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Clinical Trials Transformation

Sponsor handbook

Clinical Trial Information System (CTIS) user guidance on the sponsor's workspace

Version 6.4

The most Frequently Asked Questions (FAQs) on CTIS can be found in the Sponsor FAQs, which complements the present document.

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Introduction and general principles

The EMA Clinical Trials Information System (CTIS) Sponsor Handbook provides clinical trial (CT) sponsors representing pharmaceutical industry, SME (small and medium-sized enterprises), academia, research organisations and other clinical trial sponsor organisations with the **operational guidance** they need to create and submit clinical trial information to the member states of the European Union/European Economic Area (EU/EEA) through the CTIS. Those actions and the process is displayed through the Clickable table of contents. The summary of changes of the present document can be found in chapter 7. Annex I: acronyms and definitions can be consulted for acronyms and definitions and Annex II: lists of resources, videos and bitesize talks contains the full list of useful resources and videos, including a dedicated bitesize talk on the description of the structure of the present handbook. A Sponsor Frequently Asked Questions (FAQs) document is also available to users, see Sponsor FAQs.

CTIS serves to implement the EU pharmaceutical law under the Clinical Trial Regulation (EU) No 536/2014, hereinafter 'CTR'. The CTR applies to interventional trials with medicinal products for human use, including low-interventional trials. It does not apply to non-interventional studies (see definition in Art 2(2)(4) of the CTR) or to trials not involving medicinal products.

CTIS is the online system for the regulatory submission, authorisation and supervision of clinical trials in the EU/EEA. CTIS acts as the single-entry portal in the EU/EEA **for all trials on investigational medicinal products** involving human subjects. If a trial is performed on human subjects, but it is **observational or it is performed only on a medical device, it cannot be recorded in CTIS**. CTIS allows a unified application dossier for submissions by clinical trials sponsors to one or more EU/EEA Member State (National Competent Authorities (NCAs) and Ethics Committees (ECs)). Information exchange between sponsors and Member States is fully electronic. Most of trial data and a set of trial documents submitted through CTIS are accessible on the CTIS public website as per CTIS publication rules (see section 2.1.).

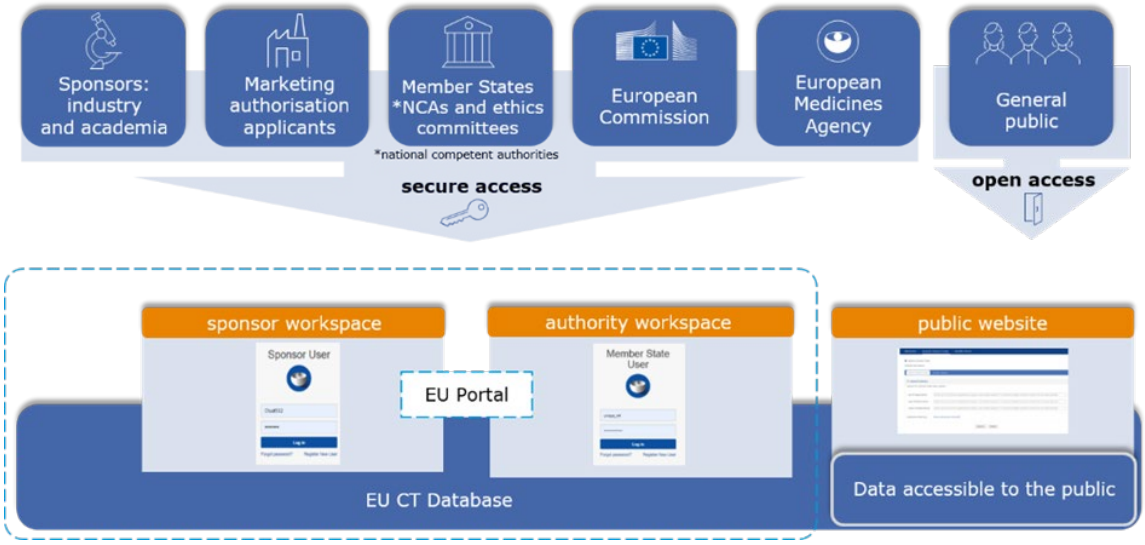
While CTIS streamlines end-to-end electronic application procedures across the EU/EEA, it **is not a clinical trial management system**. Although CTIS offers a secure archive for documents and decisions, **sponsors must use their own systems for storing trial-related data for compliance purposes.**

CTIS consists of two secured workspaces, only accessible to registered users, and a public website:

- sponsor workspace: accessible to sponsors to prepare and submit clinical trial data for its assessment by Member States, and to marketing authorization applicants to submit Clinical Study Reports, in line with Art 37 of the CTR. The CTIS sponsor workspace is only accessible to registered users and allows them to perform the actions displayed in the Clickable table of contents throughout the clinical trials lifecycle
- authority workspace: accessible to national competent authorities, ethics committees, the European Commission, and the European Medicines Agency (EMA). It allows the assessment and oversight of clinical trials by Member States and the European Commission.
- public website: open to any member of the public, including patients, healthcare professionals, and researchers, it provides searchable clinical trial information, including CT results in both technical and lay language. Users can search for specific trials or treatment-related details through a specific advanced search as well as through a more patient-oriented trial map.

The system enhances patient safety in clinical trials by offering an end-to-end electronic solution for safety reporting and a harmonized safety assessment across the EU/EEA, through delivering a

repository of Annual Safety Reports (ASRs). The electronic reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to EU/EEA Member States is done by sponsors through EudraVigilance.



→ on this topic: see also the video on CTIS technical environment.

The two CTIS secure workspaces store various data types to support user activities:

- **User-entered data**: information added during any clinical trial application (CT application) completion by the sponsor or assessment by the Member States, which includes **structured data fields** that are populated in CTIS (written values, selections made by radio buttons or dropdown lists) and **documents** that are uploaded in CTIS, which allows users to upload, view and download documents (e.g. for sponsor: protocols, informed consent forms, and safety reports, and for authorities: assessment reports). Documents can be uploaded, but not created, within CTIS.
- Data retrieved from **external databases** that are linked to CTIS:
    - **User data** from the **EMA Account Management portal**, managing user access and credentials (e.g. name, email, user ID). See section 1.1.
    - **Organisation data** from **Organisation Management Service (OMS)**, providing organisation details (e.g. name, location) and being updated from CTIS when new organisations are created directly in CTIS. See section 1.2.
    - **Medicinal product data** from the **eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD)**, supplying data on authorised/unauthorised products. See section 1.4.

  Data from XEVMPD and OMS are retrieved by sponsors when filling in the CT application and copied into CTIS at the time of retrieval. **These data and are not automatically updated when they are amended in XEVMPD and/or OMS**. This is due to legal security grounds, ensuring records match the state during submission or assessment. **In case sponsors wish to change those data, they first need to change them in those external databases** and then update the CT application through a Request for Information (RFI, see section 3.3.), a substantial modification (SM, see section 4.3.), or a non-substantial modification (NSM, see section 4.8.), depending on the field (see the document CTIS application fields).

Before starting to draft their clinical trial application in CTIS, sponsors should perform all the necessary **pre-submission steps** which **may take more than a week to be finalised** (see section 1.) and be

aware of the relevant regulatory requirements (see below box). In addition, section 6. provides useful information on CTIS release notes and known issues, information and training and contact points.

The following resources need to be consulted before compiling a CTIS CT application:

- Regulation (EU) No 536/2014
- CTR Questions & Answers (CTR Q&A)
- Quick guide for sponsors - Regulation 536/2014 in practice
- Documents listed in EudraLex - Volume 10 - Clinical trials guidelines
- Documents listed in European Commission website containing information on clinical trials in the context of Regulation EU No 536/2014
- Documents listed among the Clinical Trials Coordination Group (CTCG) Key Documents list
- National Competent Authorities (NCA) websites containing national requirements of each Member State Concerned (fees, templates, etc)

Important: once the trial is ended, sponsors must submit its summary of results and a lay-person summary of results to CTIS. This is to comply with Article 37(4) of the CTR. Relevant timelines and instructions can be found in section 5.2. of this handbook.

1. Pre-submission steps

When planning the submission of an initial clinical trial application (IN), the sponsor needs to keep in mind that **a certain time range is required for the pre-submission steps** to be completed, in terms of training and actions to be performed. Note that the Sponsor FAQs includes further guidance on this topic.

Prior to starting using CTIS, sponsors need to make sure that:

1. They have an **active EMA Account** on the EMA Account Management portal, see section 1.1.
2. Their sponsor organisation is registered in the Organisation Management Service (OMS): this can take **up to 10 days**, see section 1.2.
3. Their sponsor organisation is registered with EudraVigilance (EV), see section 1.3. Timelines for approval by the EV Registration team may vary: **timely submission for registration is advisable**.
4. All the Investigational Medicinal Products (IMPs) used in the trial are registered in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) see section 1.4.
    1) Submission of product information in the XEVMPD is possible only when the sponsor organisation is registered with EudraVigilance (i.e. the organisation profile is created, users are registered, and any technical set-up is completed).
    2) Once the product information is submitted in the XEVMPD by the sponsor user via a medicinal product message (XEVPRM), the XEVMPD confirms via an XEVPRM acknowledgement if the submission was successful or not. The XEVPRM acknowledgement is sent to the sponsor **within minutes but can take up to 48 hours**.
5. *Optional, but highly recommended:* at least one user is registered as Sponsor Admin through the EMA Account Management portal, see section 1.5.1.1. ; this will allow the sponsor to follow the 'organisation-centric approach': see section 1.5.1.

Steps 1, 2 and 3 can be performed in parallel.

To ensure optimal user experience of CTIS and of the above-mentioned EMA applications, the following is recommended:

- good **internet connectivity**. Poor connectivity may cause session timeouts when loading a page content or downloading files, require refreshing or re-login, and could lead to duplication or corruption of uploaded files in CTIS. Users can measure their internet connection quality through this link. Ethernet connection is recommended, wireless may slow uploads. (Minimum upload speed: 1 Mbit/s, Recommended download speed: 3 Mbit/s, Maximum latency: 300ms).
- use the **Google Chrome browser**. Other browsers are not recommended as they may affect user experience. If its performance is slow or not working, its browser cache should be cleared and emptied.
- **log in with a certain account once at a time.** A certain account can only be used by one person at a time. Also, users should not open multiple browser windows (tabs) with the same account credentials.
- if a user is logged into an account and needs to log into additional accounts on the same PC, they must **use separate Chrome incognito windows for each account**. Multiple accounts cannot be logged into from the same Chrome window or tabs.

- use 1080p resolution screens, especially if using dual screens.
- have an updated virus scanner installed, as well as PDF and Word software applications.
- use a PC/laptop with minimum 8 GB of RAM memory, where Windows OS runs smoothly.

Note that Mac OS devices have not been tested for the use of CTIS.

1.1. Access to EMA applications (CTIS, EV, XEVMPD)

To access the CTIS Sponsor workspace, as well as other EMA applications listed in the present handbook (EV and XEVMPD: see sections 1.3. and 1.4.), a user needs to first have an active EMA Account on the EMA Account Management portal. To do so, the user must create the account by completing the Self-service Registration form: see How to create a new EMA account.

Note that the multi-factor authentication (MFA) is enabled for EMA applications: it is recommended that each user is equipped with a mobile or an office phone that can be used for second factor authentication, see instructions. If users need to recover their credentials, they can refer to the 'Recover your credentials and re-activate your account' guide on the EMA Account Management website (this occurs in case their accounts were inactive for more than 6 months, and may imply that all associated roles are no longer assigned, see section 1.5.).

If a user already uses other EMA applications (e.g. IRIS, EudraVigilance, Eudralink), then no new account must be created, and the same access method as for other applications can be used to access CTIS.

Users can access the CTIS sponsor workspace after receiving a confirmation email, stating that their account is valid. Please note that, in some cases, it may take up to a working day until the account becomes active. **Users need to log in using their email address:** see Authentication using email address.

Once access is given to the user in CTIS, the user has a 'Default role', to which the appropriate user roles must be given, **to perform tasks** in the CTIS workspace: see section 1.5. .

Note: in case of change of employer, the user needs to register again through creating a new EMA account via the EMA Account Management portal. In addition, the user needs to disable the old account following the steps from the guide Terminate your account: further information in the EMA Account Management Frequently Asked Questions (FAQ).

With regards to the Organisation Management Service (OMS), as of 1 October 2025 its portal offers guest access to query and browse, while change requests should be submitted through the EMA Service Desk, see section 1.2.1. .

1.2. Sponsor and other organisation(s) registration in OMS

CTIS uses organisation data from the Organisation Management Service (OMS), a central source of validated organisation data for EU regulatory activities. OMS is one of the four Substance, product, organisation and referential (SPOR) master data domains and it stores master data like organisation name and address for entities in EU/EEA and outside of the EU/EEA such as marketing authorisation holders (MAHs), sponsors, third-party contractors (e.g. CRO - Contract Research Organisation), regulatory authorities, trial sites and manufacturers.

Sponsor or co-sponsor users must register their organisations in OMS before filling in their IN. In addition, any party can create a new organisation record in OMS, e.g., for clinical sites, CROs, vendors or other facilities that are required when filling in any CT application or submitting a

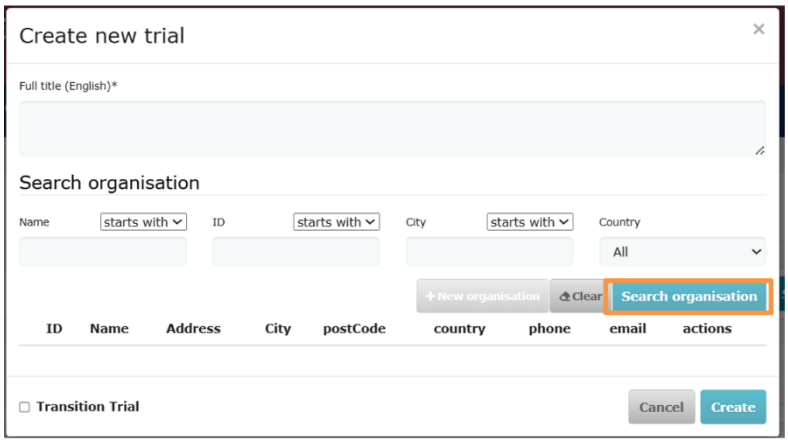
notification in CTIS. Unless the organisation is registered in a National Business Registry, all requests should also be supported by valid documentation: see section 1.2.1. **Sponsors or other organisation(s) that wish to register in OMS should be aware of its validation timelines to ensure timely registration before CTIS submission (up to 10 working days)**. See document section of OMS portal for additional information.

For all those organisations that are not sponsor organisation, the local registration in CTIS is possible: see section 2.4.3.. For sponsor organisations, **local registration** is **strongly discouraged**, as it may lead to issues during the conduct of the CT (e.g. when creating an Annual Safety Report, ASR').

If an organisation is registered in OMS, its information is public and can also be retrieved through dedicated search functionalities of CTIS in the following locations of the sponsor workspace:

- Personal profile: update employer information
- Request a role: Add sponsor organisation
- Create new trial: Add sponsor organisation
- Part I: 'Sponsor' section: Add Sponsor Legal contact / Add Third-party organisation
- Part II: Trial Sites: Add site
- Notifications on Serious Breach or third country inspectorate: Add site
- ASR submission

For example, upon access to the CTIS sponsor workspace (see section 1.1.), a sponsor user retrieves their organisation from OMS through using the 'Search organisation' functionality when clicking on 'Create' a clinical trial (see section 2.3.3.). Users need to populate the 'Name' field or the 'ID' field and click on 'Search organisation'. The more characters are used, the more accurate the search results will be. It is advised to use the 'contain' option when filtering, and not the value 'starts with'. Note: organisations can have multiple addresses (linked to the same main Organisation Identified (ORG-ID)), though only one can be selected in CTIS. After performing the search, users can select the relevant organisation by clicking the radio button.



If the organisation is not listed, or if its details are incorrect, the sponsor user should submit an EMA Service Desk request to create a new organisation in OMS (see section 1.2.1.) or to modify an existing one (see section 1.2.2.).

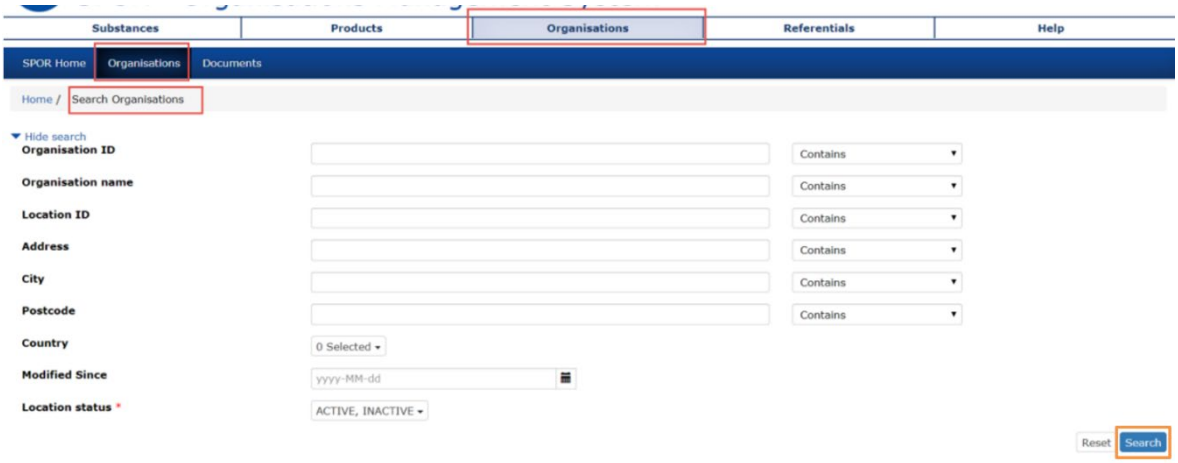
Note: the option to create a new organisation locally in CTIS (button '+ New organisation') should not be chosen by sponsor or co-sponsor organisations, which need to be present in OMS, but could be chosen in other cases, e.g. third-party organisations registration (see section 2.4.3.).

Below are the steps to follow to add a new organisation's record in OMS (see section 1.2.1.), or to modify an existing one (see section 1.2.2.), through submitting a 'change request' directly on the OMS portal.

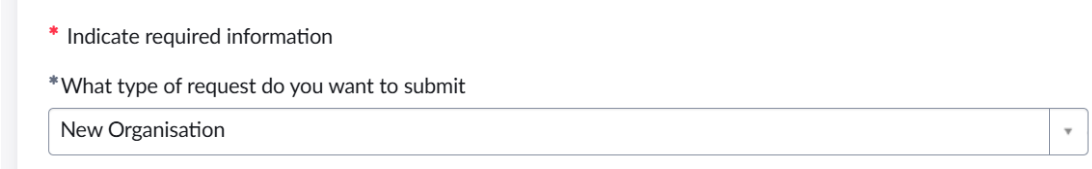
1.2.1. Add a new organisation's record in OMS

The below steps describe the actions to be performed to add a new organisation's record in the OMS portal:

1. **Search if your organisation is already registered in OMS**, by clicking on the 'Organisations' sub-tab, found on the 'Organisations' tab of the OMS search interface, using the search fields to retrieve the organisation and clicking on the 'Search' button.



2. Depending on the outcome of the search:
   - ***If you can see your organisation*** *as correctly registered in OMS*, **no further action is needed**, since no new organisation needs to be created. The following steps are not applicable.
   - *If you can see your organisation but its* ***details are incorrect***: see section 1.2.2. .
   - *If* ***no results*** *are retrieved from the search*, continue with the following steps.
3. Create a new organisation through submitting a request through the EMA Service Desk, and choosing 'New organisation', for the 'What type of request do you want to submit'. Refer to document 'A6 - Alternative access solution' in the OMS portal document repository (click on 'Documents' and then 'View')

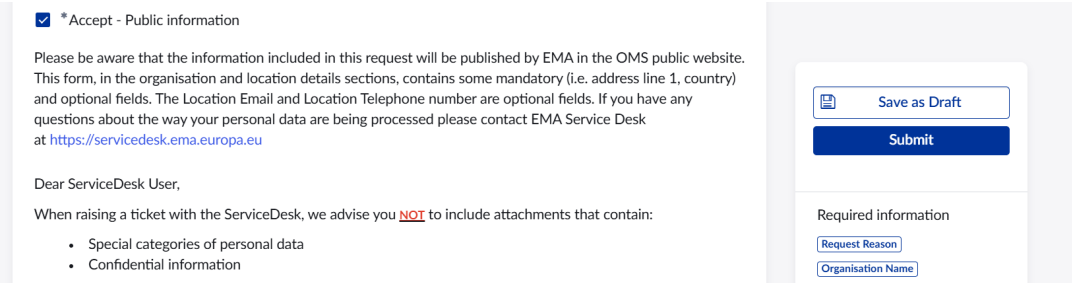


The following steps depend on whether your organisation is present in a National Business Registry (an official government-managed database that records and maintains key

information about businesses operating within a country) or not. **Refer to document 'C - OMS Data Quality standards' in the OMS portal document repository** (click on 'Documents' and then 'View'), where there is a section on the 'Reference of National Business Registry websites, within and outside the EEA':

- *In case your organisation is not present in a National Business Registry*: continue with step 3.
- *If your organisation is registered in a National Business Registry*, no document is needed, and you can directly submit the form as per step 4.

4. *If your organisation is not listed in a National Business Registry,* **then you need to include valid documentation** in the 'Add Attachments' section of the EMA Service Desk request: only those entities that have the necessary documents should perform the registration. To know which documentation should be submitted in the change request, see the document 'E - OMS Change Requests' (section 'Request of a new Organisation', table on 'Required Documentation') in the OMS portal document repository (click on 'Documents' and then 'View'). The documentation varies depending on the organisation; for example, for Hospitals, Universities, and research institutions it can be the EudraGMDP site reference number or document for the GxP certificate, or otherwise a 'CT registration Headed Letter' (found as template on the OMS portal document repository). The 'CT registration Headed Letter' must be always attached in case the sponsor is not an organisation but a person (e.g. practitioner, entrepreneur). Note: **if the documentation attached to the request is not compliant with OMS's requirements, it may lead to the rejection of the request.**
5. Once all fields of the **'New organisation request' have been populated** as per step 2 (and any appropriate documentation attached, if applicable, as per step 3) you need to **select the checkbox** under the information fields, acknowledging that you are aware that the information included in the request **will be published** by the EMA on the OMS public website. Afterwards, click on the '**Submit'** button in the **right corner**.



The validation and approval of the requests can take up to 10 working days: see document 'X - SPOR SLAs' available in the OMS portal document repository (click on 'Documents' and then 'View'). **The more correct the provided documentation is, the shorter the approval timeline will be**.

Once the change request is validated and processed by the EMA OMS team, the user will receive an email acknowledgement with the outcome through the EMA Service Desk:

- **Approved Change request:** acknowledgement that will contain the outcome and the correspondent **ORG-ID**.

- **Rejected Change Request:** acknowledgement that will contain the outcome, reason for rejection and, where applicable, guidance on the necessary steps for successful approval of the change request.

The ORG-ID is automatically generated by OMS at the time of the creation of an organisation. This ID is specific for each organisation. It is composed of ORG-1000 plus a random number created by the system (e.g. ORG-100001234). If users do not have this information at hand and would like to view it, they can retrieve it by searching for their organisation in OMS.

Multiple requests for various organisations (also, without waiting for prior requests to be handled) can also be submitted (also, not necessarily for the user's organisation, it can be a registered organisation the user represent). In case there is no registered organisation in OMS to be affiliated with (either the user employer or an organisation to be represented), the user needs to submit a request for a new organisation as per above steps and wait until the request is approved. After approval of the request, the following ones can be submitted, also in parallel.

In case the organisation has different departments and clinics:

- *If the departments and clinics belong to multiple legal entities*, each one will need to be registered separately in OMS.
- *If all the departments belong to the same legal entity*, users need to register in OMS only one organisation with one ORG-ID.
- *If all the clinics and departments belong to the same legal entity but are located at different physical addresses* (i.e. clinic A is located to XYZ Street 03 and clinic B is located to XYZ Street 13), then users need to register in OMS as many different locations as the number of the different physical addresses, always under the same ORG-ID.

With regards to **details** of the departments or clinics, those are not to be inserted in OMS, but in CTIS Part II of any CT application ('Investigator information' section, 'Department' field: note that the Department field has a limit of 100 characters when filling it in any CT application), see section 2.2.

1.2.2. Updating an existing organisation in OMS

To update the details of an existing organisation or to add a new location, a user needs to submit a request to the EMA Service Desk. Anyone can submit a change in OMS, regardless of the organisation they are affiliated with, as long as they are affiliated to an organisation available in OMS. Nonetheless, the change request is validated by the EMA OMS team and therefore valid supporting documentation should be provided to support it. The process could **take up to 10 working days**: see also listed document 'X - SPOR SLAs' available in the OMS portal document repository (click on 'Documents' and then 'View'). Instructions on updating existing organisations in OMS are provided in the document 'E - OMS Change Requests' (section 'Request of a new Organisation', table on 'Required Documentation') in the OMS portal document repository.

1.3. Sponsor registration in EudraVigilance (EV)

Sponsors must be registered with EudraVigilance (EV) to report medicinal product information in XEVMPD (see section 1.4.), as well as to report Suspected unexpected serious adverse reactions (SUSARs) to EV (see section 4.12.): see EudraVigilance website and EudraVigilance: how to register. Sponsors of clinical trials should be able to report SUSARs in a timely manner. For this reason, even if the medicinal product information is already present in XEVMPD, **it is necessary for the sponsor to be registered in EV before submitting an IN**. To do so, the Responsible Person (RP) of the sponsor

(see this page) needs to provide a Notification of successful completion of the EudraVigilance ICSR training (see EudraVigilance training on electronic reporting of ICSRs) and a Notification of a successful completion of the XEVMPD knowledge evaluation (virtual or e-learning). Both are requested from at least one user from the sponsor organisation during the organisation's registration with EudraVigilance; this person does not necessarily have to be the RP (i.e. the notifications can be in the name of any active user of the organisation who has completed the above courses). Timelines for approval by the EV Registration team depend on several factors, including the correct submission of the necessary documents: **timely submission for registration in EudraVigilance is advisable**.

1.4. Medicinal product registration in XEVMPD

Before filling in the 'Product' section of any CTIS CT application (see section 2.4.5.), **the sponsor must ensure that information about the medicinal products used in the trial is available in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD)**. The XEVMPD (also known as 'Article 57 database') includes all EU/EEA-authorised medicinal products as well as unauthorised ('development') medicinal products that are linked to clinical trials, including those without an EU/EEA marketing authorisation for their specific strength or form. Information on medicinal products that are already authorised in the EU/EEA is submitted in the XEVMPD by MAH. Information on medicinal products that are not authorised in the EU/EEA is submitted in the XEVMPD by sponsors. Note: placebo details are to be added directly in CTIS without XEVMPD registration. A **timely registration of product information in XEVMPD is essential** not only when applying for an IN, but also when updating information when replying to RFI (see section 3.3.) or when submitting an SM (see section 4.3.)

To submit medicinal product data in the XEVMPD, sponsor organisations must be registered in the Organisation Management Service (OMS, see section 1.2.) and also with EudraVigilance for medicinal product reporting (see section 1.3.). Sponsors can submit medicinal product information either via Gateway or via the XEVMPD web application (XEVMPDweb). **At least one user from the sponsor organisation needs to have completed XEVMPD training before the sponsor can submit medicinal production information in the XEVMPD**. The XEVMPDweb application allows registered users to create and send Extended EudraVigilance Medicinal Product Report Messages (XEVPRMs), receive XEVPRM acknowledgements which confirm their submissions, view medicinal product information and perform queries.

See the Guidance on the electronic submission of information on investigational medicinal products for human use in the XEVMPD for information on how to submit information for each data field of your investigational product. The document also includes information on how to add missing information (for example, substance or sponsor details) in the XEVMPD.

When registering medicinal products in the XEVMPD**, sponsors should take into account the publication requirements of the relevant CTIS product data fields**, as specified in the document CTIS application fields. The publication modality and timelines of product-related fields are defined in Annex I of the Guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System (CTIS). Note that fields taken from the XEVMPD cannot be further amended in CTIS before publication; as per the XEVMPD guidance, due to the CTIS publication rules, it is recommended that **the product name created and entered in XEVMPD is not considered commercially confidential and does not contain the strength of the product**.

Providing that the insertion of the medicinal product information was successful, an EV Code is assigned to the medicinal product record by the XEVMPD; the XEVPRM acknowledgement will reference the assigned EV Code, which is considered the EU MP Number in CTIS. In case the XEVPRM

acknowledgement is not received by the sponsor, a query to the XEVMPD Service Desk can be raised by the sponsor. Once the EV Code assigned to the medicinal product record is available in the XEVMPD, **the sponsor will be able to search and retrieve its relevant product details through CTIS application within 48 hours**: see section 2.4.5.

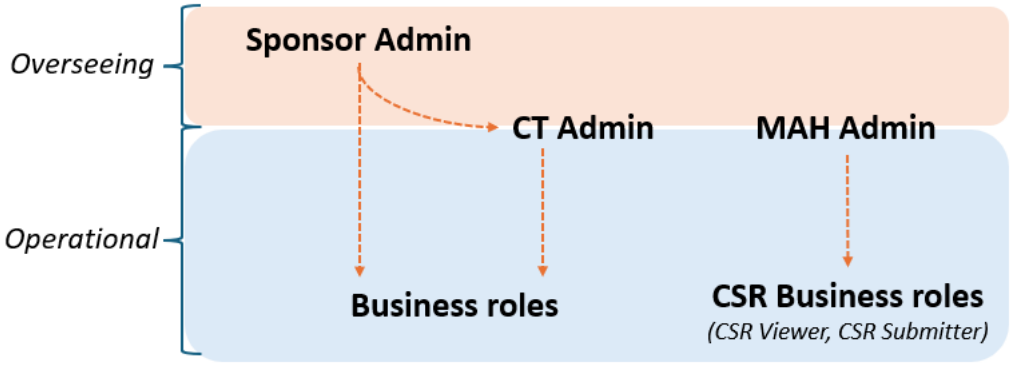
1.5. CTIS user management: Organisation-centric vs Trial-centric

CTIS is a role-based system that enables users to perform specific actions based on their responsibilities and the permissions assigned to them within a clinical trial.

All registered users via EMA's Account Management Portal (see section 1.1.) **receive a default role in CTIS** that enables them to access the CTIS sponsor workspace. The default role enables users to manage their user profile information. By clicking on their name at the top right corner of the CTIS interface, users can update their personal profile (e.g. contact details, or employer's info), **view and request a role** (through the 'My roles' sub-tab, see section 1.7.2.) or log out of the system. **Default users that have no role assigned can only see the 'Clinical trials' tab** on the top left of the page. However, to have visibility of other tabs and perform actions in the system, roles must be given to registered users. The tabs that can be seen once the appropriate roles are given are the 'Notices & alerts' tab, the 'RFI' tab, the 'User administration' tab, the 'Annual safety report' tab and the 'Clinical Study Report' tab (see section 1.6.).

There are two main types of sponsor roles in CTIS:

- **Administrator roles**, allowing users to assign and oversee roles of other users through the 'User administration' tab (3 in total: Sponsor Admin, CT Admin, MAH Admin).
- **Business roles**, allowing users to operate on the trial (15 in total, including Part I preparer, CT Submitter, ASR Submitter, Clinical Study Report (CSR) Submitter, etc.).

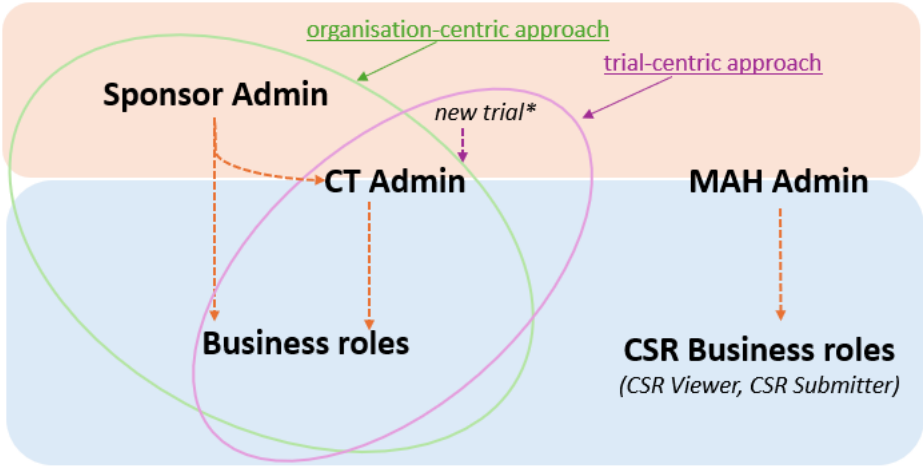


CT Admin and MAH Admin are Administrator roles that also have operational permissions: CT Admin has all business roles except ASR Submitter, CSR Viewer and CSR Submitter, while the MAH Admin has the CSR Viewer and the CSR Submitter roles. For a full overview of their characteristics and of the permissions allowed for each role, see section 1.6.

There are **two user management approaches** of CTIS, which enable organisations to manage their users according to their needs and resources: the **Organisation-centric approach** and the **Trial-centric approach**.

The **approach is established automatically** when the user performs certain actions in the system:

- once a **Sponsor Admin role is given to a user of a specific organisation** (with a certain ORG-ID), all trials sponsored by that ORG ID will follow the **organisation-centric approach** (see section 1.5.1.
- if a **user with no role assigned** logs in the CTIS Sponsor's workspace and **creates an IN for an ORG-ID that does not have a Sponsor Admin user appointed**, the trial will follow the **trial-centric approach** and the user automatically gains the role of 'CT Admin' (see section 1.5.2. 1.5.2.).



**new trial created from an ORG-ID for which a Sponsor Admin was not appointed, see section 1.5.2.*

Pros and cons of the two approaches need to be evaluated by a sponsor before starting a new trial in CTIS: detailed descriptions of the two approaches are available in sections 1.5.1. and 1.5.2. Based on the current experience, **it is recommended that commercial and non-commercial sponsors use the organisation-centric approach** (preferably by centralising the activity within a dedicated internal team).

→ on this topic: watch also the video on Creating a clinical trial: Clinical trial-centric approach vs organisation-centric approach.

1.5.1. Organisation-centric approach

The organisation-centric approach allows the **management of user roles at the organisation level**, ideal for sponsors running multiple trials. Once the sponsor organisation is registered in OMS (see section 1.2.), in order to follow this approach **a Sponsor Admin (high-level administrator) must be registered through the EMA Account Management** portal (see section 1.5.1.1.).

This type of user management approach follows a top-down model, where the **Sponsor Admin assigns medium-level administrator (i.e. CT admin) and business roles** to users to perform user management or business activities in CTIS. Upon role's assignment, **users become affiliated with the organisation's ORG-ID (as registered in OMS) of the relevant Sponsor admin in CTIS**.

The organisation-centric approach is particularly useful for organisations that (will) conduct trials on a regular basis, even if with a low frequency. This approach ensures centralised access management, since access and roles can be managed centrally across trials, ensuring good visibility of an organisation's CTIS user pool and workload. It supports data quality and integrity and enhances security, as access to CTs is enabled by role assignment/approval for a certain ORG-ID (as registered in OMS). However, this approach requires a formal registration process. The first Sponsor Admin for an organisation needs to be validated through the EMA Account Management portal (either by the EMA or by the

External Organisation Administrator, who is also validated by EMA and can approve or reject requests to become an administrator for other EMA-run systems, see section 1.5.1.1.).

If the organisation for which a CT is going to be created already has a Sponsor Admin associated with the respective ORG-ID, the applicable approach will automatically be the organisation-centric and all of the organisation's users will need to have roles assigned by the Sponsor Admin to perform any action in the system (or by the CT Admin, with an 'all trials' role, once appointed by the Sponsor Admin, see section 1.7.1.).

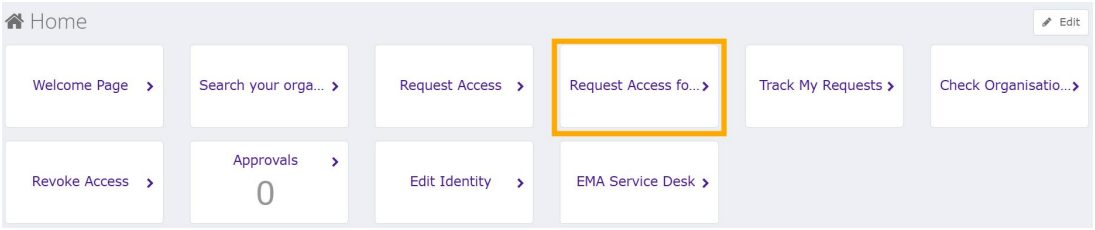
1.5.1.1. Sponsor Admin registration through the EMA Account Management portal

The CTIS Sponsor Admin ('Sponsor Admin') is a high-level administrator role that is applicable only to the organisation-centric approach.

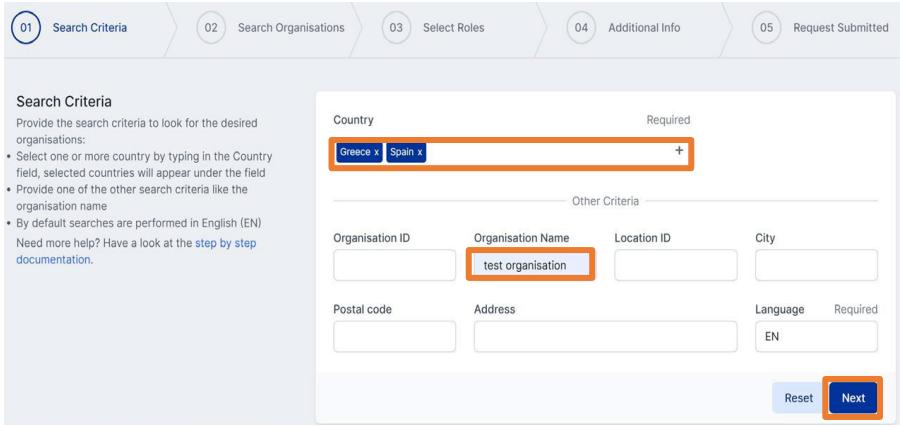
The request for the Sponsor Admin is submitted and managed through Identity and Access Management (IAM) section of the EMA Account Management portal by the user that will become the Sponsor Admin for an organisation with a specific ORG-ID.

Steps that a user with a 'Default' role (see section 1.1.) needs to do to request a Sponsor Admin role:

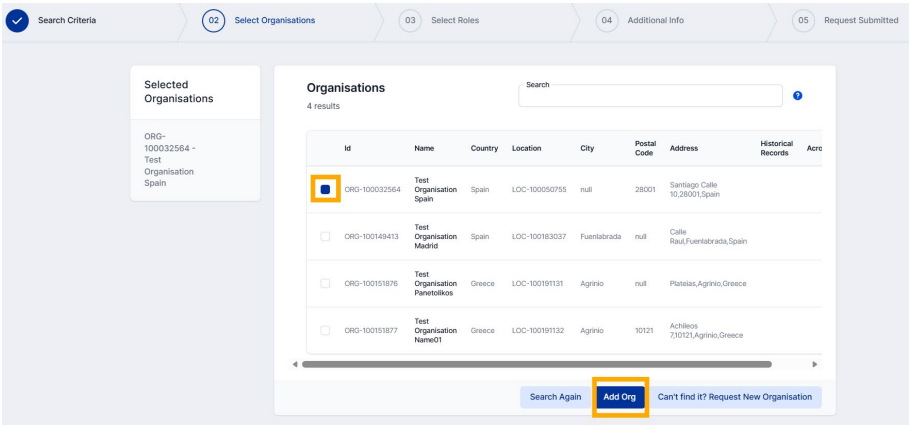
1. Sign in the EMA Account Management portal (see section 1.1.) by clicking on 'Single Sign on' at the top right of the webpage. Then, click on the 'Request Access for Organisations' tile in the EMA Account Management portal dashboard.



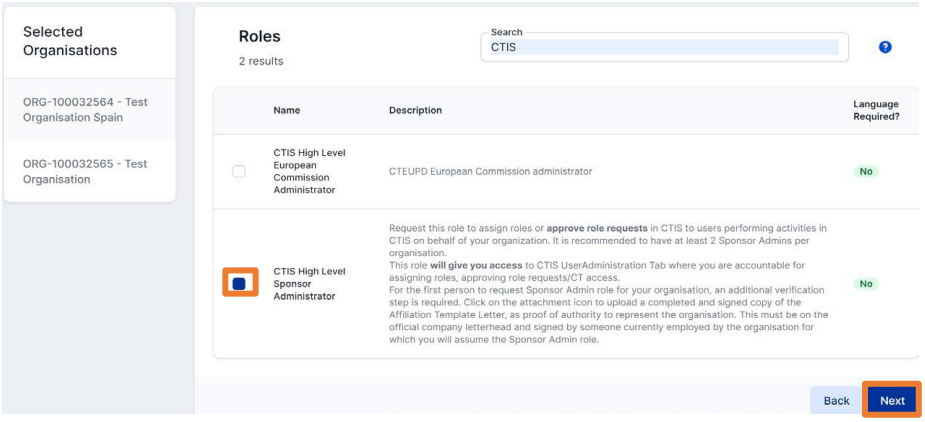
2. Once in the Request Access for Organisations page, add at least two search criteria: 'Country' (required) and organisation ID or Organisation name (the same as for OMS registration, see section 1.2.) and click on 'Next'.



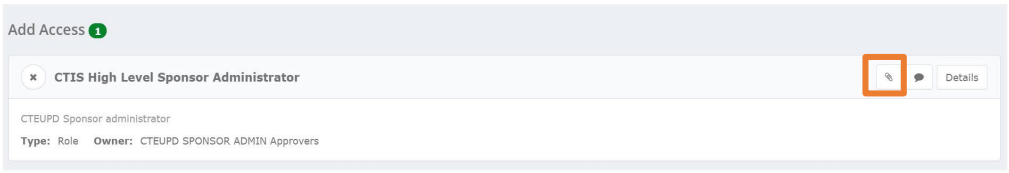
3. Select the organisation or organisations for which the role needs to be requested and click on 'Add Org'.

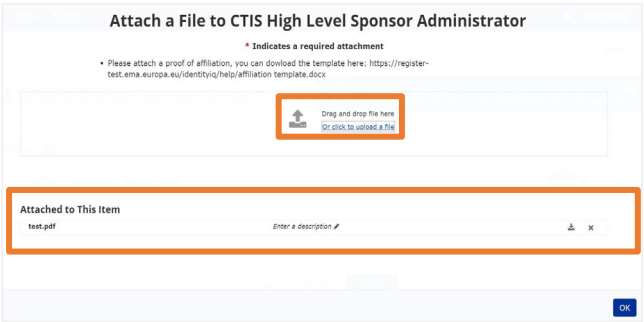


4. Search the keyword 'CTIS' to perform the search in the 'Roles' section. Select the tick box for the 'CTIS High-level Sponsor Administrator' role and click on the 'Next' button.



5. *If no other Sponsor Admin or [External Organisation Administrator] exists for the relevant ORG-ID,* then download the [affiliation letter] template, copy paste its content onto a Sponsor company's letterhead and attach it by clicking on the 'Attach' button (paper clip icon) at the left of the 'CTIS High Level Sponsor Administrator'. This affiliation letter must be signed by someone currently employed by the organisation and can represent it legally, for which the user will assume the Administrator Role (i.e. a person working for the organisation and who can legally represent it). You can add a description of the document by selecting the 'Pencil' icon next to the

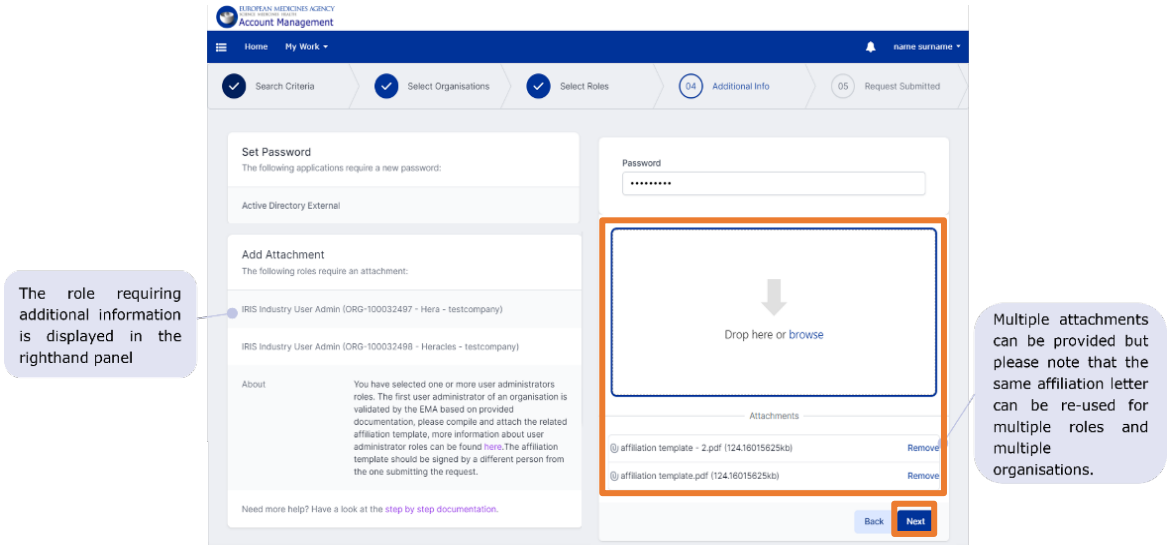




document. Once attached, click on 'OK'. If no document is attached while requesting the role, the request will be denied by the EMA system.

If there is already a Sponsor Admin or External Organisation Administrator, the necessity of the above step is defined internally by the organisation's internal procedures. The proof of affiliation letter is not required once an External Organisation Administrator has been validated in the EMA Account Management for a certain ORG-ID.

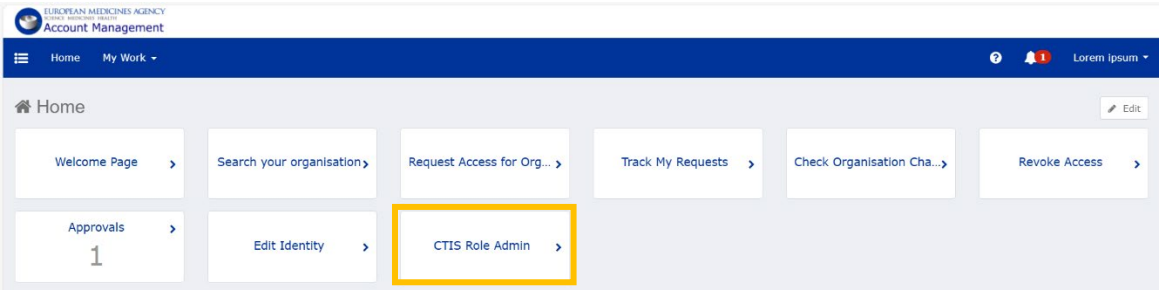
6. *In some cases (depending on the combination of selected organisations and roles),* an 'Additional Information' page is displayed. After adding the requested info, or *if no additional information is required*, click on the 'Submit' button and the request is submitted.



7. After the completion of the request, the Request ID is generated.

The request is then **processed** either by the EMA or by the External Organisation Administrator (if this already exists for the relevant ORG-ID, as described in the EMA Account Management portal), *in case no other Sponsor Admin was already appointed for the same organisation*; *if the same organisation already has a Sponsor Admin*, this user will be the one approving the request (see section 1.5.1.2.). Note: the appointment of the Sponsor Admin is tied to the ORG-ID. **If multiple ORG-IDs exist for the same organisation, separate requests must be submitted for each**, although the same affiliation letter can be reused and attached for each individual request.

When a request is approved, the user receives a confirmation email and the title 'CTIS Role Admin' is displayed in the EMA Account Management portal **Home dashboard**.



Once the EMA or the External Organisation Admin approves the first Sponsor Admin, **this Sponsor Admin (or the External Organisation Administrator) manages subsequent requests from users of the same organisation seeking the same role via the EMA Account Management portal**

(see section 1.5.1.2.). Those requests are received via automated email notifications. The EMA does not handle these requests once the first Sponsor Admin (or an External Organisation Administrator) has been assigned by the EMA.

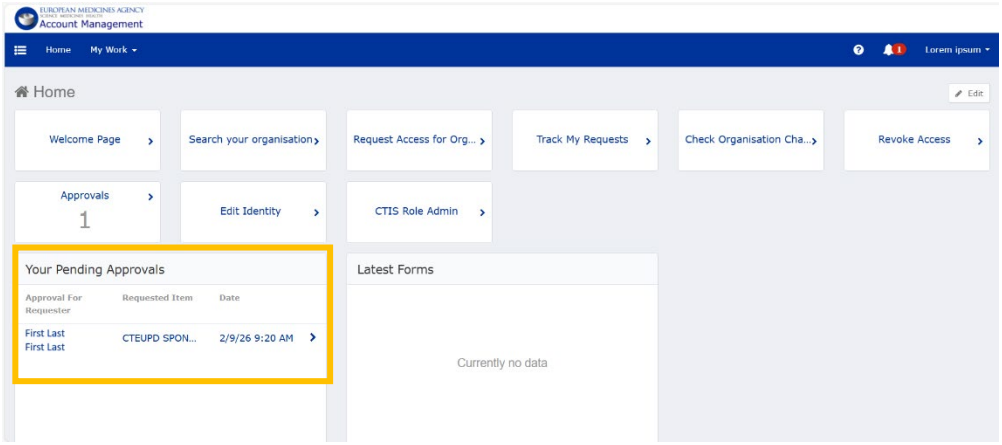
There is no limit to the number of Sponsor Admins that a sponsor organisation can have. It is up to the sponsor to decide the number of Sponsor Admin roles. Every organisation is advised to have more than one Sponsor Admin, as every one of them can manage the other Sponsor Admin users of his/her organisation (i.e. approve or reject a request or remove an existing one). Note: any Sponsor admin can remove the role of the other Sponsor Admins, regardless of the order in which they were assigned the role.

1.5.1.2. ***Sponsor Admin role assignment to another user by the Sponsor admin***

An already assigned Sponsor Admin user can approve or reject a request to have a Sponsor Admin role by another user, (see section 1.5.1.1. on how to submit a request to be a Sponsor Admin). The request is received by the Sponsor Admin users via email and this assignment can be given by the Sponsor Admin to a user of their affiliated ORG-ID or working on behalf of such organisation.

Steps that a user with a **Sponsor Admin** role (see section 1.5.1.1.) needs to take to assign a Sponsor Admin role to another user through the EMA Account Management portal:

1. Log in the EMA Account Management portal and click on the relevant request in the 'Your pending approvals' section



2. Review the request details, select 'Approve' or 'Deny' and click on 'Complete'. *If multiple requests were received*, they can all be processed at once by using the 'Approve all' or 'Deny all' buttons.

The changes regarding a Sponsor Admin role can be administered internally by another Sponsor Admin. To that end, **it is advised to have at least two Sponsor Admins per organisation**.

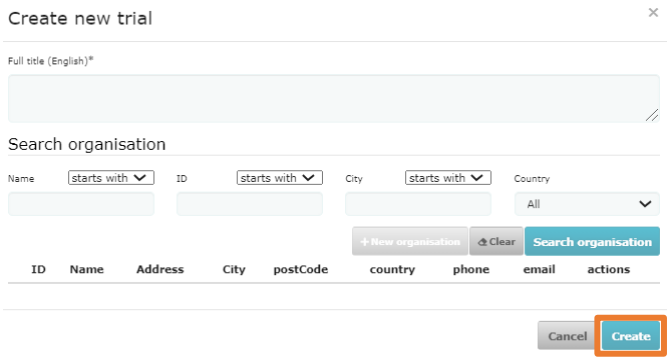
1.5.2. Trial-centric approach

The trial-centric approach applies **when no Sponsor Admin was registered in the EMA Account Management portal for a specific ORG-ID**, see section 1.5.1.

The same steps described to create a new CT (see section 2.3.3.) are applicable to a user with a 'Default' role (see section 1.1.) that is implementing the trial-centric approach:

1. Log in the sponsor workspace, and in the 'Clinical trials' tab click on the '+ New trial' button at the bottom right corner.

2. Populate the information of the new trial (title, organisation, choosing the specific ORG-ID previously recorded in OMS, see section 1.2.) and click on 'Create'.



3. The system checks if there is already an appointed Sponsor Admin with that specific ORG-ID:
   - *if no Sponsor Admin exists*, **the user automatically becomes the CT Admin for that particular trial**. Access is strictly restricted to the trials created by the user, regardless of the existence of other CTs created by other users using the same ORG-ID.
   - *if the specific ORG-ID has already a registered Sponsor Admin*, the user will not be able to create the IN, and **an error message is displayed**. In this case, the user will need to ask for a role to the already appointed Sponsor Admin, and the trial will follow the organisation-centric approach, (see section 1.5.1.).

Through the trial-centric approach, **further allocation of other CT Admin or business roles is then done at trial level by the CT Admin**, who can manage users and can perform sponsor business activities in CTIS related only to that particular trial (with the exception of activities related with ASR and CSR submission, for which the specific roles need to be requested, see section 1.7.1.).

Note: in case a Sponsor Admin is nominated afterwards, for the same organisation where the CT Admin had previously created a trial under 'CT centric approach', that trial will subsequently follow the 'organisation-centric approach'.

This user management approach follows a **bottom-up model with roles assigned at trial level, rather than organisation level**. This approach could suit small organisations and specifically academic sponsors, which may initiate very limited number of trials and on an *ad hoc* basis. It enables faster submissions but **poses security risks**, as any user can create a trial on behalf of a sponsor organisation that has not previously registered a Sponsor Admin. Moreover, it lacks central oversight as no user can view all trials, nor all users involved, at the level of a specific ORG-ID. In case of future change of legal entity of the sponsor, this approach causes further burden to the original sponsor regarding the administration of roles: see bottom of section 4.1.1.

1.6. User roles in CTIS ('role matrix')

A role is a function with one or more permissions. In this context, a permission is an approval to do something on data or other system resources. As mentioned in section 1.5. , user roles in CTIS can be Administrator roles or Business roles. The CTIS Administrator Roles (Sponsor Admin, CT Admin and MAH Admin) are the ones that can assign other business roles in CTIS, while business roles are the ones that have the permissions to view/create/update or complete certain tasks in the trial lifecycle. In the organisation-centric approach, the **Sponsor Admin assigns other users the roles of Sponsor Admins, CT Admins and Business roles** (e.g. Part I Preparer, ASR Submitter), see section 1.7.1. . In the trial-centric approach, the CT Admin nominates other CT Admin and business roles (e.g. Part I Preparer, ASR Submitter). The MAH admin (either in an organisation-centric approach or trial-centric approach) cannot be nominated by the Sponsor admin or by the CT Admin, but can only request the role through the EMA CTIS Service Desk (see section 5.3.1.); once nominated, the MAH Admin nominates CSR-related Business roles (CSR Viewer, CSR submitter)

The present section provides details on the permissions related to the different kinds of roles. With the exception of the Sponsor Admin role, all other roles can be 'trial specific' (only allowed for a certain trial) or 'all trials' (for all trials of a specific ORG-ID). In addition, the same user can have multiple roles at the same time, although **having roles with overlapping permissions is discouraged**, see section 1.6.2. .

Important: users should only be assigned the roles necessary for their activities. If a role is no longer required for a sponsor user, the relevant Sponsor Admin or CT Admin should revoke it (see section 1.7.1.). Retaining unnecessary roles may contribute to system performance degradation and should be avoided.

It is recommended that Sponsor Admins are limited to a small number of users (e.g. 2 or 3 users). The number can be higher for the CT Admins depending on whether other organisations are given access to the system (e.g. CROs). A business user cannot have the same role twice.

→ on this topic: watch also the CTIS bitesize talk: User access and role management.

See also document Notices and alerts per role.

1.6.1. Administrator Roles

See below the specific characteristics for each of the CTIS Administrator roles.

The **Sponsor Admin** (classified as 'high level Sponsor administrator'):

- needs to request the role through the EMA Account Management portal (see section 1.5.1.1.) or have the role assigned by another Sponsor Admin (see section 1.5.1.2.).
- is the first role that can be requested in case of organisation-centric approach (see section 1.5.1.).
- has the full overview and can manage all users of the affiliated organisation.
- has only administrator permission and not business permissions: to operate on a trial, a user that only has the Sponsor Admin needs to assign other roles to him/herself (e.g. CT Admin, or other business specific roles.

The **CT Admin** (so called 'medium level administrator'):

- can be first assigned only by the Sponsor Admin in case of organisation-centric approach (see section 1.5.1.), or by other CT Admins if at least one CT Admin was assigned by the Sponsor Admin.
- is the first role automatically assigned in case of trial-centric approach (not recommended, see section 1.5.2.).
- has administrator permissions and can assign other roles to users, either proactively or upon request of those users (see section 1.7.) and can manage a number of users for a specific trial or for all trials of the affiliated ORG-ID, depending on whether their scope assigned is 'specific trials' or 'all trials', respectively.
- has all business permissions except those related ASR and CSR processes. Note: a user needs to be given the role of CT Admin with scope 'all trials' in order to be able to create one or more new IN, and to copy or resubmit a trial for that ORG-ID.

The **MAH Admin** (also classified as 'high level administrator'):

- can be assigned upon request by the EMA CTIS Service Desk, following the submission of a valid affiliation template (see section 5.3.1.).
- has administrator permissions (limited to other CSR related roles) as well as business permissions (CSR Viewer and CSR Submitter).
- can only operate in the creation and submission of CSR (see section 5.3.2.) for one or more trials and does not have any other business role (contrary to the CT Admin).

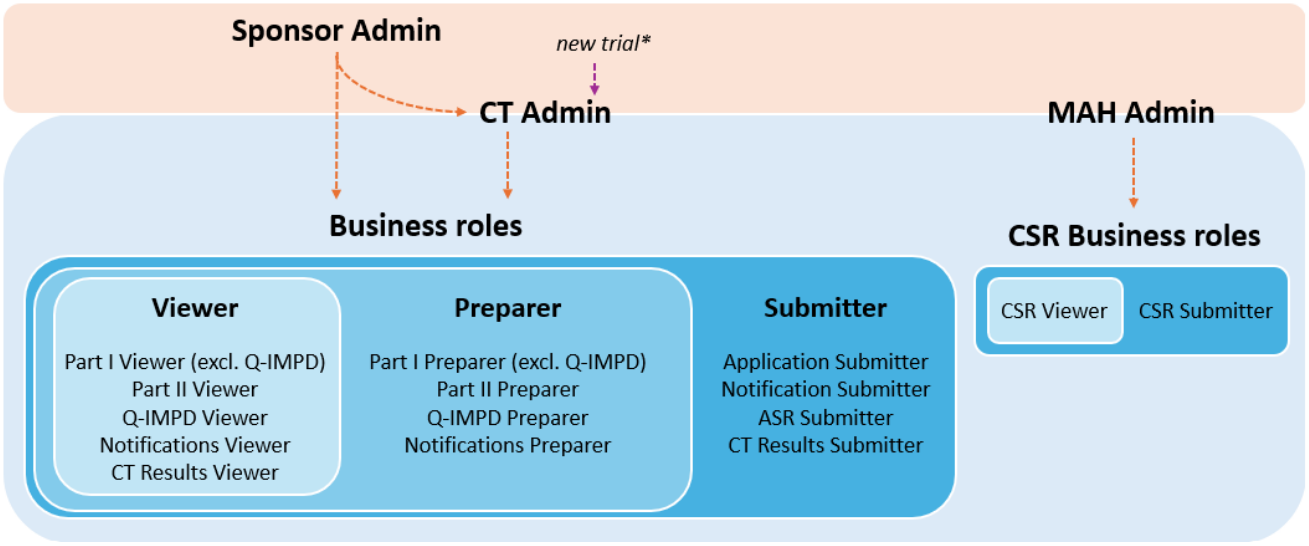
1.6.2. Business roles

Business roles are assigned to users by Administrator users and cannot assign roles to other users. Users with those kinds of roles can perform specific activities in CTIS, for a specific CT or for all CTs, within their organisation. As mentioned, a user can have more than one role.

In total, there are 15 Business roles. They can be assigned by the Sponsor Admin, the CT Admin or the MAH Admin; those roles can be grouped according to 3 main sets of permissions:

- **Submitting** permissions allow users to submit and withdraw data/documents, and to update submitted data/documents (including all preparing and viewing permissions listed below).
- **Preparing** permissions allow users to create, edit, upload documents, save and copy information from an existing CT application to create a new one, as well as deleting or cancelling draft items (including also viewing permissions listed below).
- **Viewing** permissions allow users only to view and download structured data and documents in different formats.

Those permissions are structured in a cascade approach (i.e. each permission level includes the permissions of the previous levels):



**new trial created from an ORG-ID for which a Sponsor Admin was not appointed, see section 1.5.2.*

The names of the business roles reflect the area of action of a CT (e.g. Part I, ASR) in which users are involved, and their access level permissions (e.g. Viewer, Preparer, or Submitter). The different business roles allow users to perform specific activities in CTIS for a specific CT or all CTs of their affiliated organisation. For example: Part II Preparer role can create and delete drafts of Part II of the application dossier of a CT; the Application Submitter can share, submit, withdraw and update the final version of an application while the Part II Viewer can only view the information of Part II, but not edit it.

It is up to the administrator users to decide how many roles a user can have. There is, in principle, no limit to the number of business roles a user can have simultaneously. However, as best practice, **assigning overlapping roles**—such as Viewer in addition to Preparer, or Viewer/Preparer in addition to Submitter—**is discouraged**, as it may negatively impact system operability.

1.6.3. Administrator, Preparer and Submitter roles

The table below gives an overview of the permissions linked to the Sponsor workspace for the three **Administrator roles**, and for all **Preparer and Submitter roles**, covering sponsor roles and the marketing authorisation holder ones. For an explanation of the specific permissions within the step-by-step guides, refer to the relevant sections in this handbook (see Clickable table of contents).

Allowed permissions

		Sponsor Admin	CT Admin	Part I Preparer (excl Q-IMPD)	Q-IMPD Preparer	Part II Preparer	Application submitter	Notification Preparer	Notifications Submitter	ASR Submitter	CT Results Submitter	MAH Admin	CSR Submitter
Roles Admin	Manage role assignment: view and allocate roles and trials	■	■										
	Assign CSR viewer and/or CSR submitter roles											■	
Create initial application (IN)	Create/Edit/copy/resubmit IN		■										
	Form: add cover letter, Compl. Reg. 2016/679 and CT category		■					■					
	Form: proof of payment		■	■		■		■					
	MSC: add MSCs involved		■					■					
	Part I: populate information Part I (excl. Q-IMPD)		■	■				■					
	Part I: populate information Part I (Q-IMPD)		■		■								
	Part II: populate information for Part II		■			■		■					
	Timetable: modify Winter clock stop		■					■					
	Cancel/submit/withdraw an IN		■					■					
Request for Information (RFI) Response	Add supporting documentation – General		■	■		■		■					
	Add supporting documentation - Quality		■		■								
	Change CTA Part I excl. Q-IMPD/add CTA changes		■	■				■					
	Change CTA Part I Q-IMPD/add CTA changes		■		■								
	Change CTA Part II/add CTA changes		■			■		■					
	Reply to Part I excl. Q-IMPD considerations/add doc		■	■				■					
	Reply to Part I Q-IMPD considerations/add doc		■		■								
	Reply to Part II considerations/add document		■			■		■					
	Discard CTA changes/Submit RFI response		■					■					
Notifications	Create trial notifications on CT events (e.g. trial start) or other (e.g. unexpected event)		■						■	■			
	Submit/update/withdraw notification		■							■			
Additional Member State Concerned (AM)	Create/Cancel/Submit/Withdraw AM		■					■					
	Form: cover letter/ Compliance Reg. 2016/679		■					■					
	Form: proof of payment		■	■		■		■					
	MSC: add the expected number of subjects		■					■					
	Part I: add Translations to Part I (Q-IMPD)		■		■								
	Part I: add Translations to Part I (excl. Q-IMPD)		■	■				■					
	Part II: create Part II		■			■		■					
	Timetable: modify Winter clock stop		■					■					
Create substantial modification (SM)	Create/Cancel/Submit/Withdraw SM		■					■					
	Form: cover letter/SM description		■					■					
	Form: proof of payment		■	■		■		■					
	MSC: modify the expected number of subjects		■					■					
	Part I: modify Part I (Q-IMPD)		■		■								
	Part I: modify Part I (excl. Q-IMPD)		■	■				■					
	Part II: modify Part II		■			■		■					
	Timetable: modify Winter clock stop		■					■					
Create non-substantial modification (NSM)	Create/Cancel/Submit/Withdraw NSM		■					■					
	Form: NSM description		■					■					
	Form: proof of payment		■	■		■		■					
	Part I: modify Part I documents (Q-SA)		■		■								
	Part I: modify Part I documents (excl. Q-SA)		■	■				■					
	Part II: modify Part II		■			■		■					
Ad hoc ass. or Corrective Measure	Respond to RFI raised during an ad hoc assessment or as opinion on a Corrective Measure		■						■	■			
ASR	Create/submit ASR & ASR RFI responses										■		
Results	Create/submit/update/withdraw summary of results and lay person summary of results		■									■	
Clinical Study Report (CSR)	View trial (list and summary) of the CSR and View trial's notices and alerts for the CSR, Download CSR												■
	Create CSR, Submit/update/withdraw CSR												■

1.6.4. Viewer roles

The table below gives an overview of the permissions linked to the Viewer roles, covering not only the sponsor roles but also the MAH ones.

What can be viewed		Part I Viewer (excl. Q-IMPD)	Q-IMPD Viewer	Part II Viewer	Notifications Viewer	CT results Viewer	CSR viewer
Tabs	**CT list and summary tab**	■	■	■	■	■	■
	Full trial information tab	■	■	■		■	
	Notifications tab				■		
	CT Results tab (Result summary)					■	
	Corrective measures tab (including request for opinion, view of the opinion)				■		
	Assessment additional information tab (RFI and RFI response)				■		
	Users tab	■		■	■	■	
	Notices and alerts tab	■	■	■	■	■	
	Clinical Study Report (CSR) tab and **Notices and alerts on the CSR**						■
Creation of CT	**Form:** cover letter, proof of payment, Compliance Reg. 2016/679 and trial category	■		■			
	MSC	■		■			
	Part I dossier: Q-IMPD/ scientific advice restricted document		■				
	Part I dossier: excl. Q-IMPD	■					
	Part II dossier			■			
Evaluation of CT	**RMS selected** (from the summary tab)	■	■	■	■	■	
	Validation information: RFI/RFI response - Q-IMPD		■				
	Validation information: RFI/RFI response – excl. Q- IMPD	■		■			
	Validation information: validation conclusion	■	■	■			
	Assessment Part I information: assessment Part I information – quality-related information		■				
	Assessment Part I information: assessment Part I information - excluding quality-related information	■					
	Assessment Part I information: part I conclusion	■	■				
	Assessment Part I information: part I disagreement	■	■	■			
	Assessment Part II information (RFIs, responses to RFIs, final Part II AR and Part II conclusion)			■			
	MSC Decision (including Revert decision)	■	■	■	■	■	
	Timetable	■		■			
Download CT (only information that users have access to according to role permissions, e.g. a Part II role can download Part II information, CSR viewer can only download CSR)		■	■	■	■	■	■

1.7. Role(s) assignment and how to request a certain role

Sponsor Admin users need to obtain their role by submitting relevant requests via the EMA Account Management portal (see section 1.5.1.1.), while MAH Admin roles are requested via the EMA CTIS Service Desk (see section 5.3.1.). The rest of the roles are assigned by users with the relevant Administrator role (Sponsor Admin, CT Admin, MAH Admin, as applicable) either proactively or upon request (see section 1.7.1.). User roles can be requested to the Sponsor Admin or to the CT Admin: see section 1.7.2. .

Note: when new roles are granted or updated, the user must log out and log back in to apply the changes, since **role assignments are synced during login**. If actions are performed, and the data is not visible, users should refresh the page.

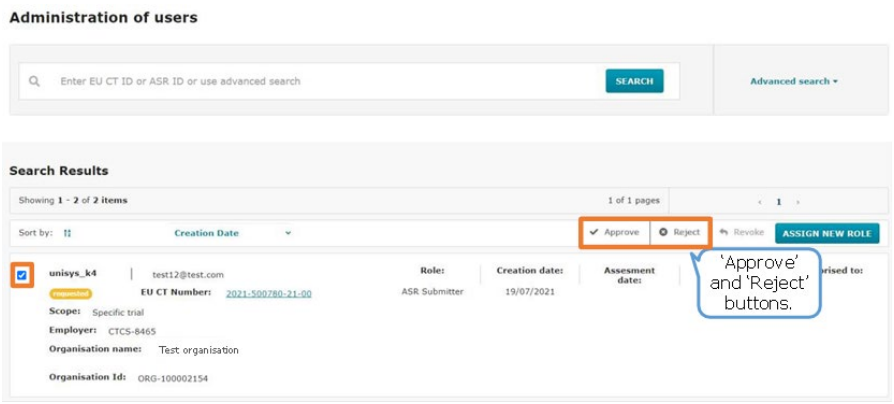
1.7.1. Role(s) assignment by the Administrator(s) to other users

This section is applicable to both organisation-centric and trial-centric approaches and it describes how a Sponsor Admin, a CT Admin or a MAH Admin can assign a specific role to a user. Note that MAH Admin can only assign CSR-related roles (see section 1.6.1.). In case the request for assignment comes from a user (requested as per section 1.7.2. , it would appear in the 'User administration' tab and it would not be received via email; the administrator does also not receive any notice or **alert**, but the request appears in the with the 'Requested' value as the status. For this reason, **Administrators need to check the User administration tab regularly**.

The below steps are applicable to a user with **Sponsor Admin**, **CT Admin** or **MAH Admin** role(s), who needs to assign roles to himself/herself or to other users:

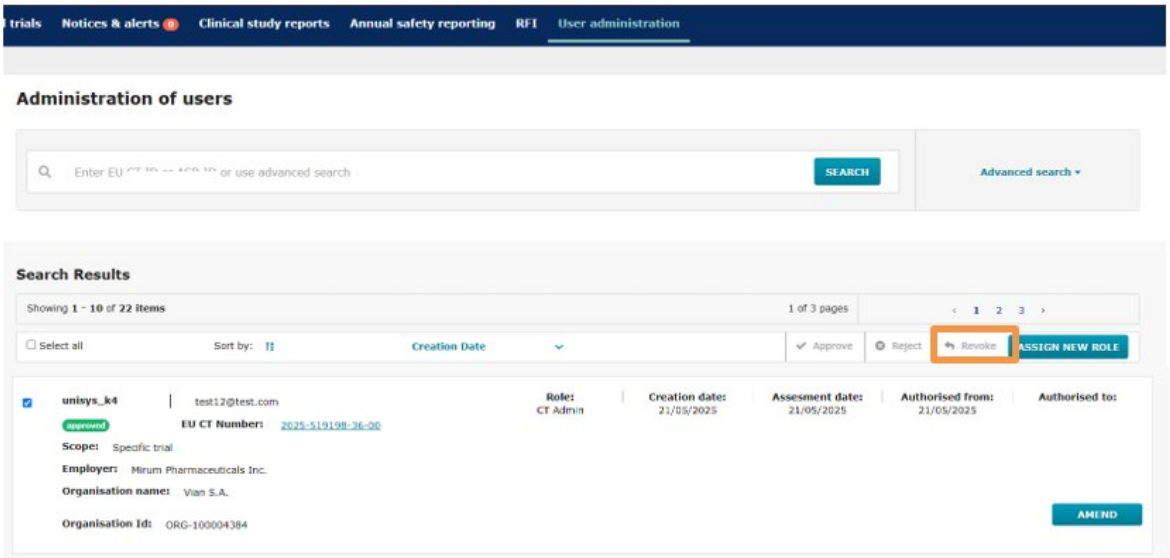
1. Click on the 'User administration' tab displayed at the top of the CTIS sponsor workspace screen. In this tab, you can manage user roles for CTs submitted by your organisation or affiliated organisations (to which your sponsor organisation assigns roles to users in order for them to perform clinical trial actions on your organisation's behalf).
2. *If requests for roles appear in the 'User administration' tab list*: you can click on the checkbox next to the role and click on 'Approve' or 'Reject' .
3. *If no request for the relevant role appears in the 'User administration' tab:* click on 'Assign a new role' and fill in the relevant data (such as user ID, EU CT number of a clinical trial, date, etc.) to assign a role, choosing it from a predefined drop-down list of roles. When proactively assigning a role, you need to define the scope as well, which could be:
    - All trials: the role assigned to the user covers all trials under the umbrella of the affiliated organisation of the administrator (organisation-centric approach, see section 1.5.1.).

- Specific trial: the role assigned to the user is only applicable to a specific clinical trial. This option is available in both user management approaches (organisation-centric approach and trial-centric approach, see section 1.5.).



More than one role can be added at the same time, either to the same user or to different users. This allows you to establish the roles of the whole process of a trial.

Administrator users can perform all the actions from the 'User administration' tab, approving/rejecting any incoming requests, assigning/revoking/amending roles, and searching for users by various criteria using a basic or advanced search. In the results page of this tab, an administrator user can view all the roles that have been assigned in his/her organisation, or for the CTs under his/her role scope. In order to **revoke a role**, the user needs to select the role from the list of results by clicking on the tick box on the left-hand side of the relevant role, and then click on the 'Revoke' button, next to the 'Assign new role' button:



If needed, administrator users can also **amend the authorised date of** a given role through clicking on the 'Amend' button at the bottom left of each role (see above screenshot).

Any role can be revoked or its assignment date can be amended except for high-level administrator roles (Sponsor Admin, MAH Admin): these roles are managed through EMA Account Management portal and cannot be revoked through CTIS – for this reason, the tick box and the 'amend' option are not displayed for such users. Instructions to revoke Sponsor Admin role are here, while to revoke an MAH

Admin role an EMA CTIS Service Desk ticket needs to be opened. A CT Admin role can be revoked directly in CTIS by another Sponsor/CT Admin.

→ on this topic: watch also the video on How to request roles and how to assign roles to registered users in CTIS and How to amend and revoke roles of registered users in CTIS.

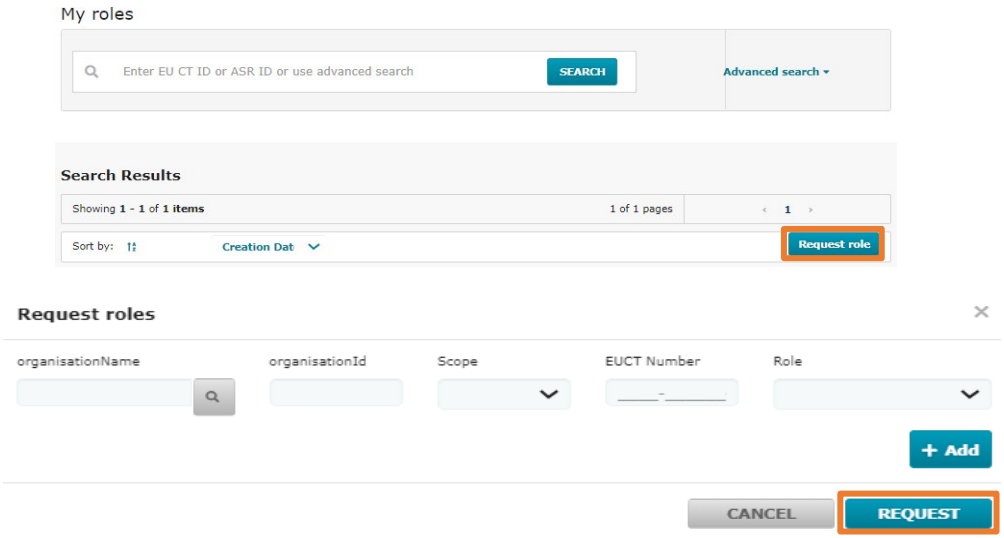
1.7.2. Request sponsor user role(s) to the Sponsor Admin or to the CT Admin

In the organisation-centric approach, role requests can be submitted by any user to either the Sponsor Admin or the CT Admin. In the trial-centric approach, roles can only be requested to the CT Admin.

As mentioned in section 1.5. , all users with an EMA account have a 'default' role in CTIS enabling them to access the landing page of the CTIS sponsor workspace. The following steps are applicable to any user that has EMA Account (either with already assigned roles or with no other role) and that needs to request one or more roles in CTIS:

1. Log in the sponsor workspace, click on your name at the top-right corner of the landing page and choose 'My roles'.

2. In 'My roles' page, click on 'Request role'.
3. Populate the fields of the pop-up window (all mandatory) and click on 'Request'. You can limit the role to one trial (by selecting 'specific trial') or request the role for all trials that your organisation manages (by selecting 'all trials') from the scope drop-down menu (see section 1.7.1.).



4. Once the requested role is approved by the Sponsor Admin (see section 1.7.1.), **you need to log out and log in again** in order to have the role assigned to you in the system.

From the moment a role has been assigned to a user, that user becomes automatically affiliated to that Sponsor ORG-ID. Sponsor users can view their roles by clicking on their name button at the top-right corner of the CTIS interface and then on 'My roles'. After clicking on 'Search', users can view all the role(s) they have been assigned by an administrator user. Roles can be sorted by

alphabetical order, user ID, email, employer, organisation name, ORG-ID, role type, scope, EU CT number, creation date, assessment date, status, authorised from and authorised to dates.

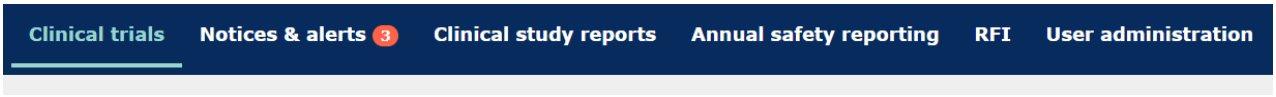
To know **how long a role will last**, in 'My roles' section, among the information displayed for each role, on the right side of the screen, users will find the date from which the role is authorised ('Authorised from') and the date in which this role will finish ('Authorised to'). This period is determined by the administrator when assigning a role and can be amended by Administrator users. Note: the authorisation period is not a mandatory field. If the administrator user does not fill it out when assigning the role, the date of the field 'Authorised from' will correspond to the date when the role is granted.

→ on this topic: watch also the video on How to request roles and how to assign roles to registered users in CTIS and on How to amend and revoke roles of registered users in CTIS, and the CTIS bitesize talk: User access and role management.

1.8. Accessibility of CTIS tabs depending on the user role

See list of tabs that can be accessed in the sponsor workspace and relevant user roles that can access them:

- **Clinical trials:** all users (Sponsor Admin, CT Admin, Part I Preparer (excl. Q-IMPD), Q-IMPD Preparer, Part II Preparer, Application Submitter, Part I Viewer (excl. Q-IMPD), Q-IMPD Viewer, Part II Viewer, Notifications Viewer, Notification Preparer, Notifications Submitter, CT results Viewer, CT Results Submitter, ASR Submitter, MAH Admin, CSR Viewer, CSR Submitter)
- **Notices & alerts:** CT Admin, Part I Preparer (excl. Q-IMPD), Q-IMPD Preparer, Part II Preparer, Application Submitter, Part I Viewer (excl. Q-IMPD), Q-IMPD Viewer, Part II Viewer, Notifications Viewer, Notification Preparer, Notifications Submitter, CT results Viewer, CT Results Submitter, ASR Submitter, MAH Admin, CSR Viewer, CSR Submitter
- **Clinical study reports:** MAH Admin, CSR Viewer, CSR Submitter
- **Annual safety reporting:** ASR Submitter
- **RFI:** CT Admin, Part I Preparer (excl. Q-IMPD), Q-IMPD Preparer, Part II Preparer, Application Submitter, Part I Viewer (excl. Q-IMPD), Q-IMPD Viewer, Part II Viewer, Notifications Viewer, Notification Preparer, Notifications Submitter, ASR Submitter
- **User administration:** Sponsor Admin, CT Admin, MAH Admin



End of chapter: jump to Clickable table of contents.

2. Apply for a clinical trial authorisation

Before applying for a CT authorisation through the instructions below, the following resources should be consulted: documents listed in the 'Chapter I - Application and application documents', 'Chapter III – Quality' and 'Chapter V - Additional documents' of the EudraLex Vol. 10 guidelines, the Quick guide for sponsors - Regulation 536/2014 in practice, the CTCG Key Documents list on 'Cover Letter template', 'Best practice for the naming of documents', 'Frequently asked questions related to Clinical trials submitted under the Regulation EU 536/2014','Complex clinical trials' and 'CTCG Guidance for Sponsors on Article 11 workaround', the CTR Q&A, and the relevant National Competent Authorities (NCA) websites containing national requirements of each Member State (fees, templates, etc). For questions on the **content** of a CT application, refer to the relevant MSC(s) national contact point(s). In addition, the Sponsor FAQs includes further guidance on the topic.

Once all the necessary pre-submission steps are performed (section 1.), users with the correct roles are ready to prepare their IN, the first step of the trial life cycle. **Detailed Information on how a user with the appropriate roles can create, fill in and submit an IN** is provided in **section** 2.3.

Once the user creates an IN (see images in section 1.5.2.) and accesses its application page, six sections are shown:

1. Form: includes cover letter, proof of payment, GDPR compliance, and trial publication category
2. MSCs: contains details about the Member States Concerned (MSCs), proposed Reporting Member State (RMS), estimated number of participants in each MSC, and copied from Part I section: non-EU/EEA trial locations and number of participants.
3. Part I: provides trial-specific information, including protocol, trial design, trial objectives, eligibility criteria, therapeutic area, previous scientific advice and agreed Paediatric Investigation Plan (PIP), sponsor details, and trial products details.
4. Part II: contains list of participating sites and regulatory documents for each MSC, such as informed consent form, subject recruitment arrangements, suitability of trial sites and principal investigators (PIs), compliance with national data protection requirements.
5. Evaluation: details the phases of application evaluation by the MSC(s), allowing Member State users to document assessment outcomes and upload assessment reports.
6. Timetable: offers a visual overview of evaluation status and progression of the CT application post-submission.

The first four sections (Form, MSCs, Part I, Part II) are completed by the sponsor:

- the **content** of those sections reflect the one of **Annex I of the CTR** (letters A to R). **Section** 2.2. of the present handbook gives an overview on structured data to be filled in and documents to be uploaded for each section. A more detailed view can be found in the document CTIS application fields, which also applies to other types of applications besides an IN (i.e. Additional Member State Applications (AMs), SM and NSM, see Annex I for abbreviations).
- The **language** used for the structured data and documents can be **in one or more of the official languages of the EU** and as per MSC(s) requirements (for part I: see 'Annex II: Language requirements for part I documents' of the CTR Q&A), in line with Article 26 of the CTR.

Important: before starting to draft the IN, users must thoroughly review the publication rules for each structured data field and document that needs to be inserted. Failure to do so may result in unintended publication of Commercially Confidential Information (CCI) and personal data. See section 2.1.

Depending on the number of MSC(s) in the application, an IN can be:

- **Mononational**: CT application which concerns only one Member State. These applications aim at receiving the authorisation to conduct a CT in the territory of a Member State.
- **Multinational**: CT application which concerns 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.

Multinational trials applications will have **several part II sections**, depending on the number of Member States involved in the trial.

The full list of values present in the CTIS structured data forms can be found here.

The **Evaluation and the Timetable sections** are informative sections on the progress of the trial lifecycle, once submitted (see section 3.).

2.1. CTIS Publication rules

The sequence of events occurring during the trial life cycle requires the collection and processing of personal data and might contain information that is considered commercially confidential. As defined in Article 81(4) of the CTR, both personal data and CCI should be exempted from publication.

When preparing any CTIS application (IN, AM, SM, NSM, see sections 2.3. , 4.2. , 4.3. , 4.8. and Annex I for abbreviations**) the sponsor should redact CCI and anonymise any personal data of:**

- **All structured data** where publication appears as '**yes' in column H** of the CTIS applications fields document.
- **All documents** where publication appears as **'yes' in column H** of the CTIS applications fields document: Protocol, Protocol Synopsis, Summary of product characteristics (SmPC), Subject information and informed consent form, Recruitment arrangements, (see the CTIS applications fields document for exceptions based on trial category).

The same principles should apply when the sponsor submits notifications or Final summary of results, Lay person summary of results and Clinical study reports documents to CTIS (see sections 4.1. 4.9. 5.2. 5.3.): see column H of the Notifications, ASR and Results document to know their publication rules. Note: when submitting a notification on Unexpected event, Urgent safety measure, or Serious breach since only the relevant structured data is published, sponsors should not refer to the documents in those data (see section 4.9.1.).

After a decision of any kind has been issued by the MSC(s), the data and documents submitted to CTIS by the sponsor are made available to the public **as per the modality and timelines described in Tables I and II of Annex 1** to the Guidance document on how to approach the protection of personal data and CCI while using the CTIS. Table III of Annex 1 also lists the documents that are subject to publication, links to their standard templates and provides examples of commonly included personal data which must be anonymised in those documents. The mentioned **Guidance document should be thoroughly reviewed by the sponsor before submitting information to CTIS** since it details the rules to follow when inserting data and documents to CTIS, their publication rules and how to manage personal data and CCI contained in those data and documents.

The disclosure rules of CTIS structured data and documents depend on the trial category, on the population age (in case of category 1 trials) and on the trial phase (in case of category 2 trials that are integrated phase 1 and 2). **The trial category is chosen by the sponsor when filling in the 'Form' section** of the IN, based on definitions provided in Table V of Annex I of the Guidance document. Note that this field, as well as the 'justification for trial category' cannot be modified through subsequent SMs, NSMs and AMs. **Exceptions to these disclosure rules apply to all trials submitted before 18 June 2024 (referred to as 'historical trials'**), where only their structured data were published as of this date; for those '**historical trials', any document that is submitted as part of a modification will be published in line with the CTIS publication rules** (with an exception, see section 2.3 of Guidance document and Table IV of its Annex I).

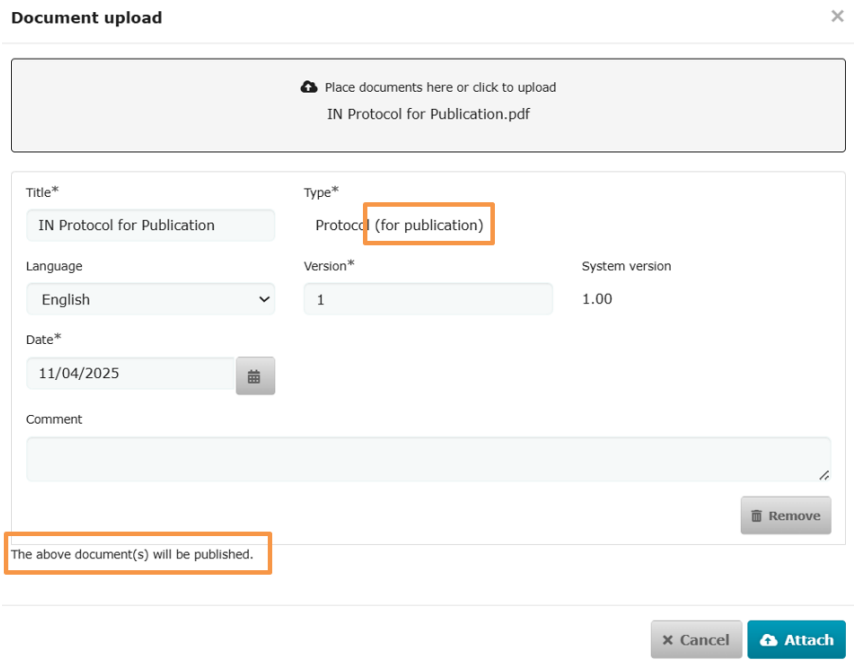
With regards to **personal data** inserted in **structured data and documents**, they should generally be removed, or pseudo anonymised. **Exceptions apply to certain names and surnames** (see section 3.3.1. of the mentioned Guidance). Note: **any contact detail inserted in CTIS should be a functional contact detail and not containing personal data** (e.g.: clinicaltrials@companyX.com). This includes details of the Principal Investigators, which are also subject to publication.

For **all documents uploaded in CTIS** (regardless of whether they are subject to publication or not), **personal data should also not be present in their metadata**: see section 2.3.2.

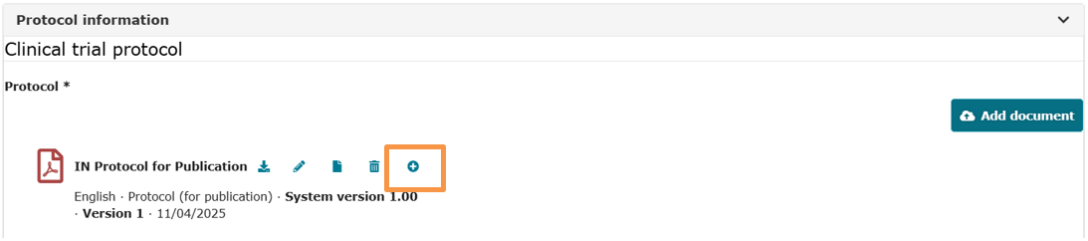
See below the steps applicable to a user with the appropriate permissions that is preparing an IN (as per section 2.3.), an AM (as per section 4.2. , an SM (as per section 4.3. , or a NSM (as per section 4.8.) and needs to upload document(s) that will be subject to publication:

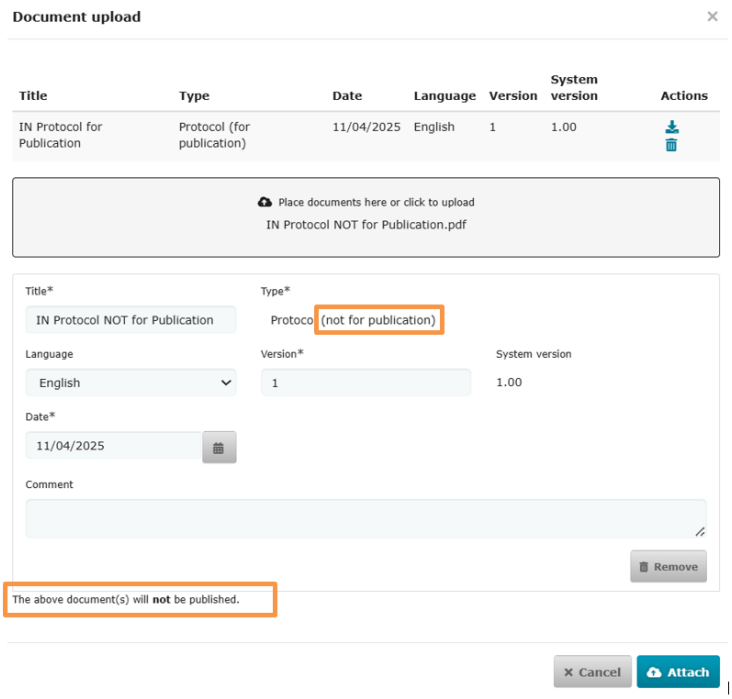
1. You should **prepare two versions** of the same document:
    - one **'for publication'** where CCI and personal data should not be present (with the exceptions on personal data mentioned in section 3.3.1. of the mentioned Guidance), as well as metadata (see section 2.3.2.)
    - another one **'not for publication'** where **CCI** are included, in order to provide the entire set of information that is deemed necessary for the assessment by the RMS/MSC(s). Note that **personal data** also need to be removed or pseudo anonymised in this version with some exceptions (see Guidance document and Q&A on the protection of CCI and Personal Data while using CTIS). This version should also not contain any metadata (see section 2.3.2. . Note: in case no CCI or personal data are present in the version 'for publication', the preparation of this document is not necessary.
2. After having accessed the sponsor workspace and found relevant CT application (see section 2.6.), lock the relevant part of the CT application where the document needs to be uploaded through clicking on the padlock on the right, and click on the relevant arrow to display the relevant section.
3. Click on 'Add document' on the right.

4. Upload the **first version** that is the one 'for publication', where CCI and personal data should not be present.

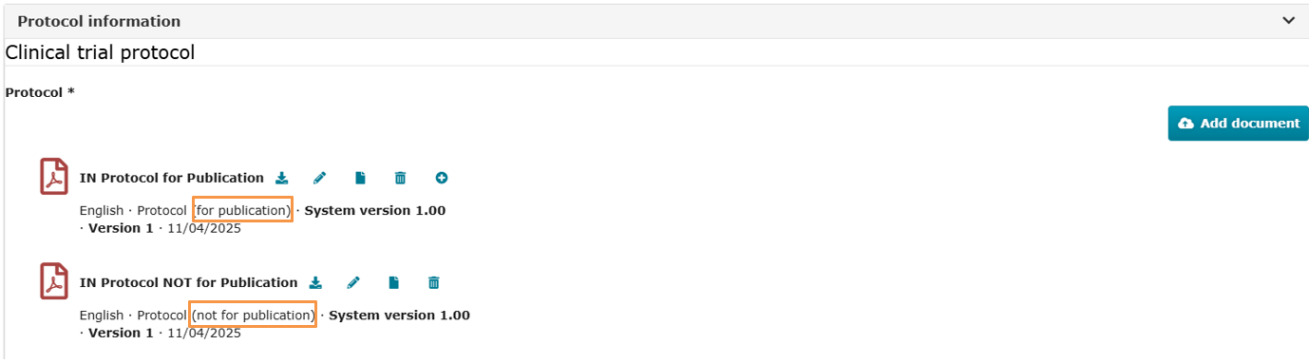


5. Click on the **'+' button** and upload any **additional version** that is the version 'not for publication' (as detailed above). *Note that this step is not applicable in case the 'for publication' version does not contain CCI or personal data*.



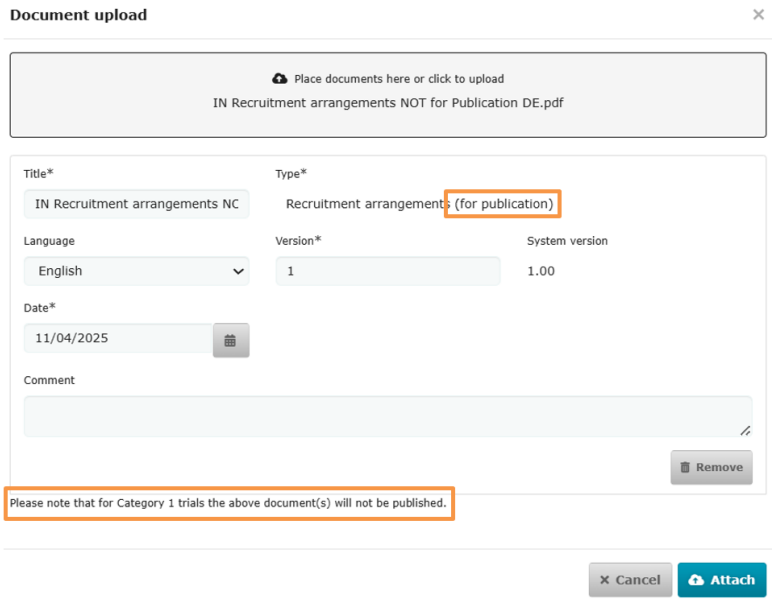


Both versions of the same document are then displayed in the appropriate documents sections:



Important: any document inadvertently uploaded as first document for those documents sections that are 'for publication' will be published. It is the responsibility of the sponsor to ensure that in those documents CCI and personal data are removed and can be published. For example, if an Investigator's Brochure (IB) is uploaded into the SmPC section of a Category 2 or 3 trial, the IB will be made public if the sponsor does not correct this oversight before the decision on the application.

Note: for category 1 trials, Recruitment arrangements and Subject information and informed consent form documents are not subject to publication, even if the relevant message in CTIS displays them as 'for publication' in the uploading window.



CTIS publication updates are processed overnight, and therefore publication changes to the CTIS public portal appear the next day from when they are inserted in the CTIS secure website**, including changes to the approval of a clinical trial application** (see section 3.1.6.), **trial status** (section 4.1.), **or submission of summary of results** (see section 5.2.), except for when a later publication if foreseen (see **Tables I and II of Annex 1** to the Guidance document on how to approach the protection of personal data and CCI while using the CTIS.).

A useful summary of the CTIS publication rules can be found in the quick user guide. All the mentioned reference documents reflect the current publication rules for CTIS, defined in the Revised CTIS transparency rules, and provide guidance on the protection of personal data and CCI submitted to the system, in accordance with the requirements of Article 81(4) of the CTR. A Q&A document on this topic is also available to users (see Q&A on the protection of CCI and Personal Data while using CTIS).

Notes from the List of known issues and workarounds:

- In case a sponsor user needs **to remove a document 'for publication',** the user needs to **delete first all the associated documents 'not for publication'** (even the ones of the previous versions) before deleting the associated "for publication" document. After removal of the "for publication" and "not for publication" versions, the corrected documents can be uploaded in the appropriate order. Note that in this case, previously submitted documents are not removed from any previously existing application(s): the removal only applies to the relevant draft application. In addition, the action can also be reversed by cancelling the draft application and creating a new draft application. See instructions in the linked List of known issues and workarounds.
- In case it is **not possible to delete a document** because of an error message informing there is a 'not for publication' version linked to it that is not visible to the user: the users can proceed without deleting the document and providing an explanation to the authorities.
- When two '**not for publication**' protocol documents are uploaded at the same time by clicking on the '+' button, they may not appear under the 'for publication' document for which they were added. Please upload the 'not for publication' protocol documents one-by-one.

→ on this topic: watch also the videos on Clinical Trials Information System (CTIS) bitesize talk: Revised transparency rules and the new CTIS public portal and Data protection in CTIS.

2.2. Clinical Trial (CT) application data fields and documents

This table gives an overview of the data fields and documents of a CTIS application:

- **Documents** are highlighted in **bold**. **When creating documents** to be uploaded in CTIS, a sponsor user should consult the **'Best practice guide naming of documents in CTIS',** available in the 'Key document list' section on the CTCG page.
- **Mandatory fields and documents** are marked with an **asterisk (*)**. Conditionally required fields and documents are marked with two asterisks (**).
- **Column 'Pub?'** marks which are the fields or documents that **are subject to publication** in line with the publication rules (see section 2.1.).

Detailed fields descriptions can be found in the document CTIS applications fields. Section 2.4. specifies further details for their completion. Note: **do not include terms in '< >' brackets** when filling in structured data (see 2.3.1.2.).

Important: to help shorten MSC assessment and approval timelines and reduce the risk of unnecessary rejections, **sponsors should submit high-quality applications: refer to the Recommendation paper on frequent issues identified during assessment of Part I and Part II.**

Field or Document	Pub?	Comment
Form		
Cover letter*	No	Refer to the following templates, available in the 'Key document list' section on the CTCG page: • 'Initial application cover letter' for IN, and • 'Cover letter' + 'Modification description' for SM Refer to the CTR Q&A and CTR document on content requirements.
Transition trial: EudraCT number	Yes	Should no longer be used
VHP number and Comments	No	Should no longer be used
Proof of payment of fee	No	Used where applicable. Refer to '**Fees for clinical trials submitted under CTR'** available in the 'Key document list' section on the CTCG

Field or Document	Pub?	Comment
		page and national requirements from the relevant National Competent Authorities (NCA) websites.
Compliance with Regulation (EU) 2016/679*	No	Refer to EudraLex Vol. 10 template statement on compliance Regulation (EU) 2016/679: PDF/Word
Trial Category and Justification*	Yes	See Table V of Annex I: Guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System (CTIS). Trial Category, together with population age and trial phase, determine the publication rules (see section 2.1.). **Note that these fields can only be edited when drafting the IN**. They cannot be modified through a subsequent SM, NSM or AM.
MSCs		
Member states*, Subjects*	Yes	Indicate the Member State(s) where the trial is going to be conducted and the number of subjects involved.
Select Proposed RMS*	No	Indicate the proposed RMS, if the trial is going to be conducted in more than one country.
Rest of the world subjects, Estimated EEA subjects, Estimated Rest of the world subjects, Estimated Total subjects	Yes	These are all 'read only' fields: they all show data specified in Part I.
Trial specific information - Part I - Trial details		
Full title* (+translations), Public title*(+translations), Protocol code	Yes	Provide identifiers of the trial. The protocol code corresponds to the name or acronym assigned to the protocol by the sponsor.
Secondary Identifying Numbers: WHO UTN ID, ClinicalTrial.gov ID, ISRCTN ID	Yes	These fields need to be mandatorily completed only in case there is a Secondary ID (unique clinical study identifiers) assigned by other publicly available clinical trial registries.

Field or Document	Pub?	Comment
Additional Registries: Registry Name and Identifier	Yes	
Trial category: Low intervention trial* and justification, Trial phase*	Yes	See definition of low intervention trial in Art 2(2)(3) of the CTR. Trial phase, together with trial category and population age, affects the publication rules, see section 2.1.
Attachment of justification of low interventional clinical trial	No	Only required in case of Low intervention trial.
Medical condition* (+translations), Is the medical condition considered to be a rare disease?*, Therapeutic Area*	Yes	See definition of a rare disease.
Medical condition(s) MedDra information: Version, Level, Classification code, Term name, System organ class	Yes	More info on MedDRA here
Trial scope*, Main objective*(+translations)	Yes	
Secondary objective (+translations)	Yes	
Eligibility criteria: Principal inclusion criteria* (+translations), Principal exclusion criteria* (+translations)	Yes	When entering inclusion and exclusion criteria, the users are advised to insert a number in front of the text of the criterion, to indicate the desired order.
Primary end points* (+translations), Secondary end points	Yes	
Trial duration: Estimated recruitment start date in EEA*, Estimated end of trial date in EEA*, Estimated global end date of the trial**	Yes	
Source of monetary support or material support: Organisation name	Yes	
Individual Participant Data (IPD) Sharing Statement: Plan to share IPD*, Plan description	Yes	Statement regarding the intended sharing of deidentified individual clinical trial participant-level data (IPD). Should indicate whether IPD will be shared, and how.

Field or Document	Pub?	Comment
Population of trial subjects: Age range*, Age range secondary identifier**, Are subjects male?*, Are subjects female?*, Clinical trial group*, Vulnerable population*	Yes	
Recruitment population group**, Subjects incapable of giving consent personally**, Emergency situation description**, Other description**	No	
Protocol*, Protocol synopsis*	Yes	**The first version uploaded for each document is the one 'for publication', where CCI and personal data must be removed, see section 2.1.** The main version of the Patient-facing materials (**not the translations**) may be uploaded in the 'Protocol' document section. Note that **video files cannot be uploaded**: in this case, the URL to the video may be included in a PDF or Word document, together with any relevant explanatory screenshot(s). Translations of patient facing materials, if any, are to be uploaded in part II section on compliance with national requirements on data protection (see below), in line with the CTR Q&A
Data Safety Monitoring Committee Charter (DSMC)	No	
Study design	No	
Study design: Period details, Arm details	Yes	This field may contain CCI: note that is an optional field and it is always subject to publication when filled in.
Scientific Advice: Competent authorities that provided scientific advice	Yes	

Field or Document	Pub?	Comment
Scientific Advice: **Summary of scientific advice**/ Scientific advice–Quality**	No	
Paediatric Investigation Plan (PIP): EMA PIP number**	Yes	This field is only mandatory in case the trial is part of a PIP. If the trial is not part of a PIP, this field should not be filled in. Note: in case the decision is negative, no EMA PIP number should be inserted as it would affect publication rules.
Paediatric Investigation Plan (PIP): **PIP opinion**	No	
Associated Clinical trials: EUCT/EUDRACT Number, Sponsor**, Full title	Yes	Sponsors can refer to data generated in another trial run under the regime of Clinical Trial Directive (CTD) or CTR. See how to fill in this part in section 2.4.1.
Sponsor agreement	No	The written agreement from the sponsor of the submitted applications that are associated with this clinical trial application, in case the associated trial is owned by a different sponsor
References: Online reference to publication and link	Yes	Provide the PMID (PubMed identifier) number if available
Countries outside the European Economic Area and Rest of the world subjects	Yes	Add non-EEA country if trial is also conducted outside of EEA. These fields are copied in the 'Form' section, see above.
Trial specific information - Part I - Sponsor		
Sponsor details: Name*, Organisation Type*, Address*, contact details*	Yes	See definition of 'Sponsor' in Art 2(2)(14) of the CTR. The value is taken from OMS and it is automatically filled in depending on details inserted when creating the IN. Further details need to be provided: contact details need to be functional (not personal ones). Refer to the CTR Q&A on the content requirements. Co-sponsor details should also be inserted here: see how in section 2.4.2.

Field or Document	Pub?	Comment
Scientific contact point: Organisation name*, Functional contact point name* and contact details*	Yes	Provide only functional details (not personal ones).
Public contact point: Organisation name*, Functional contact point name* and contact details*	Yes	Provide only functional details (not personal ones).
Legal Representative: Name**, Organisation Type**, Address**, contact details**	No	This field is only required if the sponsor of the trial is not based in the EU. Provide only functional details (not personal ones).
Third-Party Organisation(s) associated with the trial: Name, Address, contact details, duties	Yes	Provide only functional details (not personal ones). See how to fill in this part in section 2.4.4.
Contact point for union: Name*, Address*, Functional contact point name* and contact details*	No	Contact point used by regulatory authorities for communications with the sponsor.
Sponsor(s) responsible for compliance*, sponsor responsible for being a contact point*, Sponsor(s) responsible for implement the measures taken in accordance with Article 77*	Yes	
Trial specific information - Part I - Products		
Medicinal products details: Name*, EU medicinal product number/medicinal product unique ID, Marketing Authorisation, Pharmaceutical form, Active substance name, EU Substance Number, Active Substance other descriptive name, Medicinal product other name, Is this a specific paediatric formulation*, Authorisation status, Medicinal product role in trial*, Sponsor's product code, ATC code**	Yes	Details for authorised or development products are all extracted from XEVMPD, see section 1.4. See how to fill in this part in section 2.4.5.
Medicinal products details: Product Strength	No	Taken from XEVMPD

Field or Document	Pub?	Comment
Dosage and administration details: Route of administration*, Maximum duration of treatment*, Maximum daily dose allowed and unit of measure*, Maximum total dose allowed and unit of measure*	Yes	The 'Maximum daily dose allowed' corresponds to the maximum amount of the Investigational Medicinal Product (IMP) that a participant is allowed to receive per day, based on the study protocol; the Maximum total dose allowed' corresponds to the maximum cumulative dose of the IMP that a participant can receive over the entire course of the treatment in the clinical trial. Modalities of protection of Commercially Confidential information for these fields are specified in the Q&A on the protection of CCI and Personal Data while using CTIS.
Has the medicinal product been modified in relation to its Marketing Authorization?*, Description of the modification**	Yes	
IMPD Quality*: **IMPD-Q, Simplified IMPD-Q** or Justification for no IMPD upload	No	Investigational Medical Product Dossier (IMPD) – provides information related to an IMP and is divided into Quality (IMPD-Q) and Safety and Efficacy (IMPD-S and -E)
IMPD - Safety and efficacy*: **IMPD - Safety and Efficacy, Simplified IMPD - Safety and Efficacy** or Justification for no IMPD upload	No	As above. Role: 'test' - Include comparator, placebo or investigational product as necessary
Content labelling of the IMP's	No	
Product authorization details**: Marketing authorization (MA) country, Marketing Authorisation number, Centralised procedure/MRP/DCP/registration procedure number	Yes	Taken from XEVMPD, see section 1.4.
Orphan designation**: Does this product have an orphan product designation, Designation number for orphan product	Yes	

Field or Document	Pub?	Comment
Active substance: Classification, Active substance name, Active substance name synonyms, Active substance other descriptive name, EU active substance code, Sponsor substance code	Yes	Taken from XEVMPD, see section 1.4.
Active substance strength	No	Taken from XEVMPD, see section 1.4.
Advanced therapy: Advanced therapy classification, CAT reference number, Somatic cell origin, Somatic cell type, Species origin for xenogeneic cell, Specify type of differentiated cells, Specify other somatic cell type, Tissue engineered cell type, Origin of the engineered tissue, Cell specification, Tissue Engineered xenogeneic species of origin, Gene of interest, Type of gene transfer product, Gene therapy type, Additional description, Genetically modified cells present, Specify type of cells, Origin of genetically modified cells, Species origin for xenogeneic cell - genetically modified cells	Yes	See how to fill in this part in section 2.4.5.2. Reference the ATMP authorisation number (Committee for Advanced Therapies - CAT reference number)
Device associated with medicinal product: Product use in combination with a device, Type of device, Device has CE mark, Device trade name, Device notified body, Description of device	Yes	See how to fill in this part in section 2.4.5.3.
Investigator brochure for the medicinal product*: **Investigator brochure****	No	IB: A multifunctional regulatory document essential for the conduct of clinical trials that summarises the physical, chemical, pharmaceutical, pharmacological, and toxicological characteristics of an investigational medicinal product (IMP) as well as any clinical experience.
Investigator brochure for the medicinal product*: **Summary of product characteristics (SmPC)****	Yes	SmPC: This is the product information document which is made available to all prescribing physicians in the EU for marketed products **The first version uploaded is the one 'for publication', where CCI and personal data must be removed, see section 2.1.**

Field or Document	Pub?	Comment
Compliance with GMP for the medicinal product: **Authorisation of manufacturing and import, QP GMP certification**	No	Documentation about good manufacturing practice (GMP) for the investigational medicinal product.
Compliance with GMP for the medicinal product: Authorisation number of manufacturing and import	Yes	
IMPD-Q, Simplified IMPD-Q **,** Justification for no upload**	No	
IMPD-Safety and Efficacy, Simplified IMPD-Safety and Efficacy****, Justification for no upload**	No	
Auxiliary Medicinal Product Dossier, Reason for no upload**	No	
IMPD-Q Placebo	No	
Content labelling of the IMPs*, and of linked products	No	
Part II		
Trial site(s)*: Organisation OMS ID, Organisation name, Site location, Site Street address, Site city, Site post code, Site country. Investigator Information*: Title, First name, Last name, Department, Phone, Email	Yes	It includes 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 details for the investigator must be **functional contact details**, and not personal ones**.** Note that they are made public. See how to fill in this part in section 2.4.6.
Recruitment arrangements*	Yes	Refer to 'Part II application document templates' (chapter I of EudraLex vol.10). For the content: refer to the relevant NCA website(s). For category 2 and 3 trials: **the first version uploaded is the one 'for publication', where CCI and personal data must be removed.** For category 1 trials: this document is not published.

Field or Document	Pub?	Comment
Subject information and informed consent form*	Yes	Refer to EudraLex Vol. 10 template 'Informed consent and patient recruitment procedure': PDF/Word. For the content: refer to the relevant National Competent Authorities (NCA) website(s). For category 2 and 3 trials: t**he first version uploaded is the one 'for publication', where CCI and personal data must be removed.** For category 1 trials: this document is not published.
Investigator CV*, Suitability of the investigator	No	Refer to EudraLex Vol. 10 templates: • Investigator Curriculum Vitae template: PDF/Word • Declaration of interest template: PDF/Word
Suitability of the facilities*	No	Refer to EudraLex Vol. 10 Site suitability form: PDF/Word.
Proof of insurance cover or indemnification*	No	Only the certificate of insurance (avoid adding CCI in these documents).
Financial and other arrangements*	No	Refer to national requirements, e.g. some Member States require signed Clinical Trial agreements.
Compliance with national requirements on Data Protection	No	Translations of patient facing documents, if any (see relevant question in the CTR Q&A and the 'Best practice guide naming of documents in CTIS' available in the 'Key document list' section on the CTCG page; further details in the requirements on translations of patient facing documents) The compliance document is only required by some countries.
Compliance with use of Biological samples	No	Optional, only if biological samples are collected. Refer to EudraLex Vol. 10 template 'Compliance with applicable rules for biological samples': PDF/Word

2.3. Create and submit an Initial CT application (IN)

Users should familiarise themselves with CTIS before interacting with the system. It is recommended that a small team of sponsor users first gains experience in the CTIS Training environment to navigate and perform activities effectively (see section 6.2.3. for instructions on how to gain access to this environment). This approach enhances readiness and facilitates dossier preparation for smoother member state assessment. **As a general rule, sponsors are encouraged to include in the IN all Member States where the trial is planned to be conducted to promote alignment of the Part I dossier (see 'Substantial Modification' section of the CTR Q&A).**

Section 2.3.1. is on practical matters the users should be aware of, when using CTIS, while section 2.3.2. explains how to remove metadata from any document that needs to be uploaded on CTIS (regardless of whether will be made publicly available or not). Both sections are **applicable to any action performed** through the system, including the preparation of **any kind of application** (IN, AM, SM, NSM, see sections 4.1. 4.9. 5.2. 5.3.).

2.3.1. Practicalities when using CTIS

2.3.1.1. CTIS Cross-systems buttons and icons

A group of buttons can be found across CTIS to support users' main activities. These cross-system buttons share the following set of characteristics that will help users to understand their behaviour:

- **Dependencies**: some action buttons in the system are only available after specific steps are completed. For example, 'Submit' may only become active after pressing 'Save'. These dependencies are often shown through button colours: light grey or light blue means inactive, while dark grey or dark blue indicates the button is active.

- **Users' permissions:** certain action buttons are only visible to users with specific permissions. If a button is missing, the user may not have the required role (see section 1.6. . For example, only users with the ASR Submitter role can see the 'Annual safety reporting' tab in the sponsor workspace.
- **Similarities:** some buttons, such as 'Cancel' and 'Withdraw', are illustrated with the same 'cross' icon but have different functions.
- **Locations:** the buttons' placement in CTIS varies by process and section. For example, when creating an IN, 'Check', 'Save', 'Cancel' and 'Submit' appear at the top of the page. However, while in a Request for Information (RFI), 'Submit' appears at the bottom.

Important: users can **update and complete any CT application section** by **clicking on the relevant 'Padlock' button (this will lock the section to the specific user)**. Once they have finished editing the section, they need to click on the 'Padlock' button again to save the changes and make them visible to other users. If a user locks a section, this section cannot be accessed by others. Note that the **session timeout limit of CTIS is 45 minutes**. If users stay more than 45 minutes idle, they will be logged out automatically.

The main CTIS cross-system buttons and icons are:

Search: allows users to search and retrieve clinical trials, clinical trial applications, notices and alerts, tasks and other information across the system.

Padlock: allows users to lock a field in CTIS and work on it. This prevents other users from accessing a field/subsection in which another user is working.

Save: allows users to save their work and makes it visible to others who were assigned the necessary permissions in the same workspace.

Check (also 'Accept'): allows users to check whether all mandatory fields were completed

Cancel or 'Withdraw': cancel an action and prevent the changes from being saved before the submission or withdraw information that was already submitted to the system.

Upload (also 'Add' or 'Submit'): the same icon is used to allow users to add documents into the system and to progress with submission.

Add document: it is used to upload a new document for which no earlier version is already present in the application. A document added through the 'add document' button should not replace a previously submitted document

Download: allows users to download data and documents that they have permission to view.

Edit ('pencil icon'): allows users to edit the data referred to documents before submission.

Update: allows users to upload new versions of a document once the application and the documents are submitted. Note: to replace a document when the CT application is still in draft, users need to first to remove it and then add a new document.

Remove: this enables the user to remove previously uploaded information.

Add: this is a cross-system functionality that appears after uploading the first version of the document intended for publication. It is only available in CTIS sections where the uploaded documents are published, and it allows users to submit a document version 'not for publication'.

Versioning: allows users to see the version of documents, applications, or records submitted.

Share: Allows users to share data and documents with other Member States within the workspace.

Below there are specificities regarding filling in some of the structure data's free text fields (section 2.3.1.2.) and uploading documents (section 2.3.1.3.).

2.3.1.2. Limits of characters for structured data free-text fields

Generally, there is **a limitation of 4000 characters** for manual data free-text fields. Nevertheless, there are certain fields following masked values, i.e. PIP number (EMEA-111111-PIP11-11) or fields with smaller sizes. These are further detailed below.

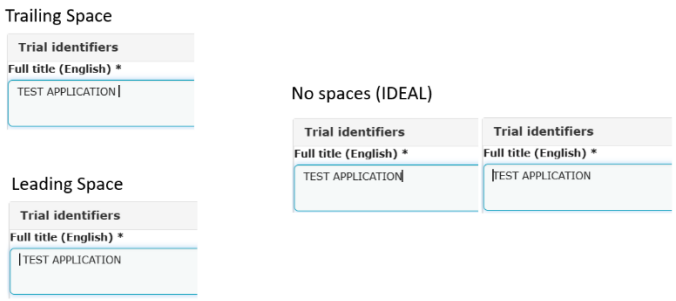
Text field	Character limitation
Manual data free-text fields (general rule)	4000
Numeric fields (e.g. dose) maximum decimals digits	2, separated by a dot (.)
Phone number	15
Protocol code, registry identifier, designation number for orphan product, CAT reference number	20
Sponsor internal identifier for unexpected event, serious breach, urgent safety measure, 3rd country inspectorate inspection notifications	20
Registry name, source of monetary support, period title, arm title, sponsor contact person first name and last name, address, town/city, department, email address, product code, gene of interest, species origin for the xenogeneic cells, tissue-engineered xenogeneic species of origin, device trade name, device notified body, authorisation number of manufacturing and import	100
Primary and secondary end points	500
Description of the device	2000
Plan description (IPD sharing)	1000

Notes from the List of known issues and workarounds:

- In the structured data fields, any entered text that is between two **angle brackets ('<>')** will be deleted. For example, 'Today is the <seventh> of June' becomes 'Today is the of June'. It is advised to use other brackets such as **() {} []** or **add a space** between the angle brackets and the text.
- In order to prevent technical issues with the download of an application, ensure to **remove leading and trailing spaces** when copying and pasting text from other sources into CTIS data fields. In order to check for this, after pasting text into a CTIS field, click inside the field and ensure there are no gaps between the body of the text and the cursor:

- Place the cursor at the end of the pasted text and press 'Backspace' button on your keyboard until it deletes the last character (you can type it back).

- Place the cursor at the beginning of the pasted text and press 'Delete' button on your keyboard until it deletes the first character (you can type it back).



2.3.1.3. Characteristics of documents upload

Every time users upload a document in CTIS, they should name them as per **'Best practice guide naming of documents in CTIS',** available in the 'Key document list' section on the CTCG page. In addition, users should keep in mind that the **system allows for storage of clinical trial data with a maximum size of 220 GB** and particularly permits the following characteristics for document upload:

Document details	System limitation
Document file name	100 characters. None of these 7 special characters (/,.;|) allowed
Document version	10 characters, it can be numerical or not
Document comment free text field	4000 characters
Document file maximum size	50 MB
Maximum number of documents uploaded in one batch	25

Users can upload documents using any external/internal/cloud storage location and using an appropriate dialog box or the drag-and-drop upload functionality. There is currently no limit in time for which documents will be no longer accessible; however, sponsors should not use CTIS as a clinical trial management system. Sponsors should have their own systems to track and archive any document submitted through CTIS.

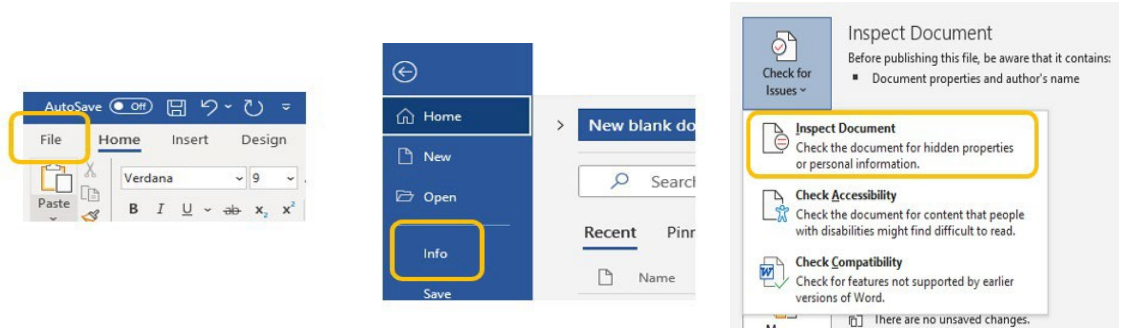
2.3.2. How to remove personal information from properties of CT application documents

When filling in any CT application, users need to upload several documents in Word or PDF format. After preparing the documents in their computers and **before uploading them to their CTIS application**, sponsor users need to make sure that they have removed any personal information from the properties of their documents. This is **applicable to any document, regardless of whether it will be made publicly available or not,** see Guidance document on how to approach the protection of personal data and commercially confidential information while using the CTIS. Users can follow the below steps to remove the data from the properties of their documents: section 2.3.2.1. specifies the steps to perform if the documents are in Word format, while section 2.3.2.2. gives instructions in case the documents are in PDF format. Be aware that the described steps are indicative and might differ depending on the application used.

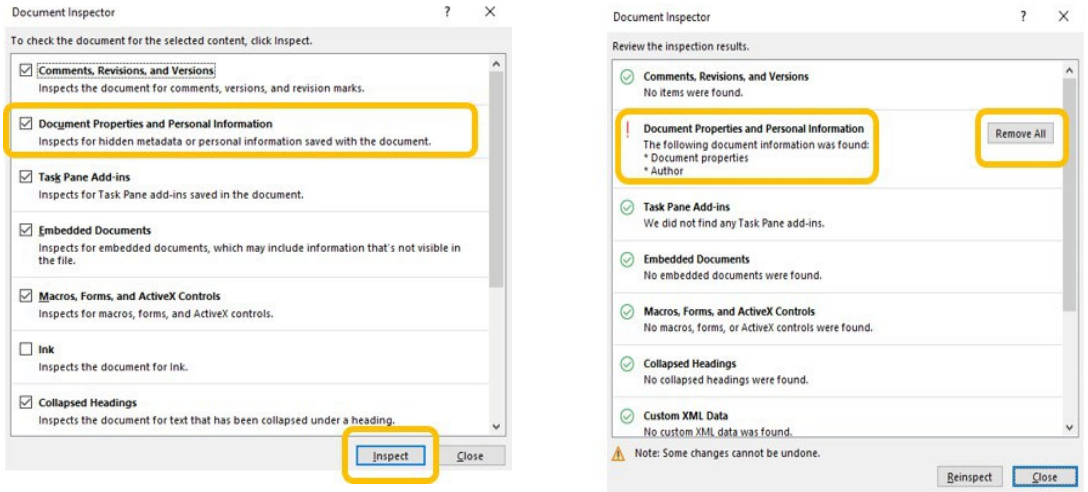
2.3.2.1. Removing personal information from properties of Word files

See below the steps applicable to a user who needs to remove personal data as metadata from the properties of Word files before converting them to PDF files:

1. Click on the 'File' tab of the Word document, then on the 'Info' and 'Check for issues' (at the right of 'info') and select 'Inspect Document' option.



2. Make sure that **'Document Properties and Personal Information'** option is ticked in, and then click on the **'Inspect'** button. Document inspector will run and if personal information is found on the properties of the document, an **exclamation mark** and a **'Remove all'** button will appear on the 'Document Properties and Personal Information'.



3. Click on the **'Remove all'** button. A **green tick** sign will appear on the 'Document Properties and Personal Information' section **indicates that personal information has been removed**.

4. Save the document.

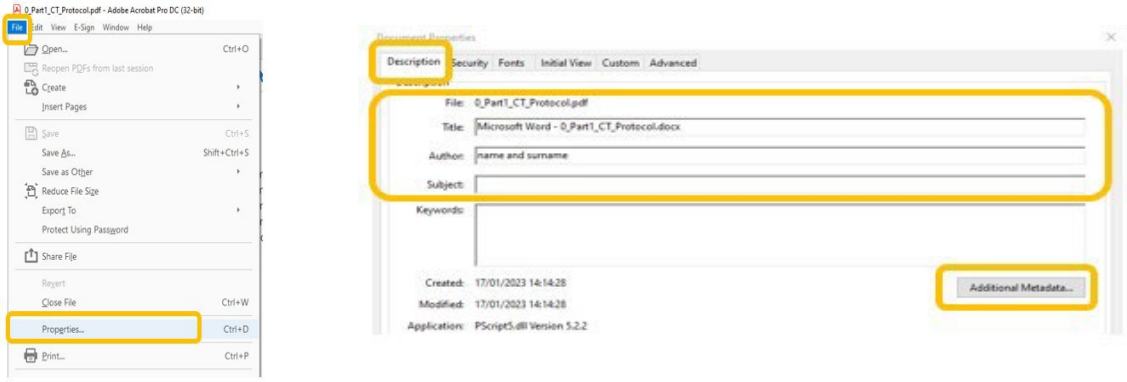
Now you are **ready to upload** the document to your trial in CTIS, or to convert it to PDF format. In case your document is subject to publication, refer to instructions of section 2.1.

2.3.2.2. Removing personal information from properties of PDF files

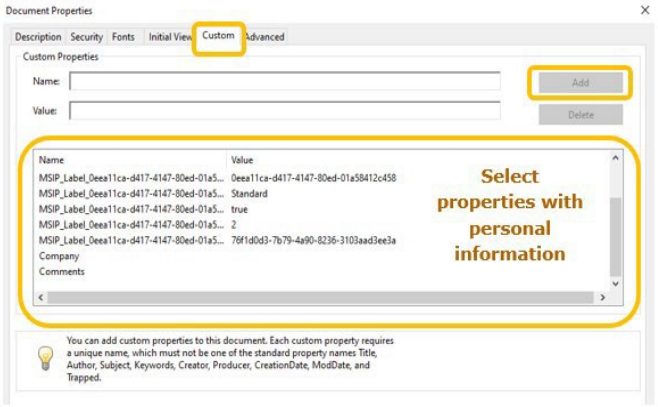
Users are advised to remove the personal information from the properties of Word files before converting them to PDF files. By doing so, users most probably won't find any personal information in the properties of the PDF files, unless the application they used for the conversion maintains any personal data in the resulting PDF file (i.e. a username that might be indicative of the user's full name). Therefore, users are advised to check the properties of their PDF files even after having removed any personal information from the properties of the sourcing word files, as per steps below:

1. Open the PDF file, click on tab 'File' on the top right corner and then on 'Properties'. Note: you need to open the PDF files with an application **that is not just a PDF reader**, to be able to edit the fields with personal information.

2. The 'Document Properties' window will pop up. Click on the tabs **'Description'** to see if any personal information is included in the document properties. **Edit the fields** that have any personal information appropriately. Please be aware that additional fields can be seen if you click on the **'Additional Metadata'** button.



3. Click on the **'Custom'** tab, to see if any personal information can be found in the listed properties. If yes, **select one of the properties** that contain personal information, to **activate the 'Delete'** button and click on it to remove the selected property from the listed ones. You will need to repeat the step for any other property that might have personal information.



4. Save the PDF document.

Now you are **ready to upload** the PDF document to your trial in CTIS. In case your document is subject to publication, refer to instructions of section 2.1. .

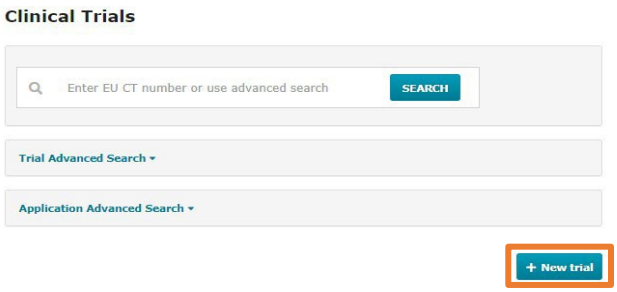
2.3.3. How to create and submit an IN

The below steps describe how to create and submit an IN and can be performed by a user who has the following **roles**, depending on the action:

- Create/copy an IN: **CT Admin** (scope: 'all trials')
- Draft/edit an IN/any CT application: **CT Admin**, **Part I Preparer (excl. Q-IMPD), Part II Preparer**, **Q-IMPD Preparer**, **Application Submitter**
- Submit/cancel/withdraw an IN/any CT application: **CT Admin**, **Application Submitter**

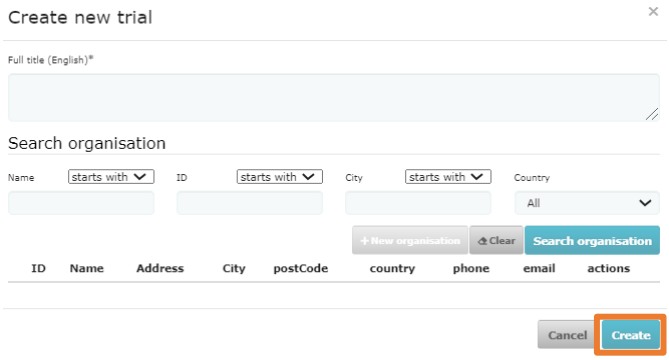
After having accessed the sponsor workspace:

1. In the Clinical trial tab, select the **'+ New trial'** button at the bottom right corner.



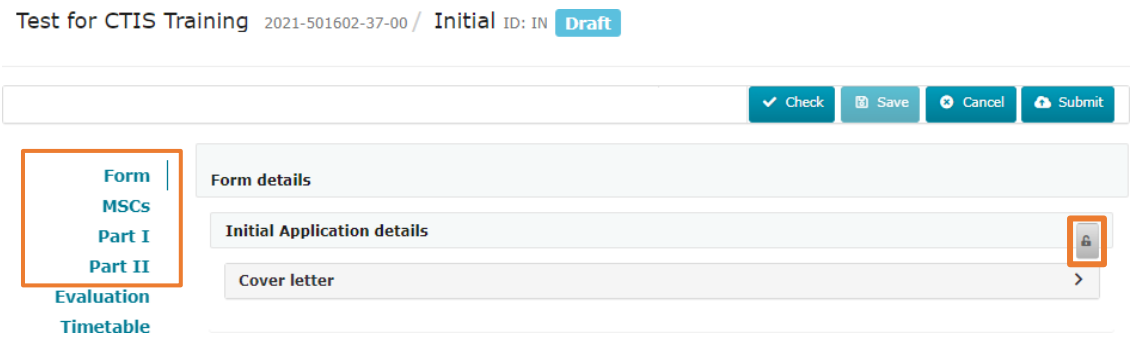
2. Populate the fields 'Full title' and 'Sponsor organisation': search for the sponsor organisation by clicking on the 'Search Organisation' button. This **data is retrieved from the OMS**: if the sponsor organisation is not registered, you need to register it, refer to section 1.2.

3. Click on '**Create**'.

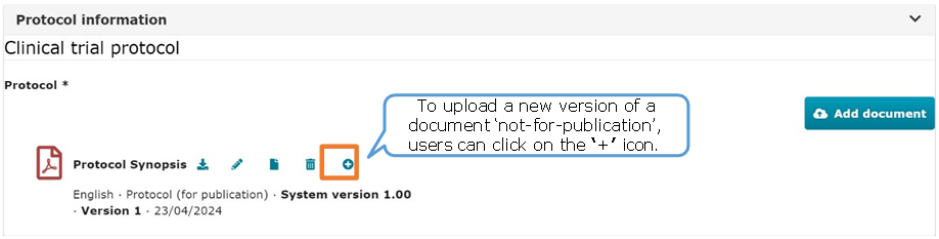


4. An IN is created. You can now populate structured data fields and upload documents in the sections 'Form', 'MSCs', 'Part I' and 'Part II' through **clicking on the padlock** on the right (this locks each subsection). Note:

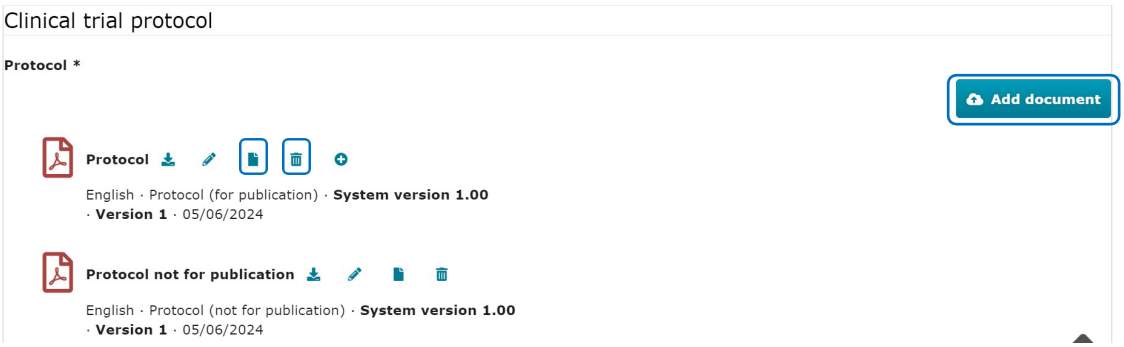
   - Section 2.1. : **most of the structured data fields** and **some documents are made publicly available**, refer to the list of CTIS applications fields, columns H to L to know their publication rules.
   - Table in section 2.2. , giving an overview of an IN data fields and documents
   - section on 'practicalities' 2.3.1.
   - the 'Best practice guide naming of documents in CTIS', available in the 'Key document list' section on the CTCG page to know how to name documents to be uploaded, and section 2.3.2. on how to remove personal data from documents' metadata
   - Section 2.4. on filling in specific sections of the application, including the product section.



5. *In case of documents that are going to be publicly available*, **when selecting the 'Add document' button in each section, the first uploaded document is the one that will be published**. The '+' icon can be used to upload versions 'not for publication' of these documents (in case the 'for publication' version contained redactions of CCI and anonymised personal data); more details in section 2.1. , including references on how to redact documents and relevant publication timelines.



6. After uploading a document, you can **edit** its information through clicking on the 'Edit' button and can remove it through the 'Remove' button. Note: the 'Update' button becomes active once the IN is submitted. **To update a document in a draft IN, you need first to remove it and then add a new document**.

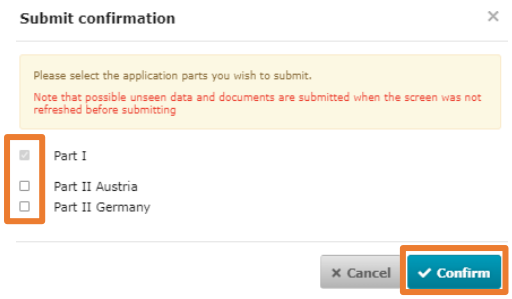


7. The IN can **be saved** as a draft at any point in time before submitting it. To **continue editing it**, see section 2.3.3.1.

8. After populating all the fields**, unlock the padlock button of the relevant subsection** and click on the '**Check'** button on the top-right corner of the CT application page to see if any required field was not populated (it will appear marked in red). After all the required fields are populated, select the **'Submit'** button.

9. Select the application parts that are to be submitted and click on the '**Confirm'** button. Note: as per Article 11 of the CTR, IN submissions could also be limited to Part I: in this case, the relevant Part II needs to be submitted within **two years**, see section 2.5.

10. After reading the confirmation text, select the 'I agree' box and then click on '**Confirm'**. At this point the IN is submitted and the MSC(s) will start the evaluation process. The trial status changes from 'pending' to 'under evaluation'.



The full content of **a CT application could also be cancelled** at any point during its drafting, through clicking on the 'Cancel' button on the upper-right corner of the page: in this way, all populated data and documents will be deleted from CTIS. Note: **once an application is cancelled, it is not possible to retrieve it back** (not even through opening an EMA CTIS Service Desk ticket). If an application is drafted but then cancelled, **the EU CT number cannot be reused:** the sponsor will need to issue a new number and change it in all the corresponding CT documentation where the CT number is needed.

After its submission, there is the possibility of **copying** the IN to create a similar one: see section 2.3.4. After submitting the IN, if users want to update the dossier, they need to **create and submit an SM or a NSM application**, as applicable (refer to section 4.3. and 4.8.).

Note from the List of known issues and workarounds: when clicking on the 'Check' button, the system may not highlight the following fields that however **must be completed**: telephone and the email address for the third-party organisation(s) and presence of the scientific and public contact points, and the individual participants data (IPD) field**.**

→ on this topic: watch also the CTIS bitesize talk: Initial clinical trial application and the videos:

- *Fill in the Form and the MSC sections*
- *Fill in the Part I section*
- *Fill in the trial details of Part I section*
- *Fill in the Sponsor details of Part I section*
- *Fill in the Product details of Part I section*
- *Fill in the Part II section*

2.3.3.1. How to apply a change to a CT application during its drafting

Users can edit the application while it is in draft status (i.e. before submission). To do so, they should navigate to the CT summary page and select the relevant Application ID under the 'ID' column in the 'Application and Non-Substantial Modification' section (see section 2.6.1.). To populate or upload the required information and documentation, **users must lock each subsection by clicking on the padlock icon**.

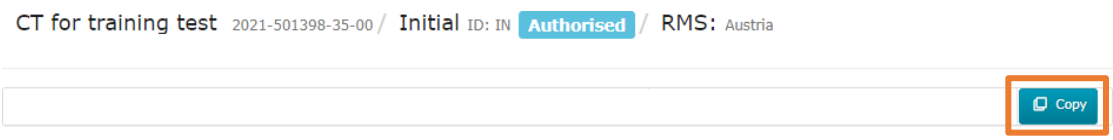
If a document needs to be updated while the application is still in draft, users must **first remove the previously uploaded document** and then upload the new version. Users can also edit document metadata such as the title, date, version, and comments. To do this, they can click on the pencil icon, which makes the relevant fields editable. Once the necessary updates are made, users can either save the application by clicking on the 'Save' button in the upper-right corner of the page or submit the application, provided all required fields have been completed.

2.3.4. How to copy a submitted IN

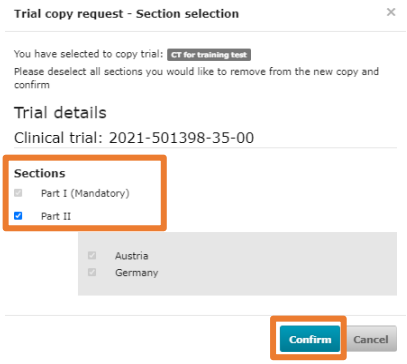
The copy functionality allows users to create a new IN starting from an **already submitted** application, where, for example the same medicinal products were used. The new application will have **a new and unique EU CT number**. Any section of the new IN can then be modified as relevant.

The below steps can be performed by a user who has a CT Admin user role. After having accessed the sponsor workspace:

1. Search for the clinical trial (see section 2.6.1. on how to search for a trial), click on the relevant CT number and scroll down to see the 'Application and Non-substantial modification' section; click on the IN of the application under the 'ID' column (see section 2.6.2. on how to view a submitted trial).
2. On the top right corner of the page, select **'Copy'**



3. Part I of the IN will be copied by default; you can select/deselect to copy or not copy Part II of a specific MSC. Select then the '**Confirm'** button.



The new IN will be in draft, and you will be able to edit it before submitting it. Note: only data and documents of the **last submitted version** of the original application will be copied and not those of previous versions. If multiple RFI responses with application's changes had been submitted during assessment of the original application (see section 3.3.), the copied IN draft will contain the details and documents of the last submitted application version.

2.4. Fill in specific IN sections (e.g. product section)

The below steps detail how to complete specific sections of a CT application and can be performed by a user who has the following roles, depending on the action and of the part of the application:

- Create/copy an IN: **CT Admin**

- Draft/edit an IN/any application: **CT Admin, Part I Preparer (excl. Q-IMPD), Part II Preparer, Q-IMPD Preparer, Application Submitter**
- Submit/cancel/withdraw an IN/any CT application: **CT Admin, Application Submitter**

2.4.1. Adding an Associated Clinical Trial

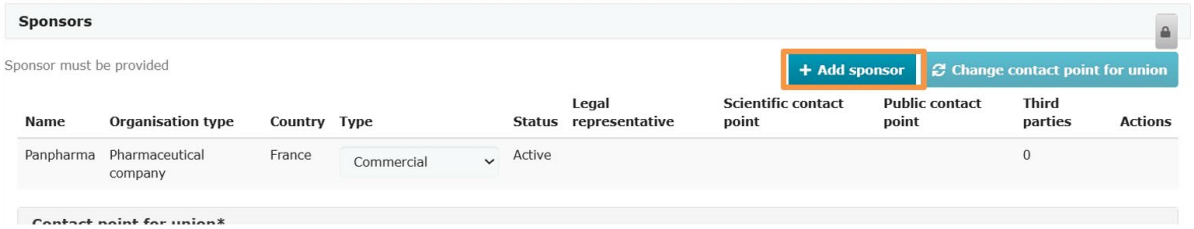
In line with Article 25(4) and (5) of CTR, sponsors can refer to data generated in another trial conducted under the regime of CTD or CTR. This is particularly required in certain cases mentioned in the CTR Q&A (look for keyword 'Associated clinical trials' throughout the Q&A document). Note: this is different from the 'Transition trial' field, which is no longer applicable and should not be used. Steps are the following:

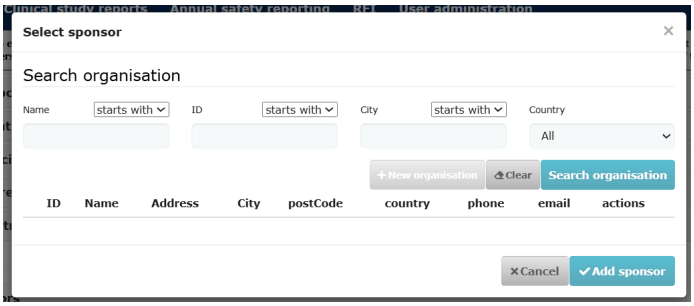
1. Access the 'Associated clinical trials' tile under the 'Trial details' subsection of Part I, and click on the '+ Associated clinical trial' button.
2. Retrieve the trial number (EudraCT, if it was conducted under the regime of the CTD or EU CT, if conducted under the regime of the CTR) using the search functionality and associate it.
3. *In case the associated trial is owned by a different sponsor,* an agreement from the sponsor owner needs to be provided: click on the '+' icon and on the 'Add document' button. Note: while structured data fields of this section are subject to publication, the uploaded document is not.

2.4.2. Adding a co-sponsor organisation

Sponsor and co-sponsor organisations **must be registered in OMS** before they initiate an IN in CTIS, see section 1.2. The sponsor organisation is already pre-filled in the relevant 'Sponsors' section of the CT application, however further details need to be added (e.g. Scientific/public contact points), after clicking on the table that displays the sponsor name. In case a CT is **sponsored by more than one organisation**:

1. **Click on 'Add Sponsor'** and look for the relevant sponsor organisation that acts as co-sponsor.
2. The field 'Responsibilities of the sponsors' is displayed: specify the responsibilities of each sponsor organisation through clicking on 'Manage responsibilities'.





2.4.3. Organisation registration locally in CTIS for use in CTIS

Apart from the sponsor(s) section, the CT application includes several other entries that refer to organisation entities. In a limited number of cases and **only in the below mentioned CTIS sections**, if users do not retrieve an organisation in OMS when looking for it in CTIS and cannot register the organisation as per section 1.2., it is possible for users to create an organisation entry directly in CTIS. Note that **the present section is not applicable to the fields of sponsor and co-sponsor**, which have to be registered in OMS and have an associated ORG-ID, see section 1.2.

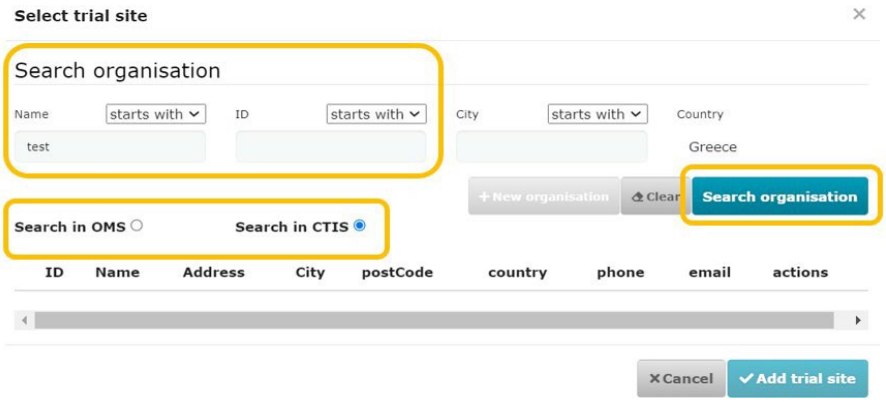
Organisations created locally in CTIS are not validated by the EMA SPOR team and therefore they will only be registered in CTIS and not in OMS. When registering organisation locally, **users should follow OMS data quality standards** (see section 1.2.) to avoid RFIs from assessing authorities due to inaccurate data.

Below there are the steps to be performed in order to register an organisation locally in CTIS. The following steps refer to the example of adding a trial site in Part II of a CT application, however they can be applicable to other sections where an organisation can be searched (see step 1).

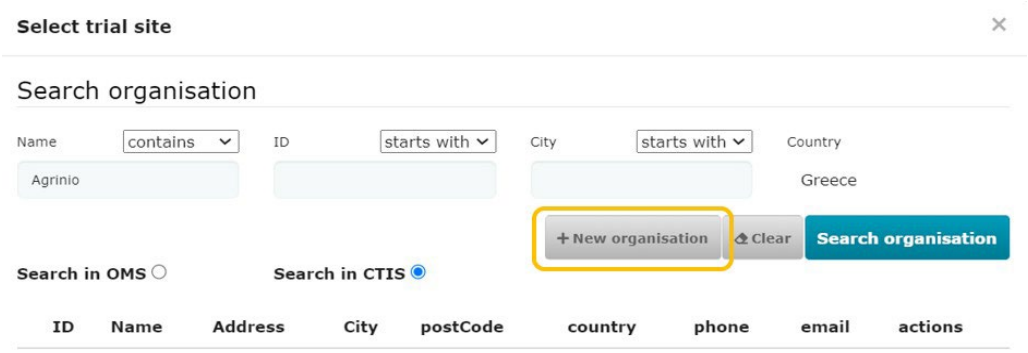
1. Verify that the organisation is not present in either OMS and or CTIS, through selecting 'Search in OMS' and then 'Search in CTIS' in any of the following sections:

   - Part I Sponsor section – Third-party organisations
   - Part II – Trial sites
   - Serious Breach notifications – Details of the site where the serious breach occurred
   - Third Country Inspectorate Inspection – Third country inspection site

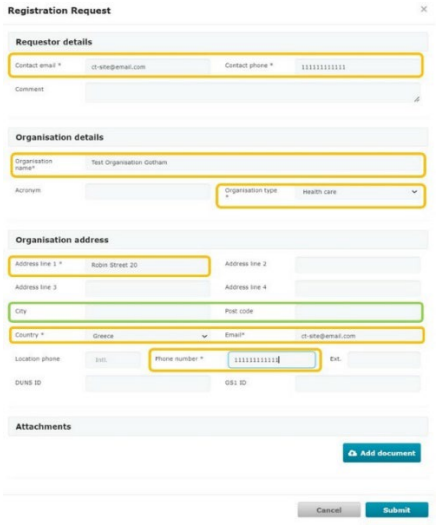
   This is to avoid creating unneeded organisations in CTIS. To increase the scope of your search, you could use the 'contain' filter and not the default 'starts with' filter.



2. If you do not find the site when searching in OMS or in CTIS, a red message will be displayed on the upper right corner, and you need to create the site in CTIS by clicking the button '+ New Organisation'.

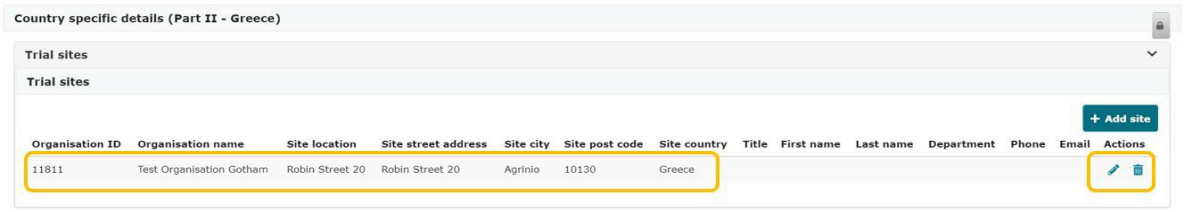


3. Complete the registration form through following the OMS data quality standards, as mentioned above. Mandatory fields are indicated with an asterisk. You are advised to enter the city and postcode, although these fields are not highlighted as mandatory, to ensure notifications that include sites registered in CTIS pass the technical validation. Moreover, in the case of trial sites/third-party vendors, this is required information in case of inspections.



4. Submit the registration form through clicking on 'Submit' button at the end of the form and confirming the pop-up confirmation window. Note: Organisation IDs for organisations registered in CTIS start with 'ORL-' (while OMS-originated organisations' IDs start with 'ORG-'). You may wish to take note of this ORL-ID for future reference. The ORL-ID will also appear when using the relevant organisation name or other organisation details in the search fields.

5. The organisation and its details will appear immediately in the overview for the relevant CT application. You can now click on the 'Add trial site' button (as applicable, depending on the CT application section, or i.e. 'Add third party').



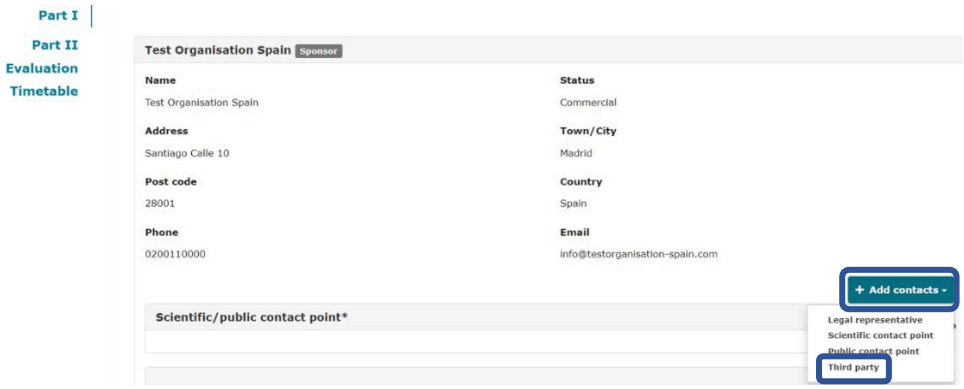
Once the trial site is added to the CT application, you could also remove it (e.g. in case details are mistyped) by using the bin icon or edit it to fill in additional information related to the organisation by using the pencil icon under the 'Actions' tab placed on the right side of the table. For examples, for a trial site in Part II, you can use the pencil icon to populate the Principal Investigator related information. In the same way, after having created a third-party organisation in the 'Sponsor' section of Part I, you could populate the activities assigned to the third-party (see below section). In some other cases (i.e. Serious Breach notification), the pencil icon might not appear as there are no further details to be added. When an organisation is created locally in CTIS, it starts in DRAFT status and is visible only within the associated draft CT application or notification, i.e. it does not appear when other sponsors (or even the same sponsor who created the organisation) search in CTIS.

Important: **once the relevant CT application or notification is submitted, the locally registered organisation in CTIS changes from DRAFT status to ACTIVE status, becoming searchable by other users**, including users from different organisations such as other sponsors. **Organisations registered locally in CTIS with ACTIVE status can be edited through a NSM or SM** (to modify details of the organisation such as address or name or country etc).

2.4.4. Adding a third-party organisation

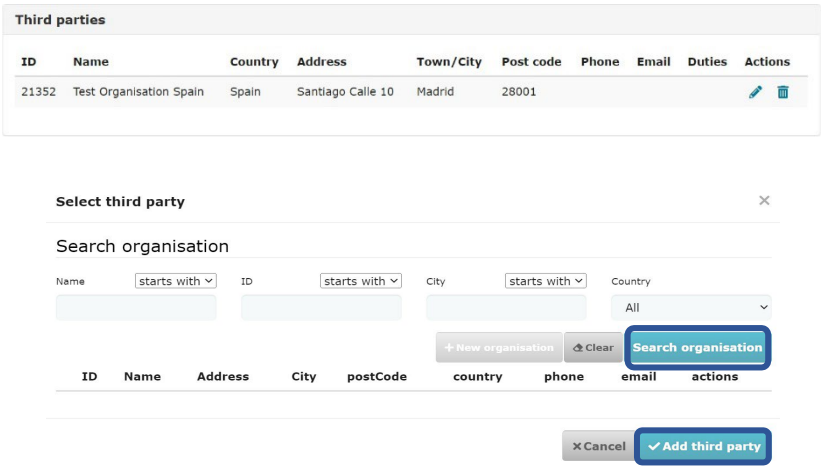
In case the sponsor has delegated any of their responsibilities to one or more third-party organisations (e.g. Clinical Research Organisations) these entities can be included in the application once they are registered in OMS (refer to section 1.2.) or they can be added locally (see section 2.4.3.):

1. In the 'Sponsor' section of 'Part I', click on the '+ Add contacts', choose the 'Third party' option



2. Search for the relevant organisation and click on the 'Add third party' button.

3. Click on the pencil icon to modify the information regarding that third-party (assigned duties and contact details). **Functional contact details must be used** since **they will be made publicly available** (see section 2.1.).



2.4.5. Adding medicinal product(s) in CTIS

Before filling in the 'Products' section of Part I of the IN or of any CT application**,** the user needs to **make sure that the relevant medicinal products are present in XEVMPD**: see section 1.4. on adding a medicinal product in XEVMPD.

For each trial in CTIS, in the Part I of an IN **the user must add at least one medicinal product with the 'Test'** role, which is the IMP being tested during the trial. Users can add several 'Test' IMPs in a CT application. It may be that several products share common documentation (see step 8 below).

Besides the 'Test' role, the following other roles can be associated to a product, as applicable:

- Comparator: medicinal Product used as a reference in a CT to be compared to the 'test' medicinal product.
- Placebo (could also not be in XEVMPD): product with no therapeutic effect, used as a control when testing new medicinal products.
- Auxiliary: Auxiliary Medicinal Product (AxMP) 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). See document Auxiliary Medicinal Products in Clinical Trials

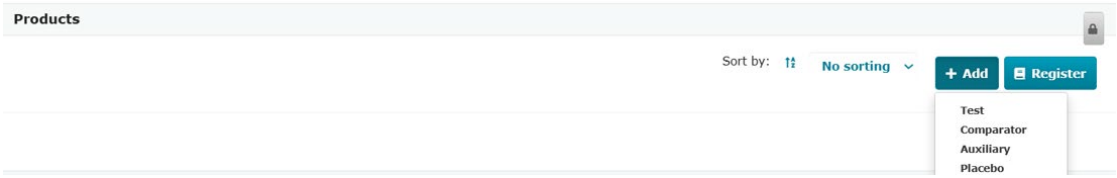
In CTIS, the product information (for test product, comparator and AxMP) is retrieved from the XEVMPD, and this is enabled by a search and selection functionality available for an authorised product (i.e. a product with a marketing authorisation in the EU/EEA), an active substance, an Anatomical Therapeutic Chemicals (ATC) code or an unauthorised product. Only for placebo, the product details are generally specified locally in CTIS and are usually not retrieved from XEVMPD.

Below there are the steps that a user with one of the following **roles** needs to perform when adding product(s) in the 'Product' section of the CT application: **CT Admin, Part I Preparer (excl. Q-IMPD), Q-IMPD Preparer, Application Submitter**.

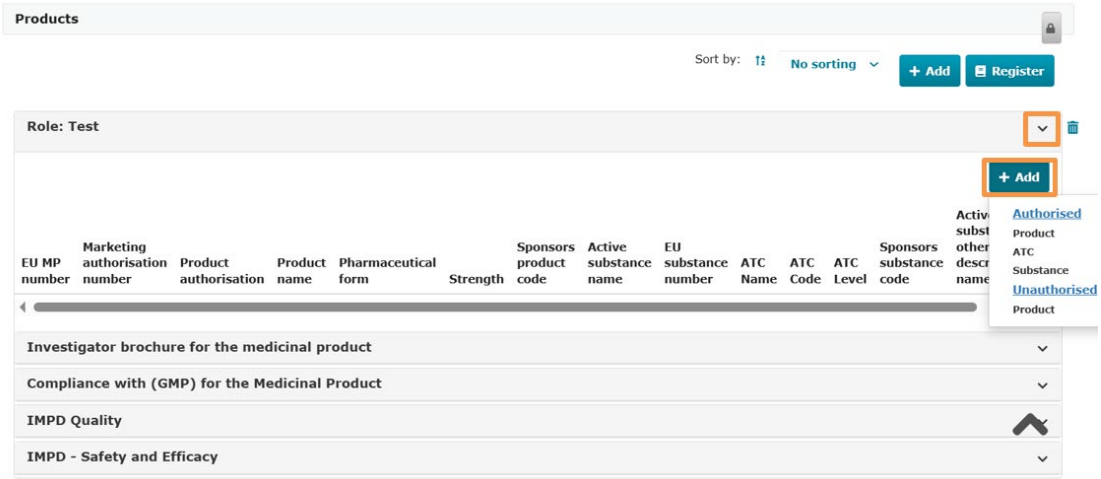
After having accessed the sponsor workspace and having created the IN as per section 2.3.3. :

1. Select 'Part I' and click on the padlock at the top right of the 'Products' section to lock it.

2. Select the **type of product** that needs to be added (as per above descriptions) through clicking on '+ Add'. The 'Register' option can be selected in case the product needs to be added to XEVMPD, see section 1.4. .



3. After selecting the kind of product, click on the arrow on the right to open the menu and then on the '+ Add' button. Select here the authorisation status of the product ('Authorised' or 'Unauthorised') to be searched and the kind of **search** parameters ('Product', 'ATC' or 'Substance').



4. When searching, you 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. Search fields are different depending on the type of product:

   Authorised:

   - Product: EU Medicinal Product (MP) number (i.e. EV Code assigned to a specific medicinal product record by XEVMPD), Pharmaceutical form, Marketing authorisation number, Strength, Name of product, Active substance name, EU substance number, and/or ATC code.
   - ATC: ATC code (level 3, 4 or 5) and ATC name
   - Substance: Name, EU Substance Number, Pharmaceutical form, Strength

   Unauthorised:

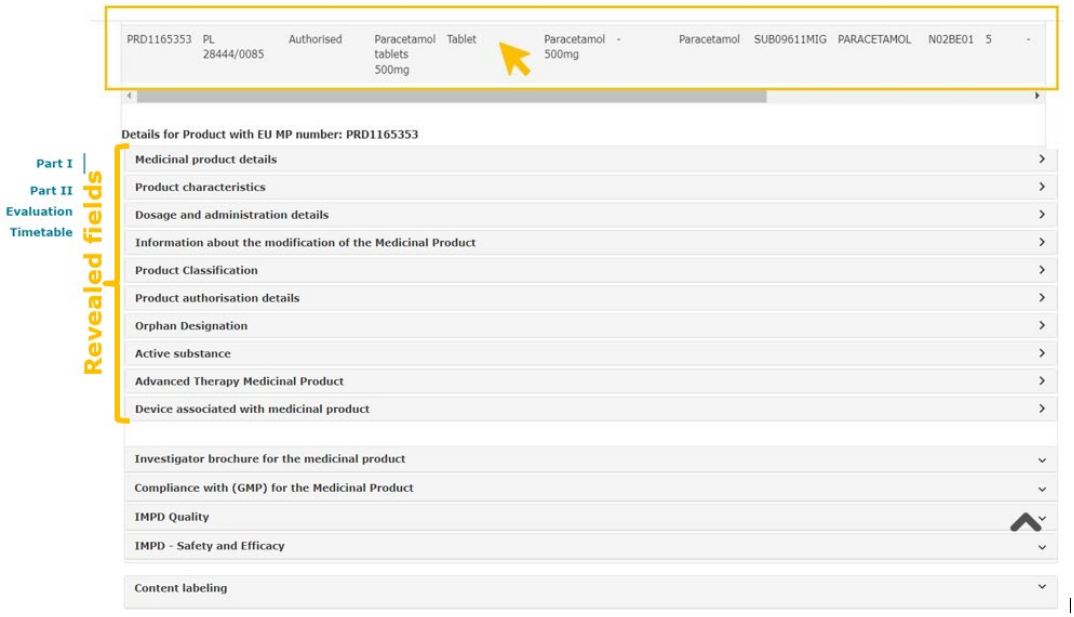
   - Product: EU Medicinal Product number and EU substance number (both fields are mandatory)

   For unauthorised medicinal products, refer to section 2.4.5.1. .

Depending on the parameters used to run the search, you can get a unique search result returned, or multiple results can be retrieved. For example, in case of search by EU MP number only one result is returned. However, if the user is searching for an active substance, a pharmaceutical form or strength, then multiple results may be returned.

5. Once the authorised or unauthorised medicinal product is retrieved from XEVMPD, select it and **click on 'Add product'**. Some pre-populated data appear in the CTIS form, which are extracted from XEVMPD (as applicable: EU MP number, Marketing authorisation number, Product authorisation, Product name, Pharmaceutical form, Strength, Active substance name, EU substance number, ATC Name, ATC Code, ATC level, Type), while others would need to be filled in (e.g. Sponsor's product code, from the 'Medicinal product details' tile).

6. **Click on the ribbon where those pre-populated product data are displayed**, to **show all fields** related to the selected product.

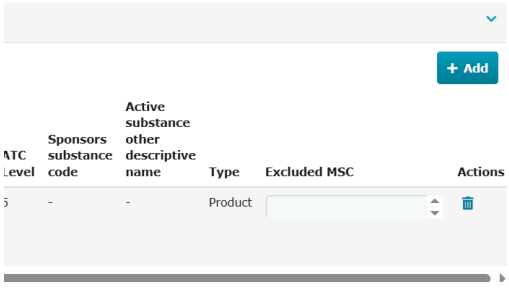


7. All **structured data fields** need to be populated as applicable, see table in section 2.2. In addition, **for each product you have to provide** the following **documents** foreseen in the CTR, as applicable: Investigator Brochure (IB) or the Summary of Product Characteristics (SmPC); Investigational Medicinal Product Dossier (IMPD) Quality; Investigational Medicinal Product Dossier (IMPD) Safety and Efficacy; GMP documentation, Content labelling. Among them, **only the SmPC is subject to publication and should not contain any CCI or personal data** (see section 2.1.). Important: **in case you add another document in the SmPC slot (e.g. the IB), this document will be published**.

8. Populating the **IMPD Quality and IMPD Safety and Efficacy** sections*:* users with Q-IMPD Preparer role are able to populate only the IMPD Quality part, including the addition of any quality-related document. Users with the Part I Preparer (excl. Q-IMPD) role are not able to complete

the IMPD Quality part, but can complete everything else that concerns Part I, including IMPD Safety and Efficacy. The CT Admin can complete all fields, irrespectively of the type. Note: if you have already uploaded the IMPD-related documents (IMPD Quality or IMPD Safety and Efficacy) to other clinical trials, you might not need to upload any documents again. In that case, you 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 CT application). If you upload at least one document to any of the document sections, the free text field disappears, and you need to upload all the mandatory documents to be able to submit your application.
For guidance on **IMPD-Q only submissions** and **on protecting IMPD-Q confidentiality when the Sponsor is not the Product Owner or Substance Owner**, refer to the Sponsor FAQs, and the CTR Q&A (look for 'IMPD-Q' as a keyword), the 'Frequently asked questions related to Clinical trials submitted under the Regulation EU 536/2014' available in the 'Key document list' section on the CTCG page and *watch the Clinical Trials Information System (CTIS) bitesize talk: IMPD-Q only submission*. For more information on Alternate IMPD-Q and New Guidance AxMP, consult the Q&A from CTIS Bitesize Talk on Alternate IMPD-Q and new guidance AxMP (24/04/2024) and *watch the corresponding CTIS Bitesize Talk: Alternate IMPD-Q and new guidance AxMP*.

9. *In case a product is not used in a specific Member State Concerned:* by default, the product is applicable to all MSCs. However, sponsors can choose to exclude a product from an MSC when foreseen by the protocol, for example in case of concurrent medication for underlying disease treatment. This can be done by clicking the 'Excluded MSC' box from the ribbon that hosts the overview details of the medicinal product and selecting the MSC in a drop-down list of the MSCs involved in the trial.



Note: The "Excluded MSC" dropdown displays 10 values at a time. To view and select additional countries, users should initially select all countries shown in the dropdown, even those they do not intend to exclude. As each country is selected, another country becomes available in the list. Once all required countries have been selected, any countries that were selected only to reveal additional options can be removed before saving.

10. **Any placebo** product must be **linked to products** that have the role of 'Test/Comparator' by clicking on the button '+ Link products' displayed in the section with the same name.

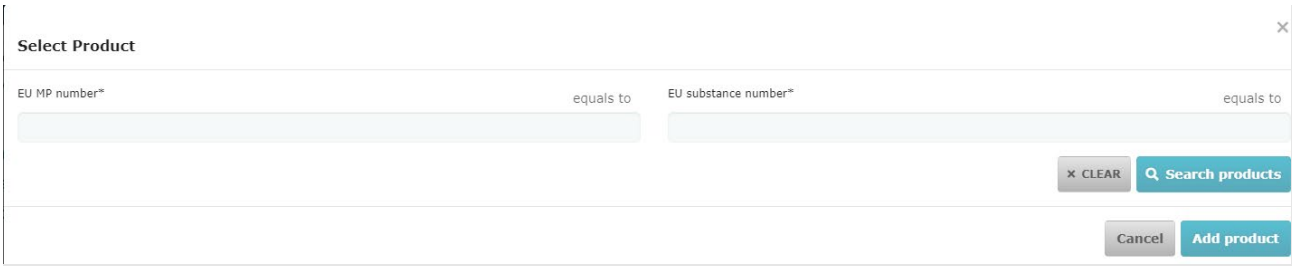
11. In case the added product is an **Advanced Therapy Medicinal Product (ATMP)** and/or it is **used in combination with a medical device**, the relevant sections need to be completed: see section 2.4.5.2. and section 2.4.5.3. for specific instructions

2.4.5.1. Adding an unauthorised medicinal product in CTIS

As explained in section 1.4. , unauthorised products include those that have not received a marketing authorisation in the EU/EEA. This is also valid in case they have a specific strength and/or pharmaceutical form, which differs from a product that is already authorised in EU/EEA.

Registration of unauthorised medicinal products **in XEVMPD** is independent of the role of the medicinal product in the clinical trial (i.e. test, comparator etc.), however it **needs to be done before** they can be used to populate dossier Part I of the CT application in CTIS. Note: if an active substance is used in a clinical trial in a new pharmaceutical dose form and/or new strength, a new development medicinal product must also be entered in the XEVMPD by the sponsor organisation. However, if a medicinal product not yet authorised in the EEA, that is already present in XEVMPD, is used in a clinical trial for different indications and/or routes of administration(s), the sponsor can update the existing unauthorised medicinal product in XEVMPD with the new indication/route of administration.

Users can retrieve unauthorised products information in CTIS only by searching for EU MP number (medicinal product EV Code) together with the EU substance number (substance EV Code) referenced for this product in the XEVMPD. A medicinal product EV Code is a unique number assigned by the XEVMPD to each medicinal product record successfully inserted in the dictionary and it is used to identify this medicinal product in the XEVMPD. It should be noted that **both parameters**, namely the medicinal product EV Code and the substance EV Code, **are mandatory** to run the search in CTIS for unauthorised medicinal product data, and therefore users must be cognisant of the required information in order to be able to add the product in the CT application.

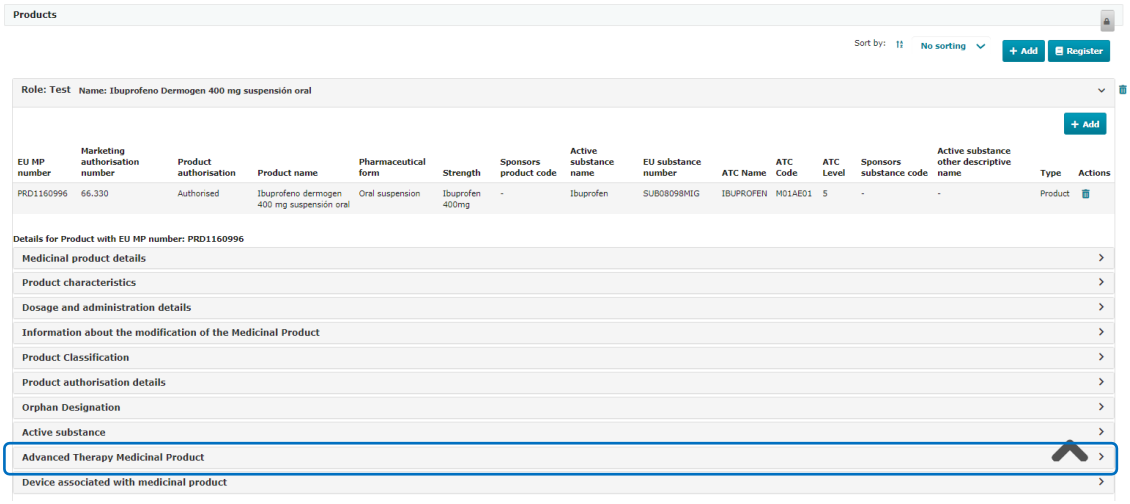


Once the medicinal product of interest is identified, users will see some pre-populated information, as it is available in the XEVMPD. Note: the strength and pharmaceutical form of the retrieved unauthorised product are not displayed in the draft CT application dossier Part I. This information only becomes visible following the submission of the application to the MSC(s).

More details on the registration of medicinal products in XEVMPD are provided in section 1.4. of this handbook.

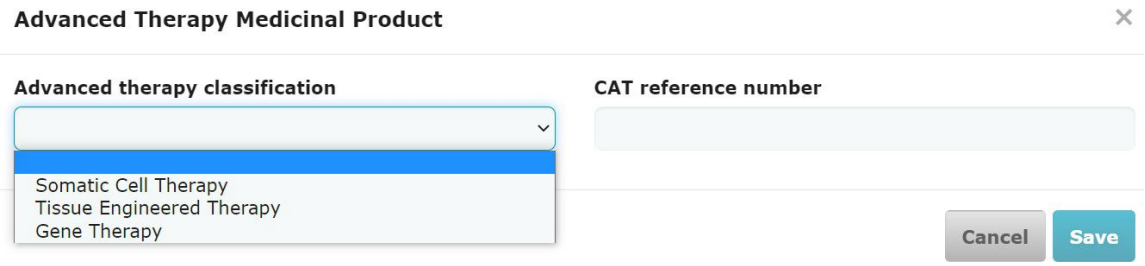
2.4.5.2. Advanced Therapy Medicinal Products section

In case the product used in the trial is an Advanced Therapy Medicinal Product (ATMP), users need to populate the relevant information in the tile 'Advanced Therapy Medicinal Product', since the confirmation of whether a medicinal product is classified as ATMP is not captured in XEVMPD.



The below steps are applicable to a user with the following roles: **CT Admin, Part I Preparer (excl. Q-IMPD), Application Submitter**. After having accessed the sponsor workspace and having completed the product section as described in section 2.4.5. :

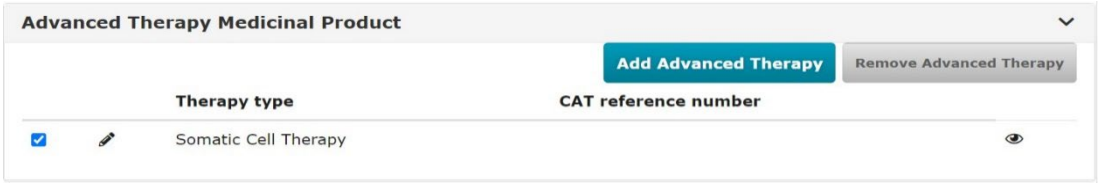
1. Expand the 'Advanced Therapy Medicinal Product' tile, click on the 'Add Advanced Therapy' button. In the pop-up window, select an option from the 'Advanced therapy classification' drop-down menu, and populate the Committee for Advanced Therapies (CAT) reference number, if applicable.



2. Based on the selection of the type of advanced therapy, relevant fields might be expanded below, that will allow you to record additional information regarding a specific ATMP. The selection of the first fields might affect subsequent fields and under specific circumstances, some of them might be mandatory. Mandatory fields are indicated with an asterisk. The available fields for each Advanced therapy classification option are:

   - Somatic Cell Therapy: Somatic cell origin (Autologous; Allogenic; Xenogeneic); Somatic cell type (Stem; Differentiated; Other).
   - Tissue Engineered Therapy: Tissue engineered cell type (Stem; Differentiated; Other); Origin of the engineered tissue (Autologous; Allogenic; Xenogeneic).
   - 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).

3. After populating the relevant details, save the information recorded in the ATMP tile.
4. Once saved, you can edit the information by using the 'Pencil' icon, or you can remove it and add new data by using the 'Remove Advanced Therapy' button. The 'Eye' icon allows you to view all the details entered for a specific ATMP.

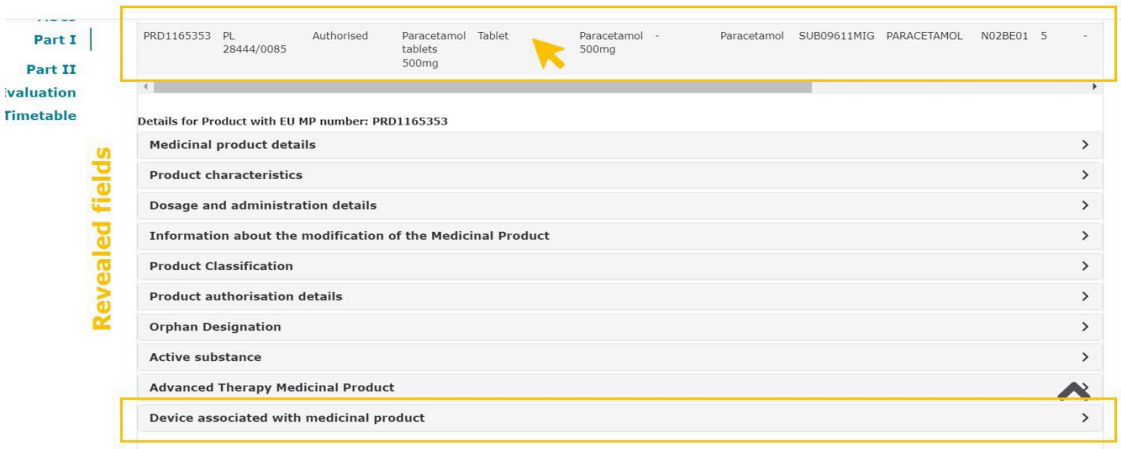


2.4.5.3. Medical device associated with a medicinal product

The CTR Q&A indicates under which circumstances a medical device, in combination with a medicinal product, can have a role in a clinical trial and be assessed under the CTR. If the medical device (in combination with the medicinal product, or ATC or substance) is indeed the **object of the study** under the CTR, the details of the medical device need to be populated in the details for the respective medicinal product that is combined with the device.

The below steps are applicable to a user with the following roles: **CT Admin, Part I Preparer (excl. Q-IMPD), Application Submitter**. After having accessed the sponsor workspace and having completed the product section as described in section 2.4.5. :

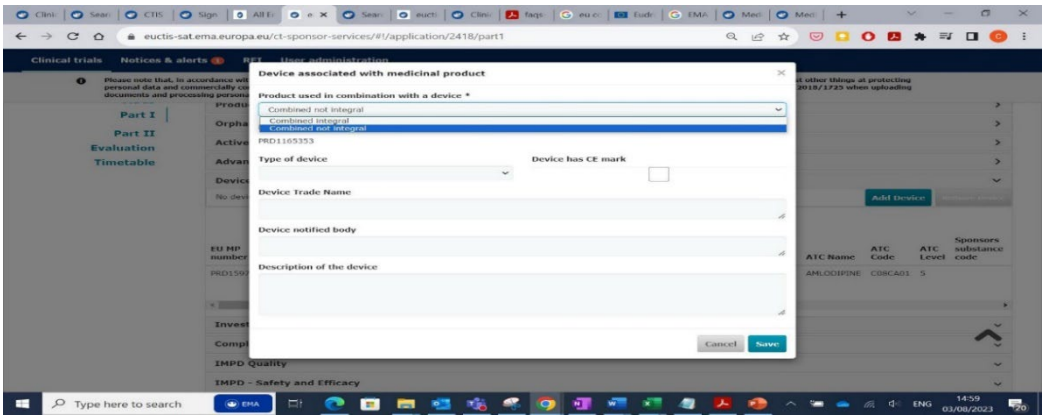
1. Click on the ribbon that hosts the overview details of the medicinal product (or ATC, or substance) that is combined with the medical device. Fields related to the selected product will be revealed below. Among them, at the end, you can see the tile 'Device associated with medicinal product'.



2. Open the tile and click on the 'Add device' button

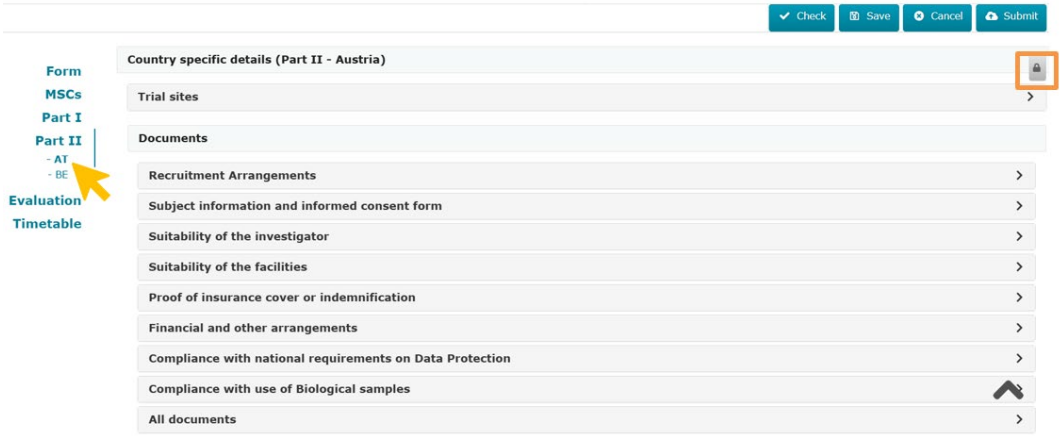
3. Populate the details of the device. The first field, 'Product used in combination with a device', is a drop-down list for which users need to indicate whether the device is combined as an integral item with the product or not. Then, you can use the following fields to indicate the type of the device (drop-down list), whether there is a CE mark 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).

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



2.4.6. Populating Part II section of a CT application

The information covered in the Part II section of a CT application includes structured data and documents **applicable to each of the MSC(s)** where the sponsor is applying for authorisation of a clinical trial. If the trial is a multinational trial, **those details need to be populated for each of the Member States** involved:

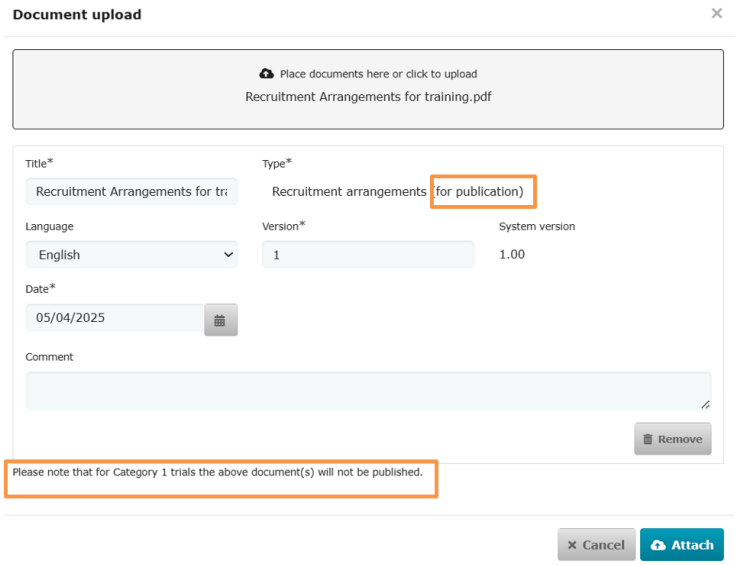


The **structured data** that need to be populated consist of details of the **trial sites**, including name and address of the site, and details of the **principal investigator** conducting the trial at the site (name, department, department contact points: phone number and email address. All those details **are made public** and need to be **functional** contact details (see section 2.1.). The **documents** that need to be uploaded (for which templates can be found on the EudraLex Volume 10 page) are:

- Recruitment arrangements (publicly available for category 2 and 3 trials, see below)
- Subject information and Informed consent form (publicly available for category 2 and 3 trials, see below)
- Suitability of the investigator
- Suitability of the facilities
- Proof of insurance cover or indemnification

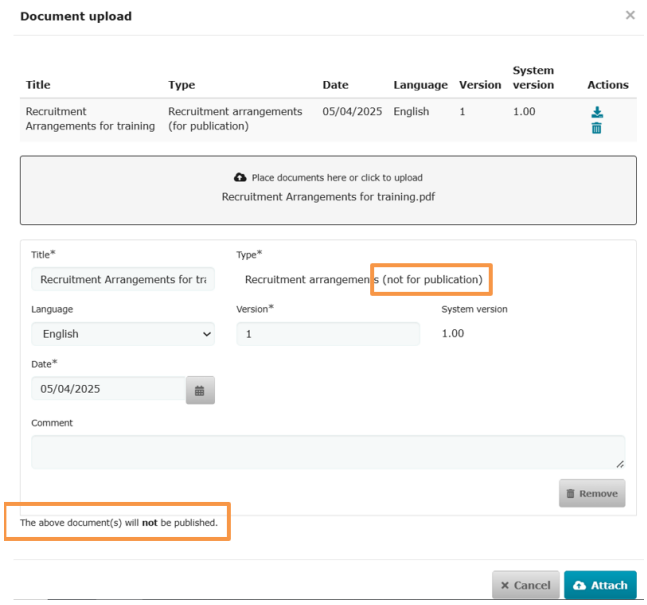
- Financial and other arrangements
- National requirements for data protection, as applicable
- Use of biological samples, as applicable

Recruitment arrangements and Subject information and Informed consent form documents are made publicly available for category 2 and 3 trials: for these trials, the first uploaded document is the 'for publication' one and needs to be redacted of CCI and personal data, see section 2.1.



In case of Category 1 trials, even if the system displays the document as 'for publication', note that those documents are not published, in line with the publication rules (see section 2.1.).

The document added when clicking on the '+' button is the one 'not for publication' and can contain CCI as needed for the MSC(s) assessment.



Note that placeholder Part II data/documents are allowed only when strictly adhering to the 'CTCG Guidance for Sponsors on Article 11 workaround' listed among the 'Key documents list' of the CTCG website (see section 2.5.1.).

Once all fields are filled in, sponsor users can refer to section 2.3.3. to know how to submit the application.

2.4.7. Transition from Directive to Clinical Trial Regulation

Clinical trials authorised under the CTD (Clinical Trials Directive 2001/20) that are ongoing beyond 30 January 2025 should have been transitioned to the CTR. The transition of clinical trials from the CTD to the CTR was open to sponsors from the day of the entry into application of the CTR, on 31 January 2022, until the end of the 3-year transitional period, on 30 January 2025, without the need to discontinue a clinical trial or put a trial on hold.

***For trials that should have been transitioned CTR from the CTD but** were not, sponsors are advised to* see CTCG Best Practice Guide for sponsors who have missed the transition timeline.

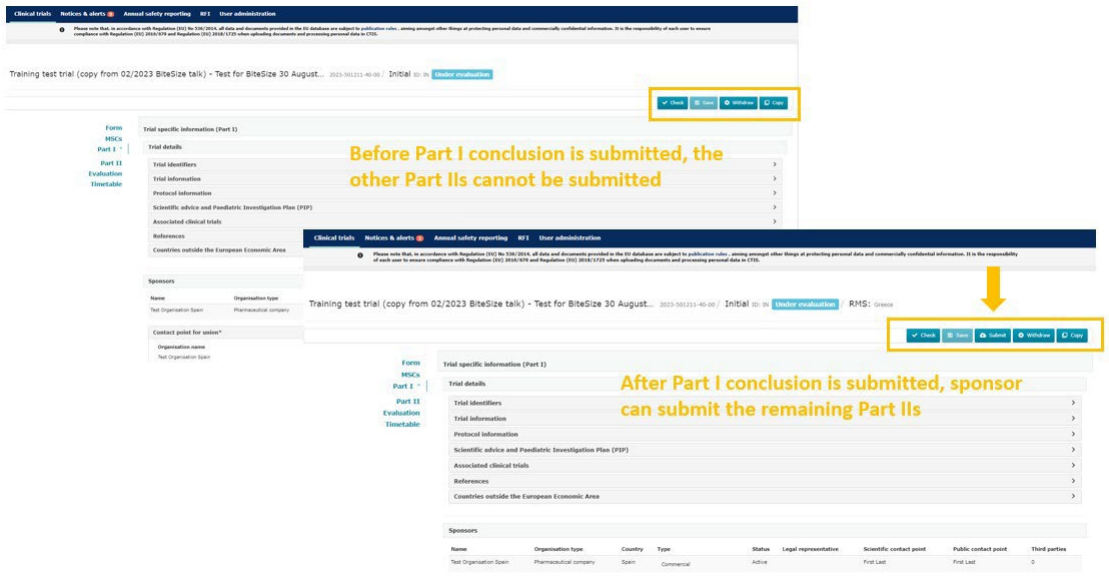
With regards to trials that were transitioned to the CTR from the CTD, once the transition trial has a recorded authorisation in CTIS, all the requirements of the CTR apply from the date of approval of that application under the CTR. More information in the Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation. The sponsor needs to comply with their CTR obligations for the management of the trial and submit notification information as required. These include start of trial notification and start of recruitment that may have occurred prior to authorisation but could also include further events as they are likely to take place. Also, **any changes to the dossier need to be reflected in line with the requirements of the CTR**. Therefore, any subsequent SMs submitted to the MSC(s) need to comply with CTR's requirements. More information on submitting SMs in a clinical trial application through CTIS can be found in section 4.3. Additionally, specific guidance for the first substantial modification after a trial application transition is available in the Clinical Trials Coordination Group (CTCG) website, including the relevant Annex I Cover Letter Template, Annex II Substantial Modification Description Template and Annex III - First SM Part II after transition. Submission of results documents must also comply with the CTR requirements, including any interim results whose due dates fall after the trial was transitioned to CTIS.

***Regarding new application submissions in CTIS**, sponsor users should not use the "transition" tick box displayed at the beginning of the application process. If used, the application will not be treated as a transitioned trial, but rather as a new application that must meet all standard CTR requirements, as outlined in the **CTCG best practice guide**.*

2.5. Partial submission of an IN

Before applying the below instructions, the CTR Q&A (search for the keyword 'article 11') should be consulted. For questions, refer to the relevant MSC(s) national contact point(s).

Sponsors should submit high-quality applications that are complete and comply with regulatory requirements, through performing a full submission in line with Article 5 of the CTR (including Part I and Part II). However, it is also possible for sponsors to perform a **partial IN submission** of Part I only under **Article 11** of the CTR. In case of a partial submission, sponsors need to wait for the RMS/MSC(s) 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 (status: 'lapsed').



When submitting an application limited to the aspects covered by **Part II** of the dossier, the sponsor needs to declare 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(s). The list of the documentation and information required to be provided in Part II is set out in CTR Annex I (sections K to R).

Note that a CTCG Guidance for Sponsors on Article 11 workaround has been published on 27 April 2026 to allow the submission of an SM Part I also to MSCs initially intended to receive Part I only (partial IN): see section 2.5.1.

→ on this topic: watch also the CTIS Bitesize talk: Part I-only applications and Part II requirements.

2.5.1. Partial submission of IN: submission of a subsequent SM or AM

In CTIS it is not possible for sponsors to submit an SM for a partially submitted IN until Part II has been submitted for all MSCs and all MSCs have issued their decisions (see section 2.5. above). Where

decisions have been issued only by some MSCs (i.e. those for which Part II has already been submitted by the sponsor), no SM or AM can be submitted for the trial. **To proceed with an SM or AM, the sponsor should submit Part II applications for all remaining MSCs, and wait until all the decisions have been issued.** *Note that,* ***in those cases where an SM/AM needs to be submitted urgently for a partially submitted IN the sponsor may proceed as follows***:

- Follow the CTCG Guidance for Sponsors on Article 11 workaround available under 'Key Documents List' on the CTCG page and referenced in the CTR Q&A (keyword: 'Article 11 workaround'):

    1. contact the relevant MSC(s) (contact details are in Annex III of CTR Q&A) to determine whether submission of placeholder Part II data/documents to complete the earlier partial submission would be acceptable. Note that this approach is not acceptable in France

    2. *if acceptable,* submit Part II applications for the remaining MSCs including placeholder Part II data/documents

    3. Once all relevant decisions have been issued, the sponsor may submit the SM or AM. **Important: the trial is neither allowed to start nor recruit participants in an MSC until the Part II actual data/documents have been submitted in an SM Part II and subsequently authorised**

- In alternative, or if the workaround is not acceptable for the MSC(s):

    1. withdraw the trial application for the remaining MSC(s) for which no decision has been issued (see section 2.7. on how to withdraw an application)

    2. submit an SM for the MSCs that have already issued a decision. After a decision on the SM has been issued, the sponsor can submit AM(s) for the MSC(s) whose applications were previously withdrawn. Note that an AM cannot be submitted also while the evaluation of an SM including Part I is ongoing (see section 4.2.).

For new partial IN where the submission of an SM Part I is expected to take place after the submission of the partial IN, sponsors may instead use the Article 11 workaround by submitting a full IN to all MSCs, including those intended to be in Part I only, with placeholder data/documents in Part II. Note: this procedure is acceptable in all EU/EEA Member States except for France, where a full Part II submission should occur (placeholder data/documents would not be accepted in France). The Article 11 workaround facilitates alignment among MSCs on the Part I assessment. Note that **the clinical trial may neither start nor recruit participants in an MSC until the actual Part II data/documents have been submitted in an SM Part II and subsequently authorised.** Details of the procedure are provided in the CTCG Guidance for Sponsors on Article 11 workaround, available under "Key Documents List" on the CTCG page. Additional background information is available in the CTR Q&A (keyword: "Article 11 workaround"), which also refers to the CTAG minutes of November 2025.

2.6. Search, view and download a CT or CT application

The search functionality enables users to retrieve clinical trials and/or associated applications, and view and download structured data and documents associated with them.

Users are only able to retrieve, view and download CT and CT application information for those trials in which they have been assigned a role by an administrator within their organisation. This means, for example, that a user that only has Part II Preparer role will not be able to view or download Part I information of the CT application. Sponsor users cannot view CTs or CT application of other sponsors, but a CRO working for multiple sponsors is able to search for all trials they are working on. In

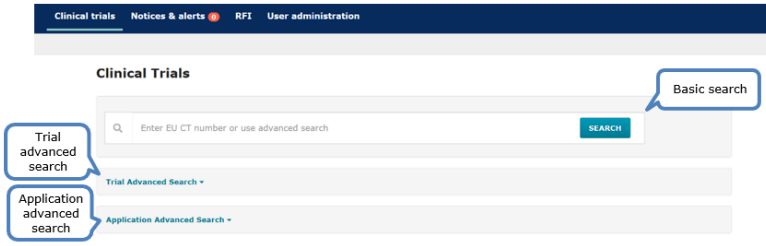
addition, some information may be restricted based on user group, such as ongoing Member State's assessments being hidden from sponsor users or draft trials being inaccessible to Member State users prior to submission.

The following sections describe how to search for a CT or a CT application through CTIS (section 2.6.1.), and, once found, how to view them (section 2.6.2.) and download the relevant information (section 2.6.3.).

→ on this topic: watch the video on How to search for a clinical trial in the CTIS sponsor workspace and How to view and download clinical trial information.

2.6.1. Searching for a draft or submitted clinical trial

The 'Clinical trials' tab in the CTIS landing page allows users to search for trial information stored in the CTIS workspace. A **basic search** can be done by EU CT number or **advanced search** options (per trial and per application) can be used to filter results by parameters like trial status, Member State(s) involved, therapeutic area or active substance. Through clicking on 'Search' without specifying other parameters, all CTs for which the user was granted permissions appear in the results list.



In both advanced searches, **multiple values can be specified** within each criterion. When multiple search fields are used with a single value each, the search operates as an 'AND' condition, retrieving CTs that meet all specified criteria (e.g.: authorised trials in a certain therapeutic area with a specific RMS). If multiple values are used within the same field, the search operates as an 'OR' condition, retrieving CTs that match any of the defined values. For example, searching for CTs with statuses 'authorised' and 'under evaluation' in two Member States will return trials from either status in either of the Member States. Using multiple values broadens the search, yielding more results. No minimum of search criteria is required in the advanced search functionality.

Search results are displayed in a table, each one with basic details on the trial, while further details are accessible by clicking the EU CT number. The results can be sorted by the EU CT number, evaluation process, sponsor, trial title or status. Draft CT applications that have not yet been submitted to the MSC(s) can also be seen (their status is viewed as 'pending'). There is no feature that allows users to either download the search results or save a search and its criteria. To view multiple CTs, it is advised to open them in different browser windows by right-clicking on the EU CT numbers.

Note that the basic and advanced search functionalities of CTIS are accessible across different tabs such as Clinical trials, Notices & alerts, RFI, Annual safety reporting (ASR) and User administration, depending on the user's role and therefore visibility of those tabs in the user's workspace. The search features vary depending on the tab, with each providing a unique set of criteria relevant to its content. **When searching for an ASR ID**, the search needs to be performed **without the ASR prefix** ('2024-12345' instead of 'ASR-2024-12345'), see section 4.13.

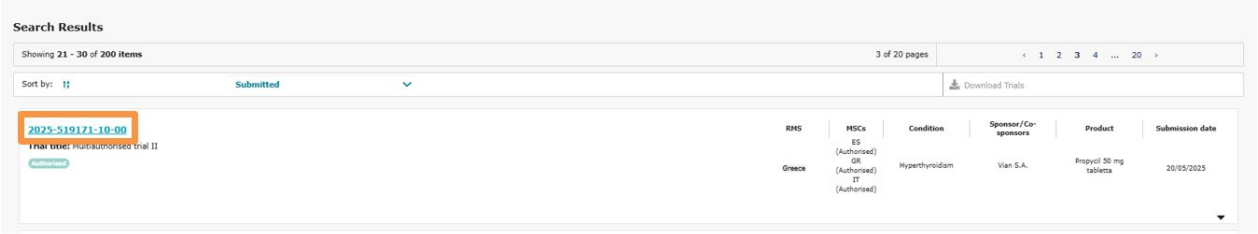
Any search functionality retrieves a maximum of 200 results per search and the results page can display a maximum of 100 results per page. For this reason, organisations with a high volume of CTs data are advised to narrow down their searches when using the advanced search functionalities.

2.6.2. Viewing a draft or submitted clinical trial

On a search results list, users can view the **status** of each CT or CT application shown among the results. A CT or a CT application can have the following statuses:

- **Pending**: the CT application is being drafted by the sponsor.
- **Expired**: no start of recruitment date was inserted within 2 years from the notification date of the authorisation (see section 3.1.7. and section 4.3.3. on how to extend the start of recruitment date).
- **Under evaluation**: the CT application was submitted by the sponsor, and it is under assessment of the MSC(s), see section 3.
- **Withdrawn**: the CT application was withdrawn by the sponsor, during its assessment: see section 2.7.
- **Lapsed**: during the evaluation phase any of the RFI was not responded in time by the sponsor (as per MSC(s) deadlines, see section 3.3.) or no Part II application was submitted after the partial submission of Part I (see section 2.5.),
- **Not valid**: the CT application did not pass the validation phase of the MSC(s) assessment.
- **Not authorised**: the assessment outcome is negative in all MSC(s), see section 3.1.7.
- **Authorised**: the assessment outcome is positive in one or more MSC(s), see section 3.1.7.
- **Halted**: the sponsor applies a temporary halt of the trial, see section 4.1.
- **Suspended**: MSC(s) suspends the trial for a corrective measure while the sponsor submits an SM, see section 4.11.
- **Revoked**: MSC(s) revoke the authorisation of the trial, as a result of a corrective measure (see section 4.11.): the trial is no longer authorised.
- **Ended**: the sponsor notifies the trial end, see section 4.1. and 5.1.

Users can click on each EU CT number shown in the search results list to open the relevant CT page.

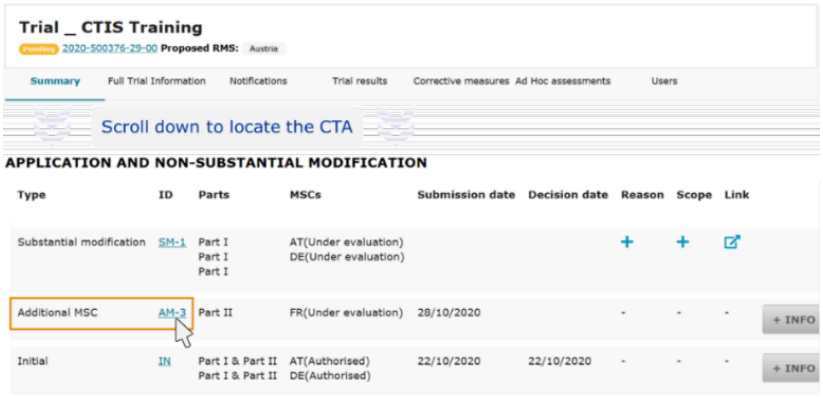


The **CT page** displays the latest authorised or drafted information on a trial. The following subtabs are visible to users depending on their assigned roles:

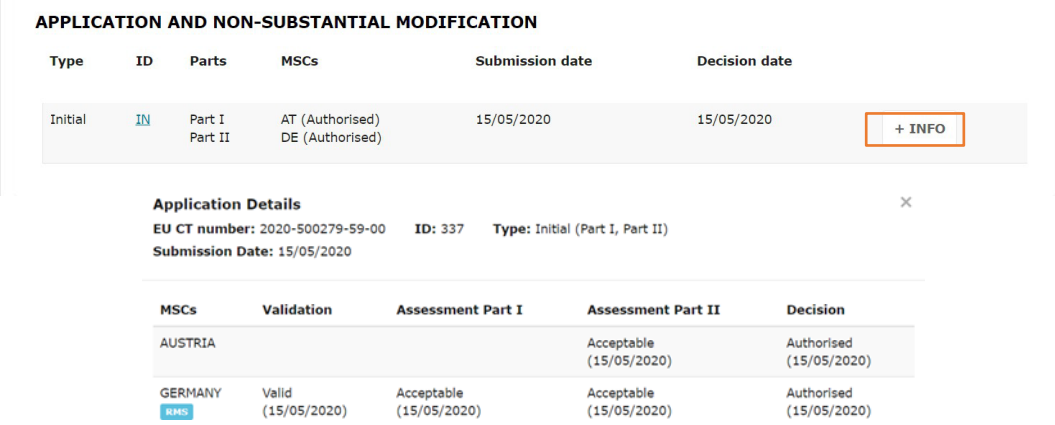
- **Summary:** displays key information of the CT, such as the trial status in each MSC, the therapeutic area, the medical condition(s), and, in consecutive order (starting with the most recent one), the full list of CT application.
- **Full Trial information**: displays comprehensive data and documents on the latest authorised or draft application and includes six sections: Form, MSCs, Part I, Part II, Evaluation and Timetable. See sections 2.3.3. , 3.1. and 3.1.8.

- **Notifications**: enables to view and manage the relevant events in the life cycle of an authorised CT which have been notified to the MSC(s) (e.g. trial and recruitment periods such as trial start date or temporary halt, unexpected event, serious breach, urgent safety measure, third country inspectorate inspection). See sections 4.1. and 4.9.
- **Trial results:** shows the summary of results of any intermediate analysis of data or the summary of results, with the corresponding layperson summary of results, submitted by the sponsor at the end of the trial and the CSR submitted by the Marketing authorisation applicant, if applicable. See section 5.2. and 5.3.
- **Corrective measures:** displays any measure taken by MSC(s) as part of their supervision activities to ensure adherence to the CTR (i.e. suspension of the CT, revocation of the CT authorisation, or request to the sponsor to modify any aspect of the CT). See section 4.11.
- **Ad hoc assessments**: lists the assessments done by the MSC(s) on ad hoc basis as part of their supervision activities, following, for example, the submission of notifications or safety-related information by the sponsor. See section 4.10.
- **Users:** lists all the users associated with a CT, as well as their role(s), sponsor organisation or authority organisation, and employer. See section 1.6.

On a CT page, a **specific CT application can be opened** by scrolling down and clicking on the CT application ID reference.



Moreover, the status of an application in each MSC can be viewed by clicking on '+ Info', on the right-hand side of the ribbon that hosts the overview details of the CT application.



Once having clicked on a specific CT application page, **all of the most recently submitted information** on the application can be viewed, which users can manage by navigating through the sections on the left of the page: refer to section 2.3.3. 2.2. for a description of how to fill in this part. Previous versions of the application and their respective data can be accessed by using the 'Versions' button, found on the upper right corner of each CT application page.

To **go back** to the CT page, a user can click on the **EU CT number at the top** of each CT application page.

2.6.3. Downloading a draft or submitted clinical trial

There are two ways for downloading CT information: either from the CT page or from each CT application page.

2.6.3.1. CT page

Once in the CT page (as per section 2.6.2.), through clicking on the 'Download' button in the upper right corner users can see a tree menu from which the part of the application the users wish to download can be selected (either related to the application dossier –Form, MSC, Part I and Part II– or related to the evaluation/assessment). Note that only one application per time can be selected. The **latest version** of the submitted structured data and documents will be downloaded. To download earlier versions of the structured data, users can view them by clicking on the 'Versions' button on the CT application page and using the browser's functionalities to print as PDF the CT application pages of interest. In addition, information on notifications, corrective measures and trial results, if applicable, can be included in the download zip file. After having selected the relevant information and the file type, to download the file users need to click on 'Start download' at the top-right corner of the CT page.

2.6.3.2. Downloading documents from each CT application page

Documents submitted in the various sections of a CT application can be downloaded from the sponsor workspace through the download icon displayed on the right side of each document. Any previous version of the documents can also be viewed and downloaded through clicking on the arrow on the right side of each document ('Previous versions'), and then on the download icon. The CT application's documents can also be viewed and downloaded from the 'All documents' tile in the end of Part I and Part II sections and clicking on the respective word or PDF icon on the right side of each document. The RFI documents can only be downloaded individually using the blue download icon next to each document of an RFI.

The above is applicable to CT application related documents. With regards to CT results documents (summary of results, lay person summary and CSRs), these can be downloaded in case by users who have the appropriate user role, through the respective download icons from the CT 'Trial results' page.

Note that the above instructions are referred to the sponsor's secure website of CTIS. It is not possible to download previous versions of a document from the CTIS public website.

2.7. Withdraw a submitted IN and resubmit it

Before applying the below instructions, the CTR Q&A (search for the relevant keywords) should be consulted. For questions, refer to the relevant MSC(s) national contact point(s).

The below sections describe how to withdraw (section 2.7.1.) and resubmit (section 2.7.2. an IN, after its submission. Note: to cancel an IN or any CT application while in draft status (i.e. before submission), refer to section 2.3.3.

2.7.1. Withdrawing a submitted IN

As per Article 12 of the CTR, **a withdrawal of a full IN can be done:**

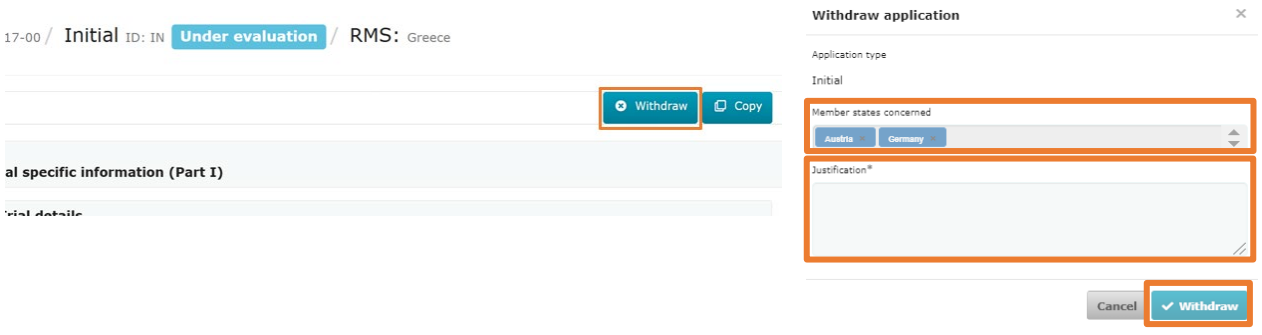
- **until a conclusion on Part I** (reporting date) **is submitted by the RMS.** In case of a multinational trial, the withdrawal done before the reporting date would apply **to all MSC(s).**
- **after the reporting date** and while the IN is still under evaluation**, but before a decision has been issued by the relevant MSC.** The application can be withdrawn from each MSC separately, so users need to **select the MSC** for which the application should be withdrawn.

Section 3. provides a description of the different evaluation phases. The first scenario above also applies in case of partial submission of a CT application (see section 2.5.). In addition, for a partial submission of Part I only, the CT application may be withdrawn at any time after the reporting date, even if the trial has already been authorised in one or more other MSC(s) that received a full application.

Once the decision regarding an IN is taken, a sponsor no longer has the possibility to withdraw the application. If, after authorisation of the trial, the sponsor does not insert the start of recruitment notification (see section 4.1.) within two years from the notification date of the decision of authorisation, **the application will expire**. If, instead, the recruitment starts and the sponsor decides to terminate early an ongoing CT in one of the MSC(s) (i.e. after the decision is issued in that MSC), the sponsor should **notify the MSC of the early termination**.

Below there are the steps that a sponsor user with a **CT Admin and/or Application Submitter** role can perform in order **to withdraw an application** (they are also applicable to a SM or AM, see section 4.5.). After having accessed the sponsor workspace:

1. Search for the relevant CTA: once in the CT page, click on the **IN** of the application under the 'ID' column of the 'Application and non-substantial modification' part (see section 2.6.1.)
2. From top right, select 'Withdraw' option.
3. Provide a justification in the relevant pop-up window (mandatory field) and click on 'Withdraw': the application is withdrawn.



2.7.2. Resubmitting an IN

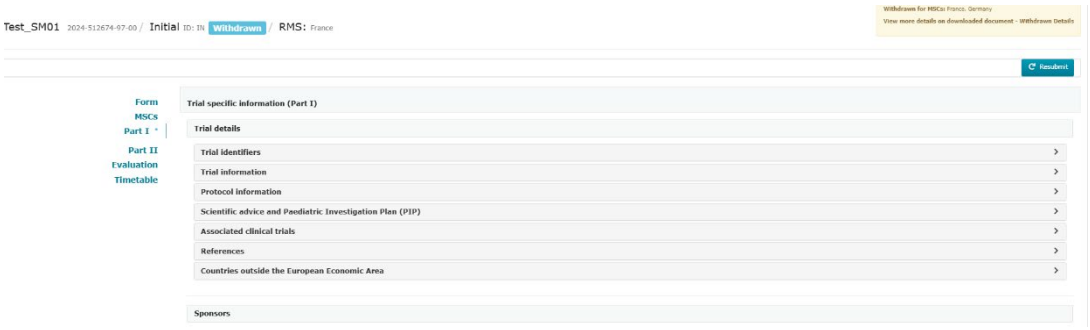
As per Article 13 of the CTR, following the refusal of authorisation or the withdrawal of an application, an IN can be resubmitted to any intended MSC. See also CTR Q&A. The resubmitted application shall be deemed **a new application** subject to authorisation and will maintain the same EU CT number, apart from the last two digits which will correspond to the number of times the application has been resubmitted (e.g.: from 2025-123456-12-00 to 2025-123456-12-01). In order to save the time of the user, the CT application fields of the former IN will be appearing as filled in in the resubmitted IN.

Note that **only applications with statuses 'Not valid', 'Withdrawn', 'Lapsed', 'Expired' or 'Not authorized' can be resubmitted**. Applications with other statuses (e.g. 'Revoked') cannot be resubmitted. For these applications the sponsor could choose to 'copy' the trial, however this will mean that the trial will have a different EU CT number (see section 2.3.4.).

Below there are the steps that a sponsor user with **CT Admin** role (with 'all trials' scope, or with the relevant 'specific trial' scope) can perform in order **to resubmit an application** (they are also applicable to a SM or AM, see section 4.5.). Note: the **CT admin role the only role which allows a resubmission of an IN application**; the 'application submitter' role does not allow an IN application resubmission, while it allows a resubmission of SM or AM, since no new EU CT number is created in those cases (see 'role matrix' in section 1.6.3.).

After having accessed the sponsor workspace:

1. Search for the clinical trial application: once in the CT page, click on the **IN** of the application under the 'ID' column of the 'Application and non-substantial modification' part (see section 2.6.1.)
2. Click on the 'Resubmit' button: a new draft application is created. The new draft will include all of the **most recent information** in the structured data and the documents that were submitted in the previous application, even if they were updated by responding to an RFI. Only the most recent information is shown, not the historical one(s). Note: in case the 'Resubmit' button does not appear, it could be that the application was already resubmitted, or the trial has a status that is different from the ones stated above.



3. Modify the new application as needed. Note that once the resubmission version is created**, all metadata, including the documents dates are reset** as it is considered a new submission. You would need to **modify the relevant metadata as appropriate**.
4. Submit the application as described in section 2.3.3.

The application is submitted.

End of chapter: jump to Clickable table of contents.

3. Evaluation phase

The evaluation phase starts as soon as the IN is submitted. It includes:

1. **Reporting Member State (RMS) selection** phase, *in case of multinational clinical trials*: to select the RMS for the trial. The RMS is the MSC that **leads** the validation and assessment of Part I, which includes sending the RFI and entering the conclusion for both the validation phase and Part I assessment phase. See section 3.1.2.

2. **Validation** phase: to verify that the clinical trial falls under the scope of the CTR and that the IN documentation is complete and in line with the requirements of Article 25 and Annex I of the CTR. In case of multinational trials, this phase takes place parallel to the RMS selection. See section 3.1.3. The MSC(s) could raise an **RFI** during this phase, to which the sponsor needs to reply.

3. **Assessment** phases: to review the content of the application provided by the sponsor. For an IN, the assessment phase is divided into two parts: Part I and Part II. These phases are performed in parallel but only start after the validation phase is completed. The MSC(s) could raise an **RFI** during this phase, to which the sponsor needs to reply. Each assessment phase ends with an assessment report and the submission of a conclusion by the MSC(s). The main objective of each part is:

    a. Part I: to review the scientific and medicinal product documentation, as defined in Article 6 of the CTR (e.g. completeness and adequateness of the investigator's brochure, compliance with labelling requirements, protocol, etc.). This review is performed by the MSC(s) and coordinated by the RMS. The RMS enters the conclusion on Part I, which applies to all MSC(s). See section 3.1.4.

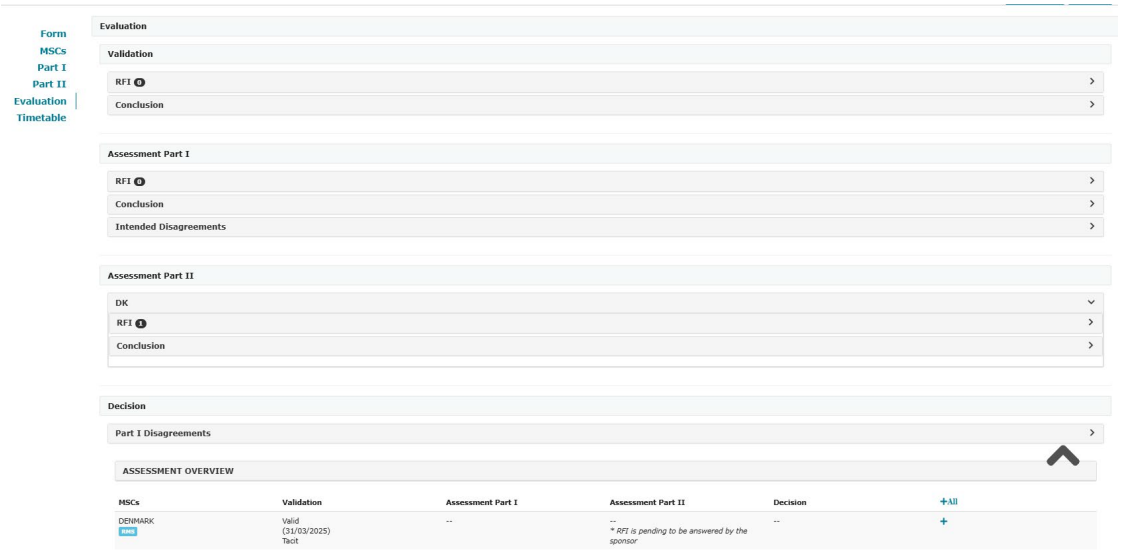
    b. Part II: to evaluate the regulatory aspects of the IN that are of a more national/local nature. In this case, the assessment is performed individually by the MSC for its own territory without any involvement of the RMS, and each MSC enters their own Part II conclusion. The MSC reviews the requirements for informed consent, the arrangements for recruiting and compensating the trial participants, the data protection rules, etc., amongst other documents set out in Article 7 of the CTR and the General Data Protection Regulation. See section 3.1.5.

4. **Decision** phase: to establish the **outcome** of the assessment of a IN for the start of the clinical trial in an MSC territory. The Decision is made by each MSC and may result in authorisation, authorisation subject to conditions or rejection of the CT. See Article 8 of the CTR and section 3.1.6.

Each phase has specific **time limits** for both Member States and sponsors, that are defined in the CTR, which can however be shorter: see section 3.1.

Important: after submitting an IN, sponsors should monitor the 'Notices & alerts' tab on a daily basis to see if there is any RFI sent by the MSC(s) or opt-in to receive email notifications. Failure to respond to an RFI before the due date causes the application to lapse. See sections 3.2. and 3.3.

The Evaluation tab of the CT application page presents the assessment overview of the IN, reflecting the four phases mentioned above. The validation, Part I and Part II sections include an RFI and a conclusion subsection.



Within the evaluation phase, CTIS requires:

- Member States to undertake **tasks**, which are classified as: **hard tasks** (mandatory: if they are not executed the system applies a tacit decision) and **soft tasks** (non-mandatory: if not executed, the system does not apply immediate consequences on the process).
- sponsors to perform **actions** (e.g. respond to RFI).

The following sections define the timelines applicable to each task and action for each evaluation phase. Both tasks and actions are reflected in the 'Timetable' tab of the CT application page, see section 3.1.8. However, sponsors are not able to see the soft tasks of Member States.

Note that the Sponsor FAQs includes further guidance on the evaluation topic.

3.1. Evaluation steps, outcome and timetable

Timelines during the evaluation phase are measured in **calendar days** and adhere to Regulation 1182/71, for all application types: **INs, AMs and SMs**, see sections 4.2. and 4.3. All timelines are visible in CTIS secure workspaces, see section 3.1.8. , where the following is ensured:

- The reference time zone is the **Central European Time (CET)**.
- Start of a task: a task will start on the **day after** it has been created. Note: a task is created when its precondition is met in the respective workflow (i.e. RMS selection, validation, assessment Part I, assessment Part II, or decision phase).
- All activities with a due date shall be due at **23:59:59 CET** on that day.
- The **due date** must fall on a **working day**. If it falls on a weekend or bank holidays, it will automatically be moved to the following calendar (working) day. Note: for multinational trials, the **official holidays of the reporting and concerned Member States are considered** based on their respective responsibilities. The public holidays in the sponsor territory are not taken into account in the calculation. See table below.
- **A period of at least two consecutive working days shall be foreseen** for completing a task or action.

An informally agreed **winter clock stop** is observed from 22nd December at 23:59:59 CET to the 8th of January the following year at 00:00:01 CET. Tasks won't have their due date falling during that

period. Any day during that period is not counted towards the timelines. If the sponsor has any objections to this pause, they must inform the RMS in advance. No other clock stops are applied within the procedures.

Depending on the type and phase of the application, **in case of multinational clinical trials CTIS takes one calendar into account for any given task,** as presented in the following table:

Process	Day Count Starts	Day Count Ends	Calendar		
			IN	Substantial modification	Additional MSC
Select RMS	Application submitted	RMS selected	Longest calendar[1]	N/A	N/A
Validate Application	Application submitted	Validation concluded	RMS	RMS (for SM Part I/II or Part I only) MSC (for SM Part II only)	N/A
Assess Part I	Application validated	Part I concluded	RMS calendar	RMS calendar	RMS calendar
Assess Part II	Application validated	Part II concluded	Each MSC calendar	Each MSC calendar	Each MSC calendar
Submit Decision	Part I concluded Part II concluded	Decision submitted	Each MSC calendar	Each MSC calendar	Each MSC calendar

Note that the above is only applicable to Member States tasks, and not sponsor's actions (e.g. RFI response due date).

Completion of tasks affects the timeline of the application process (i.e. timers in CTIS are dynamic). The timelines shown in CTIS correspond to the maximum deadlines foreseen for each task/action and the maximum timeframes between the end of a task and the end of the following one. If a task/action is completed before its deadline, the corresponding deadlines for the following tasks/actions are recalculated. For certain tasks, performed by the MSC(s), their earlier completion will result in shorter timelines of the following tasks/actions and potentially, in a shorter evaluation period. **A task completed earlier will shorten the timelines** in the following cases:

- **Validation**, if the task 'Submit validation conclusion' is completed earlier by the RMS (maximum deadline: day 10, or day 10 +15 days, in case of an RFI)
- **Part I assessment**, if the task 'Submit Part I conclusion' is completed earlier by the RMS (maximum deadline: day 45, or day 45 + 31 days, in case of an RFI). Within the Part I assessment workflow, if the soft task 'Document considerations' is completed earlier than day 38, it will trigger the next task 'Consolidate considerations' earlier than the initial projected due date. However, if the due date for the final task of this workflow ('Submit Part I conclusion') will remain as originally calculated, the RMS can conclude earlier than the indicated due date.
- **Part II assessment**, if the task 'Submit Part II conclusion' is completed earlier by the MSC(s) (maximum deadline: day 45, or day 45 + 31 days, in case of an RFI).

The timeline for the task 'Submit Decision' is always 5 days and never shorter. This task is released once both Part I & II conclusion are submitted. However, in the case of AM and for SM Part II, the 5-day timeline starts from the due date of the Part II conclusion, even if this task is completed earlier.

[1] Each MSC has a different holiday calendar. In case of a multinational trial, the process of the RMS selection will follow the longest calendar of the MSCs involved.

Timelines could also be shorter in case the MSC(s) indicate a shorter period for sponsors to respond to the RFIs. For this reason, when receiving an RFI, **sponsors need to check the deadlines imposed by the MSC for responding to it.** Examples of timelines calculations are provided in section 3.1.8.

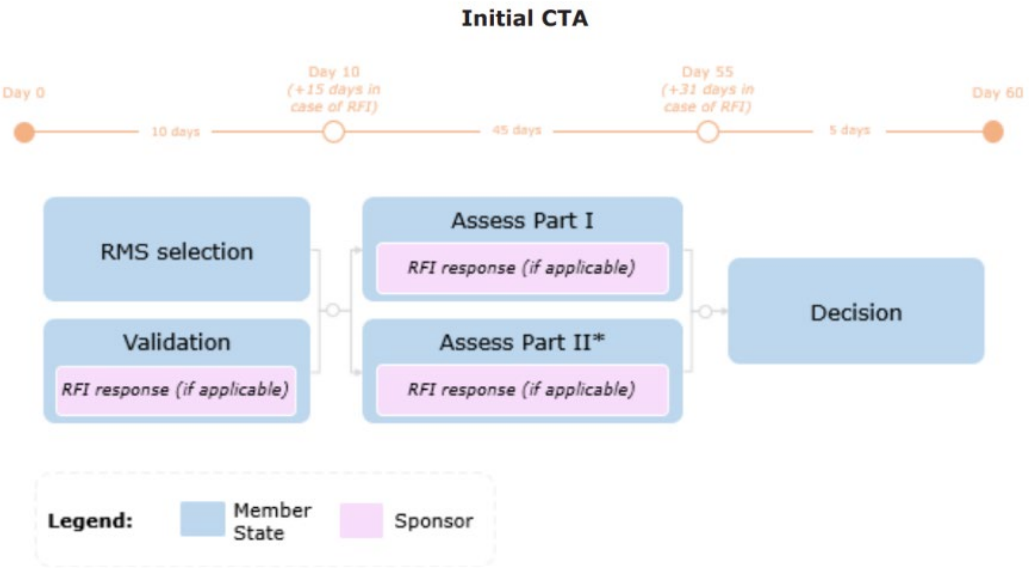
3.1.1. IN: general timelines

The CTR sets a **60-day deadline for Member States to submit their decision on an IN**. However, this timeline **may be extended if RFIs are raised** by one or more MSC(s) during the evaluation:

- **Validation Phase:** the timeline can be extended by up to 15 days (10 days for the sponsor to respond and 5 days for the MSC(s) to review the response).
- **Assessment Phases:** the timeline can be extended by up to 31 days (12 days for the sponsor to respond, 12 days for the MSC(s) to review the response and 7 days for the RMS to consolidate the review).

Multiple RFIs can be raised at different stages throughout the IN, but if several are raised within the same assessment phase, the overall timeline will be extended only once, even though each RFI has its own individual deadline.

The **timelines displayed in CTIS represent the maximum deadlines for each task or action**, as well as the maximum intervals between consecutive tasks. CTIS operates with a dynamic workflow: see section 3.1.



* In case of applications limited to Part I, the sponsor has two years from the notification of the conclusion of Part I to submit an application for Part II, see section 2.5.

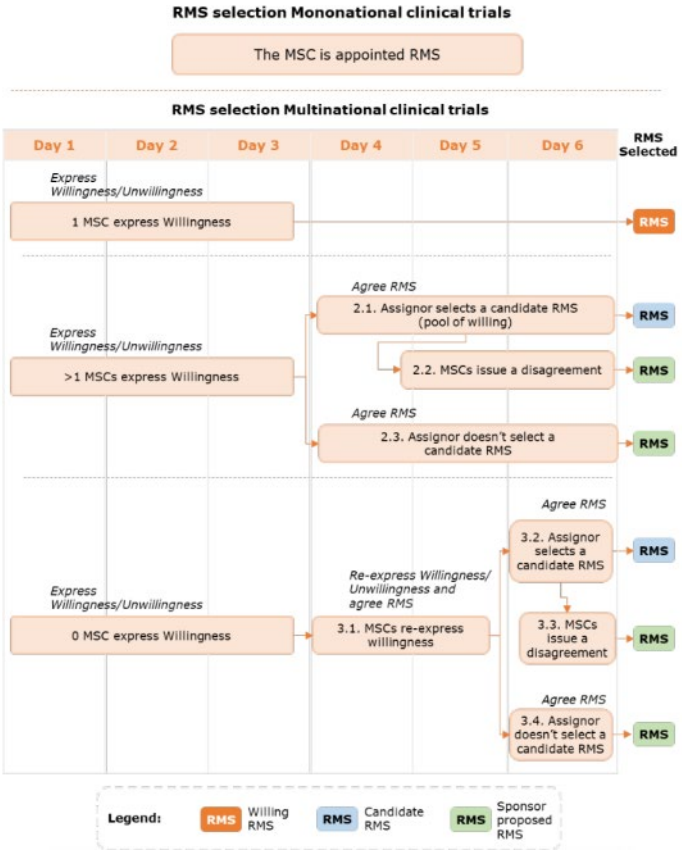
3.1.2. IN: RMS selection

The RMS selection process is the responsibility of the Member State(s) participating in the assessment of the IN, and it is triggered as soon as the application is submitted by the sponsor:

- In **mononational trials,** the MSC is automatically appointed as RMS after the submission of the application and no other actions are necessary.
- In **multinational trials**, the RMS selection process runs parallel to the validation phase. However, the selection of an RMS is required before a validation RFI can be sent or the validation

conclusion can be entered, as the RMS is responsible for this. The **RMS must be selected within six days** from the IN submission, as outlined in Article 5(1) of the CTR.

The different scenarios within the RMS selection process are shown in the image below:



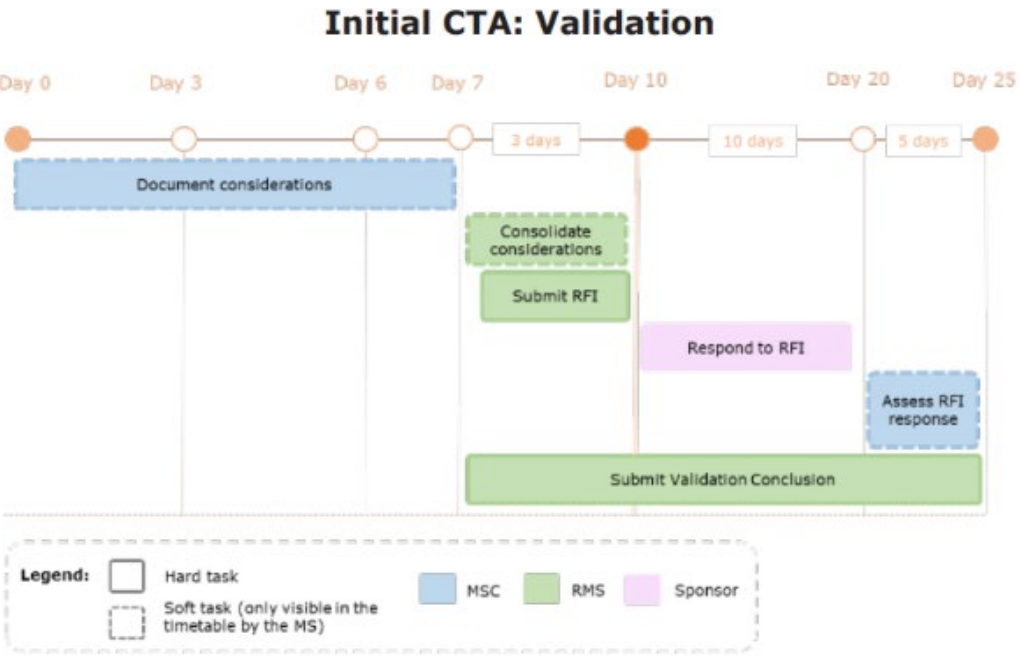
The MSC(s) have until day 6 from the application submission to disagree with the candidate RMS selected by the assignor.

Task	Deadline *(dynamic workflow)*
MSC(s) **express willingness/ unwillingness**, *hard task*	Up to day 3 (day 0+3), or earlier if all MSC(s) conclude the 'Express willingness' task and if more than 1 MSC is willing at day 3. If no MSC is willing at day 3, the task is labelled 're-express willingness and agree RMS'. Having two consecutive working days and falling on a working day (longest MSC calendar)
MSC(s) **agree RMS**, *hard task*	Up to day 6 (day 0+6) or at the end of 'Express willingness/unwillingness' task if completed earlier. Having two consecutive working days and falling on a working day (longest MSC calendar)
MSC(s) **re-express willingness and agree RMS**, *hard task*	Up to day 6 once all MSCs have concluded the 'Express willingness' task. Having two consecutive working days and falling on a working day (longest MSC calendar)

More information on RMS selection process can be found in the module 6 of the training materials on the Authorities workspace.

3.1.3. IN: Validation

The validation **starts as soon as the IN is submitted** and must be **completed within 10 calendar days,** with the submission of a validation conclusion by the RMS. This period may be **extended by up to 15 additional days if an RFI is issued.** In an IN, the MSC(s) can start documenting any needed considerations about the application before the RMS selection process is concluded (as per section 3.1.3.). Once considerations are consolidated by the RMS, an RFI is issued to the sponsor through CTIS. The sponsor has **up to 10 calendar days** to respond. Upon receipt, the MSC(s) assess the RFI response within an additional 5 days and the RMS issues a validation conclusion by day 25. Sponsors should **carefully check the deadlines** set by the MSC(s) for responding to RFIs, as MSC(s) may impose a shorter response period. **Note: in case the sponsor does not respond to an RFI before the due date, the application will lapse.**



Note: in mononational trials, the MSC and RMS are the same actor

Task or action	Deadline *(dynamic workflow)*
MSC(s) document considerations, *soft task*	Day 7 (day 6 + 1 day): up to 7 days after the IN with Part I and Part II or Part I (only) has been submitted by the sponsor. **In case of multinational trials**: 1 day after the RMS has been agreed, falling on a working day. Note that there is no necessity of 2 consecutive working days rule, because the lifecycle of this task started at Day 0, so this rule is already satisfied between Day 0 and 7. **In case of mononational trials**: day 7 is calculated as Day 0 + 7 days, falling on a working day and keeping the two consecutive working days rule.
RMS consolidates considerations, *soft task*	Day 10 (day 7 + 3 days): up to day 10 from the application submission and after the consideration has been shared, falling on a working day.

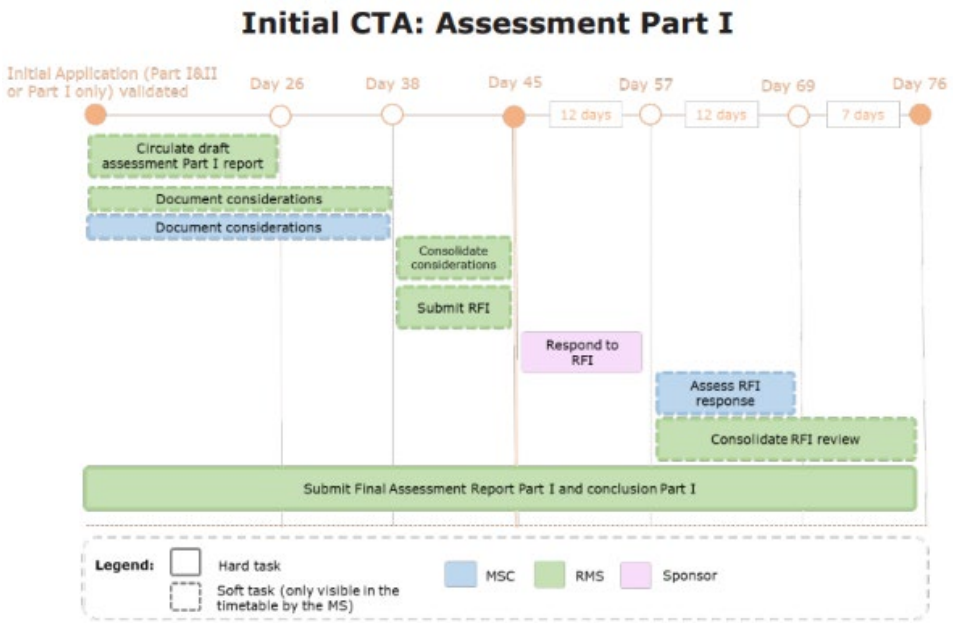
Task or action	Deadline *(dynamic workflow)*
	In case of multinational trials: day 7 + 3 (submit validation decision) = Day 7 (document considerations for validation due date) + 3 days, keeping 2 consecutives working days during the task lifecycle and falling on a working day (RMS calendar). **In case of mononational trials**: day 10 is calculated as day 7 + 3 days, falling on a working day.
RMS submits RFI (if applicable), *soft task*	Day 10 (day 7 + 3 days): up to day 10 from the IN submission, once an accepted, adapted, or merged consideration has been shared. **In case of multinational trials**: day 7 + 3 (submit validation decision) = Day 7 (document considerations for validation due date) + 3 days, keeping 2 consecutives working days during the task lifecycle and falling on a working day (RMS calendar). **In case of mononational trials**: day 10 is calculated as day 7 + 3 days, falling on a working day.
Sponsor responds to RFI (if applicable)*, action*	Day 20: (day 10 + 10 days): sponsors have 10 days to respond once the RFI has been submitted by the RMS. **Failure to respond to an RFI before the due date causes the application to lapse.**
MSC Assess RFI response (if applicable), *soft task*	Day 25 (day 20 + 5 days): up to day 25, task triggered if and when an RFI response is received. The MSC(s) have up to 5 days to assess the RFI response.
RMS submits Validation Conclusion, *hard task*	Day 10 or day 25 (in case of a submitted RFI). Triggered at day 7, or earlier if the RMS is selected. Up to 25 days from the application submission in case of an RFI.

3.1.4. IN: Assessment of Part I

Once the validation phase is concluded, the RMS starts the assessment of Part I structured data and documents submitted by the sponsor through CTIS, which can take up to 45 days (or up to 76 days if RFIs are raised). The RMS may also extend the period up to 50 days for consultation with experts. In case of multinational trials, the RMS needs to circulate the Part I Draft Assessment Report by day 26 from the end of the validation phase. In parallel, if needed, the RMS and the MSC(s) document considerations on Part I by day 38 from validation phase. By day 45, considerations are then consolidated by the RMS and sent to the sponsor as an RFI. Upon receipt, the sponsor generally has 12 days to respond, although this timeline could be shortened by the RMS. The MSC(s) have then an additional 12 days to assess the response to the RFI. The RMS then has another 7 days to consolidate the review of the response to the RFI by day 76. The Part I Final Assessment Report Part I and relevant conclusion are submitted by the RMS to CTIS by day 76. **Note: in case the sponsor does not respond to an RFI before the due date, the application will lapse.**

If the RMS does not complete the task 'Submit Part I conclusion' by the due date, Part I will remain labelled with 'No conclusion' and the overall application will remain 'Under evaluation'.

For more information on how the RMS performs the Assessment of Part I, see the Quick Guide of Module 8: How to evaluate a Clinical Trial Application: Assessment and Decision - Part I.



Note: in mononational trials, the MSC and RMS are the same actor.

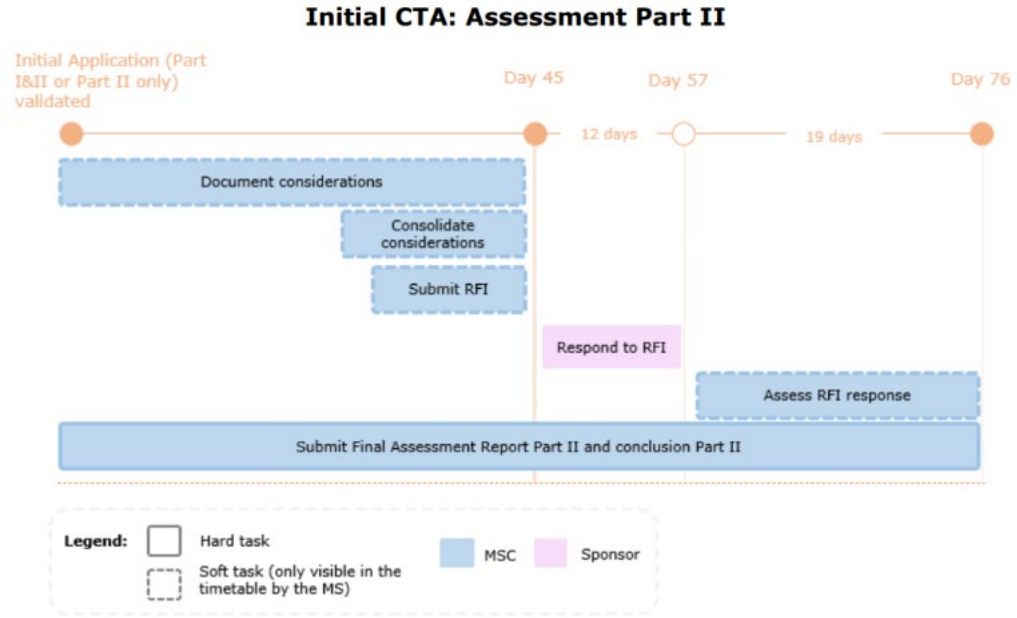
Task or action	Deadline *(dynamic workflow)*
RMS circulates Draft Assessment Report (DAR) Part I, *soft task*	Day 26 (day 0 + 26 days): up to 26 days from the Validation of the IN.
RMS & MSC document considerations, *soft task*	Day 38 (day 26 + 12 days): up to 38 days from the Validation of the IN and once the RMS has completed the 'Circulate DAR' task.
RMS consolidates considerations, *soft task*	Day 45 (day 38 + 7 days): up to 7 days after the considerations are shared.
RMS submits the RFI (if applicable), *soft task*	Day 45 (day 38 + 7 days): up to 45 days from the validation of the IN.
Sponsor responds to RFI (if applicable), *action*	Day 57 (day 45 (or RFI submission date, set by RMS) + 12 days): up to 12 days to respond from the RFI submission. **Failure to respond to an RFI before the due date causes the application to lapse.**
RMS & MSC assess an RFI response (if applicable), *soft task*	Day 69 (day 57 + 12 days): up to 12 days after the response is sent by the sponsor for the MSC, and up to 19 days for the RMS.
MSC submits Final Assessment Report (FAR) Part I and Part I conclusion, *hard task*	Day 45 or day 76: up to 45 days or 76 days (if RFIs are raised), from the Validation of the IN.

3.1.5. IN: Assessment of Part II

The assessment of Part II **runs parallel to the assessment of Part I** and can take **up to 45 days**, by which the Part II Final Assessment Report and conclusion need to be submitted by each MSC. However, **in case considerations are documented**, those are consolidated at the level of each MSC and **RFIs are submitted by day 45** to the sponsor through CTIS. **The Sponsor has then 12 days to reply**, after which the MSC has 19 days to assess the RFI response and submit to CTIS the Part II Final Assessment Report and conclusion by day 76 from the validation of the IN. **Note: in case the sponsor does not respond to an RFI before the due date, the application will lapse**.

If the MSC does not complete the task 'Submit Part II conclusion', Part II of the application will remain labelled as 'No conclusion'. Nonetheless, the application will proceed to the Decision phase.

For more information on how the MSC(s) perform the Assessment of Part II, see the Quick Guide of Module 8 – How to evaluate a Clinical Trial Application: Assessment and Decision - Part II.



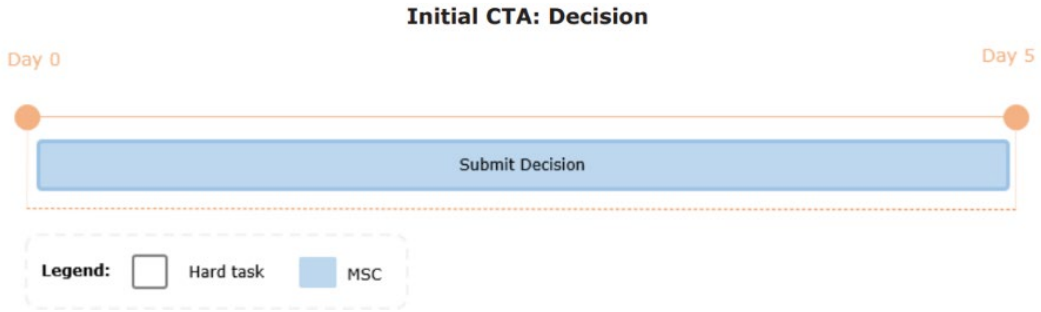
Task or action	Deadline *(dynamic workflow)*
MSC documents considerations (application documents), *soft task*	Day 45: up to 45 days from the Validation of the IN.
MSC consolidates considerations, *soft task*	Day 45: up to 45 days from the validation of the IN. This task must be performed right after the considerations have been documented and before submitting an RFI to the sponsor.
MSC submits RFI (if applicable), *soft task*	Day 45: up to 45 days from the validation of the IN. This task will be performed after the considerations have been consolidated.
Sponsor responds to RFI (if raised by MSC)	Day 57 (day 45 (or RFI submission date) + 12 days): up to 12 days to respond from the RFI submission. **Failure to respond to an RFI before the due date causes the application to lapse.**

Task or action	Deadline *(dynamic workflow)*
MSC assesses RFI response (if applicable), *soft task*	Day 76 (day 57 + 19 days): up to 19 days after the response is sent by the sponsor.
MSC submits Final Assessment Report (FAR) Part II and Part II conclusion, *hard task*	Day 45 or day 76: up to 45 days or 76 days (if RFIs are raised), from the Validation of the IN.

3.1.6. IN: Decision

Each MSC enters a decision that applies only to their own MS. Each MSC has a **maximum of 5 days to submit its decision**[2], starting from when the conclusions on both Part I and Part II have been submitted. The decision status can be 'authorised', 'authorised with conditions' or 'not authorised' (see section 3.1.7.). An MSC can actively insert the decision status within the 5 days deadline. If an MSC does not submit its decision, a tacit decision is automatically entered for that MSC, with an authorisation status that follows the part I conclusion. Note that the sponsor does not have to await positive decisions from all MSC(s) before starting the trial: the trial can already start in the MSC that has authorised the trial, even if the assessment is still ongoing in the other MSC(s).

For more information on the Decision phase, see the Quick Guide of Module 8 – How to evaluate a Clinical Trial Application: Assessment and Decision - Decision.

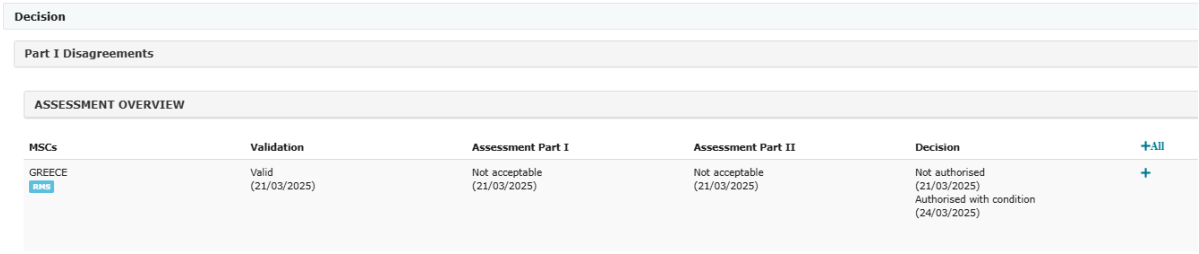


Task or action	Deadline *(dynamic workflow)*
MSC submits decision, *hard task*	Day 5: 5 days after the trigger of the task (e.g. conclusion part II, or no conclusion part II), as long as there are two consecutive working days and it is falling on a working day for each MSC calendar3.1.7.

3.1.7. Evaluation outcome

Once a decision of any kind has been issued on the clinical trial application, the conclusion of the validation and the assessment phases can be viewed in the 'Evaluation' tab of the CT application page. At the bottom of the page, in the assessment overview table, the information is recorded for each MSC and includes each MSC's respective decision. In the event that an MSC would have disagreed to the conclusion 'acceptable' or 'acceptable with conditions' to Part I, this information would have been also recorded in this section.

[2] Note that in view of the rules mentioned in section 3.1 , the decision may take more than 5 calendar days



All documents and data assessed for the trial, as referred to in the latest submitted application, can be consulted in the tab 'Full Trial Information'.

The assessment of an IN can have the following outcomes:

- **Lapsed**: during the evaluation phase, any of the RFIs was not responded in time by the sponsor (as per MSC(s) deadlines, see section 3.3.)
- **Not valid**: the CT application did not pass the validation phase of the MSC(s) assessment
- **Not authorised**: the assessment outcome is negative in all MSC(s), based on any of the grounds specified in Article 8(4) of the CTR. In line with the CTR, after the receipt of the decision on the clinical trial**,** the sponsor has the right to **appeal** against the decision (refusal). The Member States shall provide an appeal procedure in respect of a refusal related to Article 8 (Decision on the clinical trial). In this situation, the respective national laws apply to each MSC.
- **Authorised with conditions:** the authorisation of a clinical trial is restricted to conditions which by their nature cannot be fulfilled at the time of the decision. Refer to CTR Q&A in order to know what should be understood by 'conditions'.
- **Authorised**: the assessment outcome is positive in one or more MSC(s). Note that a trial can be authorised in one MSC, while not being authorised in another.

A full overview of trial statuses can be found in section 2.6.2.

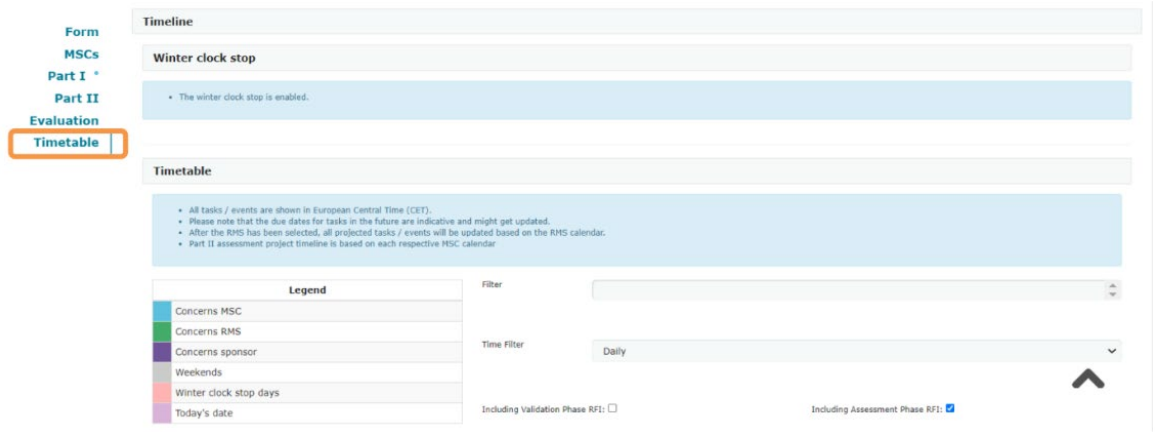
From the date the IN is authorised or authorised with conditions in an MSC, the 'first visit of the first subject' in that MSC must be within 2 years. As per section 4.1. a sponsor user with the appropriate roles needs to notify the 'First visit of the first subject' via the 'Start recruitment' notification. The 'Start of recruitment date' entered must be within the 2-year timeline, while the notification can be submitted within 2 years plus 15 additional days. Failure to notify the 'Start recruitment' within the timeline will change the trial authorisation status in that MSC to 'Expired', according to Article 8.9 of the CTR. If needed, **sponsors can request an extension to start the recruitment beyond 2 years via an SM** Part I & II or SM Part II only. Note that an SM Part I-only cannot be used to request the extension of start of recruitment. Refer to section 4.3.3. for instructions on how to extend the start of recruitment date.

3.1.8. Timetable section in CTIS

Once an application has been submitted, sponsor users with relevant roles can see the timetable of any CT applications they are involved in through clicking on the relevant tab on the left-hand side of the CT application page. The 'Timetable' tab allows users to **monitor the progress of the assessment** of a particular CT application, by displaying the actual completion dates of each completed assessment phase, and the expected completion dates of the remaining ones. To calculate the expected due dates, the system applies a set of rules stemming from Regulation 1182/71, see section 3.1. Member States' hard tasks (mandatory) and soft tasks (non-mandatory), as well as sponsors' actions (see section 3.)

are reflected in the timetable overview, however sponsors are not able to see the soft tasks of Member States.

Note: the timetable does not cover ASR functionality (see section 4.13.)

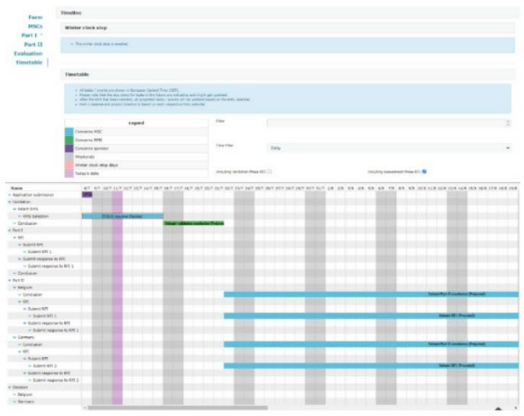


Users can also download the timetable as a CSV file, which will display the dates of the completed tasks and the dates foreseen for the remaining ones.

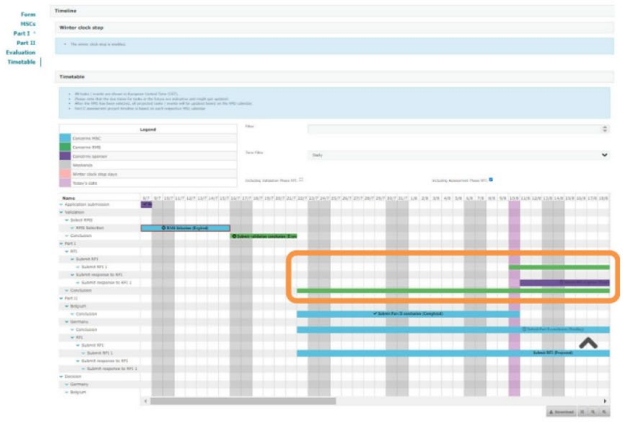
The Timetable displays a **projection of dates** for each evaluation phase based on the deadlines set out in the CTR, however reflecting the CTIS dynamic workflow by keeping updated the current and projected due dates. Rules are detailed in section 3.1. A projected due date is an estimated calculation of when a task/action will take place based on the maximum deadlines set out in the CTR. This means, for example, that users can view from the beginning which is the maximum due date of the decision. This is indicated in the functionality with the label 'Projected'.

Users can also filter the visibility of the timetable according to the **time scale** they are interested in (daily, monthly or yearly), or according to the different phases of the assessment process. It is also possible to filter to include or not the timelines of RFIs raised during the assessment.

In case a new task/action is triggered by the sponsor or Member state, the system will automatically include it in the timetable:



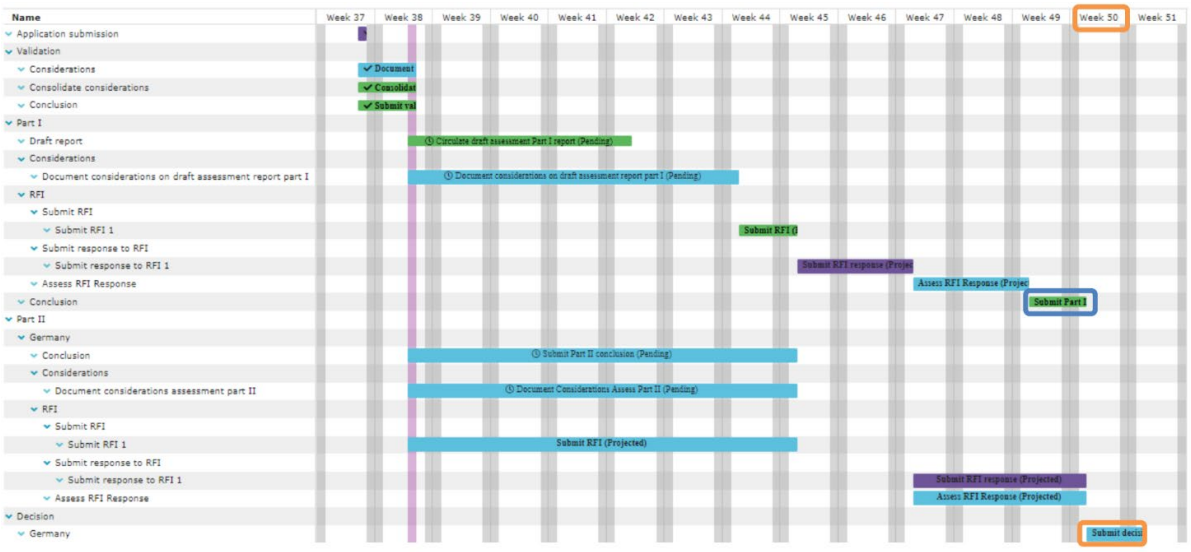
Sponsor's timetable



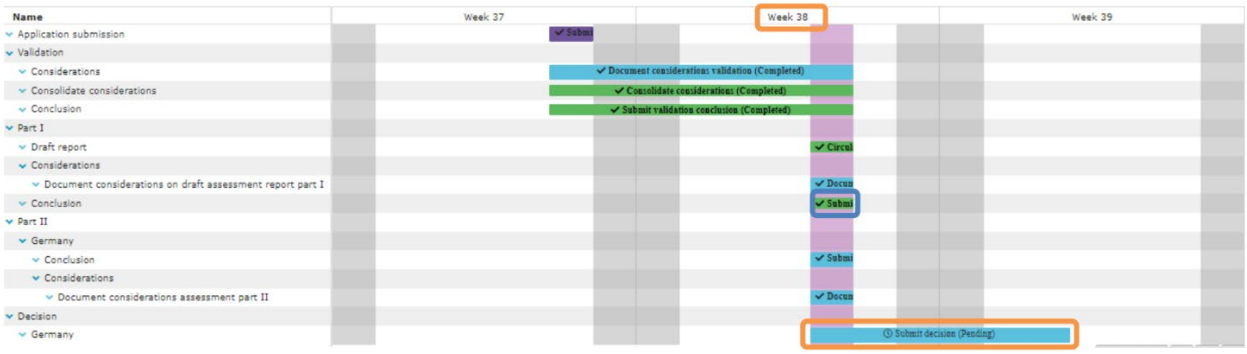
Sponsor's timetable with RFI

Once each phase has been completed, the timetable is automatically adjusted, maintaining the maximum days established in the CTR for the evaluation of each phase. Also, when new tasks/actions are triggered, their new due dates are adjusted, and they can have an impact on sponsors. **Users are advised to consult on a regular basis the tasks/actions due dates** and the timetable, in order not to miss any mandatory step that could lead to the lapse of the CT application.

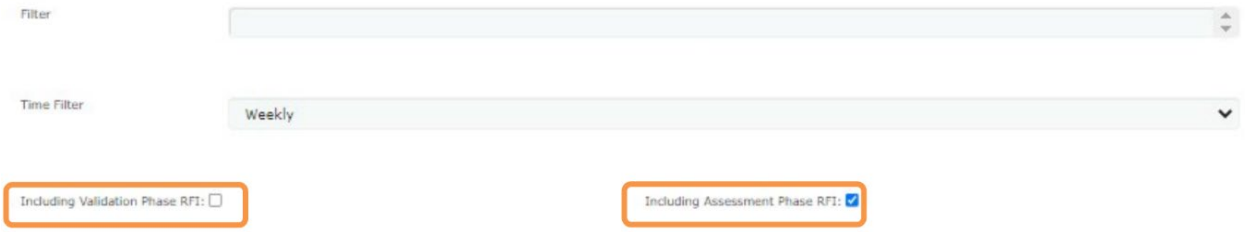
For example, in the image below the task 'Submit decision' (orange box) is projected for week 50:



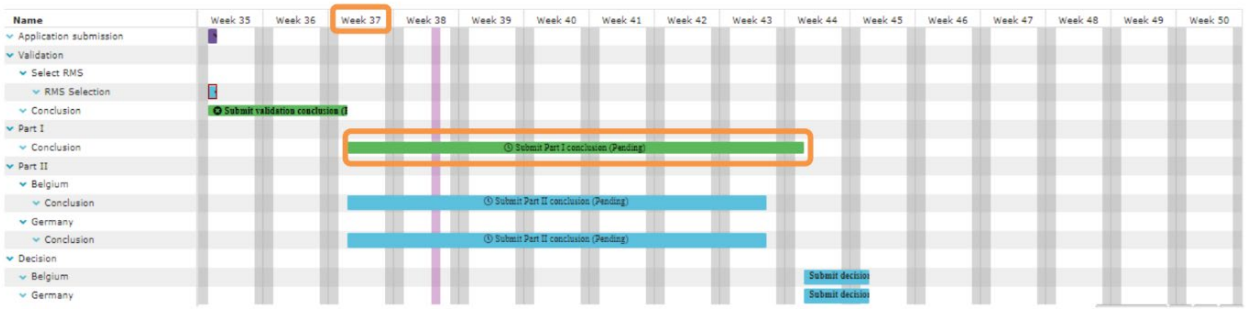
However, after the earlier completion of the task 'Submit Part I conclusion' (blue box), the 'Submit decision' task will need to be completed within 5 days from week 38 (orange box), and no longer from week 50:



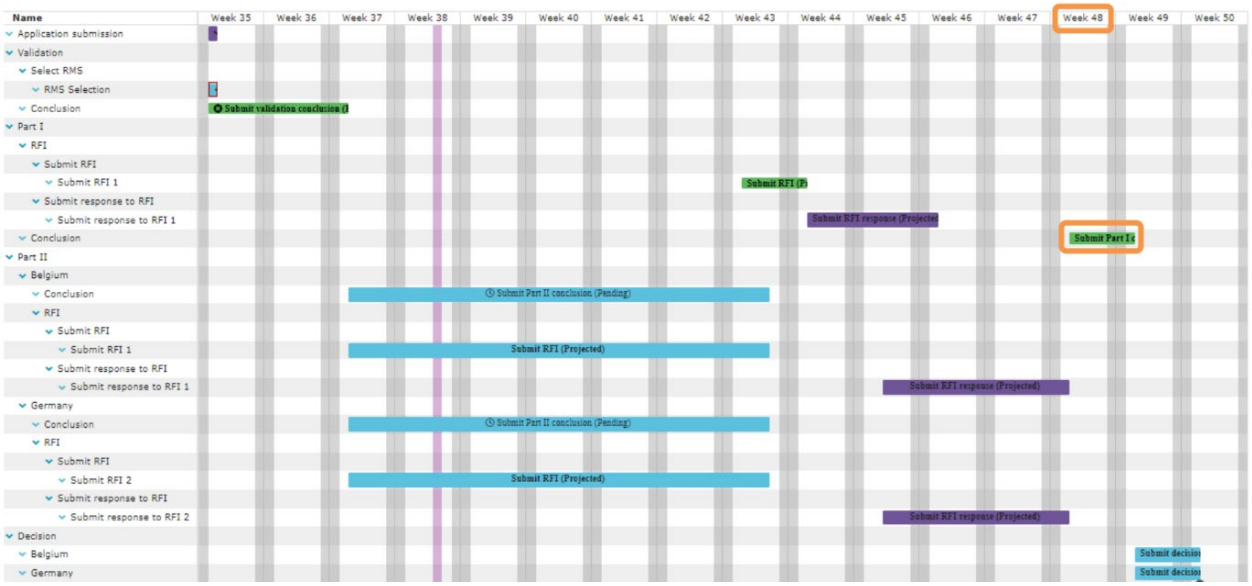
The 'Timetable' functionality also allows sponsor users to consult projected timelines with or without RFIs submitted for each phase (see section 3.3. on how to respond to an RFI). To view the projected RFIs' impact on the due dates, users can click on the tick boxes for each phase, as shown in the image below:



In the example in the image below, the timelines are shown without the RFI projected due dates. In this scenario the 'Submit Part I' due date is on week 37.



If the projected timelines for the RFI of the assessment phase are included, the 'Submit decision' projected due date for the MSC(s) is moved to week 48. Note that, while the timelines are extended when the first RFI is submitted, they are not extended subsequently in case more RFIs are submitted.



Below, some examples and images of due dates calculations are presented using the example of a multinational trial submitted on 17/07 (Day 0 of the timeline), with a public holiday on 21/07, before the RMS is agreed (longest calendar applies).

- MSC Task 'Express Willingness/Unwillingness' might take up to three days from the submission date (Day 0): due date of the task is on 20/07 (Day 3).
- MSC Task 'Agree on RMS' might take up to six days from the submission date (Day 6). This task is released after the task 'Express Willingness/Unwillingness' is completed. The timeline continues after Day 3, and the 4th day is on 21/07. In the graph below, Day 6 should be on the Sunday 23/07. However, as per section 3.1. , '**a period of at least two consecutive working days shall be foreseen** for completing a task' and therefore Day 6 falls on the Tuesday 25/07 (being Monday and Tuesday the two consecutive working days).

Day	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su
Month	17/07	18/07	19/07	20/07	21/07	22/07	23/07	24/07	25/07	26/07	27/07	28/07	29/07	30/07
Day #	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 6	Day 6	Day 7	Day 8	Day 9	Day 10	Day 10
Task / Action	CTA Submission			Express Willingness	Public Holiday				Agree on RMS	Document Validation Consider.				

- MSC Task 'Submit validation RFI' (or 'Submit Validation Conclusion' if RFI is not submitted) might take up to 10 days from Day 0 (the submission date), so taking into account the previous step of this example, Day 10 should fall on 29/07. However, this is a Saturday. Since '**The due date must fall on a working day**' (see section 3.1.), then Day 10 falls on 31/07.
- Sponsor's action 'Submit RFI response' should be completed by the 20th day since the trial submission date (considering that all tasks are performed on their due dates and not earlier). The timeline continues from where it was left, therefore Day 20 falls on 10/08.

Day	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su
Month	31/07	01/08	02/08	03/08	04/08	05/08	06/08	07/08	08/08	09/08	10/08	11/08	12/08	13/08
Day #	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23
Task / Action	Submit Valid. RFI or Conclusion										Submit RFI response (sponsor)			

Day	Mo	Tu	We	Th
Month	14/08	15/08	16/08	17/08
Day #	Day 24	Day 25	Day 26	Day 27
Task / Action		Submit Validation Conclusion		

Due dates of tasks
Weekend days
Public Holiday

MSC's task 'Submit validation conclusion' might take up to 25 days from the trial submission date. Continuing the established timeline, Day 25 falls on 15/08. Earlier completion of the related soft tasks (i.e. submit RFI, assess RFI response) or sponsor's actions do not shorten the maximum timeline of the MSC (hard) task 'Submit validation conclusion'. The timeline of the tasks and actions that comprise the Part I assessment phase starts from the Validation conclusion task completion (Day 0). Due to the rule 'The due date must fall on a working day', the timeline of the tasks 'Circulate DAR' & 'Document considerations' is extended to 11/09.

The maximum due date for sponsor's action 'Respond to RFI' in Part I is Day 57 from the Validation conclusion task completion by the MSC. If the sponsor responds earlier than the due date (i.e. on Day 54, instead on Day 57), the due date of the MSC(s)' task 'Assess an RFI response' will be recalculated and it changes from Day 69 to Day 64. If another RFI is submitted, due dates might be recalculated.

The due date of the MSC(s)' (hard) task does not change. According to the same rules, the due date of the 'Submit Part I conclusion' task is not affected by earlier completion of the related soft tasks or sponsor's actions. It remains on Day 76.

Day	Mo	Tu	We	...	Sa	Su	Mo	...	Fr	Sa	Su	Mo	Tu	...
Month	15/08	16/08	17/08	...	09/09	10/09	11/09	...	22/09	23/09	24/09	25/09	26/09	...
Day #	Day 0	Day 1	Day 2	Day ...	Day 25	Day 26	Day 26	Day ...	Day 37	Day 38	Day 38	Day 38	Day 39	Day ...
Task / Action	Submit Valid. Concl.			→			Circulate DAR	→				Document considerations		→

Another example is presented below on winter clock stop and calculation of due dates.

Day	Su	Mo	…	We	…	Mo	…	Mon	…	Mo	…	Su	Mo
Month	01/10	02/10	…	11/10	…	16/10	…	23/10	…	30/10	…	05/11	06/11
Day #	Day 44	Day 45	Day …	Day 54	Day …	Day 57	Day …	Day 64	Day …	Day 69	Day …	Day 75	Day 76
Task / Action		Consolid. Consider. & submit RFI	→	Respond to RFI (sponsor) earlier	→	Respond to RFI (sponsor)	→	Assess an RFI response earlier	→	Assess an RFI response	→		Submit Part I Conclu-sion

Three CT applications are submitted before, or during the winter clock stop. The due date of the first task of the MSC(s) ('Express Willingness/Unwillingness' has the Day 03 from application submission date as its due date) is indicated with yellow. As it can be seen, no days of the timeline are consumed during winter clock stop period.

Day	Th	Fr	Sa	Su	Mo	…	Su	Mo	Tu	We	Th
Month	21/12	22/12	23/12	24/12	25/12	…	07/01	08/01	09/01	10/01	11/01
Day #			WCS*	WCS*	WCS*	WCS*	WCS*				
Task / Action	CTA1 submission	Day 01					End of WCS*	Day 02	Day 03		
		CTA 2 submission					End of WCS*	Day 01	Day 02	Day 03	
					CTA 3 submission		End of WCS*	Day 01	Day 02	Day 03	

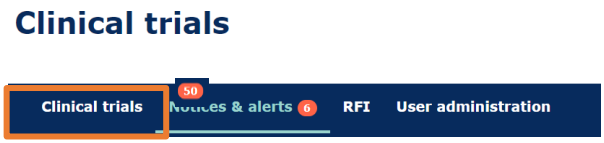
* Winter Clock Stop

Note from the List of known issues and workarounds: during the assessment of a clinical trial application, **the timetable may show different due dates**/status/information than the actual due dates/status on the Tasks page and RFI page. This **does not impact on** the workflow and the actual due date of the task and RFI. **Users are recommended to comply with the due dates recorded with the individual tasks and RFI.**

→ *on this topic: watch the video on How to manage the workload in CTIS - Timetable.*

3.2. Notices and alerts

The Notices & alerts tab is a general tab where the sponsor receives a wide list of messages related to events occurring during the trial life cycle, either with an informative purpose or with an actionable purpose, including alerts **related to the RFIs** raised by the MSC(s) during the evaluation of any CT application (see section 3.3.). The present section is applicable to notices and alerts raised during the evaluation of any application (IN, AM and SM).



Sponsor users need to monitor system-triggered messages related to clinical trials they are involved in, from creation to reporting. These messages can be:

- **Notices**: messages aiming to inform the user of an event related to a clinical trial. Examples: task completed by a MS, Part I and Part II or Part I (only) or Part II (only) submitted, etc.

- **Alerts**: messages informing the user of an **action to be performed**. Examples: RFI submitted by the MSC(s) etc. CTIS includes a subtype of alerts ('alert reminders') which are specifically aimed at reminding sponsor of actions or tasks, respectively, which are about to expire.

The first sub-tab on top of the page ('New!') shows messages received since the last login of the user, while the second sub-tab ('All') shows all the role-related messages once their role in a clinical trial started (i.e. users that are assigned a new role will see the "old" notices and alerts of such role in the 'All' sub-tab). Old notices and alerts cannot be deleted and are kept in the system for traceability purposes.

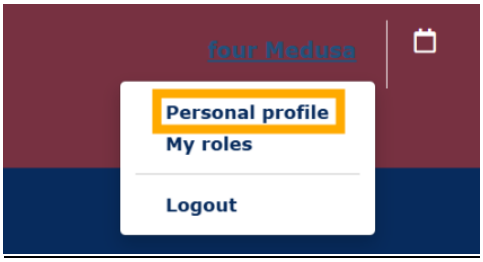
Users only receive the notices and alerts relating to the clinical trial to which they have been given a **specific role**. Users with the same role in a given trial will receive the same notices and alerts. All users who are registered in the system with a certain role continue to receive notices and alerts based on their profile for the whole duration of the role authorization period. There is no option to redirect notices and alerts to another user.

Sponsors can **search** the notices and alerts by using the basic search or advanced search to use criteria such as type, reference number, title of the notice, dates received, source type, etc. In addition, they can **sort** the results alphabetically. Important: all notices and alerts will **no longer be visible** in the system **after 90 calendar days** from their generation.

Of note, 'notices' are different from 'notifications', which are actively reported by the sponsors to CTIS to update on the clinical trial (e.g. start of recruitment, or safety notification: see section 4.1.).

Email notifications are sent to the recipient address recorded in the user's Personal Profile: Sponsor users may activate receipt of such messages through a dedicated opt-in check-box within their Personal Profile.

Users are, by default, opted out, and the opt-in setting applies uniformly to all Notices and Alerts. The opt-in preference applies to all Notices & Alerts relevant to the user's role.



Notes from the List of known issues and workarounds:

- Any malfunction affecting the Notices and Alerts feature in CTIS will be reflected in the corresponding email notifications: e.g., if a Notice is not generated, no email notification will be sent; if multiple Notices are generated instead of one, multiple email notifications will be sent.
- CTIS automatically generates an alert when a due date to submit the Start of Recruitment or Summary and Lay summary of Results is approaching. These alerts are meant as general reminders and are generated irrespective of the current status of the trial lifecycle. As such, an alert for 'Start of Recruitment due…' may be generated even if the Start/End of Recruitment date has already been submitted. In such cases, the alert can be ignored, providing the Start of Recruitment has been correctly submitted as per section 4.1. , or the Summary and Lay summary of Results was submitted as per section 5.2. .

→ *For more information on Notices and alerts see also*: Notices and alerts per role.

3.3. Respond to a Request for Information (RFI)

Before applying the below instructions, the following resources should be consulted: the CTCG Key Documents list on 'RFI Response template', and the CTR Q&A (search for the relevant keywords). For questions, refer to the relevant MSC(s) national contact point(s).

A CT application RFI is a **request for additional information regarding an application** that the MSC(s) could address to the sponsor when evaluating any submitted CT application, as per Articles 5(5) and 6(8) of the CTR. The present section is applicable to RFIs raised during the evaluation of any application (IN, AM and SM).

An RFI can include questions related to the aspects covered in both the validation and the assessment phases, but it can also refer to one specific part of the application. In an IN with Part I and Part II, an RFI can be raised by the RMS as part of the validation and assessment of Part I and by each MSC following assessment of Part II. To **minimise the need to raise an RFI**, sponsors should submit **high-quality** CT applications.

RFI can be raised by the RMS and MSC at any point in time during the evaluation phase. There are no predicted timelines and period of time when RFI can be raised, therefore the sponsors should be vigilant in monitoring the notices and alerts and the RFI tab.

The **60-day evaluation timeline of a CT application is extended in case RFIs are raised** by up to 15 days if the RFIs are raised in the Validation phase (of which maximum 10 days can be given for the sponsor's response), and up to 31 days if the RFIs are raised in the Assessment phase (of which maximum 12 days can be given for the sponsor to reply). Note: if multiple RFIs are raised during any given phase of the evaluation, the extension of the timelines applicable to that phase occurs only once. Additionally, the timelines do not change if the sponsor responds to the RFIs earlier. For more information on timelines, see section 3.1. Sponsors need to **check the due date of each RFI set by the MSC(s)/RMS** in the RFI ab or in the evaluation section of the CT application, since the deadline could be shorter than the maximum number of days allowed. **The sponsor must respond to an RFI before the deadline. Failure to respond will lead to the full application lapsing** and it can no longer be considered for evaluation (i.e. the sponsor will need to resubmit the application. See section 2.7.2.)**.**

Users can access RFIs through: CT application page, Notices & alerts tab, and RFI tab. The 'RFI' tab lists all the RFIs received during the entire life cycle of a CT, including CT application RFIs and other types of RFIs. A specific RFI can be found through basic and advanced search functionalities, as well as sorting options, which are available in both the Notices & alert tab and the RFI tab. See section 3.3.1. on steps to follow to search for an RFI and to modify a CT application as part of the RFI response. **Submitting an RFI response is mandatory even if no changes to the CT application are required.**

RFIs generate corresponding notices in CTIS and may also trigger **email notifications** where the user has actively opted in, noting that users are opted out by default, as described in section 3.2.; however, **users remain responsible for monitoring RFIs directly within the Sponsor Workspace, irrespective of email receipt**.

Note that the RFI tab also displays requests done by MSC(s) for additional information to the sponsor when supervising an authorised CT, i.e. in the context of ad hoc assessments, requests for opinions before applying a corrective measure and the assessment of ASRs (see sections 4.10. , 4.11. and 4.13.). For ad hoc assessment and corrective measures RFIs, authority users in charge of the supervision of a clinical trial describe the set of questions they have and submit the RFI for sponsors to respond in the dedicated subsection in a clinical trial page (ad hoc assessment, corrective measures, etc.).

In the context of a CT application evaluation, RFIs are raised by the RMS/MSC(s) via the considerations documented in the system, which are consolidated by the RMS/MSC(s) (accepted/merged/adapted or rejected) and used as the basis for the RFI. RMS/MSC(s) can also upload documents in CTIS as supporting documentation to the RFI being raised.

Once raised, sponsors have the possibility to download from CTIS the considerations part of the RFI, as well as any supporting documentation, so the RFI can be allocated to be addressed by relevant team members that have specific roles. In accordance with his/her roles, each sponsor user can also have access to the considerations in the RFI and any documents directly from CTIS and can provide the reply directly in the system.

Notes from the List of known issues and workarounds:

- For an overview of the required actions, sponsor users are advised to regularly consult the tabs '**Requests for Information (RFI**)' instead of relying solely on the notices and alerts.
- **To prevent applications lapsing**, sponsors are advised to **submit responses to RFIs ahead of the due date**. This allows time to provide support if any issue is highlighted upon submission.
- In case an RFI response is **not possible** due to technical limitations of the system - **submit a ticket** to EMA CTIS Service Desk.
- In case of technical issues in completing a **response to RFI** (e.g., uploading a certain document, or updating the IMP code in XEVMPD), sponsors are advised to **submit the RFI response despite this pending action**. Sponsors should then reach out to the MSC(s) and request an additional RFI to be raised. This allows more time for the sponsor to coordinate with the EMA CTIS Service Desk to resolve the technical issue from the first RFI.

→ on this topic: watch also the videos on How to manage the workload in CTIS - RFI tab (sponsor workspace), How to access and view an RFI in CTIS, How to change a Clinical Trial Application as part of an RFI response, How to respond to RFI considerations and submit an RFI response and the CTIS bitesize talk: Requests for information.

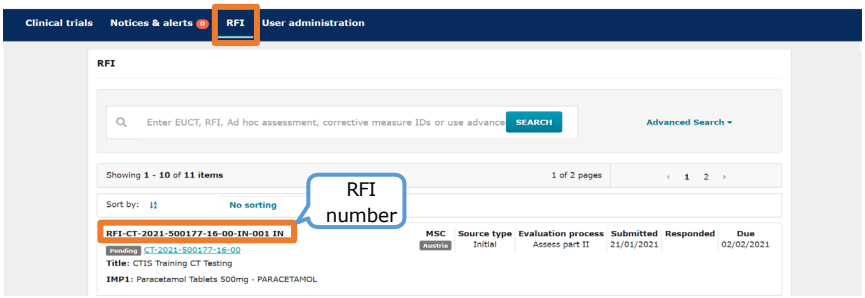
3.3.1. How to respond to an RFI

Sponsor users can view/download RFIs or create RFI responses as long as the RFI corresponds to the section of the application in which they have a role (e.g. Part II Preparer can create an RFI response if the RFI corresponds to Part II; Q-IMPD Preparer can create an RFI response if the RFI corresponds to Part I Quality, etc). The below steps can be performed by a user who has the following roles, depending on the action:

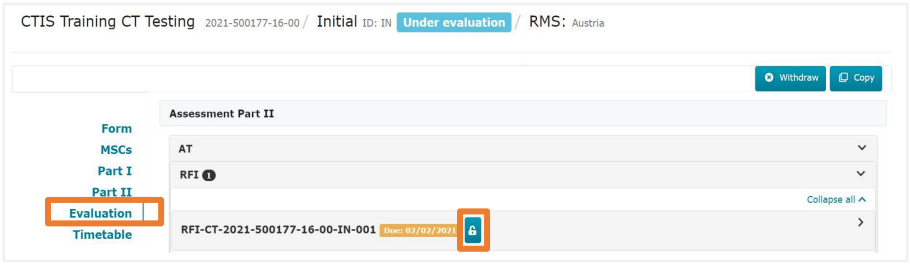
- View and download an RFI: **CT Admin, Part I Viewer (excl. Q-IMPD), Part I Preparer (excl. Q-IMPD), Part II Viewer, Part II Preparer, Q-IMPD Viewer, Q-IMPD Preparer,** and **Application Submitter**.
- Create an RFI response: **CT Admin, Part I Preparer (excl. Q-IMPD), Part II Preparer, Q-IMPD Preparer,** and **Application Submitter**.
- Submit an RFI response: **CT Admin** and **Application Submitter**.

After having accessed the sponsor workspace:

1. Click on the 'Notices & alerts' tab and see the alert stating that an RFI has been received. The same RFI can also be seen in the 'RFI' tab. Note: users only receive the RFI alert if they have the **appropriate role** for the relevant CT application part that is affected by the RFI (e.g. Part I Preparers will receive alerts regarding RFIs concerning Part I).
2. **Click** on the **alert** and display the RFI in the evaluation section of the relevant CT application page; alternatively, you can access the 'RFI' tab and click on the RFI number to access the RFI.

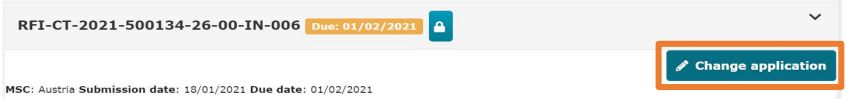


3. Once in the evaluation section of the CT application, you need to identify the relevant RFI from the listed RFIs and expand its menu to view it.



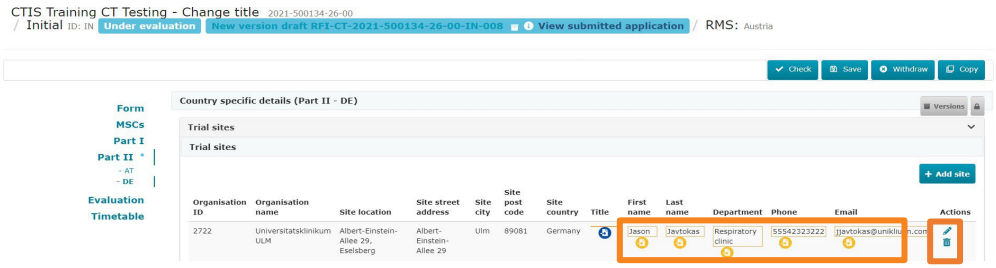
4. Once in the RFI, **review the comments** from the RMS/MSC(s), any supporting documentation, if attached, and the considerations raised as part of the RFI.
5. Click on the **padlock button** to lock the session and **respond to the RFI**. The approach to respond to an RFI depends on the content of the request raised by the RMS/MSC(s).

   If no changes to the CT application are needed (e.g. when simple clarifications are requested to the sponsor), skip steps 6 to 10 and go to step 11. *In case you need to modify the structured data and/or documents of the application*, follow next steps.
6. *If a CT application requires changes*, **click on the 'Change application'** button to create a new CT application version on top of the already submitted one.

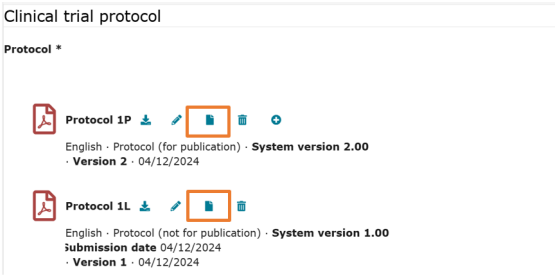


Once the draft application version is created, the '**Discard changes'** button will appear: if selected, the system will revert the draft and remove the performed changes.

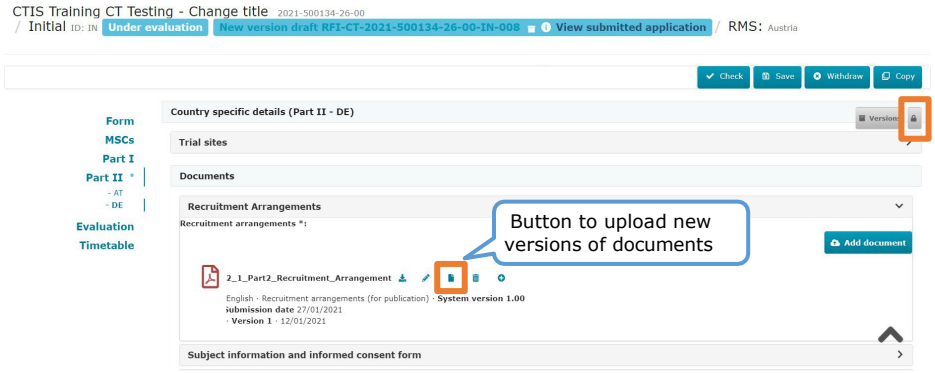
7. *If **changes** are required to the **structured data of the CT application***, click on the **pencil icon** to edit the fields. Such changes can be related to the sections Form, Part I and Part II, depending on the information provided in the RFI.



8. *If **changes** are required to the **submitted documents of the CT application,** you need to* draft new versions of those documents. Once the relevant document is ready, click on the sheet icon in the relevant document section and upload it in the same location of the CT application. Previously uploaded documents can be deleted when responding to an RFI or can be updated through the use of '**update' icon** (in this case, documents will have the same document type, language and title). When uploading a new document, you can specify the date and the version of the file, and a new system version will be generated sequentially by the system, independently of the sponsor's version number. Note that the name of the document cannot be replaced when uploading the new document, but only its version's number/coding.

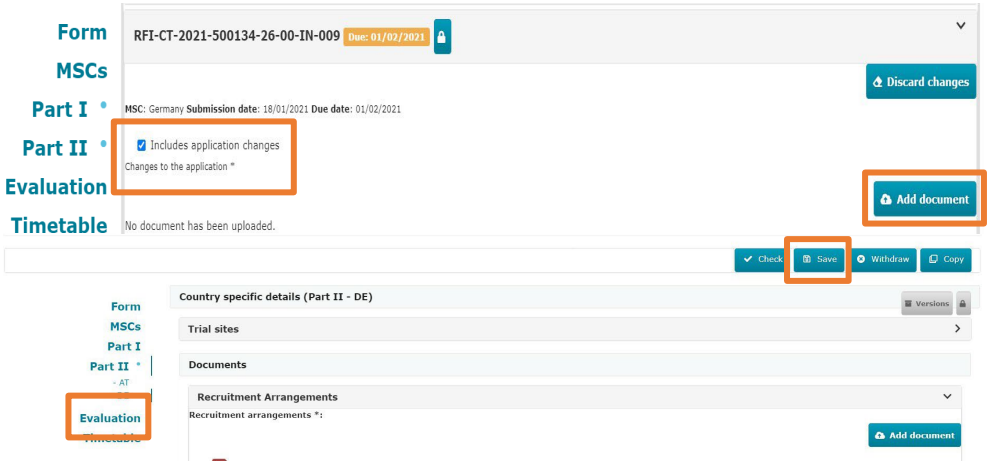


If needed, **a new document of the same type** can also be attached by clicking on the **'Add document'** button. Note: the cover letter cannot be updated as part of an RFI response. Relevant document template 'RFI Response List of Changes to the Application' is available in the 'Key document list' section on the Clinical Trials Coordination Group page.



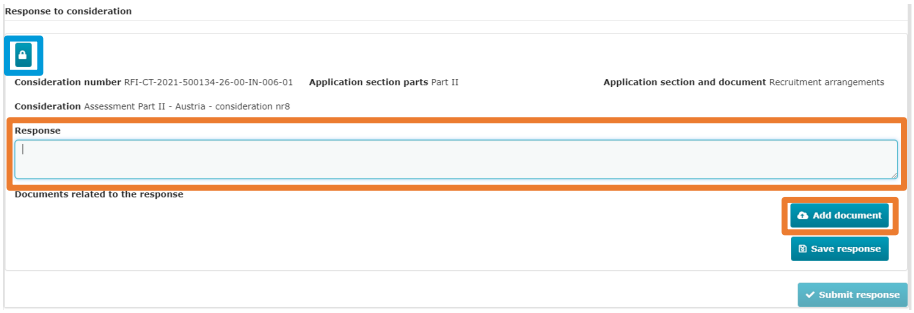
9. After the required changes are included, **save the draft CT application** by clicking on the **'Save'** button. A blue ribbon appears at the top of the CT application page showing that the updated application is in draft mode. To modify it further, you can click on the version displayed after clicking on the blue ribbon. Alternatively, you can go back to the RFI working area under 'Evaluation' section and progress with the submission of the updated application and RFI responses.

10. Within the 'Evaluation' section, *in case you have included changes in the structured data/documents of the CTIS application,* **confirm that the tick box 'Includes application changes'** is checked. To include a description of those changes, click on **the 'Add documents'** button (see



template RFI 'Response List of Changes to the Application' – mandatory if changes to the application were made, available in the 'Key document list' section on the CTCG page). Note: the **'Add document' functionality shall not be used to upload updated CT application documents.**

11. **Respond to the considerations** raised by the MSC(s) and click on '**Save response'** button**. This step is mandatory,** even if no changes were included as part of the application (steps 6 to 10). You can also include one or more supporting documents, if needed, by clicking on the **'Add document'** button.

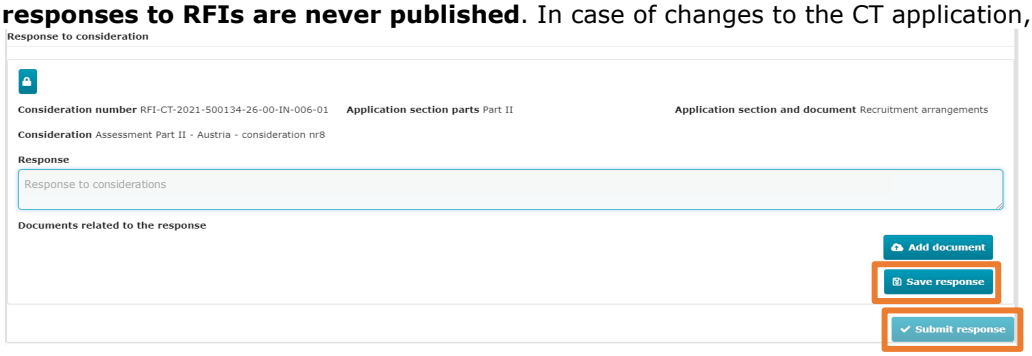


12. Once responses to all raised considerations are included, click on **'Submit response'** button and then on **'Confirm'**, once the pop-up window is displayed. Note: the button 'Submit response' is not visible if the user has not clicked on the padlock that is above the considerations in order to unlock it, or if the user has not responded to all raised considerations.

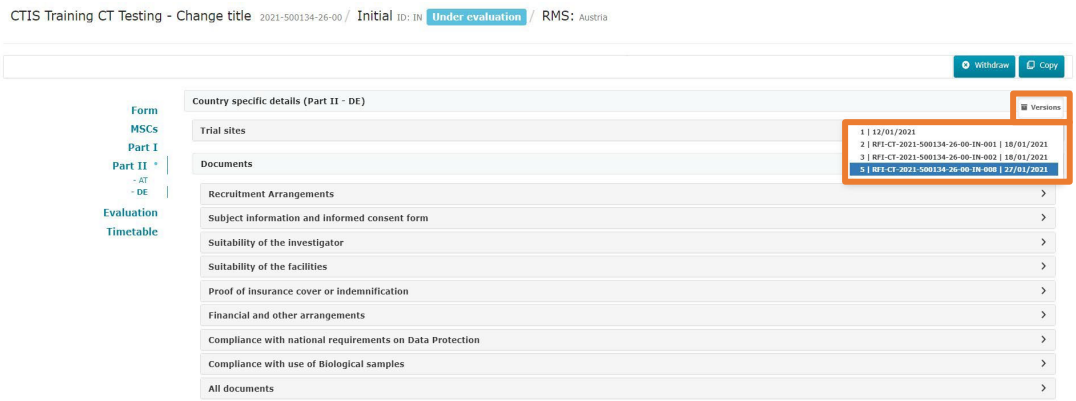
Once the submission is confirmed, the **RFI status** will change to **'responded'**. Sponsors do **not receive an email** to confirm that an RFI response was successfully sent to the RMS/MSC(s). For that, users can go to the 'Notice & alerts' tab and check the notice that the response was sent to MSC(s).

An RFI response cannot be edited after it has been submitted to the RMS/MSC for review, nor can it be withdrawn. If an MSC deems that the RFI response provided by the sponsor is incomplete, the MSC submits another RFI.

RFIs and responses to RFIs are never published. In case of changes to the CT application, the latest version of structured data and documents submitted in an RFI response will become visible to the public, if subject to publication as per CTIS publication rules (see section 2.1.).



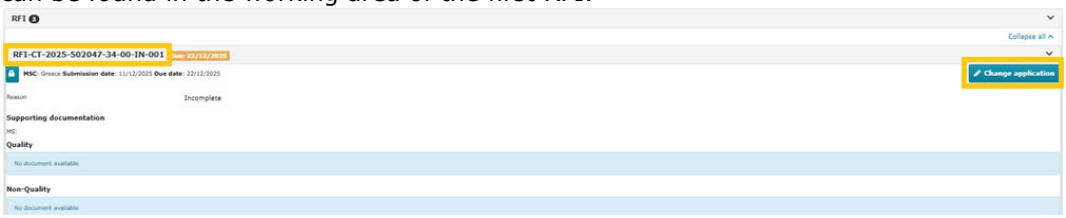
View submitted versions: you can view all the RFIs responses submitted for a CT application in the evaluation section of the CT application page and in the RFI tab. In addition, if your RFI required changes to a CT application, changes made to the data in the application are highlighted in yellow after you click on the 'Padlock' button to unlock it. All CT application versions are also displayed by clicking on the 'Versions' button.



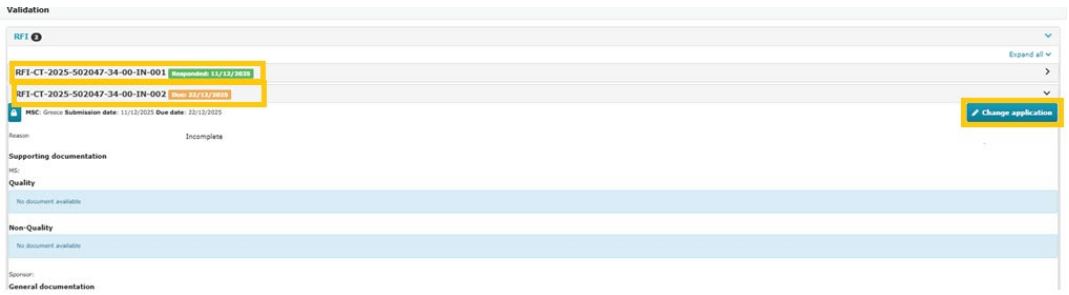
If **more than one RFI** is received:

- *if no changes to the CT application dossier are required*, the user can respond simultaneously to more than one RFI.
- *if more than one change is needed **in the same part of the application***, corresponding to two or more RFIs, CTIS only allows the user to have one draft application opened at a time. This is so to ensure traceability of the changes made to an application. The 'Change application' button

can be found in the working area of the first RFI.



The **'Change application'** button on the subsequent RFIs becomes available once the first RFI has been responded to.



Where multiple RFIs are open and the sponsor needs to respond to a subsequent RFI before addressing the first one, the response should be limited strictly to the considerations raised in that subsequent RFI and submitted without introducing any changes to the application. Amendments to documents or structured data should only be made when the sponsor starts preparing the response to the first RFI, which remains pending.

- *if more than one change is needed **in different parts of the application***, e.g. in case RFIs are simultaneously raised in relation to both Part I and Part II, different users may work on two simultaneous drafts of the application to address the changes needed (a user can work on Part I RFI at the same time as other users are working on Part II RFI). Since they concern different parts of the application, the traceability of changes is assured. Also, Part II RFIs raised by different MSC(s) can be addressed simultaneously by different users, if needed. Note: in case of simultaneous RFIs, users should be mindful to work on their respective RFIs.

End of chapter: jump to Clickable table of contents.

4. Conduct a clinical trial

Once the trial is authorised, and during its conduct, the sponsor may perform any of the following actions:

- **Notifying** each MSC **about events** that occurred while the trial is conducted, or of any applied measure in case of unforeseen events. These notifications can be 'trial and recruitment periods' notifications (section 4.1.) and other types of notifications (section 4.9.).
- **Adding an additional MSC to the IN** through an **AM**: see section 4.2.
- **Applying a change to the IN** through an **SM** (see section 4.3. or a **NSM** (see section 4.8.), as applicable.
- Responding to an **RFI** raised during an **ad hoc assessment**: see section 4.10.
- Responding to an **RFI** raised as **request for opinion on a corrective measure**: see section 4.11.
- Reporting **SUSARs**: see section 4.12.
- Drafting and submitting **ASRs**: see section 4.13.

When **drafting an AM, an SM or an NSM**, sponsors should first consider:

- Which are the **CT dossier's fields/documents that can be updated.** The detailed list of structured data and documents that can or cannot be modified through an AM, SM or NSM can be seen in columns N, O and P of the CTIS application fields document.
- The applicable **publication rules**, including the ones for trials submitted before 18 June 2024 ('historical trials'), see section 2.1.
- Whether there are already **draft applications on that trial.** Sponsors should avoid creating new draft applications while a previous draft already exists. Draft applications copy the documents and data from the last authorised application, which means updates in parallel or later applications will not be reflected automatically: **see example below**.
- Whether there are already **ongoing evaluations on that trial**, which could prevent the submission of those applications, see below table.

Sponsors are advised to **avoid creating draft applications of SM, NSM, or AM** not only **while a previously submitted application is still under evaluation**, but also **when a draft already exists**. This is because when a draft application is created, it copies the documents and data from the last authorised application. The following provides an example on the impact of draft application creation timing:

1.	IN authorised	16-Oct-2025
2.	AM draft application created (it copies structured data and documents from the authorised IN) / or AM-1 under assessment	17-Oct-2025
3.	Part I+II SM draft application created (it copies structured data and documents from the authorised IN)	18-Oct-2025
4.	Part I+II SM application submitted	19-Oct-2025
5.	Part I+II SM application authorized	25-Oct-2025

6. AM application submitted / or AM-1 authorised (will not contain SM changes) 26-Oct-2025

In the above example, the AM application submitted/authorised on 26-Oct-2025 will not contain the changes submitted in the Part I+II SM. **CTIS does not retrospectively apply changes authorised in applications that were already created**. It is the user's responsibility to create and submit applications in a logical, sequential order.

The below table summarises the **allowed submissions** whilst there are **ongoing evaluations**:

Ongoing evaluation of	Submission of an AM	Submission of an SM to Part I and Part II	Submission of an SM to Part I	Submission of an SM to Part II	Submission of a NSM
IN	Not until a decision is issued by all MSC(s)	Not until a decision is issued by all MSC(s)	Not until a decision is issued by all MSC(s)	Not until a decision is issued by all MSC(s)	Part I only: Only after one MSC in the IN issues a positive decision Part I & Part II: Only after one MSC in the IN issues a positive decision; Part II only to that MSC that have issued a positive decision Part II only: Only possible for the MSC that have issued a positive decision.
Part I & Part II SM application	No	No	No	No	No
Part I only SM application	No	No	No	No	No
Part II only SM application	Yes	No	No	Only to that MSs without an SM Part II only under evaluation	No
AM	Yes (to different MSs)	No	No	Yes, provided that the MS is different from the MS of the AM	No

Note: the Sponsor FAQs includes further guidance on the topics of this chapter.

4.1. Notify on trial events (e.g. CT start, start of recruitment)

Before applying the below instructions, the CTR Q&A (search for the relevant keywords) should be consulted, as well as the 'Frequently asked questions related to Clinical trials submitted under the Regulation EU 536/2014' available in the 'Key document list' section on the CTCG page. For questions, refer to the relevant MSC(s) national contact point(s).

Notifications can only be submitted for trials that have been **authorised in at least one MSC**. Trial and recruitment periods notifications are different from other types of notifications (section 4.9.) and refer to events related to the CT life cycle such as the start, restart and end of the trial, start and restart of recruitment, temporary halt, end of trial in EU/EEA and global end of the trial. Relevant definitions can also be found in the CTR Q&A. Data fields to be completed and documents to be uploaded can be seen in the list of CTIS fields on Notifications, ASR and Results document. These types of notifications must be made **within 15 days from the start of the event** (Articles 36-38 of the CTR). They can be classified into two kinds.

1. Notifications that need to be submitted **for every CT**:

- **Start trial:** the first **act of recruitment** of a potential subject for a specific CT, unless defined differently in the protocol (as per Article 2(25) of the CTR). It is the date of initiation of the first trial site in an MSC.
- **Start recruitment:** the first visit of the first subject (see definition in the CTR Q&A). The date could be the same as for the start trial. The recruitment of subjects **shall start within two years from the CT authorisation**. If the start recruitment notification is not submitted within that period, the trial expires, unless the sponsor submits an SM for an extension of this period beyond two years, which needs to be authorised by the MSC, see section 4.3.3.
- **End recruitment:** the act of stopping recruitment of subjects in an MSC. It corresponds to the date on which the last patient is enrolled in each Member State (MS). Reporting this within 15 days of the actual event can be challenging: it is recommended to plan accordingly.
- **End trial:** the last visit of the last subject, or a later point in time as defined in the protocol (as per Article 2(26) of the CTR). *The trial could also be **early terminated***: see below.
- **Global end of trial:** *in case the trial is conducted in countries outside of the EEA*, the sponsor shall also notify this date by clicking on 'Submit global end' button.

Early termination means the premature end of a CT due to any reason, before the conditions specified in the protocol are accomplished (as per CTR). When the protocol specifies circumstances that would determine an early termination of the CT, should such circumstance(s) occur, the sponsor needs to also notify an early termination of the CT, clarifying the reasons to the MSC(s). The sponsor shall notify each MSC of the early termination:

- **within 15 days**, when the reasons **do not affect the benefit-risk balance** (e.g. low recruitment, shortage of product supply, end of development) and the treatment options for subjects still participating in the CT will not be compromised or no subjects within EU/EEA states have been included in the CT. The reasons and any follow-up measure should also be included in the notification.
- **without undue delay** but not later than 15 days, when the CT is ended **based on an impact on the benefit-risk balance**. The reasons and follow-up measure should also be specified.

The date of the early termination is the date of the end of the CT. In all cases, except when no subject was included in the CT, a summary of results with the relevant available information is expected within

one year of the early termination of the CT (or within 6 months, in case the trial includes paediatric subjects), including post-trial follow-up data, where applicable (see CTR Q&A): see section 5.2.

2. Notifications that need to be submitted **only when the sponsor needs to interrupt a CT** on specific grounds **with a view to resuming it** afterwards:

- **Temporary halt:** an interruption not provided in the protocol of the conduct of a CT with the intention of the sponsor to resume it. This kind of notifications can be related to a matter of subject safety and/or benefit-risk balance, or to other reasons. In some cases (e.g. impact on subject safety, or risk-benefit balance), an SM may be needed in order to restart a trial after a temporary halt. If the trial is not restarted within two years or within the extension period requested through an SM, the trial will be deemed ended, see CTR Q&A. Important: **the text inserted by the sponsor in all the structured data fields for a temporary halt is all made publicly available**, see column H of the Notifications, ASR and Results document: no CCI or personal data should be inserted in such fields.
- **Restart trial:** the act of restarting the trial, after a temporary halt or after a suspension of the CT as part of a corrective measure by an MSC.
    - If the halt was not related to reasons regarding subject safety/benefit-risk balance, the sponsor can restart the trial within two years since the halt and notify the relevant MSC(s) within 15 days of the restart of the trial. It is also possible to **extend the date of the restart of a trial beyond 2 years** from the halt if an SM is submitted for authorisation before the two years deadline from the temporary halt date (see section 4.3.3.).
    - To restart a trial which was halted in an MSC for reasons of subject safety/benefit-risk balance, the sponsor needs to **submit an SM that includes part II** of the relevant MSC, and have it authorised by the MSC. The sponsor shall provide a justification for the restart, including conclusions of the analysis, the mitigation measures (if applicable), and an updated benefit- risk assessment. When creating an SM application, the sponsor needs to select 'Restart trial' as the justifying reason. Afterwards, in order for the user to submit the restart trial notification, the previously authorised SM needs to be linked to the notification in the restart form (Note: only authorised 'Restart trial' SMs will be displayed so that the user can link them to the notification).
- **Restart recruitment:** the act of restarting the recruitment of subjects. The trial must have been first restarted to be able to restart the recruitment.

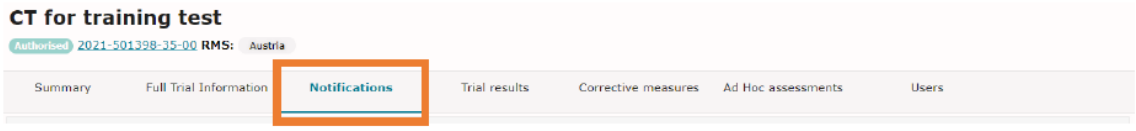
Trial and recruitment periods notifications are published on the CTIS public portal upon submission. When an update for these types of notifications is submitted, including their withdrawal, the update is reflected in the CTIS public website within 24 hours.

→ on this topic: watch also the CTIS bitesize talk: Notifications - Part 1 and the video on How to manage a clinical trial in CTIS (Sponsors) – Trial and recruitment periods notifications.

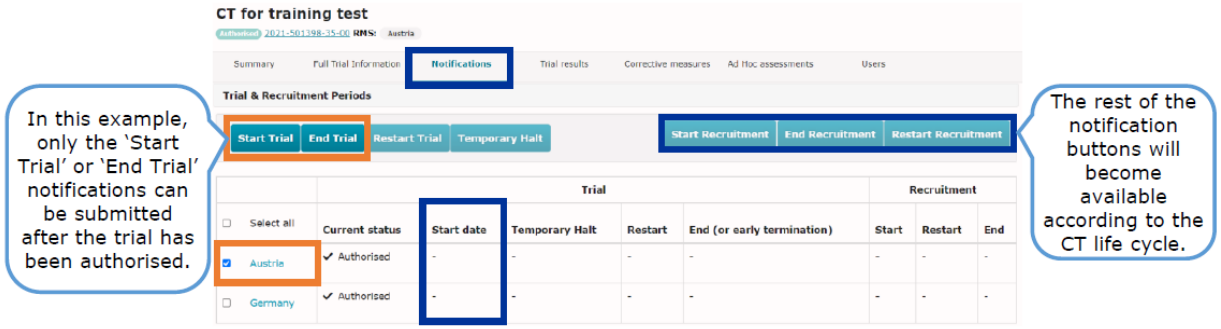
4.1.1. How to submit trial and recruitment period notifications

Below there are the steps that a sponsor user with the role of **CT Admin, a Notification Submitter** or **Notification Preparer** (who however cannot submit) can perform in order to insert a notification. After having accessed the sponsor workspace and searched for the relevant CT (see section 2.6.1.) and selected the relevant CT (see section 2.6.2.):

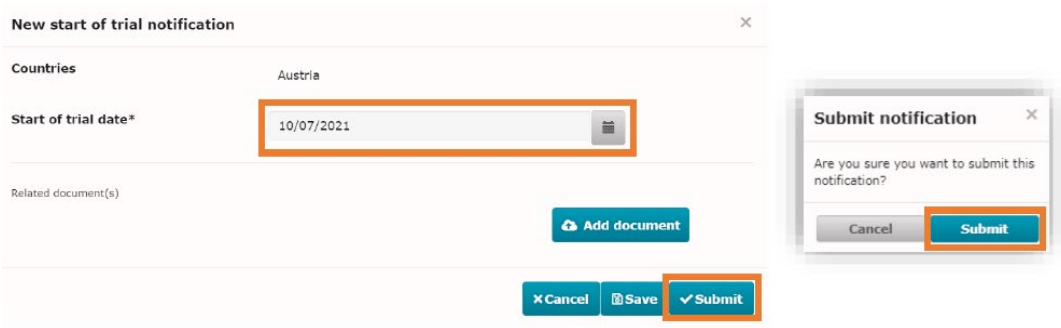
1. In the CT page, click on the **'Notifications'** sub-tab.



2. In the 'Trial & Recruitment Periods' notifications section **select the MSC** where the notification needs to be submitted to. If the same date applies across more than one MSCs, they can all be selected.

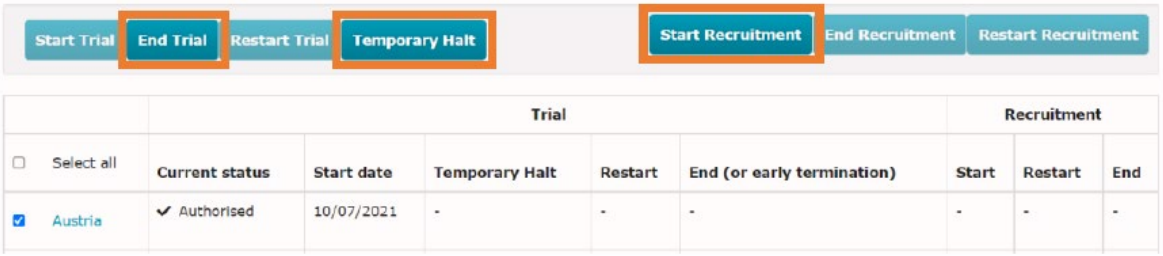


3. After selecting **'Start Trial'**, fill in the **details,** add **supporting documents** in the pop-up window Data fields to be completed and documents to be uploaded can be seen in the list of [CTIS fields on Notifications, ASR and Results].



4. Click on the **'Submit'** and the 'Confirm' buttons.

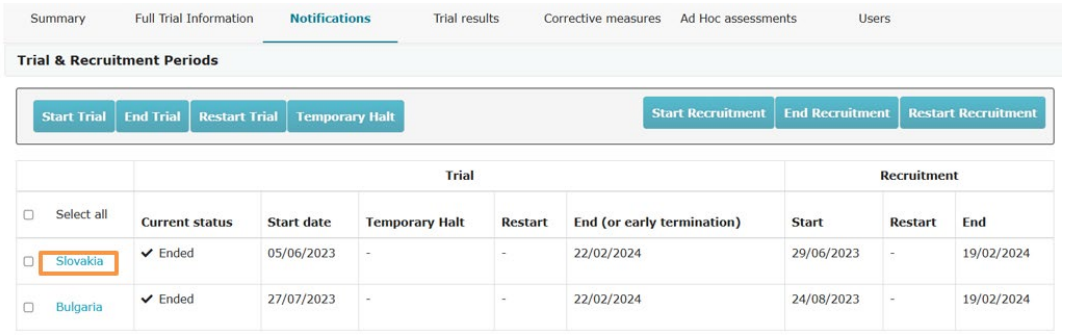
5. Once **the trial has started**, other notifications can be submitted, such as a **temporary halt** or the **start of recruitment** of a trial.



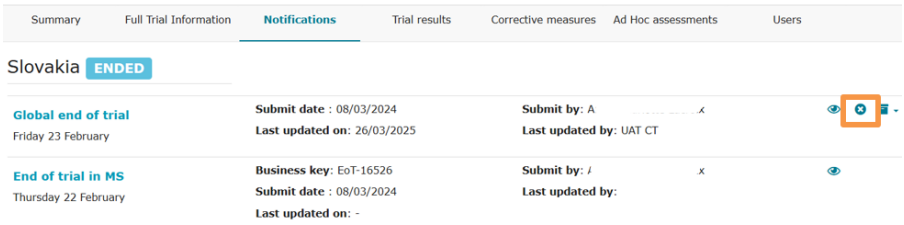
4.1.1.1. How to update a trial and recruitment periods notification after its submission

A sponsor user can update any trial and recruitment periods notification after its submission. For the most recently submitted notification (including if it is a 'global end of trial'), the following options will be available and can be chosen as appropriate: **view, update and withdraw**. It is possible to only edit the last submitted notification: to edit a previously submitted notification, the user needs to withdraw it and then resubmit it. See steps below.

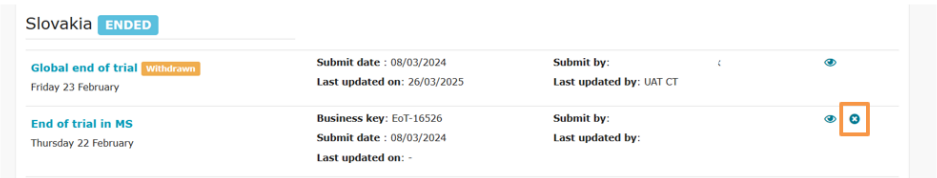
1. Click on 'Notifications' and on the relevant MSC to access the relevant notifications history.



2. For the last notification listed (including if it is a 'global end of trial'), the following options will be available and can be chosen as appropriate: view, update and withdraw. To edit previously submitted notifications, you need to withdraw the most recently submitted one(s), until the one that you would like to edit.

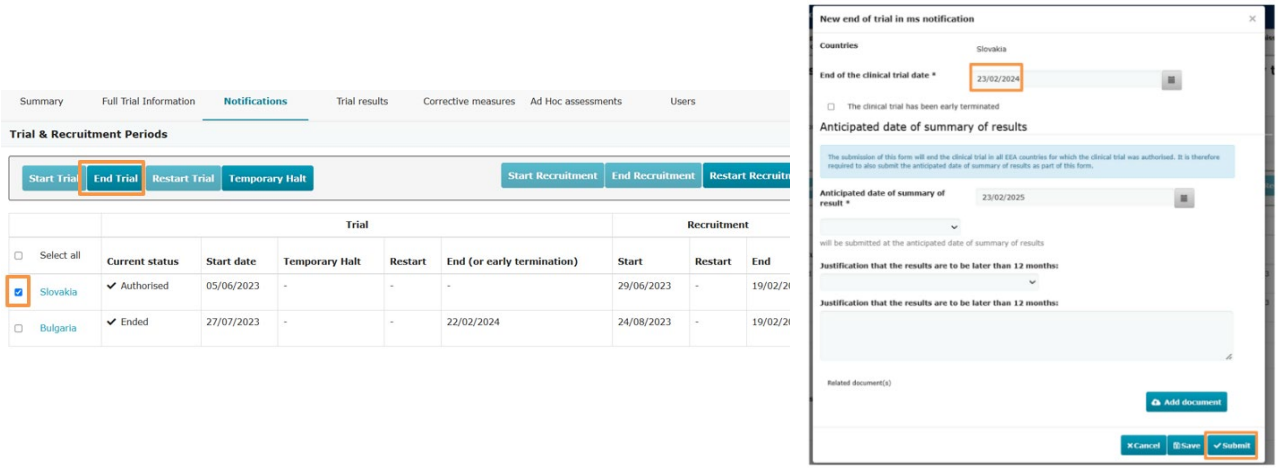


3. After having inserted the justification and having clicked on 'confirm' when the system asked for further confirmation, click on the 'withdraw' of the remaining notification(s) until the one you would like to edit. The system will ask again for a justification for withdrawal and to confirm the withdraw.



4. Once the former notification is withdrawn, you need to resubmit it in its corrected version.

5. Afterwards, you need to re-submit all the more recent notifications, which were previously withdrawn (including the global end of trial one, in the example shown).



4.2. Create and submit an Additional Member State application (AM)

Before applying the below instructions, the following resources should be consulted: the CTCG Key Documents list on 'Best practice guide naming of documents in CTIS' and 'Frequently asked questions related to Clinical trials submitted under the Regulation EU 536/2014', and the CTR Q&A (search for the relevant keywords). For questions, refer to the relevant MSC(s) national contact point(s).

As a general rule, sponsors are encouraged to include in the IN all Member States where the trial is planned to be conducted to promote alignment of the Part I dossier (see CTR Q&A).

An AM is an application for **extending** a previously authorised CT to the territory of one or more other Member State(s). Structured data and documents that are modified through an AM are all **published in line with the CTIS Publication rules**, see section 2.1. . When an AM is submitted on a so called '**historical trial'** (trial submitted before 18 June 2024), only Part II documents that concern the additional MSC are published, while Part I documents are not published since they cannot be updated through the AM. For more details see Table IV of Annex I to Guidance document on how to approach the protection of personal data and CCI while using the CTIS.

The detailed **list of structured data and documents that can be or cannot be modified through an AM** can be seen in column N of the CTIS application fields document. In essence, when submitting an AM, the following parts of the existing CTIS application can be modified/added:

- **Form**: Cover letter, Proof of payment.
- **MSCs**: MSC(s) included in the AM and the estimated total population for the CT in each MSC.
- **Part I**: translations of specific Part I sections for the AM (if required by the MSC); for example, translations of fields such as the CT title, the medical condition, the CT objectives, the eligibility criteria, etc. and documents such as the protocol, data safety monitoring committee charter, investigator brochure, etc.
- **Part II**: information related to aspects that concern the AM, and relevant translations. These includes Trial sites information, Recruitment arrangements, Subject information, Informed consent form, 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.

An AM can be submitted if the IN for the clinical trial has been authorised in at least one MSC, and while there are no other applications where Part I is under evaluation. It is possible to submit an AM if there is an assessment ongoing for an SM Part II in other MSC, or if there are other AM under evaluation. While the user can submit separate AM to each new MSC, it is advisable to combine the requests and include the different AMs in a unique submission. See relevant table in section 4. (page 104).

A sponsor should also **avoid creating draft application of AM, when a draft application of any kind already exists**. This is because when a draft application is created, it copies the documents and data from the last authorised application: see section 4. (page 104).

There is no limitation to the number of MSC(s) that can be included in an AM. By clicking on the 'Create' button on the upper-right side of the CT page and 'Additional MSC', a sponsor can select one or multiple MSC(s) to add to the AM (see step 2 below). Once created, sponsor users will have to provide MSC details for each MSC to be added. Once submitted, the application will be evaluated by each of the newly added MSC.

→ on this topic: watch also the CTIS bitesize talk: Additional Member State concerned (MSC) application.

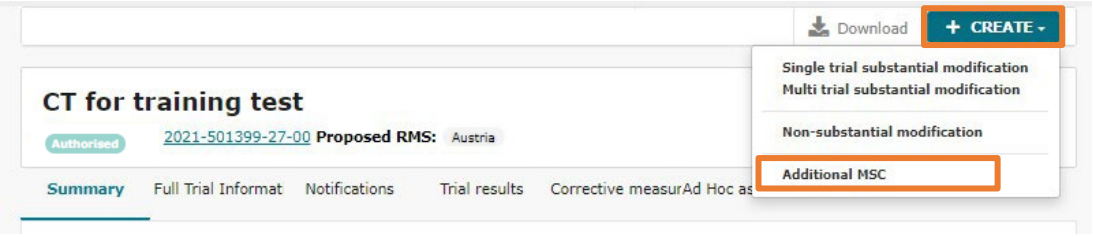
4.2.1. How to create and submit an AM

The below steps can be performed by a user who has the following roles, depending on the action:

- Submit/cancel/withdraw an AM/any CT application: **CT Admin** and **Application Submitter**.
- Edit/draft an AM/any CT application: **CT Admin, Part I Preparer (excl. Q-IMPD), Part II Preparer, Q- IMPD Preparer** and **Application Submitter**.
- Create an AM or any CT application and copy it: **CT Admin**.

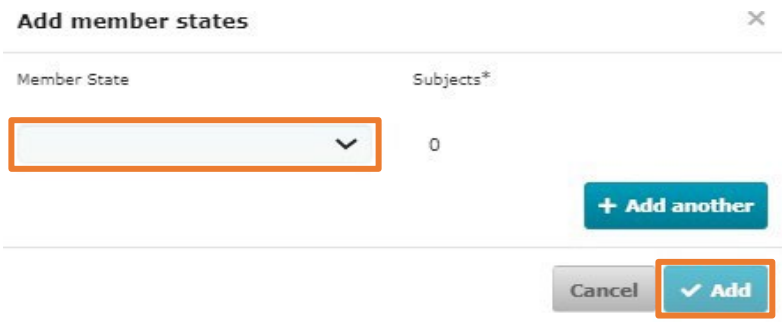
Before creating a draft application, ensure there are no other draft applications or applications under assessment for the same part of application (see section 4.). After having accessed the sponsor workspace and searched for the relevant CT (see section 2.6.1.) and selected the relevant CT (see section 2.6.2.):

1. In the 'Summary' subtab of the CT page, select the **'+ CREATE'** at the top right corner and choose 'Additional MSC'.

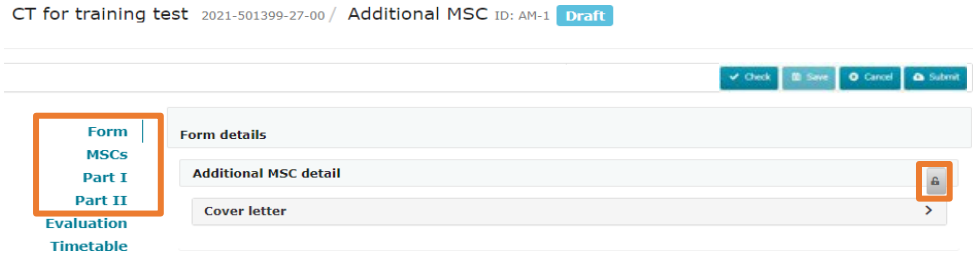


2. Confirm that are no other draft applications or applications under assessment for the same part of application (see section 4.)

3. In the pop-up window, **select the new MSC(s)** to which you wish to extend an authorised clinical trial and populate the foreseen number of subjects for the trial in each new MSC. After that, click on the '**Add**' button.

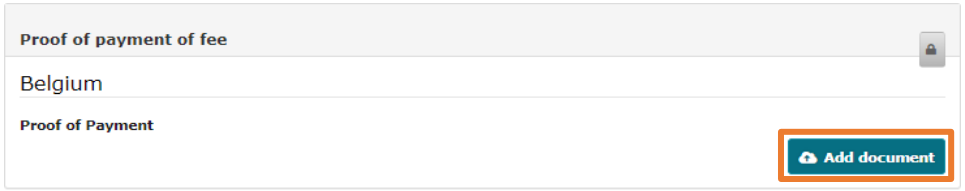


4. Add the Cover Letter in the 'Form' section. Afterwards, start to **populate all the required fields** of the sections 'MSCs', 'Part I' and 'Part II' found on the left side of the screen. **Refer to specificities detailed the 'Notes' of step 4 of section 2.3.3.** . In order to populate a field, you can click on the padlock button in each subsection. See details on **structured data and documents that can or cannot be modified through an AM** in column N of the CTIS application fields document. Refer to section 2.3. to know how to populate each field.



5. Additionally, you can include **translations** of the data and documentation related to Part I (click on Part I to add translations). You can only add data and documents in Part I that correspond to the translations applicable for the added member states, since all the rest of Part I data and documents have already been evaluated. **Translations of documents that are subject to publication need to be redacted of CCI and personal data when added**: refer to section 2.1. . For those documents, the '+' (plus) icon can be used by users to upload versions 'not for publication'.

6. You can upload other **documents** to other parts of the AM application by selecting the 'Add document' button available in the respective sections.



7. After populating all the fields, click on the padlock to lock the relevant section(s). Select the '**Check'** button on the top-right corner of the AM page to see if any required field has not been populated (the missing fields will appear marked in red). After all the required fields are populated, select the 'Submit' button.

8. After reading the confirmation text, select the 'I agree' box and then click on 'Confirm'.

If after submission there are missing or incorrect documents, for instance, because of wrong information or language, **an RFI will be issued by the MSC(s)** to request the sponsor to update the application accordingly: refer to section 3.3. to know how to reply to an RFI.

→ on this topic: watch also the video on How to submit an additional Member State concerned application in the CTIS sponsor workspace.

4.3. Create and submit a Substantial Modification application (SM)

Before applying the below instructions, the following resources should be consulted: the CTCG Key Documents list on 'Cover letter template', 'Best practice guide naming of documents in CTIS' and 'Frequently asked questions related to Clinical trials submitted under the Regulation EU 536/2014', and the CTR Q&A (search for the relevant keywords). For questions, refer to the relevant MSC(s) national contact point(s).

As per Article 2(13) of the CTR, an SM is a request by the sponsor for a change of a CT dossier that is likely to 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 the sponsor needs to make a change to the CT dossier that is not likely to substantially impact the subjects' safety or rights or the reliability/robustness of the generated in the CT, the sponsor could perform an NSM, see section 4.8. Examples of whether an application should be considered an SM are provided in section 4.3.1. In case of doubt on whether a change should be submitted as an SM or as a NSM, the sponsor shall consult the RMS/MSCs.

Structured data and documents that are modified through an SM are all **published in line with the CTIS Publication rules**, see section 2.1. **.** Important: when an SM is submitted on a so called '**historical trial'** (trial submitted before 18 June 2024), **all documents that are subject to publication** as per publication rules **are published**, see Table IV of Annex I to Guidance document on how to approach the protection of personal data and CCI while using the CTIS, not only those ones that were modified as part of the SM. This means that the sponsor needs to make sure that **all documents** uploaded in all the **'for publication'** document sections of the SM **are redacted of CCI** and that their **personal data are anonymised, including those documents that are not strictly in scope of the SM**.

The detailed **list of structured data and documents that can or cannot be modified through an SM** can be seen in column O of the CTIS application fields document. The scope of an SM can be Part I only, Part II only, or Part I and Part II (see more details below). Documents and structured Data Fields that may be populated through an SM are listed here:

	Form	MSCs	Part I*	Part II*
Document for upload	Cover letter		Documents	Documents
	Modification description		Document translations	Document translations
	Supporting information			
	Proof of payment			
Structured data field	Supporting information	Number of subjects per MSC	Data	Trial site(s)
	SM reason		Data translations	PI contact details
	SM scope		Third-party entity	
			Sponsor contact details	
			Description of changes	

* *If there are any changes to the dossier*

After selecting the scope of the SM, users need to prepare the SM application, adding required information, editing already submitted structured data and updating submitted documents depending on the changes they would like to perform to the dossier. 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 tracked changes**, to facilitate the assessment of SMs.

A sponsor should **avoid creating draft application of SM, when a draft application of any kind already exists**. This is because when a draft application is created, it copies the documents and data from the last authorised application: see section 4. (page 104).

A sponsor can only **submit an SM to an MSC where the trial was authorised and that does not have an ongoing assessment** of the same part of the dossier for the concerned trial. As per the table in section 4. (page 106), an SM can still be submitted when there is a parallel assessment of SMs for Part II in different MSCs, or if it regards Part II only and there is a parallel assessment of an AM for Part II in another MSC.

4.3.1. Types and scope of an SM application

Chapter III of the CTR refers to three types of SMs:

- SM of **Part I only** (Articles 17 to 19): sponsor users are able to make changes to any section of the application, except Part II.
- SM of **Part II only** (Article 20): sponsor users can select the MSC for which they want to submit an SM, and modify the relevant Part II. **Users can select only one MSC at a time.**
- SM of both **Part I and Part II** (Articles 21 to 23): **users can select multiple MSCs at the same time.**

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, see list of detailed fields in document CTIS application fields.

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.

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. A non-exhaustive list of examples of modifications that should be regarded as substantial is provided in **Annex IV of the CTR Q&A**.

Note that in case of a **change of sponsor**, an SM is not applicable when:

- Changes to the **legal entity of the sponsor** need to be performed through a **change of sponsor SM and cannot be performed through an SM Part I** (see section 4.4. on 'Change of sponsor SM'). This is to facilitate the MSC(s) evaluation of this SM.
- Changes to the **details of the sponsor** (that are classified as changes of 81.9 NSM (according to Annex IV of CTR Q&A can be done through a NSM, see section 4.8.1. .

An **SM may also 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 MSC(s) 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.

The sponsor should also assess whether an SM leads to changes in the CT to the extent that it has to be considered a completely new CT. Some scenarios would require **an IN to be considered instead of an SM**, for example: a change of the 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 IN).

In case **the SM regards a trial that was transitioned** from the CT Directive (see section 2.4.7.) specific guidance for the first substantial modification after a trial application transition is available in the Clinical Trials Coordination Group (CTCG) website, including the relevant Annex I Cover Letter Template, Annex II Substantial Modification Description Template and Annex III - First SM Part II after transition.

→ on this topic: watch also the CTIS bitesize talk: Modifications.

4.3.2. How to create and submit an SM

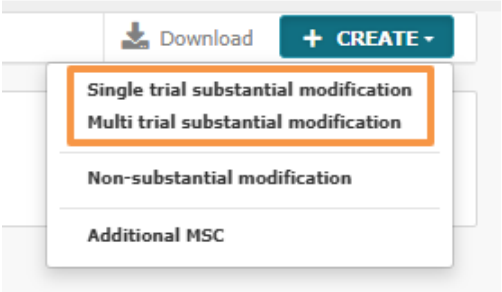
The below steps can be performed by a user who has the following roles, depending on the action:

- Create an SM/any CT and CT application and copy it: **CT Admin**.

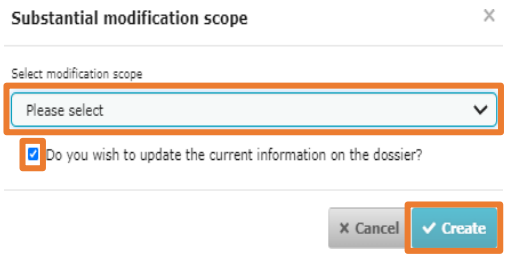
- Edit/draft an SM/any CT application: **CT Admin, Part I Preparer (excl. Q-IMPD), Part II Preparer, Q- IMPD Preparer,** and **Application Submitter**.
- Submit/cancel/withdraw an SM/any CT application: **CT Admin** and **Application Submitter**.

Before creating a draft application, ensure there are no other draft applications or applications under assessment for the same part of application (see section 4.). This also includes ASR assessments (see section 4.13.). After having accessed the sponsor workspace and searched for the relevant CT (see section 2.6.1.) and selected the relevant CT (see section 2.6.2.):

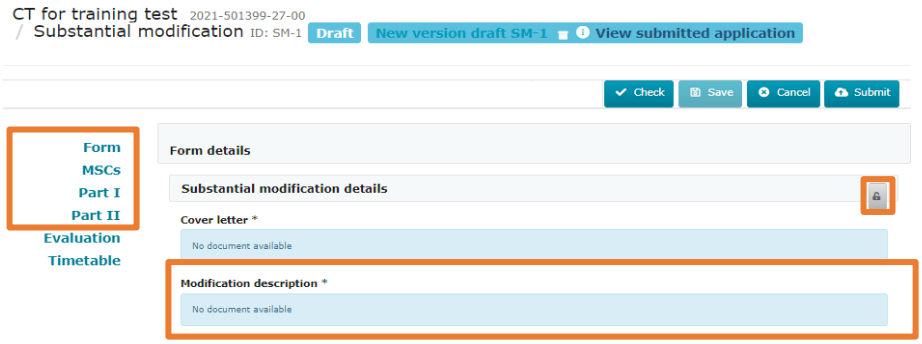
1. In the 'Summary' subtab of the CT page, select the **'+ CREATE'** button and at the top-right corner e and choose 'Single trial substantial modification' or 'Multi trial substantial modification' depending on whether the modification corresponds to one or more clinical trials (see explanation in section 4.3.1.).



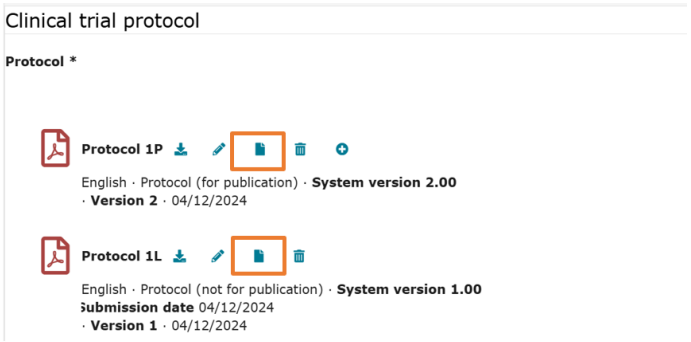
2. Confirm that are no other draft applications or applications under assessment for the same part of application (see section 4.)
3. In the pop-up window, you can **select the scope** of the modification, if it is for Part I only, Part II only, Part I and Part II (see above explanations), and select the checkbox on updating the current information of the application dossier. **You are strongly advised not to untick this checkbox** (otherwise you will not be able to change the application upon request of the MSC(s) through an RFI, see below 'List of known issues and workarounds'). After that, click on the '**Create**' button: the SM is created.



4. In the 'Form' section, add the Cover Letter, populate the field 'Modification description' and add a document explaining the changes that are brought to the trial through the SM. Note that specific information on SMs on 'Extension to start trial recruitment beyond 2 years' , 'Restart of trial', or 'Extension to restart trial beyond 2 years' can be found in section 4.3.3. . In order to populate a field, click on the padlock button in each subsection. 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.



5. **Populate all the relevant and required fields** of the sections 'MSCs', 'Part I' and 'Part II' through clicking on the padlock button in each subsection. The list of **structured data and documents that can be or cannot be modified through an SM** can be seen in column O of the CTIS application fields document. Refer to section 2.3. to know how to populate each field and to the 'Notes' of step 4 of section 2.3.3. When updating an existing document, **click on the 'update' icon and not on the 'Add document' button** on the right, which should not be used to update already existing documents, but to add new documents which were not previously part of the dossier:



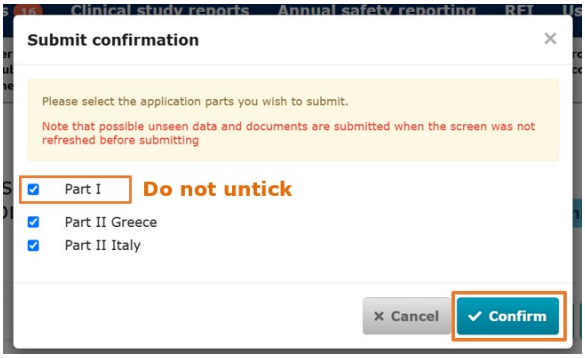
Additional 'not for publication' version(s) of the updated document can be uploaded through clicking on the '+' icon on the right of the relevant document (e.g. the track changes version from the document uploaded in the previous application, in addition to the clean 'not for publication' version which includes CCI).

6. You can include a description of the changes applied in the 'Section changes description' tile of the respective section. If your trial was originally submitted before 18 June 2024, **make sure all documents (including those ones that are not strictly in scope of the SM) do not contain CCI and are anonymised of personal data**: see section 4.3.

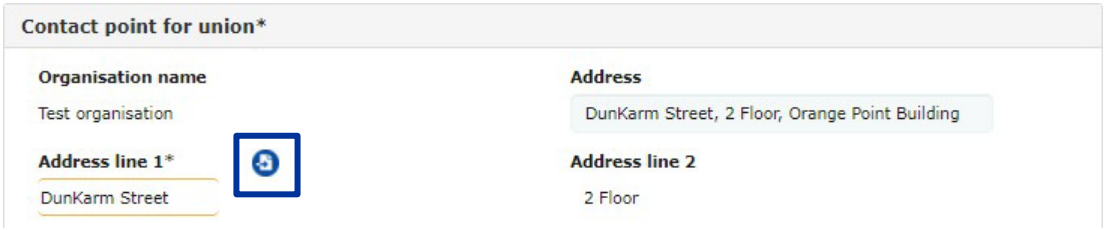
7. Once you have included your comments, an exclamation mark will appear in the modified sections. Note that in the 'MSCs' section of the SM application you can only modify the expected number of subjects to be recruited in a CT, but you cannot include any additional MSC, as this is done via an AM (see section 4.2.).

8. After populating all the required fields, click on the padlock to lock the relevant section(s). Select the '**Check**' button on the top-right corner of the SM page to see if any required field has not been populated (the missing fields appear marked in red) . Examples of fields that may need to be updated are the 'Plan to share IPD' or the 'Estimated end date of the trial' in the 'Trial information' section. Lastly, select the '**Submit'** button.

9. Click on '**Confirm'** in the 'Submit confirmation' pop up window. In case of multinational SM Part I and II: **do not untick the 'Part I' tick box**: an SM part II cannot include more than one member state (see section 4.3.1.).



After submitting the SM application, the changes to the trial dossier will be indicated with a blue icon:



The SM will be evaluated by the MSC(s) after it has been submitted.

Notes from the List of known issues and workarounds:

- If an SM is created and submitted after an End of Trial notification took place for a particular MSC, that MSC will not be included in the assessment of the SM. If the **SM is created before the End of Trial notification but submitted after**, that MSC will still be included in the SM application. In such cases, it is advised to cancel the draft SM and create a new SM. This will ensure that the MSC where the trial has ended will not be included in the SM application.
- When submitting an SM to **restart a trial** after a temporary halt due to safety/risk-benefit reasons, make sure to **select the option 'Restart trial'** as reason for the SM.
- After an SM is submitted, while preparing a response to validation RFI, the **proof of payment** documents already submitted have **disappeared**. Please add the documents back in before submitting the RFI response.

- When creating an SM, make sure **not to untick the box** '*Do you wish to update the current information on the dossier?*'. If you untick this box, it will not be possible to make changes to documents or structured data, even in response to RFIs (see above step 2).
- When **deleting a draft SM***,* the next SM created will be assigned the next consecutive **number (+1)**. This is expected behaviour of the system and thus the numbers of the SM cannot be changed*.*

When creating an SM draft containing both Part I and Part II for a multinational trial, sponsor should not remove the Part I before submission: if this occurs, a single Part II application for multiple MSCs is generated, which is corrupted as it is not foreseen in the CTR: see section 4.3.1. . Where this occurs, the corrupted SM part II application involving multiple MSCs should be cancelled or withdrawn, and separate SM part II applications should be, instead, created and submitted in every MSC.

→ on this topic: watch also the video on How to submit a single trial substantial modification in the CTIS Sponsor workspace.

4.3.3. SM to extend the recruitment start date, SM to restart a trial and SM to extend the restart trial beyond 2 years

The below kinds of SMs are to be performed as **SM Part I & II** or an **SM Part II in the specific MSC(s):**

- **SM to extend the recruitment start date**: according to Article 8(9) of the CTR, a trial authorisation expires in an MSC if no subject has been included in that MSC within two years from the authorisation date, unless an extension of the recruitment start date via an SM has been authorised
- **SM to restart a trial**: in line with Article 38(2) of the CTR, in case of temporary halt for reasons of subject safety/benefit-risk balance, the sponsor needs to submit an SM to restart the trial, so that **a notification of a trial restart can be submitted in the relevant MSC** as per section 4.1. (within two years and 15 days from the temporary halt, see below note)
- **SM to extend the restart trial beyond 2 years**: according to Article 37(7) of the CTR, a trial that is in 'temporary halted' status and is not resumed within two years, is deemed as 'ended'. In line with the CTR Q&A, the sponsor can submit within the two-year period following a temporary halt an SM requesting that the restart date occurs after the two-year period.

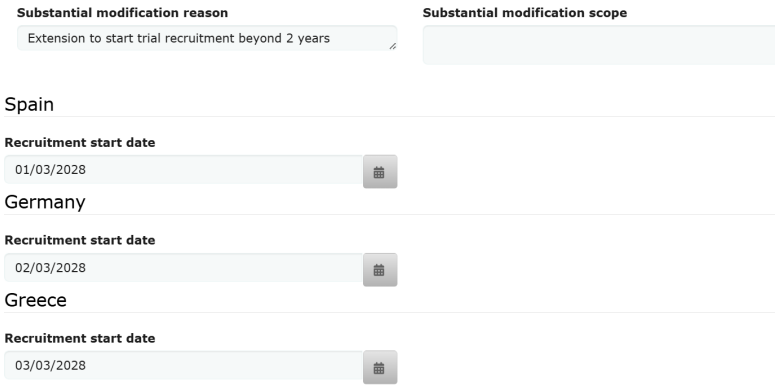
All the above SMs must be submitted well in advance, so that they can be **authorised by the 2-years deadline**. Note that an SM Part I-only cannot be used in these cases.

To perform an SM such as the one above, once logged into CTIS:

1. Perform steps 1 to 3 of section 4.3.2., selecting '**Part I & II'** or **'Part II'** as scope.
2. Proceed with step 4: in the 'Form' section, **select the relevant reason** (e.g. 'Extension to start trial recruitment beyond 2 years' , 'Restart of trial', or 'Extension to restart trial beyond 2 years') as the reason for the SM,
3. A new field appears per MSC(s)**:**
    - in case of the 'Extension to start trial recruitment beyond 2 years', insert the relevant **foreseen deadline of the start of recruitment** in the mandatory field 'recruitment start date'
    - in case of 'Restart of trial', insert the **anticipated trial restart date** in the mandatory field 'Anticipated trial restart date'

- in case of 'Extension to restart trial beyond 2 years', insert the relevant **deadline when the trial is foreseen to be restarted** in the mandatory field 'restart date'

Note in case of multi-national trials for SM Part I and Part II, this date must be filled in for at least one MSC.



4. Continue until step 8 of the instructions in section 4.3.2.

Once the SM on the extension of the recruitment start date, or on the extension of the restart date of the trial is authorised and the original two year deadline has passed, the trial remains 'Authorised' in the relevant MSC(s), allowing the sponsor to submit the 'Start recruitment', or 'Trial restart' notification as applicable. Note that the 'Start of recruitment' or 'Start of trial' date entered in the notification must be within the extension period authorised in the SM, while the notification can be submitted within the extension period granted, plus additional 15 days.

4.3.4. Substantial modification (SM) or Additional MSCs (AM) for a partial submission application

Sponsors cannot submit an SM for a partially submitted IN before Part II for all MSC(s) have been submitted and all MSC(s) have issued decisions. Similarly, the sponsor cannot submit any AM 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 AM applications can be submitted. Refer to section 2.5.1. and to the *CTIS Bitesize talk on Partial submitted trials*.

4.4. SM to change the sponsor

Detailed guidance on this type of SM is provided in the CTCG Guide for Change of Trial Sponsor, in the CTR Q&A (search for the relevant keywords), in the 'Frequently asked questions related to Clinical trials submitted under the Regulation EU 536/2014' available in the 'Key document list' section on the CTCG page and in the relevant CTIS bitesize talk.

In line with Annex IV of the CTR Q&A, sponsor users can submit an SM Part I to request the change of the sponsor ORG-ID, in order to **transfer the ownership of the trial** to a different sponsor **with a different legal entity**. This type of SM is the 'Part I only – change of sponsor' SM and is different from the 'Part I only' SM, where this change is not permitted. Also, in case the change regards only an address change but the legal entity remains the same, the sponsor can submit a NSM (see section 4.8.3.).

The change of sponsor SM is only intended to be used for the change of sponsor ORG-ID and **not for any other reasons**. In case the sponsor needs to include other changes to the CT dossier, an SM needs to be submitted (see section 4.3.) in addition to the change of sponsor SM, since this kind of SM does

not allow other changes to the CT dossier, and since the SM Part I does not allow changes to the legal entity of the sponsor. In addition, in case the change of sponsor substantially impacts other documents updates, a subsequent SM (Part I and/or Part II) should be submitted without undue delay: see CTCG Guide for Change of Trial Sponsor,

Below are presented the sections of the dossier that can be modified and completed through this kind of SM, that correspond to the only sections where the user will find a padlock (section 4.4.1.):

Form

- Documents to be uploaded (no placeholders allowed): 'Cover letter' (mandatory), 'Modification description' (mandatory), 'Supporting information documents', 'Proof of payment of fee'. Note: in case the IN of the relevant trial was submitted before 18 June 2024, the cover letter needs to specify that the Part I documents 'for publication' do not contain personal data/CCI.
- Structured data: 'Supporting information'.

The SM fields 'Reason' and 'Scope' are pre-populated and cannot be modified.

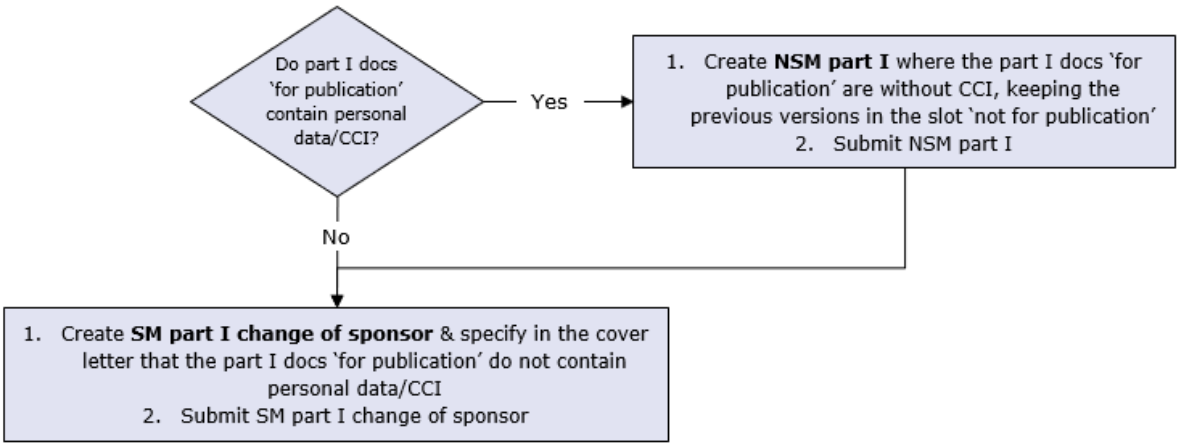
Part I - 'Sponsors' section

All the structured data fields in this section can be modified, including those dedicated to contact points. All filled in information is going to be publicly available, except for the Legal representative (if appointed, in case the sponsor is located outside of the EU/EEA). Contact details therefore need to be functional contact details and not personal contact details.

Note that the change of sponsor SM **does not allow replacement of Part I documents**.

Important: in case the trial is an **'historical trial'** (the IN was submitted before 18 June 2024), **and no part I documents were published yet, you need to review the Part I 'for publication' documents** to see if they contain CCI or personal data. If they do, **you need to submit first an NSM Part I** to update those documents so that they can be published (see section 4.3.), and then submit the change of sponsor SM.

For a trial submitted to CTIS **before 18 June 2024**:



The change the ownership of a trial is possible in case:

- The new sponsor is registered in OMS, see section 1.2.1.
- All documents uploaded in the 'for publication' document sections of Part I (see Table II of Annex I) can be published, even in case the trial was submitted before 18 June 2024 (see below).

- The trial is authorised by all MSC(s)
- There **are no draft SM, NSM, AM or ASRs** on the trial, **or ongoing evaluations** of these.
- There are no pending RFIs for Ad hoc assessments, Corrective measures, or ASRs (see sections 4.10. and 4.11.).

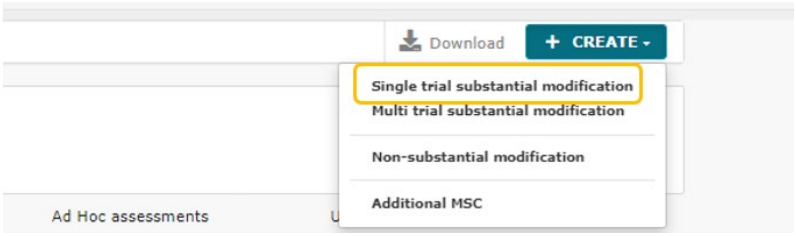
If all the above conditions are met, the sponsor can proceed with the change of sponsor SM as per the instructions below.

4.4.1. How to change the sponsor's legal entity

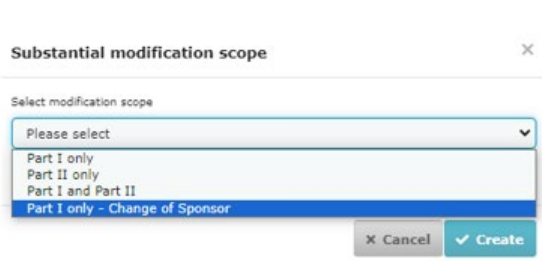
Sponsor users with the roles of **CT Admin** or **Application Submitter** need to follow the following steps to prepare and submit a request for sponsor ORG-ID change. Users with the role of **Part I Preparer (excl. Q-IMPD)** can perform steps 0 to 8 (they cannot submit).

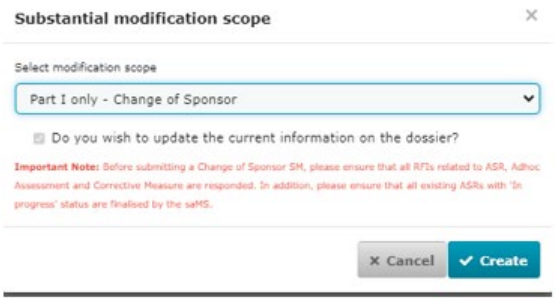
After having accessed the sponsor workspace and searched for the relevant CT (see section 2.6.1.) and selected the relevant CT (see section 2.6.2.):

1. In the 'Summary' subtab of the CT page, select the **'+ CREATE'** at the top right corner and choose "Single trial Substantial Modification".



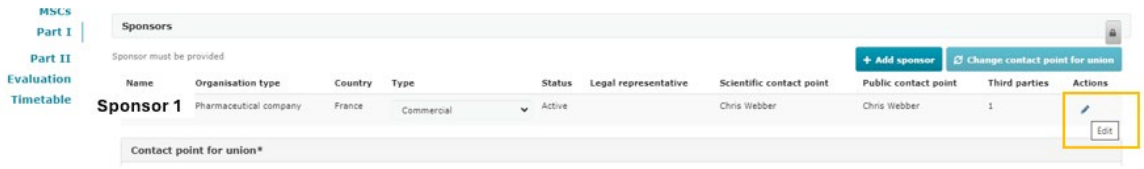
2. Select **'Part I only – Change of Sponsor'** from the dropdown menu. A red warning message appears. Note: the tick in box regarding the change of dossier appears checked by default and cannot be unticked, since the structured data for Part I/sponsor section will be modified).





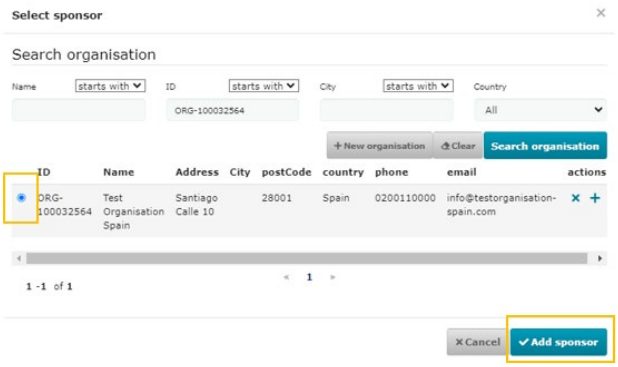
3. Click on 'Create' to create a draft of the SM application.
4. **Modify those sections** where you will find a padlock (Form: 'SM details' and 'Proof of payment fee' and Part I: 'Sponsors' sections) and upload the relevant **documents** ('Cover letter' and 'Modification description' are mandatory: see details above). See section 2.3. on how to use the common functionalities to complete the draft application before submitting it.

5. In the 'Sponsors' section, after having made sure that the new sponsor has an ORG-ID in OMS (see section 1.2.), click on the padlock at the top right. An **edit** button (pencil icon) appears on the right side of the ribbon that includes the main sponsor details.



6. Click on the pencil icon and search for the new sponsor's organisation in the pop-up menu. Once found, **select the correct organisation** from the search results, by using the radio button on the left side. The 'Add sponsor' button is activated.

7. Click on the '**Add sponso**r' button: now the details of the initial sponsor were overwritten with those of the new selected organisation, intended to be the new sponsor of the trial after the authorisation of this SM by all MSC(s). Details of the new selected sponsor are displayed in the structured data of the 'Sponsor' section in Part I.



8. Make sure that all other fields of the 'Form' section and of the 'Sponsors' section are correctly filled in.

9. Click on '**Submit'** and confirm the submission through the following two pop-up windows.

The actual change of sponsor will occur only after the authorisation of the SM by all MSC(s). Users need to take care of the role management prior the authorisation of the SM. **Roles under the initial sponsor will be rendered obsolete after the authorisation of the SM by all MSC(s).**

If the new sponsor follows the organisation-centric approach (see section 1.5.1.), the Sponsor Admin has access to the trial immediately after the authorisation of the SM by all the MSC(s). It is recommended that the Sponsor Admin of the new sponsor organisation **assigns roles** with scope "all trials" to other users **in advance to the approval** of the change of the sponsor SM by the MSC(s). In this way, once the change of sponsor SM is authorised, those users will be automatically granted with access permissions to this specific trial without any further intervention of the Sponsor Admin.

If the new sponsor organisation follows the CT-centric approach (see section 1.5.2.), i.e. no Sponsor Admin has been delegated), the initial sponsor user roles will be all revoked once the SM is approved. **CT Admin users of the initial sponsor** (those ones that were holding the CT Admin role before the authorised change of sponsor) need to **contact the EMA CTIS Service Desk** and request that the CT Admin role is assigned to a user that represents the new sponsor organisation, otherwise the ticket does not pass the EMA validation. The new sponsor's users cannot open this Service Desk ticket.

The evaluation of a Change of sponsor SM follows expedited timelines: see the CTCG Guide for Change of Trial Sponsor.

4.5. Withdraw a submitted SM or AM and resubmit it

The sponsor can withdraw an AM or an SM application by accessing the CT application and selecting the 'Withdraw' button. The sponsor must provide a justification. The withdrawal can only be done **before the MSC(s) have issued a decision**.

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

- For an **AM,** the withdrawal can be done separately for each MSC involved, before the decision has been issued, and it applies to the entire application (including Part I).
- In the case of an **SM Part I only** or **Part I and Part II**, the withdrawal applies to all MSC(s) if requested before Part I conclusion (reporting date). If Part I conclusion was already issued, then the withdrawal can only be done separately for each individual MSC.
- In the case of an **SM Part II only**, the application can be withdrawn from one or more MSC(s), at any point before the decision is issued.

Users should refer to section 2.7.1. for specificities and steps to follow.

4.5.1. Resubmitting a submitted AM or SM

Both SM and AM applications can be resubmitted by a user with a CT Admin role or an 'application submitter' role, bearing in mind the following principles:

- The **status** of the application to be resubmitted should be: 'Not valid', 'Withdrawn', 'Lapsed', 'Expired', or 'Not Authorised' (similarly to INs).
- The last submitted SM can be resubmitted if there is **no other SM in draft**. The same applies to **AM**.

Users should refer to section 2.7.2. for specificities and steps to follow. Note that, while an IN application can be resubmitted exclusively by a user with a CT admin role, an SM or an AM can also be resubmitted by a user with an 'application submitter' since no new EU CT number is created in those cases (see 'role matrix' in section 1.6.3.).

4.6. Evaluation of an AM

The evaluation of AM application includes an assessment of Part II and the Decision, since on Part I of the application a conclusion has already been reached. The additional MSC(s) will have access to Part I of the application and will be able to document considerations, which will reach the RMS. However, the assessment made by the additional MSC on Part I, and its Decision on the evaluation of the whole application will have no bearing on the Decision issued by the RMS and the other MSC(s) at the time of the evaluation of the IN. The evaluation of an AM application does not involve the Validation step. An explanation of the scope of each phase is provided in section 3.

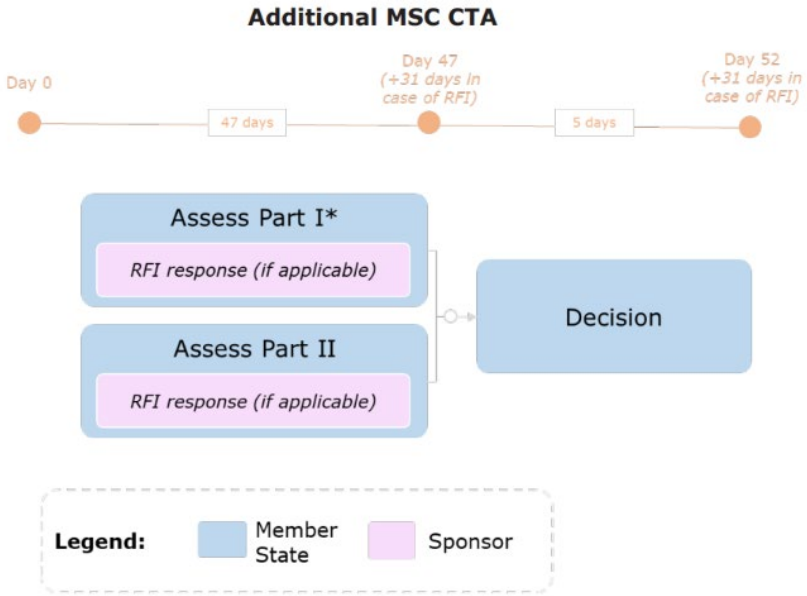
Refer to section 3.1. for general principles of the evaluation timelines in CTIS, that are valid for all application types.

The CTR establishes an **overall timeline of 52 days for the MSC(s)** to evaluate an AM application. This deadline **may be extended in case RFIs** are raised by MSC(s) throughout the evaluation process.

Timelines can be extended up to 31 days if RFIs are raised in the assessment phase. Multiple RFIs can be raised during the different phases of the evaluation process. However, it should be noted that when multiples RFIs are raised, each of them will have its own deadline, and the **overall timeline will be only extended once** (see image below for further reference).

The dates shown in the figure below **correspond to the maximum deadlines foreseen for each task/action**. However, the system includes a **dynamic workflow** by which, if a task/action is completed before its deadline, the corresponding deadlines for the following tasks are recalculated, but the maximum timeframes are still respected.

For more information on the AM evaluation process, refer to the Step-by-step guide of Module 08: How to evaluate an Additional Member State Concerned clinical trial application.

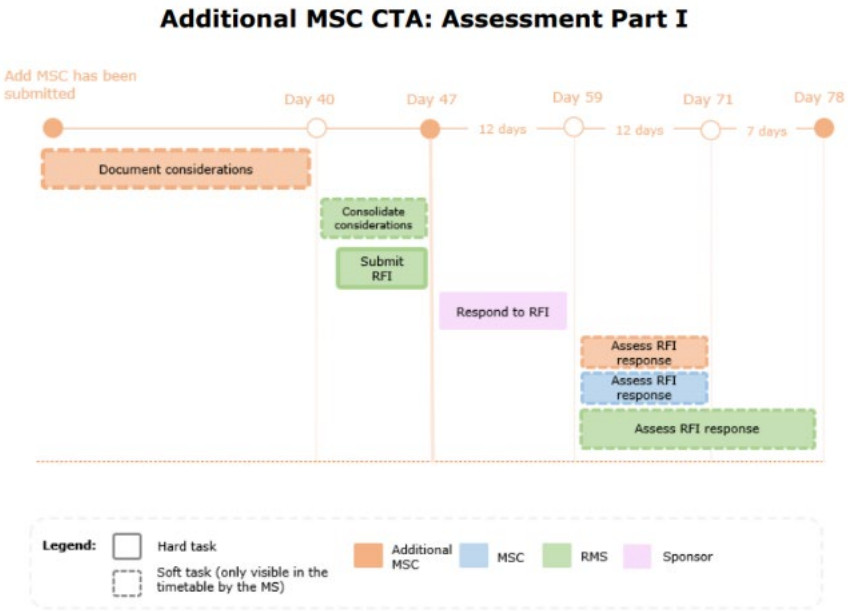


**Step in the process that may occur depending on the CT application submitted. For an AM application, users may raise considerations for Part I, but the Part I conclusion cannot be modified.*

Part I RFIs are allowed in an AM. Added MSC(s) can raise Part I considerations. The RMS will then consolidate them and submit an RFI, even though Part I assessment was previously concluded.

4.6.1. AM: Assessment of part I

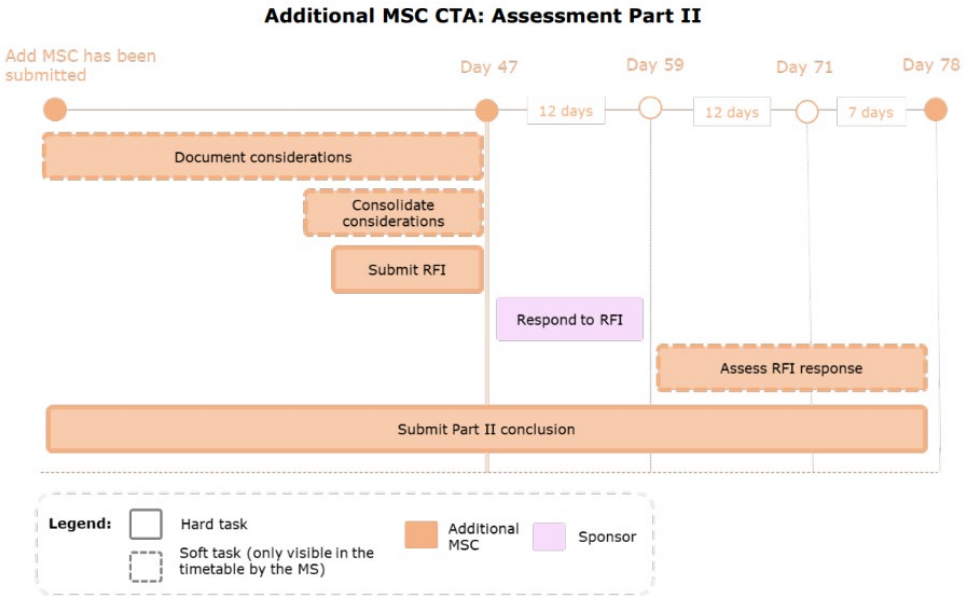
The **assessment of Part I** of an AM application can take **up to 47 days, or up to 78 days if RFIs are raised.** In case the sponsor does not respond to an RFI before the due date, it will cause the application to lapse (see image and table below for further reference).



Task or action	Deadline *(dynamic workflow)*
Additional MSC document considerations, *soft task*	Day 40 (day 0 + 40 days): up to 40 days from submission (having two consecutive working days and falling on a working day).
RMS consolidates considerations, *soft task*	Day 47 (day 0 + 47 days): up to 47 days from submission (having two consecutive working days and falling on a working day).
RMS submits RFI (if applicable), *soft task*	Day 47 (day 0 + 47 days): up to 47 days from submission (having two consecutive working days and falling on a working day).
Sponsor responds to RFI (if applicable), *action*	Day 59 (day 47 + 12 days): up to 12 days from the submission of the RFI.
All MSC(s) assess RFI response (if applicable), *soft task*	Day 71 (day 47 + 12 days +12 days): up to 12 days from the RFI response (having two consecutive working days and falling on a working day).
RMS assess RFI response (if applicable), *soft task*	Day 78 (day 47 + 12 days +12 days + 7 days): up to 19 days from the RFI response (having two consecutive working days and falling on a working day).

4.6.2. AM: Assessment of Part II

The **assessment of Part II** of an AM application can take **up to 47 days, or up to 78 days if RFIs are raised**. In case the sponsor does not respond to an RFI before the due date, it will cause the application to lapse (see image and table below for further reference).

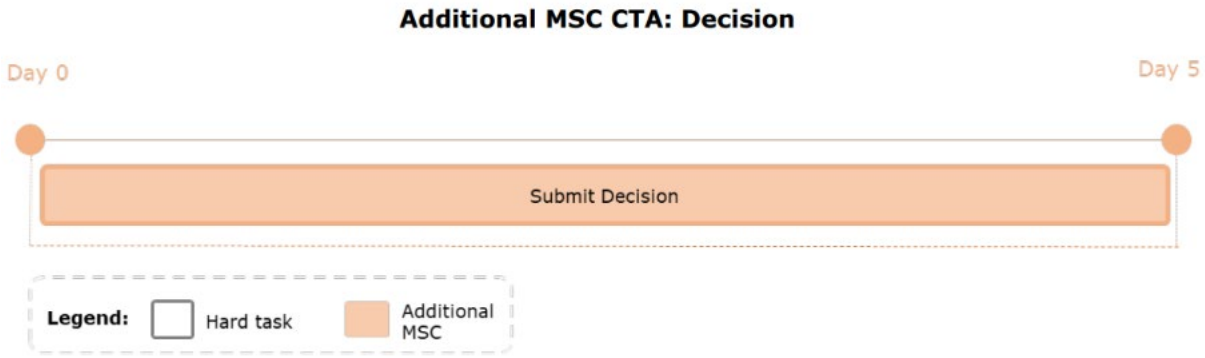


Task or action	Deadline *(dynamic workflow)*
Additional MSC documents considerations, *soft task*	Day 47 (day 0 + 47 days): up to 47 days from submission (having two consecutive working days and not falling on a non- working day).
Additional MSC consolidates considerations, *soft task*	Day 47 (day 0 + 47 days): up to 47 days from submission (having two consecutive working days and not falling on a non- working day).
Additional MSC submits RFI (if applicable), soft task	Day 47 (day 0 + 47 days): up to 47 days from submission (having two consecutive working days and not falling on a non- working day).
Sponsor responds to RFI (if raised by MSC), *action*	Day 59 (day 47 + 12 days): up to 12 days from the submission of the RFI.
MSC assesses RFI response (if applicable), *soft task*	Day 78 (day 47 + 12 days +12 days + 7 days): up to 19 days from the RFI response (having two consecutive working days and falling on a working day).
MSC submits Final Assessment Report (FAR) Part II and Part II conclusion, *hard task*	Day 78 (day 47 + 12 days +12 days + 7 days): up to 19 days from the RFI response (having two consecutive working days and falling on a working day).

4.6.3. AM: Decision

The **Decision** phase of an AM application can take **up to 5 days.** For this type of application, the timeline of the task 'Submit Decision' is not shortened if the previous hard task is completed earlier (in this case, the 'Submit Part II conclusion'), as it would happen in the cases of the IN and SM applications.

The due date for the '**Submit Decision'** in an AM application will be on Day **52 (47 + 5),** or day 83 (78 + 5) in case RFIs are raised during assessment phase, and will not change, regardless of an earlier completion of previous tasks occurs during the assessment.



Task or action	Deadline *(dynamic workflow)*
Additional MSC submits decision, *hard task*	Day 5: up to 5 days from the submission of Part II conclusion (having two consecutive working days and falling on a working day). If no conclusion has been submitted, the task is still triggered.

4.6.4. AM evaluation outcome

The AM assessment can have the following outcomes:

- **Lapsed**: during the evaluation phase any of the RFIs was not responded in time by the sponsor (as per MSC(s) deadlines, see section 3.3.)
- **Not authorised**: the assessment outcome is negative in the MSC(s) to which the AM was submitted, see section 3.1.7. ., based on any of the grounds specified in Article 14(4) of the CTR. After the receipt of the decision on the clinical trial**,** the sponsor has the right to **appeal** against the decision (refusal). The relevant MSC(s) shall provide an appeal procedure in respect of a refusal related to Article 14 (subsequent addition of a Member State concerned). In this situation, the respective national laws apply to each MSC.
- **Authorised with conditions:** the authorisation of a clinical trial is restricted to conditions which by their nature cannot be fulfilled at the time of the decision. Refer to the CTR Q&A to know what should be understood by 'conditions'.
- **Authorised**: the assessment outcome is positive in the added MSC(s), see section 3.1.7.

A full overview of trial/application statuses can be found in section 2.6.2.

4.7. Evaluation of an SM

The evaluation phases of an SM application include Validation, Assessment (Part I and/or Part II), and Decision. Note that some SM may concern only Part I, Part II, or both, depending on the scope of the modification. An explanation of the scope of each phase is provided in section 3. Refer to section 3.1. for general principles of the evaluation timelines in CTIS, that are valid for all application types.

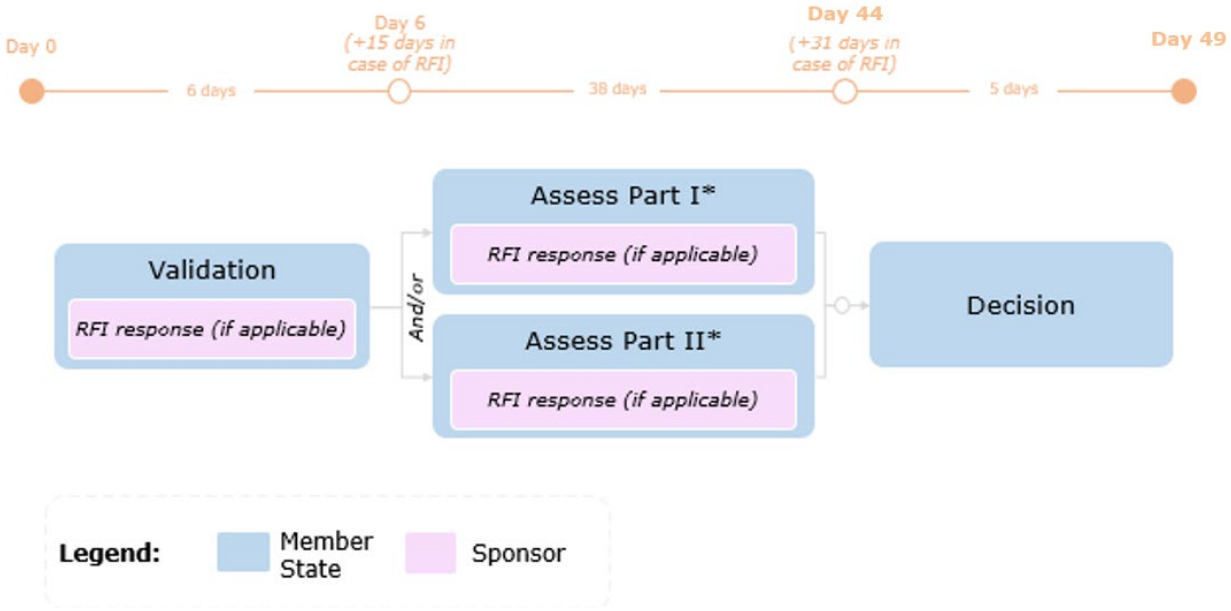
The CTR establishes an **overall timeline of 50 days for the MSC(s)** to evaluate an SM application. This deadline **may be extended in case RFIs** are raised by MSC(s) throughout the evaluation process.

Timelines can be extended up to 15 days for RFIs raised in the **validation phase** (10 days for sponsors to respond and 5 days for MSC(s) to review the response), **and up to 31 days** for RFIs raised **in the assessment phase**. Multiple RFIs can be raised during the different phases of the evaluation

process. However, it should be noted that when multiples RFIs are raised, each of them will have its own deadline, and the **overall timeline will be only extended once** (see image below).

The dates shown in the figure correspond to the **maximum deadlines foreseen for each task/action.** However, the system includes a **dynamic workflow** by which, if a task/action is completed before its deadline, the corresponding deadlines for the following tasks are recalculated, but the maximum timeframes are still respected.

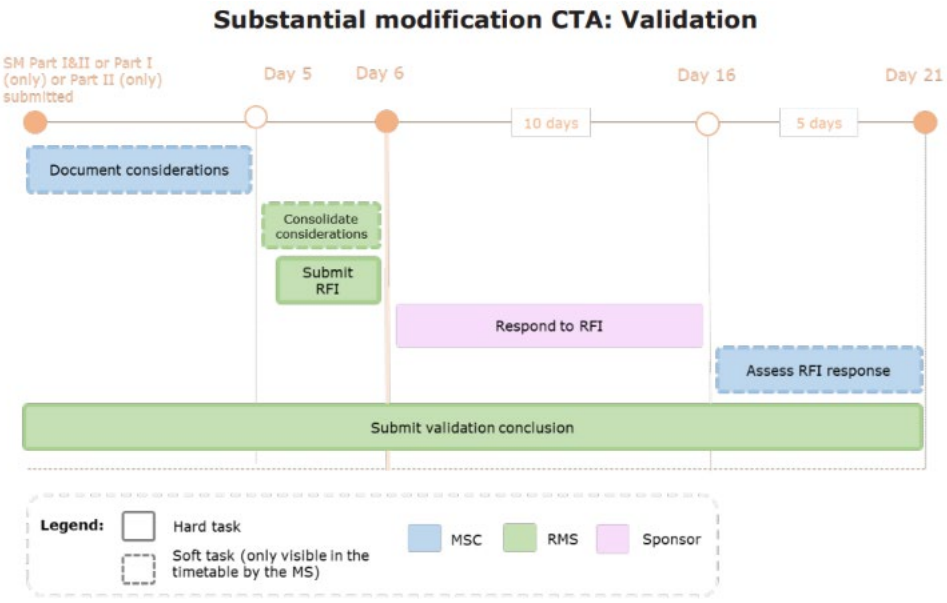
For more information on how the MSC(s) evaluate an SM, see: How to evaluate a Substantial Modification clinical trial application.



**Step in the process that may occur depending on the CT application submitted. An SM can include Part I and Part II, Part I only or Part II only.*

4.7.1. SM: Validation

The CTR establishes that the **validation phase** for an SM should take **up to 6 days**. This timeline can be further **extended by a maximum addition of 15 days if an RFI is submitted**. This deadline comprises an additional time for the sponsor to reply (10 days) and MSC(s) to assess the RFI responses (5 days). Sponsors need to check the deadlines given by the MSC(s) for responding the RFIs in the system, as MSC(s) can determine a shorter period for sponsors to respond to the RFIs. In case the sponsor does not respond to an RFI before the due date, it will cause the application to lapse (see image and table below).



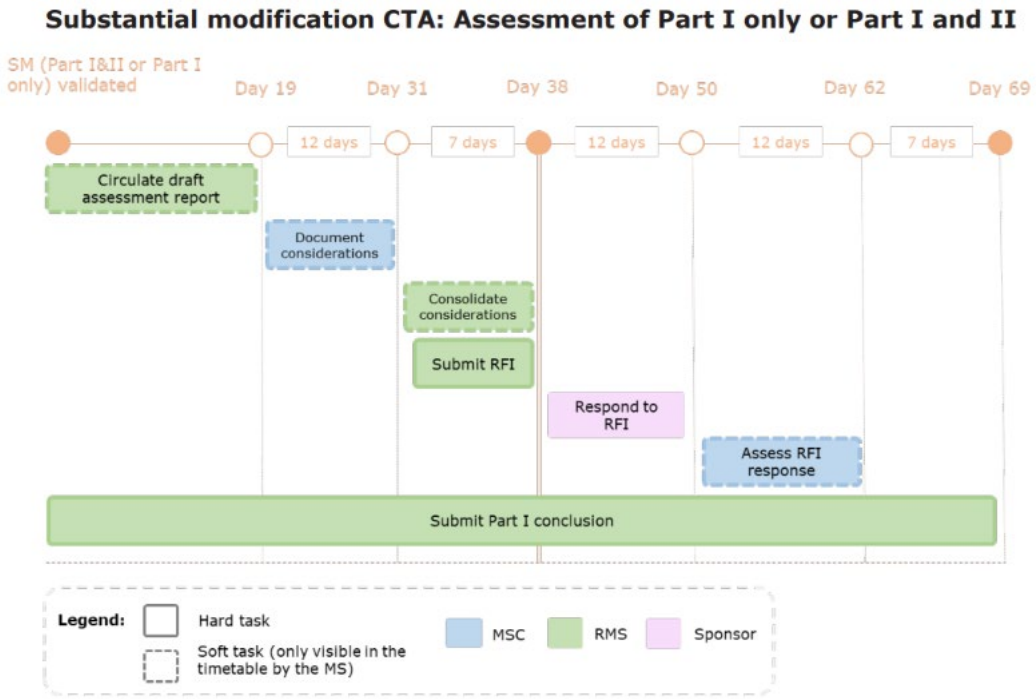
Note: In case of SM applications limited to Part II only, all tasks will be performed by the MSC.

Task or action	Deadline *(dynamic workflow)*
MSC document considerations, *soft task*	Day 5 (day 0 + 5 days): up to 5 days from the submission of an SM from the sponsor (having two consecutive working days and falling on a working day).
RMS consolidates considerations, *soft task*	Day 6 (day 5 + 1 day): up to 1 day from the 'Document consideration' task (falling on a working day).
RMS submits RFI (if applicable), *soft task*	Day 6 (day 5 + 1 day): up to 1 day from the 'Document consideration' task (falling on a working day).
Sponsor responds to RFI (if applicable), *action*	Day 16 (day 6 + 10 days): up to 10 days from the submission of the RFI.
MSC assess RFI response (if applicable), *soft task*	Day 21 (day 6 + 10 days + 5 days): up to 5 days from the date when the sponsor responded to an RFI, up to day 21 (having two consecutive working days and falling on a working day).
RMS submit validation conclusion, *hard task*	Day 6 or day 21 if an RFI is submitted: up to 1 day from day 5 (falling on a working day). Day 21 if an RFI is submitted.

4.7.2. SM: Assessment of Part I only or Part I and II

The **assessment of Part I** of an SM can take **up to 38 days**, or **up to 69 days if RFIs are raised.** In case the sponsor does not respond to an RFI before the due date, it will cause the application to lapse (see image and table below).

If the RMS does not complete the task 'Submit Part I conclusion' by the due date, Part I will remain labelled as 'No conclusion', and the overall application will remain 'Under evaluation'.



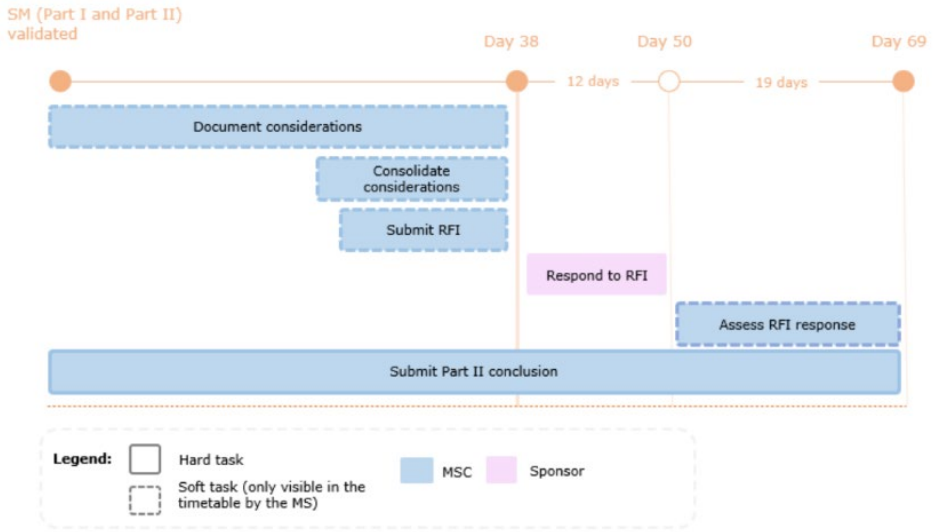
Task or action	
RMS circulates Draft Assessment Report (DAR) Part I, *soft task*	Day 19 (day 0 + 19 days): up to 19 days from the validation of the SM (having two consecutive working days and falling on a working day).
MSC document considerations, *soft task*	Day 31 (day 19 + 12 days): up to 12 days from the circulation of the draft assessment report (having two consecutive working days and falling on a working day).
RMS consolidates considerations, *soft task*	Day 38 (day 19 + 12 days + 7 days): up to 7 days from the document consideration task (counted in a staggered approach as stated and falling on a working day).
RMS submits the RFI (if applicable), *soft task*	Day 38 (day 19 + 12 days + 7 days): up to 7 days from the document consideration task (counted in a staggered approach as stated and falling on a working day).
Sponsor responds to RFI (if applicable), *action*	Day 50 (day 38 + 12 days): up to 12 days from the submission of the RFI.
MSC assess an RFI response (if applicable), *soft task*	Day 62 (day 38 + 12 days + 12 days): up to 12 days from the RFI response (having two consecutive working days and falling on a working day).
MSC submits Final Assessment Report (FAR) Part I and Part I conclusion, *hard task*	Day 69 (day 38 + 12 days + 12 days + 7 days): up to 7 days from the assessment of the RFI response (falling on a working day).

4.7.3. SM: Assessment of Part II

The **assessment of a Part II SM** can run parallel to the assessment of Part I and can take **up to 38 days, and up to 69 days if RFIs are submitted** to the sponsor (12 days for the sponsor to respond and additional 19 days for the MSC(s) to assess the RFI). In case the sponsor does not respond to an RFI before the due date, it will cause the application to lapse (see image and table below).

If the MSC does not complete the task 'Submit Part II conclusion', Part II of the application will remain labelled as 'No conclusion'. Nonetheless, the application will proceed to the Decision phase.

Substantial modification CTA: Assessment of Part II



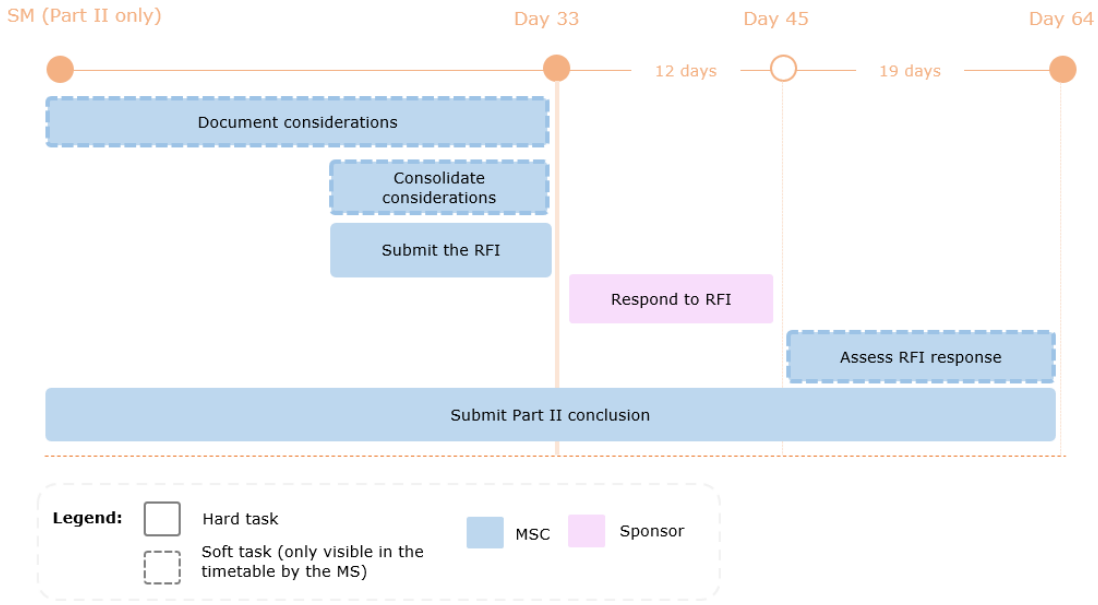
Task or action	Deadline *(dynamic workflow)*
MSC documents considerations, *soft task*	Day 38 (day 0 + 38 days): up to 38 days from the validation of the SM (having two consecutive working days and falling on a working day).
MSC consolidates considerations, *soft task*	Day 38 (day 0 + 38 days): up to 38 days from the validation of the SM (having two consecutive working days and falling on a working day).
MSC submits RFI (if applicable), *soft task*	Day 38 (day 0 + 38 days): up to 38 days from the validation of the SM (having two consecutive working days and falling on a working day).
Sponsor responds to RFI (if raised by MSC), *action*	Day 50 (day 38 + 12 days): up to 12 days from the submission of the RFI.
MSC assesses RFI response (if applicable), *soft task*	Day 69 (day 50 + 19 days): up to 19 days from the date when the sponsor responded to the RFI (having two consecutive working days and falling on a working day).
MSC submits Final Assessment Report (FAR) Part II and Part II conclusion, *hard task*	Day 38 or day 69 if an RFI is submitted (Day 0 + 38 days + 12 days + 19 days). Having two consecutive working days and falling on a working day.

4.7.4. SM: Assessment of Part II only

The assessment of a Part II only SM can take **up to 33 days**, **or up to 64 days** if RFIs are raised (see image and table below).

If the MSC does not complete the task 'Submit Part II conclusion', Part II of the application will remain labelled as 'No conclusion'. Nonetheless, the application will proceed to the Decision phase.

SM: Assessment of Part II only

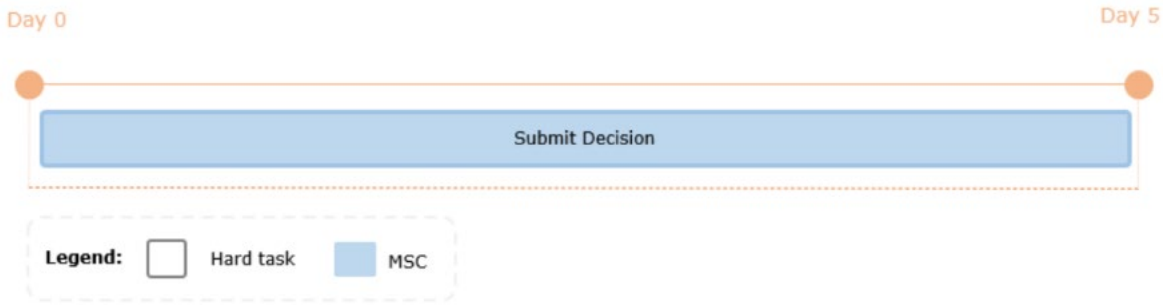


Task or action	Deadline *(dynamic workflow)*
MSC documents considerations, *soft task*	Day 33 (day 0 + 33 days): up to 33 days from the validation of the SM (having two consecutive working days and falling on a working day).
MSC consolidates considerations, *soft task*	Day 33 (day 0 + 33 days): up to 33 days from the validation of the SM (having two consecutive working days and falling on a working day).
MSC submits RFI (if applicable), *soft task*	Day 33 (day 0 + 33 days): up to 33 days from the validation of the SM (having two consecutive working days and falling on a working day).
Sponsor responds to RFI (if raised by MSC), *action*	Day 45 (day 33 + 12 days): up to 12 days from the submission of the RFI.
MSC assesses RFI response (if applicable), *soft task*	Day 64 (day 33 + 12 days + 19 days): up to 19 days from the RFI response (having two consecutive working days and falling on a working day).
MSC submits Final Assessment Report (FAR)	Day 64 (day 33 + 12 days + 19 days): up to 19 days from the RFI response (having two consecutive working days and falling on a working day).

Task or action	Deadline *(dynamic workflow)*
Part II and Part II conclusion, *hard task*	

4.7.5. SM: Decision

The **Decision** phase of an SM application can take **up to 5 days** (see image and table below).



Task or action	Deadline *(dynamic workflow)*
MSC submits decision, hard task	Day 5: up to 5 days from the submission of Part II conclusion (having two consecutive working days and falling on a working day). If no conclusion has been submitted, the task is still triggered.

Note: For SM Part II only, the due date is day 38 from validation conclusion (or day 69, in case of RFI) and the timelines will **not** be shortened if the previous task in the evaluation process ('Submit Part II conclusion') is completed earlier.

4.7.6. SM evaluation outcome

The SM assessment can have the following outcomes:

- **Lapsed**: during the evaluation phase any of the RFIs was not responded in time by the sponsor (as per MSC(s) deadlines, see section 3.3.).
- **Not valid**: the SM did not pass the validation phase of the MSC(s) assessment.
- **Not authorised**: the assessment outcome is negative in one or more MSC(s), see section 3.1.7. , based on any of the grounds specified in Article 23(2) of the CTR. After the receipt of the decision on the clinical trial, the sponsor has the right to **appeal** against the decision (refusal). The Member States shall provide an appeal procedure in respect of a refusal related to Article 20 (validation, assessment, and decision regarding an SM of an aspect covered by Part II of the assessment report) and Article 23 (Decision on the SM of aspects covered by Parts I and II of the assessment report). In this situation, the respective national laws apply to each MSC.
- **Authorised with conditions:** the authorisation of a clinical trial is restricted to conditions which by their nature cannot be fulfilled at the time of the decision. Refer to CTR Q&A to know what should be understood by 'conditions'.
- **Authorised**: the assessment outcome is positive in one or more MSC(s), see section 3.1.7.

A full overview of trial/application statuses can be found in section 2.6.2.

4.8. Create and submit a Non-Substantial Modification (NSM)

In line with Article 81(9) of the CTR, a **NSM is any change to the CT dossier that is not likely to substantially impact the safety or rights of the subjects, or the reliability and robustness of the data generated in the CT but is relevant for the supervision**. A NSM is not subject to evaluation by the MSC(s) and those changes performed as part of the NSM are applicable as of its submission date. Sponsors can submit NSMs to keep the information of the dossier up to date: **see examples of NSM 81.9 in Annex IV of the CTR Q&A**. NSM changes can also be provided as part of RFI responses in relation to other CT applications, where so required (see CTR Q&A). **In case of doubt** on whether a change should be submitted as an SM or as a NSM, **the sponsor shall consult the RMS/MSCs.**

Structured data and documents that are modified through a NSM are all **published in line with the CTIS Publication rules**, see section 2.1. When a NSM is submitted on a trial submitted before 18 June 2024 ('historical trial'), all documents that are subject to publication as per publication rules are published, see Table IV of Annex I to Guidance document on how to approach the protection of personal data and CCI while using the CTIS. This means that **the sponsor needs to make sure that all documents uploaded in the 'for publication' document sections are redacted of CCI and that their personal data are anonymised, including those documents that are not strictly in scope of the NSM**.

The detailed **list of structured data and documents that can or cannot be modified through a NSM** can be seen in column P of the CTIS application fields document. The scope can be Part I only, Part II only, or Part I and Part II (see more details below). After selecting the scope of the NSM, users need to add/edit the required information as applicable throughout the dossier.

Important: it is possible to update documents such as the protocol and synopsis through a NSM. Those updates should be in line with Art 81(9) of the CTR and should not be performed in place of an SM. It is the responsibility of the sponsor to assess whether a modification is to be regarded as 'non-substantial' and can therefore be submitted as NSM. Annex IV of the CTR Q&A, includes a non-exhaustive list of examples of modifications that should be regarded as non-substantial. This assessment is to be made on a case-by-case basis.

Documents and Structured Data Fields that may be populated with a NSM application type:

	Form	MSC	Part I[a]	Part II[a]
Document for upload			Documents	Documents
			Document translations	Document translations
Structured data field	Modification description	Number of subjects per MSC	Data[b]	Trial sites details update[c] Trial sites deleton[d]
			Data translations	PI contact details
			Third party entity	
			Sponsor contact details	
			Description of changes	

[a] *If there are any changes to the application dossier*

[b] *Structured data fields can be modified with limitations*

[c] *Trial sites details can be edited through a NSM. If the trial site is registered in OMS, a change request to OMS needs to be approved: see section 1.2.2. If the site is registered locally, the update can be done directly: see section 2.4.3.*
[d] *Trial sites cannot be added through a NSM, they need to be added through an SM.*

A sponsor can only submit a NSM under certain circumstances: refer to the table of section 4. A sponsor should **avoid creating draft application of NSM, when a draft application of any kind already exists**. This is because when a draft application is created, it copies the documents and data from the last authorised application: see section 4. (page 104).

4.8.1. Types and scope of an NSM

A NSM can include Part I and II, Part I only or Part II only. A NSM Part II can include multiple MSCs (this is different from the SM Part II, which can only include one MS at a time, see section 4.3.1.). A NSM cannot affect multiple trials (this is different from multi-trial SMs). In case a sponsor wants to apply non-substantial changes to multiple CTs, separate NSMs, one for each CT, need to be submitted.

A non-exhaustive list of examples of modifications that should be regarded as non-substantial is provided in **Annex IV of the CTR Q&A**: **in this Annex, changes that are classified as 'NSM' only (and not '81.9NSM') are to be submitted with the subsequent submission and do not need an ad hoc NSM for them.** With regards to the changes on the sponsor's name (without change of the legal entity), refer to section 4.8.3. .

→ on this topic: watch also the CTIS bitesize talk: Modifications.

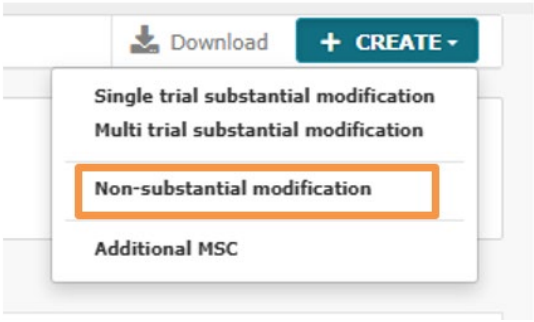
4.8.2. How to create and submit a NSM

The below steps can be performed by a user who has the following roles, depending on the action:

- Submit/cancel/withdraw a NSM: **CT Admin** and **Application Submitter**.
- Edit/draft a NSM: CT Admin, **Part I Preparer (excl. Q-IMPD), Part II Preparer, Q- IMPD Preparer,** and **Application Submitter**.
- Create a NSM and copy a NSM: **CT Admin**.

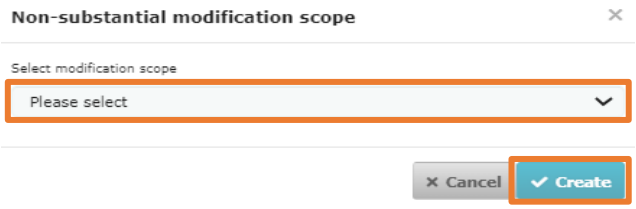
Before creating a draft application, ensure there are no other draft applications or applications under assessment for the same part of application (see section 4.). After having accessed the sponsor workspace and searched for the relevant CT (see section 2.6.1.) and selected the relevant CT (see section 2.6.2.):

1. Select the '+ CREATE' button at the top-right corner of the CT page and choose 'Non-substantial modification'.

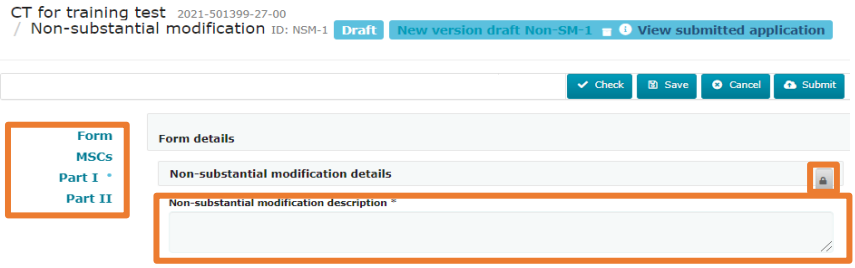


2. Confirm that are no other draft applications or applications under assessment for the same part of application (see section 4.)

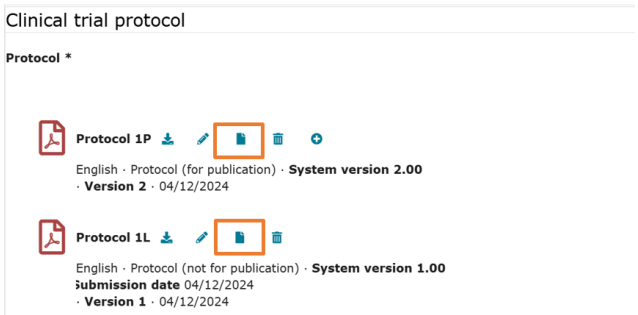
3. In the pop-up window, select the scope of the modification and can click on the 'Create' button.



4. In the 'Form' section, populate the field 'Non-substantial modification description' to describe what is being modified through the NSM (click on the padlock button to modify the fields). Note: a cover letter or a document on the NSM updates is not required (this is different from AM and SM applications).



5. **Populate all the relevant and required fields** of the sections 'MSCs', 'Part I' and 'Part II' through clicking on the padlock button in each subsection. The list of **structured data and documents that can be or cannot be modified through a NSM** can be seen in column P of the CTIS application fields document. Refer to section 2.3. to know how to populate each field and to the 'Notes' of step 4 of section 2.3.3. When updating an existing document, **click on the 'update' icon and not on the 'Add document' button** on the right, which should not be used to update already existing documents, but to add new documents which were not previously part of the dossier:

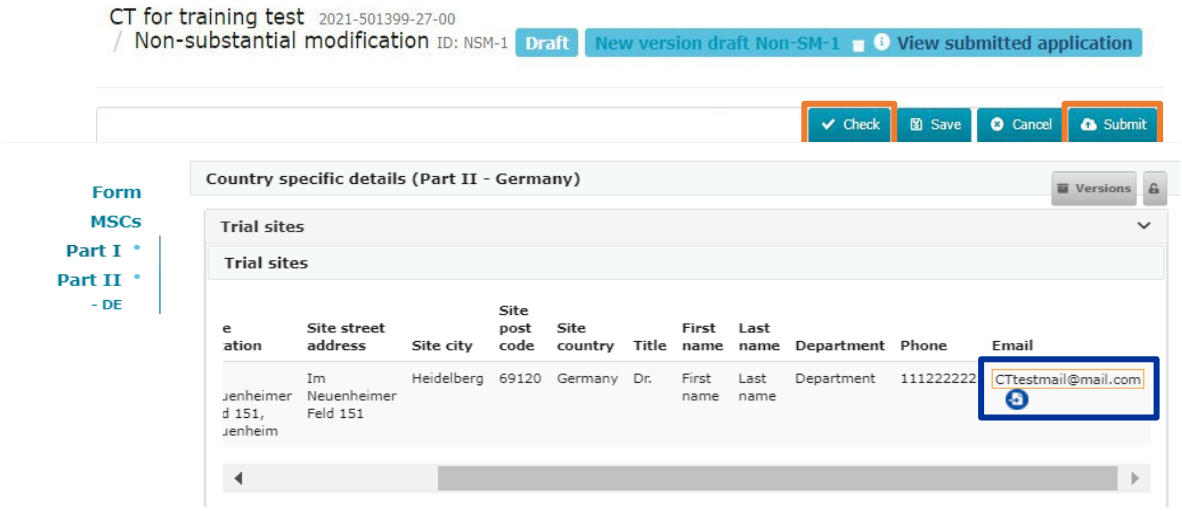


Additional 'not for publication' version(s) of the updated document can be uploaded through clicking on the '+' icon on the right of the relevant document (e.g. the track changes version from the document uploaded in the previous application, in addition to the clean 'not for publication' version which includes CCI).

6. You can include a description of the changes applied in the 'Section changes description' tile of the respective section. If your trial was originally submitted before 18 June 2024, **make sure**

all documents (including those ones that are not strictly in scope of the SM) do not contain CCI and are anonymised of personal data: see section 4.3. For steps on how to change sponsor details: see section 4.8.3.

7. After populating the fields, click on the padlock to lock the relevant section(s). Select then the '**Check' button** on the top-right corner of the CT application page. Examples of fields that may need to be updated are the 'Plan to share IPD' or the 'Estimated end date of the trial' in the 'Trial information' section. In case any information was unintentionally removed, the missing fields will appear marked in red. Lastly, select the 'Submit' button and click on 'Confirm' after agreeing with the confirmation text.



After submitting the NSM, changes to the application are indicated with a blue icon. A NSM is not subject to evaluation by the MSC.

4.8.3. NSM to update the sponsor details

As per column '81.9NSM' of Annex IV of the CTR Q&A, changes to the sponsors details that do not require a change of its legal entity can be performed through a NSM. This includes change of the sponsor's name, contact details, or address**. In case, however, the legal entity of the sponsor changes, a specific SM needs to be submitted**, refer to section 4.4.

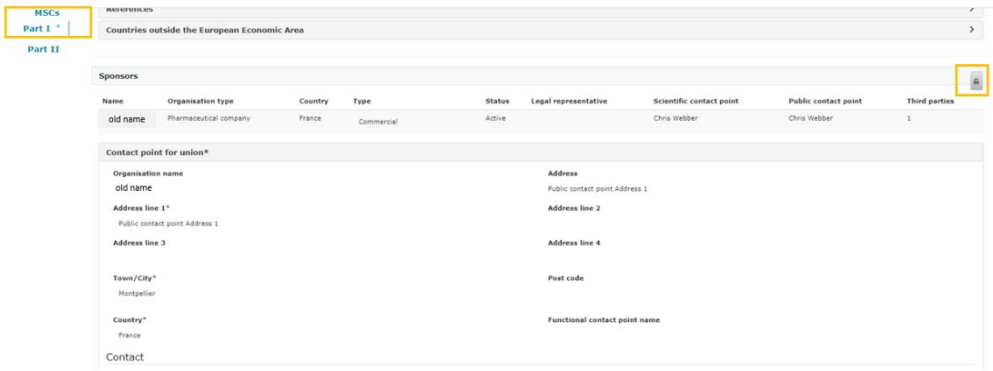
Before recording the changes in CTIS, sponsor users need to update the relevant OMS data by submitting a request to update the organisation details in OMS (see section 1.2.2. and document E - OMS Change Requests in OMS document repository). Following validation and approval of the change request by the OMS team, the sponsor can then start drafting the NSM by following the instructions below.

The below steps can be performed by a user who has the following roles, depending on the action:

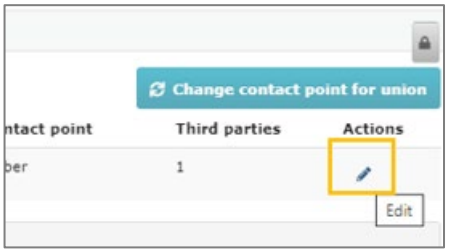
- Submit/cancel/withdraw a NSM: **CT Admin** and **Application Submitter**
- Edit/draft a NSM: **CT Admin, Part I Preparer (excl. Q-IMPD)** and **Application Submitter**
- Create and/or copy a NSM: **CT Admin**

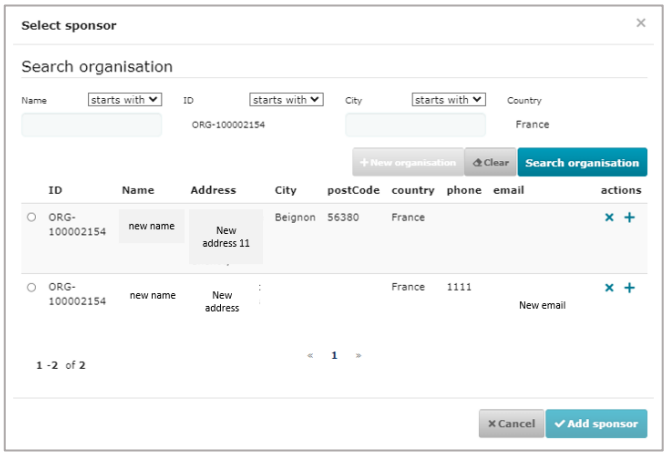
After having accessed the sponsor workspace and searched for the relevant CT (see section 2.6.1.), selected the relevant CT (see section 2.6.2.), and performed steps 0 to 5 of section 4.8.2. through either choosing a Part I only NSM or a Part I and Part II NSM (in case other changes in Part II are also performed):

1. Click on the 'Part I' section and click on the padlock of the 'Sponsors' section to edit it



2. After clicking on the padlock, click on the '**edit'** button on the right side of the ribbon that includes the main sponsor details, and a pop-up window appears where you can **search for the relevant organisation**. The fields 'ID' and 'country' are already populated and cannot be edited. Changes to these fields imply a change of legal entity, see section 4.4. You can use the non-mandatory fields 'Name' or 'City' to search for the organisation. If the OMS change request has been approved, the new entry with the updated sponsor details will appear in the search results.





3. Select the correct result using the radio button on the left, to activate the 'Add sponsor button'.
4. After clicking the 'Add sponsor' button, the updated sponsor details will overwrite the previous ones. Save the draft NSM and **submit** it.

After the change of the sponsor details is submitted in CTIS, **any new application**, ASR, Ad hoc assessment or Inspection that is created **will reflect the updated sponsor details**. Previous applications (or ASRs or Ad-hoc assessments), submitted before the change of sponsor information in CTIS, will keep the previous sponsor details and will not be impacted by the change.

4.9. *Notify on an Unexpected event, Urgent safety measure, Serious breach or a Third-Country Inspectorate Inspection*

Before applying the below instructions, the CTR Q&A (search for the relevant keywords) should be consulted, as well as the 'Frequently asked questions related to Clinical trials submitted under the Regulation EU 536/2014' available in the 'Key document list' section on the CTCG page. On serious breaches notifications, refer to Guideline on reporting serious breaches and Appendix III b – Information to be submitted with a notification of a serious breach, and look for the relevant notification's keywords in the CTR Q&A. For questions, refer to the relevant MSC(s) national contact point(s).

Besides the notifications listed in section 4.1. , other types of notifications are:

- **Unexpected event:** incident that might influence the benefit-risk balance of the medicinal product, or that would lead to changes in the administration of a medicinal product or in overall conduct of a clinical trial (e.g. a significant hazard to the patient population). Such notifications must be made without undue delay but **no later than 15 days** from the date the sponsor became aware of the event (Article 53 of the CTR).
- **Urgent safety measure:** where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor can take an urgent safety measure without awaiting prior authorisation by the MSC. The sponsor shall notify the measure without undue delay but no **later than 7 days** from the date on which the measures were taken (Article 54 of the CTR). If such a measure constitutes a temporary halt of the CT, it shall be notified within 15 days.
- **Serious breach:** on a breach that is likely to affect to a significant degree the safety and rights of one or more subjects, or the reliability and robustness of the data generated in the clinical trial. These notifications must be made without undue delay but **no later than 7 days** from the date on which the sponsor became aware of the breach (Article 52 of the CTR). Further guidance can be found in the CTR Q&A (search for the keyword 'serious breaches').
- **Third-Country Inspectorate Inspection:** on any inspection reports of third-country authorities concerning the CT. As per Article 53 of the CTR, the sponsor shall submit **all** inspection reports performed by third country authorities concerning the clinical trial. **This also includes inspections conducted after the trial has ended.** Further guidance can be found in the CTR Q&A (search for the keyword 'third-country Inspection Reports').

Notifications on Unexpected events, Urgent safety measures or on Serious breaches are published after MSC(s) assessment, with timelines depending on the trial category, see section 2.1. and Table I of Annex I to Guidance document on how to approach the protection of personal data and CCI while using the CTIS. The detailed list of structured data and documents that are, or are not subject to publication is specified in the list of CTIS fields on Notifications, ASR and Results. In essence:

- **All fields filled in by the sponsor are subject to publication: sponsor should not include CCI or personal data in any of those fields**.
- Any attached **document** is not subject to publication: **sponsors should not refer to the attached documents in the structured data fields,** otherwise the content of the fields would not be understandable once published.

These notifications can be removed from the CTIS public website only if the sponsor withdraws them, which is possible even after assessment (see steps below), as long as the MSC(s) agree with the sponsor that the notification can be withdrawn.

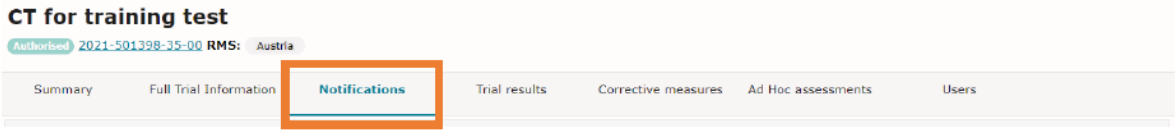
Third-Country Inspectorate Inspection notifications are never subject to publication.

→ on this topic: watch also the CTIS bitesize talk: Notifications - Part 2, and the second part of CTIS bitesize talk: Notifications including serious breach.

4.9.1. How to submit other types of notifications

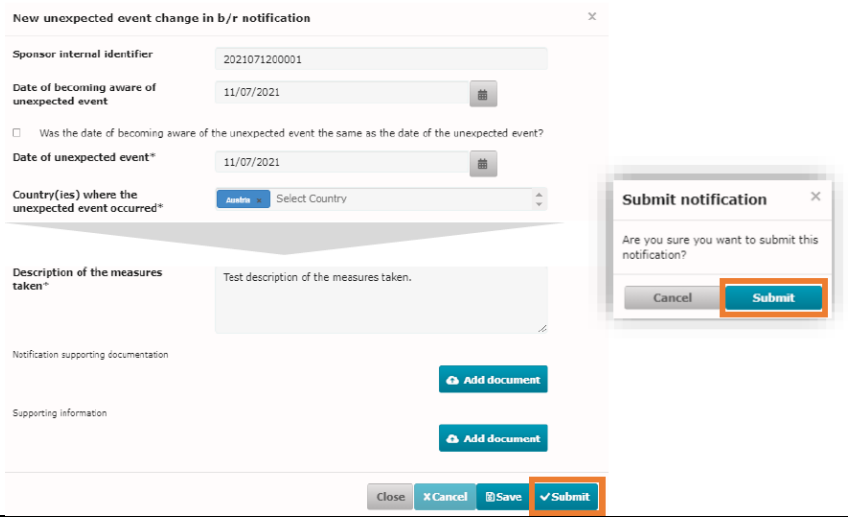
Below there are the steps that a sponsor user with the role of **CT Admin, a Notification Submitter** or **Notification Preparer** (who however cannot submit) can perform in order to insert a notification. After having accessed the sponsor workspace and searched for the relevant CT (see section 2.6.1.) and selected the relevant CT (see section 2.6.2.):

1. In a **CT page**, click on the **'Notifications' sub-tab**.



2. Scroll **below the 'Trial & Recruitment Periods'** notifications section and you will be able to see the other types of notifications. Click on the '**+ New**' button for the notification of interest.

3. Fill in the **details of the notification** to be submitted and upload any needed **document**. Data fields to be completed and documents to be uploaded can be seen in the list of CTIS fields on Notifications, ASR and Results. When filling in structured data, **since none of the uploaded documents is published, do not refer to them in the relevant structured data** (i.e. **do not write 'see pdf attached'**), otherwise it would not be clear on the CTIS public portal. Note: in the Serious breach notification, site details are taken from OMS (see section 1.2.) or from CTIS if the site was registered locally (see section 2.4.3. in case site details cannot be retrieved, one of those two routes of registration should be performed. In the example below, a notification of an unexpected event is shown.



4. When populating the pop-up form of a notification, you could also **save i**t as a draft before submitting it. Until you click on the 'Submit' button, the notification remains as a draft and is only visible to you and other sponsor users with appropriate role(s). At this stage, the draft notification can be modified through clicking on the pencil icon nearby. You could also delete the draft notification, through clicking on the 'Cancel' button.

5. Once the notification is ready, click on 'Submit' and then on 'Confirm'.

6. Once submitted, *if needed* **you can use the icons to perform various actions**: the **eye icon** to view the information of the notification, the **pencil icon** to update data (e.g. to correct errors, provide additional information, etc.) and the **cancel icon** to withdraw the notification. In order **to update a notification**, the pencil icon must be clicked. Afterwards, a pop-up will display the information populated when creating the notification. This allows the user to make the changes needed, including if there is an impact on subject safety and/or benefit-risk balance. Finally, the user needs to click on the 'Update' button. After updating a notification, a button to list previous versions will become available. Note that **only the latest version of a notification is published**. In case a published notification is modified upon its assessment, former versions are removed from public view.

6. *If needed,* **to withdraw a notification** following endorsement by the MSC(s), you need to click on the withdraw icon, provide a justification and confirm. Afterwards, the withdrawn notification will still be visible in the 'Notifications' sub-tab of the CT page, but it will no longer appear on the CTIS public website.

→ on this topic: watch also the video on How to manage a clinical trial in the CTIS sponsor workspace – Other notifications.

4.10. Respond to an RFI raised during an ad hoc assessment

Supervision by the MSC(s) of a clinical trial is foreseen in the CTR. An ad hoc assessment is the process that enables the Member States to discuss and assess information related to a submitted notification (temporary halt, serious breach, unexpected event, urgent safety measure), a suspected unexpected serious adverse reaction (SUSAR), safety of an IMP or class of IMPs (i.e. with a similar mode of action), or any other information relevant to the supervision of a trial. During this process**, a Member State can request additional information from the sponsor in the form of an RFI** and consult with other Member States.

MSC(s) can create, update and complete an ad hoc assessment through CTIS, or search, view, and download an ad hoc assessment that was already completed. The assessing Member State is the MSC that starts the ad hoc assessment and the discussion with other MCSs, and that can raise an RFI to the sponsor. The sponsor participates in the ad hoc assessment process only in case the assessing MSC raises an RFI.

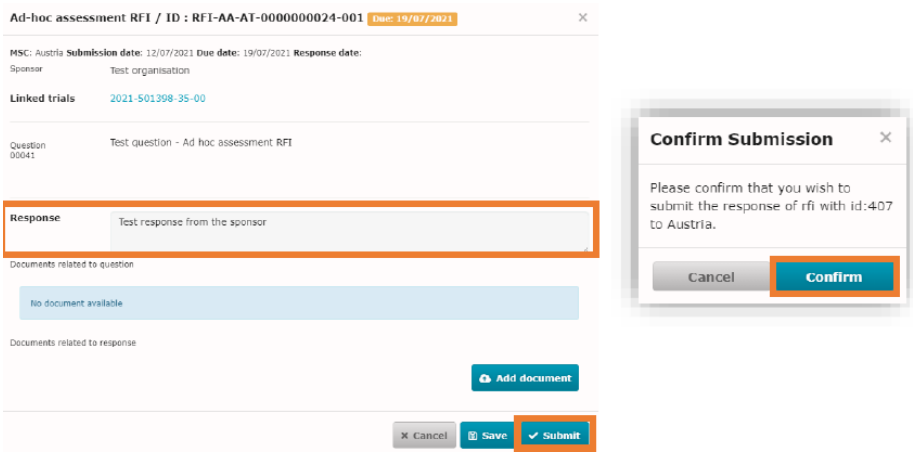
Once received, the sponsor needs to reply to the RFI as per deadlines given by the MSC(s). The **sponsor needs to proactively monitor the 'Notices & alerts' tab on a daily basis,** especially after submitting a notification of a temporary halt, serious breach, unexpected event, urgent safety measure or SUSAR, **or opt-in to receive email notifications** (see section 3.2.).

The ad hoc assessment submitted RFI and the corresponding responses are **not subject to publication**.

The below steps describe how a sponsor user with the **role of CT Admin, Notification Preparer or Notification Submitter** needs to respond to ad hoc assessment RFI through CTIS. **Note that the sponsor user receives the RFI and is able to perform the below steps only if the user has the above detailed role(s) for each of the trials that are linked in the Ad Hoc assessment** (e.g. if an ad hoc assessment is linked to two different trials, a user is able to perform the below steps if he or she has a CT Admin, a Notification Preparer or a Notification Submitter for both of the trials).

After having accessed the sponsor workspace:

1. Click on the 'Notices & alerts' tab and see the alert stating that an RFI has been received. Note: you only receive the RFI alert if you have appropriate role.
2. **Click on the alert** and display the RFI raised by the MSC(s) as part of an ad hoc assessment. Alternatively, you can access the **'RFI' tab** and click on the **RFI number**.
3. Once in the RFI, **review the comments** raised by the MSC(s) and any supporting documentation, if attached.
4. To answer the RFI, fill in the **respective details** in the pop-up window. Click on '**Submit**' and then select the 'Confirm' button in the pop-up window. In addition, supporting documentation can be provided in support of the responses. Note: **through the RFI responses provided as part of an ad hoc assessment, it is not possible for the sponsor to update the CT dossier**.



5. *In case of an ad hoc assessment RFI related to a notification*, the response submitted by the sponsor does not automatically update the notification. **If the notification requires to be updated, this needs to be done through a separate action** (see section 4.1. in case of temporary halt, or section 4.9. in case of other notifications).

Once the RFI is submitted, to access all the ad hoc assessments performed in relation to a CT and responses to the respective RFIs, you can click on the '**Ad Hoc assessments**' sub-tab on a clinical trial page and scroll down to the Ad-hoc assessment.

4.11. Respond to an RFI raised on a corrective measure

The corrective measure is a process defined in the Article 77 of the CTR, that allows the MSC(s) to **request a modification of a CT dossier or to modify its status to ensure compliance** of clinical trials with the requirements set out in the CTR, if the MSC considers that those requirements are no longer met. A corrective measure could be deemed necessary by the MSC(s) as a result of an ad hoc assessment, an inspection or a safety assessment, when becoming aware of additional information provided after the assessment conclusion, or after assessing a notification submitted by the sponsor (temporary halt, unexpected event, serious breach or urgent safety measure).

The corrective measure is therefore a supervision activity that is taken individually by each MSC. Both the RMS and the MSC(s)) can create and submit corrective measures in their territory regardless of their role. As part of the process, MSC(s) can consult each other or consult other Member States that are not part of the trial before taking any corrective measure. Depending on the measures taken by an MSC in case of non-compliance, a corrective measure can consist of:

- **Require modification**: if the MSC creates a 'Require modification' corrective measure and submits it, the sponsor is notified via the 'Notices and alerts' tab that an SM to the CT is required. This type has no impact on the trial status.
- **Suspend** (see section 2.6.2.): if the MSC creates a 'Suspend' corrective measure and submits it, the CT status changes to suspended (only for that MSC).
- **Suspend & Require modification**: if the MSC creates a 'Suspend & Require modification' corrective measure and submits it, the status of the clinical trial will be changed to suspended. The sponsor needs to submit an SM to address the changes required by the MSC (only for that MSC).
- **Revoke** (see section 2.6.2.): if the MSC creates a 'Revoke' corrective measure and submits it, the CT status changes to revoked (only for that MSC). In case the **overall status (i.e. applicable to all MSC(s))** of a CT changes to **'revoked'**, sponsor users need to populate the 'Anticipated summary of Results' date: see the bottom of this section.

The sponsor can refer to section 4.3. in case an SM is required as part of a corrective measure. The required SM needs to be evaluated by the one or all MSC(s) (e.g., if a Part I SM is required, it needs to be evaluated by all MSC(s).

The system also allows MSC(s) to cancel a draft corrective measure in case it is no longer deemed necessary by the MSC(s) (for example, after consultation with other MSC(s) or assessment of the sponsor's opinion, see below), by selecting 'No further action needed'.

The CTR foresees that the **MSC(s) shall request the sponsor's opinion before applying the corrective measure**, except where immediate action is required. That opinion shall be **delivered by the**

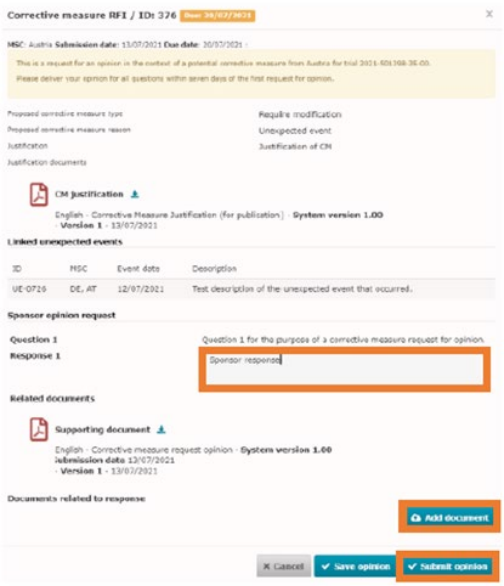
sponsor within 7 days. If the sponsor does not respond within the expected timeline, the MSC(s) can decide to apply the corrective measure. The sponsor receives an alert for any opinion raised as part of a corrective measure under the 'Notices & Alerts' tab. The **sponsor needs to proactively monitor the 'Notices & alerts' tab on a daily basis,** especially after receiving the outcome of an inspection or submitting a notification of temporary halt, serious breach, unexpected event, urgent safety measure or SUSAR, **or opt-in to receive email notifications.**

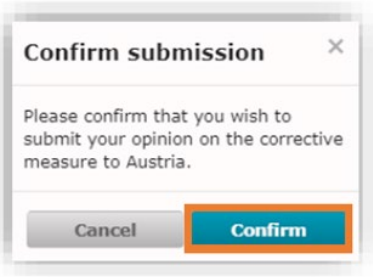
Only the corrective measure structured data **fields inserted by the MSC(s) are subject to publication**. The RFIs to request the sponsor's opinion on an intended corrective measures and the sponsor's responses are not subject to publication.

The below steps describe how a sponsor user with the **role of CT Admin, Notification Preparer or Notification Submitter** needs to respond to requests for opinion regarding corrective measures through CTIS.

After having accessed the sponsor workspace:

1. Click on the 'Notices & alerts' tab and see the alert stating that a 'Sponsor Opinion on a Corrective Measure' has been received. Note: you only receive the alert if you have appropriate role.
2. Access the **'RFI' tab** and click on the **RFI number**.
3. Once in the RFI, **review the comments** raised by the MSC(s) and any supporting documentation, if attached.
4. To answer the RFI, fill in the **respective details** in the pop-up window. Click on '**Submit opinion**' and then select the **'Confirm'** button in the pop-up window. Supporting documentation can be provided in support of the responses.



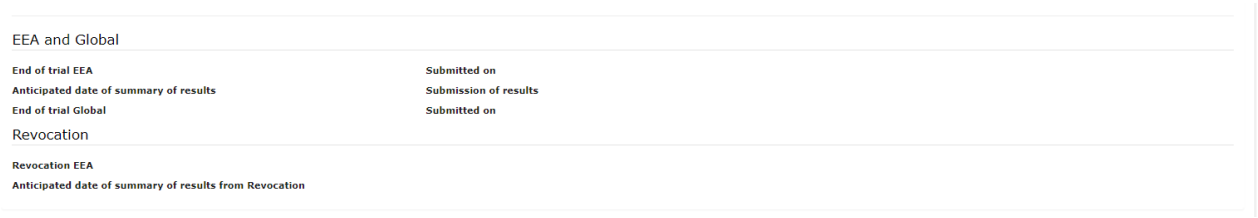


The MSC(s) will assess the answer and decide to apply or cancel the corrective measure, or if a new request is needed: in case the MSC is not satisfied with the sponsor's response, **the MSC may resubmit a request for opinion** to the sponsor through the corrective measure form.

To access the corrective measures that have been already applied, click on the 'Corrective measures' sub-tab on a clinical trial page. Here only corrective measures submitted (i.e. applied) are displayed. Note that an MSC may have requested an opinion to the sponsor but may not have applied any corrective measures yet.

When a corrective measure is updated, the system allows users to view previous version(s) via a button next to the eye icon.

Note: when the overall status (i.e. applicable to all MSC(s)) of a CT **changes to 'Revoked'** as a result of a Corrective measure, sponsor users need to **populate the field 'Anticipated summary of Results' date**. In the 'EEA and Global' section, the title 'Revocation' is displayed as in the image below:



The field 'Revocation EEA' is automatically populated with the date of revocation in the last MSC and the 'Anticipated date of summary of results from Revocation', is populated by default with a date set to 12 months after the revocation of the trial in the last MSC for adult trials or 6 months for paediatric trials. Sponsors can select the 'Update results date' button to update the 'Anticipated date for summary of results from Revocation', as applicable. Refer to section 5.2. for instructions on results submission.

4.12. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Refer to the information regarding reporting safety information on clinical trials that can be found on the EMA webpage. Search for the relevant keywords in the CTR Q&A (reporting of adverse events/adverse reactions). For questions, refer to the relevant MSC(s) national contact point(s).

As per Article 42.1 of the CTR, sponsors have the **legal obligation** for the electronic reporting of SUSARs through the clinical trial module of EudraVigilance (EV) for a CT performed in at least one Member State of the EU/EEA. As per section 1.3. **the EV registration is mandatory** for sponsors. Refer to the relevant page on planned training performed on EudraVigilance: see EudraVigilance training on electronic reporting of ICSRs. Where a sponsor, due to a lack of resources, does not have the possibility to report to EudraVigilance, and the sponsor has the agreement of the MSC, the reporting may be done to the MSC where the SUSARs occurred. That MSC shall then report the SUSARs to EudraVigilance (Art 42.3 of the CTR).

Note that sponsors are no longer required to report SUSARs directly to Member States, as was the case under the Clinical Trials Directive. **Sponsors should report SUSARs to EudraVigilance only**, regardless of whether the trial has been approved under the CTR or CTD. This allows a single submission process and harmonised procedures. Member states have the ability to set up SUSAR rerouting rules in EudraVigilance if they wish to receive copies of SUSARs for their national systems.

4.13. Submit an Annual Safety Report (ASR) and respond to ASR RFI

Before applying the below instructions, the following resources should be consulted: ICH E2F DSUR - Guideline, 'Clinical Trial Safety' section in the CTCG Key Documents list, search for 'ASR' on the CTR Q&A, the Commission Implementing Regulation (EU) 2022/20. For questions, refer to the relevant MSC(s) national contact point(s).

According to Article 43 of the CTR, sponsors shall submit annually a report on the safety of each IMP used in a trial, other than placebo. The ASR (formerly known as 'DSUR') is a document provided by sponsors to authorities regarding the monitoring and evaluation of the evolving safety profile of an IMP and mitigation of potential risks. The obligation of submitting an ASR starts with the first authorisation of a trial and it ends with the end of the last trial conducted by the sponsor with the concerned IMP. More information in the CTR Q&A. The sponsor is also responsible to **respond to the RFIs** raised by the MSC(s) or by the safety assessing Member State (saMS) on the ASR.

For a mononational CT, the assessment of the ASR is usually under the responsibility of the MSC. For a multinational trial, a saMS is nominated as the MSC that leads the safety assessment and assesses the ASR or, in some situations (e.g. academic trials), it is the RMS that assesses the ASR. For the purpose of this section, the ASR assessing member state is referred to as the saMS in all mentioned cases.

If applicable, the saMS can create RFIs after consolidating the MSC(s)' considerations regarding the draft assessment report. In addition, the saMS is expected to assess the ASR RFI responses from the sponsors and provide a finalised assessment of the ASR.

The ASR document, any ASR RFI and their structured data are **never published**. However, all Member States (also those that are not MSC(s) for the trials that are in scope of the ASR) have access to the submitted ASR information.

→ on this topic: watch also the CTIS bitesize talk: Annual safety report (ASR).

4.13.1. How to submit an ASR

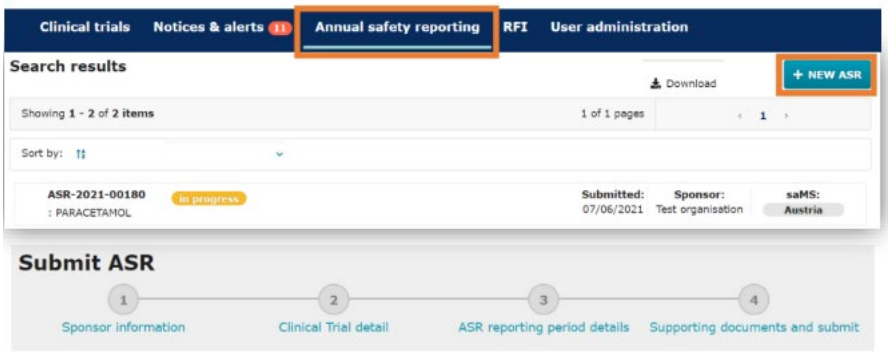
The below steps describe how a user with **ASR Submitter role** can create and submit an ASR for a trial. Note that:

- ASR Submitter users can only see the ASRs of CTs for which they have been given an ASR related role.
- CT Admin user does not have any ASR permissions to its role. To be able to perform ASR related activities, the CT Admin should assign the ASR Submitter role to him/herself.

Before proceeding, the ASR Submitter should make sure that there is no ongoing assessment of a 'change of sponsor' for the relevant trial(s) (see section 4.4.). In addition, the ASR Submitter should have the **ASR document** in PDF **prepared** to be submitted and **know all the relevant information to populate** the ASR submission form (e.g. Investigational medicinal products, relevant events that occurred, reporting period, etc), since **the ASR needs to be completed in a single session** (see below). Note that the maximum allowed size for the ASR document is 50 MB. A template for this document can be found in the 'Clinical Trial Safety' section in the CTCG Key Documents list.

After having accessed the sponsor workspace:

1. Open the 'Annual safety reporting' tab and click on the **'+ New ASR'** button.



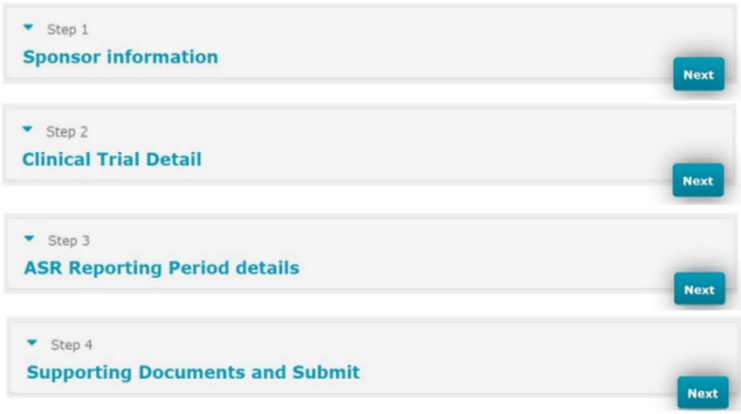
2. Fill in the mandatory fields of the ASR submission form (see full list of fields in the document CTIS fields on Notifications, ASR and Results). Those fields are grouped into four steps, see below. Note that neither the ASR submission form nor the relevant RFI responses can be saved during their completion and before submission. Therefore, they **have to be filled in and submitted in one session, otherwise the information already populated will be lost**. The 'Clear' button allows erasing the information populated on the form and start over without closing the form. The 'Cancel' button allows the user to erase the information populated on the form and go back to the ASR tab. The following four steps need to be completed in this step:

   a. **Sponsor Information ('Step 1')**: select the sponsor organisation to include the organisation details and the contact details for ASR submission.

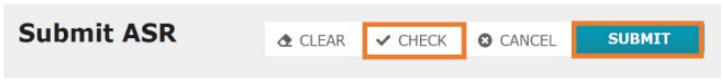
   b. **Clinical Trial Detail ('Step 2')**: add here those trials that are in the scope of the ASR and select the IMP(s) and any AxMP of interest from the clinical trial selection. **Search and add trial(s)** to which the ASR is applicable through searching the relevant IMP in all the authorised trials for which you have an ASR Submitter role. Note that CTs that are not authorised will not be retrieved. From the list, users can select all the trials related to the ASR, which can involve multiple IMPs. After the selection of trials involved in the ASR, **you must also select at least one IMP per trial**. You can also add more than one AxMP per trial by clicking on the respective button below the IMPs. An ASR can be related to **more than one trial**, as well as to **more than one IMP, and can involve more than one MSC**. If you want to search by multiple MSC(s) in the search functionality, you can keep the 'CTRL' key pressed on your keyboard, click on the Member States, and then launch the search. From that list, you can select all the trials related to the ASR.

   c. **ASR Reporting Period details ('Step 3')**: add the ASR data lock point, the reporting period, what the ASR includes, and other relevant reporting period details. You need to specify here if any events occurred during the reporting period of the ASR. Question 'Substantial Modification on RSI submitted and approved during the reporting period' refers to section 'Changes to Reference Safety Information' of the relevant ICH guideline E2F on DSURs. A drop-down list allows you to select one or more of the following values: 'Novel combination', 'New combination', 'First in class product/IMP (in EU)', 'Advanced therapy medicinal product (ATMP)', 'New signals or concerns or risk for the product', 'Temporary halt or suspension of any trial due to safety reason', 'Premature ended trial/s', 'Unexpected event changing benefit risk of any trial', 'Substantial modification of protocol or IB for risk mitigation any trial', 'Refused approval due to safety reason', 'Serious breach safety related or impact on safety' and 'Urgent safety measure'. Definitions of 'Novel-Novel Combination' and 'New Combination' can be found in Annex I: acronyms and definitions (see ASR section).

d. **Supporting Documents and Submit ('Step 4')**: upload the ASR document (only PDF file types are allowed), as well as any relevant supporting documents in PDF format (i.e. SmPC, IB etc.). None of the uploaded documents in this section is subject to publication.



3. Once all fields are completed and documents are uploaded, scroll up to the top of the form and click on the '**Check'** button to test if the form is complete and then click on '**Submit'**



An **ASR ID code is created once the ASR has been submitted.** The ASR ID code is the unique identification number of the ASR that can be used, for example, to search for it using the basic search functionality of the 'Annual safety reporting' tab. The ASR ID is a composition of unique details separated by a hyphen: 'ASR' Acronym, Year of submission and Sequential number of ASRs created (e.g. ASR- 2024-00001).

You can access a submitted ASR by clicking on the 'Annual safety reporting' tab, where you can see a list of all the ASRs submitted by the sponsor (where the sponsor user has the ASR Submitter role). To retrieve a specific ASR, you can use the basic or advanced search and then click on 'Search ASRs'. Note: **when searching for an ASR ID**, the search needs to be performed **without the ASR prefix** ('2024-12345' instead of 'ASR-2024-12345'). Users can then click on the ASR ID on the search results list to open the ASR page. In addition, through clicking on the 'Download' button on the top right side of a search results list of the 'Annual safety reporting' tab, you can download all the results from the search results list in a spreadsheet file type.

→ on this topic: watch also the video on How to create, cancel or clear, and submit an annual safety report.

Note from the List of known issues and workarounds: CTIS users may encounter issues during the submission of ASRs for trials under those OMS ORG-IDs which were deleted in OMS (since they were identified as duplicates, see 22/12/2023 Newsflash). In this case you need to submit ASRs for trials under deleted ORG-IDs, you need to submit a SM to change the sponsor of the trial to a valid ORG-ID (see section 4.4.). After the full authorisation of the change of sponsor SM, you can proceed with ASR submission. .

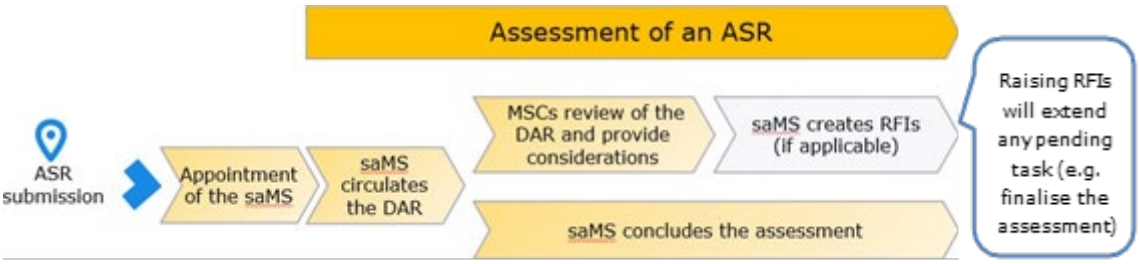
4.13.2. Assessment of the ASR by the saMS

A submitted ASR can have three possible statuses:

- ASR submitted: the ASR has been submitted, but the assessment has not started (i.e. the saMS appointment process is ongoing).

- ASR Assessment in progress: the saMS has been appointed and the assessment is ongoing.
- ASR Assessment completed: the assessment has been finalised.

After the sponsor submits an ASR, the appointment of the saMS process starts (in case the ASR involves multiple MSC(s)). Once appointed, the saMS can start the assessment tasks of the ASR. The saMS can decide to extend, only once, some of the tasks related to the ASR assessment.



During the assessment of the ASR, the **saMS could submit an RFI to the sponsor, which results in an extension of the deadline for finalising the assessment**. This generally happens once the saMS has circulated the ASR Draft Assessment Report (DAR) among the MSC(s) and the process of consolidating considerations is completed.

According to the implementing regulation member states should conclude the ASR assessment within 42 days or 84 days in case an RFI is raised. Currently, there is no technical restriction in CTIS that limits when the saMS may issue RFIs during the ASR workflow.

4.13.3. How to respond to RFIs raised by the saMS on an ASR

When the saMS creates an RFI, the **due date** for the sponsor to respond to the ASR RFI **is set automatically to 14 days**. However, the saMS could also reduce the deadline before submitting the ASR RFI to the sponsor. The ASR Submitter receives an alert for any RFI raised as part of an ASR assessment under the 'Notices & alerts' tab. The **ASR Submitter** needs to **proactively monitor the 'Notices & alerts' tab on a daily basis** after submitting an ASR, or opt-in to receive email notifications (see section 3.2.). In addition, the ASR Submitter should notice **the due date** of the ASR RFI. The ASR Submitter user could access the ASR RFIs through either the 'Annual safety reporting' tab, the 'RFI' tab or the 'Notices & alerts' tab. Note: the ASR Submitter **is the only role** that can view an ASR RFI and reply to it (not even the CT Admin can see if an RFI was submitted on one of their trial's ASRs), see section 4.13.1.

Below there are the steps that sponsor user with **ASR Submitter** role should follow to access and submit responses to RFIs created by the saMS in the context of the ASR assessment.

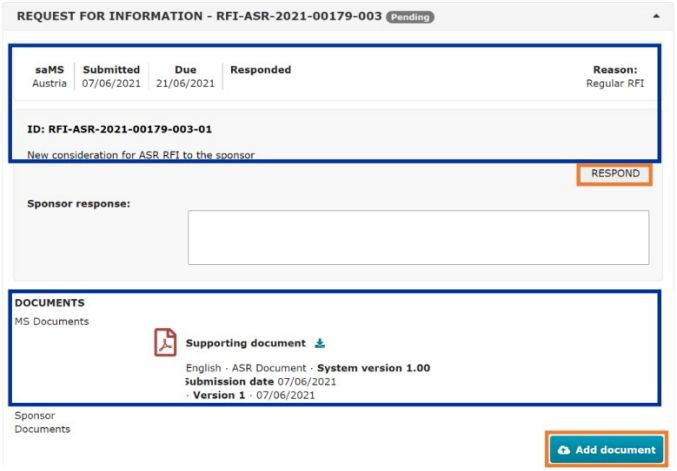
After having accessed the sponsor workspace:

1. **Check for an alert** in the 'Notices & alerts' tab, the 'RFI' tab, or the 'Assessment' sub-tab of an ASR page of the 'Annual safety reporting' tab.

2. **Click on the alert** and then expand the RFI to show the details, such as considerations submitted by the saMS and any supporting documents.
3. **Review** the requested RFI details and documents.

4. Write a response to each consideration in the field 'Sponsor response' in the considerations section of an ASR RFI by clicking on the '**Respond'** button on the right side of each consideration. In the same way as the ASR form, **an RFI response cannot be saved before the submission**. Therefore, it has to be populated and submitted in one session.

5. Upload any supporting document through clicking on '**Add document**' (only PDF format is allowed) and classify it by using the 'Type' drop-down list (i.e. 'Additional document', 'ASR document', 'IB', 'Protocol', 'Sponsor Discussion Response Supporting Document', 'SmPC'). It is possible to add more than one document, if necessary. Note: **submitting a new document (e.g. a new ASR document) as an ASR RFI supporting documentation does not replace the original document, neither create a new version of it.** To replace it, the already submitted ASR needs to be deleted, and a new one needs to be uploaded. To access the new documents, both sponsor and authority users will need to go to the ASR RFI response section on the 'Assessment' sub-tab of an ASR page.



6. Tick the checkbox to agree with the ASR RFI response submission statement and click 'Submit'

An **ASR RFI ID code is created. It is different to the above-mentioned ASR ID**. The ASR RFI ID code is a unique identification number for the RFIs received in the context of an ASR, which can be used, for example, to search for it using the basic search functionality in the RFI tab. The ASR RFI ID is a composition of unique details separated by a hyphen: Acronym, Year of submission, Sequential number of ASR created, Sequential number of the RFI, Sequential number of each consideration (e.g. RFI-ASR -2024-00001-001-01).

The ASR RFI response from a sponsor **follows an assessment process** similar to the responses to other types of RFIs (see section 3.3.). An ASR RFI response is assessed by the **saMS**, which has the responsibility to **perform an assessment of the ASR RFI response**. The saMS can reply to each sponsor response individually and after the saMS has assessed the response, the MSC(s) can comment on the assessment of the ASR RFI response made by the saMS.

When the assessment is completed by saMS, the status of the ASR changes from 'Under assessment' to 'Finalised'. The ASR assessment tab includes a field with the final summary and conclusion of the saMS. This section is visible once the assessment is complete.

→ on this topic: watch also the video on How to search and view an annual safety report (ASR), and respond to requests for information (RFIs) received during the ASR evaluation.

End of chapter: jump to Clickable table of contents.

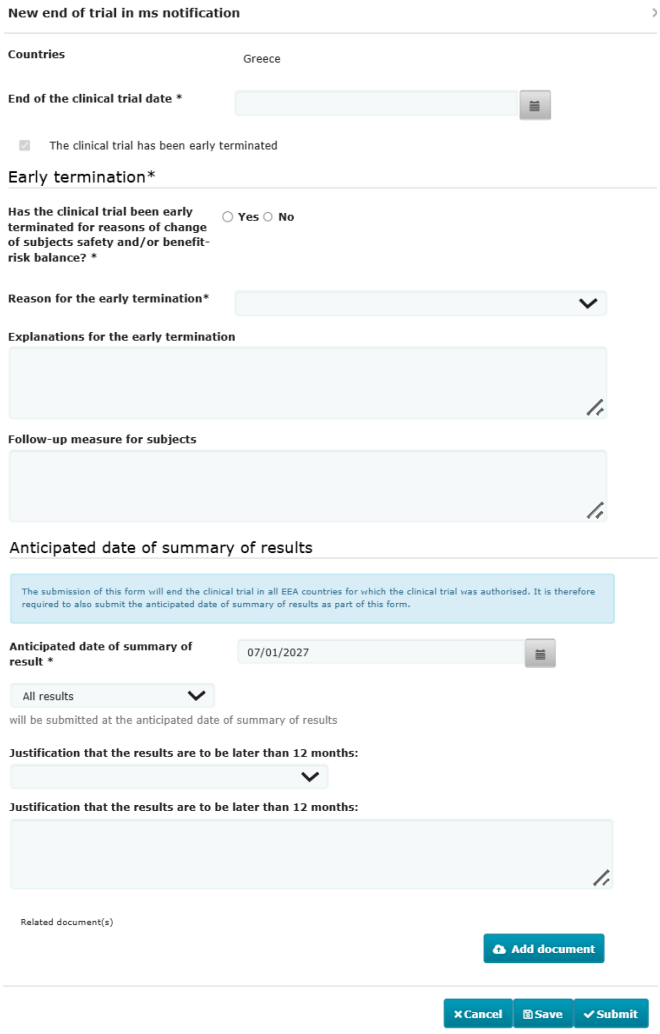
5. End the clinical trial and submit results

Note: the Sponsor FAQs includes further guidance on the topics of this chapter.

5.1. Notify the end of a CT

Within 15 days from trial end or early termination, the sponsor needs to submit the relevant notification, see section 4.1. for instructions and refer to 'end trial', 'global end of trial' and 'early termination' notifications.

When submitting the end of trial notification, *in case there is going to be a delay in the submission of results* the sponsor is responsible to notify regarding it in the field 'Anticipated date of summary of results', through filling in both of the fields 'Justification that the results are to be later than 12 months:' (or 6 months, in case of paediatric trials).



5.2. Submit interim results, summary of results and layperson summary

Before applying the below instructions, the following resources should be consulted: documents on results submission listed in 'Chapter V - Additional documents' of the EudraLex Vol. 10 guidelines, relevant questions in the CTR Q&A (search for the keyword 'results') and in the 'Frequently asked questions related to Clinical trials submitted under the Regulation EU 536/2014' available in the 'Key document list' section on the CTCG page. For questions, refer to your MSC(s) national contact point(s).

Details on the submission of results documents and relevant publication are provided in the list of CTIS fields on Notifications, ASR and Results.

Important: Article 37(4) of the CTR states that, irrespective of the outcome of a clinical trial, the sponsor must submit to CTIS a summary of the results of the trial, which shall always be accompanied by a summary written in a manner that is understandable to laypersons (people without expert knowledge). When defined in the protocol, an intermediate summary of results (also called 'interim results') should also be submitted. Further guidance on this topic is provided in the CTR Q&A (look for keywords 'results' and 'intermediate data analysis').

5.2.1. Timelines of submission

Summary of results and layperson summary of results need to be submitted within **one year** from the end of a clinical trial in all EU/EEA Member States concerned. For a trial in **paediatric** population (subjects aged from 0 to 17 years) and/or if the clinical trial is part of a paediatric investigation plan, the deadline for submitting the summary of results is shortened to within **six months** from the end of a clinical trial in all EU/EEA Member States concerned.

Where it is not possible to submit the summary of results within the defined timelines, for example when the CT is still ongoing in third countries and data from that part of the trial are not available, which would make a statistical analysis not possible, the **sponsor should justify this in the protocol** and specify when the results are going to be submitted. In addition, this date needs to be mentioned in the field in the 'Anticipated summary of Results' date, when filling in the End of trial date for all Member States, see section 4.1.1. In addition, the sponsor should indicate the expected end of the trial date when filling in the IN (see table in section 2.2.). Also, when the overall status of a clinical trial changes to 'Revoked' after a corrective measure is applied, the sponsor should indicate the 'Anticipated summary of Results' date, see section 4.11.

If the CT protocol provides for an intermediate data analysis date prior to the end of the CT and the results are available, an **intermediate summary of results** shall be submitted within one year of the intermediate data analysis date. The intermediate data analysis date is not provided at the time of the IN as structured data, but it is populated by the user when recording the submission of the intermediate data analysis results. In this case, a layperson intermediate summary of results should not be uploaded. After the submission of the intermediate summary of results, the MSC(s) receive a notice that the document has been submitted by the sponsor.

5.2.2. Contents and publication rules

Section 'Submission of results of clinical trials' of the CTR Q&A details the requirements and reference documentation that a sponsor should consult when drafting a summary of results and layperson summary to be submitted in CTIS. This includes the definition of the endpoints to be reported and language requirements for the Lay person summary of results.

Annex IV of the CTR defines the content of the **summary of results** of a clinical trial:

- **CT information:** clinical trial identification; identifiers; sponsors details; paediatric regulatory details; results analysis stage; general information about the clinical trial; population of subjects.
- **Subject disposition:** recruitment; pre-assignment period; post assignment periods.
- **Baseline characteristics:** age and gender (required); study specific characteristic (optional).
- **End points:** end point definitions; statistical analyses for each end point.
- **Adverse events (AEs):** AE information; adverse events reporting group; serious adverse event; non-serious adverse event.
- **Additional information:** global SMs; global interruptions and re-starts; limitations, addressing sources of potential bias and imprecision and caveats; declaration by the submitting party on the accuracy of the submitted information.

According to Annex V of the CTR, **the summary of results for laypersons** must include:

- CT information
- Sponsors name and contact details
- General information about the CT
- Population of subjects
- Investigational medicinal products
- Description of adverse reactions and their frequency
- Overall results
- Comments on the outcome
- Indication if follow up CTs are foreseen
- Indication where additional information could be found

This document may only be submitted as a version of the final results (not intermediate).

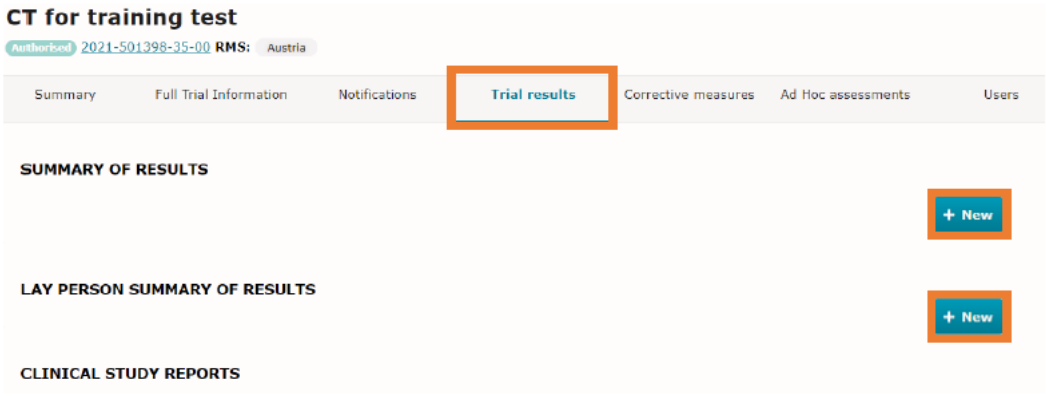
With regards to their publication rules, **summary of results and layperson summary are both subject to publication** as per publication timelines outlined in Table II of Annex 1 to the Guidance document (see section 2.1.). They therefore need to be submitted in their version 'for publication', and 'not for publication' (in case the 'for publication' version contains CCI/personal data that need to be visible to the MSC(s)), and the 'for publication' version is published overnight following submission (for most trials: see Table II of Annex 1). The **intermediate summary of results is not subject to publication** (note that the system mistakenly marks the intermediate summary of results as 'for publication': this is not correct and only the final summary of results is 'for publication', see image in section 5.2.3.).

5.2.3. How to submit trial results in CTIS

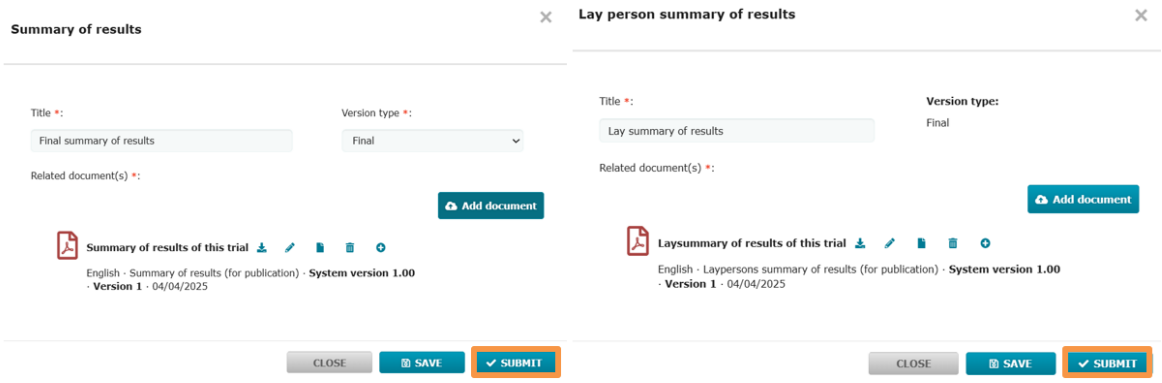
This section describes the steps that a sponsor user with **CT Admin** or **CT Results Submitter** role need to perform to submit trial results. They can be submitted if a notification on the end of trial was submitted as per section 5.1. , except for interim results that can be submitted also while the trial has not ended yet.

After having accessed the sponsor workspace and searched for the relevant CT (see section 2.6.1.) and selected the relevant CT (see section 2.6.2.):

1. Access the 'Trial results' sub-tab in the CT page and click on the **'+ New'** button.

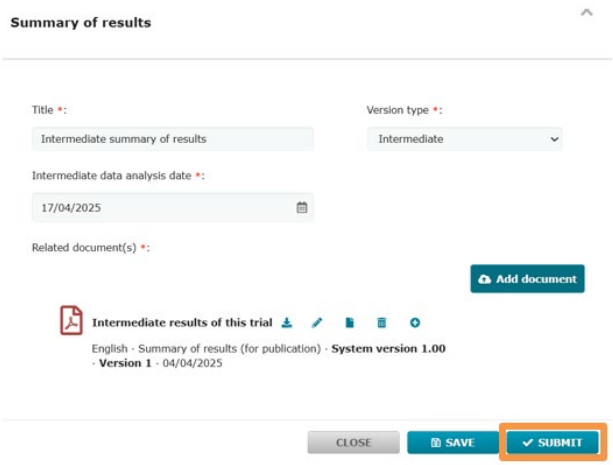


2. Populate the details according to each case (summary of results and lay person summary of results). *In case you need to submit interim results,* this is possible through selecting 'intermediate' in the 'version type' dropdown menu. The document will **not** be subject to publication, see below note. **For final summary of results and layperson summary: note that the first version of the uploaded document is the one 'for publication'** and therefore must be redacted of CCI and/or personal data (see section 2.1.). In case a redacted version is uploaded, you then also need to upload an unredacted version of the documents in the 'not for publication' slots by selecting the '+' button next to the document uploaded 'for publication'.
3. Click on '**Submit'** button and then select the 'Confirm' button in the pop-up window.



Once the summary of results is submitted, you can view it under the 'Trial result' sub-tab. From there, the previously submitted documents and fields can be **viewed and updated**. Note that only the **latest submitted** version of the summary of results document is subject to publication (former versions are not published and are kept in the secure workspaces).

Note: **the intermediate summary of results can be submitted both before the trial has ended and after it is ended. In both cases, this document is NOT subject to publication**. The wording 'for publication' displayed by the system refers to the final summary of results and never to the intermediate summary, even if it is also (incorrectly) displayed when the intermediate summary of results option is selected from the dropdown menu:



5.3. Submit the Clinical Study Report (CSR) and update it

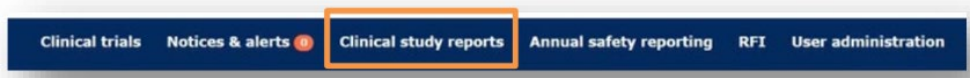
As per Article 37(4) of the CTR, 'where the clinical trial was **intended to be used for obtaining a marketing authorisation** for the investigational medicinal product, the applicant for marketing authorisation shall submit to the EU database the clinical study report within 30 days after the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application'. This applies to centralised authorisation procedures and national authorisation procedures.

A CSR is a report of an individual study of an IMP, in which the clinical and statistical description, presentations, and analyses are integrated. The **content** of the CSR submitted to CTIS must be in line with ICH E3: further details are provided in **chapter 5 of the Sponsor FAQs**, including those cases where the same CSR is subject to transparency requirements under EMA Policy 0070 and in CTIS.

The 'for publication' version of the submitted CTIS CSR is made publicly available in line with the CTIS revised transparency rules. and should not contain CCI or personal data (see section 2.1.).

Note that sponsor **users do not receive an alert from CTIS** when the due date for submitting a CSR is approaching.

CSRs can be created, searched, updated or withdrawn in the 'Clinical study reports' tab, as per below described processes. To be able to view this tab and submit a CSR, the appropriate role is needed.



5.3.1. Roles needed to view, prepare and submit a CSR

As described in section 1.6. of this handbook, in relation to the CSR process there are three sponsor roles involved: MAH Admin, CSR Viewer, and CSR Submitter. The MAH Admin can perform all the CSR related tasks (view, create, edit, submit, update, and withdraw a CSR), as well as assign CSR Viewer or CSR Submitter roles to other CTIS users to perform their activities. The CSR Submitter can perform all the tasks related to the management of CSRs, except for managing CSR related roles. However, the CSR Viewer can only view CSRs that are in draft or submitted, but cannot submit, update or withdraw CSRs. Further details on allowed permissions are provided in section 1.6.3.

The MAH Admin role should be requested by raising a ticket to EMA CTIS Service Desk (see section 6.3.). In their ticket, users need to attach an affiliation letter (filling in this affiliation template provided by the EMA) signed by a representative of the MAH/MAA (Marketing Authorisation Holder/ Marketing

Authorisation Applicant). Users need to fill in the affiliation letter details such as the clinical trial for which the MAH Admin role is requested, as well as personal data (full name, email) and sponsor organisation data. After receiving the request, the EMA will validate it and will proceed with assigning the MAH Admin role for the trials listed in the affiliation letter.

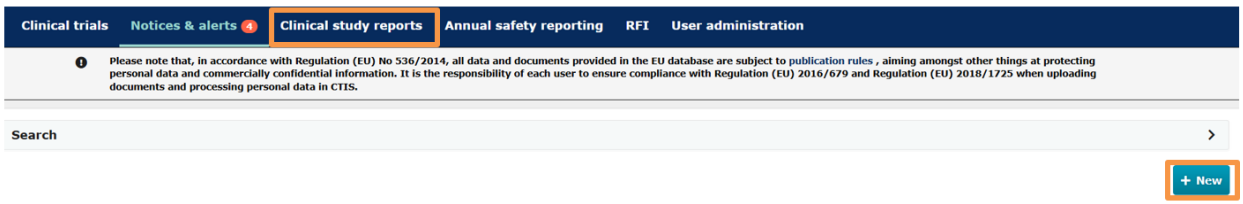
Note that sponsor users (who are not MAH users) can view the CSRs only in the 'Trial Results' sub-tab of a clinical trial page. They cannot see the 'Clinical Study Report' sub-tab as it is meant for the MAH users to manage the application. Member States users can also view any submitted CSRs in the 'Trial results' tab of the clinical trial page.

5.3.2. Create and submit a CSR

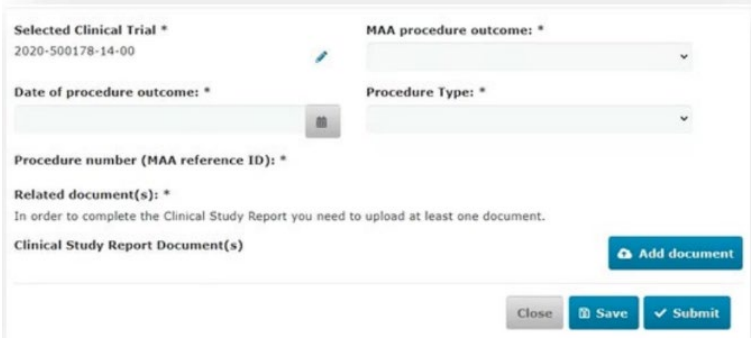
The below process describes how users with **CSR Submitter** and/or **MAH Admin** roles can create and submit a CSR for a clinical trial that has been authorised.

After having accessed the sponsor workspace:

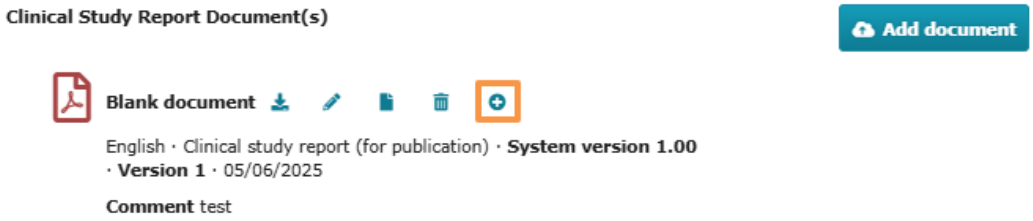
1. From the 'Clinical study reports' tab, click on the '+ New' button displayed on the left of the screen:



2. **Search** for the trial for which you intend to submit the CSR through the advanced search functionality.
3. Select the trial of interest and then click on the '**Confirm'** button at the end of the results page.
4. A pop-up window is displayed in which you can populate the CSR required fields and upload the appropriate document(s).



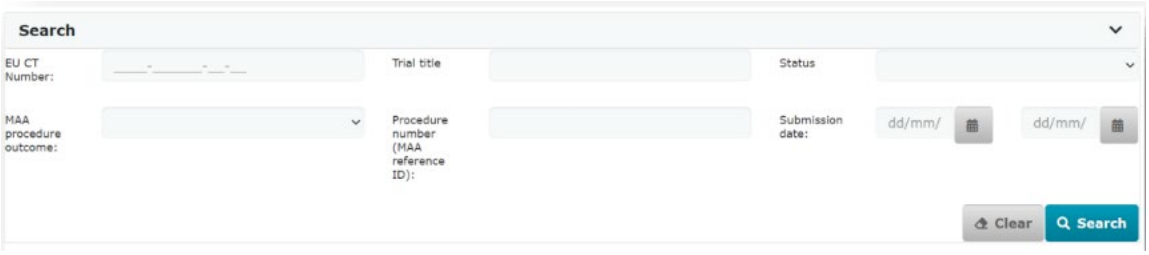
5. **Note that the first version** of the uploaded document is the one **'for publication'** and therefore must be redacted of CCI and/or personal data (see section 2.1.). In case there are CCI/personal data in the 'for publication' version, you also need to Upload an unredacted version of the CSR in the 'not for publication' slot by selecting the '+' button next to the document uploaded for publication.



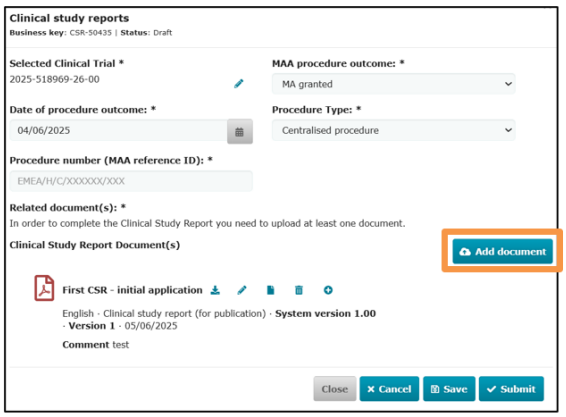
6. Once fields are completed and documents are uploaded, you can click on the '**Submit'** button. If you want to cancel the submission while it is in 'Draft', you need to select the button 'Close'. You can also save drafts of uncompleted CSRs by selecting the 'Save' button. Saved drafts can be retrieved in the CSR tab search functionality.

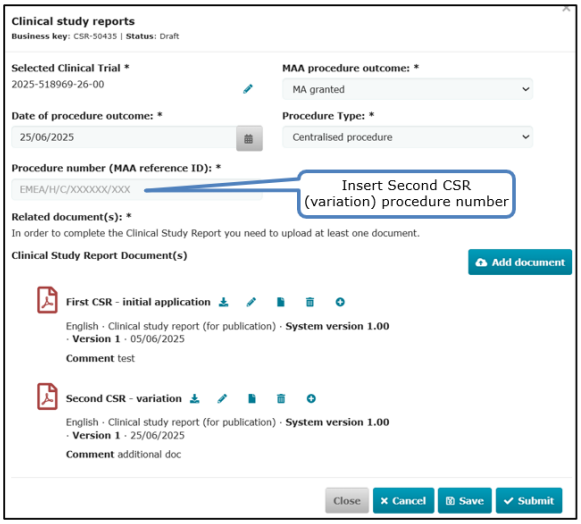
Once a CSR is submitted, **a notice is generated in the 'Notices & alerts' tab** informing the sponsor of the relevant clinical trial (provided that the sponsor user has been assigned CSR related roles), that a corresponding CSR has been submitted.

From the 'Clinical study reports' tab, users with the appropriate roles can **search** for a submitted CSR through opening the search functionality by clicking on the drop-down button displayed on the right side of the 'Search' field.



Sometimes users need to submit multiple CSRs for a specific trial (e.g. in the case of a variation to the terms of the initial marketing authorisation). In such case, the user needs to click on 'add document' after having uploaded the first document 'for publication'. The 'not for publication' version can also be uploaded as usual, through clicking on the little plus button. However, the content of the structured data fields to be filled will need to correspond to the latest finalised marketing authorisation procedure (e.g. a variation).





5.3.3. Update a submitted or draft CSR

The below process describes how users with **CSR Submitter** and/or **MAH Admin** roles can update and submit an already submitted CSR.

After having accessed the sponsor workspace:

1. From the 'Clinical study reports' tab, search for a CSR (see section 5.3.2.) and identify the CSR that needs to be updated.

1. Click on the pencil icon on the right side of the CSR.

2. A pop-up window is displayed where those required fields (marked with an asterisk, see previous section) can be updated. Examples of updates:

   - the CSR document can be updated by clicking on the pencil icon of the already present CSR, in case for example a new version of the same CSR is available (if the current version is an 'interim' CSR and needs to be replaced with a 'final' CSR).

   - new versions of the CSR could be uploaded through the 'Add document' button. In this case, the current version will remain as a separate document from the newly added document. This scenario is applicable when different interim versions of a CSR are used to support different marketing authorisation procedures, e.g. initial MAAs, variations or line extensions that included the same trial. In this case, the structured data in CTIS should be updated with the latest EMA procedure number to which the most recently uploaded CSR version refers to: more information on this in section 5.3.2.

3. Afterwards, click on the 'Update' button on the bottom left corner of the pop-up window and confirm the message that the system displays.

When a CSR is updated, the new version of that CSR will be the one subject to publication.

5.3.4. Downloading a CSR

Users with the appropriate role (**CSR Viewer, CSR Submitter, MAH Admin**) have three options to download a submitted CSR:

- From the overview page of the 'Clinical study reports' tab:

  1. Search the CSR from the search functionality of the 'Clinical study reports' tab.

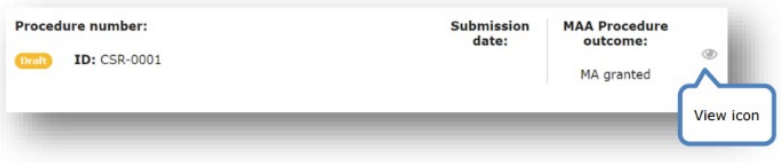
  2. Select the eye icon on the right side of the CSR.

  3. A pop-up window is displayed, containing all the CSR-related information, including any uploaded document(s).

  4. Users can download the documents by selecting the download icon.

- From the 'Trial results' sub-tab of the 'Clinical trial' page:

1. Search a specific CT from the 'Clinical trials' tab and click on the EU CT number.
2. Select the 'Trial results' sub-tab of the clinical trial page.
3. Go to the section 'Clinical Study Reports'.
4. Select the eye icon on the right side of the CSR.



5. A pop-up window is displayed, containing all the CSR-related information, including any uploaded document(s).
6. Users can download the documents by selecting the download icon.

- Downloading the documentation from the CT: see instructions in section 2.6.3.2. , selecting 'Clinical Study Reports'.

5.3.5. Withdrawing a CSR

Users with **CSR Submitter** or **MAH Admin** role can withdraw an already submitted CSR, provided appropriate justification is given.

1. Search for a CSR (see previous section) and identify the CSR to be withdrawn.
2. Click on the pencil icon on the right side of the CSR.
3. A pop-up window is displayed, where you are requested to add a justification for the withdrawal request.
4. Click on the 'Withdraw' button at the bottom right corner of the pop-up window and once again in the confirmation pop-up message that appears.

A notice is automatically generated informing the sponsor responsible of the CT (provided the user has CSR related roles) that a CSR corresponding to it has been submitted or withdrawn in CTIS. If a CSR is withdrawn, users may submit a new CSR for that trial.

If a CSR is withdrawn, it will not be published. However, it will remain visible and flagged as withdrawn in the 'Clinical Study Report' tab for MAH users and in the 'Trials results' sub-tab of the clinical trial page for sponsors users. A published CSR that is withdrawn is removed from public view within 24 hours from withdrawal.

If a CSR is withdrawn, the MAH users are still required to comply with the requirements of Article 37(4) of the CTR and **submit a new CSR within 30 days** after the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for the marketing authorisation has withdrawn the application.

End of chapter: jump to Clickable table of contents.

6. CTIS training & support

6.1. Release notes and known issues

The EMA regularly performs technical updates to CTIS to improve its features and functionality. When significant updates are made to CTIS, the EMA publishes release notes that outline what has changed in the system. Updates may include improvements to existing features and functionality, the addition of new features as well as functionality and technical improvements. In addition, in the same page, the EMA publishes known issues that sponsor and authority users may encounter when using the CTIS secure workspaces. Where possible, the workarounds to apply are proposed.

All versions of the release notes and known issues documents can be found on the 'Website outages and system releases' available on the EU Clinical Trials page: CTIS users are advised to make use of the latest version of the lists of known issues published on this page.

6.2. Information and training

6.2.1. Clinical Trials Highlights Newsletters

To stay up to date with the latest developments, plans and system improvements, users need to consult the Clinical Trial Highlights newsletter, available on the EMA corporate website. Users can subscribe here to stay updated on the evolving clinical trials landscape in the EU/EEA.

6.2.2. CTIS information events

The events page on the EMA corporate website displays information on events organised by the EMA on CTIS (search words e.g. CTIS; SME).

In order to further support CTIS sponsor users after CTIS go-live, the EMA has launched series of virtual events that can be seen in the EMA's webpage on CTIS Training and information events:

- CTIS walk-in clinics provide an opportunity for sponsors to receive practical guidance about CTIS by asking questions to CTIS experts.
- CTIS bitesize talks are themed events offering users live system demonstrations on a specific CTIS functionality, with additional question and answers on the specific theme.
- In addition, the EMA introduced OMS troubleshooting sessions for CTIS users, another series of virtual events aiming to address and clarify outstanding issues and questions related to registering organisation and/or location data in OMS for use in any CTIS CT application.

All of these events are open to everyone. The recorded videos of past events become available for the public on the EMA's YouTube channel and can be accessed also through the dedicated event pages as of 2 weeks from the relevant event.

6.2.3. The CTIS training environment

The CTIS training environment is a copy of a recent version of CTIS, and it may not always be identical to the latest version. The purpose of the CTIS training environment is to enable knowledge acquisition of the already implemented functionalities of CTIS, by the future CTIS users and their organisations, in a practical way and in a safe environment. The CTIS training environment use is directed by conditions, instructions and guidance, and is made available by the EMA.

The CTIS training environment is intended for individuals and organisations that are the already using or intending to use the secure workspaces of CTIS (authority and sponsor workspace). More information on deployment activities can be found on the following link: https://euclinicaltrials.eu/website-outages-and-system-releases/#lists-of-known-issues-and-proposed-workarounds

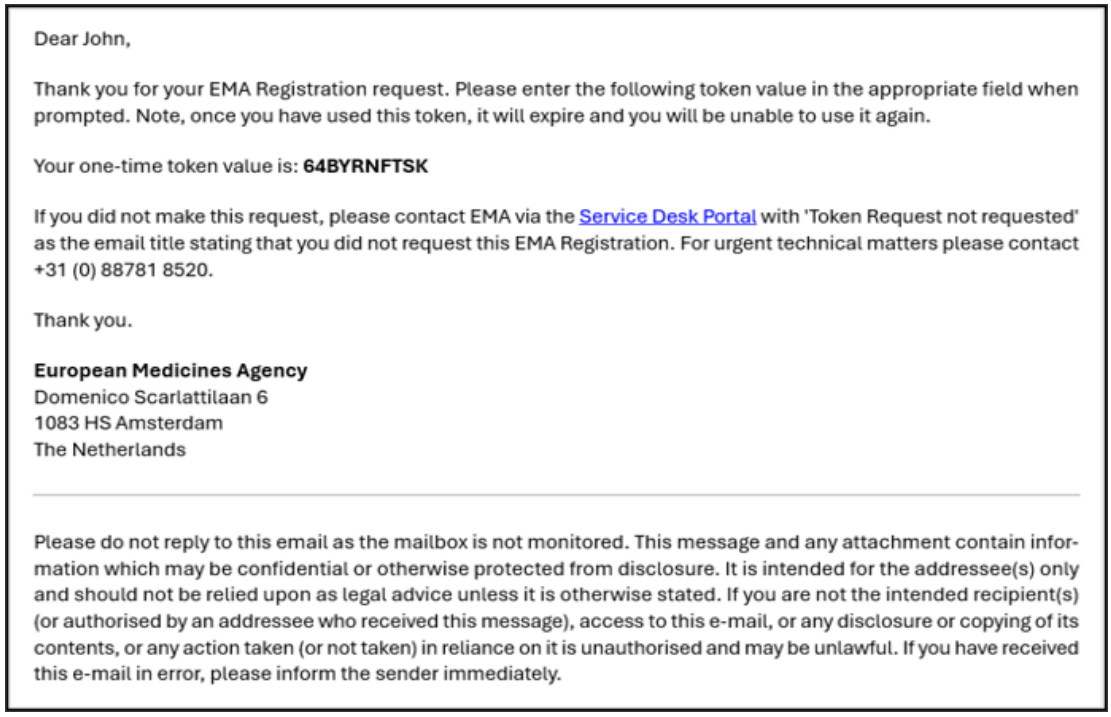
As of July 2026, the CTIS Training Environment uses the same authentication approach as the CTIS production environment. Access is based on personal user accounts linked to individual email addresses and requires multifactor authentication (MFA). Artificial or shared user accounts are not supported.

How to register and get access for users without an EMA account

Users who do not yet have an EMA account must first register in the EMA Account Management system through the EMA production registration portal. This step needs to be completed at least a day before requesting the Training access role, to allow sufficient time for account creation and activation.

To register:

- Go to the EMA registration portal: https://register.ema.europa.eu/.
- Select **Sign up** and complete the registration process.
- Confirm your registration using the token received by email:



Dear John,

Thank you for your EMA Registration request. Please enter the following token value in the appropriate field when prompted. Note, once you have used this token, it will expire and you will be unable to use it again.

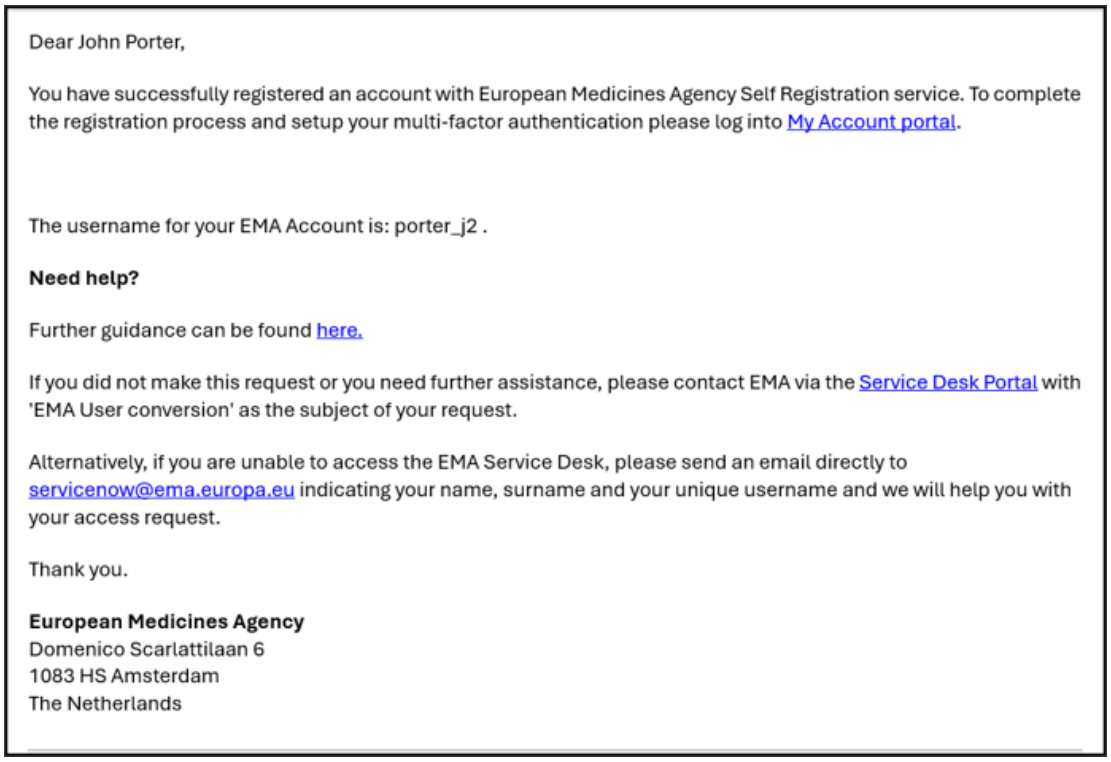
Your one-time token value is: **64BYRNFTSK**

If you did not make this request, please contact EMA via the Service Desk Portal with 'Token Request not requested' as the email title stating that you did not request this EMA Registration. For urgent technical matters please contact +31 (0) 88781 8520.

Thank you.

European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

- Once the EMA account has been created and activated, complete the account registration using the instructions provided in the subsequent email communication.



Dear John Porter,

You have successfully registered an account with European Medicines Agency Self Registration service. To complete the registration process and setup your multi-factor authentication please log into My Account portal.

The username for your EMA Account is: porter_j2 .

Need help?

Further guidance can be found here.

If you did not make this request or you need further assistance, please contact EMA via the Service Desk Portal with 'EMA User conversion' as the subject of your request.

Alternatively, if you are unable to access the EMA Service Desk, please send an email directly to servicenow@ema.europa.eu indicating your name, surname and your unique username and we will help you with your access request.

Thank you.

European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

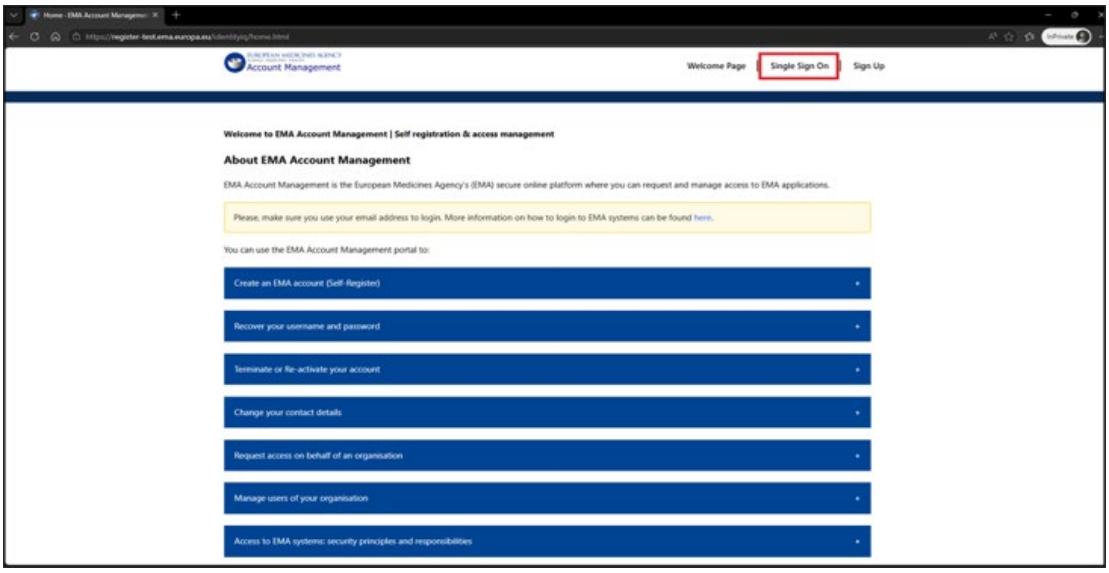
- Sign in using the registered email address.
    - User information is propagated within approximately 5 minutes.
    - The user is created with Member (EXT) status.

Requesting training access role

Users who already have an EMA account for the CTIS Production Environment may use the same account credentials to access the CTIS Training Environment. However, access is not granted automatically. Users must first request the dedicated *training access* role. This *training access* role can only be requested the day after the EMA account has been created.

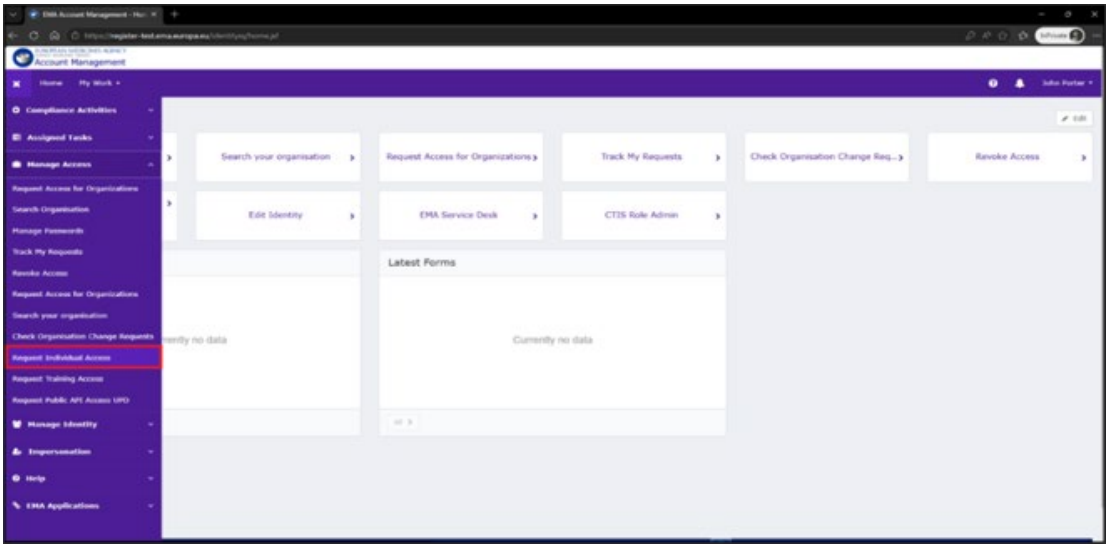
To request the role:

- Navigate to Register (Test)
- Select **Single Sign-On** (**SSO**).
- Complete the two-factor authentication (**2FA setup)** if required.
- Submit the request for the dedicated *training access* role.

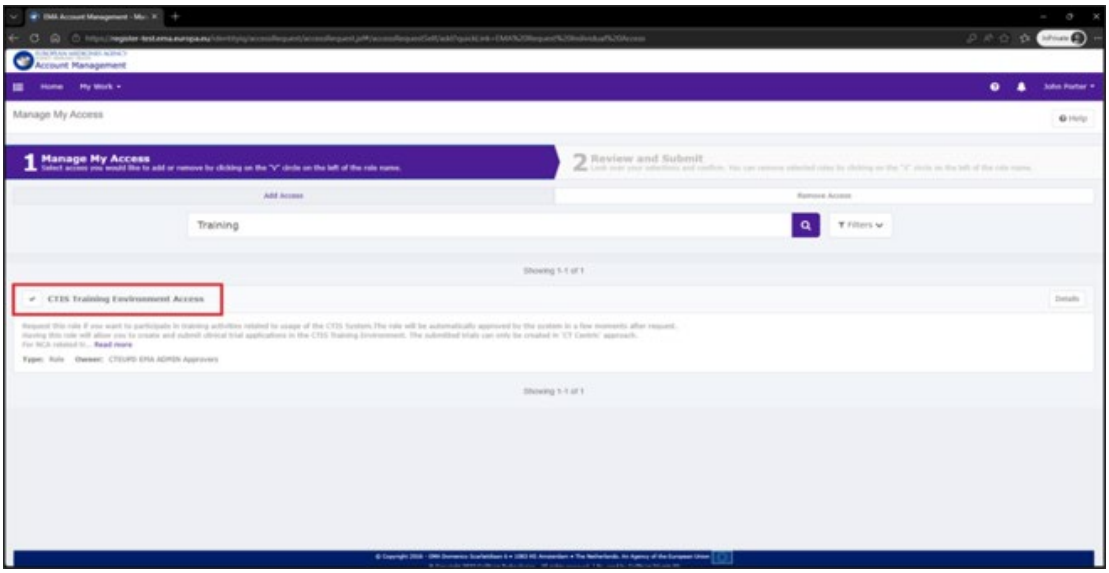


Requesting access to the CTIS Training Environment

- Open the user menu and select **Request Individual Access**.



- Search for **Training**.
- Select **CTIS Training Environment Access**.



- Review the request details and select Submit.

This access request can be submitted no earlier than the day following the creation of the EMA account.

First-time access requests

If the EMA account has not previously been used to request access, users may be asked to complete an additional form requesting user information. This for should be completed and submitted as part of the access request process.

Approval and role activation

Users may monitor the status of their request through **Track My Requests**.

Requests for access to the Training Environment are approved automatically. Approval is typically granted within a few minutes and does not require further action from the user. Following approval, the synchronisation and activation of the *training role* may take approximately 30 minutes. Once the role has been activated, users can access the CTIS Training Environment using their EMA account credentials.

Key changes

The revised access process introduces the following changes:

- Authentication in the CTIS Training Environment follows the same approach as in the CTIS Production Environment.
- Multifactor authentication is mandatory.
- Personal user accounts linked to individual email addresses are required.
- Artificial user accounts are no longer supported.
- Both new and existing users must request the dedicated CTIS Training Environment Access role before gaining access to the training environment.

If support is needed for this environment, users should contact the EMA CTIS Service Desk, see section 6.3.

6.2.4. Other useful websites

More information on CTIS is also available through consulting the following websites:

- Clinical Trials Information System – EMA webpage
- Clinical Trials Information System training and support– EMA webpage
- CTIS website
- ACT EU website: Implementation of the Clinical Trials Regulation
- EudraCT (European Union Drug Regulating Authorities Clinical Trials Database)

6.3. Need help? Contact us

Depending on the kind of questions a user may have, the appropriate channel needs to be used.

For questions on the **content of clinical trial applications** (structured data and documents), users should refer to the relevant Member States contact points.

For questions **related to the CTR** that cannot be answered through consulting CTR Q&A, users should submit their question via the regular CTIS public events or refer to the relevant Member States contact points.

If the **behaviour of CTIS is different from the one described in the present handbook**, users should first check:

- In case of downtime: the planned system interruptions timeframe and any unplanned outage.
- In case of a specific issue (e.g. tabs not showing, time outs, empty warning messages): the list of known issues and workarounds and see if the issue is present.
- in case of a log in issue, if it can be solved as per EMA account management.

If none of the above applies, users can make use of the EMA CTIS Service Desk, **mentioning the EU CT number of the relevant trial** application and providing as many information as possible (who you are, CTA/RFI number, application ID, your location, described the steps taken, indicate any due date and attach screenshots of the issue). More information on the Support page.

For issues with **the search function of sponsor or product**, report an issue with SPOR functionalities (see details on XEVMPD support in Annex II of the relevant Guidance on XEVMPD).

For technical support with **other EMA IT systems** (e.g. XEVMPD, EudraVigilance, IRIS, EudraCT), see EMA General Service Desk.

General questions on CTIS functionalities from sponsors that have not yet created an EMA account, should be directed through sending a question to the EMA.

End of chapter: jump to Clickable table of contents.

7. History and summary of changes of the sponsor handbook

This handbook has been developed by the EMA in collaboration with representatives from industry and Member States. It is regularly updated, particularly to reflect changes in CTIS functionalities. The handbook is intended to be used alongside the various reference documents it cites as well as the Volume 10 of the publication 'The rules governing medicinal products in the European Union' that contains guidance documents applying to clinical trials (EudraLex - Volume 10 - Clinical trials guidelines).

Since its initial publication in July 2021, the handbook has undergone several updates. The most recent revision was the most substantial to date, as described in the table below.

Document version and publication date	Changes introduced in the text
6.4, 7 July 2026	Guidance on new way to access the CTIS Training environment (section 6.2.3)
6.3, 26 June 2026	New information introduced by CTR Q&A v7.2 incorporated Information on email notification of notices and alerts was added
6.2, 26 March 2026	References to the newly published Sponsor FAQs added. The use of the 'update' icon was specified when drafting a SM/NSM Detailed instructions were added in section 4.3.3.
6.1, 7 November 2025	Clarifications were included in section 1.1. on the Multi Factor Authentication and in section 1.2. on submitting a change request for OMS. Sponsor users can now modify a broader set of fields and documents within NSM: section 4.8. was updated accordingly. Further amendments were performed in this section and in section 4.3.1. for clarity purposes
6.0, 9 July 2025	Version 5.0 was updated to Version 6.0 in order to fully integrate the content of the former CTIS training modules that were used by sponsors when operating on CTIS
5.0, February 2025	Multifactor Authentication (MFA) (former section 2.1.1) *updated* Transition from the Clinical Trials Directive to the Clinical Trials Regulation (former section 5) *updated* CTIS Highlights and Newsflash Newsletters (former section 10.2) *updated*

Annex I: acronyms and definitions

See also 'Definitions' Article 2 of CTR, EMA General Glossary of regulatory terms and EMA Medical Terms Simplifier.

Acronym	Definition
AM – Addition of a Member State concerned application	Refer to Article 14 of the CTR and to definition of CT application.
ASR - Annual Safety Report	Document on the monitoring and evaluation of the evolving safety profile of an IMP and the mitigation of potential risks. When submitting an ASR, the following two terms are mentioned, in step 2: **Novel-novel combination**: a combination of two or more innovative (investigational) medicinal products, neither of which has been authorised or thoroughly studied before, either individually or in combination **New combination**: a new pairing (or grouping) of already known/authorised medicinal products that have not previously been studied together in a clinical trial. Even though the individual components are not innovative per se, their combined use introduces a novel therapeutic strategy that requires separate evaluation for safety and efficacy.
ATC code - Anatomical Therapeutic Chemical code	International classification system for medicines that is maintained by the World Health Organisation (WHO).
ATMP - Advanced Therapy Medicinal Product	Medicine for human use that are based on genes, tissues or cells, offering ground-breaking new opportunities for the treatment of disease and injury.
CAT - Committee for Advanced Therapies	EMA committee responsible for assessing the quality, safety and efficacy of advanced therapy medicinal products (ATMPs) and following scientific developments in the field. More information here.
CCI - Commercially confidential information	Information whose publication might prejudice the commercial interests of individuals or companies to an unreasonable degree. The Agency cannot disclose commercially confidential information unless there is an overriding public interest in disclosure.
CET – Central European Time	A standard time observed in Central Europe, 1 hour ahead of Coordinated Universal Time (UTC).
Clinical study	Refer to Article 2(2)(1) of the CTR.
CT - Clinical trial	Refer to Article 2(2)(2) of the CTR.
CRO - Clinical Research Organisation	A contract research organisation, also called a clinical research organisation is a service organisation that provides support to the pharmaceutical and biotechnology industries in the form of outsourced pharmaceutical research services (for both medicinal products and medical devices).

Acronym	Definition
CSR - Clinical Study Report	Report of an individual study of an investigational medicinal product, in which the clinical and statistical description, presentations, and analyses are integrated.
CT application - Clinical Trial Application	A request (made by the sponsors) for the authorisation (by the Member States concerned), to perform an action related to clinical trials conducted in the EU. It can be a request to start a clinical trial (IN), the extension of a clinical trial to another MSC territory and subjects (AM), or to perform an important modification to an already started CT.
CTCG - Clinical Trials Coordination Group	The CTCG is a European Heads of Medicines Agencies (HMA) working group of experts in the classification, assessment and oversight of clinical trials from National Agencies. This working group also promotes harmonisation of clinical trial assessment decisions and administrative processes across the national competent authorities (NCAs). More information here.
CTD - Clinical Trial Directive 2001/20/EC	Former Clinical Trials' legislation applicable in the EU, repealed by the Clinical Trial Regulation (EU) 536/2014.
CTIS - Clinical Trial Information System	Online system for the regulatory submission, authorisation and supervision of clinical trials in the EU/EEA. CTIS acts as the single-entry portal in the EU/EEA for all trials on investigational medicinal products involving human subjects. Trial data and documents are accessible on the CTIS public website.
CTR - Clinical Trial Regulation (EU) 536/2014	EU pharmaceutical legislation aiming to harmonises the processes for assessment and supervision of clinical trials throughout the EU. On 31 January 2022, the Regulation repealed the Clinical Trials Directive (EC) No. 2001/20/EC and national implementing legislation in the EU Member States, which regulated clinical trials in the EU until the Regulation's entry into application. More information here.
CV	Curriculum Vitae
EC - Ethics Committee	Refer to Article 2(2)(11) of the CTR.
EEA - European Economic Area	Economic area composed of Member States of the EU and three countries of the European Free Trade Association (EFTA) (Iceland, Liechtenstein and Norway; excluding Switzerland).
EMA - European Medicines Agency	Agency of the EU responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU, as well as for the maintenance and further development of the CTIS. More information here.
EU - European Union	Supranational political and economic union of 27 member states that are located in Europe.
EU CT number - EU Clinical Trial number	Trial identifier code, unique to each clinical trial conducted in CTIS.

Acronym	Definition
EU MP number - EU Medicinal Product number	A unique number assigned by the XEVMPD to each medicinal product record successfully inserted in the dictionary; it is used to identify this medicinal product in the XEVMPD and it is also called EV code.
EV - EudraVigilance	Refer to definition here.
GDPR - General Data Protection Regulation	The EU general data protection regulation (GDPR) governs how the personal data of individuals in the EU may be processed and transferred.
GMP - Good Manufacturing Practices	Aset of regulatory guidelines and quality assurance principles designed to ensure that products—such as pharmaceuticals are consistently produced and controlled according to set quality standards
IAM – Identity and Access Management	User registration system that provides individuals with access to the applications that are managed by the EMA, including CTIS, XEVMPD, OMS, EV.
IB - Investigator Brochure	A multifunctional regulatory document essential for the conduct of clinical trials that summarises the physical, chemical, pharmaceutical, pharmacological, and toxicological characteristics of an investigational medicinal product (IMP) as well as any clinical experience.
IMP - Investigational Medical Product	Refer to Article 2(2)(5) of the CTR.
IMPD - IMP Dossier	Dossier that provides information related to the quality of an IMP(IMPD Q), and to the Safety and Efficacy (IMPD S and E).
IN - Initial Clinical trial Application	Refer to definition of CT application. The elements to be included in the application dossier for an IN are defined in Annex I of the CTR.
IPD – Individual Patient Data	Raw data collected from each individual participant in a study.
MAH/MAA - Marketing Authorisation Holder/MA Applicant	The company named on the Marketing Authorisation for a medicinal product in a country or in the EU/EEA, or the applicant of a marketing authorisation for a medicinal product.
MSC - Member State Concerned	An EU Member State that has received a CT application for its assessment and therefore is responsible for its assessment. Refer to Article 2(2)(12) of the CTR.
NCA - National Competent Authority	National regulatory agency in an EU Member State.
NSM - Non-Substantial Modification	A change implemented to a Clinical trial with the purpose of correcting information that is not expected to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the Clinical trial. Refer to Article 81(9) of the CTR.

Acronym	Definition
OMS - Organisation Management Service	EMA management system managed providing a single source of organisation data, such as their names and addresses. More information here.
PI - Principal Investigator	Refer to Article 2(2)(15) of the CTR.
PIP - Paediatric investigation plan	A paediatric investigation plan (PIP) is a development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children. More information here.
PMID - PubMed identifier	Unique identifier number of PubMed.
QP	Qualified Person
RFI - Request for Information	CTIS functionality through which the MSC(s) ask sponsors to provide additional information in the context of validation and assessment of a CT application, ad hoc assessments, corrective measures and ASR.
RMS - Reporting Member State	Member State Concerned with a leading role in the assessment of Part I of a CT application and in the monitoring of a CT during the clinical trial lifecycle
RP - Responsible Person	Person responsible to register a sponsor in EudraVigilance: more information here.
RSI – Reference Safety Information	Refer to the CTR (Annex I, section E, numbered item 30).
SM - Substantial Modification	Refer to Article 2(2)(13) of the CTR and to definition of CT application
SPOR - Substance, product, organisation and referential (SPOR) master data domains	EMA management system managed providing a single source of data on substance, product, organisation and referential. More information here.
SmPC - Summary of Product Characteristics	This is the product information document which is made available to all prescribing physicians in the EU for marketed products.
SUSAR - Suspected Unexpected Serious Adverse Reaction	An untoward and unintended response to a study medication, that is fatal or life-threatening.
XEVMPD - eXtended EV Medicinal product data dictionary	Data base that stores and provides quality data on authorised or investigational medicinal products to CTIS. This information is requested to sponsors when filling out a clinical trial dossier/application.
XEVPRM - eXtended EV medicinal product message	Message through which the product information is submitted in the XEVMPD by the sponsor.

Annex II: lists of resources, videos and bitesize talks

Resources

- Regulation (EU) No 536/2014
- CTR Questions & Answers (Q&A)
- Quick guide for sponsors - Regulation 536/2014 in practice
- Documents listed in EudraLex - Volume 10 - Clinical trials guidelines
- Documents listed in European Commission website containing information on clinical trials in the context of Regulation EU No 536/2014
- Documents listed among the Clinical Trials Coordination Group (CTCG) Key Documents list
- National Competent Authorities (NCA) websites on each MSC requirements

Videos

Section	Video
Introduc-tion and general principles	CTIS technical environment
1.5.1.	Creating a clinical trial: Clinical trial-centric approach vs organisation-centric approach
1.7.1. 1.7.2.	How to request roles and how to assign roles to registered users in CTIS How to amend and revoke roles of registered users in CTIS.
2.1.	Data protection in CTIS
2.3.3.	Fill in the Form and the MSC sections Fill in the Part I section Fill in the trial details of Part I section Fill in the Sponsor details of Part I section Fill in the Product details of Part I section Fill in the Part II section and submit the application
2.6.	How to search for a clinical trial in the CTIS sponsor workspace How to view and download clinical trial information
3.1.8.	How to manage the workload in CTIS - Timetable
3.3.	How to manage the workload in CTIS - RFI tab (sponsor workspace) How to access and view an RFI in CTIS How to change a Clinical Trial Application as part of an RFI response How to respond to RFI considerations and submit an RFI response

Section	Video
	CTIS bitesize talk: Requests for information
4.1.	How to manage a clinical trial in CTIS (Sponsors) – Trial and recruitment periods notifications
4.2.1.	How to submit an additional Member State concerned application in the CTIS sponsor workspace.
4.3.2.	How to submit a single trial substantial modification in the CTIS Sponsor workspace.
4.9.	How to manage a clinical trial in the CTIS sponsor workspace – Other notifications
4.13.1.	How to create, cancel or clear, and submit an annual safety report
4.13.3.	How to search and view an annual safety report (ASR), and respond to requests for information (RFIs) received during the ASR evaluation

Bitesize talks

Section	Bitesize talk
Introduction and general principles	CTIS Bitesize talk: Redesign of the CTIS training material for sponsor users
1.7.1. 1.7.2.	CTIS bitesize talk: User access and role management (24/02/2022)
2.1.	CTIS bitesize talk: Revised transparency rules and the new CTIS public portal (20/06/2024)
2.3.3.	CTIS bitesize talk: Initial clinical trial application (23/03/2022)
2.4.5.	CTIS bitesize talk: IMPD-Q only submission (10/05/2023) CTIS Bitesize Talk: Alternate IMPD-Q and new guidance AxMP (24/04/2024)
2.5.	CTIS bitesize talk: Part I-only applications and Part II requirements in CTIS (30/08/2023)
3.3.	CTIS bitesize talk: Requests for information (28/04/2022)
4.1.	CTIS bitesize talk: Notifications - Part 1 (28/09/2022)
4.2.	CTIS bitesize talk: Additional Member State concerned (MSC) application (23/06/2022)
4.3.1.	Clinical Trials Information System (CTIS) bitesize talk: Modifications (31/05/2022)
4.9.	CTIS bitesize talk: Notifications - Part 2 (23/11/2022) CTIS bitesize talk: Notifications including serious breach (16/10/2024)
4.13.	CTIS bitesize talk: Annual safety report (ASR) (15/12/2022)