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Clinical Trials Information System (CTIS) Programme

Clinical Trials Information System (CTIS) - Sponsor Handbook

A compilation of key guidance, technical information, recommendations and references for getting ready for use of CTIS

Executive summary

The aim of the EMA CTIS Sponsor Handbook ("Handbook") is to provide clinical trial (CT) sponsors representing pharmaceutical industry, SME, academia, research organisations and other clinical trial sponsor organisations with the information they need for getting ready for use of the Clinical Trials Information System (CTIS) when the Clinical Trial Regulation [CTR: Regulation (EU) No 536/2014] comes into application. The Regulation harmonises the assessment and supervision processes for clinical trials throughout the EU/EEA, via CTIS. CTIS will contain the centralised EU portal and database for clinical trials foreseen by the Regulation.

The Handbook addresses key questions on CTIS and provides a compilation and references to key guidance, technical information, recommendations, training materials and supportive documentation to facilitate planning.

It has been developed by the European Medicines Agency (EMA) in collaboration with some representatives of industry stakeholders.

The Handbook will be revised as more information becomes available or system functionalities are updated. It is best used in conjunction with the many references to which it points, including e.g. 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](#)).

Proposals and comments for needs to be addressed and for evolution of the document can be provided to EMA:

References	Location (area or document)
Proposals and comments on the Sponsor Handbook	https://ec.europa.eu/eusurvey/runner/CTIS_Sponsors_Handbook_Feedback



Document evolution

Version	Version description	Date
1.0	This first version of the CTIS Sponsor Handbook contains prioritised topics. Additional topics will be inserted/completed in the document and updates provided in next versions.	28 July 2021
2.0	Updated handbook sections: <ul style="list-style-type: none">- Editorial changes across the document- OMS registration process (section 3.2.1) <i>updated</i>- User personas and organisation models (section 4.5) <i>updated with new links</i>- Product management in CTIS (section 5) <i>updated</i>- Transition from Directive to Regulation (section 6) <i>updated</i>- Data fields and documents specifications (sections 7.1.3) <i>new</i>- SUSARs reporting (section 8.1) <i>updated</i>- Training environment for user training and organisation preparedness (section 10.4) <i>new</i>	30 November 2021

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1. What CTIS is and what it does

1.1. A brief introduction to CTIS

*Digitalisation
& Improved
Efficiency*

When live, CTIS will be the **single entry point** for clinical trials information in the European Union (EU) and in the European Economic Area (EEA).

This will include a single clinical trial application dossier, covering clinical trial applications submitted to EU/EEA Member States (including submission to National Competent Authorities (NCAs) and Ethics committees) and registration of the clinical trial in a public register; all in one integrated submission.

CTIS provides harmonised and simplified **end-to-end electronic application procedures** over the lifecycle of clinical trials across the EU/EEA.

CTIS is, however, not a clinical trial management system. It should therefore not be relied upon by sponsors to store information on a clinical trial. Although CTIS provides a digital secured archive of documents, decisions and information on a clinical trial, sponsors should ensure they utilise their own information management system to store information needed for compliance purposes.

The exchange of information between sponsors and Member States will be fully **electronic in CTIS**.

In CTIS, Member States will collaborate and **coordinate amongst themselves for the evaluation and supervision of clinical trials resulting in** one single decision per Member State Concerned.

Documents can be uploaded but not created in CTIS.

*Increased
Transparency*

CTIS will offer searchable **clinical trial information** to the patient, the healthcare professional and the general public. Clinical trial **results will be available both as a technical summary and in lay language**.

Information can be retrieved by searching for a particular trial or across trials for treatment-related details.

*Enhanced
Patient
Safety*

Patient safety in clinical trials is enhanced as CTIS provides an end-to-end electronic solution for safety reporting of trials.

CTIS facilitates a harmonised safety assessment in Europe, supported by agreed assessment report templates.

The clinical trial module of EudraVigilance will provide for the electronic reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) by sponsors and re-routing to Member States.

CTIS delivers an electronic Annual Safety Reports (ASRs) repository.



CTIS is a unique intuitive tool that facilitates submission of clinical trial applications including those for multi-national trials and therefore facilitating investigation of e.g. rare diseases. It thereby also supports academic innovative work.

CTIS offers search and export of structured clinical trial data to allow efficient reporting for scientists.

A clinical trial can be extended to more Member States e.g. to enhance recruitment rates.

1.2. Overview of Clinical Trial Application (CTA) process in CTIS – from submission to decision and reporting

CTIS is structured in two restricted and secured workspaces (Sponsor and Authority), only accessible to registered users, and a website openly accessible to the general public.

The sponsor workspace provides clinical trial sponsors with the functionalities for submission of CTAs to Member States and management of information throughout the life cycle of clinical trials.

CTIS allows sponsors to manage system users and their roles within their organisations, compile clinical trial dossiers including document upload for new and updated trials, cross-refer in the application to other trials, where for example the same product was used, receive alerts and notices for ongoing trials, respond promptly to requests for information, view deadlines, search and access clinical trials and record a summary of clinical study results.

At the top of the sponsor workspace landing page, users view a menu bar with tabs that correspond to the various functionalities that reflect the roles and related permissions assigned to the user in CTIS depending on their responsibilities regarding the clinical trials.

- The **clinical trials** tab provides search functionalities that facilitate users to find specific trials and view information (see module 9 of the CTIS training programme).
- The **notices and alerts** tab shows the messages triggered by activities that occur during the life cycle of a clinical trial.
- The tab for **requests for information –RFI** tab– provides access to such requests made by Member States Concerned for clinical trials, and enables users to view their status, due dates and other relevant information.
- The **User administration** tab allows management of roles and permissions for all users that are registered in the system.

The CTIS Training Material Catalogue Module 02 provides a High-level overview of CTIS workspaces.

References	Location (area or document)
Clinical Trial Regulation (EMA website)	Clinical Trial Regulation European Medicines Agency (europa.eu)
CTIS Training Material Module 02 'High-level overview of CTIS workspaces and	https://www.ema.europa.eu/documents/other/quick-guide-overview-ctis-workspaces-common-system-

common system functionalities: User Quick Guide'	functionalities-ctis-training-programme-module-02_en.pdf
CTIS Training Material Module 02 'High-level overview of CTIS workspaces and common system functionalities: CTIS common functionalities, Part A'	https://youtu.be/EgIRpL17WaU
CTIS Training Material Module 09 'Search, view and download information on clinical trials and clinical trial applications: User Quick Guide'	https://www.ema.europa.eu/en/documents/other/quick-guide-how-search-view-download-clinical-trial-clinical-trial-application-ctis-training_en.pdf

2. CTIS Go-Live date

The Clinical Trial Regulation was adopted and entered into force in 2014, however the timing of its application depends on confirmation of full functionality of CTIS through an independent audit.

On 21 April 2021, following an independent, successful audit of CTIS, the EMA's Management Board confirmed that CTIS is fully functional and meets the agreed functional specifications.

The European Commission considered that the conditions set by the Regulation were met and published a notice in the Official Journal (OJ) of the European Union on 31 July 2021.

Six months after this notice, the Regulation will start to apply and CTIS will go live.

The CTIS will go live on 31 January 2022.

References	Location (area or document)
Information on clinical trials in the context of Regulation EU No 536/2014, including the notice published in the OJ (European Commission website)	https://ec.europa.eu/health/human-use/clinical-trials/regulation_en
Information in the context of Regulation EU No 536/2014 (EMA website)	https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

3. Getting access to CTIS – registrations

3.1. User self-registration

In order to access the CTIS Sponsor workspace, a user will need to have an active EMA Account.

If the user already uses other EMA applications (e.g. Eudralink, SPOR, IRIS, EudraVigilance, OMS), the user already has an EMA Account and could access the CTIS Sponsor workspace using his/her existing EMA Account credentials.

If the user does not have an active EMA Account, (s)he needs to create one, by self-registration.

The self-registration process is described on the EMA Account Management (IAM) homepage and in Module 03 of the CTIS Training Material Catalogue.

References	Location (area or document)
EMA Account Management homepage	https://register.ema.europa.eu/identityiq/home.html
CTIS Training Material Module 03 'User Access Management: Quick Guide'	https://www.ema.europa.eu/en/documents/other/quick-guide-user-access-management-ctis-training-programme-module-03_en.pdf
CTIS Training Material Module 03 'User Access Management: Frequently Asked Questions (FAQs)'	https://www.ema.europa.eu/en/documents/other/faqs-user-access-management-ctis-training-programme-module-03_en.pdf
CTIS Training Material Module 03 'User Access Management: Videoclip'	https://www.youtube.com/watch?v=VSLYv9I-LcE&ab

3.2. Organisation and High-level administrator registration

3.2.1. Organisation registration in OMS for use in CTIS

CTIS consumes organisation data from Organisation Management Service (OMS). OMS provides a single source of validated organisation data that can be used as a reference to support EU regulatory activities and business processes. It stores master data comprising organisation name and location address for organisations such as marketing authorisation holders, sponsors, regulatory authorities, trial sites and manufacturers.

If an organisation has already been successfully registered in OMS, a user can retrieve its details within CTIS to populate the clinical trial application, submit notifications or to use it for other sponsor-related activities in CTIS (i.e. populate employer's details in personal profile).

If an organisation is not yet registered in OMS when starting to use CTIS, it is recommended first to register the organisation via a change request¹ directly on the [OMS portal](#).

It may also be possible to submit a request to register an organisation in OMS while working within CTIS. This functionality in CTIS is offered to facilitate sponsors that need to submit, within very tight deadlines, clinical trial applications and/or notifications including details of organisations that are not yet available in OMS. The validation of a change request, raised in OMS directly or via CTIS, takes up to a maximum of 10 working days.

Regardless if the details of a new organisation are created via OMS directly or by accessing OMS via CTIS, it is paramount that such requests are supported by a valid documentation to achieve a successful OMS validation, therefore it is expected that the entity in possession of the valid documentation proceed with the registration in OMS.

Depending on the type of organisation to be registered in OMS, different types of documentation can be provided to support the registration process in OMS. Guidance is published on the OMS portal, [E - OMS Change Requests](#).

¹ The term 'change request' for OMS refers to an addition of new or modification of existing records in OMS.

In case the request raised is incorrect, or it is not supported by the appropriate accompanying documentation, this will result in the OMS validation being failed and the organisation's details will not be retrievable in a subsequent search in OMS for that organisation.

It should be noted that when populating organisation details via CTIS, it is strongly discouraged to provide incorrect/incomplete documentation, although, in terms of system functionalities, CTIS still allows users to progress with submission.

Note: Registration of clinical investigator sites in CTA, part II: it should be noted that CTIS requires sponsors to populate details of clinical investigator sites in part II of the dossier by retrieving the information from OMS, therefore clinical investigator sites also qualify as organisations that should be registered in OMS, as needed.

In case the required organisation is not already available in OMS, the sponsor can create a new organisation record directly from CTIS while compiling a CTA, as explained above. To support the registration in OMS of a clinical investigator site/ facility, a headed letter document signed and dated by a representative of that organisation, stating the full company name and address, should be provided.

Of note, any party can create a new organisation record in OMS for a clinical investigator site in part II. However, as explained above, the request should be supported by a valid documentation, otherwise it will not be possible for the sponsor user to search, select and find that organisation details again if the OMS request has failed.

Please note that the same applies for registration of other organisations in OMS, used when completing a CTA or submitting a notification in CTIS, such as details of CROs, vendors or other facilities that take part during the conduct of the trial. They will also need to be correctly registered in OMS to be retrievable when completing the CTA.

More details can be found in the Module 03 of the CTIS Training Material Catalogue.

References	Location (area or document)
EMA Organisation Management Service (OMS) homepage	https://www.ema.europa.eu/en/human-regulatory/research-development/data-medicines-iso-idmp-standards/spor-master-data/organisation-management-service-oms
Submission of change requests in OMS	https://www.ema.europa.eu/en/human-regulatory/research-development/data-medicines-iso-idmp-standards/spor-master-data/organisation-management-service-oms#submitting-change-requests-section
CTIS Training Material Module 03 'User Access Management: Videoclip'	https://www.youtube.com/watch?v=tUKA44v3P4Y&ab
Industry Webinar Introduction to OMS services and activities	https://www.youtube.com/watch?v=fxMpsgDnWZY&ab

3.2.2. High-level Administrator registration

The CTIS High-level Administrators are roles that are requested and managed through the EMA Account Management portal.

Two high-level administrators are required to initiate the management of users in the sponsor workspace:

A) Sponsors group of users:

The Sponsor Administrator role is considered to be the high-level Administrator for sponsors. The request for the Sponsor Administrator is submitted by the user that will become the Sponsor Administrator for an organisation and will be handled via EMA Account Management portal.

The registration process for the Sponsor Administrator (Admin) role, via the EMA Account Management portal, started on 1 September 2021 and needs to be supported by an appropriate "Affiliation letter" submitted to EMA at the time of registration.

It should be noted that the appointment of the high-level Admin for a sponsor, namely the sponsor Admin for an organisation, will be processed in IAM based on the organisation ID (Org-ID).

If different Org-IDs for the same organisation exist, they cannot be grouped together in the request to appoint a sponsor Admin for the purpose of using CTIS, and therefore each request should be raised individually. However, the same affiliation letter can be used and attached for each individual request.

Once the Sponsor Administrator role is assigned by EMA to one person, on basis of the validation of the request, the Sponsor Administrator will manage any following requests from other users who wish to become Sponsor Administrator for the same organisation.

EMA will not handle these requests once the first Sponsor Administrator has been assigned by EMA. The necessity of an "Affiliation letter" or any other supporting documentation for these subsequent requests will be decided by each organisation internally.

Explanatory training material is available in the CTIS Training Material Catalogue, in Module 07 – "Management of registered users and Role matrix" and on the EMA Account Management homepage.

B) Marketing Authorisation Holder (MAH) group of users:

A MAH Administrator role is also available to support the submission of clinical study reports into CTIS when a trial has been included in a marketing authorisation application. The registration process for MAH Administrator will take place via Service helpdesk and the process is currently under development. Further information will provided in the next updates of this document.

References	Location (area or document)
EMA Account Management homepage	https://register.ema.europa.eu/identityiq/home.html
Affiliation letter template	https://register.ema.europa.eu/identityiq/help/affiliation%20template.docx
CTIS Training Material Module 07 'Management of registered users and Role matrix: Step-by-step Quick Guide (high level Admin)'	https://www.ema.europa.eu/en/documents/other/step-step-guide-high-level-ctis-administrator-management-roles-permissions-ctis-training-programme_en.pdf
CTIS Training Material Module 07 'Management of registered users and Role matrix:	https://www.ema.europa.eu/en/documents/other/faqs-management-roles-permissions-ctis-training-programme-module-07_en.pdf

Frequently Asked Questions (FAQs) – specific ones’	
CTIS Training Material Module 07 ‘Management of registered users and Role matrix: Videoclips’	https://www.youtube.com/watch?v=SWvMeCnBhz0&ab https://www.youtube.com/watch?v=a02SfPT3fWY&ab

4. Management of users and organisations in CTIS

4.1. Key user management concepts in CTIS

There are two approaches to user management in CTIS: The organisation-centric approach and the trial-centric approach.

These approaches have been designed according to the needs of the different types of sponsor organisations that will use CTIS.

Before using CTIS, sponsors should carefully consider which user management approach best fits their organisation.

A full description of each of these approaches, and the advantages and disadvantages of choosing each one, are explained in the reference documents listed below, as well as in section 4.3 (organisation centric approach) and section 4.4. (clinical trial centric) of this document.

References	Location (area or document)
CTIS Training Material Module 07 ‘Creating a clinical trial: Clinical trial centric approach vs organisation centric approach’ (Video)	https://www.youtube.com/watch?v=hfzZxwX2W-Y
CTIS Training Material Module 07 ‘Management of registered users and role matrix’	https://www.ema.europa.eu/en/learning-module/management-roles/story.html

4.2. User roles concept in CTIS

In order to perform an action in CTIS, such as preparing, submitting or viewing a clinical trial application, notifications, summary of results and clinical study reports, a user must be assigned with a CTIS user role to obtain appropriate permissions.

Up to 18 sponsor user roles are foreseen for CTIS. The profile of a user can be built with a combination of different roles, to allow the user to complete various actions in CTIS. Users with administrator roles (high-level administrator, clinical trial administrator) can assign roles to other users, enabling them to perform actions.

Each role in CTIS comes with a specific set of permissions, which are predefined levels of actions that users can perform on data and documents stored in CTIS. These permissions are at user management level (reserved for administrator user roles) and access level, ranging from viewing to preparing and submitting clinical trial information in CTIS.

EMA has prepared a document to describe the concept of user roles and permissions in detail, a Role Matrix, which outlines the permissions linked to each user role, and a summary of roles document. These documents can be found at the links below.

References	Location (area or document)
CTIS Training Material Module 07 'Management of registered users and role matrix	https://www.ema.europa.eu/en/learning-module/management-roles/story.html
Guide to using holistic overview document	https://www.ema.europa.eu/documents/other/guide-using-holistic-overview-document_en.pdf
Sponsor workspace: summary of roles	https://www.ema.europa.eu/documents/other/sponsor-workspace-summary-roles_en.pdf
Sponsor workspace: summary of role permissions - Sponsor Workspace Roles - permission matrix summary	https://www.ema.europa.eu/en/documents/other/sponsor-workspace-summary-role-permissions_en.pdf

4.3. Organisation centric approach - Sponsor administrator

The organisation-centric approach is one of two user management approaches in CTIS that can be used by sponsors of a clinical trial. It is intended to serve the needs of organisations and/or sponsors that run multiple clinical trials.

The organisation-centric approach means that user management is done at organisation level.

Under the organisation-centric approach, the sponsor needs to appoint a high-level administrator (sponsor administrator). The sponsor administrator must be registered in EMA Account Management platform (see section on High-level administrator registration).

Before a user can register as a high-level administrator for a sponsor organisation, this organisation needs to be registered with the Organisation Management Service (OMS); see section 3.2.1 on Sponsor organisation registration.

Management of users within the organisation is done at the organisation level with a top-down model. Once appointed, sponsor administrators can assign medium-level administrator (i.e. clinical trial administrator) and business roles to users in CTIS to perform user management or business activities. In the organisation-centric approach, users become affiliated to the organisation (in particular, the user becomes affiliated to the Org-ID number as registered in OMS) of the sponsor administrator in CTIS when they are assigned with a role by this administrator.

The organisation-centric approach is particularly useful for organisations that will conduct trials on a regular basis, even if the frequency is low. The advantages of this approach are that it allows the management of access and roles across trials within one organisation thus, supporting data quality and integrity through a top-down validation process, as well as ensuring security as a user can only create a new CTA for that organisation-ID, as registered in OMS, if it has been previously assigned the clinical trial administrator (CT Administrator) role by the sponsor administrator.

Note: a user needs to be given the role of CT Administrator with scope 'all trials' in order to be able to create one or more new clinical trial applications for that organisation-ID .

Additional information is published on the EMA Corporate website under the Training Programme - User access management (Module 3).

References	Location (area or document)
EMA Account Management homepage	https://register.ema.europa.eu/identityiq/home.html
CTIS training material module 03 'User access management: User Quick Guide'	https://www.ema.europa.eu/en/documents/other/quick-guide-user-access-management-ctis-training-programme-module-03_en.pdf

4.4. Trial centric approach – Clinical Trial Administrator

The trial-centric approach is one of two user management approaches in CTIS. A user will automatically be guided to use this approach in CTIS only in the case a sponsor administrator has not been registered and appointed in the EMA account management system for a specific organisation.

In this approach, when the user initiates the creation of a new clinical trial application, the system will check if a sponsor administrator has been appointed for the sponsor organisation selected for that initial Clinical Trial Application. If that is not the case, the user will be able to proceed becoming the clinical trial administrator for that particular trial.

Further allocation of other CT Administrator or business roles to users is then done at trial level. The clinical trial administrator can manage users only for the trial(s) of his/her concern and can perform all sponsor business activities in CTIS related only to that particular trial(s).

In the trial-centric approach, users follow a bottom-up model that supports an easy way of submitting a limited number of clinical trial applications and straightforward management of a small number of users at trial level, not organisation level.

This approach is intended to serve the needs of small organisations and specifically academic sponsors, which may initiate trials on an *ad hoc* basis. It allows for the management of a smaller number of users and one or very limited numbers of clinical trials. This allows a faster process (no need for registration of a high-level sponsor administrator) when submitting a first initial, and subsequent applications, as applicable. However, it is less secure as any user can, potentially, create a trial on behalf of a sponsor organization that has not previously registered a sponsor administrator. Moreover, no individual user will have a centralised oversight of the trials being conducted for that sponsor organization nor the users involved.

Additional information is published on the EMA Corporate website under the Training Programme - User access management (Module 3).

References	Location (area or document)
CTIS training material module 03 'User access management: User Quick Guide'	https://www.ema.europa.eu/en/documents/other/quick-guide-user-access-management-ctis-training-programme-module-03_en.pdf

4.5. CTIS user personas and organisation models

Sponsors have various processes, structures and partnerships for managing clinical trials. In order to facilitate the completion of processes in CTIS, sponsors must understand the CTIS User Management functionalities and how to best make use of these functionalities in their organisational environment. Sponsors also need to understand user roles so that they can ensure that they have the correct confidentiality agreements in place.

To assist sponsors in understanding the CTIS User Management functionalities and how to organise in CTIS, EMA has published CTIS user personas linked to CTIS user roles and permissions, and example sponsor organisation models in CTIS.

References	Location (area or document)
CTIS sponsor user personas	https://www.ema.europa.eu/documents/other/clinical-trial-information-system-ctis-sponsor-user-personas_en.pdf
Principles for sponsor organisation modelling in CTIS	https://www.ema.europa.eu/documents/other/principles-sponsor-organisation-modelling-ctis_en.pdf

5. Product management in CTIS

5.1. Medicinal product registration in XEVMPD

Before completing the clinical trial application in CTIS, the sponsors should ensure that the details of the medicinal products used in the clinical trials are already registered in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD). It should be noted that a placebo can be added manually in CTIS directly; sponsors do not need to submit information on a placebo to the XEVMPD.

The dictionary includes all medicinal products that are authorised in the EU/EEA and un-authorised medicinal products (referred to in the XEVMPD as 'development' products) that are associated with clinical trials. Un-authorised products include those that have not received a marketing authorisation in the EU/EEA for the strength and/or pharmaceutical form.

To submit medicinal product data in the XEVMPD, sponsor organisations must be registered in the Organisation Management Service (OMS) and also with EudraVigilance either via Gateway or the EudraVigilance web application (EVWEB). This application allows registered users to create and send Extended EudraVigilance Product Report Messages (XEVPRMs), receive XEVPRM acknowledgements, view medicinal product information and perform queries.

Consolidated guidance on the electronic submission of information on un-authorised medicinal products for human use in the XEVMPD is now available on the 'Data submission on investigational medicines: guidance for clinical trial sponsors' webpage. The guidance was drafted based on the processes already in use and on information available in existing documentation.

Some high-level details specific for the registration of medicinal products in XEVMPD, to then be used in CTIS, are also presented below to describe the business flow.

The active substance for the development medicinal product must be available in EMA SMS (Substance Management Service).

Substance data is entered and maintained in the XEVMPD by the EMA; when substance information is successfully inserted in the XEVMPD, a substance EV Code is generated by the XEVMPD.

To request the addition of new substance information, or an amendment of existing substance information, in the XEVMPD, sponsors should follow the process described in the '[Changes to some business rules of the eXtended EudraVigilance Medicinal Product Dictionary \(XEVMPD\)](#)' document.

The EMA will validate the request and the substance EV Code will be provided to the sponsor via an e-mail confirmation from the EMA Service Desk within 4 working days.

If a development medicinal product needs to be entered in the dictionary by the sponsor, the sponsor should submit the medicinal product data in the XEVMPD via an XEVPRM with the operation type 'Insert'.

The medicinal product data must be submitted in accordance with the principles described in section 1 'Initial submission of a development medicinal product' of the '[Guidance on the electronic submission of information on investigational medicinal products for human use in the Extended EudraVigilance medicinal product dictionary \(XEVMPD\)](#)' document. The document also includes information on how to add missing information (for example substance or sponsor details) in the XEVMPD.

Providing that the insertion was successful, an EV Code will be assigned to the medicinal product record by the XEVMPD and sent automatically to the sponsors' sender organisation ID via an XEVPRM acknowledgement.

Once the EV Code assigned to the medicinal product record is available in the XEVMPD, the sponsor can search and retrieve the product details in CTIS. More information to associate an un-authorized medicinal product to a CTA can be found in section 5.4 of this handbook.

Training for clinical trial sponsors on how to enter and maintain product information into the XEVMPD is also available.

References	Location (area or document)
Data submission on investigational medicines: guidance for clinical trial sponsors webpage	https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/data-submission-investigational-medicines-guidance-clinical-trial-sponsors
Guidance on the electronic submission of information on investigational medicinal products for human use in the Extended EudraVigilance medicinal product dictionary (XEVMPD)	https://www.ema.europa.eu/en/documents/other/guidance-electronic-submission-information-investigational-medicinal-products-human-use-extended_en.pdf
Electronic submission of investigational medicinal product (IMP) data to the Extended EudraVigilance medicinal product dictionary (XEVMPD) - Frequently asked questions and answers (FAQs)	https://www.ema.europa.eu/en/documents/other/electronic-submission-investigational-medicinal-product-imp-data-extended-eudravigilance-medicinal_en.pdf
Extended EudraVigilance medicinal product dictionary (XEVMPD) training webpage	https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/extended-eudravigilance-medicinal-product-dictionary-xevmpd-training

eXtended EudraVigilance Medicinal Product Dictionary (XEVMPPD) Data-Entry Tool (EVWEB) user manual	https://www.ema.europa.eu/en/documents/other/extended-eudravigilance-medicinal-product-dictionary-xevmpd-data-entry-tool-user-manual_en.pdf
eXtended EudraVigilance Medicinal Product Report Message (XEVRPM) Step-by-Step Guide: Insert of a Development Medicinal Product (DMP)	https://www.ema.europa.eu/en/documents/other/extended-eudravigilance-medicinal-product-report-message-step-step-guide-insert-development_en.pdf

5.2. Medicinal product in CTIS extracted from XEVMPPD

For each trial in CTIS, the sponsor has to associate at least one medicinal product with the role as 'test' and populate this information in the part I of an initial clinical trial application.

Other product roles that can be associated to a clinical trial application, as applicable, are: comparator, placebo and auxiliary medicinal product.

In CTIS, the product information (for test product, comparator and auxiliary medicinal product) is retrieved from the XEVMPPD 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 and an un-authorised product.

5.3. Adding an authorised medicinal product in CTIS

Medicinal products details in an application form are mandatory. The users can add product details in a CTA for any product role in the trial (test, comparator, auxiliary) by searching and selecting the product details from XEVMPPD. Only for placebo, the product details can be specified locally in CTIS.

A user can add an authorised product by searching per product details, active substance or ATC code, as applicable.

The following parameters are displayed to a user that can search in XEVMPPD, via CTIS, for an authorised medicinal product:

×

Select Product

EU MP number <input style="width: 90%;" type="text"/> starts with ▼	Pharmaceutical form <input style="width: 90%;" type="text"/> ▼
Marketing authorisation number <input style="width: 90%;" type="text"/> starts with ▼	Strength <input style="width: 90%;" type="text"/> starts with ▼
Name of product <input style="width: 90%;" type="text"/> starts with ▼	Active Substance Name <input style="width: 90%;" type="text"/> starts with ▼
EU substance number <input style="width: 90%;" type="text"/> starts with ▼	ATC Code <input style="width: 90%;" type="text"/> starts with ▼

X CLEAR
🔍 Search products

Cancel
Add product

Depending on the parameters used to run the search, the user can get a unique search result returned, or multiple results can be retrieved.

For example, in case of search by EU MP number (i.e. EV Code assigned to a specific medicinal product record) only one result will be returned.

If, however, the user is searching per pharmaceutical form or strength of a medicinal product, then multiple results may be returned.

The following parameters are displayed to a user that can search in XEVMPD, via CTIS, for an active substance used in an authorised medicinal product:

Select Substance x

Name * EU Substance Number

Pharmaceutical form Strength

x Reset Search substances

Cancel Add Substance

The following parameters are displayed to a user that can search in XEVMPD, via CTIS, for an ATC code (level 3, 4 or 5) associated with an authorised product:

Search ATC x

ATC Code ATC Name

x Reset Search ATCs

Cancel Add ATC

5.4. Adding an un-authorised medicinal product in CTIS

Un-authorised medicinal product details may contain confidential information and therefore access to this information is restricted.

As explained in section 5.1 above, un-authorised products include those that have not received a marketing authorisation in the EU/EEA for the strength and/or pharmaceutical form.

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 be entered in the XEVMPD by the sponsor organisation.

If a medicinal product not yet authorised in the EEA is used in a clinical trial for different indications and/or routes of administration(s), the sponsor can update their existing development medicinal product in XEVMPD with the new indication/route of administration.

Registration of development medicinal products in XEVMPD is independent of the role of the medicinal product in the clinical trial, i.e. test, comparator before they can be used to populate dossier part I of the CTA in CTIS.

Users can retrieve un-authorised 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 in 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; 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 un-authorised medicinal product data.

Users will have to be cognisant of the required information in order to be able to run the search for development products in XEVMPD and add the product in the CTA of CTIS.

Select Product X

EU MP number* equals to EU substance number* equals to

X CLEAR Q Search products

Cancel Add product

Once the medicinal product of interest is identified, the user will see some pre-populated data, as it is available in the XEVMPD. The strength and the pharmaceutical form of the retrieved un-authorised product will not be displayed in the draft CTA dossier part I. It will only become visible following the submission of the application to the MSCs.

More details on the registration of medicinal products in XEVMPD is provided in section 5.1 of this handbook.

5.5. Medicinal product details in CTIS

For both authorised and un-authorised product, once that the desired medicinal product details are retrieved from XEVMPD, users will see some pre-populated data in CTIS extracted from the XEVMPD.

Some additional details, such as the dosage and administration details, information about of the medicinal product, Advance Therapy Medicinal Product (ATMP) details (as applicable), combination with medical device (as applicable), will have to be populated in CTIS.

In addition to the population of the structured data fields in CTIS, for each product, users will have to also provide the documents foreseen in the Clinical Trials Regulation, as applicable, namely:

- 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

Part I	Medicinal product details	>
Part II	Product characteristics	>
Evaluation	Dosage and administration details	>
Timetable	Information about the modification of the Medicinal Product	>
	Product Classification	>
	Product authorisation details	>
	Orphan Designation	>
	Active substance	>
	Advanced Therapy Medicinal Product	>
	Device associated with medicinal product	>
	Investigator brochure for the medicinal product	∨
	Compliance with (GMP) for the Medicinal Product	∨
	IMPD Quality	∨
	IMPD - Safety and Efficacy	∨
	Content labeling	∨

For more information, see also training module 10.

References	Location (area or document)
CTIS training module 10 'Create, submit and withdraw a clinical trial': e.g. Videoclip How to submit an initial clinical trial application in the CTIS Sponsor workspace – Fill in the Product details of Part I section	https://www.youtube.com/watch?v=e-JTvFoBICs

6. Transition from Directive to Clinical Trial Regulation

6.1. Transition period

There is a 3-year transition period that starts on the CTIS go-live date.

Year 1 (31 January 2022 to 31 January 2023):

- During the first year after CTIS go-live, sponsors will be able to choose whether to apply for a new clinical trial application (CTA) under the regime of the Clinical Trial Directive (CTD: Directive 2001/20/EC) including using EudraCT or to apply under the new legislation, the Clinical Trial Regulation (EU) No 536/2014, using CTIS.
- Both options will be possible, and sponsors will be able to choose for themselves which system to use.
- Member States will be ready to use CTIS and accept applications under the new legislation (CTR) from day 1 of CTIS go-live.

Years 2 and 3 (31 January 2023 to 31 January 2025)

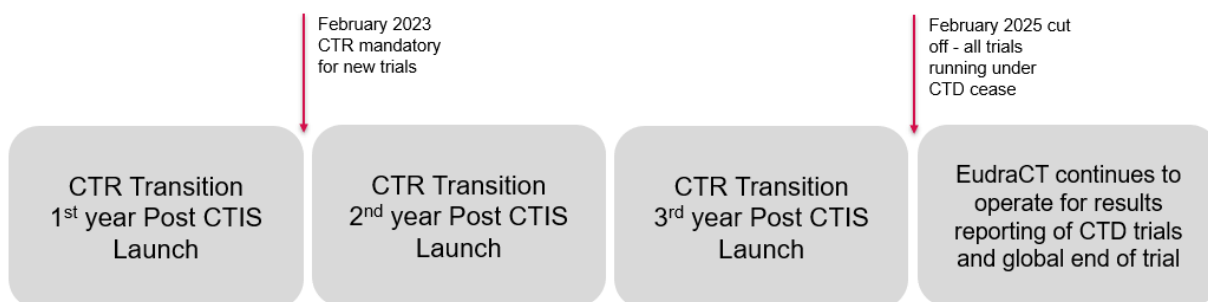
- Submission of new CTAs under the CTD in EudraCT will not be available for new CTAs. From 31 January 2023 all new CTAs must be submitted under the new legislation (CTR) using CTIS.
- CTAs that were submitted under the old legislation (CTD) utilising EudraCT prior to 31 January 2023, will be able to continue to run and complete under that Directive for a further two years maximum, until the end of the 3-year transition period, occurring on 31 January 2025. Processes will remain unchanged, and sponsors will therefore be able to submit end of trial and

substantial amendments, as needed during the course of the trial, under the Directive. EudraCT will remain operational throughout the transition period to enable these trials to continue.

- By 31 January 2025, these clinical trials, authorised under the CTD, must either have ended in the EU/EEA or have been transitioned; they cannot continue running under the old legislation utilising EudraCT beyond the end of the 3-year transition period (31 January 2025). Thus, if sponsors are running trials that they expect to continue in EU/EEA beyond 31 January 2025, sponsors will need to transition them to the CTR before the transition period expires. EudraCT will remain active after the end of the transition period for sponsors to notify global end of the trial and submission of summary results of trials completed under the Directive.
- Clinical trials applications to be transitioned have already been approved under the Directive. Member States Concerned (MSC) may therefore choose to approve transition trials within or in less than 60 days. However, MSC are also permitted to raise RFIs on the transition application (leading to a maximum approval period of 106 days) and applications for trials with some types of investigational medicinal product (e.g. ATMPs) can be extended further. Therefore sponsors are required to submit their transition applications to CTIS early enough before the end of the transition period, to ensure that trial conduct is not interrupted.
- Transition applications can be submitted at any time during the 3-year transition period and sponsors are urged to ensure that they complete the process early enough in the transition period to ensure continuity of the clinical trial beyond 31 January 2025, taking account of statutory holidays and the two-week winter clock stop.
- Once a clinical trial has switched to the CTR, all the requirements of the CTR will apply from the date of approval of the transition application under the CTR.
- Details of the requirements for transitioning of single-country and multi-national trials are provided in the Eudralex Volume 10 Q&A mentioned in the table below. Multi-national clinical trials (trials conducted under the same EudraCT number in different Member States) should be transitioned as a single multi-country clinical trial application under the CTR, utilising a harmonised or at least consolidated protocol (refer to Eudralex Volume 10 Q&A 11.7). Sponsors may need to consider harmonising the protocol by substantial amendments under the CTD before they transition them as one trial under CTR with one EU Clinical Trial number (refer to Eudralex Volume 10 Q&A 11.8). Consolidation of a protocol to only reflect what is already approved in each MSC prior to submission of a transition application does not require prior approval via submission of a substantial amendment under the Directive since no changes to the protocol content are made during the consolidation process.

Voluntary Harmonisation Procedure (VHP) trials:

- The VHP will discontinue as of entry into application of the CTR; it should be noted that the ability to submit new applications or substantial amendments under the VHP terminated already on 15 October 2021. The clinical trials included in the VHP will, in principle, qualify to transition as multi-national clinical trials. More details are provided in Eudralex Volume 10 Q&A 11.9.



References	Location (area or document)
Link to EudraLex - Volume 10 - Clinical trials guidelines	https://ec.europa.eu/health/documents/eudralex/vol-10_en#fragment1
Link to EudraLex - Volume 10 - Clinical trials guidelines - QUESTIONS & ANSWERS draft	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
Conclusion of VHP Procedure - Deadline for submissions to VHP in the context of the Christmas Break 2021/2022 and transition to CTIS/CTR starting with the CTR application	https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2021_07_CTFG_Conclusion_VHP_Deadlines_for_VHP_Submissions.pdf
CTFG_Best_Practice_Guide_for_sponsors_of_transition_multinational_clinical_trials	https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2018_05_CTFG_Best_Practice_Guide_for_sponsors_of_transition_multinational_clinical_trials.pdf

6.2. Points to consider on transitional arrangements

Some aspects have been included here of what the sponsor should consider when defining a submission strategy for CTIS during the transition period.

Key dates:

Event	Date
Earliest date for submission of a new clinical trial application under the Regulation.	31 January 2022
Earliest date for submission of a clinical trial application to transition a trial from the Directive to the Regulation.	31 January 2022
Latest date for submission of a new clinical trial application under the Directive.	30 January 2023

Does the trial need to be transitioned?

- Sponsors need to consider whether a trial needs to be transitioned.

- Only trials that are still running under the Directive on 30 January 2025 that meet the following criteria need to be transitioned:
 - ❖ Are interventional clinical trials in humans and
 - ❖ Involve at least one site in the EU/EEA where the trial is still ongoing and
 - ❖ Are not on hold
 - ❖ Have not submitted a notification that the trial has ended in the EU/EEA.

If an end of trial notification has been submitted in all EU/EEA member states, but the global end of the trial has not been notified, the trial does not need to be transitioned. Global end of the trial and trial summary results should be posted via EudraCT under the Directive.

Trials that are very old and started prior to the Directive 2001/20/EC coming into application do not benefit from the transition process. If they are truly interventional and need to continue to run after the end of the CTR transition period, then a new CTA under the CTR needs to be submitted.

Paediatric trials that are being conducted entirely outside the EU/EEA but for which a EudraCT number has been created should also not be transitioned.

Trials that are on hold beyond the end of the transition period cannot be transitioned. In these circumstances restarting the trial would require submission of a new application under the CTR.

General considerations:

- Sponsors will need to ensure that all documentation is available in electronic format for submission via CTIS.
- The workflow in CTIS for transitioning a trial follows the workflow of submitting an initial application. Therefore, transitioning a trial from the Directive to the Regulation can take up to a period of 60 days [(if no Member States intervene during the workflow) and up to a maximum of 106 days (in situations where a Member State raises an Request for Information (RFI)]. However, it should be noted that it is possible for a Member State to intervene in the workflow and approve a transition application before 60-day automatic workflow is completed. In addition, the timelines may be extended beyond 106 days if the product falls within the definition of an Advanced Therapy Medicinal Product (ATMP).
- Transitioning trials from the regime of the CTD into the regime of the CTR, must be carried out when there are no substantial amendments ongoing in any Member State Concerned (MSC) under the Directive.
- The trial will be required to comply with the requirements of the Regulation as of the CTA decision date captured in CTIS. Prior to that date the trial continues under the CTD.
- Where a mandatory document is expected to be uploaded into the CTIS that does not exist for the transitioning trial, then a blank document is expected to be uploaded with a comment that the document does not apply and it has been provided to allow transition from the CTD to the CTR Regulation.

If a substantial modification affecting this part of the CTA follows approval of the transition application, the required documentation would need to be provided as part of the substantial modification.

- In addition, if a sponsor intends to transition a multi-national clinical trial as a single multi-country clinical trial application under the CTR, only data field information and documents for the MSCs where the trial is still ongoing need to be entered in CTIS.
- When completing the CTA and providing the CT data and documents in CTIS, consideration should be given to the transparency requirements of the CTR, including the need to remove personal data from submitted documentation and to apply for a deferral of publication, if applicable.
- Notifications information, even if they have already occurred (e.g. start and end of the trial, start of recruitment, temporary halt) will need to be completed in CTIS since they trigger other events in the system.
- For example, start of recruitment is relevant since transition trials can expire for any MSC if recruitment has not started within 2 years of the decision date registered in CTIS.
- However, retrospective documentation does not need to be submitted to CTIS (e.g. interim CSRs, inspection reports or earlier versions of IBs or Protocols that have been superseded under the CTD). Only current approved versions should be included in the transition application.
- Submission planning during the active phase of the trial will be critical to ensure trials are not interrupted.

Mono-national trials:

- The trial is transitioned from the CTD to the CTR by submitting a new application in CTIS that reflects the content of the dossier that is currently approved and has been assessed by the MSC. Documentation required is specified in Eudralex Volume 10 Q&A #11.6 in addition to the cover letter and CTIS field information.

Multi-national Trials:

- It is preferable to transition multi-national trials to the CTR under a single CT number in CTIS provided they have a consolidated protocol that corresponds to what is already authorised in each of the MSCs.
- The trial is transitioned from the Directive to the Regulation by submitting a new application in CTIS that reflects the dossier that is currently approved and has been assessed by ALL the MSCs. If the protocol is not consolidated, the sponsor should first submit a substantial amendment under the Directive in order to align and obtain a harmonised protocol authorised by all Member States before submitting a transition application under the CTR.
- Documentation required is specified in Eudralex Volume 10 Q&A #11.7 in addition to the cover letter and CTIS field information.
- Once the application to transition the trial has been submitted to CTIS, a reporting Member State (RMS) will have to be selected. The RMS will be required to coordinate the oversight of the trial under CTR.
- All ongoing trials, including VHP trials, can be submitted for transition to CTIS as from 31 January 2022, and during the review/approval time no substantial amendments or substantial modifications can be submitted via the Clinical Trial Directive or Clinical Trial Regulation respectively.
- In the period from the end of the VHP procedure submission (15 October 2021) until submission of the transition application, any substantial amendments submitted to VHP trials will be assessed in accordance with the Clinical Trial Directive by individual MSCs.

7. Data, documentation and processes

7.1. Clinical Trial Application (CTA) and Notification Forms

This section intends to provide information on the data fields and documents that sponsors need to complete, as applicable, in the context of clinical trials applications and notifications to be submitted to CTIS. These forms provide an overview of the data fields to be completed and documents to be provided with the aim to help sponsors to prepare in advance the information required for the submission of an initial CTA, adding Member State Concerned application (AMSC), Substantial Modification (SM), non-Substantial Modification (non-SM) and notifications.

The forms referred to in this document have been prepared based on the audit version of the system and further updates are planned for the Go-live and post-Go-live versions. Next review also envisages to include the CTIS structured data form for Request for Information (RFI) and the Annual Safety Report (ASR).

7.1.1. Clinical Trial Application Form overview of the data fields to be completed and documents to be provided

In the table below there are two excel documents, one providing the forms for initial Clinical Trial application, adding Member State Concerned application, Substantial Modification (for a single trial) and non-Substantial Modification, and a separated one for a Multi trial Substantial Modification application.

Each document contains an overview with some relevant instructions followed by the list of the data fields to be completed and documents to be uploaded for each of the CTIS sections to be prepared for an application: the form section (4 tabs included, one per application type), MSC, Part I and Part II sections. Moreover, the documents include the different searches that the sponsor will need to perform through interfaces with other systems.

For each of the sections mentioned previously, the following columns with the information indicated, have been included per data field:

- ID: reference of the field referring to.
- Field Type: type of field referring to (Header, Lookup list, Radio button, Text, Numeric, Document upload).
- Field Name: field name in CTIS.
- Field Description: brief description of the field.
- Cardinality: information whether the data input in the field is 0, 1, or many.
- Conformance: information whether the field/document is Conditionally required, Optional, Mandatory, Read Only.
- Document format: specific format (.PDF, .Doc, etc) in which the document may be uploaded, when applicable.
- Publication: information whether the field/document will be made public (yes/no).
- Deferrable: information whether deferral to the publication can be applied (yes/no).
- Editable: information whether the field is editable under a given type of application (yes/no). This is not applicable for the Multi trial Substantial Modification application.

References	Location (area or document)
CTIS structured data form - Applications (IN, AMSC, SM, non-SM)	https://www.ema.europa.eu/documents/template-form/ctis-structured-data-form-initial-application-additional-member-state-concerned-substantial_en.xlsx
CTIS structured data form - Applications (Multi trial SM)	https://www.ema.europa.eu/documents/template-form/ctis-structured-data-form-multi-trial-substantial-modification_en.xlsx

7.1.2. Notification forms: overview of the data fields to be completed and documents to be provided

The document provided in the table below contains an overview with some relevant instructions followed by the overview of the data fields to be completed and to be uploaded for each notification form present in the notifications section implemented in the system: start of trial, start of recruitment, end of recruitment, end of trial, global end of trial, temporary halt, restart of trial, restart of recruitment, anticipated date of summary of results, unexpected event, serious breach, urgent safety measure and 3rd country inspectorate inspection.

For each of the notifications mentioned previously, the following columns with the information indicated, have been included per data field:

- ID: reference of the field referring to.
- Field Type: type of field referring to (Header, Lookup list, Radio button, Text, Numeric, Document upload).
- Field Name: field name in CTIS.
- Field Description: brief description of the field.
- Cardinality: information whether the data input in the field is 0, 1, or many.
- Conformance: information whether the field/document is Conditionally required, Optional, Mandatory, Read Only.
- Document format: specific format (.PDF, .Doc, etc) in which the document may be uploaded, when applicable.
- Publication: information whether the field/document will be made public (yes/no).
- Deferrable: information to which a deferral to the publication date can be applied (yes/no).

References	Location (area or document)
CTIS structured data form - Notifications	https://www.ema.europa.eu/documents/template-form/ctis-structured-data-form-notifications_en.xlsx

7.1.3. Data fields and documents specifications

Data fields and documents specifications can be found in the overview section of each CTIS Structured data form.

When populating clinical trial information in CTIS, the following points should be considered:

As a general rule, 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 (EMA-111111-PIP11-11) or fields with smaller sizes. These are further detailed below.

- **Smaller number of characters allowed in free text fields in CTIS:**
 - o Phone number: 15 characters
 - o Protocol code, registry identifier, designation number for orphan drug, CAT reference number: 20 characters
 - o Sponsor internal identifier for unexpected event, serious breach, urgent safety measure, 3rd country inspectorate inspection notifications: 20 characters
 - o 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 characters
 - o Primary and secondary end points: 500 characters
 - o Description of the device: 2000 characters
 - o Substantial modification part I, part II, part I and II reason and scope: 2000 characters
- **Characteristics of documents upload:**
 - o Document file name: 100 characters. No special characters (/,:|) allowed.
 - o Document version: 10 characters, it can be numerical or not
 - o Document comment free text field: 4000 characters

The system allows for storage of clinical trial data with a maximum size of 220 GB.

7.2. Download options

Download options will be described in a later version of the Handbook.

7.3. Document modifications

Document modifications will be described in a later version of the Handbook.

7.4. Handling of Requests for Information (RFIs) in CTIS

During the evaluation of CTAs, Member States Concerned (MSC) have the possibility to require clarifications to the sponsors by raising RFIs that should be addressed within the defined timelines. It should be noted that failing to provide responses within the timelines will lead to the application being lapsed. It is encouraged that high quality dossiers are submitted in CTIS with each application, to minimise, where possible, the need to raise a request for information.

RFI can be identified by the sponsors via monitoring the notices and alerts tab and the RFI tab in CTIS Sponsor workspace. For example, in an initial application with Part I and part II, an RFI can be raised by the reporting Member State (RMS) as part of the validation and assessment of part I and by each MSC following part II assessment. RFI can be raised by the RMS and MSC at any point in time during

the evaluation phase. There are not predicted timelines and period of time when RFI can be raised, therefore the sponsors should be vigilant on monitoring the notices and alerts and the RFI tab.

RFIs are raised by the RMS/MSC via the considerations documented in the system as part of the evaluation. Documented considerations are then consolidated by the RMS/MSC (accepted/merged/adapted or rejected) directly in CTIS and used as the basis for the RFI. RMS/MSC can also upload documents into CTIS as supporting documentation to the RFI being raised.

Sponsors have the possibility to download from CTIS the considerations part of the RFI, as well as any supporting documentation, so RFI can be allocated to relevant team members to be addressed. Users can also have access to the considerations in the RFI and any documents, directly from CTIS and work on their reply directly from the system.

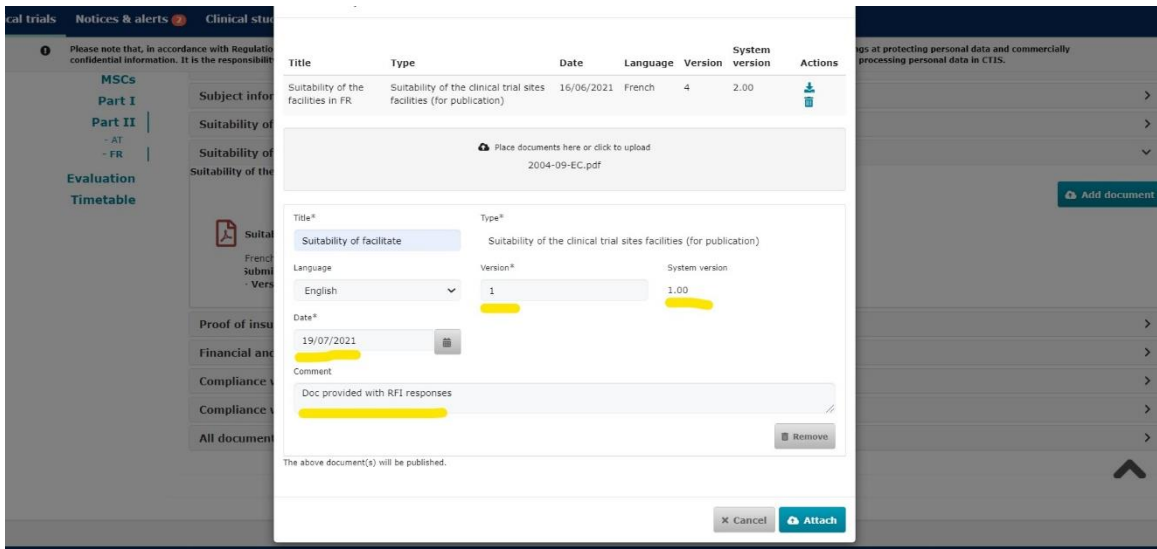
In order to address an RFI, the sponsor will have to provide a response in the free text displayed after each consideration raised by the RMS/MSC as part of the RFI, that can be complemented by supporting documents. RFI responses can be saved as draft before submission.

The screenshot shows a form for responding to an RFI. At the top, it displays the 'Consideration number' (RFI-CT-2021-500869-24-00-IN-003-02), 'Application section parts' (Part I - Clinical), and 'Application section and document' (Justification low Intervention). Below this, there is a 'Consideration' field with the value 'consideration'. A large 'Response' text area is provided for the user to enter their reply. At the bottom, there is a section for 'Documents related to the response' with two buttons: 'Add document' and 'Save response'.

The sponsor will also have the possibility to apply changes to the dossier, both structure data and documents, depending on the nature of the request raised. If changes to the dossier are applied, the sponsor should also provide a document containing a description of the changes made.

This screenshot shows a more detailed view of the RFI response form. On the left, there is a navigation menu with 'Part I *', 'Part II', 'Evaluation', and 'Timetable'. The main content area shows the RFI ID 'RFI-CT-2021-500869-24-00-IN-003' with a 'Open: 19/07/2021' status. A 'Discard changes' button is visible. A checkbox labeled 'Includes application changes' is checked and highlighted with a yellow circle, with the text 'Changes to the application *' below it. There are sections for 'Supporting documentation' (MS: Quality and Non-Quality), 'Sponsor: General documentation', and 'Quality related documentation', each with an 'Add document' button. A 'No document has been uploaded.' message is also present.

Previously uploaded documents can be deleted when responding to an RFI or a new version of a document can be provided (in this case documents will have the same document type, language and title). When uploading a new document, the sponsor can specify the date and the version of the file, and a system version will also be generated sequentially by the system.



Completely new documents can also be submitted when replying to an RFI, for the section of the application dossier in question and subject to the RFI.

Access to the RFI, as well as download functionality, will depend on the user profile, for example part I only users will only have access to RFI pertaining to part I of the dossier. Each user can download the RFI and RFI responses that the user has access to. It should be noted that CT Administrators can assign to themselves access to Part I and Part II and therefore can have access to all RFIs.

CTIS enables sponsors users to address RFI simultaneously in the different sections of the CTA, namely a user can work on part I RFI at the same time as users working on part II RFI. Also, part II raised by different MSC can be addressed simultaneously by different users, if needed.

RFI raised and the responses provided are subject to publication rules, except for RFI raised for sections of the application that are exempted from publication, such as the quality section of the dossier or questions related to quality in general.

Training material on how to address incoming RFIs related to the evaluation of a Clinical trial application has been published on the CTIS Training Material Catalogue, Module 11.

Finally, RFI mechanisms have also been implemented in the system to enable exchange of information between MSC and sponsors as part of an ad hoc assessment, following for example a notification of a serious breach, or in case of evaluation of an annual safety reports (ASRs) or when a sponsor opinion needs to be provided in the context of a corrective measure.

Training material on how to address other types of incoming RFIs (Ad hoc assessment, Corrective measures) has been published on the CTIS Training Material Catalogue, Module 04 and 05. Training material on how to address incoming RFIs related to ASR will be published on the CTIS Training Material Catalogue, Module 18.

References	Location (area or document)
CTIS Training Material Module 04 'Support with workload management in the sponsor workspace: eLearning – RFI section'	https://www.ema.europa.eu/en/learning-module/workload-management-sponsor/story.html
CTIS Training Material Module 04 'Support with workload management in the sponsor workspace: FAQs – RFI section'	https://www.ema.europa.eu/en/documents/other/faqs-support-workload-management-workspace-ctis-training-programme-module-04_en.pdf

CTIS Training Material Module 04 'Support with workload management in the sponsor workspace: Videoclip'	https://www.youtube.com/watch?v=6z-Q6-LK8Ws&ab
CTIS Training Material Module 05 'Manage a CT through CTIS: eLearning – various references to types of RFI'	https://www.ema.europa.eu/en/learning-module/manage-ct/story.html
CTIS Training Material Module 05 'Manage a CT through CTIS: FAQs – various references to types of RFI'	https://www.ema.europa.eu/en/documents/other/faqs-how-manage-ct-ctis-training-programme-module-05_en.pdf
CTIS Training Material Module 11 'Respond to requests for information received during the evaluation of a clinical trial application: eLearning'	https://www.ema.europa.eu/en/learning-module/respond-to-rfis-ctis/story.html
CTIS Training Material Module 11 'Respond to requests for information received during the evaluation of a clinical trial application: FAQs'	https://www.ema.europa.eu/en/documents/other/faqs-how-respond-requests-information-received-during-evaluation-clinical-trial-application-ctis_en.pdf
CTIS Training Material Module 11 'Respond to requests for information received during the evaluation of a clinical trial application: Videoclips'	https://www.youtube.com/watch?v=vbQVki3pGI&ab https://www.youtube.com/watch?v=DXrQMStp2a0&ab https://www.youtube.com/watch?v=sO8YRSatsDA&ab
CTIS Training Material Module 18 'How to create and submit an annual safety report and respond to related requests for information: Step by Step guide'	https://www.ema.europa.eu/en/documents/other/step-step-guide-how-create-submit-annual-safety-report-respond-related-requests-information-ctis_en.pdf

8. Safety reporting obligations

8.1. Suspected Unexpected Serious Adverse Reactions (SUSARs)

The reporting of SUSARs by the sponsor to the Agency in the context of the CTR is outlined in Article 42. The most relevant change for sponsors is the legal obligation for the electronic reporting of SUSARs to the clinical trial module of EudraVigilance for a clinical trial performed in at least one Member State (Art 42.1).

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 Member State concerned (MSC), it may report to the Member State where the SUSARs occurred. That Member State shall then report the SUSARs to EudraVigilance (Art 42.3).

In April 2021 the Clinical Trials Expert Group (CTEG) announced that CT-3 final arrangement for SUSARs will apply also to all trials approved through the CTD from when CTIS goes live. This means that from 31 January 2022, sponsors **will report SUSARs only to EudraVigilance**, regardless of whether the trial has been approved through the CTR or CTD. This will bring the benefit of a single submission process and harmonised procedures to the area of SUSAR reporting. Member States will have the ability to set up SUSAR rerouting rules in EudraVigilance if they wish to receive copies of

SUSARs for their national systems. This will apply for all trials approved under the Clinical Trial Directive and the Clinical Trials Regulation.

The section 7c (REPORTING OF ADVERSE EVENTS/REACTIONS) of the Eudralex Volume 10 Q&A published by the Commission may address some further questions in the context of SUSAR reporting.

References	Location (area or document)
Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536
Link to EudraLex - Volume 10 - Clinical trials guidelines - QUESTIONS & ANSWERS draft	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
Detailed guidance on the collection, verification and presentation of adverse events/reactions arising from clinical trials on medicinal products for human use ("CT-3")	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52011XC0611(01
CTEG announcement that CT-3 final arrangements for SUSAR reporting will apply from when CTIS goes live	https://ec.europa.eu/transparency/expert-groups-register/core/api/front/document/56534/download
EudraVigilance: electronic reporting	https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-electronic-reporting

8.2. Annual Safety Report (ASR)

The reporting of ASRs by the sponsor to the Agency in the context of the CTR is outlined in Article 43, applicable to trials registered in CTIS and managed under the CT Regulation. The sponsor shall submit annually through CTIS a report on the safety of each investigational medicinal product (IMP) used in a clinical trial, other than placebo, for which it is the sponsor. This obligation referred to in paragraph 1 starts with the first authorisation of a clinical trial in accordance with the CTR. It ends with the end of the last clinical trial conducted by the sponsor with the IMP.

The section 7d (ANNUAL SAFETY REPORTS) of the draft Q&A published by the Commission in Eudralex Volume 10 may address some of the questions in the context of ASR reporting.

The documents referred to in section 7.1 apply also to this section. In addition, you can find the link to the ASR submission training module using the url below:

References	Location (area or document)
Link to EudraLex - Volume 10 - Clinical trials guidelines - QUESTIONS & ANSWERS draft	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
CTIS Training Material Module 18 'How to create and submit an annual safety report and respond to related requests for information: Step by Step Guide'	https://www.ema.europa.eu/en/documents/other/step-step-guide-how-create-submit-annual-safety-report-respond-related-requests-information-ctis_en.pdf

9. Data transparency

The clinical trial information processes and flows in CTIS start with a clinical trial application (CTA) submitted by the sponsor, or delegated entities, via CTIS secure domain (see section on Overview of Clinical Trial Application process in CTIS), to carry out a clinical trial in the EU/EEA, and the corresponding evaluation performed by the Member States Concerned (MSCs).

Following this evaluation, a decision is issued by each MSC for the CTA, on whether the trial is authorised, authorised with conditions, or not authorised. After a decision, of any kind, has been issued by the MSCs, the data and documents submitted to CTIS for the trial will be made available to the public, unless the sponsor has applied for a deferral (see link to disclosure rules in the reference table below).

When populating the data fields of CTIS, the sponsor user will be able to request a deferral. When requested by the sponsors at the time of submission of an initial application and if granted by the RMS/MS during the evaluation of the application, a deferral will delay the publication of a set of data and documents (e.g. protocol, investigator brochure, informed consent information sheet). The documents that can be deferred from publication and the deferral timelines are listed in the Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database" (see link to disclosure rules in the reference table below).

Article 81(4) of the Regulation is clear in defining the publication aspect of the clinical trial information contained in the EU Database that is part of CTIS:

"4. The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:
(a) protecting personal data in accordance with Regulation (EC) No 45/2001
(b) protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure
(c) protecting confidential communication between Member States in relation to the preparation of the assessment report
(d) ensuring effective supervision of the conduct of a clinical trial by Member States."

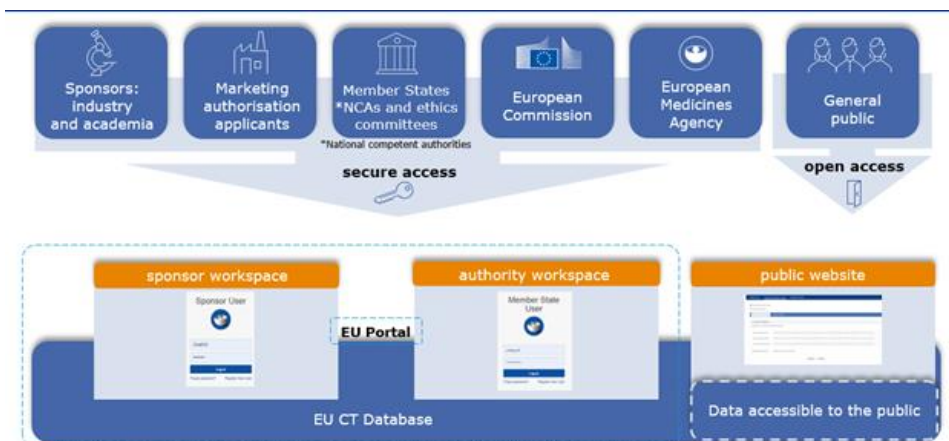
The sequence of events occurring during the trial life cycle might require the collection and processing of personal and non-personal data. Also, data and documents provided by the users in CTIS might contain information that is considered commercially confidential.

As defined in Article 81(4), both personal data and commercial confidential information are exempted from publication.

In order to address this requirement, CTIS provides several functionalities:

- ability to defer publication to protect Commercially Confidential Information (CCI). This is taking into account the marketing authorisation of a medicinal product and phase of a trial;
- ability to upload a document into a placeholder that will never be subjected to publication (e.g. financial arrangements, IMPD-Quality, RFI related to quality);
- ability to upload alongside a document 'for publication', a version 'not for publication' to protect personal data and CCI, if the submission is needed for the assessment by the MSC.

Access to data and document in CTIS secure domain is regulated depending on the user's profile. Part of the clinical trial information contained in CTIS secure domain will also be made available to the general public, via the public website.



A version 'for publication' of the mandatory documents as outlined in the data fields for clinical trial information submitted to CTIS in an initial application or during the trial lifecycle, must be provided, regardless whether a deferral for publication will be requested or not, as applicable for the document in question. If a sponsor has requested deferral of publication for a document, it will be the 'for publication' version of that document that will be deferred.

The need to have in CTIS a version of the documents 'for publication' and 'not for publication' will depend on document content and might not be necessary in every instances. In case both versions are needed, then they should be provided at the same time. Only the 'for publication' version of the document will be published, with timing depending on the deferral rules –as applicable. CTIS will not allow the uploading of a 'not for publication' version of a document without having already uploaded a 'for publication' version.

It should be noted that the deferral functionality has been implemented as a tool available for sponsors to protect CCI aspect in the documents uploaded in CTIS and avoid extended redaction to be carried out by sponsors.

However, it should be noted that the deferral mechanism is optional for the sponsor to choose, if they wish to delay the publication of data and documents via CTIS. Sponsors are allowed to submit a 'for publication' and 'not for publication' version of documents that are not subject to deferral rules. If no deferral is selected, the data and documents (for publication version) will be published at the first opportunity: the time of the decision of the first MSC.

In the version of the documents 'for publication' the user shall remove/omit information on personal data and may remove/omit any relevant information still considered to be CCI even after the deferral period has passed, as applicable.

The ability to upload a version 'not for publication' is made available to the sponsor, in order to provide information on personal data and CCI that are deemed necessary for the assessment by the RMS/MSCs. It is not expected that such version is provided by the sponsor for all document types, as again, the need will depend on the document content.

This functionality gives the freedom to exchange information in CTIS secure domain between users with regulated access depending on their profile, and at the same time protect personal data and the legitimate interest of sponsors for what concerns CCI.

The public domain will enable members of the public to have access to clinical trial information, that can be retrieved via a search mechanism that can be customised according to the needs.

For a list of the data and documents that will, or will not, be published via CTIS please consult the files mentioned in section 7.1 of this document.

Search criteria Search results Display options

Basic Criteria

Contain all of these terms:

Contain any of these terms:

Does not contain any of these terms:

Hide Advanced Criteria

Trial status	<input type="text" value="--Select Multiple--"/>	Country	<input type="text" value="--Select Multiple--"/>
Trial number	<input type="text"/>	Age group	<input type="text" value="--Select Multiple--"/>
Trial title	<input type="text"/>	Therapeutic area	<input type="text" value="--Select Multiple--"/>
Conditions	<input type="text"/>	Trial phase	<input type="text" value="--Select Multiple--"/>
Sponsor/co-sponsor	<input type="text"/>	Sponsor type	<input type="text" value="--Select Multiple--"/>
End point	<input type="text"/>	Gender	<input type="text" value="--Select Multiple--"/>
Product	<input type="text"/>	Protocol code	<input type="text"/>
Product role	<input type="text" value="--Select Multiple--"/>	Rare disease	<input type="checkbox"/>
Population type	<input type="text" value="--Select Multiple--"/>	PIP	<input type="text"/>
Orphan designation number	<input type="text"/>	Events	<input type="text"/>
Does this product	<input type="radio"/> Yes		

References	Location (area or document)
Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536
Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014"	https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf
CTIS Training module 12 'Data protection: e-learning course'	https://www.ema.europa.eu/en/learning-module/data-protection-ctis/story.html

10. Support

10.1. CTIS Highlights Newsletters

To stay up to date with developments and plans, please see EMA CTIS Highlights Newsletters on EMA corporate website: to subscribe write to CT.communication@ema.europa.eu

References	Location (area or document)
CTIS Highlights NewsLetters	https://www.ema.europa.eu/en/news-events/publications/newsletters#clinical-trials-information-system-(ctis)-highlights-section

10.2. CTIS information events

The events page on the EMA corporate website will collect information on information events organised by EMA on CTIS (search words e.g. CTIS; SME).

References	Location (area or document)
EMA corporate website Events page	https://www.ema.europa.eu/en/search/search/ema_editorial_content/ema_event?sort=field_ema_computed_date_field&order=desc

10.3. CTIS training

Training is available from EMA on how to use the Clinical Trials Information System (CTIS) ahead of its planned launch. EMA's training resources are tailored for clinical trial sponsors and staff of the European Union (EU) Member States, European Commission and other organisations who will use the system.

The EMA CTIS training programme is mainly composed of **online training modules** available for use from the CTIS training programme page on the EMA corporate website. A wide selection of materials in different formats are available on introductory modules, common functionalities for all registered users, modules on the authority (Member States, EMA and European Commission) workspace and on the sponsor workspace. It also includes recordings from virtual training sessions organised by EMA and a section with information about the Master trainer programme.

When starting to use the training materials, it is advised that organisations and users first make use of the Guide to CTIS Training Material Catalogue.

Reproduction and/or distribution of the content of the published training materials is authorised for non-commercial or commercial purposes, provided that the EMA is acknowledged as the source of the materials (©2021 European Medicines Agency).

The European Medicines Agency has developed the training materials to enhance public access to information on CTIS. The training materials describe initially a preliminary version of CTIS and while the material will undergo revision it may therefore not entirely describe the system as it is at the time of use of the material. The Agency does not warrant or accept any liability in relation to the use (in part or in whole) or the interpretation of the information contained in this training material by third parties.

Limited end user training events will be organised by EMA and announcements will be made on the events page of the EMA corporate website (search e.g. with word "CTIS" or "SME").

References	Location (area or document)
Clinical Trials Information System (CTIS) training programme page (EMA corporate website)	https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-ctis-online-modular-training-programme
Guide to CTIS Training Material Catalogue (EMA corporate website)	https://www.ema.europa.eu/en/documents/other/guide-ctis-training-material-catalogue_en.pdf

10.4. CTIS training environment for user training and organisation preparedness

The Clinical Trial Information System training environment (CTIS Sandbox) is typically a copy of a recent version of CTIS albeit not always identical to latest version. The purpose of CTIS Sandbox 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. CTIS Sandbox use will be directed by conditions, instructions and guidance and is made available by EMA. EMA will maintain support for the CTIS Sandbox users through a CTIS User Support Service.

Access to CTIS Sandbox is based on need and urgency and is therefore intended for, and limited to, those individuals and organisations that are the future users of the secure workspaces of CTIS (authority, sponsor workspace) and who are already trained on the system through the CTIS Training Programme (MS Master Trainer, online training modules, thorough self-study).

A phased rollout of the training environment will be provided to defined user groups in sequence, starting with Member States and the European Commission and followed by Sponsors.

More specifically, EMA will provide access to the CTIS Sandbox in 3 waves:

- **Wave 1** (15 October 2021): EU/EEA Member States (MS) and European Commission;
- **Wave 2** (22-26 November 2021): Clinical trial sponsor organisations that have sponsor Master Trainers who were fully trained in the CTIS Sponsor Master Trainer Programme offered by EMA in 2021;
- **Wave 3** (*timing to be confirmed*): other sponsors and CTIS users that will operate in the respective secure workspaces of CTIS.

In this third wave, access to CTIS Sandbox will be provided to representatives of sponsor organisations on the basis of the need and urgency to plan their user configuration, and to experience how to create an initial clinical trial application. Organisations were offered an initial opportunity in October 2021 to complete a self-assessment through a survey that collected information on contact details of individuals, the organisations that they represent, and their plans for the use of CTIS.

The data collected allow EMA to understand their need and urgency for access to CTIS Sandbox and to consider when access will be granted to ensure the Agency is in a position to support the CTIS Sandbox users effectively. Access in wave 3 will be granted in phases and a queuing system will apply based on the outcome of the self-assessment survey. Once wave 3 has started, the survey may be reopened to allow additional representatives of clinical trial sponsor organisations to express their interest for access to the CTIS Sandbox. Information on the survey will be provided in the CTIS Highlights Newsletters.

Before accessing CTIS Sandbox, users will need to be thoroughly trained on CTIS to get the best out of their access.

Version deployments (and times off line) will be communicated to CTIS Sandbox users in advance through the EMA website to enable planning of activities by sponsor organisations having access to CTIS Sandbox.

10.5. Questions and answers on CTR/CTIS

Frequently Asked Questions on CTIS functionalities are available as part of the published training material modules. These will be merged into one document and published for easier use.

Until the dedicated CTIS service desk is operational, questions on CTIS functionalities can be directed through AskEMA by use of the general form (see table below for a link). The use of this will enable EMA to improve the Frequently Asked Questions on CTIS.

For technical support with other EMA's IT systems than CTIS (e.g. Eudravigilance, IRIS, EudraCT), please use the EMA Service Desk portal (see table below for a link). The EMA Service Desk will not respond on CTIS questions.

Questions and answers on the CTR are available in Eudralex Volume 10 Q&A.

References	Location (area or document)
Frequently Asked Questions on CTIS functionalities - within training modules on the Clinical Trials Information System (CTIS) training programme page (EMA corporate website)	https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-ctis-online-modular-training-programme
New questions on CTIS functionalities (AskEMA)	https://www.ema.europa.eu/en/about-us/contact/send-question-european-medicines-agency
Technical support with EMA's IT systems <u>other than CTIS</u> (e.g. Eudravigilance, IRIS, EudraCT)	Assistance with information technology (IT) systems EMA Service Desk
Questions on CTR - Link to EudraLex - Volume 10 - Clinical trials guidelines - QUESTIONS & ANSWERS draft	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

10.6. CTIS Helpdesk at EMA

Information on the CTIS Service desk will be made available in a later version of the Sponsor Handbook.

10.7. Support for SME and academia sponsors

Specific events and dedicated training materials will be organised for SME and academia sponsors.

References	Location (area or document)
CTIS Training Module 19 'CTIS for SMEs and academia'	https://www.ema.europa.eu/en/documents/other/quick-guide-introduction-ctis-smes-academia-ctis-training-programme-module-19_en.pdf

11. Other references

References	Location (area or document)
Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536
Link to Commission website containing information on clinical trials in the context of Regulation EU No 536/2014	https://ec.europa.eu/health/human-use/clinical-trials/regulation_en
Link to EudraLex - Volume 10 - Clinical trials guidelines	https://ec.europa.eu/health/documents/eudralex/vol-10_en#fragment1
Link to EudraLex - Volume 10 - Clinical trials guidelines - QUESTIONS & ANSWERS draft	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) - the European database for interventional clinical trials on medicinal products authorized in the European Union (EEA) and outside the EU/EEA if they are part of a Paediatric Investigation Plan (PIP) from 1 May 2004 onwards; established in accordance with Directive 2001/20/EC	https://eudract.ema.europa.eu/

12. Acronyms and Glossaries

References	Location (area or document)
CTIS Training: List of Acronyms	https://www.ema.europa.eu/en/documents/other/ctis-training-list-acronyms_en.pdf
EMA General Glossary of regulatory terms	https://www.ema.europa.eu/en/about-us/about-website/glossary