Clinical Trial Information System: overview, opportunities and challenges

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KEYWORDS

Clinical Trial Information System; CTIS; clinical trial portal and database; clinical trial regulation; EU CTR; European Medicines Agency; EU; sponsor.

ABSTRACT

The implementation of the Clinical Trial Information System (CTIS), from 31 January 2022, will facilitate the day-to-day business of sponsors of clinical trials by harmonising submission and maintenance of trial applications, assessment and supervision of trials, while promoting patient safety and transparency. But what about the potential challenges, and how are sponsors preparing for these? This article reviews the CTIS structure, user management, data transparency and confidentiality, as well as other CTIS functionalities, and outlines challenges and potential mitigations for sponsors of clinical trials.

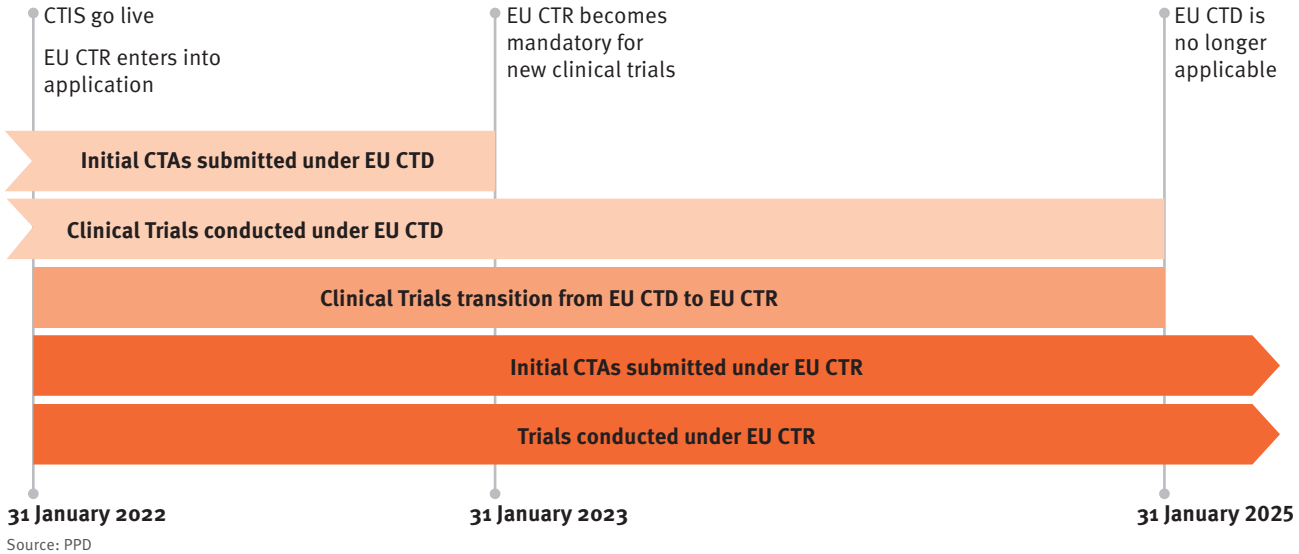
Introduction

The application of the EU Clinical Trial Regulation 536/2014 (EU CTR) and the Clinical Trial Information System (CTIS) from 31 January 2022 will result in considerable changes to the way clinical trials are regulated in the EU (see Figure 1). The CTIS is expected to harmonise and streamline the submission process across EU member states (MSs) and EEA countries (Iceland, Liechtenstein and Norway), referred to together as the Member States Concerned (MSC). Through the CTIS, sponsors will be able to submit a single Clinical Trial Application (CTA) to MSC. This will provide a joint assessment coordinated by a Reporting Member State (RMS) issuing a single decision for Part I of the application, which covers general trial, sponsor and product information. It will also serve as an electronic submission and communications portal; support collaboration and oversight by MSs; and facilitate increased transparency of clinical trial information and results.

CTIS interaction with other EU databases

The CTIS interacts with different existing databases and systems managed by the EMA and retrieves data from the Organisation Management Service (OMS).[5] The 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 comprised of the organisation's name and location address, such as marketing authorisation holders (MAHs), sponsors, regulatory authorities, trial sites and manufacturers. If an organisation is registered in the OMS, a user can retrieve its details from within the CTIS to populate the CTA or to use it for other sponsor-related activities in the CTIS (eg, to populate employer's details in a personal profile).[4] Therefore, it is recommended to register the organisation via a request in the OMS before using the CTIS.[1,2,4] Sponsor organisations or co-sponsor organisations, third-party contractors (eg, contract research organisations [CROs]), EU and EEA trial sites, and MAHs must be registered

Figure 1 **Transition to EU CTR**



Source: PPD

Figure 2 **Organisation-centric approach**

Pros	Cons
Management of users is done at an organisation level with a top-down model	All trials can be viewed by users under the specific organisation
Management of users working on several clinical trials across an organisation	Decreased confidentiality when several vendors have access to CTIS
Decreased user management	
Good visibility of the organisational workload	

Source: PPD

in the OMS in order to use the CTIS. It may also be possible to submit a request to register an organisation while working within the CTIS.[4] This, however, is not recommended, as the entry in the OMS is temporary and will be deleted if the OMS entry is not validated by the organisation itself. Populating organisations, such as trial sites, directly in the CTIS if not already registered in the OMS, could lead to a specific trial site being registered several times with varying details. It is therefore recommended that trial sites are registered in the OMS as soon as they have been selected for participation and well in advance of populating an application in the CTIS, as this will ensure the correct site is selected in an application. Depending on the organisational structure that has been implemented, this could be checked by central submission teams or the local affiliates that will be involved in the compilation of part II of the application.

Another system that interacts with the CTIS is EudraVigilance Human (EV Human) and, in particular, its component EudraVigilance Medicinal Product Dictionary, which provides the CTIS with information about the medicinal product (MP) used in the trial (investigational MP or auxiliary MP). This includes information for unauthorised MPs in the EU.[2,5] EV Human manages and analyses information on suspected adverse reactions to medicines that have been authorised or are being studied in clinical trials in the EEA.[2]

CTIS registering and user roles

The CTIS has two restricted and secured workspaces: the sponsor workspace and the authority workspace, which will only be accessible to registered users.[3,7,8,9] The general public, including patients, healthcare professionals, scientists, clinical research associations, the media and any other members of the public, will have access to a public workspace, where they will be able to view published information in everyday language.[2]

Users need to have EMA accounts to access the CTIS restricted workspaces. Users of other EMA applications (eg, IRIS, EudraVigilance, SPOR), who have already created EMA accounts, can use these credentials to access CTIS-restricted workspaces.[7]

The CTIS has 49 roles across the sponsor and authority workspaces, including administrator and business roles; up to 18 roles in the sponsor workspace and up to 31 roles in the authority workspace.[11] Initially users receive a default role ('birth-right permissions') enabling them to access the system and perform a limited number of actions. To perform additional actions, users need to be assigned specific CTIS roles by a user called 'clinical trial administrator'. One user can have more than one role, enabling each organisation or MS to structure their work in a flexible way, according to their organisational model, needs and resources.

The sponsor workspace provides the functionality to submit CTAs to MSs and to manage information throughout the life cycle of clinical trials.

There are multiple roles and access rights for the sponsor's users, depending on the type of activity required to be performed within the CTIS. The sponsor's clinical trial administrator (CT-admin role) is a high-level role and, once appointed, they will be able to assign all other medium-level administrator and other business roles, including those of preparer, submitter and viewer.[8]

User management in CTIS

To meet the needs of the different types of sponsor organisations that will use the CTIS, two management approaches have been designed: the organisation-centric approach and the trial-centric approach.[4] Before using the CTIS, sponsors should carefully consider the advantages and disadvantages of each approach before deciding which to apply (see Figure 2).

Organisation-centric approach: Intended to serve the needs of organisations with a large number of users, clinical trial applications and/or clinical trials. User management is completed at the organisation level. The sponsor needs to appoint a high-level CT-admin. Management of other users is controlled at the organisation level, with a top-down model.[10] Once appointed, sponsor administrators can assign medium-level administrator and business roles to users in the CTIS to perform user management or business activities, respectively.[4,10]

Trial-centric approach: Intended to serve the needs of small organisations and specifically academic sponsors, which may initiate trials on an ad hoc basis (see Figure 3). It allows for the management of a smaller number of users and one or a very limited number of clinical trials. Users follow a bottom-up model that supports an easy way of submitting a limited number of clinical trial applications and the straightforward management of a small number of users at the trial level, rather than the organisation level.[4,10]

Evaluating trial-specific organisational models is essential to ensure that user roles can be assigned as required and to efficiently conduct a trial. The CT-admin role is permitted to perform all tasks within the CTIS and has the right to grant user access. When multiple organisations are involved in populating an application, sponsors may want to hold the CT-admin role to create a study within the CTIS prior to providing access to several roles. When more than one organisation is involved in compiling Part II of the application in the CTIS, it should be noted that these organisations will be able to access all of Part II within the CTIS. In this scenario, sponsors may want to consider assigning a lead organisation that will be responsible for populating the Part II portion of the CTIS. In a scenario where the investigational medicinal product dossier IMPD-Quality (IMPD-Q) access is provided to a co-sponsor or a different organisation, only the role with the IMPD-Q role will be able to receive requests for information (RFI) on the IMPD-Q. Having a confidentiality agreement in place will allow the sponsor organisation to still receive RFI.

How sponsors can prepare for CTIS

- *Processes:* Centralising access and communication via a dedicated team that closely monitors timelines and the CTIS for incoming communications and handles document/data entry and downloads for trial master file (TMF) compliance will decrease the user access management burden and will ensure coordination of responses to RFI within tight timelines
- *Technology:* Sponsors/CROs may want to upgrade their electronic trial master file (eTMF), regulatory information management and clinical trial management systems to meet the new demands of EU CTR. To achieve an effective upgrade, completing a comprehensive impact assessment and planning in advance is essential
- *People:* Stakeholders must be trained to use the CTIS and an efficient change management process must be in place to implement new ways of working
- *Transitioning:* Evaluating the book of work and implementing a robust transition plan from the EU Directive 2002/20/EC to the EU CTR must be a priority. Sponsors may want to consider executing pivotal trials through the CTIS towards the end of the first year of implementation once the system and processes have been established
- *Lack of experience:* Even though a great selection of training materials are available for sponsors and all stakeholders, with the delay in the issuance of the sandbox environment, practical experience with the CTIS submission is lacking.

Data transparency and confidentiality

One of the main goals of the EU CTR is to increase data transparency. The EU CTR creates transparency on the conduct of trials in the EU from the point of authorisation to the publication of the results. The clinical trial information processes in the CTIS starts with a CTA submitted by the sponsor/delegated entities, via the CTIS, and the corresponding evaluation performed by the 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. The default is always to make public at the first opportunity. However, sponsors have options to defer the timing of publication of specific data/documents.[4,6] There are certain pieces of information, such as the EU clinical trial number, sponsor name and address, nature of the clinical trial and the date of the start of the trial, which are always published regardless of trial category.[4,6]

It will be possible for the sponsor to request a deferral when populating the data fields of the CTIS. The deferral mechanism is optional for the sponsor to choose if they wish to delay the publication of data and documents via the CTIS. Sponsors can submit a 'for publication' and a 'not for publication' version of documents that are not subject to deferral rules. If no deferral is selected, the data and documents (version for publication) will be published at the first opportunity, which will coincide with the time of the clinical trial decision, announced by the first MSC. [4,6]

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

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. All the required information should be available in the version 'not for publication' for access and evaluation by the RMS/MSC. A period of deferral of five (or seven) years, depending on the trial type, is considered appropriate as it ensures that adequate up-to-date investigator brochures and IMPDs can be submitted with confidence to the EU portal.[4,6] It also gives sponsors sufficient time before publication to protect their economic interests, but information is nonetheless made public, including when IMPs did not reach marketing authorisation. It therefore balances the economic interests of the sponsor with the overall objective that information contained in the database is made public.

Technical challenges for sponsors

The introduction of the CTIS to the clinical trial submission process creates certain technical challenges for sponsors and CROs. One of them is that the system requires manual data entry. The system does not have an application programming interface (API) available, nor does it allow for an upload of structured data (eg, an XML file accompanied with a submission package) that would populate data and document elements in the CTIS. Almost all sponsors prepare and maintain the same data in their systems and assemble submission documents within their IT environment. The ability to upload or directly transfer data and documents via an API from the sponsor environment into the CTIS would save a lot of time and effort and would contribute to the ultimate data quality and compliance.

Another challenge with the CTIS is the fact that the system does not allow for sending alerts and notifications to the user's email address, forcing users to continuously check their studies for incoming alerts, RFI and notifications. Taking into consideration the narrow timelines for some of the activities in the process (eg, RFI responses), immediate access to

Figure 3 **Trial-centric approach**

Pros	Cons
Management of users at a trial level with a bottom-up approach	Access to be provided on a trial-specific basis = increased user management
Allows management of a smaller number of trials within organisation	Organisational administrator is not required, reducing organisational oversight regarding the creation of a new application for a trial
Flexibility in maintaining confidentiality when several vendors are involved	

Source: PPD

incoming communication within the CTIS is business critical.

The EU CTR and good clinical practice require sponsors and investigators to maintain TMF compliance. Although the CTIS is a secure archive of documents and data, sponsors are still required to keep all records in their own eTMF for compliance. Certain aspects of this requirement are challenging within the CTIS as it does not support 'document like' (formatted) exports/printouts of certain fields in the system (eg, RFI, approval letters, etc). Filing screenshots has potential risks of not having consistency in the format and could affect their validity in an audit. It also remains to be seen how clinical trial sponsorship changes will be dealt with for an ongoing trial from a system perspective.

Conclusion

The CTIS implementation will start with the minimal capabilities necessary to allow sponsors to make submissions while adhering to the EU CTR. During the user acceptance testing, many issues were identified with the system, resulting in the need for future enhancements post go-live. The EMA plans to consult with stakeholders to compile a list of priorities post go-live to add to a timetable for system upgrades. Sponsors should be ready to ensure that their organisations are prepared for any future upgrades to be implemented in training, and to make amendments to internal standard operating procedures and guidance documents, as required.

Although the CTIS rollout is a major milestone on the path to streamlining clinical trial management process in the EU, technical capabilities will need to go through several rounds of improvements to achieve process efficiency. Considering the CTIS go-live timing and allowed transition period, companies should be proactive and analyse the current business processes, adapt and upgrade their information systems, or transform operations to prepare and avoid disruptions of start-up and maintenance of all clinical trials, new and ongoing.

To mitigate the risks associated with the new processes mandated by the EU CTR, it will be crucial for sponsors to implement robust strategic planning by partnering early with experienced CROs/service providers. They will be able to recommend appropriate solutions to respond to the changing clinical trial regulatory landscape and to adapt quickly to the operational shifts posed by the CTIS.

It will be useful to share pragmatic examples/tips and lessons learned from practical experience with using the CTIS once it is live. ■

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