Regulatory Factsheet

The Clinical Trials Regulation and the Clinical Trials Information System

The Clinical Trials Regulation (CTR)

The way clinical trials (CTs) are conducted in the European Union (EU) will undergo a major change when the CT Regulation (CTR) (Regulation (EU) No 536/2014) comes into application on 31 January 2022. The CTR replaces and expands the scope of the existing EU CT Directive (CTD) 2001/20/EC. The CTR will also apply to all CTs previously authorised under the CTD if still ongoing after 31 January 2025 (see also transition period). The CTR does not apply to non-interventional studies.

The CTR will introduce:

- **A simplified application process:** a single, harmonised, fully electronic CT application (CTA) submission and assessment process for CTs conducted in one or multiple EU/EEA Member States (MS).
- **A streamlined process for review and authorisation:** there will be a coordinated 2-part assessment procedure (Figure 1) within the MSs concerned, with a single decision per MS (National Competent Authority [NCA] and Ethics Committee combined). For multinational trials, there will be a coordinated assessment with one Reporting Member State and involvement of all Member States Concerned.
  The processes and timelines are defined: up to 60 days for decision on an initial application (where there is no request for information [RFI]), rising to maximum 106 days (with RFI). For CTs involving advanced therapy investigational medicinal products the timelines may be extended by 50 days to a total of 156 days. A tacit approval is assumed where timelines are missed.
- **A category of "low-intervention trials":** where trials fall into this category, they are afforded less stringent requirements for monitoring and documentation.
- **New rules on the protection of subjects and informed consent:** these intend to harmonise requirements but still allow national rules in some aspects, including who may act as a legal representative of a subject or legal age of consent. There are also additionally provisions for CTs in emergency situations and cluster trials.
- **Transparency requirements:** ensuring greater involvement of the public and patients, with the mandatory introduction of laypersons(s) or patient organisations into the testing team and the publication of a final report in lay language.

Figure 1. Content of the CTA dossier in CTIS

Part I Coordinated assessment, Internal Involvement of different bodies (i.e. NCA +EC)	Part II National Evaluation, Ethics Committee
• Benefit vs. risks for subjects, including relevance of CT, reliability and robustness of data • Manufacturing and importation for IMP • Labelling requirements • Investigator's Brochure	• Informed consent, subject recruitment, data protection • Reward/compensation investigators/subject • Suitability of investigators and of trial sites • Damage compensation • Collection/storage/use of biological samples

The Clinical Trials Information System (CTIS)

CTIS is the system enabling the implementation of the CTR. From the "go-live date" (31 January 2022) CTIS becomes
the single-entry point for CTA submission, authorisation and supervision in the EU and EEA.
There will be a 3-year transition period:

- Year 1: from 31 January 2022 to 31 January 2023 sponsors may choose to submit a CTA under the CTR in CTIS or under the CTD in EudraCT.
- Years 2-3: from 1 February 2023 to 31 January 2025 all new CTAs must be submitted under the CTR in CTIS, whereas trials authorised under the CTD and which are still ongoing may continue under the CTD in EudraCT.

From 1 February 2025 all CTs authorised under the CTD must either have ended or been transitioned to CTR via CTIS. EudraCT will remain active after the end of the transition period for submission of summary results of trials completed under the CTD. Transition applications can be submitted any time during the 3-year transition period. A transition application is expected to take around 60 days to be approved.

Figure 2. Content of a transition submission from CTD in EudraCT to CTR in CTIS

- New cover letter
- New application form (Part I and II)
- Consolidated protocol
- Investigator's brochure (IB)
- GMP relevant documents
- Investigational medicinal product dossier (IMPD)
- Existing documents related to auxiliary medicinal products, submitted for the assessment in the context of the initial application (if applicable)

Figure 2 shows the requirements for a transition application. Sponsors should allow sufficient time in case a substantial amendment is required to create a consolidated protocol before transitioning your multi-national trial from the CTD in EudraCT to the CTR in CTIS.

There are two user management approaches in CTIS, which enable organisations to manage their users according to their needs and resources.

Sponsors must choose between the two approaches:

- Organisation-centric approach: a general user management approach in which a high-level administrator, previously validated by EMA, is required. This approach is intended for big organisations managing a high number of users and CTs.
- Trial-centric approach: is only expected to be used by non-commercial sponsors managing a small number of users and CTs.
- There are up to 18 roles in the CTIS sponsor workspace, including 15 roles for sponsor users and 3 for Marketing Authorisation Holders (MAH) users. For a role to be assigned to a user in CTIS, the administrator user needs to define the scope as well. There are two scopes available for a user role:
- All trials: the role assigned to the user covers all trials within the organisation. This option is only available in the organisation-centric approach
- Specific trial: the role assigned to the user is only applicable to a specific clinical. This option is available in both user management approaches
- All roles in CTIS can be split into the following two principal categories:
- Administrator roles: users with this role are responsible for the management and oversight of other users within their organisation, or in the context of a specific CT. These roles have the permissions to assign, amend, or revoke roles/trial access to other users to be able to perform actions in CTIS.

- Business roles: are roles that reflect the responsibilities of users during the life cycle of a CT, as defined in the CT Regulation. Business roles are assigned by administrator users, and they are linked to specific business permissions, such as submitting-, preparing-, or only viewing-permissions.
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How to prepare for the Regulation and CTIS

To successfully adapt to the new processes, systems and timelines, sponsor organisations should urgently assess current capabilities and ways of working against what is required to become compliant with the CT Regulation.

- Review all the key areas, including clinical management, governance, information and data flow, and technology capability
- Include key stakeholders and externally manged roles, such as consultants or contract research organisations (CROs), in the assessment to determine the right strategy that is fit-for-purpose for your organisation
- Develop your regulatory and operational strategy
- Reflect changes in updated SOPs and quality management system
- CTIS will introduce new processes for managing CTs.
- Decide on the management approach: organisation-centric vs trial-centric
- If not already done, register your organisation in EMA's organisation management service (OMS) system
- Define and assign your sponsor administrator(s) and (for the organisation-centric approach) register the high-level administrator in EMA's identity access management (IAM) system. Registrations are now open for CTIS Sponsor administrator, this must be supported by an affiliation letter (See 'EMA Affiliation Template Letter')
- Decide who is/are the master trainer(s) in your organisation
- Train all applicable staff of your new ways of working
- Encourage organisation users to practice in the CTIS "sandbox" environment when it becomes available