

Clinical Trials HIGHLIGHTS

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The next issue of the Newsletter, due in July 2023, will only be sent via email to readers who signed up and agreed to the data privacy policy [here](#).

Welcome to Clinical Trials Highlights

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Welcome to the April 2023 issue of Clinical Trials Highlights.

The use of the Clinical Trials Information System (CTIS) became mandatory for initial clinical trial applications on 31 January 2023. Since this milestone, over 400 initial clinical trial applications (CTAs) have been submitted in CTIS, with the weekly number of submissions steadily increasing towards the weekly average in EudraCT during previous years. In total, over 1000 initial CTAs have been submitted in CTIS since its launch on 31 January 2022 and over 400 clinical trials authorised under the Clinical Trials Regulation (CTR) are available in the system.

Sponsors are already preparing for the next phase of implementation of the CTR. By 30 January 2025, any ongoing trials approved under the Clinical Trials Directive will fall under the CTR. Therefore, any trials will need to be transferred to CTIS and approved before 30 January 2025 if they are ongoing. Sponsors have already submitted 120 transitional trials to CTIS. More information on transitional trials is available under Module 23 of the [CTIS online training programme](#) and the CTCG's [best practice guide](#) for multinational sponsors of transitional trials.

- EMA CTIS Team

Commercial sponsors' perspective

Mandatory application of the CTR in the EU

This commercial sponsor perspective was developed by clinical trial experts from a working group of pharmaceutical companies and associations coordinated by EFPIA (European Federation of Pharmaceutical Industries and Associations).

A key milestone in the implementation of the CTR was reached on 31 January 2023, when application of the CTR and submission via CTIS became mandatory for all new clinical trials conducted in the EU.

The much awaited, single, EU-wide clinical trial application submission and approval framework enshrined in the CTR was implemented in 2022 with the launch of CTIS. The system was developed by EMA in close collaboration with the Member States and European Commission and in consultation with all stakeholders including commercial and non-commercial sponsors, and patient organisations. As commercial sponsors we acknowledge and thank EMA, Member States and the European Commission for the commitment and extensive work conducted so far to develop and implement CTIS.

In parallel, Sponsors have been working hard to ensure that they too are fully prepared to meet the requirements of the CTR as its application entered this new phase. Commercial sponsors have already submitted clinical trial applications through CTIS, with many having completed the submission and approval process successfully. Sponsors are also using the system to manage interactions with Member States during the conduct of their clinical trials.

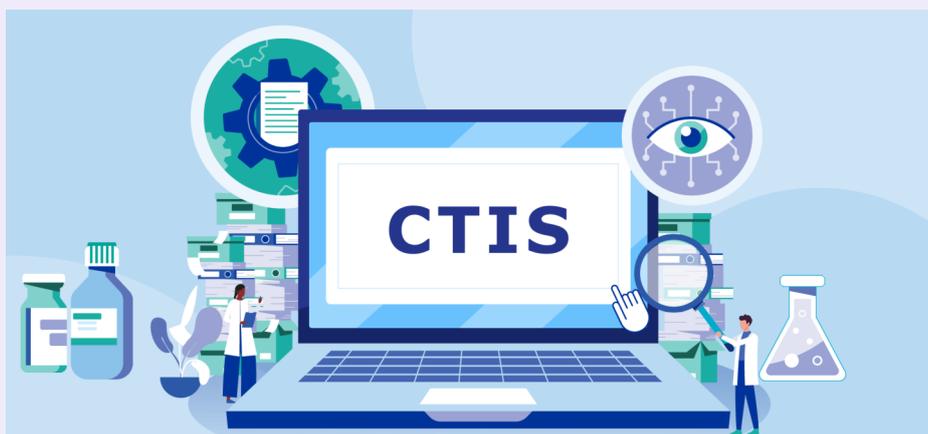


Image 1.
Since 31 January 2023, sponsors submit all new clinical trial applications in the EU/EEA via CTIS.

With CTIS as the cornerstone of CTR, EMA, the European Commission and Member States in consultation with sponsors (commercial and non-commercial) have worked diligently to enhance the system and resolve any issues. All change involves some challenges and with CTIS initial problems were mostly minor and quickly rectified. Some issues have required more extensive work to achieve resolution, and EMA has been pivotal in ensuring fixes were implemented as soon as possible. In this context it is important to acknowledge the intensive work undertaken by EMA to ensure readiness of CTIS for 31 January 2023.

As CTIS becomes a routine but vital tool necessary for Sponsors to successfully complete their clinical development plans in EU, we would urge EMA, Member States, and the Commission to continue their work in further developing and enhancing the usability and functionality of the system. The first year of implementation of the CTR has highlighted additional opportunities for collaboration. From a commercial sponsor's perspective, there is a need for further harmonisation of requirements for the assessment of Part II of the clinical trial application, and for an efficient process to ensure the seamless transition of clinical trials previously authorised under the Clinical Trial Directive to the CTR.

As commercial sponsors we continue to believe that the CTR will play a part in making the EU a competitive location to conduct clinical research in the future. We are committed to work with EMA, the Member States, the European Commission, and all stakeholders to support the future development of CTIS and the success of the CTR.

CTIS Development

Recent Improvements in CTIS

The latest CTIS releases have resolved several issues, enhancing the user experience and delivering system improvements in the following areas:

- Improvements to **application creation/preparation of documents and data**, enhancing the search functionality and allowing users with trial-specific roles to create subsequent clinical trial applications (CTAs).
- **Communication between Sponsor and Member State users**, with enhancements to the notices and alerts functionality and the selection of dates in the calendar when submitting a second Request for Information (RFI) in Part II.
- Enhancements to the **authorisation and supervision of clinical trials**, enabling the creation of corrective measures by a Member State Concerned (MSC) added after the non-authorization of the initial CTA, preventing the generation of the workflow tasks for a withdrawn MSC, and ensuring the due date of the "Submit validation decision" task is correctly displayed in all substantial modification application types.
- Improvements to the **Member State application programming interface (MS API)**, including enabling multiple versions of the MS API to allow MS to adopt changes at their own pace.

EMA has also initiated the process to register CTIS as a WHO data provider. Further updates will be provided in upcoming issues of this Newsletter.

For more details on recent improvements, please refer to the [Website outages and system releases](#) page of the CTIS website, where you can find the latest release notes and lists of known issues. The release notes reflect the updates implemented in the most recent technical release of CTIS, while the known issues documents outline the issues that sponsor and authority users may encounter when using the CTIS secure workspaces, with possible workarounds.

EMA and the EU Clinical Trials Regulatory Network remain focussed on improving the user experience in CTIS and providing support to sponsors in the transition to the CTR. EMA is continuously monitoring user feedback to prioritise the resolution of issues and the enhancement of functionalities that are most impactful for the user community.

Launch date: Multi-factor authentication in CTIS

The multi-factor authentication (MFA) strategy for user logins to CTIS, for both Sponsor and Member State workspaces, will be launched on 1 June 2023. This strategy will further reinforce the security of user accounts.

In preparation for the introduction of MFA, it is recommended that each user is equipped with a mobile or an office phone that can be used for second factor authentication. Users can already log into the [EMA ServiceNow portal](#) to set up their MFA for EMA systems, which will work also for CTIS once deployed and activated. Further instructions on setting up MFA for EMA systems are available [here](#).

The activation of MFA is currently not planned for the CTIS Training Environment. Information about a possible future implementation of a MFA in the CTIS Training Environment will be announced in the [CTIS Newsflash](#). For the MS API, the MFA will be rolled out at a later date and MS users will be informed in advance.



*Image 2.
Multi-factor authentication in CTIS will
reinforce the security of user accounts.*

CTIS Events

EMA and the [EMRN](#) continue to provide training events and information sessions to support CTIS users. All EMA-run events are live broadcast and a video recording is made available after each session on the respective [event pages](#).

EMA continues the series of half-day **informational webinars**, organised twice a year, aiming to share some practical advice regarding transitioning clinical trials from the Clinical Trials Directive (2001/20/EC) to the Clinical Trial Regulation (536/2014) as well as best practices on CTIS. The next informational webinar is planned for early July 2023. More details will be available shortly on the [EMA website](#).

Regular **CTIS bitesize talks** are still being held as part of EMA CTIS event series, where sponsor users can learn from CTIS experts about a specific CTIS functionality and have their questions answered live. CTIS users can submit and upvote questions in advance as well as live during the events via Slido. All video recordings are published on the respective [event pages](#). The next CTIS Bitesize talk on the Part I only submission of the quality part of the **Investigational Medicinal Product Dossier (IMPD-Q)** is scheduled for 10 May 2023. More details will be available on the dedicated [event page](#).

More dates have been announced for the **CTIS walk-in clinics**, which provide sponsor users with the opportunity to raise questions about any CTIS functionality and receive advice from CTIS experts. CTIS users can submit and upvote questions in advance as well as during the live sessions via Slido as described on the [event pages](#), where the event recordings are also available. The first sessions for 2023 took place on [18 January](#), [16 February](#), [16 March](#), [19 April](#).

The next CTIS walk-in clinic events:

- [17 May 2023](#)
- [14 June 2023](#)

The **Sponsor end user training** programme continues and the next events dates are:

- [2 - 5 May 2023](#)
- [27 - 30 June 2023](#)

CTIS Training

Training material update

A new version of the [CTIS Sponsor Handbook](#) has been published, including changes in several sections of the document. New content includes a section on the multi-factor authentication in CTIS, links to the latest CTIS Bitesize Talks, recent Q&A documents and an updated glossary. A more detailed description of the recent changes can be found in the 'Document evolution' section of the Sponsor Handbook.

Users are reminded that dates in CTIS are always displayed in Central European Time (CET), despite the change to daylight savings time during spring/summer in Europe. Users are also reminded that the Request for Information (RFI) response due date cannot fall on a weekend or during the clock stop. However, the date may fall on a Member State bank holiday.

A revised version of the [Q&A document](#) providing preliminary guidance to users on how to protect personal data and commercially confidential information (CCI) in CTIS is now available on the [EMA website](#). The new Q&A item 1.9 clarifies that documents with track changes can only be submitted in CTIS in the slot 'not for publication'.



Access to CTIS Training environment

Sponsors may express their interest in accessing the CTIS training environment via the open survey ([Survey 4.0](#)). This survey collects information and contact details of representative individuals, the organisations that they represent and their planning regarding the use of CTIS. These details serve to identify the needs and intention for use of CTIS and support decisions on granting access to the CTIS Training Environment. Once granted, access will expire after a limited time period (6 months) to allow as many sponsors as possible to benefit from the training environment.



ACT-EU

Priority Action (PA) 3: Multi-stakeholder platform kick-off meeting date

The public consultation on the development of a multi-stakeholder platform (MSP) to promote collaboration for improving clinical trials in the EU was launched in February and concluded in March 2023. Over 200 stakeholders responded, expressing their support for the establishment of the platform and providing valuable input regarding priority topics for discussion.

The kick-off meeting of the platform is scheduled for 22 and 23 June 2023, and will be held as a hybrid meeting including a significant on-site presence at the EMA building in Amsterdam. This event is intended to be the first of a series of workshops to establish the platform and discuss the priorities set out by the stakeholders. Stakeholder groups who, during the public consultation, expressed their interest in being part of the MSP will be invited to send a representative to the kick-off event.

Further details on the multi-stakeholder platform meeting will be published on the dedicated [event page](#).



Image 3.
The kick-off meeting of the Multi-stakeholder platform will take place on 22-23 June 2023.

PA4 update: GCP modernisation – ICH E6 R3 Public consultation workshop

The revision of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R2) guideline on Good Clinical Practice (GCP) aims to address the application of GCP to the increasingly diverse range of clinical trial types and data sources.

As part of the published ACT EU multi-year workplan and acknowledging the important role of ICH E6 as the global regulatory guideline for GCP, a multi-stakeholder workshop on ICH E6 R3 public consultation is being organised by Priority Action 4 (PA4). The workshop aims to engage and hear the views of stakeholders of ICH E6 R3, including patients, healthcare professionals, assessors, inspectors, industry and academia. It is envisaged that future discussion with stakeholders on the implementation of ICH E6 R3 will take place under the auspices of the ACT EU Multi-stakeholder platform, after it is launched.

The workshop is scheduled to take place on 13 - 14 July 2023 as a virtual event, to enable wide participation.

Day 1, 13 July: 13:30 - 18:30 CEST. The sessions will be live broadcast and include in-depth presentations on both the principles of ICH E6 R3 and Annex I, panel discussions with relevant stakeholders and Q&As.

Day 2, 14 July: 09:30 - 15:00 CEST. Discussions will take place in multiple breakout sessions and will therefore not be broadcast. Pre-registration will be required. The breakout sessions will run on five different tracks held simultaneously, twice during the day, allowing relevant stakeholders with more than one topic of interest to attend two different breakout sessions.

Further details on the workshop, including on the registration process and agendas, will be published on dedicated [event page](#). Early registration is recommended to facilitate the planning and allocation of the breakout sessions especially.



*Image 4.
The stakeholder workshop on the ICH E6 R3 public consultation will take place on 13-14 July 2023.*

PA8 update: Open consultation on single-arm trials reflection paper



In some marketing authorisation applications the pivotal clinical data stems from single-arm trials. This is observed across different therapeutic areas, particularly for rare and ultra-rare diseases. A reflection paper has been drafted to outline considerations on single-arm trials that are submitted as pivotal evidence for establishing efficacy in marketing authorisation applications.

The reflection paper is anchored in the work plans from the [Committee for Medicinal Products for Human Use](#), the [Committee for Advanced Therapies](#), the [Methodology Working Party](#) and the [Oncology Working Party](#).

The reflection paper has been released for public consultation on the [EMA website](#). Stakeholders are invited to send their comments by 30 September 2023.

PA9 ICH E19 Training of CT assessors

The new [ICH E19 guideline](#) was endorsed by the CHMP in September 2022 and has been effective in the EU since March 2023. The guideline provides internationally harmonised guidance on the use of selective safety data collection that may be applied in specific late-stage interventional clinical trials that may be pre-approval or post-approval. The guideline details factors that should be considered to support with adequate justification in the protocol a reduced collection of certain data in a clinical trial.

In the context of the implementation of the new guideline, an information session for clinical trial assessors was organised by the Clinical Trials Coordination Group (CTCG) on 21 March 2023. During this session the ICH E19 key principles and an overview of risk proportionate approaches in clinical trials, as per [EudraLex Volume 10](#), were presented, together with examples of reduced safety data collection and reporting.

General Updates

Clinical Trials Raw Data Pilot: application of EMA's data transparency principles

The Clinical Trials Raw Data Pilot team, in consultation with the Industry Focus Group on Raw Data, has developed a [paper on the application of EMA's data transparency principles to the pilot](#). This paper was produced to support and provide clarifications to interested applicants and marketing authorisation holders (MAHs) on EMA's existing data transparency principles, including its current practice and processes that will apply during the conduct of the pilot.

The pilot has now selected its second regulatory procedure to assess the place of raw data in regulatory decision making. This procedure will entail a biosimilar application in the area of endocrinology. Applicants or MAHs that are about to submit marketing authorisation applications or post-authorisation applications are welcome to register their interest in participating in the pilot with a specific procedure by contacting rawdatapilot@ema.europa.eu.

Participation in the pilot offers a unique opportunity to applicants and MAHs to contribute to the pilot's learnings which will in turn assist the EU medicines regulatory network to make an informed decision on the place of raw data in regulatory decision-making. Pilot related guidance for applicants and MAHs can be found on [EMA's Big Data webpage](#).

ICH M11 Scientific guideline

The purpose of this new ICH harmonised guideline is to introduce a clinical protocol template and a technical specification to ensure that protocols are prepared in a consistent fashion and enable an harmonised data exchange format acceptable to the regulatory authorities.

The public consultation in Europe ended on 26 February 2023 and the consolidation of received comments will be published shortly. In total, the guideline underwent public consultation in ten regions. The ICH Expert Working Group is currently consolidating all received comments from the ten corresponding regulatory authorities. More information is available on the [ICH website](#).

EMA GCP IWP publication on clinical trials impacted by major disruptions

At the end of March 2023, the Good Clinical Practice Inspectors Working Group (GCP IWG) adopted a [points to consider document](#) regarding the management of ongoing clinical trials impacted by political conflicts, natural disasters or other major disruptions. This document draws from the experience of past major disruptions in society such as the Covid-19 pandemic and the most recent developments of the Russo-Ukrainian War; these disruptions are varied in nature but may have similar, multiple consequences on clinical trials performed in the affected geographical areas.

The document aims to help sponsors address the resulting challenges and mitigate risks to the rights, safety, dignity, and well-being of trial participants and to the scientific value of the clinical trials. It is complementary to several documents already published, including the [CTCG recommendation to sponsors on managing the impact of the war in Ukraine on clinical trials](#), the [Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials](#), and the [Guidance on the management of clinical trials during the Covid-19 \(coronavirus\) pandemic](#).

The new points to consider document can be found on the [EMA website](#).



Upcoming consultation on CTIS transparency rules

A public consultation on the CTIS transparency rules is foreseen to be launched in May 2023 on the [EMA website](#). The review of existing rules aims at simplification to improve user experience while also reducing the risk of data breaches and maintaining high levels of transparency.



A weekly [CTIS Newsflash](#) is circulated to all CTIS users and Newsletter subscribers

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