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The EU CTR: Opportunities, challenges, and lessons learned

Bettina Goldberg, MPharm • Esther Gil, MSc, BSc Pharmacy • Celina González-Colaço, BSc Pharmacy • Cristina Lupo, BSc Pharmacy

The EU Clinical Trials Regulation (EU CTR) became mandatory for all new interventional, Phases 1-4 clinical trials on 31 January 2023, presenting fundamental changes for trial sponsors, vendors, and EU member state regulators and ethics committees. This article highlights the opportunities and challenges of the regulation as part of the wider EU pharmaceutical strategy. It is based on practical experience and shares lessons learned, provides guidance for transitioning trials by the 31 January 2025 deadline, and assesses the outlook for the overall EU CTR trajectory.

Keywords – harmonization, transparency rules, transition trials

Introduction

The EU Clinical Trials Regulation, also known as Regulation (EU) No. 536/2014,[1] should be understood in the broader context of the European medicines agencies network strategy to 2025[2] and the pharmaceutical strategy of the European Commission. The aim is to maintain and develop an innovative clinical trial landscape in the EU for the benefit of all research stakeholders, including patients, investigators and sponsors. The Accelerating Clinical Trials in the EU (ACT EU) strategy paper listed 10 priority actions for 2022-2023, including enabling innovative trial methods, establishing a multistakeholder platform, and supporting the modernization of good clinical practice.[3] The EU CTR is an integral part of the ACT EU priority actions and aims to harmonize and supervise clinical trials throughout the EU while maintaining the high-level protection of trial participants, data robustness, and transparency.[4] After a significant multiyear effort by the European Medicines Agency (EMA) and stakeholder groups, the Clinical Trial Information System (CTIS), a centralized European database and portal for the submission, monitoring, and assessment of clinical trials, launched on 31 January 2022 for a 12-month voluntary phase. It became mandatory for all new interventional clinical trials, Phases 1-4, on 31 January 2023.

The next major milestone is 31 January 2025 for all clinical research stakeholders with ongoing clinical trials approved under the EU Clinical Trials Directive (EU CTD; Directive 2001/20/EC)[5] and active sites in the European Economic Area (EEA, comprising the EU countries, plus Iceland, Liechtenstein, and Norway). By that date, those trials will either automatically terminate because of the complete repeal of the CTD or be transitioned into the CTIS according to EU CTR requirements.

The regulation represents a transformational change for the entire research industry from an operational and IT system perspective, and its goal is to achieve a centralized, simplified, and fully harmonized clinical trial application approval and management process. However, stakeholders report a steep, ongoing learning curve for the adoption and implementation of the new processes and systems. In response, multistakeholder platforms have been established to ensure the continuous sharing of experience to achieve ease of use and CTIS functionality improvements.

In this article, the European medicines agency network includes the national competent authorities of the 27 EU member states, plus those of Iceland, Liechtenstein, and Norway, which come together under the aegis of the Heads of Medicines Agencies and the centralized regulator and coordinating body, the European Medicines Agency (EMA).The European Commission provides EU legal and supervisory authority to the network's decisions.

The evolution of the EU CTR

The EU CTR has been supplemented with further guidance since its initial publication. The EC released implementing and delegated acts,[6] along with a comprehensive question-and-answer document.[7,8] Although not legally binding, the Q&A document is updated regularly and provides detailed and helpful information. The EMA also set up a website to access CTIS and to provide training and support as well as stakeholder-specific sections.[9]

CTIS is an entire workflow and workspace system for global sponsors and EEA competent authorities. It was originally due to be implemented in 2016 but the launch was delayed until 2022 because of the complexity of the system's scale and scope. Functionality concerns were raised soon after the launch. However, the number of issues has decreased considerably since the early implementation in 2022. The authors estimate that by May 2023, only around 10% required further data fixes and that some of the tickets submitted to the EMA during 2023 were being addressed and resolved more quickly.[10]

In addition to comments about the functionality and user-friendly application of CTIS, the industry also raised concerns about the lack of legal interplay between the EU CTR, EU Medical Devices Regulation, and EU In Vitro Diagnostic Medical Devices Regulation and trials with genetically modified organisms, which require

a parallel national submission to each member state concerned. Those approvals need to be aligned to avoid prolongation of full clinical trial approval.

High-level process

The EU CTR uses the electronic, web-based CTIS as a single-entry point to submit, evaluate, and authorize clinical trial applications across the 30 EEA countries participating in a trial. Applications will undergo and initial review of the scientific-technical dossier (Part I) by a joint regulatory authority and ethics committee, led by a reporting member state (RMS). This harmonized review will be supplemented by country-level review of site documents and other country-specific information (Part II). The EU CTR also creates a harmonized legal basis for submission contents, processes, and timelines, and it increases transparency by making most trial documents publicly available. The process is streamlined with a single dossier submitted for all EEA countries participating in a clinical trial, an assessment process proposing predicted approval timelines and transparency rules. The approval timelines for initial clinical trial applications deviate from the official 106 calendar days, as the number of participating member states increases. This is because the holidays in the respective member states concerned and the associated decision tasks in the CTIS process need tob e factored in. In addition, the winter clock stop at the year-end holidays extends approval timelines. In the authors' experience, there have been average approval timelines of 109 calendar days (124 with winter clock stop) for trials spanning up to five EEA countries.

Balancing benefits and challenges

There are numrous challenges in balancing the benefits and challenges of regulating clinical trials. For example, there is a need for clinical trials across the EU to be harmonized and to have electronic submission and management processes in place, but at the same time, the highest flexibility in country selection and the set-up of innovative trial designs for all phases of clinical development must be maintained. Another example is around transparency and disclosure – from the patient perspective, there must be full transparency of available clinical trials to identify the best treatment under clinical development, whereas industry strives to protect company confidential information. The accompany **Table 1** (p. 4) presents an overview of benefits and challenges associated with the EU CTR.

Opportunities and benefits

The EU CTR includes predefined timelines, consolidated requirements, and common procedures, allowing for a harmonized structure for the presentation of technical and scientific data in a clinical trial application. The Part I assessment is performed under a synchronized procedure throughout the EEA. This coordinated evaluation of the application's scientific-technical dossier for a clinical trial application is a significant advance in minimizing differences in implementing the EU CTR across Europe, although full harmonization of the review process across all participating ethics committees still needs to be achieved. A fully harmonized assessment process would ensure consistency of

Table 1. Benefits and challenges associated with the EU Clinical Trials Regulation

Opportunities and benefits	Challenges and considerations
Harmonization of trial assessments Part I	High administrative burden – translations, redactions, complex clinical trials process
Consensus of acceptability of a trial across all participating member states	Inflexible modification process that does not facilitate agile clinical development
Strengthening the patient position – transparency rules and layperson language requirements	Low CTIS functionality requires workarounds and high system proficiency from users
Digitalization of the process	Confidentiality of transparency and disclosure rules
Paradigm shift triggers further process optimizations – EMA templates accelerate Part II finalization through standardized process	Nonalignment with parallel national and EU legislations delays approval timelines: IVDR/MDR, GMO
Multistakeholder communication platforms set up by EU organizations	No accelerated timelines for Phase 1 clinical trials for most member states

EMA, European Medicines Agency; **EU IVDR,** EU In Vitro Diagnostic Medical Devices Regulation; **GMO,** genetically modified organism; **MDR,** EU Medical Devices Regulation.

safety, efficacy, and quality evaluations and would lead to a consensus of acceptability across all member states, not only for the Part I assessment.

The CTIS streamlines the digitized process by enabling the electronic submission of a single dossier to all the member states participating in the trial. The training and support service facilitated by the EMA is both helpful and essential for users to become fully familiar with the new tool and associated processes.

The trial information is publicly available through the CTIS. The focus on using easily understood language for laypersons increases the transparency of the information and makes it more accessible. That accessibilty improves patient understanding of clinical trials and puts them in a better position to make informed decisions about their participation in clinic trials. In the authors' experience, the harmonized process and Part II country-specific templates have accelerated finaliztion of the Part II reviews.

Challenges and considerations

The EU CTR also presents challenges for clinical trial sponsors, vendors such as clinical research organizations (CROs), regulators, and ethics committees. The primary focus is the high administrative burden and associated cost of enforcing the EU CTR, although the burden may diminish as staff proficiency improves with experience gained and CTIS functionality improvements have been established.

Time delays and flexibility. Other challenges include response times for requests for information (RFIs) and accommodating the need for translation and

redaction of information, which may also require adaptation of internal processes of each member state concerned. In addition, certain aspects of the CTIS are not interoperable with other systems and require user proficiency to navigate the workarounds, which in turn generates a higher demand for administratve resources. Overall, the number of documents required for a submission has increased significantly under the EU CTR. For example, the authors report that in 2023, after implementation of the EU CTR, they submitted 500 documents for the initial application for a clinical trial in 5 countries at more than 50 sites. By comparison, in 2021, they submitted 50% of documents less for a similar sized trial in 5 countries at 50 sites under EU CTD due to higher transparency rules under the EU CTR.

Submitting information about complex clinical trials is complicated. To maintain the highest possible flexibility with modifications during the clinical trial lifecycle, such trials need to be separately submitted for each population or each investigational medicinal product (IMPD) as updates of the information would be needed for different aspects and, with few exceptions, no coincident assessment of different substantial modification are allowed at the same time. The CTIS has been programed for linear processes in which one step must be completed before the next starts, which does not align with the reality of clinical development programs. Flexibility measures need to be established and aligned with the EU CTR while still allowing a trial to progress scientifically and ensure the wellbeing and safety of patients. Currently, the sponsor must avoid overlapping evaluations of substantial modifications, except in exceptional cases. This makes careful planning and prioritizing of the included information essential in these types of applications.

Harmonisation. The harmonization of the review process and Part 1 assessments require that all member states adopt the EU CTR's common requirements, which may necessitate new ways of working for the particpating parties. The EU CTR allows member states flexibility in their assessment in line with national legislation. However, the common goal of harmonization should not be lost. Investigators and sponsors need real-world experience working under the EU CTR, harmonization should be prioritzed, and interpreations of the the regulatis shoud be aligned across member states.

In a parallel submission, there may be a content and time misalignment between the joint ethics committee assessment of Part I (the scientific and technical dossier) and the country-level assessment of Part II (the site-specific dossier). If the Part II assessment is concluded before that of Part I, it is likely that Part II will have to undergo a substantial modification before the clinical trial can be approved, which will result in a longer time to final approval. This presents another argument for the need for further harmonization across ethics committees and respective competent authorities. However, harmonization is

not easy because of differences in ethics committee competencies both across and within member states.

Aspects such as presenting information on medical devices and in vitro diagnostics as part of a clinical trial falling under the EU CTR follow a parallel applicaton submission. Also, clinical trials with GMOs require a parallel national submission to each member state concerned to obtain full approval of a clinical trial. These processes should be harmonized to streamline these types of trials.

For early development clinical trials, there is low awareness of the need to provide accelerated approval timelines. These trials are often mononational clinical trials for which coordination across member states is not required.

Transparency. A significant challenge in implementing the EU CTR is the application of transparency rules that allow access to the information in the public domain of the CTIS while protecting patient or confidential commercial data and information. It is important to strike a balance between transparency and privacy in a way that benefits research and ensures that clear and appropriate information and data are publicaly available. This can be achieved by using models that mitigate confusion for users. Information can be protected through redactions and by restricting the number of documents published and when they should be published based on trial category.

The EMA recently published revised transparency rules for the CTIS that are expected to be finalized by the second quarter of 2024.[11] The rules, based on the outcomes of an eight-week public consultation in 2023, are intended to streamline the volume of documents published to reduce complexity and workload for staff engaged in the necessary redactions. It is anticipated that the deferral mechanism for each trial category will be removed and only documents essential to patients and researchers will be published. This is expected to result in a earlier publication of key documents (including protocols) and simply the process significantly.[11]

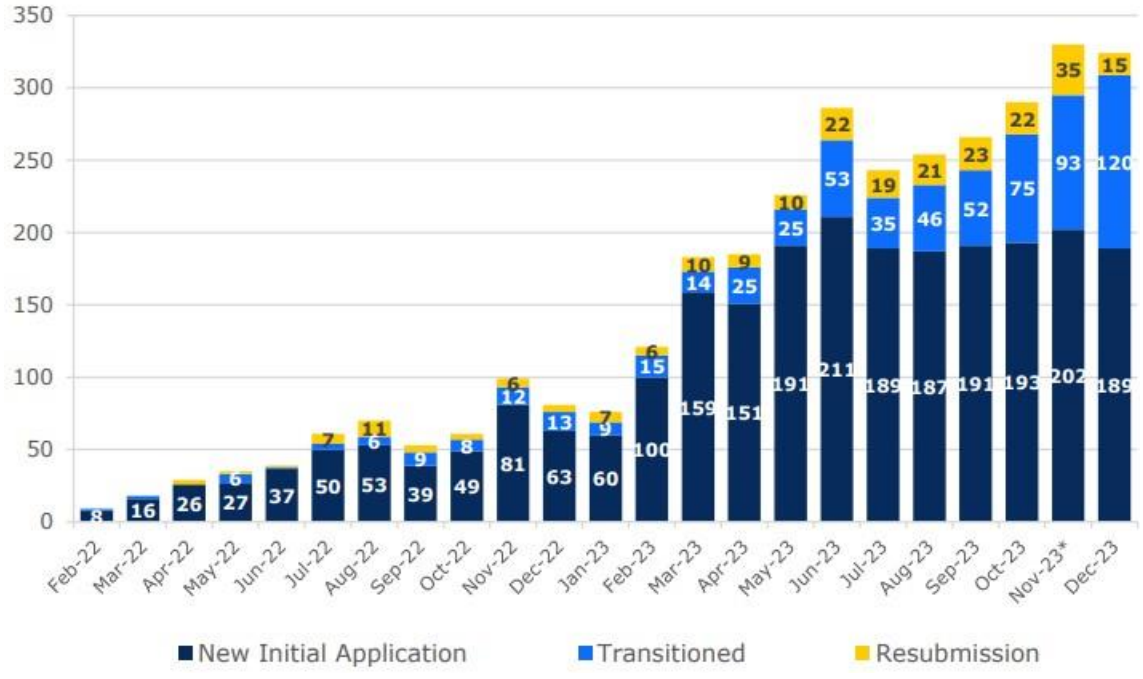
Sponsor experience trial agreement portfolio lifecycle and engage early with internal staff and outsourcing partners to maximize efficiency. It is critical to communicate clearly defined processes, responsibilities, and workflows to all contributors to stay on track with forecasted development milestones and in full compliance with the EU CTR. Sponsors may need to deploy a mix of in-house and outsourced delivery models to address company strategy, timelines, and resource demand.

When the CTIS was launched, many sponsors were hesitant to adapt to the new process during the voluntary phase from February 2022 to January 2023, expressing concerns about its impact on clinical program timelines or that they did not have an available trial to test the system. New transparency and

disclosure rules also delayed sponsors from immmediately testing the CTIS. The EMA demonstrated the late adopter behavior by comparing the number of submissions under the EU CTR's CTIS with the former EU CTD's EudraCT (**Figure 1**[12] and **Figure 2,**[13] p. 8). Sponsors continued to submit almost the same number of trials under CTD during the voluntary phase of the CTIS, with a peak in January 2023 immediately before CTIS use became mandatory. There was a month-on-month increase in CTIS use from February 2023.

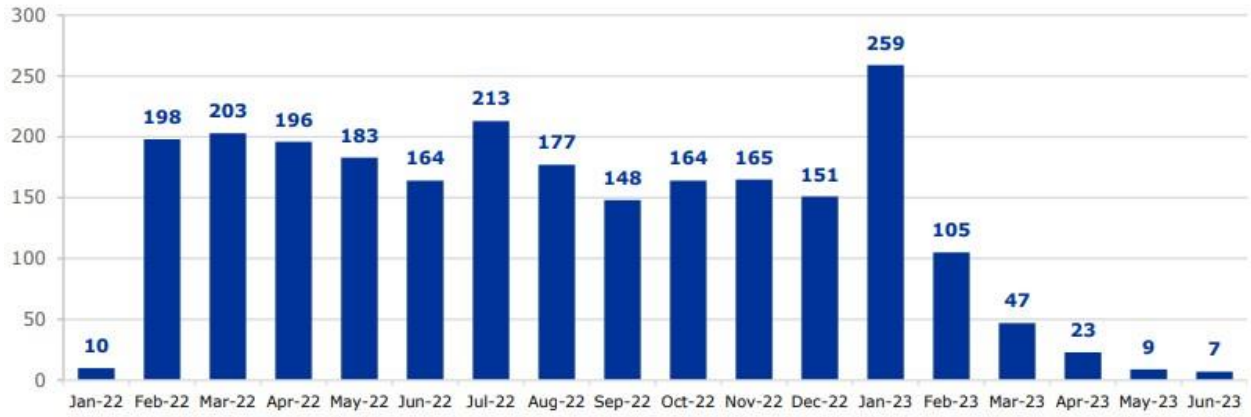
Although use of the CTIS is now mandatory for new interventional clinical trials, the authors have noted ongoing hesitancy from some sponsors to transition their clinical trials from the EU CTD to the EU CTR. Sponsors that have delayed switching until 2024 risk resource challenges as all transitions must be processed before 31 January 2025. CTIS submissions are multistakeholder undertakings. It is no longer just a regulatory submission but requires all operational functions – both in-house and external – to work toward the same goal. In the authors' experience, as respective stakeholders gain experience and proficiency in the new process there seems to be an increase in submission activity from sponsors and CROs and the EMA and member states are more proactive in addressing challenges and their turnaround times for decisions are faster.

Figure 1. Clinical trial applications submitted in the CTIS (February 2022 to December 2023)[12]



Source: European Medicines Agency

Figure 2. Clinical trial applications uploaded in EudraCT (January 2022 to June 2023)[13]



Source: European Medicines Agency

Best practices and lessons learned

The EU CTR is still in its early phase of adoption, but there are already learnings that could help inform adotpers and support them in complying with requirements and applying them efficiently. The authors have compiled the following information for adopters based on their collective experiences working through the transition period.

Country and site selection

- Be aware of the mandatory guidelines and be proactive in corrective actions, noting organizational management service and other registration requirements;[14]
- Know which countries might slow down the rate of progress within the system – the slowest country and/or selected site will determine one's submission strategy;
- Pay attention to countries that can yield faster recruitment times; and
- Plan for at least six months to transition a trial from the EU CDR to the EU CTR to allow for adding new EEA countries.

RMS selection and assessment

- Consider country selection wisely. One might not secure the desired RMS and instead receive an RMS country that may raise objections to the proposed trial. A negative RMS Part I conclusion would lead to a rejection of the whole trial. For example, one's EEA country selection may include countries that are important from a feasibility point of view but bear a risk for approval of the overall trial if selected as the RMS. In that case, it may be better to add that member state concerned after the initial trial application has been approved.

- Understand the rigidity of timelines and be proactive with RMS communication to ensure conclusion of the application and avoid misaligned between the Part I and Part II conclusions. For example, the CTIS requires member states to undertake both mandatory and nonmandatory tasks, with supporting actions from sponsors. If those tasks are not completed, then the application can lapse for technical reasons and require a resubmission which delays the overall approval timeline.
- Note which member states concerned have accelerated timelines (**Table 2**). For example, several EEA countries have accelerated assessment for either single-country Phase 1 trials or mononational trials.

Estonia, Finland, Hungary, Latvia, Lithuania, Netherlands, Norway, and Portugal have also indicated willingness to reduced timelines for mononational clinical trials.[1]

Submission stage

- There is a maximum turnaround of 12 calendar days for sponsors to respond to requests for information;
- Be aware of common process/technology pitfalls, including misalignment with EU CTR processes and requirements (e.g., communication outside of the CTIS, such as email and phone calls);
- Use the CTIS timetable to chart the sponsor tasks in the CTIS so that deadlines are met and to avoid having to resubmit the full application;[20] and
- Be familiar with the different document requirements for the EU CTR and the EU CTR.

Table 2. Accelerated assessment timelines for mononational Phase 1/first-in-human trials, from submission to application decision

Country	Timeline
Belgium	66 calendar days (+50 days for ATMPs); includes validation/content RFIs[15]
Denmark	31 calendar days after successful validation. Content RFIs will be made on Day 26 after successful validation, provided coordination with national ethics committee complete[16]
Germany	30 calendar days after successful validation; validation time may be shorter for single-center and mononational trials[17,18]
Romania	Part I – Ethics committee comments 21 calendar days after successful validation; Part II – Conclusion provided to sponsor 38 calendar days after successful validation[19]

ATMP, advanced therapy medicinal products; **RFI,** request for information.

CTIS assessment timelines

- Plan administrative resources in advance to ensure the avilability for the entire clinical trial team (sponsor and CRO),
- Monitor the CTIS often for RFIs to ensure requests are seen as soon as they are made to maximize the full turnaround period for responding, and
- Define risk mitigation strategies.

Assessment of RFIs

- Part II RFIs are delivered ahead of Part I RFIs during the assessment period. If documents in Part II have to be modified following the assessment of Part I, then the sponsor or CRO should alert the RMS of that fact so that the RMS does not close the initial application before the modification has been uploaded, otherwise the start of the trial could be delayed. In the authors' experience, member states are aware of this and have supported a quick turnaround.
- The process for requesting additional information from a sponsor is not clearly defined in the EU CTR. Some RFIs show that member states are not following the EU CTR requirements in their entirety. In that case, one should query it, but also consider whether querying the RFI will jeopardize or slowdown approval of the application.

Transition trials

Strategizing

The following clinical trials must be transitioned into the CTIS by 31 January 2025 (**Figure 3,** p. 11) or they will be automatically terminated with the complete repeal of the EU CTD:

- Clinical trials authorized under the EU CTD with the last visit of the last participant in the EU, or other trial-specific interventions with the participant specified in the protocol planned, after 30 January 2025; and
- Clinical trials in which a new EEA member state is to be added to a trial approved under the EU CTD.

In addition:

- Trials authorized under the EU CTD and with at least one active site in the EEA on 30 January 2025 need to be transitioned. *Active site* in the context of transition trials means that the last visit of the last participant, or other trial-specific interventions as specified in the protocol will take place after 30 January 2025.
- The trial does not have to be transitioned if an end-of-trial notification has been issued in the member states concerned and Iceland, Liechtenstein, and Norway, but not to the global component of the trial. In such cases, the global component and trial summaries can be uploaded to EudraCT according to the EU CTD.[21]

Figure 3. Timeline for transitioning trials from the EU CTD to the EU CTR

CT, clinical trial; **EEA,** European Economic Area; **EU CTD,** EU Clinical Trial Directive; **EU CTR,** EU Clinical Trials Regulation; **d,** day.
Source: Parexel

- There can be no pending or ongoing assessment in any of the EEA member states concerned at the time of transition, that is, no substantial amendments under review, including for country- or site-level amendments, such as a change in principal investigator or addition of a site.
- The dossier must be consolidated across EEA member states under the EU CTD.

Clinical trials that are stopped temporarily for safety or other reasons can be transitioned when they are resumed. Sponsors of these trials should flagged in the CTIS as having been halted before they transitioned.

Thousands of trials are being transitioned, creating a resource challenge for the EMA and member states in the lead up to the mandatory 31 January 2025 transition date. It is therefore important that the transition takes place as early as possible to avoid unexpected delays.

In defining the transition strategy, the following factors should be considered:

- Business approach
  - Make sure the business processes align with the EU CTR requirements;
  - Consider transition per asset to align substantial modifications to the investigator's brochure (IB) or chemical, manufacturing, and control (CMC) documents and to simplify safety reporting; and
  - Establish whether there are plans to add new EEA countries to ongoing trials.
- Dossier content planning
  - Maintain a harmonized or consolidated clinical trial protocol, IB or summary of product characteristics, and investigational medicinal product dossier (consider timelines for substantial amendment under EU CTD if required);
  - Address redaction and translation needs and timelines;
  - Consider the impact of the transition on drug supply labels (there is no need to proactively relabel released investigational medicinal products);
  - Check which documents are required under the EU CTR but not the EU CTD; and
  - The initial dossier that is submitted should not be too big and more documents can be added later.
- Safety
- Clinical supplies
- Master database registration
- Planning for implementation of transparency rules required by the EU CTR
- Planning for CTIS set-up
- Trial master file
- Notifications for trial and recruitment status milestones
- Public disclosure rules (after the tacit transition authorization date, all trial data and documents are immediately subject to the disclosure rules)

Status update

As of late December 2023, sponsors had already submitted around 580 transitional trials to the CTIS.[22] The approval timelines ranged from 106 calendar days to 22 calendar days for the expedited approval for multinational trials. The latter does not include time for potential RFIs. More time may need to factored in to accommodate the winter clock stop. (The winter clock stop is the period of time – from 22 December to 8 January the following year – when the timers within the evaluation of a clinical trial will stop. There are not due dates for tasks during that period.)[20] In the author's experience, the timelines were 60-75 calendar days, but that could increase with an increase in the volume of transitional trials. The process for transition trials is detailed and dynamic,

but there are numerous guidance and training documents, including a July 2023 EMA guidance on the transition of clinical trials from the EU CTD to the EU CTR[23] and a September 2023 guidance on transition trials from the Heads of Medicines Agencies network.[24]

Conclusion and outlook

The mission to harmonize and streamline clinical trials across the EEA while safeguarding participants' rights and data integrity under the EU ACT is a huge undertaking. The launch of the CTIS, with more than 2,500 clinical trial applications processed to date, marks a pivotal point. However, the integration of regulatory submission requirements in tandem with a dynamic clinical trial conduct environment into a an effective IT system presents numerous challenges. It is therefore essential that CTIS functionality is continually enhanced to ensure a positive user experience and a significant reduction in administrative burden while addressing innovative trial designs. It is also important that the CTIS is robust and flexible in processing the significant amount of data generated by clinical trials over their lifecycles.

Some goals have been met, but the journey is ongoing. Experiences and lessons learned must be openly communicated to advance the clinical trial environment. The focus now is to ensure that all applicable trials are transitioned to the CTIS under the EU CTR within the stipulated timeframes and factoring in the preparation and resource requirements to meet the 31 January 2025 deadline.

Abbreviations

ACT EU, Accelerating Clinical Trials in the EU; **CTIS,** Clinical Trial Information System; **EEA,** European Economic Area; **EMA,** European Medicines Agency; **EU CTD,** EU Clinical Trial Directive; **EU CTR,** EU Clinical Trials Regulation; **EudraCT,** European Union Drug Regulating Authorities Clinical Trials.

About the authors

Bettina Goldberg, MPharm, is vice president, regulatory operations, at Parexel International. She is a licensed pharmacist, with more than 30 years' experience in regulatory affairs more than two decades of proven effectiveness focused on global regulatory submission management and product labeling in clinical drug development. Goldberg provides strategic guidance and thought leadership at Parexel and is a key partner in company-wide initiatives focused on the EU CTR, decentralized clinical trials, risk management, and compliance. She co-led the Parexel taskforce on the implementation of the EU CTR delivery model. Goldberg is also engaged with the EU Scientific and Regulatory Committee of the Association of Clinical Research Organization and is an active member of the Committee for Clinical Research at the Bundesverband der pharmazeutischen Industrie. In 2016, she won Parexel's inaugural Anne B. Sayigh, PhD, Excellence in Leadership Award. She has a master of pharmacy degree from the University of Muenster, Germany. Goldberg can be reached at bettina.goldberg@parexel.com

Celina González-Colaço, BSc Pharmacy, is principal regulatory affairs consultant at Parexel International. She is a pharmacist, with more than 25 years of experience in clinical research, working in different sectors, including at the EU member state and European Regulatory Institution levels for both CROs and the pharmaceutical industry. González-Colaço has extensive

experience as a clinical trial assessor at the Spanish Agency of Medicines and Medical Devices. She also provided substantial consultation related to regulatory and clinical trials requirements, contributing to the implementation of the EU CTR by playing an active role in the development and set up of the CTIS program at the EMA. Her expertise includes an in-depth knowledge of the EU CTR and national laws related to regulatory aspects in clinical trials. In her current position with Parexel, González-Colaço has supported clients as subject matter expert in their projects, activities, and strategic and regulatory needs to work under EU CTR. She can be reached at Celina.gonzalezcolaco@parexel.com

Esther Gil, MSc, BPharm, is senior director, regulatory operations, at Parexel International, where she leads the regulatory delivery team in Europe and is the CTIS submission specialist. Gil provides strategic advice and thought leadership and has extensive experience with EU CTR implementation and supporting the requirements and implementation of the EU CTR. She is a member of industry and CRO associations and has been a speaker at Drug Information Association meetings and seminars. Before joining Parexel, she worked in a large international pharmaceutical company. Gil has a bachelor's degree in pharmacy from the Complutense University of Madrid and a master's degree in European registration procedures from the Autonomous University of Barcelona. She can be reached at esther.gil@parexel.com

Cristina Lupo, BSc Pharmacy, is director of regulatory affairs at Parexel International. She is a licensed pharmacist, with more than 20 years of experience in clinical research at CROs. During that time, she gained experience in different therapeutic areas and with clinical trials regulations working as a global regulatory leader in International clinical trials and managing access programs. Lupo manages regulatory teams that are located in different European countries and provides leadership and direction on strategizing for EU CTR implementation in projects. She also provides regulatory oversight in partnership with biotech clients and coordinates the change management needed to improve the efficiency of the sponsor and CRO procedures linked to EU CTR implementation. Lupo has a BSc pharmacy degree from the University of Genova. She is a member of the Italian Association of CROs and can be reached at cristina.lupo@parexel.com

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