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The EU Clinical Trials Regulation – Experiences from the first 18 months

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The new EU Clinical Trials Regulation represents the most significant overhaul of clinical trial requirements in Europe for a generation, and this article describes the insight gained during the months following the implementation of this new regulation. The article reviews the implications for sponsors, describes the experiences and lessons learned of an organization submitting many clinical trial applications during this time, and looks to the near future as the regulation becomes fully established.

Keywords – European Union, clinical trials, CTIS

Introduction

The EU Clinical Trials Regulation 536/2014 (EU CTR) was designed with the aim of increasing attractiveness of the EU relative to other regions where performance of clinical trials may be perceived as easier when compared with the many different requirements and timelines applying across different EU countries. By introducing greater harmonization across all EU member states, the EU CTR is designed to arrest the decline in clinical trials performed in the EU that occurred following the implementation of the EU Clinical Trials Directive 2001/20/EC (EU CTD).[1] Another key objective of the regulation is a greater degree of transparency in clinical trial–related information, such as documentation pertaining to the study and the status and location of ongoing clinical trials. It is hoped that greater awareness of the information relating to clinical trials will increase patient engagement and facilitate clinical trial participation and collaboration,[2] benefiting all stakeholders, including patients, investigators, regulators, and clinical trial sponsors.

Implications for sponsors

The significant changes within the regulation have dictated that sponsors and their partners have to adapt accordingly, and many used the eight years between 2014 and 2022 to prepare their processes and train their teams to conduct clinical trials as smoothly as possible when the regulation became

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effective. The focus of these efforts has, in most cases, been around the clinical trial application processes. Adapting from a nationally based approach to clinical trial applications to a centrally coordinated system, the Clinical Trials Information System (CTIS) has required the roles of the relevant team members to evolve. Detailed knowledge of the CTIS has become highly valuable to sponsors, as it is necessary to avoid lost time during the preparation and assessment of clinical trial applications. Likewise, it is important to understand the requirements, flexibility, and limitations of the clinical trial application structure – based on a dossier composed of Parts I and II – because trial start-up timelines can be compromised significantly by a suboptimal submission strategy. (Parts I and II focus on the trial- and country-level dossiers, respectively.) For example, the regulation permits Part I and Part II to be submitted in parallel or sequentially (as described in Article 11), so the availability of the information for each part of the application will dictate the swiftest route to authorization of the trial, but sequential approaches may limit flexibility later (as modification of documents cannot be performed at the same time as ongoing initial trial applications). Creation of a clear country-by-country strategy, based around availability of documentation and anticipated recruitment, has never been more important.

Similarly, an in-depth knowledge of the processes and requirements for the submission of annual safety reports and other trial-related notifications, such as urgent safety measures, inspection reports from third-country inspectorates, and serious breach reports, will be critical to sponsors. Performing these new activities efficiently and effectively will require detailed knowledge of the guidance and a pragmatic and solutions-focused approach to the many nuances that apply (such as whether all EU member states must be notified of an incident occurring in only one country, or an understanding of the specific types of third-country inspection reports that must be submitted through the CTIS).

Enhanced clinical trial transparency is a key objective of the EU CTR and another area that requires new or greater expertise among sponsors. Requirements to protect personal data mirror those of established EU requirements (e.g., Policy 0070[4] in relation to publication of drug information at the time of registration for sale in the EU), so many sponsors have expertise and knowledge of the principles to apply in this area. However, the protection of commercially confidential information relating to clinical trials is a significant departure from previous requirements, due to the potential release of sensitive information at an earlier stage of development. This has created many uncertainties and questions from clinical trial sponsors. The EMA anticipated this and devised a functionality within the CTIS to enable sponsors to choose to “defer” publication of different aspects of the clinical trial application dossier (and subsequent applications and notifications) based on criteria such as the likely sensitivity of the information, the value to other clinical trial stakeholders and/or patients, and the development phase of the trial. The combination of the novelty of the requirement for publication of information related to clinical trials, the complex deferral framework, and the criticality of protecting commercially sensitive

information dictates that the shift toward greater transparency has become one of the most significant areas of impact for clinical trial sponsors. It has impacted approaches to preparing documents and finalizing documents for submission, both of which now take longer due to efforts to reduce the inclusion of personal or commercially sensitive information and to redact any such information that must be included. In turn, many documents now need to be prepared for submission in duplicate, with redacted and nonredacted documents being submitted.

Given these wide-ranging implications, the EMA, member state authorities, and ethics committees have been required to co-create a significant volume of guidance and training in response to these changes, which sponsors, their partners, and other stakeholders have been required to assimilate. This has meant that a myriad of EU-level guidance and training documentation has been created and released by the EU Commission, EMA, Clinical Trials Coordination Group (CTCG, composed of member state authority representatives; **Table,** p. 4), and countless draft and temporary documents released at the member state level has not always been consistent with the EU-level guidance. Ensuring compliance with agency expectations during a time of such rapidly evolving guidance has been immensely challenging for sponsors, requiring agility, clarity of decision making, and robust planning in relation to any ongoing activities.

Despite the volume of guidance available, many details in certain areas remained uncertain, such as protection of commercially confidential information, submission document content, and transition of trials from the EU CTD to the regulation, which will be described in more detail based on the authors' specific experiences. During the first 12 months of the regulation, this general uncertainty led to application of a calculated trial-and-error-style approach, in which both sponsors and member state assessors in authorities and ethics committees attempted to apply their own practical interpretation of the regulation to the earliest applications that were made. This was likely well intentioned, but, for a commercial research community relying on predictability and hoping for simplicity and harmonization, the early experiences were somewhat frustrating for all parties – sponsors submitted dossiers that did not meet the expectations of the assessors, and the assessors requested information or documents that appeared unnecessary to sponsors. This uncertainty has also contributed to sponsor perception that timelines for authorization of trials would not meet expectations, but through efforts of the CTCG, the continued evolution of EU Commission guidance, and EMA efforts to promote harmonization, the situation is improving through 2023.

Variability in expectations and challenges with the functionality of the CTIS remain, so the early implications of the implementation of the regulation continue to impact the experiences of sponsors. Managing inconsistencies and staying abreast of the new and updated guidance and training also continue to be significant challenges for sponsors.

Table. EU-level guidance and training for the EU Clinical Trials Regulation

Document/training title	Version (current as of)[a]	Previous versions
EU Commission		
Clinical Trials Regulation (EU) No 536/2014 questions & answers[4]	6.6 (29 September 2023)	15
Quick guide for sponsors[5]	3 (14 September 2023)	2
Guidance for the transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation[6]	1 (19 July 2023)	0[b]
With EMA Complex clinical trials – Questions and answers[7]	1 (23 May 2022)	0
With CTEG Good lay summary practice[8]	1 (4 October 2021)	0
Templates for FORM and Part II clinical trial application – 7 document templates[9]	Various (from July 2019)	~12, across templates
EMA		
Clinical Trials Information System (CTIS) – Sponsor handbook[10]	3.03 (6 November 2023)	5
CTIS online training catalogue – 23 modules with multiple formats of training materials for sponsors, authorities, and the general public[11]	Ongoing publication May 2021-February 2023	NA
Guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System (CTIS)[12] and associated annexes	1.1 (10 July 2023)	2
Q&A on the protection of commercially confidential information and personal data while using CTIS[13]	1.2 (16 May 2023)	2
Revised CTIS transparency rules[14]	1.0 (5 October 2023)	0
CTIS evaluation timelines[15]	1.2 (26 January 2023)	2
Getting started with CTIS: Sponsor quick guide[16]	1 (13 December 2021)	0
Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 of the clinical trial protocol[17]	1.1 (30 June 2023)	1
Quick guide: How to use the organisation management service (OMS)[18]	1.1 (April 2022)	1
HMA CTCG		
CTCG best practice guide for sponsors of multinational clinical trials with different protocol versions approved in different member states under the Directive 2001/20/EC that will transition to the Regulation (EU) No. 536/2014[19] and associated cover letter template	2 (12 September 2023)	2
CTCG Best practice guide naming of documents[20]	2.0 (9 March 2023)	1
CTCG Q&A on submission of complex clinical trials in CTIS[21]	1.0 (14 March 2023)	0

CTCG, Clinical Trials Coordination Group; **CTEG,** Clinical Trials Expert Group; **CTIS,** Clinical Trials Information System; **EMA,** European Medicines Agency; **HMA,** heads of medicines agencies; **OMS,** Organisation Management Service; **Q&A,** question and answer.

[a]Version numbers and links included within the references section were up to date at the time of publication. Future versions, when released, can be expected to retain the titles described above and will be made available on the relevant EU Commission,[22] EMA,[23] and CTCG[24] websites. [b]This guidance was extracted from EU Commission Q&A[4] in July 2023.

Lessons learned since 31 January 2022

Although the EU CTR was implemented on 31 January 2022, clinical trial sponsors were able to submit clinical trial applications under the EU CTD for the first year after implementation. This made the EU CTR optional, and both EMA metrics and our experiences indicated an initially slow uptake of the EU CTR option among commercial clinical trial sponsors. Lack of experience among sponsors and uncertainty around the functionality of the CTIS developed by the EMA appeared to deter commercial sponsors, who require predictability around timelines for start-up of a clinical trial. During the second half of 2022, activity picked up as the mandatory deadline of 31 January 2023 approached, and our organization performed clinical trial applications on a range of clinical trials, experiencing all aspects of the CTIS for initial clinical trial applications, substantial modifications, and additional member state applications. Many different positive and challenging situations were encountered, as the member state authority approaches to the regulation have evolved.

As a directive, the EU CTD was not enacted as legislation that would be implemented directly into national law, and as a result, the principles of the EU CTD were implemented to differing degrees in different EU member states. Aspects like the proposed single opinion at the member state level and standardized timelines for authorization of clinical trials were therefore not realized in a consistent manner. One major objective of the EU CTR is greater harmonization, meaning that the nature of the legislation as a regulation is crucial. EU regulations are required to be transposed directly into national law, which should eliminate the variation in adoption and implementation experienced under the EU CTD. The goal of harmonization does face multiple challenges, and one significant challenge is the introduction of variation in situations where the regulation is "silent" on a topic – for example, variation in requirements for document content and document submission. Annex I to the EU CTR describes the requirements for submission of clinical trial documentation to regulatory authorities and ethics committees in a clinical trial application, but in many cases the description in the regulation is limited and open to interpretation. Examples include requirements for protocol synopsis, patient-facing documents, and investigator curriculum vitae (CV):

- **Protocol synopsis content requirements**. The EU Commission's EU CTR Q&A guidance[4] includes a specific question dedicated to the content of the protocol synopsis. However, this guidance states that the protocol synopsis should be a maximum of two pages, dictating that sponsors with a global protocol (that includes a much longer synopsis) must prepare a specific two-page version. However, for trials that only include EU member states, it is still necessary for the sponsor to prepare two versions of the synopsis, as some countries (e.g., Italy) require that a longer technical synopsis is also included in the clinical trial

application. Other countries also initially created their own guidance on protocol synopsis content (e.g., Czechia), creating a situation that continues to evolve.

- **Patient-facing document submission requirements.** The EU Commission Q&A[4] includes guidance to satisfy a gap in the regulation with respect to the submission requirements for certain documents handed to trial participants. Sections K and L of Annex I to the EU CTR[25] state that only documents handed to patients before the decision to participate need to be submitted in a clinical trial application, but this is not accepted consistently at this time. Some ethics committees consider this inconsistent with principles of good clinical practice (GCP),[26] which state in section 4.4.1 that the responsible ethics committee should provide a favorable opinion of any documents handed to trial participants. Several EU member states therefore created country-level guidance that describes a requirement for additional documents, handed to trial participants after the decision to consent, to be submitted in the clinical trial application.

- **Investigator curriculum vitae submission requirements.** Section M of Annex I of the EU CTR[25] states that a "[d]escription of the qualification of the investigators in current curriculum vitae" should be submitted for assessment in a clinical trial application. Some EU member states require only the CV of the principal investigator at each site, whereas others also require all subinvestigator CVs to be submitted.

The existence of these kinds of variation indicates that country-level intelligence is still necessary, diluting the benefit of the harmonization that has been achieved. The variability in documentation being required at different times in different countries also creates challenges for sponsors and their partners who are preparing clinical trial applications. For example, the variable patient-facing document submission requirements dictate that a translation of the same document may be required two to three months earlier in some EU member states than others.

Requests for information (RFIs) from authorities during the clinical trial application represent an important part of the process, and the short – 12 calendar day – timeline for response means it is critical that sponsors work together with their contract research organization on a process for responding to the questions and updating any documents that may be impacted. The EU CTR itself should not necessarily lead to an increase or reduction in the volume of RFIs received during a clinical trial application process, since the criteria for raising such RFIs have not changed relative to the prior EU CTD; however, the consolidation of submission processes for all countries does create a shorter

critical time period where all RFIs are received, meaning that availability of relevant expertise and effective collaboration is crucial during that time.

We have seen that these interactions and processes work more effectively when this has been considered up front, when all impacted parties know their roles from the point of receipt of RFIs through to completion of the response. During the first 18 months since the implementation of the regulation, we have seen a continuation of the trends experienced under the voluntary harmonization procedure, where in key trial designs considerations are raised by all member states during the Part I assessment, whereas under the directive, it was likely that not all EU countries would have challenged aspects like placebo control or dose levels proposed. So, in the past for a global trial involving many EU countries, only a small number of assessors may have challenged such aspects, jeopardizing authorization in a corresponding small number of countries; however, now, under EU CTR, authorization in all EU member states is at risk if key concerns are raised regarding the design or selection of investigational or noninvestigational (now referred to as *auxiliary*) medications. That increased level of jeopardy further intensifies the activities during the 12-calendar-day response period, as it is particularly important that protocol-level RFIs raised during the Part I assessment are satisfied.

A refusal to authorize Part I would dictate a need for resubmission for all EU countries to which the trial was submitted, leading to a significant delay in initiation of the trial at all sites in the EU. Quality of documentation prepared during that short RFI response period is therefore critical to the success of the clinical trial application. Preparing high-quality responses represents a significant challenge, particularly when there is a need for translation of the documentation before the 12-day deadline. Speed has always been a priority for translation of documentation required for clinical trial applications, but this combination of factors during the RFI period is another element of the EU CTR that intensifies that need.

Sponsors face multiple challenges stemming from the requirement to protect personal and commercially confidential information, and in many cases, this has prompted the creation of new solutions to overcome obstacles in clinical trial documentation. The EMA devised the deferral approach for protection of commercially confidential information, but many sponsors consider the deferral functionality to be insufficient protection, and specific information is being redacted in most cases. Some authorities are requesting that sponsors reconsider this choice at the RFI stage of assessment, referring to recently released guidance[12,13] that advises sponsors not to apply both deferral and redaction, but in other cases the combined approach is being accepted. The publication requirements incorporated into the EU CTR have created an extremely complex situation, with high stakes for sponsors whose clinical trial–related information is highly valuable. It will therefore remain likely that

sponsors will continue to protect documentation with redactions until there is greater clarity in the guidance available or more consistent enforcement. In turn, this situation has created a requirement for additional expertise to be introduced to the development of documentation for submission in clinical trial applications – the disclosure specialist.

The EMA has recognized the complexity created by both the rules and the mechanisms (such as deferral) introduced to help sponsors navigate the rules. A consultation with all stakeholders was opened in May 2023, and in response to the feedback received, the EMA released revised rules in October 2023. The revised rules have been designed to simplify the process of protecting personal and commercially confidential information while ensuring that information relevant to patients and researchers is made available. The new rules will eliminate the deferral mechanism and reduce the number of documents that will be published and are intended to be implemented around the second quarter of 2024 (when the required functionality is available in the CTIS). The revised rules will likely be welcomed by clinical trial sponsors, but when working with very tight timelines, these redaction-related responsibilities reduce the time that others, such as translators and clinical trial applicants, will have to complete their tasks, mandating a drive for ever-greater efficiency in all roles in addition to calling for all team members to be continually informed of the ongoing evolution of the requirements.

Case study – translation challenges and mitigations to EU CTR compliance

The significant changes in the regulation impact numerous aspects of the clinical trial application process, all of which need to be accommodated while driving a reduction in the timelines for submission; for translations, this means an acceleration of the timeframe to translate any content into multiple languages. The authors considered that it was important to incorporate translation activities into the preparation and adaptation of the integrated processes and training for the various teams preparing the RFI responses and submissions, so this was prioritized a few years before the regulation became effective in 2023.

Adapting and innovating the translation processes for the clinical trial documentation required prior to and during the RFI phases was paramount to enable successful responses within 12 calendar days. At the same time, it has been critical to maintain a high-quality process framework to ensure patient safety. Artificial intelligence technology and automation, global coverage, specialized EU CTR teams, and best practices are key components in helping to comply with the time-sensitive deadlines while mitigating any increase in cost of the translations.

Conclusion

Despite the steep learning curve experienced by clinical trial sponsors, trial site staff, the EMA, and member state agencies and ethics committees, the

implementation of a single clinical trial regulatory framework across the EU promises great benefits, some of which are starting to be realized. The consolidation of the regulatory assessment is leading to a reduction of protocol variation, and the authors are seeing only limited variation in opinion on Part I – fewer trials are being modified or rejected based on country-specific requests or decisions. There is still a significant way to go in terms of harmonization, with a range of variation still to be addressed. The same can currently be said with respect to the issues arising with the implementation of the CTIS. The system functionality limitations (as described in Q3.5 of the EU Commission Q&A guidance[4] and other EMA resources[27]) continue to create challenges for clinical trial sponsors, but the EMA is dedicating significant resources to resolving the issues in 2023. This is an important goal, as many enhancements were planned by the EMA, but none can be implemented while stabilization of the system remains the priority.

Technology developers are applying considerable effort to mitigate some of the challenges created by the short timelines and requirement for high quality dictated by the regulation. The technology development focus being applied to translation mirrors efforts in the areas of document management systems, protection of personal and commercially confidential information, analysis of clinical trial data and trial master file technologies. All of these aspects are impacted by EU CTR, illustrating the breadth of opportunities for trial sponsors to use technology to deliver improvements in efficiency, quality, and timeliness.

It remains to be seen how swiftly the aims and benefits of the EU CTR can be fully appreciated by the stakeholders involved. The will is certainly there with significant efforts being applied since 2014 by all stakeholders and commitment from EU-level agencies and CTCG to drive resolution of the challenges that remain. With the further improvements in harmonization of requirements and approaches to assessment allied with continued evolution of the CTIS, we can hope that the full objectives and advantages of the EU CTR will be realized.

Abbreviations

CTCG, Clinical Trials Coordination Group; **CTEG,** Clinical Trials Expert Group; **CTIS,** Clinical Trials Information System; **EU CTD,** EU Clinical Trials Directive; **EU CTR,** EU Clinical Trials Regulation; **CV,** curriculum vitae; **EMA,** European Medicines Agency [EU]; **HMA,** heads of medicines agencies; **ICH,** International Council for Harmonisation; **OMS,** Organisation Management Service; **Q&A,** question and answer; **RFI,** request for information.

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