Transition to the EU Clinical Trials Regulation: Trick or treat?

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doi: 10.56012/wfqf7348

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Abstract

The etiquette in clinical trial research requires companies to respect rules and to be precise and accurate. The new EU Clinical Trials Regulation 536/2014 (EU CTR) pushes companies and health authorities one step further – to be more flexible and collaborative. The EU CTR aims to harmonise clinical trial applications in the EU, bring more innovation to Europe, and enable faster approval of clinical trials. However, the novel process of clinical trial application in its early stages is fraught with technical and logistic challenges.

Introduction

Every new year brings new changes, not only in our personal lives but also in the regulatory landscape. 2021 was the final year of the transition of Medical Devices Directives (Directive 93/42/EEC and Directive 90/385/EEC) to the Medical Devices Regulation (EU) 2017/745.[1] The hottest topic in 2022 was the transition of the Clinical Trial Directive to the Clinical Trials Regulation 536/2014 (EU CTR). The aim of the regulation is to improve the transparency of conducting clinical trials, support innovative clinical trials, and simplify and harmonise the rules (see Table 1).[2]

The regulation was adopted in 2014 and the implementation was planned in December 2015. Due to various technical reasons (technical difficulties, strategical changes, and the audit of the novel system), the submission platform was officially released in January 2022.[3] As of January 31, 2023, the Clinical Trial Directive has been completely superseded by the EU CTR.[2,4] The transitional period for ongoing clinical trials that are performed under the Directive is still ongoing until 2025 (except for the non-interventional studies).

Clinical trial application then and now

THEN: Prior to January 31, 2023, a clinical trial application (CTA) submission had to be done nationally.[4] This meant that a sponsor who wants to conduct a multinational trial in 20 countries in the European Union/European Economic Area (EU/EEA) had to submit 20 national CTAs and adapt the documentation according to the different national legislations.

NOW: Under the EU CTR, all clinical trials that have been submitted nationally in the EU/EEA (except the non-interventional studies) by January 31, 2023, must be transitioned and uploaded to the new Clinical Trials Information System (CTIS) by 2025.[5] The major change is the centralised submission of clinical trial applications (CTA) in the EU through the CTIS portal. The assessments by competent authority and ethics committee can be done in parallel, and the validation/assessment questions are communicated via Request for Information (RFI) by the Member States.

Furthermore, the regulation introduced a so-called winter clock stop – a period from Decem-

Table 1. Pros and cons of the Clinical Trials Regulation

Pros	Cons
Single submission for the EU countries and to the ethics committee as well as competent authorities at the same time	New system – new challenges
Document consistency in all Member States (MSC)	Complicated procedure for smaller and less innovative clinical trials?
Channelling questions through one country – RMS (Reporting Member State)	Single substantial modification submission per clinical trial, the next submission of a substantial modification is only possible if the first procedure has been approved
Defined timelines – faster approval	Tight timelines in general
Lower documentation burden for multinational clinical trials	Other Member States (MSC) can still contact the sponsor and request documentation
Harmonisation of the rules for conducting clinical trials throughout the EU	
Simplification of safety reporting (single safety reporting for all Investigational Medicinal Products (IMPs)	
Winter clock stop	

ber 23 to January 7, when the timer of procedure temporarily stops, and no due date is allowed to be set during this period for an RFI.[6]

The new regulation is also applicable for national clinical trials, therefore smaller companies and academia which usually perform clinical trials in a single country have the same documentation burden but may cope better with the tight timelines.

The submission package: Why harmonisation really makes sense

THEN: Under Clinical Trial Directive, the general requirements for application of clinical trials with medicinal products was defined in the CT-1 Guidance Document, EudraLex Vol. 10.[7] Still, every EU competent authority had their own recommendations/naming conventions for the submission package. Table 2 shows an example of different national requirements when submitting a clinical trial application to the Health Authority in Austria,[8] Germany,[9] and Belgium.[10] As shown in Table 2, the first column contains an overview of general guidance of the submission package for the application to the competent authority as laid out in the CT-1 Guidance Document. The rows in the table compare the content of the submission package and the naming conventions for the countries mentioned above. For instance, Belgium did not require numbering of the documents which was recommended for Austria and Germany. Those two countries on the other hand requested different document numbering. Interestingly, in the Belgian guidance, the document naming convention is strictly defined.

Every Member State had their own preference for the submission system. In Austria the submission was done via email or EudraLink[11] and some countries such as Belgium and Germany were strict about the submission via Common European Submission Portal (CESP).[12] The national guidelines strictly communicated which portal was acceptable and that the correct submission channel was also essential to receive an approval of the clinical trial application.[10]

NOW: With the EU CTR the clinical trial documentation is applicable for and consistent in all countries. It is divided in two parts – Part I and Part II (see Table 3).[12] The Reporting Member State is responsible for the assessment of Part I and each Member State's Ethics Committee for Part II. The assessment of the documentation is extensively defined in the regulation.[2]

Submission of the application[2]

The application is submitted online via the CTIS, a system that has been programmed and audited by the EMA. The final rollout of the platform and the functionality were confirmed on January 31, 2022, after various delays.

Once the application is submitted, the sponsor can choose one Member state (an EU/EEA country) to be the Reporting Member State (RMS). If there are no objections or concerns, the proposal for RMS is accepted. If the proposed RMS declines, another Member State can step up

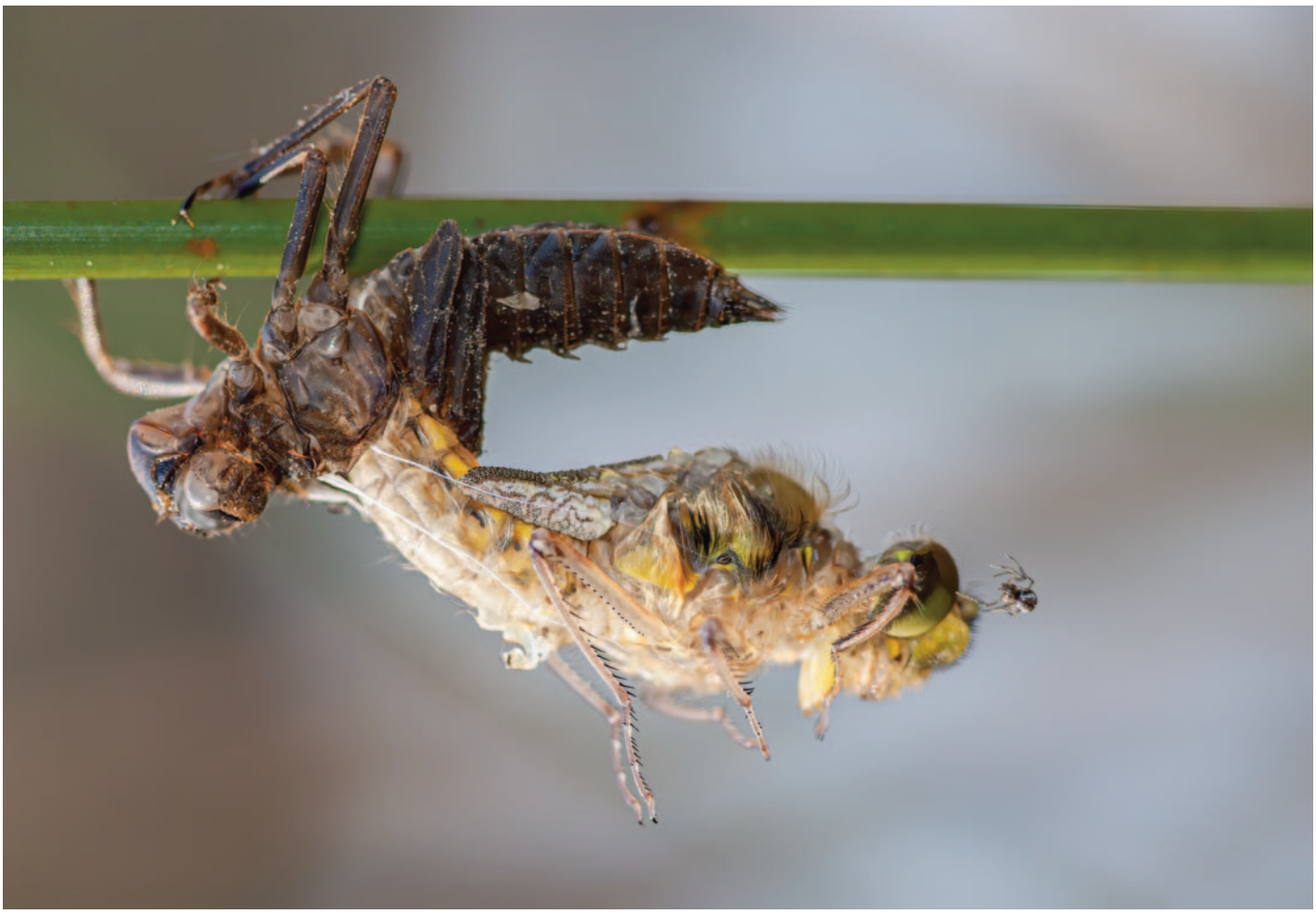


Table 2. Comparison/Overview of the European and national guidelines on the application format

CT-Guidance document, EudraLex Vol. 10	National guidance on the application format and documentation for the clinical trial submission (examples):		
General guidance:	**Austria**[8]	**Germany**[9]	**Belgium**[10]
General information	1. General information (cover letter, EudraCT)	01 Cover letter 02 EudraCT (PDF & XML)	• Cover letter • EudraCT (PDF & XML) • Signature • List of the European competent authorities to which the application has been submitted • Copy/summary of scientific advice
Protocol	2. Current version of the protocol, the synopsis, and the signature pages	03 Protocol	• Protocol
Investigator's Brochure	3. Investigator's Brochure	04 Investigator's Brochure	• Investigator's Brochure
Investigational Medicinal Product Dossier (IMPD)	4. Full IMPD, simplified IMPD or Summary of Product Characteristics (SmPC)	05 IMPD	• IMPD • Simplified dossier of the investigational medicinal product • SmPC • Copy of the manufacturing authorisation GMP certificate for biological active substance • Copy of the import authorisation • Viral safety studies • TSE certificates • Labelling examples in the national languages
Additional information	5. Patient Information, the summary of the Paediatric Investigation Plan or the summary of scientific advice	06 Risk-Benefit 07 Non-IMPD 08 GMP 09 Labelling 10 Administrative documents 11 Scientific advice 12 GMO 13 Xenogenic products 14 Other documents 15 Reporting	

Abbreviations: EudraCT, European Union Drug Regulating Authorities Clinical Trials Database

or be appointed.

The first validation of the application takes place within 10 days and the RMS contacts the sponsor to raise relevant validation issues in the form of a Request for Information. Member States have seven days to communicate requests to RMS. No contact from the RMS means that the validation is complete.

Timelines

Timelines are defined for the three different types of application – initial CTA, substantial modification (substantial changes during the study conduct phase, such as protocol amendments, IB updates and others[2]), and Additional Member State Concerned CTA (Add MSC CTA – adding a new member state for a previously approved clinical trial).[13] A procedure can be divided in three stages – validation phase (including RMS selection), assessment phase, and decision phase. RMS selection is only applicable for the initial clinical trial submission. Validation phase is valid for both the initial clinical trial submission and the substantial modification procedure. Assessment phase is valid for all procedure types (see Table 4). Every procedure has strictly defined timelines (see Table 5). An overview of the phases and submission types has been published by the EMA in their CTIS timelines overview

Table 3. Clinical Trial Submission Package according to the EU-CTR

Part I (evaluation by the Reporting Member State (RMS))	Part II (evaluation by Member States' (MSC) Ethics Committee*)
Scientific, quality, and technical aspects • Cover letter • EU Application Form • Protocol • Investigator's brochure • Good manufacturing practice documentation • Investigational medicinal product dossier/ Auxiliary medicinal product dossier • Scientific advice • EU Paediatric Investigation Plan decision • Labelling • Proof of payment	**National and ethical aspects** • Recruitment of subjects • Informed consent form and subject information leaflet • Compensation arrangements • Suitability of investigators and the clinical trial site • Proof of insurance or indemnification • Data protection • Financial agreements

* Each member state can still define/request the documents in Part II

Table 4. Types of application and phases

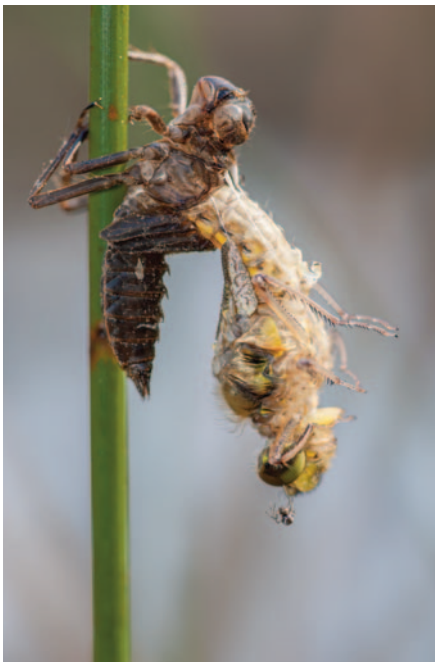
Application type	Validation	Assessment	Decision
Initial application	RMS selection and validation phase	Assessment (Part I and II)	Decision
Substantial modification	Validation phase	Assessment (Part I and II)	Decision
Additional Member State concerned (Add MSC CTA)[13]	Not applicable	Assessment (Part I and II)	Decision

handbook.[12]

Technical challenges with the new system and what can we do about it

In the *Clinical Trials Highlights* October 2022 issue, [15] the EMA acknowledged that there are certain technical difficulties with the new system.[16] In December 2022, there have been various articles published showing great concern about the functionality and official roll out of CTIS due to technical difficulties.[17,18]

I had the opportunity to participate in projects concerning EU CTR transition as a local point of contact for the competent authority and the clinical study team involved in the submission. My experience has taught me that in any case, especially with the EU CTR, collaboration is the key. If there is an issue with the portal, of course, it is possible to contact the CTIS helpdesk and try to solve the issue as soon as possible. Sometimes the deadlines are too tight



and contacting RMS is the fastest solution. It is important to have a good relationship with all internal and external stakeholders to find solutions to the technical challenges. It is of interest to both sides (EMA's and sponsor's) that the procedure runs smoothly. As stated in the EMA's *Clinical Trial Highlights* publication: "*Technical challenges encountered with the CTIS workflow for some very large multi-Member State CTAs are being managed through workarounds to minimise the impact on applications*".[15] Furthermore, they offer extensive trainings for the users and published a handbook for sponsors to ease the transition to the new CTA process.[19] After all, Rome was not built in a day.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by his employer or EMWA.

Table 5. Short overview of timelines concerning different procedures[6]

Type of application	Duration of the assessment phase	Decision
Initial Clinical Trial Application	Assessment of Part I – up to 45 days (up to 76 days if RFIs are submitted). Assessment of Part II can run in parallel	Up to 5 days
Substantial modification	Part I or Part I & II assessment up to 38 days (up to 69 days if RFIs are submitted). Part II only assessment up to 33 days (up to 64 days if RFIs are submitted)	Up to 5 days
Adding Member State concerned	Depends on the assessment. Part I or Part II assessment up to 47 days (up to 78 days if RFIs are submitted)	Up to 5 days

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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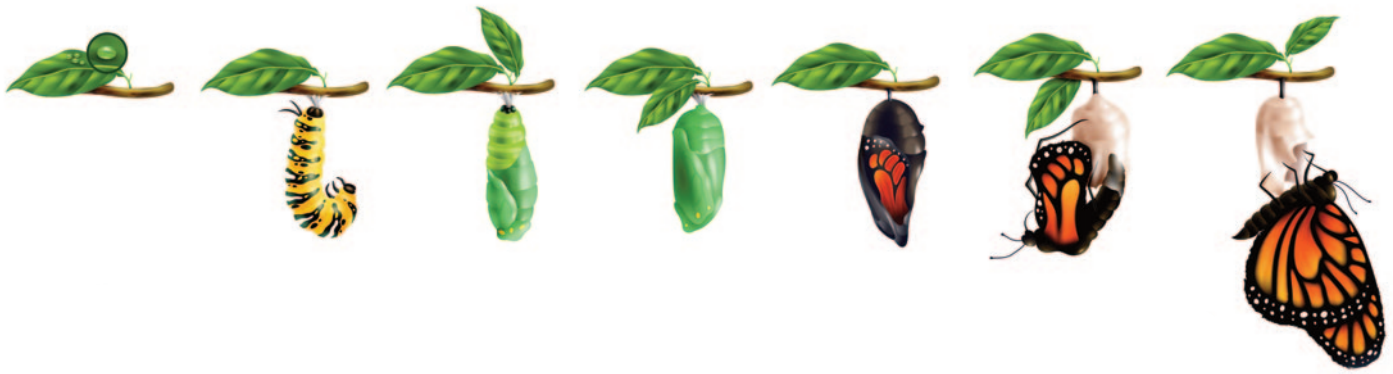

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