Implementation of the EU Clinical Trials Regulation
Update for the Swiss Federal Office of Public Health
- June 2023 -

1. European Union

CTIS

As of 31 January 2023, the Clinical Trials Information System (CTIS) is mandatory and sponsors are no longer allowed to submit clinical trials applications under the Clinical Trials Directive (CTD)[1]. In the minutes of the 118th Management Board meeting of the European Medicines Agency (EMA), it is reported that the EMA stepped up its resources and communication in the lead up to the CTIS becoming mandatory to ensure that no blocking technical issues hindered the delivery of a minimum viable product (MVP) of the CTIS, providing weekly report to the Management Board on its progress[2]. A contingency plan had also been defined to prepare for any challenges. On 7 February 2023, the EMA published a CTIS risk mitigation plan to strengthen the planning for the functioning of the CTIS to ensure users can carry out business-as-usual activities[3]. The mitigation plan seeks to identify early risks, classify and assess the risks, coordinate a rapid and effective response when issues arise, and guarantee the compliance of the CTIS user experience with the Clinical Trials Regulation (CTR)[4].

The Management Board was also provided with an update on the initiative "Accelerating Clinical Trials in the EU" (ACT EU), which oversees CTIS operations, and its key developments. ACT EU has started delivering on its 2022-2026 work program. Some of the main priority actions that were reported to the Management Board included conducting a targeted survey to identify and later tackle blocking issues. The survey helped identify several issues such as the lack of harmonization among Member States (e.g., fees, national requirements, and file naming), the rigidity of the process for the sequential submission of Part I and II of the application, the lack of preparedness in Member States, and the challenges in setting up large multi-country trials[5]. Other changes were directly implemented in the CTIS as a result of this survey. Separately, one

of the ACT EU priority actions is to establish a multi-stakeholder platform to hold regular technical discussions. On the latter, a month-long consultation was launched by the EMA on 3 February 2023[6].

Table 1: Selected KPIs on the CTR's implementation (31 January 2022 to 31 May 2023)

Number of initial CTAs submitted under the CTR in CTIS	1346			
Number of initial CTAs submitted under the CTR in CTIS per status	Under evaluation 556	Authorized CTAs 563	Non-authorized or non-valid CTAs 15	Withdrawn & lapsed CTAs 165
Number of CTs with a decision in CTIS per sponsor type & scope	Commercial		Non-commercial	
	Mono-national 148	Multinational 260	Mono-national 175	Multinational 27
Average days from submission to decision for initial CTAs	90			

Abbreviations: CT = clinical trial; CTA = clinical trial application; CTR = Clinical Trials Regulation; KPIs: Key Performance Indicators | Source: EMA[7]

The Management Board also endorsed the 2023-2024 CTIS workplan at its December 2022 meeting[8]. The workplan focuses on enhancing the CTIS user experience by implementing improvements in the most impactful functional areas of the CTIS, future proofing and minimizing risks to the technical core of the system.

The minutes of the 119th Management Board meeting in March were published on 9 June 2023[9]. At this meeting, the Management Board was updated on operational aspects of the CTIS and on recent improvements made to the system since 31 January 2023. The Management Board was also informed, among other aspects, about planned improvements to the CTIS in the area of user experience to be implemented this year.

At the same March 2023 meeting, EU Member States shared their perspectives on the CTIS implementation. Among other aspects, they highlighted that the continued collaboration with sponsors, the EMA, and the European Commission was vital to achieve a smooth transition to the CTR and its CTIS.

On February 2023, the EMA launched the CTIS Business Intelligence (BI) system and hosted a training for Member States[10]. Designed for Member States, the BI system is distinct from the CTIS and aims to help reduce query loads in the CTIS and provides a user-friendly dashboard that is said to run faster and better queries.

Challenges are said to have been experienced in the area of non-commercial trials, and the EMA reportedly found a work-around to help non-industry actors in the submission of their clinical

trials applications[11]. The EMA also reported that the ACT EU Steering Group plans to launch a support scheme for academic sponsors conducting multi-national clinical trials this year. Other priorities for 2023 of the ACT EU Steering Group include the revision of the workplan to consider learnings on the network needs and priorities, and the creation of the Multi-Stakeholder Platform (MSP). The MSP aims to be a sustainable platform enabling the collaboration between stakeholders to improve clinical trials and its kick-off meeting took place on 22-23 June 2023.

Transparency

At its December 2022 Management Board meeting, the EMA discussed an open letter, dated 17 October 2022, that highlights concerns in relation to the proposed deferral of the protocol publication for category 2 trials (i.e. phase II and III trials) by up to five years. The signatories, including non-governmental organizations (NGOs), scientific publications, and professional societies, were concerned about the detrimental impact of this measure on science, patients, and innovation, among other aspects[12]. On this point, the Management Board agreed that rules applicable to the disclosure of certain clinical trial documents and CTIS transparency measures should be reviewed[13]. A public consultation ran from 3 May to 28 June 2023[14].

On 3 May 2023, the EMA also issued an interim guidance document and an annex on CTIS transparency rules[15]. The document details how to approach the protection of personal and commercially confidential information. An updated Q&A on how to protect commercially confidential information and personal data while using the CTIS was later released on 17 May 2023[16].

Guidance and Acts

On 17 February 2023, the European Commission published version 6.4 of its Q&A documenting the rules for the governance of medicinal products in the EU under the CTR[17]. The changes include additional content on options available to the product owner in case the sponsor of a clinical trial is not said product owner of the investigational medicinal product (IMP) and should not have access to the quality IMP dossier (IMPD-Q) or associated considerations/request for information in order to protect commercially confidential information. The Q&A also includes an update to its Annex II on language requirements for Part I documents following amendments by France and Norway; the update concerns the columns on “protocol synopsis”, “patient-facing documents as part of the protocol”, and “fields of the application form” for France, and the column “labelling” for Norway.

On 21 March 2023, the European Commission issued the second version of its guidance on rules applying to clinical trials in the EU[18]. The guidance provides sponsors and investigators with a quick guide about the rules and procedures of the CTR. Changes include information on the case when the sponsor is not the product owner of the IMP mentioned in the previous

paragraph, references to the Q&A on protection of commercially confidential information and personal data, and a distinction of requirements between advanced therapy investigational medicinal products and investigational medicinal products including genetically modified organisms (GMO).

Austria

Austria's Federal Office for Safety in Health Care (BASG) updated its regulation on fees, which entered into force as of 1 January 2023[19]. Upon the CTIS becoming mandatory, the BASG signaled its willingness to take on the role of a Reporting Member State (RMS)[20]. The BASG reported that clinical trials initiated under the previous Austrian law may continue according to the previous law until 31 January 2025. An extension of the transitional period for clinical trials is not possible[21].

Following the adoption of national legislation in line with the CTR, amending also the Austrian Medicines Act (AMG) in 2022, the BASG updated information in March 2023 regarding national requirements and recommendations. It includes a list of ethics committees (ECs) evaluating clinical trials according to the CTR, as well as language requirements for application dossiers and templates documents for the FORM section of the CTIS and for national aspects (Part II). In addition, the requirements for bringing complaints against the refusal of a clinical trial application were disclosed. The complaint procedure is not linked to the CTIS, but involves the Federal Administrative Court (BVwG) of Austria.[22]

On 20 April 2023, the BASG released its statistical analysis regarding commercial/non-commercial clinical trials with medicinal products as well as performance studies with *in vitro* diagnostics from 2013 until 2022[23]. While the overall number of clinical trials in Austria remained steady between 2021 and 2022, the number of trials filed under the CTR increased by more than 70% to a total of 64 in 2022.

Several templates and background documents in line with the requirements for clinical trials under the CTR were made available by the EC of the Medical University of Graz on 14 May 2023. They include information on informed consent, recruiting materials, and patient facing documents such as questionnaires[24].

France

On 19 January 2023, France's Ministry of Health announced the launch of the work to create a national database for clinical trials. The work is said to take place during the first half of 2023. The database, open to public and private stakeholders, will feature external Application

Programming Interfaces (APIs), allowing for interconnectivity with other specialized or public registers. At a later stage, the database would be linked to the information system for research on human subjects (SI RIPH 2G), which is operated by the Ministry of Health and fed by the CTIS and the European Database on Medical Devices (EUDAMED) once it is operational. Only the SI RIPH 2G database contains all clinical trial applications for the three categories of research on human subjects (i.e. high level of intervention, minimal level of intervention, and observational research), it is currently restricted to the French administration[25]. The MVP of the national database will be called ECLAIRE.

Separately, changes in the area of pharmacovigilance obligations in clinical trials were implemented in France's law regulating research on human subjects (Loi Jardé). The changes, which became valid as of 22 May 2023, include a simplification of the reporting of unexpected serious adverse reactions (SUSARs) during clinical trials. They must now only be reported electronically via EudraVigilance[26]. The Public Health Code Art. L. 1121-1 details the form, content, and reporting modalities[27].

As previously mentioned in the last edition of this update, a draft law on innovation in healthcare is currently being discussed by the French Parliament. The text was transmitted to the lower house (National Assembly) in July 2022[28].

Germany

On 18 December 2023, Germany's Federal Institute for Drugs and Medical Devices (BfArM) updated its webpage on clinical trials announcing the end of the transitional period's application window as of 30 January 2023[29]. In parallel, BfArM made available the official list of ECs registered with the BfArM/the Paul-Ehrlich-Institute (PEI) on 7 February 2023[30]. BfArM further issued a work plan for the workload management among ECs in Germany on 14 March 2023. The plan, which takes into account the total number of ECs and their respective capacity, specifies the order according to which ECs are responsible for the assessment of applications submitted for the authorization of a clinical trials in humans[31].

BfArM and the PEI updated a joint guidance document on 15 December 2022; the document provides recommendations on the notification of observational studies and non-interventional studies[32].

On 1 January 2023, BfArM issued a publication compiling insights regarding the CTR/CTIS[33]. The contributions to the publication include articles authored in 2022 about the CTR's rule and clinical trials authorization process and the impact of the CTR on existing transparency rules from a sponsor and the industry perspective, among others[34].

Italy

The Italian Medicines Agency (AIFA) continues to roll out measures to implement the CTR. In February 2023, the AIFA reported the entry into force of a Decree dated 30 January 2023 which defines rules for the payment of the single fee for clinical trial applications to be paid via the Online Payment System (POL)[35]. Sponsors that paid fees for applications that were not submitted before 22 February 2023 must seek reimbursement. This Decree replaces a guidance document on the management of clinical trials and the related fees that was published in 2022. The AIFA also published the first version of its Q&A document on clinical trials on 12 May 2023[36]. On 16 May 2023, Italy's National Coordination Center for Ethics Committees (NCCEC) released a guide to support the preparation of Part II application documents under the CTR and that highlights aspects relevant to national legislation, which are not detailed by the CTR and the current ad-hoc Q&A [37].

Three further Decrees focusing on ECs in Italy were published on 7 February 2023 in the Official Journal by the Ministry of Health with a view to implement the CTR[38]. Those Decrees list recognized ECs, spell out evaluation and interaction rules, and define criteria for their composition and operation, respectively. ECs in Italy are organized in a tiered manner, with national ECs, so-called territorial ECs (a list of which was made available on 20 June 2023 by AIFA[39]), as well as local ECs. The Agency also released technical guidelines in May 2023 to manage, among other aspects, the ongoing transfer of competencies from the current ECs[40]. Additional guidelines applicable to ECs in Italian regions and autonomous provinces are expected to be further issued by the NCCEC[41].

The NCCEC has also been very active in providing guidance documents in line with the national legislation implementing the CTR: two contract templates related to medicinal products' trials involving medical devices and an information sheet and informed consent form for the patients' participation were issued in March 2023[42], and a document on ethical and regulatory concerns in the processing of personal health data in observational research was adopted by the NCCEC on 6 April 2023[43].

Other EU Member States and European countries

Poland

In April 2023, Poland's Act on Clinical Trials of Medicinal Products for Human Use entered into force[44]. Thanks to the entry into force, Polish legislation on clinical trials is now aligned with the CTR. The Act brings important changes to the former legislation; changes brought about include new assessment procedures for clinical trials, rules on data protection, and compensation rules.

The structure of ECs is also revamped, establishing a central EC in charge of coordinating and overseeing other Polish ECs.

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