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

1. European Union

CTIS

A continuous rise in the monthly volume of clinical trials submissions was reported at the 120th Management Board meeting of the European Medicines Agency (EMA) that took place in June 2023[1]. This trend was confirmed at the 121st Management Board meeting in October, during which it was highlighted that over 2000 initial applications have been submitted through the Clinical Trials Information System (CTIS) since the system's launch[2].

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

Number of initial CTAs submitted under the CTR in CTIS	Total 2685			
	New initials 2082	Transitioned 412	Resubmissions 191	
Number of initial CTAs submitted under the CTR in CTIS per status	Under evaluation 697	Authorized CTAs 1444	Non-authorized or non-valid CTAs 95	Withdrawn & lapsed CTAs 361
Number of CTs with a decision in CTIS per sponsor type & scope	Commercial		Non-commercial	
	Mono-national 278	Multi-national 576	Mono-national 510	Multi-national 168
Average days from submission to decision in October 2023	All ~85			

Abbreviations: CT = clinical trial; CTA = clinical trial application; CTR = Clinical Trials Regulation[3]; KPIs: Key Performance Indicators | Source: EMA[4]

At its June and October meetings, the Management Board saluted the continued efforts deployed by the Agency on the one hand to involve stakeholders in various ways, including public events and workshops and, on the other hand, to provide support to CTIS users by providing trainings, education materials, and public events. EU Member States also shared their perspective at the EMA Management Board meeting in June, highlighting the importance of a continued stakeholder dialogue and EU Member States' collaboration for a successful implementation of the CTIS. The implementation of the CTR and CTIS appears to be progressing well according to the EMA mid-year report published and discussed at the EMA Management Board meeting in October 2023[5]. The entries relating to the IT implementation of CTIS and the provision of training to CTIS users are categorized as being on track. Among other aspects, the mid-year report also states that the support for ACT EU is on track.

In the area of the transition from the Clinical Trials Directive (CTD)[6] to CTR, a number of ongoing trials will have to be transitioned to CTIS and approved at the latest on 30 January 2025; more than 4500 trials still need to be transitioned to CTIS according to the EMA[7]. To support this transition, the Heads of Medicines Agencies' (HMA's) Clinical Trials Coordination Group (CTCG) put forward a harmonized and expedited evaluation procedure for EU Member States that will remain open until 16 October 2024. Please refer to the Guidance and Acts section for guidance on the transition from the CTD to the CTR.

As reported in the previous edition of this report, the initiative "Accelerating Clinical Trials in the EU" (ACT EU) oversees CTIS operations. Following the month-long consultation held in February and March 2023, feedback from various stakeholders was gathered on the priorities to be pursued by ACT EU. The public consultation identified areas on which the ACT EU Multi-Stakeholder Platform (MSP) should initially focus, including the CTR's implementation, methodologies guidance, and regulatory support for evidence generation[8]. On the CTR's implementation, further aspects raised by stakeholders included the need for the CTR framework to keep up with modern trial designs and methods, and the need for iterative clinical trial advice. The first ACT EU MSP workshop took place in June 2023. Published in September 2023, the workshop's report lists 8 priority areas and identifies key messages including the need for improving the interface of the CTR with other legislation such as the Medical Devices and *In Vitro* Diagnostics Regulations (MDR and IVDR), the need for a greater collaboration between national ethics committees, and the need for a more flexible definition of non-commercial clinical trials, among other aspects[9]. The second version of the ACT EU workplan was published on 10 November 2023, laying out planned actions in four areas including mapping and governance, implementation of the CTR, establishment of a multi-stakeholder platform, and good clinical practice modernization[10]. Furthermore, a call was circulated in October 2023 to create an ACT EU MSP Advisory Group (ACT EU MSP AG), which aims to gather stakeholders

from patient/consumer organizations, industry players, healthcare professionals, non-commercial clinical data and translational research organizations, and research funders[11]. The ACT EU MSP AG is expected to provide strategic advice on the workplan and operational advice for specific initiatives.

Transparency

At its meeting on 5 October 2023, the EMA Management Board adopted a revised version of the rules for the publication of clinical trials information that are submitted through the CTIS with a view to improve transparency[12]. This revision was subject to a public consultation that ran in May and June 2023, as reported in the previous edition of this report. The new transparency rules will result in the sharing clinical trials information on a section of the CTIS that will be accessible to the public. Changes introduced by the new rules include a rationalization of the number of documents to be submitted by sponsors, the making available of structured data fields for data publication, and the creation of two categories (for and not for publication) for data submission in CTIS. Of note, an important change in these rules is the removal of the deferral mechanism. Through this mechanism, sponsors were able to delay the publication of selected data and documents for up to seven years after the end of the trial. Sponsored are now invited to redact commercially confidential information and personal data in the document submitted under the category “for publication” and can no longer request a deferral. The application of the revised rules is expected in the second quarter of 2024 when the CTIS technical implementation is expected to be finalized.

The European Commission, the EMA, and the HMA issued on 29 November 2023 an updated version of the question and answer (Q&A) document on the protection of commercially confidential information and personal data while using the CTIS[13]. The document was updated to reflect changes mentioned in the above paragraph and includes a new section on the revision of the CTIS’ transparency rules on how to deal with clinical trial applications submitted before the introduction of the change. This document should be read in conjunction with the EMA guidance document dated 10 July 2023 on how to approach the protection of personal data and commercially confidential information[14]. The latter aims to support users of the CTIS to understand the principles and use the different functionalities for the protection of such information.

Guidance and Acts

On 29 September 2023, the European Commission published version 6.6 of its Q&A document on the rules for the governance of medicinal products in the EU under the CTR[15]. Changes implemented in the document include a revised answer on the pre-requisites to enable the start of a clinical trial, i.e. a positive benefit-risk balance and, in exceptional cases, time-specific

requirements. A new entry was added on requirements relative to exposure to ionizing radiation for radiopharmaceuticals in clinical trials. Further updates were also made to the understanding around requirements for express informed consent from subjects, as well as annex II on language requirements for part I documents and annex III.

On 14 September 2023, the European Commission issued the third version of its guidance on rules applying to clinical trials in the EU[16]. The guidance provides sponsors and investigators with a quick guide about the rules and procedures of the CTR. Changes include a new section on how to proceed with regard to the Investigational Medicinal Product Dossier on Quality data (IMDP-Q) when adding a Member State Concerned (MSC) to the clinical trial in case the manufacturing of the Investigational Medicinal Product (IMP) concerned is done at a decentralized point of care (PoC). The introduction was also amended based on updated guidance and best practice for sponsors for the transition from the CTD to the CTR, which was updated in September 2023[17] and published alongside a template cover letter for transition trials[18].

The European Commission published further guidance dedicated to the transition from the CTD to the CTR[19]. Dated 19 July 2023, this guidance is designed to provide sponsors with guidance on aspects such as which and when clinical trials are to be transitioned, specific steps to be taken to achieve the transition, expectations regarding the documentation, and whether an MSC can be added to a clinical trial after its transition to the CTR.

Austria

For Austria, ACT EU reported a total of 161 new initial clinical trial applications submitted since 31 January 2022: 147 multinational clinical trial applications in which the country was an MSC (of which 28 where Austria was a Reporting Member State), and 14 mono-national clinical trial applications[20]. A total of 142 clinical trials have been authorized in Austria since January 2022. In October 2023, Austria's Federal Office for Safety and Health Care (BASG) made available on their website the latest version of the European Commission's quick guide released in September 2023 on the CTR's rules and procedure[21], which is also reported in the Guidance and Acts section.

France

For France, ACT EU reported a total of 718 new initial clinical trial applications submitted since 31 January 2022: 527 multinational clinical trial applications in which the country was an MSC (of which 82 where France was a Reporting Member State), and 191 mono-national clinical trial applications[22]. A total of 565 clinical trials have been authorized in France since January 2022.

Following the implementation of changes in Frances' law regulating research on human subjects (Loi Jardé) in the area of pharmacovigilance obligations in clinical trials, reported in the previous edition of this report, guidance on the reporting of adverse events, new developments and annual safety reports was issued in the second half of June 2023[23]. Two related explanatory notes on vigilance notifications were also published at the same time[24].

As previously mentioned in the last editions of this report, 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. The text is still being discussed by the Social Affairs Committee of the French National Assembly[25].

Germany

For Germany, ACT EU reported a total of 672 new initial clinical trial applications submitted since 31 January 2022: 532 multinational clinical trial applications in which the country was an MSC (of which 173 where Germany was a Reporting Member State), and 140 mono-national clinical trial applications[26]. A total of 524 clinical trials have been authorized in Germany since January 2022.

In the second half of June, Germany's Federal Institute for Drugs and Medical Devices (BfArM) updated its frequently asked questions (FAQ) covering topics including the German Register of Clinical Trials (DRKS). Of note, the updated FAQ reports that CTIS is recognized as an official data platform by the International Committee of Medical Journal Editors (ICMJE) since June 2023. Accordingly, clinical trial studies submitted through the CTIS should only be registered in the DRKS if the applicant provides an appropriate justification, such as the intention to publish studies in German[27].

Italy

On 4 August 2023, the Italian Medicines Agency (AIFA) published its report on clinical trials in Italy[28],presenting data covering the years 2020 to 2022. Of note, the document highlights that a share of 17.8% of total clinical trial applications were submitted through CTIS in Italy last year.

In July 2023, the AIFA started publishing data on clinical trials submitted pursuant to Directive 2001/20/EC[29]. The data is structured in three categories, i.e. "concluded", "in progress", and "withdrawn/unauthorized", and is updated on a monthly basis.

In the second half of the year, Italy continued to roll out measures to implement the CTR with a particular focus on ethics committees. Ethics committees in Italy are organized in a tiered manner, with national ethics committees, so-called territorial ethics committees, as well as

local ethics committees. As reported in the previous edition of this report, Italy published several Decrees defining recognized ethics committees earlier this year, laying down evaluation and interaction rules, and defining criteria for their composition and operation. In July, the AIFA published guidelines authored by the National Coordination Center for Ethics Committees (NCCEC) on the regulation of territorial ethics committees [30]. The document covers aspects such as the definition of their competence, their composition, their functioning, and the obligation to publish an annual report.

Ethics committees that are recognized by the Decrees mentioned above became effective on 7 June 2023. Some clinical trials that involve no longer recognized ethics committees are subject to a transition during which competences should be transferred to recognized territorial and national ethics committees. The AIFA made available a Q&A document dedicated to the management of this transition[31], which follows the publication of guidelines on the same topic in the same month[32].

Other EU Member States and European countries

Ireland

Ireland's Health Products Regulatory Authority (HPRA) published an updated version of its guide to conduct clinical trials under the CTR on 28 June 2023[33]. Among other aspects, the guide details the applicable Irish national legislation in line with the CTR, which was largely implemented in 2022, and provides information on the coordinated review of clinical trials information.

Slovakia

The Ministry of Health of the Slovak Republic published a notice of an organization called Ethics Committee for Clinical Trials of Human Medicinal Products, for Clinical Trial of Medical Devices, and for Performance Studies of *In Vitro* Diagnostic Medical Devices[34]. The notice, which was updated on 13 October 2023, lists the required national and EU documents to be submitted for Part II clinical trial applications.

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