Implementation of the EU Clinical Trials Regulation
Update for the Swiss Federal Office of Public Health
- August 2022 -

1. European Union

1.1 Adoption of Implementing Acts, Delegated Acts and Guidelines

The Clinical Trials Regulation (CTR, 536/2014)[1], which entered into force on 16 June 2014, became applicable on 31 January 2022. The implementation of the CTR was pending deployment of the Clinical Trials Information System (CTIS), an EU database and portal for clinical trials. Once ready, the CTIS had to undergo an audit, on which basis it was deemed fully functional in July 2021. The following transition periods apply:

- Until 30 January 2023, sponsors may choose to run a new trial under the CTR or the Clinical Trials Directive (CTD, 2001/20)[2],
- By 31 January 2025, the CTR will apply to all ongoing trials in the EU approved under the CTD.

On 10 January 2022, the Commission Implementing Regulation (EU) 2022/20[3], focused on the rules and procedures for the cooperation of the Member States in safety assessment of clinical trials, was published in the EU Official Journal (EU OJ). The text aims to avoid any duplication of work among involved EU Member States when it comes safety assessment, introducing the concept of safety assessing Member State.

On 1 June 2022, the European Commission published a draft Delegated Regulation[4] on labelling requirements for unauthorized investigational and unauthorized auxiliary medicinal products in the EU OJ. The text, once in application, will modify the CTR to allow the period of use to be omitted from the immediate packaging in specific cases. Previously, the European Commission published a Delegated Act on the basis of the CTR on 23 May 2017, which specified principles

of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections[5].

In the first half of 2022, several guidance documents were published by the European Commission to support applicants, including Questions and Answers (Q&A)[6] on the CTR, a Q&A on its interface with the *In Vitro* Diagnostics Regulation (IVDR) and Medical Devices Regulation (MDR)[7], and a Q&A on complex clinical trials[8]. In addition, guidelines on requirements for quality documentation concerning biological investigational medicinal products[9] and on requirements applicable to the chemical and pharmaceutical quality document of investigational medicinal products were published[10].

1.2 Implementation and Use of the CTIS

The implementation of the CTR is supported by two expert groups, namely the Clinical Trials Coordination and Advisory Group (CTAG)[11] and the Clinical Trials Expert Group (CTEG)[12] that provide advice to the European Commission. In addition, the implementation is also accompanied by the Accelerating Clinical Trials (ACT EU) initiative[13]. On 13 January 2022, the Heads of Medicines Agencies (HMA), the European Commission, and the European Medicines Agency (EMA) jointly announced the ACT EU, which efforts will be led by the ACT EU Steering Group (ACT EU SG). The ACT EU SG is designed to steer the transformation of clinical trials in Europe and to exercise oversight over the CTIS[14]. As a first step, it was agreed that ACT EU would discuss a draft list of Key Performance Indicators (KPIs) to monitor the CTR's implementation, which were reviewed and endorsed by the CTAG at the end of April 2022. Selected KPIs are presented in table 1 below. It is anticipated that a detailed delivery plan will be presented to the EMA Board at a future meeting.

Table 1: Selected KPIs on the CTR's implementation (31 January to 30 June 2022)

Number of initial CTAs submitted under CTR in CTIS	**130**			
Number of initial CTAs submitted under CTR in CTIS per status	Under evaluation **83**	Authorized CTAs **22**	Non-authorized CTAs **2**	Withdrawn & lapsed CTAs **23**
Number of CTs with a decision in CTIS per sponsor type & scope	Commercial		Non-commercial	
	Mono-national **7**	Multinational **3**	Mono-national **11**	Multinational **3**
Average days from submission to decision for initial CTAs	**73.9**			

Source: EMA[15]

Austria

On 14 February 2022, the Austrian Federal Law Gazette published a law that was adopted by the Austrian Parliament to bring national legislation in line with the CTR. It amends the Austrian Medicines Act and the Gene Technology Act, for the latter it foresees an accelerated procedure for therapeutic applications with genetically modified organisms. The changes to the Austrian Medicines Act allow the inclusion of trial subjects unable to consent if certain requirements are fulfilled and stipulate the requirement for dossiers of multinational trials; multinational trials applications are to be submitted in English while those for national trials can be submitted in English or German. Furthermore, the amendments regulate the interaction between ethics committees and the Federal Office for Safety in Health Care (BASG)[16].

In this context, the Federal Ministry of Social Affairs, Health, Care and Consumer Protection published a list of the ethics committees under the CTR, which constituted themselves as "Platform Ethics Committees"[17]. The platform and the BASG have defined their cooperation in an agreement[18].

In addition, the BASG is consulting with these ethics committees as to whether European templates for national documents ("Part II") in Eudralex Volume 10 need to be supplemented or replaced by national templates. The BASG has published recommendations on its website for the preparation of the CTR, which will be updated regularly. They include, among other things, information on trial sites, the CTIS and relevant training material[19].

France

In February 2022, the French Parliament continued the first reading of a draft law on health innovation, which started in November 2021[20]. Among other measures, the text aims to facilitate clinical trials in ambulatory settings, to link ethics committees to a university hospital, and to centralize the sponsor trial application's submission process to the French National Agency for Medicines and Health Products Safety (ANSM) and the ethics committee via a dedicated portal.

On 6 March 2022, Decree 2022-323 on research involving humans and clinical trials of medicines was published[21]. The legislation contains amendments to the public health code with a view to define the modalities for the evaluation of such applications under the CTR. It also specifies the functioning of ethics committees in France.

On 9 April 2022, France published Order ("Arrêté") of 28 March 2022 that updated the French template agreement for clinical trials[22]. Clinical trials sponsored by commercial actors that take place in healthcare establishments incur costs onto the latter; the template provides the details

for the agreement including the settling of such costs. This latest update aims to better implement data protection rules in the context of clinical trials. The text entered into application on 10 April 2022.

Finally, the ANSM issued a Q&A on the entry into application of the CTR[23] and updated a guidance document on the requirements for and review of clinical trial applications[24].

Germany

German legislators adopted in December 2016 main adjustments for the implementation of the CTR, namely through the Fourth Law on the Amendment of Pharmaceutical and other Regulations. This law regulates in particular adjustments to the Medicinal Products Act and the repeal of the Good Clinical Practice Ordinance, which is no longer in force as of 27 January 2022[25]. Further adjustments were made by the Ordinance of 12 July 2017 on the cooperation procedure between the higher federal authorities and the registered ethics committees in the evaluation of applications for the authorization of clinical trials[26]. In March 2022, the Federal Institute for Drugs and Medical Devices (BfArM) published a list of registered ethics committees and the order in which they are responsible for processing applications for approval of clinical trials[27;28].

In order to support harmonized application by the German federal states, the Federal Ministry of Health, the BfArM and the Paul-Ehrlich-Institut published guidance on timelines and interpretation of the CTR[29]. It includes information to facilitate the distinction of clinical trials, clinical studies and non-interventional studies. Also, any applications for approval of a clinical trial in Germany can be submitted in German or English.

Furthermore, the BfArM published a Q&A and further information on the CTIS[30].

Italy

In 2022, Italy has been continuing its reforms to implement the CTR. On 19 February 2022, Decree dated 30 November 2021 was published in the Italian official journal[31]; the text provides a legal basis for the transfer of data and results generated in the context of non-profit clinical trials to commercial entities in return for monetary payments. The text outlines the requirements for such transfers, notably in the area of data protection.

Separately, new ethics committees of national importance were established via a Decree dated 1 February and published on 16 March 2022[32]. This legislation establishes the “National Ethics Committee for Clinical Trials in Pediatric Setting” and the “National Ethics Committee for Clinical Trials Related to Advanced Therapeutics (ATMPs)” at the Italian Medicines Agency

(AIFA). The text also establishes the "National Ethics Committee for the Trials of Public Research Bodies and Other Bodies of a National Nature", which is in office since March 2022 after the nomination of its members[33]. This new body, formally under the National Health Institute (ISS), replaced the pre-existing ethics committee of the ISS and is in charge of the evaluation of clinical trials falling under the scope of the CTR as well as taking the lead in trials with a national scope[34].

The "national coordination center of local ethics committees for clinical trials concerning medicinal products for human use and medical devices"[35] was established in May 2021 and started its activities in July of the same year. Formally under the AIFA, the center coordinates, directs and monitors the evaluation activities of the ethical aspects relating to clinical trials on medicinal products for human use and medical devices delegated to the local ethics committees. Several documents were published in the first half of this year. A Regulation on the center's function and organization was published in March 2022[36] and a report on its activities was published in July 2022[37]. In addition, the center also issued guidance on collecting informed consent[38], a note inviting to the strict implementation of data protection rules in May 2022[39], and a general FAQ in June 2022[40]. Several contract and other templates relevant to clinical trials under the CTR were also issued in the first half of 2022.

Other EU Member States and European countries

Ireland

In the first half of 2022, Ireland published several pieces of legislation as part of its efforts to implement the CTR. On 4 February 2022, Statutory Instrument (S.I.) No. 41/2022 was published in the Irish official Journal[41]. In addition to implementing the CTR's content, the text sets out the responsibilities of each of the stakeholders and the powers of Ireland's Health Products Regulatory Authority (HPRA) at national level. On the same date, Statutory Instrument (S.I.) No. 43/2022 was also published, it implements several changes to existing rules[42]. On 4 March 2022, Statutory Instrument (S.I.) No. 99/2022 was issued, establishing the National Office for Research Ethics Committees and the National Research Ethics Committees[43].

Spain

In the first half of 2022, the Spanish Agency for Medicine and Health Products (AEMPS) updated and published an English version of its guidance document for conducting clinical trials in Spain. The update concerns 21 questions, which were newly added, updated or "suppressed"[44].

United Kingdom

Due to the timing of Brexit, the CTR was not automatically taken over by the UK as part of the Withdrawal Agreement dated 2020. Prior to Brexit the UK Medicines and Healthcare products Regulatory Agency (MHRA) assured that the UK's clinical trials framework would be aligned with the EU CTR. However, a public consultation on proposals to reform the clinical trials legislation in the UK that took place from January to March 2022[45] seems to indicate otherwise. The proposals are said to be more flexible than the rules contained in the CTR, including in the risk classification of and applicable penalties related to trials.

On 30 June 2022, the MHRA reported on progress made in the implementation of its plan entitled "The Future of Clinical Research Delivery"[46]. As part of the first phase of this plan, a combined review from the MHRA and the UK Research Ethics Service in collaboration with the UK Health Research Authority (HRA) was put in place. It facilitates faster set up for clinical research trials by requiring applicants to only make a single application for both CTA and ethics committee approval. Since January 2022, all new clinical trials of investigational medicinal products in the UK have been benefiting from the combined review, which is reported to have halved the approval time compared with separate applications over the period 2018 to 2021[47].

Phase two of the plan will span from 2022 to 2025. In the second phase, the MHRA reports that it will support risk-proportionate clinical trial conduct and monitoring, including through guidance in the areas of Good Clinical Practice (GCP) and pragmatic investigator guidance, among other measures. A comprehensive reference group will also be established with a view to support the generation of guidance on new legislation and ensure clear regulatory requirements. The latter goal aims to promote the UK's attractiveness for multinational clinical trials. Details on phase 3 of the plan will be issued in 2025 to 2026.

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