Implementation of the EU Clinical Trials Regulation
Update for the Federal Office of Public Health
- August 2017 -

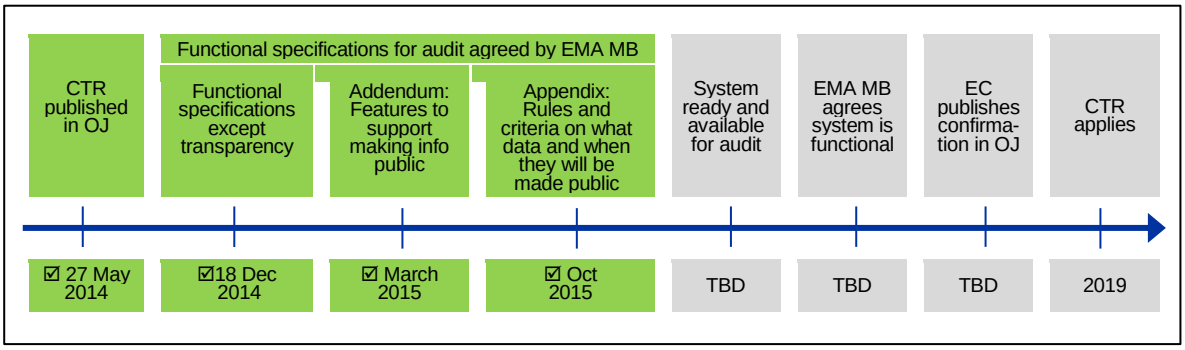
1. EU PORTAL AND EU DATABASE

1.1. EMA process and milestones

As reported earlier, the Management Board of the European Medicines Agency (EMA) announced that the application of the Clinical Trials Regulation (CTR) will be postponed from October 2018 to a still undefined timepoint in 2019. The delay is due to technical difficulties in the implementation of IT systems of the EU portal and the EU database (see report from June 2017).

It is expected that the EMA will in October 2017 communicate more details on the new timelines.

Figure 1: EMA key milestones and timelines for design and development of the EU portal and the EU database



Source: EMA 2017 (CTR: Clinical Trials Regulation; OJ: Official Journal of the EU; EC: European Commission; MB: Management Board)

1.2. EMA stakeholder meeting

The next EU portal and database stakeholders' meeting is scheduled to take place on 3 October 2017.

1.3. Implementation in France

On 22 June 2017, the French National Agency for Medicines and Health Products Safety (ANSM) published an assessment of the first 18 months of its pilot project, which started in September 2015 and aims to prepare for the enforcement of the CTR. It involves ethics committees (ECs) as well as academic and industrial sponsors. A previous assessment that focused on the pilot project's first year was published on 25 January 2017 (see report from February 2017).

This assessment of the first 18 months of the pilot project also includes the legislative and regulatory changes that took place in 2016 following the entry into force of the relevant law on research on human persons (see report from December 2016). These changes resulted in organizational adjustments, including the integration of all 39 French ECs.

In the voluntary pilot project, the ANSM and the ECs undertake to evaluate clinical trials within 60 days and to forward one single notification to the sponsor, including the ANSM decision and the EC's opinion, as required by the CTR.

During the assessment period of the pilot project (September 2015 to March 2017), the average time frame of final notifications for initiation of clinical trials was 65.5 days for those applications that were authorized by the ANSM and that received a positive opinion from the ECs. The assessment highlights that time frames were met at each stage of the process (admissibility, question submission, final notification).

During the first 18 months of the pilot project, 152 applications for clinical trials were received under the pilot project's framework, corresponding to 13.3% of total applications for clinical trials received by the ANSM during the same period. Of the 152 applications received, 128 were completed by the ANSM. Out of these 128 applications, 98 were authorized and 30 closed.

There has been an increase in the percentage of applications received compared to earlier phases of the pilot project. In the first 6 months, the applications received in the context of the pilot project represented 11% of total applications for clinical trials received by the ANSM during the same period. This percentage increased to 12.5% during the first year and reached 13.3% during the first 18 months.

The ANSM highlights that these results show positive trends in four ways:

- Collective adherence and constructive exchanges between the sponsors, the ECs and the ANSM
- Increased sponsors' contribution
- Adjustment of the organizational process following the coming into force of law no. 2012-300 dated 5 March 2012 on research on human persons, and incorporation of all 39 French ECs
- Appropriation of a process moving closer to the planned future organization with enforcement of the CTR

1.4. Implementation in the UK/Brexit

On 14 June 2017, stakeholders of the healthcare sector announced the founding of 'Brexit Health Alliance'. The alliance's membership includes actors from the National Health Service (NHS), patient representatives, medical research institutions, the industry and public health organizations.

In July 2017, the alliance published a list of "collective asks" in the context of the UK's exit from the EU (Brexit). Its stated objectives are fivefold: supporting maximum levels of research and innovation collaboration; ensuring regulatory alignment for the benefit of patients and the public's health; preserving reciprocal healthcare arrangements; ensuring robust coordination mechanisms on public health and wellbeing; and securing a strong funding commitment to the health sector and the public's health.

Among other aspects, the alliance emphasizes that it is important for the UK to be able to participate in EU systems after Brexit, which include the EU portal and database. This continued participation is depicted as a desired outcome of the Brexit negotiations.

This alliance also underlines the necessity for the UK negotiating party to take into account the delay in the implementation of the CTR and its consequences on the regulation of clinical trials in the UK.

Relocation of the EMA

EU countries interested in hosting the EMA had until 31 July 2017 to submit the candidacy of their city (see report from June 2017). In total, the European Council received 19 offers to host the EMA.

The candidates are the following cities:

Amsterdam	Brussels*	Lille	Stockholm
Athens	Bucharest	Malta	Vienna*
Barcelona	Copenhagen	Milan	Warsaw*
Bonn	Dublin*	Porto	Zagreb
Bratislava	Helsinki	Sofia	

*cities that also submitted their candidacy to host the European Banking Authority.

The final decision will be taken in a vote by the 27 EU ministers that will take place on the margins of the General Affairs Council in November 2017.

2. CLINICAL TRIAL SAFETY REPORTING

No update available.

3. ADOPTION OF IMPLEMENTING ACTS, DELEGATED ACTS AND GUIDELINES

3.1. Overview of the status of implementation measures and guidelines

The European Commission provided an update on its website about the status of its implementation measures related to the CTR:

- The Commission Delegated Act specifying principles of and guidelines for Good Manufacturing Practice (GMP) for investigational medicinal products and arrangements for inspections was adopted by the European Commission on 23 May 2017 and is expected to be published during the second semester of 2017.
- The Commission guidelines on GMP for investigational medicinal products are expected to be adopted during the second semester of 2017.

Table 1 below gives an overview of the current status of implementation measures undertaken by the European Commission and includes a guideline drafted by the EMA (see also report from June 2017).

Table 1: overview of implementation measures and guidelines

Document	Art. CTR	Status
Commission Delegated Act specifying principles of and guidelines for Good Manufacturing Practice (GMP) for investigational medicinal products and arrangements for inspections	63	• The text was adopted by the European Commission on 23 May 2017 and was under the scrutiny of the European Parliament and the Council until 23 July 2017. The publication is expected for the second semester of 2017
Commission guidelines on GMP for investigational medicinal products	63 (1)	• The guidelines are currently at the stage of preparation for the European Commission adoption procedure. The publication is expected to take place during the second semester of 2017
Commission Implementing Regulation on the detailed arrangements for Good Clinical Practice (GCP) inspection procedures including the qualification and training requirements for inspectors	78 (7)	• The final version was adopted on 24 March 2017 and published on 25 March 2017 in the Official Journal of the European Union

EMA draft guideline for the notification of serious breaches of the CTR or the clinical trial protocol	52	• The EMA put a draft guideline for the notification of serious breaches of the CTR or of the clinical trial protocol to public consultation from 23 May to 22 August 2017. Article 52 of the CTR requires the sponsor to notify the EU Member States concerned of any serious breach of the CTR or of the trial protocol
Commission guidelines on voluntary sharing of raw data	37 (4)	• The guidelines are currently in their inception phase. Their adoption is expected to take place at the end of 2018
Commission Implementing Act on the rules of cooperation of the Member States in the assessment of safety reporting information	44 (2)	• The European Commission will consider, in consultation with EU Member States, the necessity of an implementing act once the CTR becomes applicable. No target date is officially announced
Report to the European Parliament and to the Council on the application of the CTR	97	• The report will be sent 5 years from the day of entry into application of the CTR

3.2. Guidance documents

Four guidance documents were put to public consultation by the European Commission from 1 June to 31 August 2016 (see report from July 2016). On 7 August 2017, the European Commission made available the comments and replies received. Table 2 provides an overview of the results following the public consultation on guidance documents published by the European Commission.

Table 2: results from the public consultation

Draft guidance documents	Summary of public consultation
Definition of investigational medicinal product and use of auxiliary medicinal products	• 26 contributors • Comments and remarks as well as responses to questions asked by the Commission included the following topics: definition of investigational medicinal product (IMP) and use of auxiliary medicinal products (amps); medicinal products intended for research and clinical trials and investigational medicinal products (IMPs); requirements for AMPs, documentation requirements in the application dossier; and safety reporting • Comments and replies were published on 7 August 2017 and are available here
Ethical considerations for clinical trials on medicinal products conducted with minors	• 30 contributors • Comments and remarks as well as responses to questions asked by the Commission included the following topics: shortening of the text; readability and accessibility for various stakeholders; requests for overviews of EU Member State characteristics; requests for describing exceptions to the provided guidance; requests for detailed practical instructions beyond ethical considerations; requests for clarification and suggestions for rewording; definitions of assent, agreement and dissent; staggered approach; the situation when the minor becomes legally competent to give consent; trials with adolescents; and lay summary, understandable for the trial participants • Comments and replies were published on 7 August 2017 and are available here

Risk proportionate approaches in clinical trials	• 40 contributors • Comments and remarks as well as responses to questions asked by the Commission included the following topics: risk adapted approach; reorganization of the risk based quality management section; alignment of the terminology with the Integrated Addendum to ICH E6; clarification on the term 'risk assessment and mitigation plan'; clarification on the requirements for centralized monitoring; clarification on the application of risk adapted approaches to source data verification; inclusion of examples in the section on the Trial Master File content; considering more examples, for illustrative purposes; and editorial changes for consistent use of terminology and clarity purposes • Comments and replies were published on 7 August 2017 and are available here
Summary of clinical trial results for laypersons	• 46 contributors • Comments and remarks as well as responses to questions asked by the Commission included the following topics: terminology to clarify meaning or provide plain language versions; writing complex concepts in plain language; areas of duplication, health literacy principles and writing style; visuals; and template • Comments and replies were published on 7 August 2017 and are available here

4. BACKGROUND

4.1. EU Clinical Trials Regulation

In the future, clinical trials in the EU will be uniformly regulated by the EU Regulation (No 536/2014) on clinical trials with medicinal products (CTR). Under the CTR, the authorization procedure will be harmonized in the EU. According to the current Clinical Trials Directive (2001/20/EC), sponsors of a multinational clinical trial must submit separate applications to the authorities and ethics committees of each participating EU Member State, in the local language and with different application forms.

In the future, one single application per multinational trial will be submitted by the sponsor via an online portal (EU portal) run by the EMA. The CTR entered into force on 16 June 2014 and will apply as soon as the EU portal is fully functional.

4.2. Implementation of the CTR

After the CTR's entry into force on 16 June 2014, the following implementation work is envisaged:

- **EU portal and EU database:** in collaboration with the EU Member States and the European Commission, the EMA will set up and maintain an EU portal and an EU database at Union level. Furthermore, it will draw up the functional specifications for the portal and database, together with the time frame for their implementation (Articles 80 - 82 CTR).
- **EudraVigilance database:** the EMA will set up and maintain an electronic database for safety reporting (Article 40 CTR), which would be a module of the existing EudraVigilance database.
- **Secondary legislation:** the Commission has the power to adopt implementing acts, delegated acts (Chapter XVII of the CTR) and guidelines.

5. SOURCES

- Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), Enforcement of the European regulation on clinical trials on medicinal products: assessment eighteen months into the pilot phase, June 2017; http://ansm.sante.fr/content/download/106823/1353815/version/1/file/European-regulation_EC_Phase+pilote_Bilan+-june2017.pdf, last accessed on 23 August 2017.
- Brexit Health Alliance, Collective "asks" as the UK negotiates to exit the EU, July 2017; http://www.nhsconfed.org/~/media/Confederation/Files/public access/European Office/Brexit Health Alliance Asks.pdf, last accessed 23 August 2017.
- Commission Delegated Regulation (EU) of 23.5.2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections, C(2017) 3368 final; https://ec.europa.eu/info/law/better-regulation/initiative/27612/attachment/090166e5b2836df7_en, last accessed on 23 August 2017.
- Commission Implementing Regulation (EU) 2017/556 of 24 March 2017 on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council, 2017 OJ L 80/7; http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0556&qid=1493034821578&from=EN, last accessed on 23 August 2017.
- European Commission, Implementation measures by the Commission in the context of Regulation (EU) No 536/2014 – overview and state of play; https://ec.europa.eu/health/sites/health/files/files/clinicaltrials/implementation_measures_v2.pdf, last accessed on 23 August 2017.
- SFL Intelligence.