

Implementation of the EU Clinical Trials Regulation

Update for the Federal Office of Public Health

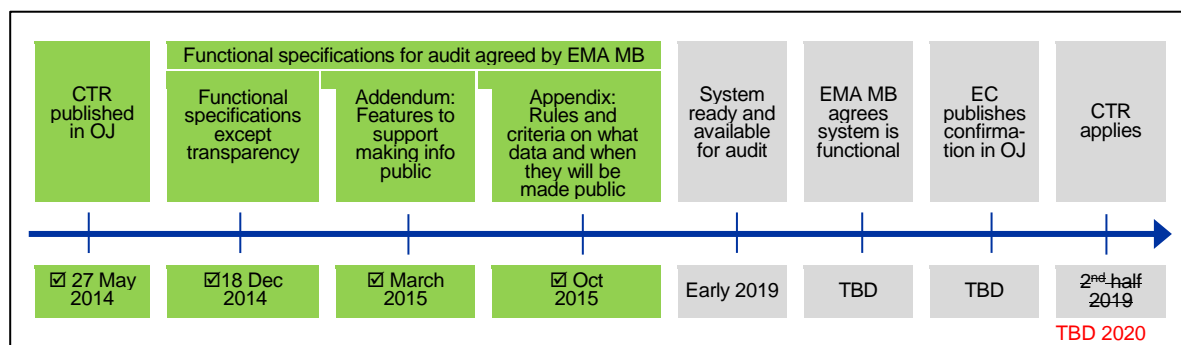
- August 2018 -

1. EU PORTAL AND EU DATABASE

1.1. EMA process and milestones

At its June 2018 meeting, the EMA Management Board confirmed that the auditable version of the EU portal and database (release 0.7) should be available for audit in early 2019 (see report from April 2018) but could be subject to further changes due to the relocation of the EMA from London to Amsterdam (refer to section 1.8). The audit report can be expected 4 to 5 months later. Consequently, the entry into application can be expected to be further pushed back to 2020; this date is also reflected on Belgium's Federal Agency for Medicines and Health Products (FAMHP) [webpage](#). Release 0.7 is reported to be in an intensive phase of testing and its release should take place in November 2018. It has been scheduled in such a way to allow for the relocation of the development data center to Amsterdam before the start of the user acceptance testing (UAT) 7 (refer to section 1.3).

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



Source: EMA 2018 (CTR: Clinical Trials Regulation; OJ: Official Journal of the EU; EC: European Commission; MB: Management Board) *red: updated timelines*

The EMA Management Board was also presented with a report on the implementation of the EU portal and database. In the context of its implementation, the portal and database are referred to by the EMA as the Clinical Trials Information System or CTIS. Notably, it was reported that a new project governance structure was endorsed in March 2018, resulting into the definition of three decision-making groups: the CTIS Expert Group, which can appeal to the EU CTR Coordination Group, the latter that reports in turn to the EMA Management Board.

1.2. External review of the implementation of EU IT systems required by the CTR

In addition, the EMA Management Board also discussed the findings and recommendations provided by an independent contractor as part of the first of 3 phases of the external review of the CTIS project, which aims to provide an “independent project assurance to [its] implementation”.

This report covered 6 topics: accountability, feasibility, purpose and specifications, users' and stakeholders' engagement and change management, expectation management and risk management. Among other aspects, the following issues are especially relevant:

- Governance structure: it is considered that modifying the new governance structure endorsed in March would be of no added value but that the mandates of the different governing bodies need to be clarified.
- Project planning and release schedule: it is reported that the complexity of the project was initially underestimated and it was recommended to further review its feasibility during the second phase of the external review process, together with an assessment of the impact of EMA's relocation to Amsterdam. To clarify the scope of the project, it was proposed to draft a new release plan to be approved by the Steering Committee and the EU CTR Coordination Group, and later endorsed by the EMA Management Board. It is recommended that all functionalities that are not strictly required to go live should be scheduled for later releases.
- Gap analysis: the EMA Management Board was invited to request the contractor who implements the portal and database to quantify the capacity gap and to assess the quality management during phase 2 of the review.

1.3. User acceptance testing

An EU portal and Union database stakeholder meeting was held at the EMA offices on 25 April 2018. Items on the agenda included an update on the planning of UAT 7, which will take place from 5 to 30 November 2018 (once the relocation of the data center has been completed) and consists of a realistic dummy trial conducted both through on- and off-site testing. The date of the next face-to-face stakeholder meeting was confirmed to be 26 September 2018.

1.4. Implementation in Belgium

In June 2018, the FAMHP provided an overview of its pilot project. It reported that 18 Ethics Committees (ECs) are currently involved in the project and that 6 ECs volunteered to participate in a working group with the college and FAMHP. The college, which was created by law in May 2017 (see report from June 2017), coordinates all accredited ECs and acts as a contact point between them and the FAMHP (see report from April 2018). It was also reported that approximately 10 pilot trials were finalized in 2017 and that this number is likely to be higher in 2018 and 2019. The agency expects the CTR to enter into application in 2020, as reported on its [webpage](#).

In addition, the FAMHP published a [new version](#) of the guidance in May 2018, which is addressed to stakeholders interested in taking part in the pilot project. The document was developed in collaboration with the college of ECs.

1.5. Implementation in France

In June 2018, the French National Agency for Medicines and Health Products Safety (ANSM) published an updated version of its guidelines for sponsors taking part in its pilot project. The ANSM previously reported on various occasions about its pilot project, which started in 2015 (see reports from February, August and December 2017).

1.6. Implementation in Germany

In May 2018, the German Federal Institute for Drugs and Medical Devices (BfArM) published guidelines for sponsors taking part in its pilot project (in [German](#) and [English](#)). The German pilot project started in October 2015 (see report from May 2016 and April 2018).

1.7. Implementation in Hungary

On 14 June 2018, the Hungarian National Institute of Pharmacy and Nutrition indicated that Hungary is taking steps to adapt its clinical trial authorization procedure ahead of the CTR's implementation. Clinical trials applicants may take part in the so-called "VHP+PILOT" procedure, which is based on the EU Voluntary Harmonization Procedure (VHP) for clinical trials authorization. The communication reports that the Hungarian Medical Research Council was to emit a final

decision on this matter.

1.8. Implementation in the UK/Brexit

This section gives an overview of recent developments on four themes and highlights their relevance in relation to the CTR, i.e. UK's clinical trials pilot project, the negotiation of a transition deal between the UK and the EU, the future relationship between both parties and the relocation of the EMA from London to Amsterdam.

UK's pilot project

In a communication last updated on 13 August 2018, the UK National Health Service (NHS) Health Research Authority (HRA) indicated that a pilot project entitled the "combined ways of working pilot" was initiated in collaboration with the UK Medicines and Healthcare products Regulatory Agency (MHRA). The pilot aims to improve the approval and ongoing management of clinical trials for medicinal products and is reported to involve a single dossier submission, combined communications to request information and a single final decision. The communication highlights that only "certain" ECs are currently involved in the pilot but that their number is increasing. The communication also includes a number of related documents including an [FAQ](#), an [application dossier guidance](#) and [instructions to sponsors](#).

Negotiations for a deal on a transition period

Intense negotiations between the UK and the EU are currently ongoing with the aim of agreeing on a "withdrawal deal". If the negotiation is successful, both parties would agree on the details of a transition period spanning from 30 March 2019 to 31 December 2020. This potential deal would mean that the CTR, if it enters into application before the end of the transition period, would be implemented into UK law through the EU withdrawal bill (or 'Brexit bill').

The UK also stepped up preparations for a "no-deal" scenario and published several technical notices addressed to individuals and businesses on 23 August 2018. The [notice](#) relevant to clinical trials highlights, among other things, the following consequences in case of "no-deal": clinical trials would be managed nationally in the UK, the CTR would not be incorporated into UK law as part of the Brexit bill given that the CTR is not set to enter into application before 30 March 2019.

In an update focused on the CTR published on 6 August 2018, the MHRA emphasized the government's intention to keep UK's legislation in the area of clinical trials aligned with that of the EU in case of a "no-deal" outcome. This position was also supported by an amendment to the UK's Brexit bill passed in April 2018 (see report from April 2018).

Whether the UK can use the CTR's EU portal and database and participate in the single assessment model depends on additional agreements between the EU and the UK irrespective of a "deal" or a "no-deal scenario".

Future relationship between the UK and the EU

The future relationship between the UK and the EU will be defined in an agreement that remains to be negotiated. In a communication published in July 2018, the European Commission reported that both parties "have started to discuss the content of a political declaration which would set out an overall understanding on the framework for a future relationship". In its update on the CTR published on 6 August 2018, the MHRA highlights that this agreement will be instrumental in determining whether the UK can use the EU portal and database and participate in the single assessment model.

In a [position paper](#) published in July 2018, the UK outlined how it wants this relationship with the EU to look like. Among other aspects, the UK would like to have an agreement that allows it to be an active member of the EMA and to take part in the "incoming clinical trials framework". The UK's participation in the EMA remains to be agreed by both parties as part of the agreement. The European Council has made clear in its "guidelines on the framework for the future EU-UK relationship" that the future relationship cannot offer the same benefits as an EU membership and that the UK as a third country cannot be involved in the decision-making of EU agencies.

Relocation of the EMA

The relocation may have an impact on the conduct of the audit described in section 1.1, which is set to start in March 2019. At its Management Board meeting in June 2018, the EMA communicated that planning adjustments were underway but were said to be expected not to have a major impact on the EU portal and database's implementation timeline. However, the Board also stated that "further impact" of the relocation will be monitored especially for aspects such as the loss of more staff than anticipated, which may have a greater impact on the general project timeline. The EU portal and database's implementation is a priority in the EMA's continuity plan. The EMA will only give an update on the timeline after the audit has taken place.

2. CLINICAL TRIAL SAFETY REPORTING

As part of the CTR's implementation, the EMA implements an electronic database for the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) and for the Annual Safety Reports (ASRs), which is a module of the existing EudraVigilance database (EVCTM) (see report from April 2018). In a document published in June 2018, the EMA reported that functionalities meant for the forwarding of SUSARs from the EVCTM to EU Member States concerned are already in place and only require to be "switched on" once the CTR enters into application. It is also reported that relevant guidance documents will be published in a staggered approach. Separately, the EMA Management Board was informed that the preparations for the development of safety reporting has started and that it will be part of release 0.9.

3. ADOPTION OF IMPLEMENTING ACTS, DELEGATED ACTS AND GUIDELINES

3.1. Overview of the status of implementation measures and guidelines

In April 2018, the European Commission released a draft [Q&A document](#) addressing a broad range of topics relevant to the CTR. Note that the document is not yet complete as it is still being discussed by the "Expert group for clinical trials", which is chaired by the Commission and composed of representatives of all EU Member States and EEA contracting parties.

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 timeframe 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.

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