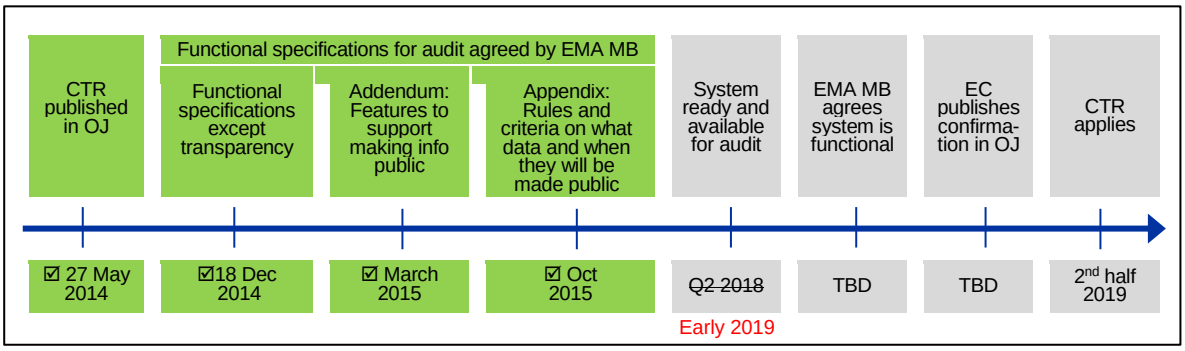
Implementation of the EU Clinical Trials Regulation
Update for the Federal Office of Public Health
- April 2018 -

1. EU PORTAL AND EU DATABASE

1.1. EMA process and milestones

At its March 2018 meeting, the Management Board of the European Medicines Agency (EMA) announced that the auditable version of the EU portal and database (release 0.7) should be available for audit in early 2019. It was also confirmed that release 0.6 was received and met the acceptance criteria. It was added that more detailed information on the timelines would be communicated after the above-mentioned audit.

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

1.2. User acceptance testing

An EU portal and Union database stakeholder meeting was held at the EMA offices on 7 February 2018. Items on the agenda included an update on user acceptance testing (UAT) 6 as well as an update on the implementation of aspects related to the portal and safety reporting (see annex 1).

UAT 6 included a total of 35 individual testers for on-site testing and 22 entities for off-site testing, including representatives from sponsors and EU Member States. The on-site testing focused on interactions between EU Member States and sponsors as part of specific scenarios while the off-site testing included the conduct of test scenarios by testers within each involved sponsor and EU Member State. Participants helped identify 456 issues and were also requested to rate different aspects of the portal in terms of (1) their own satisfaction, (2) the portal's usability and (3) design.

In addition, the dates of the next face-to-face stakeholder meetings were announced to take place on 25 April and 26 September 2018.

1.3. Training environment of the EU portal and database

The EMA gave an update on the training environment of the EU portal and database at its stakeholder meeting dated 7 February 2018. A broad introduction on this environment was first given in 2017 (see April 2017 report). The approach adopted to design the training environment consists of 4 dimensions (see details in figure 2): E-learning, guidance documentation, webinars and face-to-face trainings (see annex 2).

Figure 2: Four dimensions of the EU portal and database training environment

E-learning	Delivery format: – Most of the trainings will be delivered via **information videos** produced by the EMA – There should be approximately **15 modules**	Timelines: – The videos will be released over the course of **2018 and 2019** on the EMA's website and the Network Training Centre (NTC) website
Users guides / supporting documents	Delivery format: – Guidance documents and user guides will provide insights on how to use the system, taking a **step-by-step** approach – Documents will be available on the **EMA's website** as well as in the form of **contextual help** on the EU portal and database	Timelines: – No timelines available
Webinars	Delivery format: – Webinars will be organized for **sponsors**/Marketing Authorization Holders (**MAHs**) and **Members States** – These stakeholders will be able to send **questions** at the latest 10 days beforehand	Timelines: – The webinars will be organized between **Q4 2018 and Q1 2019**
Face-to-face	Delivery format: – Face-to-face trainings will be provided to **Member States** and **industry stakeholders** – A "**lead**" **trainer**, who will be in a position to disseminate knowledge in his/her organization, will be trained	Timelines: • No timelines available

Source: EMA, EMA stakeholder meeting, 7 February 2018

The training environment aims to comprehensively address all aspects of the EU portal and database. To that purpose, the EMA defined 8 specific 'training channels':

1. User manual
2. Overview video
3. Step-by-step process video
4. Quick guide
5. In-system help (tool tips)
6. Online presentation
7. Webinar
8. Face-to-face training

1.4. Implementation in EU Member States

On 18 April 2018, the Belgian Federal Agency for Medicines and Health Products (FAMHP) reported on the general state of implementation of the Clinical Trials Regulation (CTR) at the EU Member States' level at the DIA EuroMeeting. Differentiated progress was reported at the EU level on various components of the implementation. Some activities, such as the organization between the national competent authorities and the Ethics Committees (ECs), the enactment of national

laws, and the restructuration of ECs are showing the most progress. Other activities are less advanced, including the adaptation of the national fee structures and IT systems. The least progress was achieved in the area of safety, which still faces major hurdles in most EU Member States (see annex 3). This pattern is consistent with previous reports on progress at the national level (see report from April 2017).

1.5. Implementation in Germany

On 18 April 2018, the German Association of Research-Based Pharmaceutical Companies (VFA) gave an update on the German pilot project for the CTR at the DIA EuroMeeting (see annex 4). Within the framework of this pilot project, the respective responsible EC and the German Federal Institute for Drugs and Medical Devices (BfArM) evaluate applications for clinical examinations together in close accordance with the procedures and deadlines of the EU regulation.

The German pilot project started in October 2015 (see report from May 2016) and currently involves 34 ECs. The table below gives an overview of applications on 20 February 2018 (see figure 3):

Figure 3: Overview of applications in the German CTR pilot project*

Approved applications		Refused applications	Withdrawn applications		Other
Total: 59		Total: 2	Total: 9		Total: 5
Ongoing applications					
Assessment process: 4	Validation process: 2		Withdrawn by EC: 2	Withdrawn by applicant: 7	

*This data reflects the situation on 20 February 2018

Source: VFA, Experiences from the German Pilot as an Example for Challenges for Industry, DIA EuroMeeting, 18 April 2018

Survey conducted with companies

The VFA conducted a survey among its members on the German CTR pilot project between 12 January to 16 February 2018: 19 companies provided feedback, out of which 9 had not submitted any applications and 10 had submitted at least one application to the pilot project. The survey included 54 applications with full data sets, which represents 67% of all applications submitted in the context of the German pilot project.

Companies that completed applications highlighted that the pilot project provided for a solution-oriented collaboration with a clear focus on essential aspects during the evaluation phase. Contact persons at BfArM and the concerned ECs were also said to be easily reachable by email or phone. The survey reports that, under the process of the pilot project, the cooperation between ECs and the higher federal authorities was very good. The process also allows for the participation of local ECs and has worked well. The survey indicates that sponsors need to adapt their internal processes as well as coordination with external stakeholders (e.g. contract research organizations) to keep up with the involved timelines. Taking part in the pilot project has helped sponsors prepare for the CTR. Sponsors' preparedness is deemed a crucial factor in the success of their applications to the pilot project.

Based on its observations in the survey, the VFA considers Germany to be well prepared for the CTR.

Learnings from the pilot project's new authorization system

Surveyed sponsors reported that the authorization system under the CTR avoids contradictory objections between the ECs and the German federal authorities. Consolidated deficiency notices

or substantive queries at the national level are very helpful. However, internal processes in place in the sponsors' organizations are often not yet adapted to the CTR's authorization system.
Short deadlines for the internal coordination of responses are very challenging for the sponsors and surveyed companies underlined that it may lead to lower-quality responses to questions from authorities / ECs.

1.6. Implementation in Belgium

On 18 April 2018, the FAMHP gave an update on the implementation of the CTR in Belgium at the DIA EuroMeeting (see annex 3). The Belgian pilot project was announced in January 2017; while the procedure to authorize trials follows the Belgian national legislation of 7 May 2004, the dossier structure and its evaluation follows the spirit of the CTR (see report from February 2017).

Situation in Belgium

In Belgium, the FAMHP acts as national contact point for the CTR. The government set up a "college" that coordinates all accredited ECs and acts as contact point between the ECs and the FAMHP. Belgium has deployed a strategy that aims to involve all stakeholders, which includes: regular meetings involving the FAMHP, ECs, and the "college"; frequent updates made to guidance documents for sponsors; and information sessions organized for sponsors and ECs involved in the pilot project. Notably, it was also reported that the FAMHP was planning to involve patient representatives in the assessment of clinical trials, both before and during the assessment.

The FAMHP reported that 19 sponsors submitted applications for initial clinical trials. It also reported that final decisions were reached on 13 applications (including applications both for initial clinical trials and substantial modifications), while 3 are still under assessment and 8 are planned.

Planning ahead, the FAMHP also announced a series of measures in the context of the national implementation of the CTR. Such measures notably include the handling of applications and substantial amendments at no fee in order to create a positive incentive, the creation of a national database for healthy volunteers, and the continuation of the campaign aimed to create awareness of clinical trials among citizens and general practitioners.

The FAMHP presented some of the challenges identified in a survey conducted among stakeholders, which include:

- The full correspondence between sponsors and the "college" and between the FAMHP and the ECs is reported to be very intense as it is currently a manual process
- The processing of initial dossiers in the context of the pilot project requires more efforts
- ECs reported that they struggled with the timelines
- Sponsors reported that it was difficult to keep up with the timelines

The opportunities identified by stakeholders during the survey include the following points:

- Sponsors appreciate the fact there is a single point of contact and only one application to be submitted for trials with multiple sites
- ECs found positive to have one point of contact (i.e. the "college")

1.7. Implementation in the UK/Brexit

The implementation of the CTR in the UK was discussed at a sitting of the House of Lords dedicated to the EU withdrawal bill (or 'Brexit bill') that took place on 18 April 2018. During the debates, Baroness Annabel Goldie gave reassurances about the commitment of the UK government to implementing the CTR. Baroness Annabel Goldie also declared that if the CTR failed to come into application by March 2020, when the UK is set to leave the EU, "the Government will seek to bring into UK law all relevant parts of the EU regulation that are within the UK's control". An amendment meant to ensure the enactment of the CTR in UK law was made and later withdrawn after reassurances were provided by the government Minister.

Relocation of the EMA

On 5 March 2018, the EMA published an interactive tool to help with the monitoring of the relocation of its offices to Amsterdam. EMA offices will first be temporarily relocated in a building as the final premises will not be ready on time. The document shows that the final relocation will only be completed on 31 December 2020.
As mentioned in the previous report (see report from December 2017), there is concern that the relocation process may result in the disruption of certain EMA activities although it is yet unclear how this might affect the implementation of the EU portal and database.

2. CLINICAL TRIAL SAFETY REPORTING

In 2014, the EMA established subgroups for expert stakeholders to give input on the Clinical Trial Application (CTA), the CTA dossier, user rights and process workflow (see report from September 2014). These subgroups were later reorganized (see report from June 2015).

At its stakeholder meeting dated 7 February 2018, the EMA gave an update on the activities conducted by subgroup 6, which is concerned with the implementation of safety. Five meetings involving subgroup 6 took place between October 2017 and February 2018, addressing topics such as the submission of Annual Safety Updates (ASRs) and the remaining safety-related issues to be addressed in the EU portal and database. The subgroup will also help identify priorities for functionalities to be implemented after release 0.9.

3. ADOPTION OF IMPLEMENTING ACTS, DELEGATED ACTS AND GUIDELINES

3.1. Overview of the status of implementation measures and guidelines

In January 2018, the detailed Commission guidelines dated 8 December 2017 on good manufacturing practice (GMP) for investigational medicinal products was published by the European Commission (see table 1).

In addition, the guidance on summaries of clinical trial results for laypersons was published by the European Commission in February 2018 (see table 1). The publication of this document follows a public consultation that took place from June to August 2016 (see reports from July 2016 and August 2017).

Table 1: Overview of implementation measures and guidelines (updates in red)

Document	Art. CTR	Status
Commission Delegated Regulation (EU) 2017/1569 specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections	63	• The final document was published in the Official Journal of the European Union on 16 September 2017
Commission guidelines on GMP for investigational medicinal products	63 (1)	• The final version dated 8 December 2017 was uploaded on the European Commission's website in January 2018
Commission Implementing Regulation (EU) 2017/556 on the detailed arrangements for the good clinical practice inspection procedures	78 (7)	• The final version was published on 25 March 2017 in the Official Journal of the European Union (see report from October 2017)
EMA Draft Guideline for the notification of serious breaches of the CTR or the clinical trial protocol	52	• Based on the public consultation on the draft guideline, which was closed on 22 August 2017 (see report from October 2017), the EMA will finalize and adopt the document

Commission guidelines on voluntary sharing of raw data	37 (4)	• The guidelines are in their inception phase. Their adoption is expected to take place at the end of 2018 (see report from October 2017)
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 (see report from October 2017)
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 (see report from October 2017)
Summaries of clinical trial results for laypersons	Annex V	• The final version of the guideline was published on 22 February 2018

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.

5. SOURCES

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