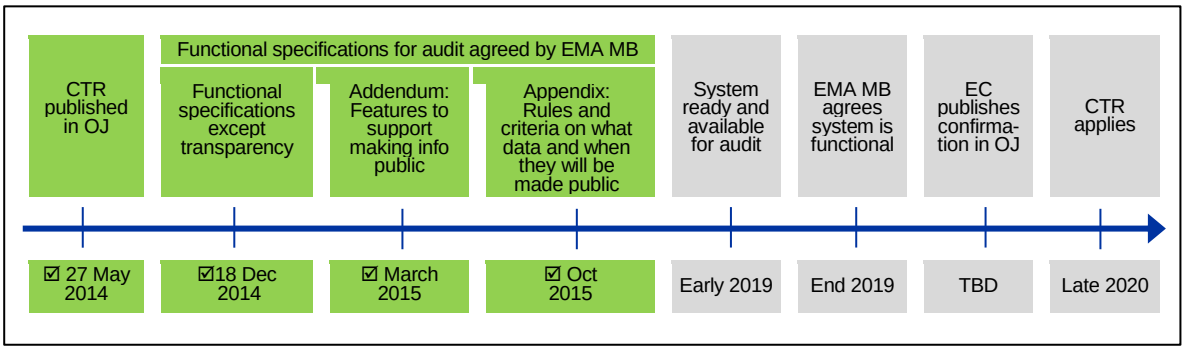
Implementation of the EU Clinical Trials Regulation
Update for the Federal Office of Public Health
- April 2019 -

1. EU PORTAL AND EU DATABASE

1.1. EMA process and milestones

At its December 2018 meeting, the EMA Management Board was informed that the delivery of the system for the User Acceptance Testing 7 (UAT 7) of release 0.7 was significantly delayed. Release 0.7 (which is the auditable version of the Clinical Trials Information System (CTIS), formerly referred to as the EU portal and database) is not ready for a full UAT. At its March 2019 meeting, the EMA Management Board reported that further announcements will be made before UAT 7 starts.

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



Source: EMA 2019 (CTR: Clinical Trials Regulation; OJ: Official Journal of the EU; EC: European Commission; MB: Management Board)

In December 2018, the EMA Management Board endorsed recommendations presented by the EU clinical trials regulation (CTR) Coordination Group in order to mitigate potential further delays. The Coordination Group was introduced as a result of the revision of the governance structure of the CTIS implementation process decided in March 2018 (see report from August 2018). These recommendations were presented and discussed along with the update on the general state of implementation of the CTIS.

The high number of bugs and issues, which could cause further delays in the CTR's implementation, prompted the Coordination Group to suggest the following recommendations:

- The current delivery approach of the CTIS be modified, with a requirement that changes are made to the team of the IT contractor. The Coordination Group identified that key factors for the success of this new approach are, among other things, strict adhesion to timelines, an adjustment of the working methodology to make it a transparent iterative process and to enable greater involvement of end-users, and an increased monitoring of progress by a small sub-group of the EU CTR Coordination Group.
- The overall progress achieved through the implementation of these changes will be assessed by the EMA Management Board.

- Supported by the Commission, the EMA was tasked with preparing a fallback solution in case such progress is deemed insufficient.

At its March 2019 meeting, the EMA Management Board reported that the restructuring of the CTIS delivery contract will allow the system to enter a phase of iterative, agile development as of June 2019.

Separately, the Belgian Federal Agency for Medicines and Health Products (FAMHP) reported on 23 January 2019 that the EMA is preparing a list containing future CTIS change requests based on the feedback received during UAT 6 and through workshops held with Member States. Such changes are prioritized following the "Moscow Technique", i.e. requests are grouped in Must haves, Should haves, Could haves, Would not haves. The FAMHP reported that this exercise has already been repeated several times.

1.2. User Acceptance Testing

A pre-UAT of release 0.7 was conducted in November 2018. Spanning from 5 to 13 November 2018, this exercise involved, among other actors, representatives of Member States, sponsors and developers. These stakeholders were able, for the first time, to complete end-to-end business scenarios and to discuss their findings directly with developers. This pre-UAT round helped identify bugs and issues; in view of their large number, the delivery of the system for the UAT 7 was significantly delayed, as reported in section 1.1.

Separately, the FAMHP provided details on the characteristics of UAT 7 in a presentation dated 23 January 2019. This round of testing will consist of two weeks of on-site and four weeks of off-site testing. The latter, whose findings will also be taken into account during the audit, is designed to test scripts that cannot be covered during the on-site testing due to limited time resources. The scripts, which were being finalized in January 2019, required a substantial amount of work. They are said to cover steps from the initial submission to the publication of clinical trials and to reflect “daily work” conducted in the CTIS, including substantial modifications and the adding of an extra Member States in a given trial.

1.3. Implementation in Belgium

On 23 January 2019, the FAMHP reported on its CTR pilot project. A new version of the guidance document dated 25 February 2019 for sponsors taking part in the Belgian CTR pilot was released.

Figure 2: Overview of mean total timelines (between submission and final decision or until all conditions met) of the FAMHP pilot project*

Phases	Number of applications	Average timeline from submission to final decision**	Average timeline from submission to fulfilment of all conditions**
Initial applications			
Phase I	8	38	54
Phase I ATMP	1	66	66
Phase II-IV	29	54	62
Applications for substantial modifications			
Phase I	2	23	23
Phase I ATMP	2	23	23
Phase II-IV	35	29	36

*This data reflects the situation on 31 December 2018; **Reported in number of days

Source: FAMHP, The BE CTR Pilot Project, 23 January 2019 (ATMP: Advanced Therapy Medicinal Product)

The main changes implemented in the document concern aspects such as: the role of the clinical trials site in the submission process, data protection based on the EU General Data Protection Regulation, and the timelines for multiple types of trials.

The FAMHP reported on its pilot activities until the end of 2018: 77 final decisions were issued over the course of the years 2017 and 2018, comprising 38 related to initial dossier applications and 39 to substantial modifications. Of note, 31 of the 38 initial dossier applications were processed in 2018. It was also reported that nine decisions were under review in January 2019 and that ten initial applications were planned to be reviewed in February 2019.

The FAMHP also reported on the average applications processing timelines, which are summarized in figure 2. By the end of this year, the FAMHP aims to have accrued 50% of all clinical trials applications to be submitted as part of the pilot.

1.4. Implementation in France

On 19 February 2019, the French National Agency for Medicines and Health Products Safety (ANSM) announced that it extended its fast track clinical authorization program to ATMPs. This fast track program was launched in October 2018 in order to improve application processing times and to prepare for the CTR's coming into application (see report from December 2018). An updated guidance document for applicants was released on 15 February 2019.

1.5. Implementation in Germany

The German Federal Institute for Drugs and Medical Devices (BfArM) released an update on its pilot project in view of preparing for the implementation of the CTR. The German pilot started in October 2015 (see report from May 2016, April and August 2018 for interim details on the pilot). BfArM reported that, in view of gaining experience in clinical trials cooperation at the European level, it and German ECs will cooperate with the Austrian Agency for Health and Food Safety (AGES). A joint evaluation of two pilot procedures is to be carried out; each country will take the lead of one procedure. The agencies were seeking interested sponsors.

1.6. Implementation in Italy

In February 2019, a draft decree was approved by the Italian Government in view of, among other things, adapting the Italian legislation to the CTR. This draft decree implements law No. 3/2018 on clinical trials of medicines for human use, which entered into force on 15 February 2018, and gave the mandate to the Italian authorities to legislate on the matter. The text was still to be discussed by the Italian Parliament at the time.

1.7. Implementation in the UK/Brexit

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

UK's pilot project

The UK National Health Service (NHS) Health Research Authority (HRA) is running a pilot project entitled the "combined ways of working pilot" (see report from August and December 2018). It reported on its website in its last update on 5 April 2019 that ten ECs are participating in the pilot. In addition, the NHS HRA updated several documents and pages, including its FAQ on the pilot project and its application dossier guidance for sponsors.

Outlook on a possible transition period

Amid the uncertainty surrounding the details of Brexit, the UK released various documents to address the topic of clinical trials. In guidance published on 20 March 2019, the UK Government emphasized that, if the CTR does not enter into application before it leaves the EU, it "will align where possible with the CTR without delay when it does come into force in the EU, subject to parliamentary approval". The document also reports that the UK will have its own equivalent clinical trials "hub" by the time the CTIS goes live. In a separate guidance first released on 3 January 2019, the UK

Medicines and Healthcare products Regulatory Agency (MHRA) states that, in a no-deal scenario, the UK "will re-align with the parts of the EU's CTR legislation that are within the UK's control". The public commitment to aligning with the CTR follows the publication of a policy paper on 22 February 2019 by the UK Department of Health and Social Care that recommends, among other things, that the UK should "explicitly commit to introducing the clinical trials transparency requirements" laid out in the CTR.

In the context of its preparation for a possible no-deal scenario, the UK also released contingency legislation on 24 January 2019 covering, among other things, clinical trials in the UK.

On 10 April 2019, the EU agreed to postpone the Brexit date until 31 October 2019. The UK could also leave the EU earlier, should its Parliament pass the current withdrawal agreement, although it is worth noting, this has already been rejected three times. In addition, if the UK is still a Member of the EU on 23-26 May 2019 (the date of the European Parliament elections) and has not ratified the withdrawal agreement by 22 May 2019, it will be required to leave the EU on 1 June 2019, if it does not hold elections to the European Parliament.

Future relationship between the UK and the EU

At the time this report was prepared, talks were ongoing in the UK and the EU on the possibility of implementing changes to the political declaration on the future relationship between the EU and the UK, endorsed by the European Council on 25 November 2018. The declaration provides an outline of the principles that will govern the relationship between both parties after a potential transition period (see report from December 2018). The formal negotiation process will commence as soon as possible after the UK's withdrawal from the EU. It is worth noting that the EU's chief Brexit negotiator, Michel Barnier, has made clear that the beginning of the talks on the future relationship is conditional to finding a satisfactory solution to the border issue between Ireland and Northern Ireland. The agreement on the future relationship will have a direct impact on how and when the UK will be able to cooperate with the EU in the area of clinical trials, following Brexit.

Relocation of the EMA

Since 11 March 2019, the EMA operates from its temporary location, the Spark building, in Amsterdam (see report from December 2018). In its business continuity plan released on 23 January 2019, the EMA highlights that projects with legal deadlines, such as clinical trials, are matters of its highest priority. It is unclear how this may affect the implementation of the CTIS.

2. CLINICAL TRIAL SAFETY REPORTING

At its December 2018 meeting, the EMA Management Board was informed that release 0.9 of the CTIS, which includes functionalities relevant to safety reporting (see report from August 2018), is progressing as originally planned.

3. ADOPTION OF IMPLEMENTING ACTS, DELEGATED ACTS AND GUIDELINES

On 10 April 2019, the European Commission released a document entitled "Question and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation (GDPR)". In addition to the interplay of the GDPR with the CTR, the document also explains the current situation with the Clinical Trials Directive.

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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