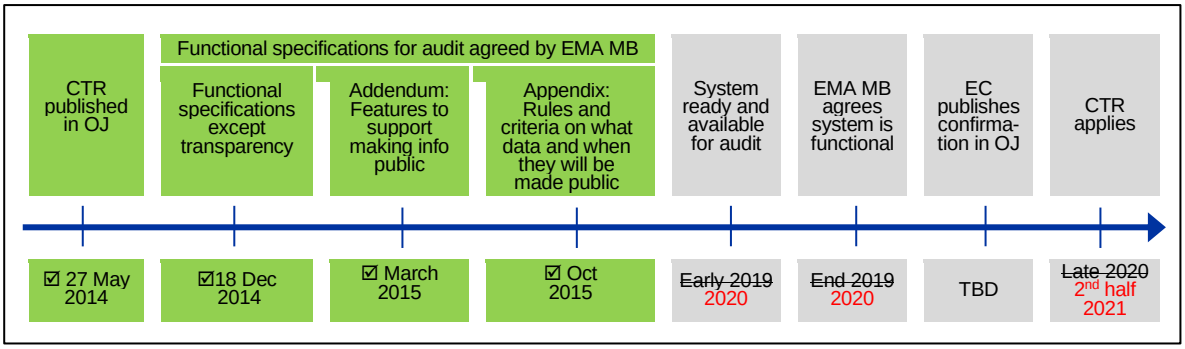
Implementation of the EU Clinical Trials Regulation
Update for the Federal Office of Public Health
- December 2019 -

1. EU PORTAL AND EU DATABASE

1.1. EMA process and milestones

At its October 2019 meeting, the EMA Management Board adopted the EMA mid-year report from the Agency's Executive Director. The document indicates that its project designed to deliver the Clinical Trials Information System (CTIS) (formerly referred to as the EU portal and database) is scheduled to run until 2021. It highlights that the implementation of the CTIS is facing further delays and is now in a "re-planning" phase in view of preparing the CTIS for the independent audit, which is planned for 2020. The causes of such delays reportedly include the change of IT contractor and the introduction of a new working model involving the stakeholders to a greater extent (see report from August 2019) and the large backlog of issues that still needs to be addressed. At its stakeholder meeting dated 25 September 2019, the EMA communicated that it does not yet have a specific date when the auditable version of the CTIS (release 0.7) will be ready for the independent audit. The topic of the audit will be discussed at the meeting of the EMA Management Board taking place from 18-19 December 2019.

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), updated timelines in red

The performance of the IT supplier in charge of delivering the CTIS was discussed in a report, which was presented to and endorsed by the EMA Management Board at its October 2019 meeting. It is reported that the document suggested follow-up actions based on the IT supplier's performance during the first 6 months after hiring, on which the EMA Management Board agreed. These suggestions notably include measures to improve the quality of the work delivered by the supplier and an extension of the monitoring period for at least three releases.

The EMA Management Board was informed that the first release of the CTIS developed following the agile, iterative delivery model contained 79 items, which were all validated in September 2019. Areas of the CTIS covered by these items include for instance the submission and assessment of clinical trials. It is reported that operational assessments of the system will be conducted in the

months following October 2019 in order to identify critical business blockers to the delivery of the auditable version, i.e. issues that prevent a successful audit outcome and for which no appropriate workaround exists.

Earlier this year, the delivery method of the CTIS was amended to follow an agile, iterative delivery model and a new IT contractor subject to a six-month trial period was hired (see report from August and April 2019).

1.2. Implementation in Belgium

On 3 December 2019, Belgium published a law that amends its rules relevant to clinical trials aimed at, inter alia, ensuring the practical implementation of the Clinical Trials Regulation (CTR) in Belgium. This royal decree amends an earlier royal decree dated 9 October 2017, which was published on 10 November 2017 (see report from December 2017) and implemented national legislation on clinical trials.

Separately, the Belgian Federal Agency for Medicines and Health Products (FAMHP) released an updated version of the guidance dated 22 July 2019 for sponsors taking part in its CTR pilot project.

1.3. Implementation in France

On 18 October 2019, the French National Agency for Medicines and Health Products Safety (ANSM) announced that it will continue running its fast track clinical authorization program for Advanced Therapy Medicinal Products (ATMPs). Launched in October 2018 with the aim of improving application processing times and to prepare for the CTR's coming into application (see report from December 2018), the fast track program was extended to ATMPs in February 2019 (see report from April 2019). In addition, this authorization program has now also been opened to complex clinical trials. The ANSM reports that as of September 2019 approximately 40 applications were submitted and processed in the context of this program.

1.4. Implementation in Germany

On 3 September 2019, the German Federal Institute for Drugs and Medical Devices (BfArM) updated its webpage on the status of the German CTR pilot project, which started in October 2015 (see report from May 2016). The page reports that a total of 181 applications were submitted by sponsors since the beginning of the pilot project, with as many as 63 received from January to early September 2019.

1.5. Implementation in Italy

On 30 October 2019, the Italian Drug Agency (AIFA) issued a contract for the conduct of clinical trials of medicinal products in order to achieve greater uniformity, quality and timeliness in defining the agreements between promoters and institutions. This publication takes place in the context of the roll out of a decree that entered into force on 27 June 2019 and is designed to, among other things, adapt the national legislation to the CTR (see report from April 2019).

1.6. 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. the UK's clinical trials pilot project, the possible transition period after Brexit, the future relationship between the UK and the EU, 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 since August 2018 entitled the "combined ways of working pilot" (see report from August 2018). It reported on its website in its last update on 4 December 2019 that 14 Ethics Committees (ECs) are participating in the pilot. In addition, the NHS HRA updated some documents and pages, including its guidance for sponsors submitting a new application, the application dossier guidance for sponsors and instructions for substantial amendments.

Outlook on a possible transition period

Amid the uncertainty surrounding the details of Brexit, the UK makes available a comprehensive Q&A document entitled "further guidance note on the regulation of medicines, medical devices and clinical trials if there's no Brexit deal", which was last updated on 3 September 2019. In line with previous communications on the topic of clinical trials (see previous editions of this report), the document emphasizes the intention of the UK Government to align its legislation with the EU CTR regardless of the Brexit outcome.

In October 2019, the EU accepted to postpone the Brexit date to 31 January 2020. The two parties also agreed upon changes to the withdrawal agreement, which remain to be approved by the EU and the UK Parliaments. At the time this report was prepared, it was challenging to give more concrete timelines with the parliamentary elections having just taken place on 12 December 2019.

Future relationship between the UK and the EU

In October 2019, EU and UK negotiators agreed on a revised political declaration on the future relationship between the EU and the UK. Implemented changes focus on the model on which the future relationship should be built, i.e. a free trade agreement model. Before the Withdrawal Agreement can enter into force, it needs to be ratified by both parties. The formal negotiation process will commence as soon as possible after the UK's withdrawal from the EU. The final 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

On a page of its website last updated on 22 November 2019, the EMA reported that the EMA's permanent building was handed over to the Agency by the Dutch Authorities on 15 November. The EMA has planned to move equipment and configure and test IT systems starting in November 2019 and continuing until January 2020 in order to allow its staff to move into the permanent building in the week of 13 January 2020. In its business continuity plan updated on 13 October 2019, the EMA highlights that projects with legal deadlines, such as clinical trials, are matters of its highest priority in line with previous versions of this document (see report from April and August 2019). It is unclear how this may affect the implementation of the CTIS.

2. CLINICAL TRIAL SAFETY REPORTING

No update is available.

3. ADOPTION OF IMPLEMENTING ACTS, DELEGATED ACTS AND GUIDELINES

On 28 November 2019, the European Commission released version 2.3 of its draft Q&A document addressing a broad range of topics relevant to the CTR. An earlier version of this document was released in June 2019 (see report from August 2019) and early November 2019.

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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