

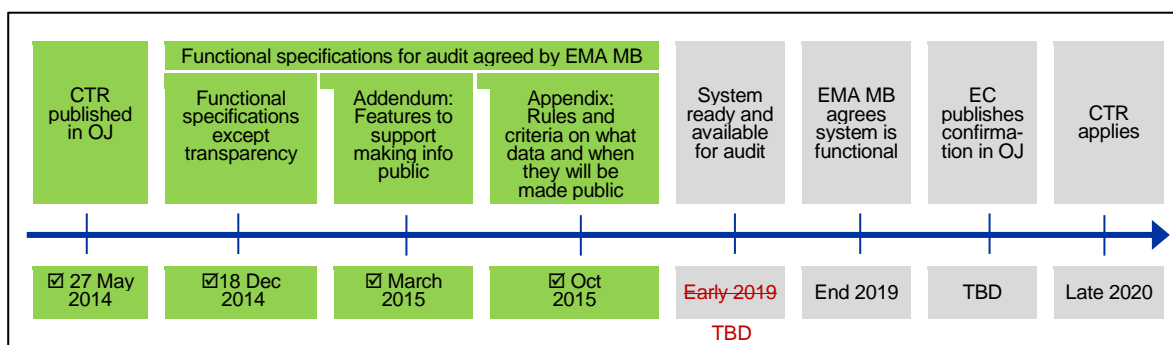
Implementation of the EU Clinical Trials Regulation Update for the Federal Office of Public Health - August 2019 -

1. EU PORTAL AND EU DATABASE

1.1. EMA process and milestones

At its June 2019 meeting, the EMA Management Board was given an update on the implementation as well as on the project methodology and plan of the Clinical Trials Information System (CTIS), also referred to as the EU portal and database. Notably, it was informed that testing and bug fixing was conducted in Spring 2019. In June 2019, a phase of "agile, iterative delivery" was initiated in order to prepare the system for the audit. Further enhancements will be carried out for and after the release of the "go-live" version of the system.

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; red: new)

At the March 2019 EMA Management Board meeting, it was reported that a "sandbox", i.e. a safe environment where untested code can be tested safely, would be created in April 2019 to allow users to familiarize themselves with the code and existing functionalities.

Since March 2019, the Management Board receives monthly high-level reports on the state of implementation of the CTIS.

In February 2019, a new IT contractor was hired for the delivery of the CTIS for a six-month trial period. In September 2019, at the end of the trial period, the services provided by the new supplier will be evaluated by the EMA Management Board, which will decide whether it should be continued. The hiring of a new contractor resulted from changes made to the governance structure and delivery plan in order to mitigate any further delay in the implementation of the CTIS (see report from August 2018). The concept of the newly developed iterative delivery model was presented to, among other actors, representatives of EU Members States (so-called champions), the EU CTR Coordination Group (see report from August 2018) and to stakeholder groups. At the March 2019 EMA Management Board meeting, the representative of the European Commission's DG SANTE expressed her confidence in the new measures taken.

Separately, it is worth noting that the EMA allocated a budget of just under €1.5M for the integration of legacy clinical trials data from EudraCT with the CTIS. In its "final programming document 2019-2021" the EMA lists deliverables for the year 2019, which include the following: preliminary business case towards the integration of legacy data with the CTIS, system and process analysis and design, final business case and start of implementation.

1.2. National implementation of the CTR

On 24 May 2019, the Belgian Federal Agency for Medicines and Health Products (FAMHP) reported on the state of the national implementation of the CTR in the different EU Member States for the period until October 2018. The overview shows that, overall, some progress is inconsistently achieved in all areas by various EU Member States. Areas such as safety, the allocation of resources, and communication and training are areas that lag behind, showing the least progress. Showing average progress are the alignment of fees, national IT systems, the roll out of pilot projects and the adaptation of national legislations. The restructuring of ethics committees (ECs) is one of the areas where the most progress was made.

1.3. Implementation in Austria

In a document authored by various Austrian Federal Ministries published in June 2019, it was reported that the interministerial and interinstitutional working group led by the Austrian Federal Office for Safety in Health Care (BASG/AGES) continues to prepare the implementation of the CTR. The Austrian Federal Ministry of Education, Science and Research made available a budget of €1.3M to build a common IT interface for all ECs that are part of the Austrian medical universities.

1.4. Implementation in Belgium

On 24 May 2019, the FAMHP reported on its CTR pilot project. A new version of the [guidance document](#) dated 22 July 2019 for sponsors taking part in the Belgian CTR pilot project 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**
<i>Initial applications</i>			
Phase I	9	37	52
Phase I ATMP	1	66	66
Phase II ATMP	1	87	87
Phase II-IV	45	55	63
<i>Applications for substantial modifications</i>			
Phase I	5	15	15
Phase I ATMP	3	38	38
Phase II-IV	75	29	33

*This data reflects the situation on 22 May 2019; **Reported in number of days

Source: FAMHP, CTR Pilot info session for sponsors, 24 May 2019 (ATMP: Advanced Therapy Medicinal Product)

The main changes implemented in the document are related to aspects such as the timing and content of the submission of clinical trials documents by the sponsors.

The FAMHP [reported](#) on its pilot project activities until the end of May 2019: 139 final decisions were issued over the course of the years 2017, 2018 and 2019 (until May 2019), comprising 57 related to initial dossier applications and 82 to substantial modifications. Of note, 62 of the 139 final decisions were taken from January to May 2019. It was also reported that 18 decisions were under review in May 2019 and that 25 initial applications were planned to be reviewed in June 2019.

The FAMHP also reported on the average applications processing timelines, which are summarized in figure 2 above.

1.5. Implementation in Portugal

On 24 May 2019, the FAMHP reported on the state of the national implementation of the CTR in various EU countries, including Portugal. It was reported that the revision of the national legislation was ongoing at the time of the update's publication in May 2019.

1.6. Implementation in Germany

On 24 May 2019, the FAMHP reported on the state of the national implementation of the CTR in various EU countries, including Germany. It reported, among other things, on the current number of clinical trials that are part of the German CTR pilot project (see figure 3). It was reported that 82% of participating sponsors are commercial entities. Figure 4 below displays the overview of the duration in days of various steps of the CTR pilot project in Germany.

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

Approved applications	Ongoing applications	Rejected applications	Withdrawn applications after GNAs	Other
77	6	4	9	14

Source: FAMHP, CTR Pilot info session for sponsors, 24 May 2019 (GNAs: Grounds for non-acceptance)

Figure 4: Overview of duration of various steps of the German CTR Pilot project*

Clinical trial application steps	Mean**	Median**	Minimum**	Maximum**
Validation	7.1	7	2	12
Elimination of validation deficiencies***	6.4	8	0	10
Verification of the elimination of validation deficiencies	3.7	4	1	5
Content check/assessment phase	23.1	24	6	29
Removal of the GNAs/RFI***	10.5	11	2	15
Final examination and decision (n=96)	9.4	10	4	13

*This data reflects the situation on 23 March 2019; **Reported in number of days; ***Under the responsibility of the sponsor

Source: FAMHP, CTR Pilot info session for sponsors, 24 May 2019 (GNAs: Grounds for non-acceptance; RFI: Requests for information)

1.7. Implementation in Italy

On 24 May 2019, the FAMHP reported on the state of the national implementation of the CTR in various EU countries, including Italy. Among other aspects, the document released shows the distribution of clinical trials applications per trial phase (see figure 5) and an overview of the outcome of the procedure of applications processed in the context of the Italian CTR pilot project.

Figure 5: Overview of the distribution of applications per trial phase in the Italian CTR pilot project

Phase I	Phase II	Phase III	Phase IV
3%	31%	63%	3%

Source: FAMHP, CTR Pilot info session for sponsors, 24 May 2019

1.8. Implementation in the UK and 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 after Brexit, the future relationship between the EU and the UK 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, and April 2019). Last updated on 12 June 2019, its website shows that 11 ECs are participating in the pilot project.

Outlook on a possible transition period

Amid the uncertainty surrounding the details of Brexit, the UK released legislation to address, among other things, the topic of clinical trials. On 19 June 2019, the UK Medicines and Healthcare products Regulatory Agency (MHRA) announced [amendments](#) to the "Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 (Statutory Instrument (SI) 2019/775)" and to its equivalent for medical devices to ensure that the published policy in relation to the regulation of medicines in a "no-deal" EU exit scenario is properly reflected. The legislation will be subject to parliamentary scrutiny and approval which the MHRA anticipates in autumn 2019. In a no-deal scenario, the MHRA would take on the roles and responsibilities currently held by the EMA.

On 10 June 2019, the HRA released its 2019-2020 [business plan](#), where it reported its intention to "implement an integrated approvals process for clinical trials of medicinal products aligned with the forthcoming CTR" by September 2019.

The UK is currently set to leave the EU on 31 October 2019, with or without a deal. At this point, it is very difficult to anticipate whether a transition period will take place or not.

Future relationship between the UK and the EU

At the time this report was prepared, the possibility of implementing changes to the political declaration on the future relationship between the EU and the UK remains open. 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, for which the EU has set clear conditions (see report from April 2019). 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

At its June 2019 meeting, the EMA Management Board reported that just below 60% of the Agency's staff have relocated to Amsterdam. A recruitment exercise is currently ongoing but the EMA does not expect to be able to reach its previous headcount. As a result, most of the activities set out for temporary suspension at the end of 2018 in the EMA's business continuity planning remain on hold. It is unclear how this may affect the implementation of the CTIS.

2. CLINICAL TRIAL SAFETY REPORTING

At its June 2019 meeting, the EMA Management Board was informed that the safety reporting functionalities were developed.

3. ADOPTION OF IMPLEMENTING ACTS, DELEGATED ACTS AND GUIDELINES

In June 2019, the European Commission released version 2 of its 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 European Economic Area (EEA) contracting parties. An earlier version of that document was released in April 2018 (see report from August 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.

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