

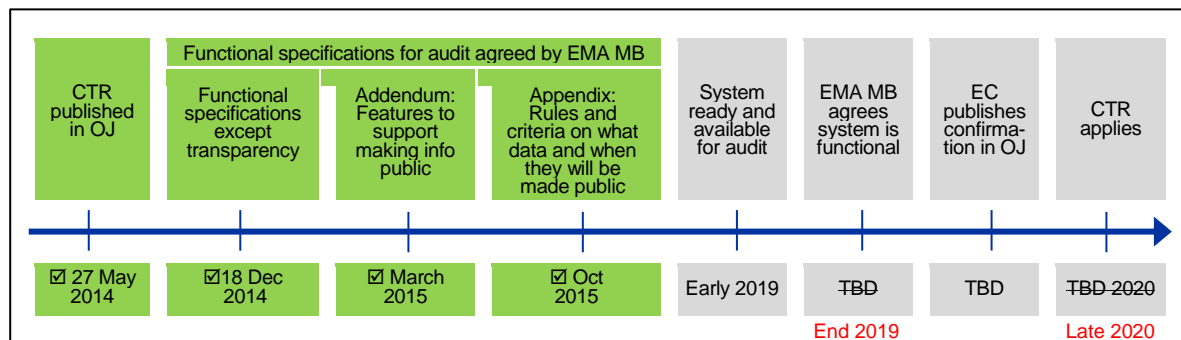
Implementation of the EU Clinical Trials Regulation Update for the Federal Office of Public Health - December 2018 -

1. EU PORTAL AND EU DATABASE

1.1. EMA process and milestones

At its October 2018 meeting, the EMA Management Board was informed that the development of the auditable version of the EU portal and database (release 0.7) was completed. Release 0.7 was reported to be undergoing an intensive phase of pre-testing prior to the formal user acceptance testing round (UAT 7), which is scheduled to be conducted in early 2019. The EMA Management Board stated that the audit will only take place after March 2019, once the EMA has relocated to Amsterdam and testing and bug fixing is finalized on release 0.7. Finally, it was also reported that the EU portal and database could go live “later in 2020”, provided that the audit and the review by the EMA Management Board are successfully concluded by the end of 2019.

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. Implementation in Belgium

On 16 November 2018, the Belgian Federal Agency for Medicines and Health Products (FAMHP) released an updated version of its guidance [document](#) designed for clinical trials sponsors who would like to take part in its clinical trial pilot project. The pilot project was started in 2017 with the aim to develop and test procedures for the review of applications for clinical trials in order to prepare for the enforcement of the Clinical Trials Regulation (CTR) (see report from February 2017). The guidance document was developed in collaboration with the college, which coordinates all accredited ethics committees (ECs) and acts as a contact point between them and the FAMHP (see report from April and August 2018).

1.3. Implementation in France

On 18 October 2018, an amendment to France’s clinical trials rules dated 17 October was published in the French official journal. It concerns the selection process of ECs for the review of clinical trial applications. French Law No. 2012-300, implemented in November 2016 (see report

from December 2016), provides for a random selection process with the aim of avoiding potential conflicts of interest. Until October 2018, the selection process was conducted without considering whether ECs had adequate competences or resources, which in turn created certain issues such as delays. The amendment aims to correct this caveat by taking into account the availability and competences of ECs while maintaining the random selection process. This change was implemented in order to adapt France's clinical trials application processing timelines ahead of the CTR coming into application.

In October 2018, the French National Agency for Medicines and Health Products Safety (ANSM) launched a new fast track clinical trial authorization program. Among other things, the program is said to drastically bring down the processing time of clinical trials applications. In addition to boosting processing times, this program aims to improve the quality and safety of applications as well as to prepare the ANSM ahead of the CTR coming into application. Among other published documents, the ANSM released a [guide](#) for applicants.

1.4. Implementation in Sweden

On 22 August 2018, the Swedish Medical Products Agency (Läkemedelsverket) published a document on the pilot project for the implementation of the CTR. The pilot project was launched by the Läkemedelsverket, the six Swedish Ethics Review Boards, Biobank Sweden and the Swedish Radiation Safety Authority. The pilot project's goal is to prepare Swedish stakeholders for the new processes defined in the CTR. The document reports that clinical trials applications received in the context of the pilot project will be reviewed following the processes defined in the CTR but authorized under the current Swedish clinical trials legislation. It also informs stakeholders that the Läkemedelsverket will be the main contact point and provides an overview of applicable timelines and necessary steps for applicants.

1.5. 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 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

Earlier this year, the UK National Health Service (NHS) Health Research Authority (HRA) reported the launch of a pilot project entitled the "combined ways of working pilot" (see report from August 2018). Last updated on 5 December 2018, the webpage indicates that 13 ECs are taking part in the pilot. In addition, the NHS HRA released a communication entitled "How the combined ways of working pilot is already making an impact", which provides [feedback](#) from two participating organizations.

Initially published on 23 August 2018, the UK Department of Health and Social Care's [guidance](#) entitled "how medicines, medical devices and clinical trials would be regulated if there's no Brexit deal" was updated on 14 September 2018. Among other issues, the guidance reports that the Medicines and Healthcare products Regulatory Agency (MHRA) intends to improve the clinical trial management process in the UK in order to allow for a single application and a single national decision, and also refers to the ongoing pilot project. A separate [document](#) entitled "life sciences sector deal 2" published on 5 December 2018 also emphasizes the UK's determination to improve the management of clinical trials and to align with processes defined in the CTR.

Negotiations for a deal on a transition period

Alongside negotiations on a transition deal between the EU and the UK, preparations for a possible no-deal Brexit scenario have been ongoing. On 4 October 2018, the MHRA [consulted](#) on contingency [legislation](#) for the regulation of medicines and medical devices for such a scenario, which also covers the field of clinical trials. The proposed contingency legislation contains a series of amendments to inter alia ensure a transition as smooth as possible in the event of a no-deal Brexit. Separately, on 6 September 2018, the European Commission published a notice to

stakeholders on Brexit and the EU rules in the field of clinical trials.

On 14 November 2018, EU and UK negotiators agreed on a draft transition deal. The agreement provides for a transition until 31 December 2020, which could be extended under given circumstances (by two years at most). During the transition period, EU law will continue to apply in the UK but membership in EU institutions will be lost for the UK. During that period, the UK cannot act as a leading authority for risk assessments, examinations, approvals or authorizations at the EU and Member States levels when it comes to, for instance, the CTR. The transition deal indicates that UK's access to networks, information systems and databases established on the basis on EU law will be interrupted at the end of the transitional period, apart from e.g. selected customs- and tax-related networks for which access is granted as defined in the document's annexes. UK's access to the CTR's EU portal and database will depend on the content of the agreement on its future relationship with the EU (see next section).

On 25 November 2018, the European Council (i.e. the EU heads of state or government) endorsed the draft transition deal. The draft deal must be approved by at least 20 EU countries with 65% of the entire EU population and ratified by the EU and UK Parliaments.

At the time of this report's finalization, the transition deal had not been discussed in the UK or EU Parliament.

Future relationship between the UK and the EU

On 25 November 2018, the European Council endorsed a political [declaration](#) dated 22 November 2018 which provides an outline of the principles that will govern the relationship between the UK and the EU after a potential transition period. Among other things, the document calls for transparent and compatible regulatory approaches as well as to explore the possibility of establishing cooperation between UK authorities and EU agencies, such as the EMA. The formal negotiation process is set to start as soon as possible after the UK's withdrawal from the EU on 30 March 2019.

Relocation of the EMA

Based on an EMA update dated 1 October 2018, the relocation of the EMA to Amsterdam is ongoing and currently on track. The update also reports that the relocation to the temporary building is scheduled to be finalized by 30 March 2019 while the relocation to the permanent building is scheduled for 31 December 2019. On 17 October 2018, the relocation of the agency was formally approved by the Permanent Representatives Committee (Coreper).

2. CLINICAL TRIAL SAFETY REPORTING

No update is available.

3. ADOPTION OF IMPLEMENTING ACTS, DELEGATED ACTS AND GUIDELINES

3.1. Overview of the status of implementation measures and guidelines

On 7 November 2018, the EMA published an updated version of its [guideline](#) on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials". The revision of this guideline was conducted by EMA with a mandate from the European Commission in order to facilitate the implementation of the CTR. The document came into effect on 1 November 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

- ANSM, Announcement - ANSM implements Fast Track clinical trial authorization program, 29 October 2018; https://ansm.sante.fr/var/ansm_site/storage/original/application/bbba0b8bdbb79e7b906b873d99b36e88.pdf, last accessed on 13 December 2018.
- ANSM, Clinical trials on medicinal products submitted to the ANSM as part of the Fast-Track procedure, Practical information guide for applicants, Test phase - October 2018, 10 October 2018 – Version 1.0; https://www.ansm.sante.fr/var/ansm_site/storage/original/application/42df327468624f1ce1862ef562c1cc30.pdf, last accessed on 13 December 2018.
- Council of the European Union, Relocation of European Medicines Agency and European Banking Authority - agreement on the legal text, 17 October 2018; <https://www.consilium.europa.eu/en/press/press-releases/2018/10/17/relocation-of-european-medicines-agency-and-european-banking-authority-agreement-on-the-legal-text/>, last accessed on 13 December 2018.
- Council of the European Union, Political declaration setting out the framework for the future relationship between the European Union and the United Kingdom, 22 November 2018; <http://data.consilium.europa.eu/doc/document/XT-21095-2018-INIT/en/pdf>, last accessed on 13 December 2018.
- EMA, EMA Management Board - highlights of October 2018, 5 October 2018; <https://www.ema.europa.eu/en/news/ema-management-board-highlights-october-2018-meeting>, last accessed on 13 December 2018.
- EMA, EMA tracking tool - relocation to Amsterdam, main milestones, 1 October 2018; <https://www.ema.europa.eu/documents/other/ema-tracking-tool-relocation-amsterdam-main->

[milestones_en-0.pdf](#), last accessed on 13 December 2018.

- EMA, Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, 7 November 2018; https://www.ema.europa.eu/documents/scientific-guideline/guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal_en-0.pdf, last accessed on 13 December 2018.
- European Commission, Notice to stakeholders - withdrawal of the United Kingdom and EU rules in the field of clinical trials, 6 September 2018, https://ec.europa.eu/info/sites/info/files/notice_to_stakeholders_brexit_clinical_trials_final.pdf, last accessed on 13 December 2018.
- FAMHP, Update on the new Clinical Trial Regulation pilot project, 16 November 2018; https://www.famhp.be/en/news/update_on_the_new_clinical_trial_regulation_pilot_project_0, last accessed on 13 December 2018.
- FAMHP, Guidance for participating parties, Voluntary Joint pilot between FAMHP, the College, accredited Ethics Committees and sponsors for processing of applications for the authorization of clinical trials and substantial modifications on medicinal products for human use in accordance with the spirit of the Regulation (EU) No 536/2014 and of the law on CTR, 16 November 2018; https://www.famhp.be/sites/default/files/content/ctr_pilot_project_guidance_for_sponsors_v5.0_16-11-2018_3.pdf, last accessed on 13 December 2018.
- Läkemedelsverket, Joint pilot project for clinical trials according to Regulation (EU) 536/2014; <https://lakemedelsverket.se/upload/foretag/humanlakemedel/klinisk-provning/Pilotprojekt%20CT%20EU-536-2014/Summary-pilot-project-clinical-trials-EU-536-2014.pdf>, last accessed on 13 December 2018.
- Loi no 2018-892 du 17 octobre 2018 relative à la désignation aléatoire des comités de protection des personnes (1), Journal Officiel de la République Française, JO No. 0241, NOR SSAX1813828L, 18 October 2018; https://www.legifrance.gouv.fr/jo_pdf.do?id=JORFTEXT000037503516, last accessed on 13 December 2018.
- MHRA, MHRA consultation on EU exit no-deal legislative proposals, 4 October 2018; <https://www.gov.uk/government/consultations/mhra-consultation-on-eu-exit-no-deal-legislative-proposals>, last accessed on 13 December 2018.
- MHRA, Draft legal text for medicines, clinical trials and medical devices EU exit no deal statutory instruments, 4 October 2018; https://consultations.dh.gov.uk/mhra/mhra-no-deal-contingency-legislation-for-the-regul/user_uploads/consultation-legal-text-1.pdf, last accessed on 13 December 2018.
- MHRA, MHRA EU exit no-deal contingency legislation for the regulation of medicines and medical devices, 4 October 2018; https://consultations.dh.gov.uk/mhra/mhra-no-deal-contingency-legislation-for-the-regul/user_uploads/consultation-printout-2.pdf, last accessed on 13 December 2018.
- NHS HRA, How the combined ways of working pilot is already making an impact, 11 December 2018; <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/how-combined-ways-working-pilot-already-making-impact/>, last accessed on 13 December 2018.
- UK Government, Draft Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community, 14

November 2018;

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/756374/14_November_Draft_Agreement_on_the_Withdrawal_of_the_United_Kingdom_of_Great_Britain_and_Northern_Ireland_from_the_European_Union.pdf, last accessed on 13 December 2018.

- UK Government, Life Sciences Sector Deal 2 - 2018, 5 December 2018; <https://www.gov.uk/government/publications/life-sciences-sector-deal/life-sciences-sector-deal-2-2018#foreword>, last accessed on 11 December 2018.
- UK Government, Guidance, How medicines, medical devices and clinical trials would be regulated if there's no Brexit deal, 14 September 2018; <https://www.gov.uk/government/publications/how-medicines-medical-devices-and-clinical-trials-would-be-regulated-if-theres-no-brexit-deal/how-medicines-medical-devices-and-clinical-trials-would-be-regulated-if-theres-no-brexit-deal>, last accessed on 13 December 2018.