Implementation of the EU Clinical Trials Regulation
Update for the Federal Office of Public Health
- October 2017 -

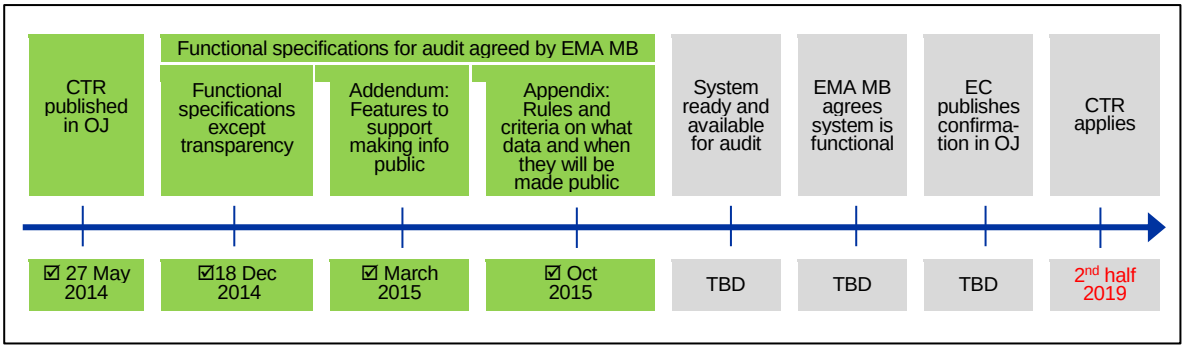
1. EU PORTAL AND EU DATABASE

1.1. EMA process and milestones

On 5 October 2017, the Management Board of the European Medicines Agency (EMA) discussed the implementation of the Clinical Trials Regulation (CTR). The development of the EU portal and the EU database remains aligned to the schedule that allows the CTR to apply as from the second half of 2019.

The EMA will be able to communicate more details on the delivery timeframe only after the completion of a cycle of testing of the system by EU Member States and sponsor representatives, and after the EMA sees that further progress with the auditable version of the system has been made.

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



Source: EMA 2017 (CTR: Clinical Trials Regulation; OJ: Official Journal of the EU; EC: European Commission; MB: Management Board; red: updated timelines)

1.2. EU clinical trials portal and Union database meeting with stakeholders

A stakeholder meeting was held at the EMA offices on 3 October 2017. Items on the agenda included an update on the EU portal and the EU database, an update on the plan regarding the sixth round of User Acceptance Testing (UAT 6) and an update from the European Commission.

- **Update on the development of the EU portal and the EU database**
  It was highlighted that the sixth test version of the system (release 0.6) is ready and provides three quarters of the system functionalities. This means that business processes specific to sponsors and EU Member States can be executed from end to end.

  The remaining functionalities will be addressed by releases 0.7 and 0.8, which are planned for the end of the first quarter 2018 and the third quarter 2018 respectively. It is also during release 0.8 that the interface specifications will be made available. Furthermore, the audit confirming that the system is functional is scheduled to take place during the second quarter

2018. The formal agreement by the EMA Management Board that the system is functional is expected during the third quarter 2018.

- **Update on UAT 6**
  UAT 6 takes place during the fourth quarter 2017 and involves 16 on-site sponsor testers and 8 off-site sponsor organizations, as well as 21 testers from EU Member States. UAT 6 consists of free-form testing as well as test scenarios.

The next EU clinical trials portal and Union database meeting with stakeholders is scheduled to take place on 17 January 2018.

1.3. Implementation in the UK/Brexit

The UK Department for Exiting the European Union acknowledged the possibility that the UK national system for clinical trials may not be aligned with the EU legislation as a result of Brexit.

This acknowledgment was made in a letter from Robin Walker, Minister at the Department for Exiting the European Union, addressed to Norman Lamb, Chair of the House of Commons Science and Technology Committee.

Dated 21 September 2017, the letter explains that “the general approach taken in the Repeal Bill […] is that EU law which applies directly in the UK legal system […] before exit, will be converted into domestic law after exit”.

As the entry into application of the CTR may not take place before the UK leaves the EU, the Repeal Bill may not cover the CTR. The letter states that, as a result, the UK’s “future alignment with the new EU Clinical Trials Regulation will be subject to negotiations”.

Separate from the above declaration, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) is organizing a Good Clinical Practice (GCP) stakeholder engagement meeting on 16 November 2017. During the meeting, the MHRA will take the role of listener to participants who will discuss and give feedback on three particular areas of the CTR that require national legislation, namely:

- Who can take consent
- Who can be an investigator
- Arrangements for exemption of Good Manufacturing Practice (GMP) for hospitals and health centers

MHRA states that the meeting will be a forum for consultation and discussion around GCP and will provide updates on operational, national and international regulatory matters. Issues touching upon the alignment of the UK laws on clinical trials with the CTR will most probably be also discussed.

1.4. Relocation of the EMA

On 3 October 2017, the EMA published comments on EU Member States’ bids for its relocation. In total, 19 bids were submitted (see report from August 2017). In its comments, the EMA looked at the following aspects (see annexes):

- Technical aspects: building layout; facilities available in the premises; and proposed relocation plans
- Other aspects: accessibility of the location; existence of adequate education facilities for the children of EMA staff; appropriate access to the labor market, social security and medical care for both children and spouses/partners of EMA staff; staff retention per location based on an internal survey launched on 4 September 2017

Better comments were attributed by the EMA to the following cities (in alphabetical order):

- Based on technical aspects: Amsterdam, Barcelona, Bratislava, Brussels, Copenhagen and Milan

- Based on other aspects: Amsterdam, Barcelona, Brussels, Copenhagen, Dublin, Milan and Vienna
- Based on staff retention survey only (>65% staff retention): Amsterdam, Barcelona, Copenhagen, Milan and Vienna

The final decision will be taken in a vote by the 27 EU ministers that will take place on the margins of the General Affairs Council in November 2017.

2. CLINICAL TRIAL SAFETY REPORTING

No update available.

3. ADOPTION OF IMPLEMENTING ACTS, DELEGATED ACTS AND GUIDELINES

3.1. Overview of the status of implementation measures and guidelines

On 16 September 2017, the Commission Delegated Regulation specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections was published in the Official Journal of the European Union (see table 1).

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 publication is expected to be published by the end of 2017 (see report from August 2017)
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 August 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 August 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 August 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 August 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 August 2017)

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

- Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections, 2017 OJ L 238/12; http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R1569&qid=1508773638124&from=EN, last accessed on 23 October 2017.
- EMA, EMA publishes comments on Member States' hosting bids, 3 October 2017; http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/10/news_detail_002819.jsp&mid=WC0b01ac058004d5c1, last accessed on 24 October 2017.
- EMA, EU Clinical Trials Portal and Union Database Stakeholder Meeting, 3 October 2017.
- EMA, EMA Management Board: highlights of October 2017 meeting, 6 October 2017; http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/10/WC500236190.pdf, last accessed on 23 October 2017.
- Gail Francis, MHRA, Upcoming GCP stakeholder engagement meeting, 21 September 2017; https://mhrainspectorate.blog.gov.uk/2017/09/21/upcoming-gcp-stakeholder-engagement-meeting/, last accessed on 23 October 2017.
- Robin Walker, Robin Walker to Norman Lamb, Leaving the EU: implications and opportunities for science and research, UK Department for Exiting the European Union, 21 September 2017; http://www.parliament.uk/documents/commons-committees/science-technology/170921-Robin-Walker-to-Norman-Lamb-DExEU%20letter.pdf, last accessed on 23 October 2017.
- SFL Intelligence.

6. ANNEXES

- EMA, Summary of EMA technical comments on the technical requirements with respect to the candidate host Member States' offers to relocate EMA, 14 September 2017.
- EMA, Other criteria essential to ensure that EMA remains operational to guarantee business continuity - EMA contributions (detailed tables), 15 September 2017.