



Clinical Trial Regulation 536/2014

Objectives, key changes and transitional arrangements

Kristof Bonnarens, DG SANTE

Webinar for SMEs and Academia on
the Clinical Trials Regulation and the
Clinical Trials Information System

29/11/2021

Objectives and key changes

Clinical Trial Regulation 536/2014 (CTR)



- The CTR was **adopted in April 2014** by the European Parliament and **published in May 2014**
- It will become **applicable on 31/1/2022**.
- Every **new clinical trial** will need to be submitted and authorised under the CTR rules 1 year after the date of application (31/1/2023)
- The **transition period** for the trials ongoing at the moment of applicability will be a **maximum of 3 years** after the date of application of the Regulation.

Purpose of the CTR

- To make Europe competitive in research considering the decline in CTs the past years by:
 - **harmonization of the approval process** for clinical trials with maximum timelines through a single electronic submission
 - Close **coordination** within and between Member States and support the conduct of multi-country trials (including countries with fewer applications at present)
 - **minimizing the scope for regulatory autonomy** at national level
 - **ensuring** the **production** of reliable and robust, high-level **scientific data and ensuring participant safety**
 - increased **transparency**



Legal form



- Existing legislation = Directive 2001/20

Binding legal requirements, which need to be **implemented by each Member State** through national legislation

- Upcoming legislation = Regulation 536/2014

Binding in its entirety, **directly applicable** to all Member States. No need for national legislation



Differences with Directive 2001/20 (1)

- Scope remains limited to **interventional research with medicinal products**, however, **adapted definitions** on clinical trial, non-interventional study, low-intervention clinical trial
- Streamlined **submission and review process via EU Portal and Database** (EUPD, part of the Clinical Trials Information System or CTIS) including a **tacit approval** system, identical for all EU/EEA Member States
- **Single decision** per Member State (= / NCA + Ethics Committee) on the basis of one single submission (identical requirements for all trials)
- **Coordinated assessment** with one **Reporting Member State**, proposed by the sponsor, and **involvement of all Member States Concerned**
- **Without prejudice** of other legislation (e.g. GMO, radiopharmaceuticals,...)



Differences with Directive 2001/20 (2)

- Persons **validating and assessing** the application should be **independent** of the **sponsor**, of the clinical **trial site** and the **investigators** involved and of persons **financing** the clinical trial, as well as free of any other undue influence.
- Strengthened rules on the protection of patients and **informed consent, specific modalities on cluster trials**
- **Coordinated safety assessment** through work-sharing and streamlined safety reporting (no more national reporting of SUSARs)
- **More transparency** on the conduct and results of the clinical trial
- The possibility for the **Commission to conduct controls** in Member States and third countries

Differences with Directive 2001/20 (3)

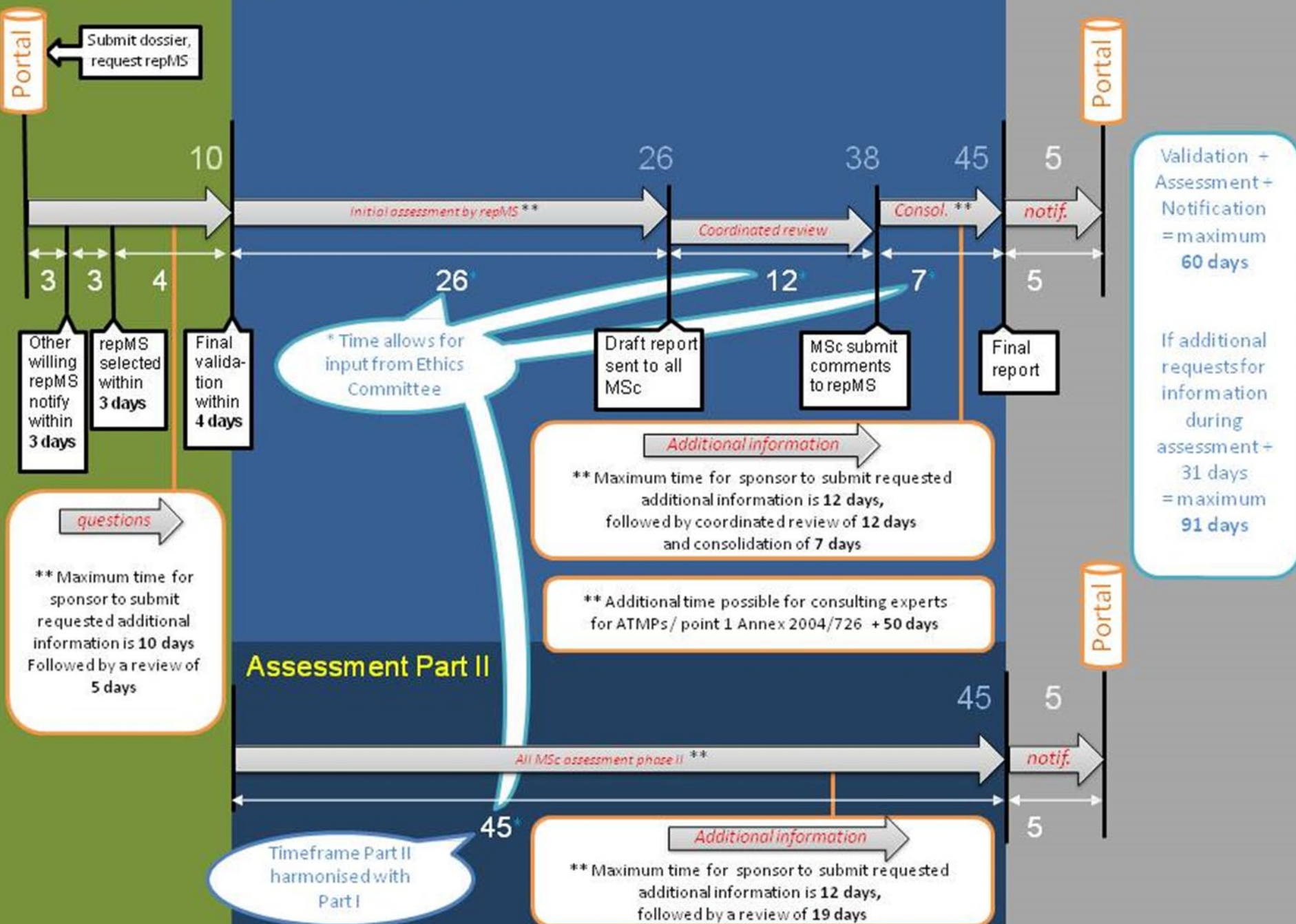
- **Low-intervention trials:**
 - the IMP are used in accordance with the **marketing authorisation** or are **evidence-based** and supported by **published scientific evidence** in any of the Member States concerned;
 - the additional diagnostic or monitoring procedures do not pose more than **minimal additional risk or burden** to the safety of the subjects **compared to normal clinical practice** in any Member State concerned
 - **Risk proportionate approaches**
- **Co-sponsorship** : a clinical trial can have **more than one sponsor**, written contract can contain divided responsibilities. Some elements need to be established jointly.

Processes in the CTR

Validation

Assessment Part I

Notification



Additional processes (1)



- **Substantial modifications**: submission and authorization of **changes** to any aspect of the clinical trial which is made **after notification of a decision** and which is likely to have a **substantial impact** on the **safety or rights** of the subjects or on the **reliability and robustness** of the data generated in the clinical trial
- Update of **changes to the clinical trial which are not substantial** but are **relevant for the supervision** of a clinical trial
- **Addition** of a Member State: **submission and autorisation**, through the EU Portal, of a proposed new Member State

Additional processes (2)



- **Notification** of start, end, temporary halt, and early termination of a clinical trial, **urgent safety measures and serious breaches**
- **Corrective measures**
- Streamlining and simplification of **safety reporting** obligations, including collaboration amongst Member States :
 - ☐ Suspected Unexpected Serious Adverse Reactions (SUSARs)
 - ☐ Annual safety reports

Union Controls



- Commission may conduct **controls** in order to verify that
 - **Member States** correctly supervise **compliance** with the Regulation
 - CT regulatory **framework in 3rd countries** offers **equivalent protection** of rights and safety of patients' and reliability of the generated data
- **Reports** with findings and recommendations resulting from Union controls shall be **submitted through the EU Portal**

Transition periods

Transition from pre-CTD to CTR

- trials that started **prior to the date of entry into application of Directive 2001/20/EC** and **not in line the CTD** cannot continue after the entry into application of the Clinical Trials Regulation. A new initial application under the CTR will be needed.

Transition from CTD to CTR



- To facilitate the change from the old to the new legislation, the CTR allows to **start and conduct a clinical trial in accordance with Directive 2001/20/EC (CTD)** during a transitional period of **1 year after application date (31/1/2022)**
- Clinical trials **authorized under the CTD before 31/1/2023** can **continue** to be conducted under the CTD until **31/1/2025**
- An application to transition ongoing trials from CTD to CTR will need to be **submitted and authorised** in time **before the end of the transitional period.**
- Trials that have the **end of trial notified in all Member States** before 31/1/2025, will **not need to be transitioned** (even when the global EoT has not been reached yet)

Transition process



- Ongoing trials which are **compliant with CTR principles** and are **not subject to any ongoing assessment** in any EU/EEA country can be transitioned
- If necessary **substantial amendments** under CTD shall be used to make the trial compliant with CTR -> this needs to be completed in time for the assessment of the compliant CTA under CTR
- It is the **sponsor's responsibility** to ensure compliance
- Member States can take **corrective measures** if the trial does not comply with CTR

http://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

Submission of an application for transition

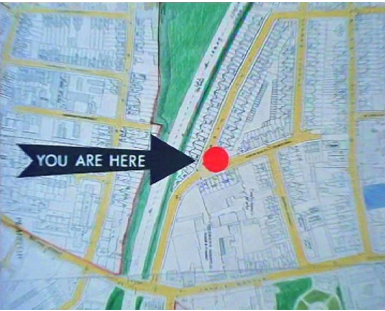
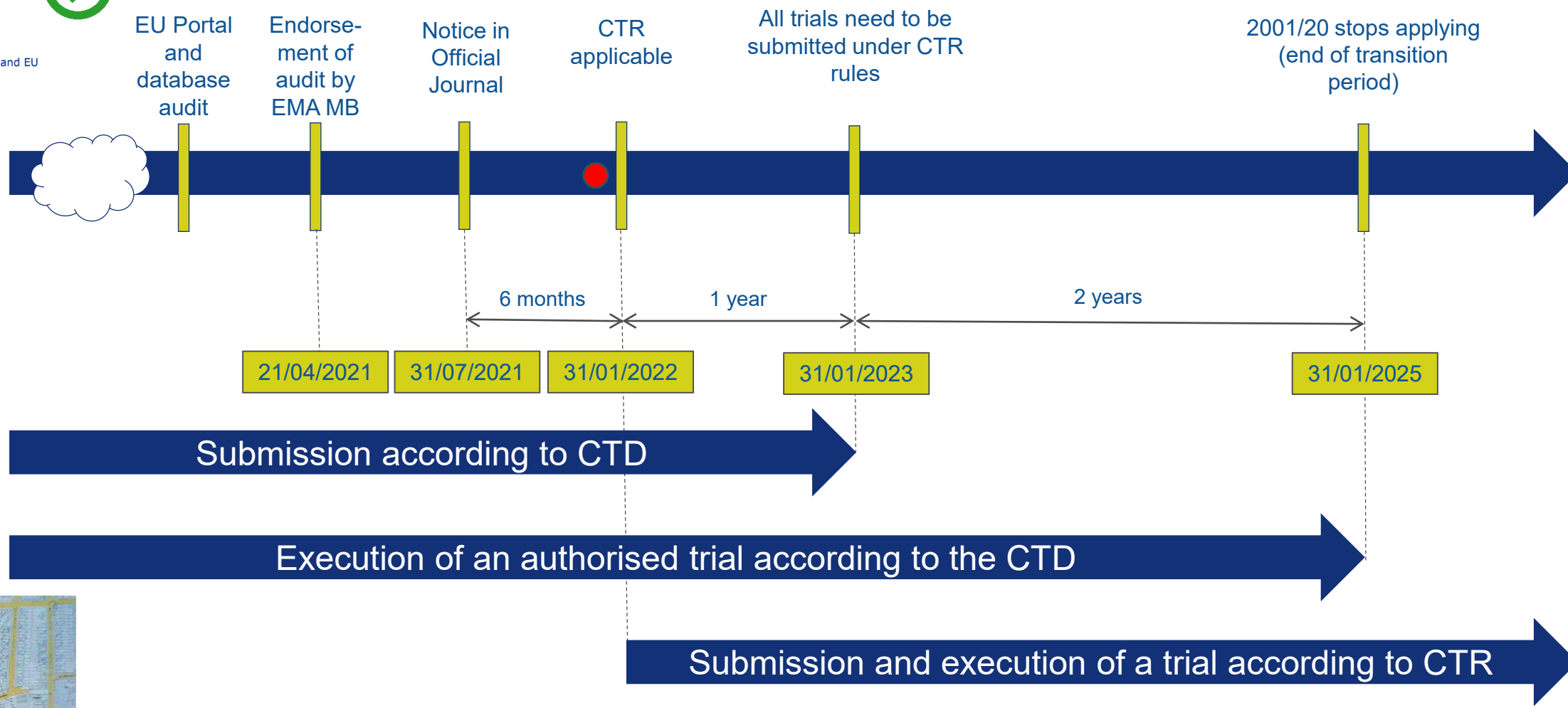
- Initial application according to the CTR, based on the latest authorized version of the dossier under CTD
- **New documents**: cover letter, CTR application (Part I and II) in CTIS, harmonised or consolidated protocol* for multi-country trials (Annex I B-D)
- **Additional mandatory documents**: all part I and II documents need to be submitted in their latest approved version (not necessary to prepare new versions for CTIS submission).
- The sponsor is not **expected to update all particulars** of the trial, including labelling, immediately after the authorisation of the trial under the CTR. Documentation should be brought in line with the CTR requirements at the time of the first revision.

* CTFG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No 536/2014).



25 March 2015
EMA/42176/2014 Rev. 1, Corr.*
Compliance and Inspections

Functional specifications for the EU portal and EU database to be audited



Information from Commission side

Eudralex volume 10 website contains a lot of information on CTR submissions and templates:

https://ec.europa.eu/health/documents/eudralex/vol-10_en#fragment1

Keep in touch



ec.europa.eu/



europa.eu/



[@EU_Commission](https://twitter.com/EU_Commission)



[@EuropeanCommission](https://www.facebook.com/EuropeanCommission)



[European Commission](https://www.linkedin.com/company/european-commission)



[europeancommission](https://www.instagram.com/europeancommission)



[@EuropeanCommission](https://www.youtube.com/@EuropeanCommission)



[EUTube](https://www.youtube.com/EUTube)



[EU Spotify](https://open.spotify.com/playlist/37i9dQZF1DX0XUx1Q8YB0l)

Thank you



© European Union 2020

Unless otherwise noted the reuse of this presentation is authorised under the [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/) license. For any use or reproduction of elements that are not owned by the EU, permission may need to be sought directly from the respective right holders.

Slide xx: **element concerned**, source: **e.g. Fotolia.com**; Slide xx: **element concerned**, source: **e.g. iStock.com**

