Clinical Trial Regulation 536/2014
General principles and new concepts

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Introduction of the Clinical Trial Regulation 536/2014 and major differences with the Clinical Trial Directive 2001/20

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Clinical Trial Regulation 536/2014

- The Regulation was **adopted in April 2014** by the European Parliament and **published in May 2014**

- The **transition period** for the trial ongoing at the moment of applicability will be a **maximum of 3 years** after the date of application of the Regulation.

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Purpose of the CTR

- To make Europe **competitive in research** considering the decline in CTs and number of patients the past years
- **Harmonization of the approval process** for clinical trials and the introduction of a common evaluation for multinational clinical trials
- To **minimize the scope for regulatory autonomy** at national level
- To ensure the pro**duction of reliable and robust**, high-level scientific data, **ensuring patient safety**

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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

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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) including a **tacit approval** system
- **Single decision** per Member State (=/ NCA + Ethics Committee)
- **Coordinated assessment** with one **Reporting Member State**, proposed by the sponsor and **involvement of all Member States Concerned**
- If no subject has been included within two years from the authorisation, the **authorisation expires**

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

Overview of the authorisation processes

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Submission and authorisation process (1)

- **One single dossier** (defined in annex I of the CTR) **and submission** for a given protocol in the EU, throught the European Portal – independent on the number of EU Member States that participate
- One **Reporting Member State (RMS)** for each trial
- **Timelines defined** by the CTR – a **tacit approval** system is in place for the validation and assessment process
- **Decision on a trial at Member State level**, on the basis of a scientific and ethical review. Exact **role and remit of ethics committee**(s) and NCA to be defined per Member State

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Submission and authorisation process (2)

- The **RMS drives the assessment** process for those aspects that are considered to be **scientifically harmonized within the EU (PART I)**
- For multinational trials, this happens in 3 phases :
    - Initial assessment phase (drafting of the assessment report by the RMS)
    - Coordinated review phase (all Member States review the draft report and share their considerations)
    - Consolidation phase (consolidation of considerations in a final part I AR)
- **Each MSC** assesses the **aspects that are of a national/local nature (PART II)**

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Submission and authorisation process (3)

- **One single decision** (part I + II) per member state
- For a **MSC, the Part I decision is the conclusion of the RMS,** except when :
  - Subjects receive **inferior treatment** compared to the normal clinical practice in that member state
  - **Specific rules** in **national** legislation are not met
  - **Considerations** on safety or reliability that were **shared during the coordinated review phase remain**
- **Disagreement** with the Part I decision of the RMS needs to be **communicated** through the EU Portal and **justified**

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Submission and authorisation process (4)

- A MSC shall **refuse** a trial if :
  - it **disagrees with the part I** decision
  - the **part II** decision is **negative**
  - An **ethics committee** has given a **negative opinion** (as defined nationally) – appeal mechanism to be foreseen
- If the **RMS opinion is negative**, it is **negative for all** MSC
- Tacit approval system means **automatic approval when the time has lapsed**
- Authorization has an **expiry date of 2 years**

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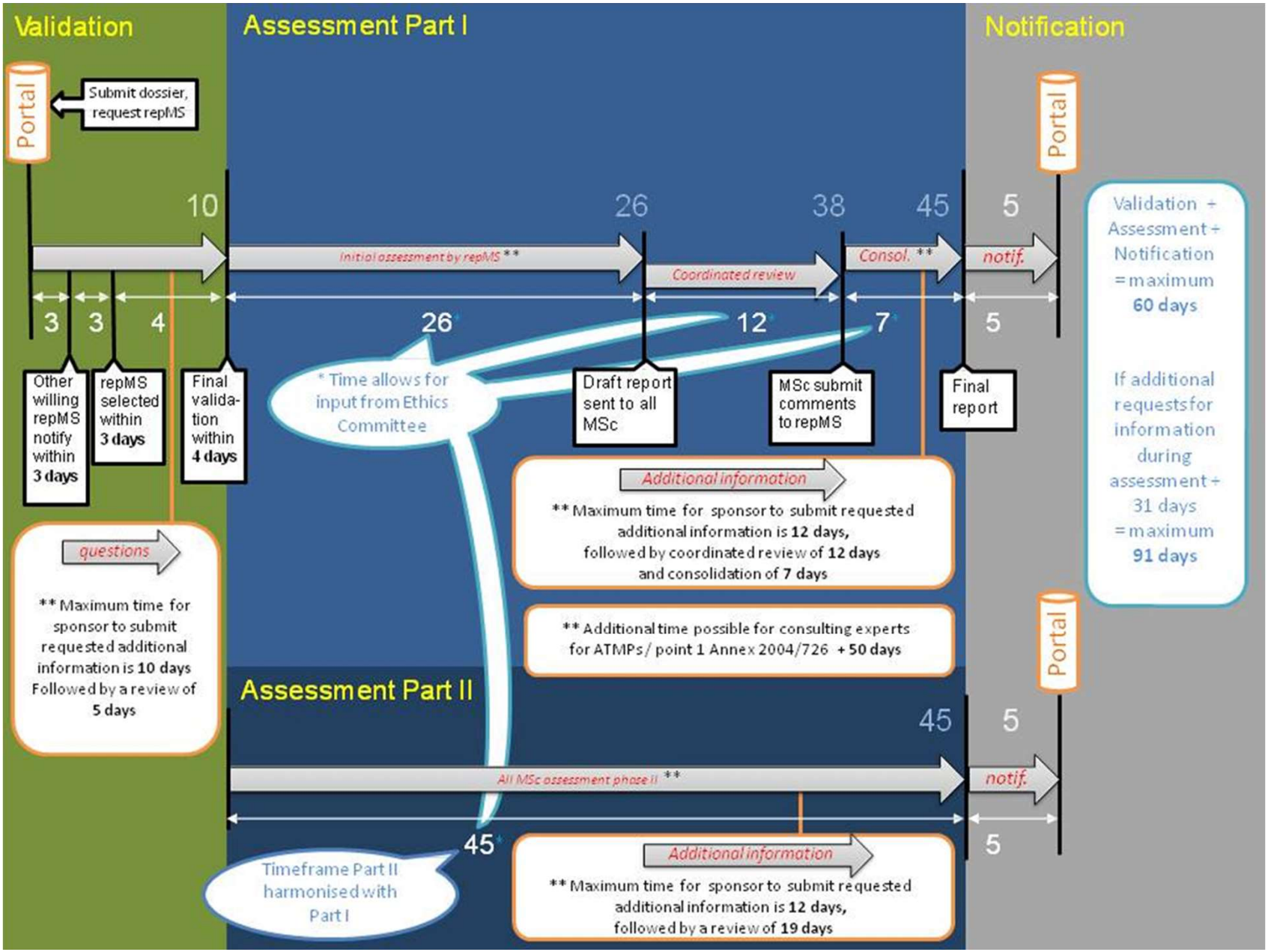

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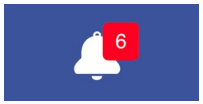
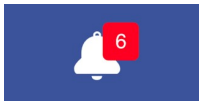
Additional processes (1)



- **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 s**tart, 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

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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**

European Portal and database Clinical Trial Information System

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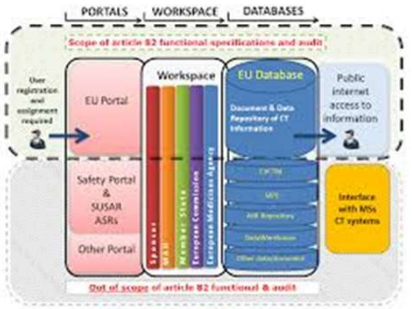
EU Portal and Database (EUPD)



- The EUPD will **enable communication on clinical trials** in Europe, and will increase efficiency of **(multinational) CTs** conducted by creating **a single entry point** for application submission and approval
- **Functional specifications** adopted by the EMA Management Board in **2014**
- Development in **collaboration with Member States** and (since May 2019) **sponsors**
- EUPD will guarantee that many of the documents submitted will be **publicly available** under the **new transparency rules.**

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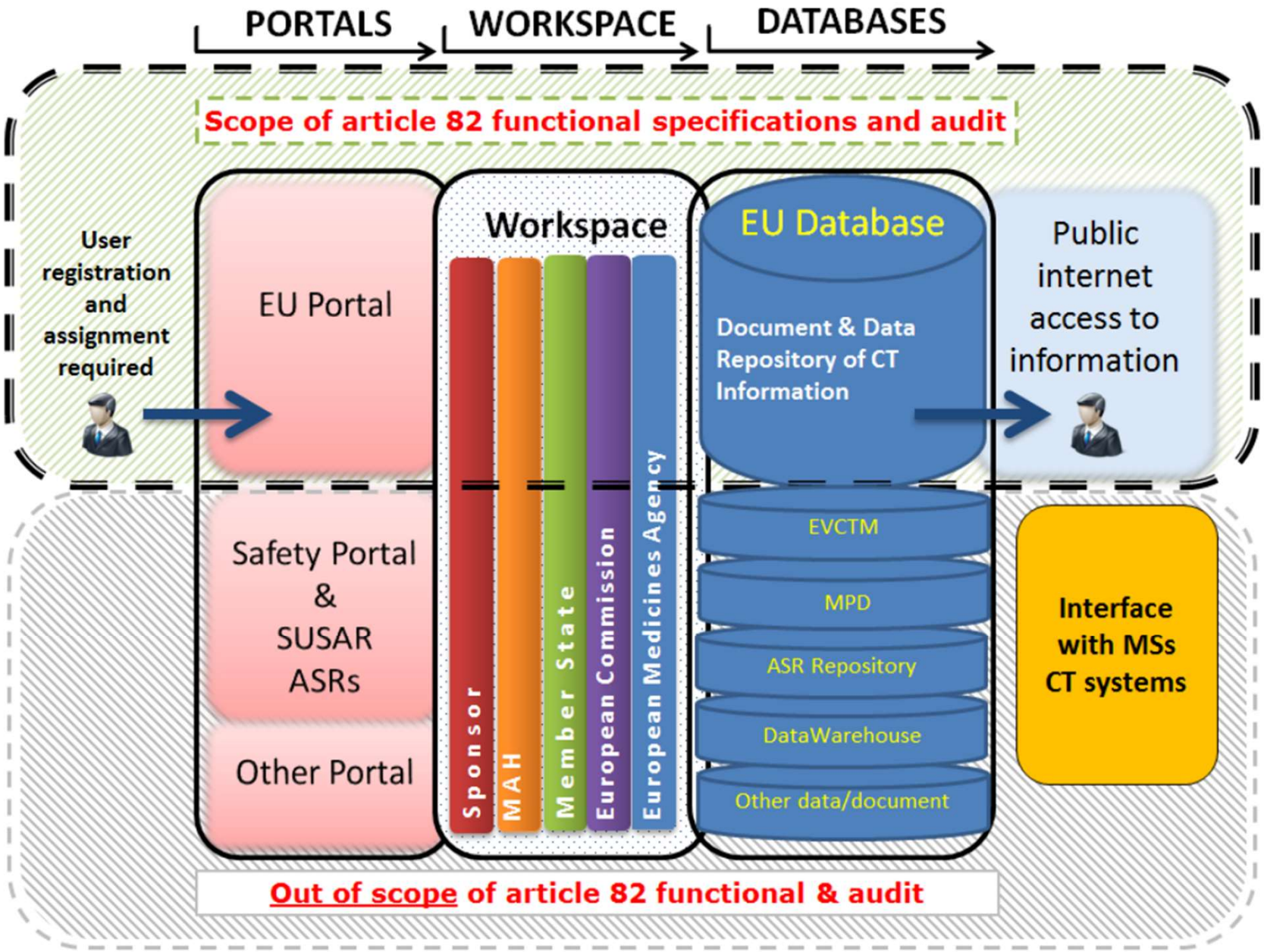

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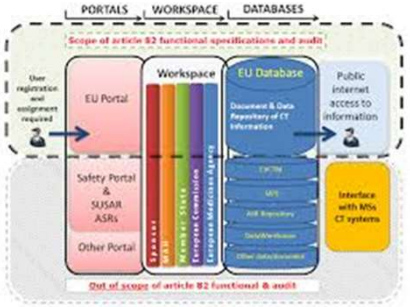
Clinical trial information System (CTIS)



- High-level functionalities:
  - ✓ **Sponsors**: application submission, supervision and update of information
  - ✓ **Member States**: authorisation of applications and supervision
  - ✓ **EU Commission**: supervision of regulatory systems in EU and in 3rd countries (union controls)
  - ✓ **General public:** access clinical trials information for transparency
  - ✓ **EMA**: database control

- **Additional key functionalities** are **not defined** in the CTR as being **part of the EUPD** (e.g. annual safety reports, reporting tools, link to the EudraVigilance database)

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CTIS - Timeframe

- **Article 99** clarifies that the CTR shall apply "**no earlier than 28th May 2016**" (6 months after successful audit of IT system).
- EUPD **audit started in November 2020**, first preliminary audit outcome was presented to the EMA MB on 23/02/2021.
- **Final audit outcome and confirmation of full functionality** of EUPD **expected in April 2021**
- **Go-live of CTIS and applicability of the CTR** likely to happen in **January 2022**

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Transparency

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Transparency

- The CTR requires **all information stored in the database to be publicly available**, unless exempted to protect:
  - **personal data**
  - commercially **confidential information**, in particular taking into account the marketing-authorisation status of the medicine, unless there is an overriding public interest
  - confidential **communication between Member** States in the preparation of their assessment
  - **supervision of clinical trials** by Member States

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Transparency

- **Disclosure rules** published in October 2015: EMA/42176/2014
- Includes descriptions of **what** and **when** documents may be made public depending on stage of development, type of trial (therapeutic vs non-therapeutic) and type of document. Publication rules based on three categories of trials
    - Category 1: Phase 1, bioequivilance / bioavailability / biosimilar trials
    - Category 2: Phase II and III (ie not Cat 1 or 3)
    - Category 3: Phase IV and low-intervention trials

Table 1:	**Overview of the timing of publication of data and documents from the clinical trial database in relation to the category of the trial as detailed in section 4.3.3** [a,b,c]		
	Category One **Phase I, Bioequivalence and Bioavailability trials and bio-similarity trials**	**Category Two** **Phase II and III trials, essentially those that are neither category one nor category three**	**Category Three** **Phase IV and low-intervention trials**
Date of decision on a trial, start of the trial, the first visit of the first subject, end date of subject recruitment, dates of temporary halts and end dates of the trial, (including early termination) (per member state, in the EU and globally as required).	Time when each date is posted in the database.		
Main characteristics of trial including WHO ICTRP data fields, cover letter and details of clinical investigators and their sites (including the summary CVs, statements of the head of the institution regarding the site and the statement regarding conditions such as economic interests and institutional affiliations that might influence the impartiality of the investigators)	Time of decision on trial.[d,c,r]		
	Sponsor may opt to have a restricted number of fields[e] made public at the time of decision on the trial and updated if applicable during the trial and defer the publication of the remainder to the time when the first summary results are made public.[c,f,g] The sponsor will be required to include a justification for the requested deferral.[h]		
Notifications occurring during	At the designated time for publication – see section 4.6 below for details		

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