



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clinical Trials Regulation (EC) No. 536/2014

Laura Pioppo, Scientific Administrator,
Clinical and Non clinical Compliance, EMA
SME workshop
20 March 2017





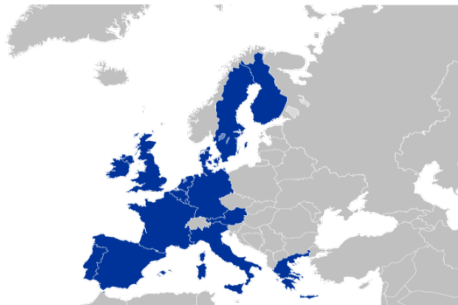
- Clinical Trials Regulation- What's new?
- Transition period from Directive 2001/20/EC to Regulation (EU) No. 536/2014
- EMA Portal and Database programme
- Portal and database project key timelines
- Transparency
- Conclusions



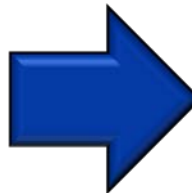
The Clinical Trial Regulation: what is new?

The Clinical Trial Regulation: what is new?

Before May 2004



Directive 2001/20/EC



Regulation (EU) No.
536/2014



Different [processes and requirements](#) for clinical trial authorisations in each Member States...

... resulted in [delays and complications](#) detrimental to effective conduct of clinical trials in the EU.

First step to harmonise [processes and requirements](#) for clinical trial authorisations.

Implementation
[1 May 2004](#).

[Concerns expressed](#) soon after its implementation.

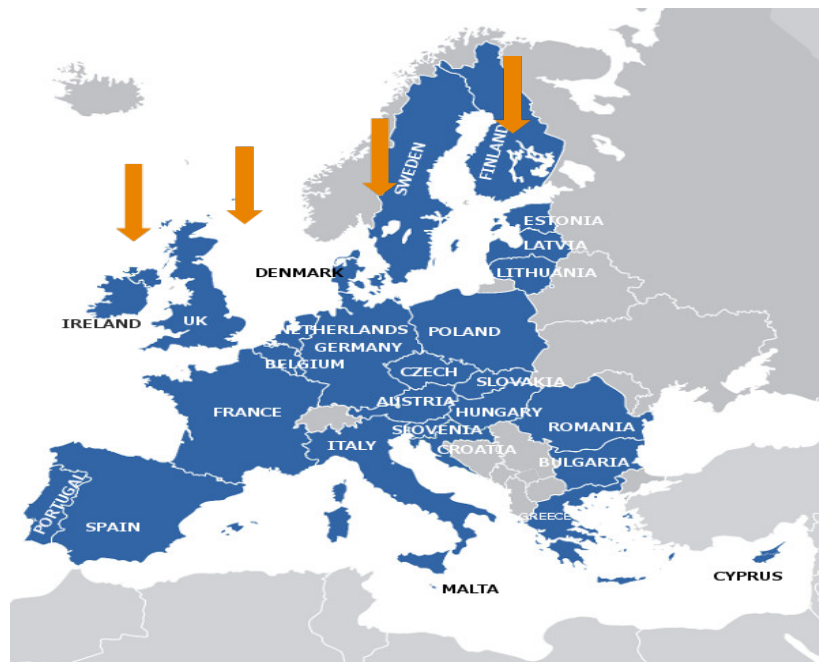
Published on
[27 May 2014](#).

[Application 6 months after](#) confirmation published in the OJ of [full functionality of EU portal and EU database](#), in any event [not earlier than 28 May 2016](#).

[Transitional arrangements](#).

Directive versus Regulation

Implemented in national laws



Directly applicable

Objectives of new CTR

- To protect the rights, safety, dignity and well-being of subjects and the reliability and robustness of the data generated in the CT;
- To foster innovation and simplify the clinical trial application process, in particular for multistate trials;
- To increase transparency, keeping the balance between protecting public health and fostering the innovation capacity of European medical research while recognising the legitimate economic interests of the sponsors.
- **Overall objective: Make EU attractive for R&D.**

- **Unchanged scope:**
 - **Interventional clinical trials with medicinal products for human use**
 - **NEW: new category of low-intervention clinical trials** with adapted requirements.
 - The investigational medicinal products (IMP) are authorised;
 - If the IMP is not used in accordance with the terms of the MA, that use is supported by published scientific evidence on S&E;
 - Minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.
- **Not covered:**
 - Non-interventional trials;
 - Trials without medicinal products (e.g. devices, surgery, etc).



- **Single e-submission to all MSCs** via an EU portal (accessible to MS NCAs and Ethics Committees);
- **Harmonised dossier** (Annex I to the Regulation / language of the documents decided by each MSC);
- **Coordinated assessment** between Reporting MS and MS Concerned;
- One **single decision** per Member State Concerned;
- Option to have **tacit decision** for the MS single decision (vs tacit approval in Dir. for NCA).



Official Journal of the European Union

ANNEX I

APPLICATION DOSSIER FOR THE INITIAL APPLICATION



- Introducing a **risk adapted approach** by applying less stringent rules to those trials conducted with medicines which are already authorised and which pose only minimal risk compared to normal clinical practice;
- **Increasing transparency** as regards clinical trials and their outcomes;
- **Simplifying safety reporting requirements**;
- **Reinforcing supervision of clinical trials** by introducing Union Controls in Member States and third countries to ensure that the Regulation is properly supervised and enforced;
- Provisions concerning **clinical trials conducted outside the EU** but referred to in a clinical trial application within the EU, which will have to comply with regulatory **requirements** that are at least **equivalent to those applicable in the EU**.



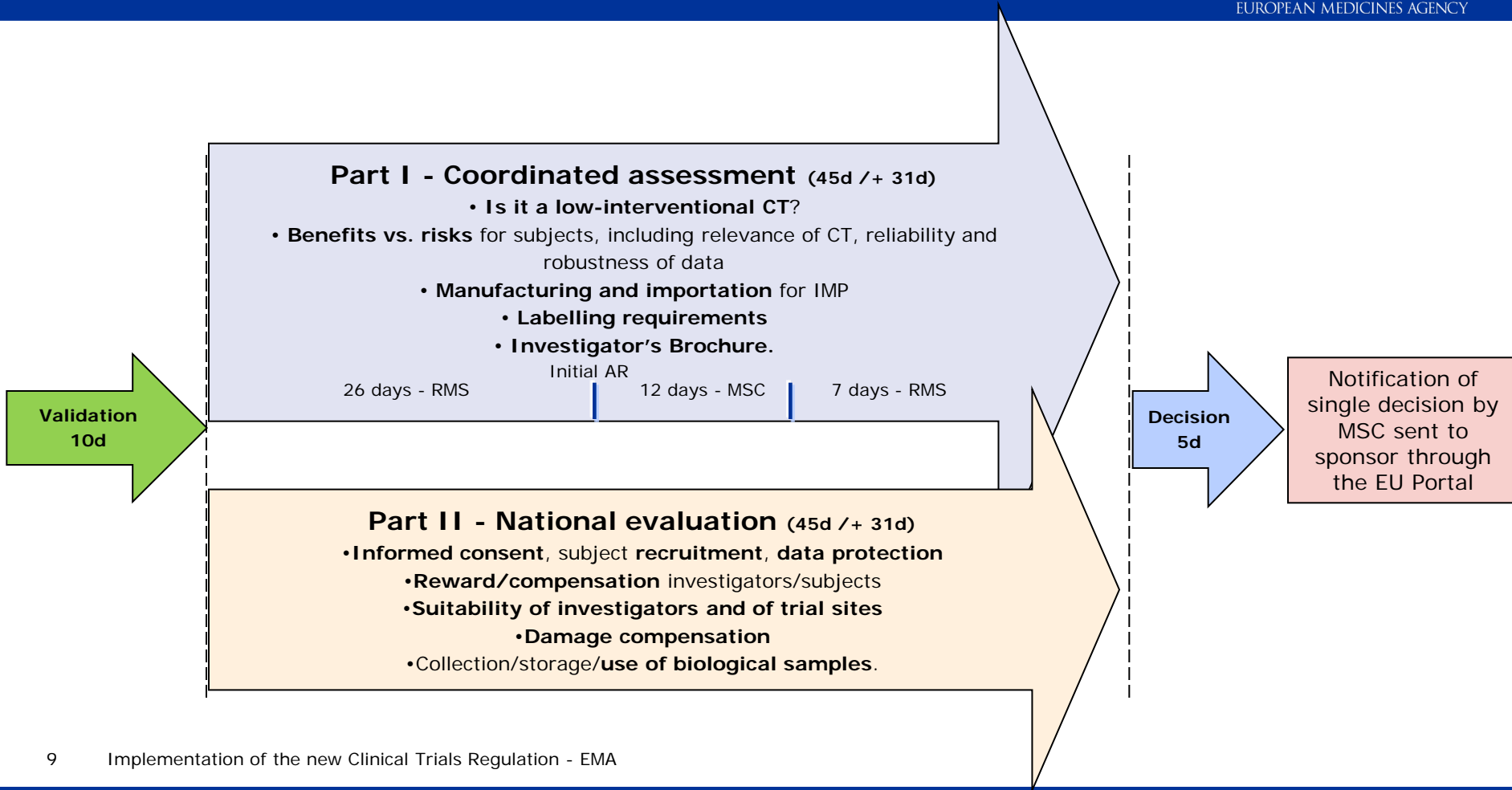
Official Journal of the European Union

ANNEX I

APPLICATION DOSSIER FOR THE INITIAL APPLICATION



- Introduce the concept of **Co-sponsorship**;
- **Informed consent** - new provisions for:
 - Broad consent (use of data outside the protocol)
 - Simplified consent for certain cluster trials
 - For trial in minors and incapacitated subjects
 - For trials on pregnant and breastfeeding women
 - Member States to maintain measures for other vulnerable groups (e.g. persons in military service, deprived of liberty)
 - Additional detail for conducting trials in the emergency setting
- Damage **compensation system** to be set up by the Member States
- Designation of **national contact points** by Member States
- Possibility for Member States to **levy a fee**
- **Archiving of the Trial master File** – 25 years





- **Reporting MS:** proposed by sponsor but proposal discussed between MSC;
- **Possibility to disagree with Part I conclusions** limited to:
 - ❖ CT will lead to patients receiving inferior treatment than normal practice in that MS;
 - ❖ Infringement of national law (e.g. CT of medicinal product forbidden in that MS);
 - ❖ Concerns as regards subject safety, data reliability and robustness.
- **Up to MS to decide who is involved in Part I and Part II** of the assessment (i.e. NCA/EC) to reach single decision;
- **Ethics Committee (EC) role and composition remains national decision**, it should take account view of **a layperson** and need to comply with procedure and timelines;
- **Refusal** : if part I/part II/both negative or if the national ethics committee has issued a negative opinion for that MS;
 - **Expiration** of the authorisation in a MSC if no subject included within two years.



As-is (Directive 2001/20) – EudraCT	To be (CT Regulation) - The EU portal and database
<ul style="list-style-type: none">• Multiple submissions for one trial (1 submission per each MSC*) /no harmonized dossier (e-submission limited to structured data and paper based submission)• Double submission within a MSC: to NCA and to Ethics Committees• Individual assessment by each MSC with no IT collaboration tool available • No single MSC decision (NCA & ECs)• Burden to NCAs in uploading information in the system• Limited EudraCT data availability to the public : structured data from the application (CTA) and summary of results	<ul style="list-style-type: none">• Single e-submission to all MSCs/harmonized dossier for one trial & e-submission of structured data and documents by MSCs • Joint assessment for Part I facilitated by collaboration tools • Single MSC decision• Distribution of the burden among users • View all CT related information <p style="text-align: right;">MSC* = member state concerned</p>



Transition period



Directive 2001/20/EC

Regulation (EU) No. 536/2014

3 year transition period

- Starts when Regulation becomes applicable
- First year: CT can be submitted under old (Dir.) or new (Reg.) systems,
- Years 2 & 3: trials authorised under old system remain under that system.

End of legacy

- All CTs to switch to new Regulation 3 years after implementation.



1. Before go live

- Any CTA submitted at this time, is still governed by the old Directive until 3 years after go live

2. Initial 12 months

- A CTA **may** still be submitted in EudraCT and governed by the old Directive
- A CTA **may** be submitted in the new EU portal and be governed by the new Regulation

3. Next 24 months

- All initial CTAs **must** be submitted in the new EU portal and be governed by the new Regulation

4. from 3 years after go live


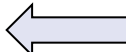
- **All CTAs are governed by the new Regulation**, regardless of their date of submission



The EU portal and database programme

The Agency has to deliver, maintain and update the IT platforms needed for the implementation as required by Regulation:

Article 81(1) "The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a EU database at Union level. The Agency shall be considered to be the controller of the EU database and shall be responsible for avoiding unnecessary duplication between the EU database and the EudraCT and Eudravigilance databases."

- **EU Portal and database project** (Art. 80, 81, 82 and 84) 
- **Safety Reporting project** (Art. 40 to 44) 
- EudraCT and EU Clinical Trial Register Legacy project (Art. 98)
- A data warehouse is part of these developments to facilitate the reporting tools between the different systems

EU Portal and database project



Submit submission package (CTA & dossier) / Address request for information

Update of Clinical Trial information re non substantial modifications

- Withdrawal
- Start of trial
- First visit first subject
- End of recruitment
- End of trial (in each MS, All MS, Global)
- Temporary halt
- Restart of trial
- Early termination
- Serious Breaches
- Unexpected events which


Submission of clinical study result summary

Submission of Inspection Reports of third country authorities

Submission of CSR

Submission of Union Control Reports


Applicant of a MA 

Commission 

 Sponsors

Member States

 General public

Search and view CT information 

 EMA

System Maintenance

Notification of willingness to be RMS(Part I)/ Decision on RMS

Submission of requests for information

Notification of the final validation (initial, additional MS or Substantial Modification)

Submission final AR Part I and II

Final single decision notification

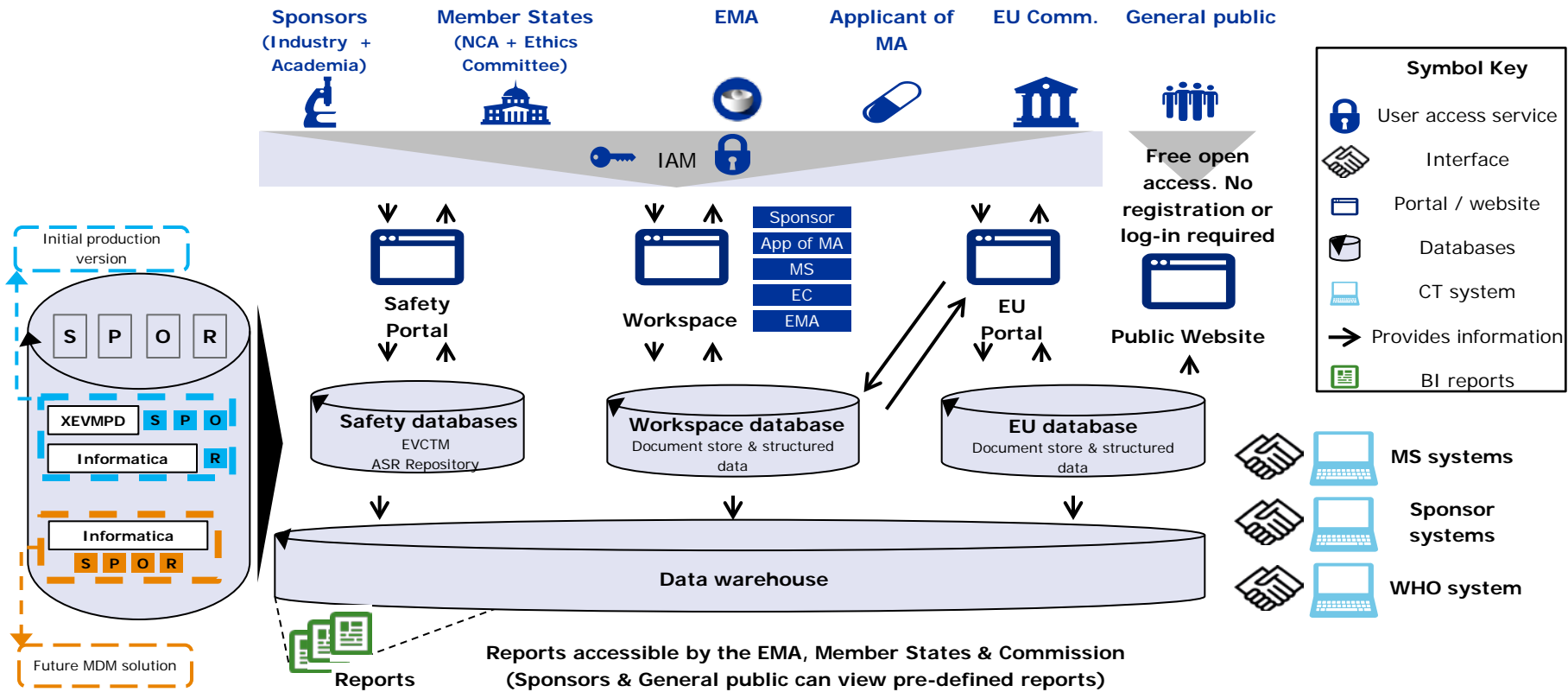
Submission Inspection Information

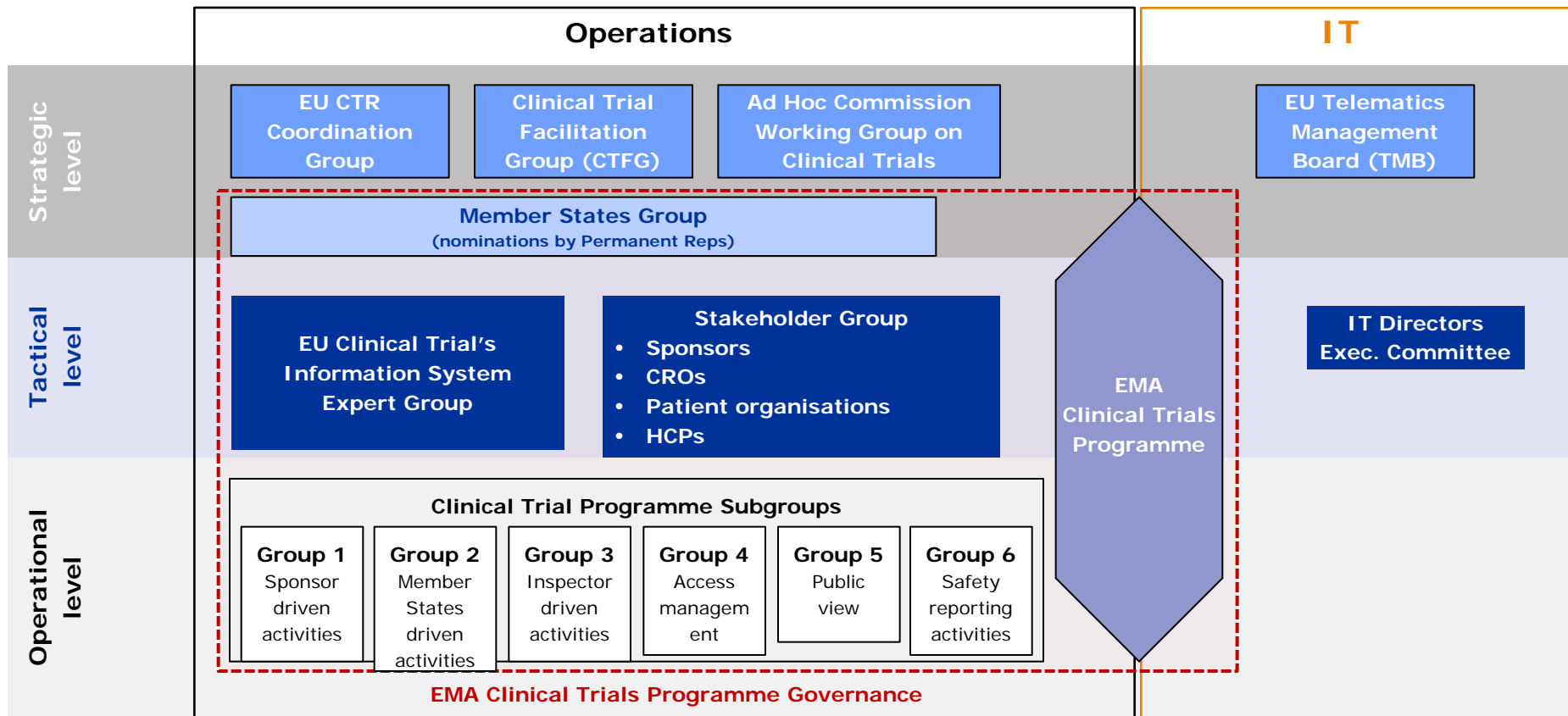
Communication disagreement to Part I assessment

Communication on implementation of corrective measures



This diagram depicts the To-Be system architecture for the clinical trial systems:

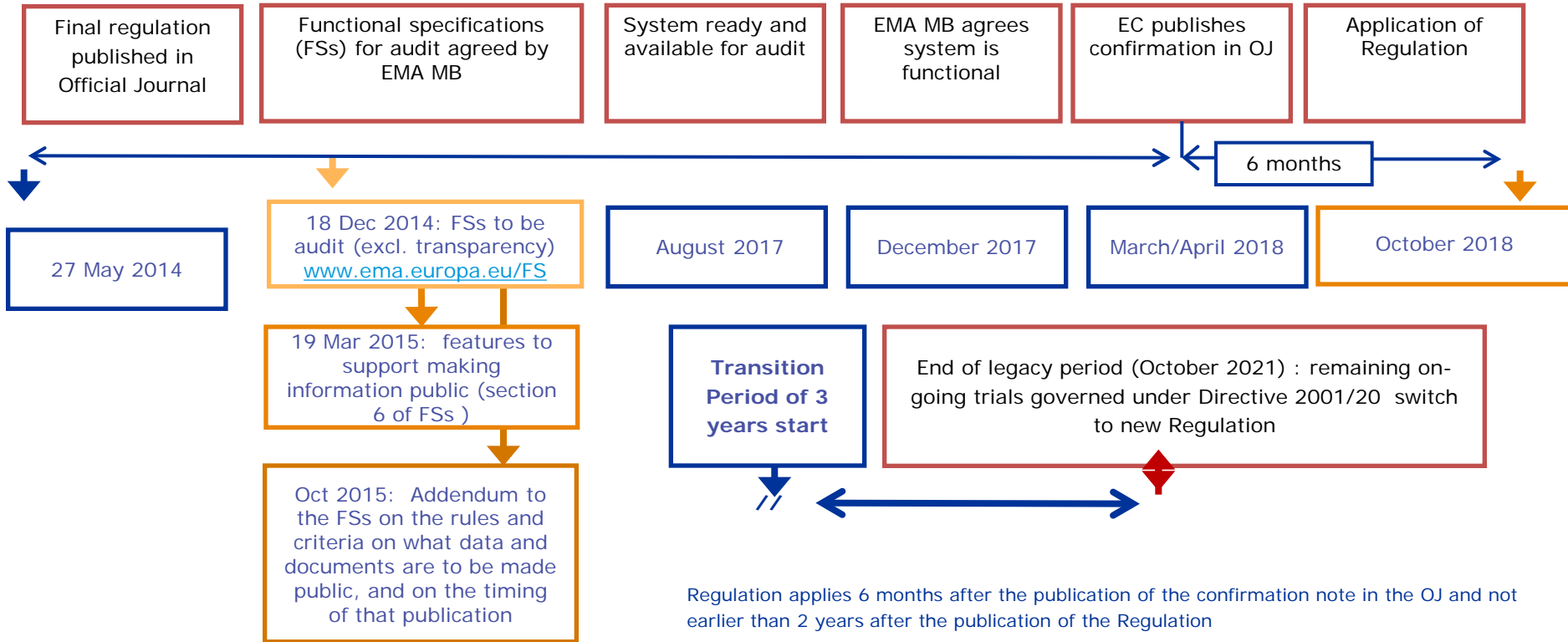






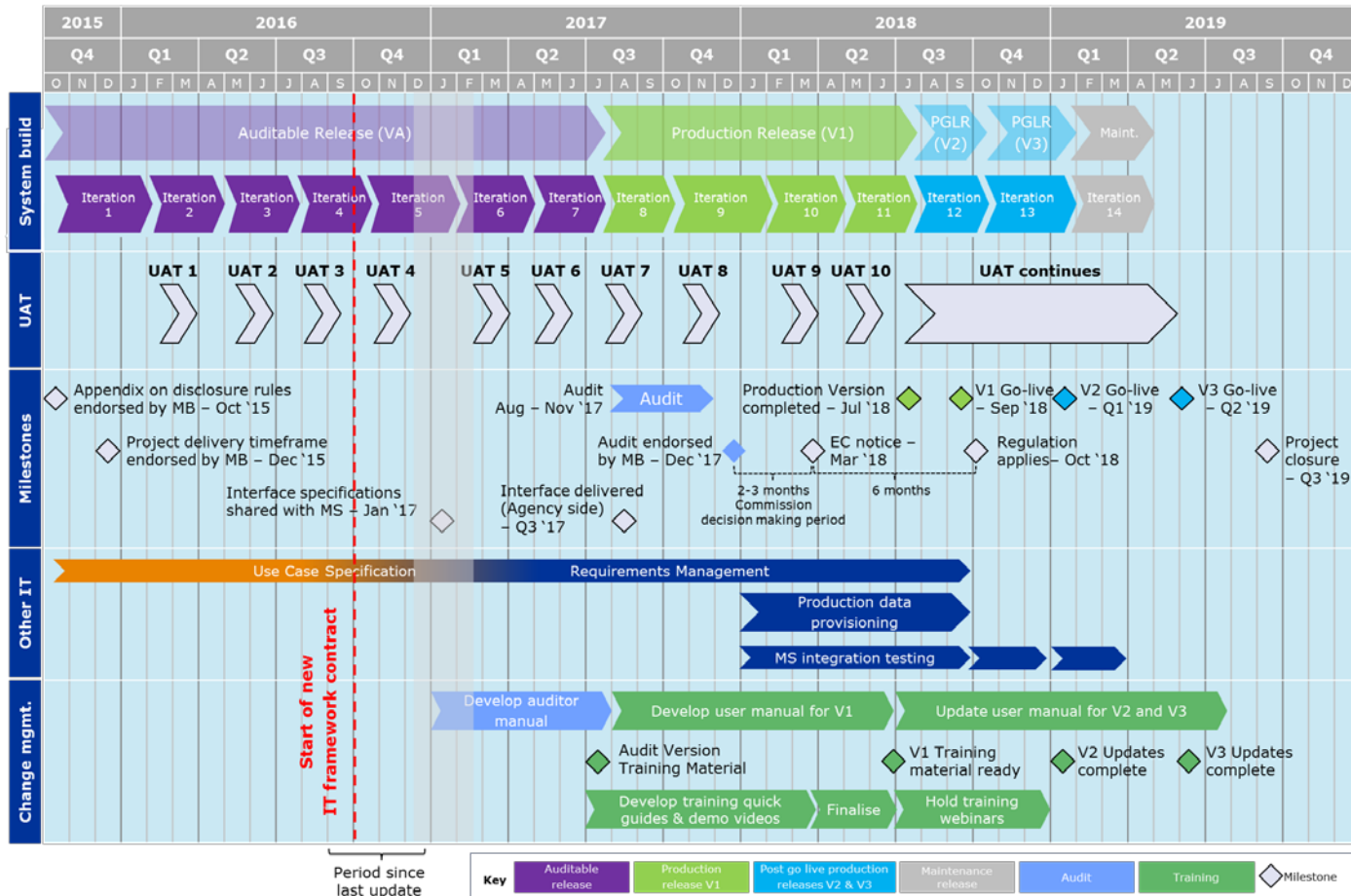
Key timelines for development

CT regulation timelines/key milestones



EU Portal and Database - Maximum project timeline

as per the delivery time frame endorsed at Dec '15 Management Board





Transparency

Article 81(4) of Regulation (EU) No. 536/2014

- EU database publically accessible by default, with exceptions justified on any of the following grounds:
 - Protection of personal data;
 - Protection of commercially confidential information in particular taking into account the MA status of the medicinal product, unless there is an overriding public interest in disclosure;
 - Protecting confidential communication between MS in relation to the preparation of the assessment report;
 - Ensuring effective supervision of the conduct of a clinical trial MSs.



- Only applications on which a decision has been reached will be made public;
- All data and documents in the system will be made public with few exceptions;
- The default is always to make public at the first opportunity;
- Sponsors have options to defer the timing of publication of specific data/documents (use of deferrals will be monitored);

- To enable public access to the database, rules for the application of the exceptions, set out in Article 81(4), are required. These rules are set out:
 - The addendum, on the disclosure rules, to the "Functional Specifications for the EU Portal and DB to be audited"
 - A balanced approach is needed to protect public health and also foster the innovation capacity of European medical research:
 - respecting patients' and doctors' needs and the public's entitlement to extensive and timely information about clinical trials;
 - and developers' and researchers' need to protect their investments;

- Is there a trial in which I could participate?
- What was the outcome of the trial I did participate in?
- What trials were the basis of the marketing authorisation, what were their results?
- What is known about the medicine I am taking/prescribing?
- Can we review the data used to support the marketing authorisation?
- Has the trial we are designing already been conducted? Were there problems with similar trials?



- The IMPD quality section will not be made public as it remains commercially confidential even after the marketing authorisation has been given;
- Draft assessment reports (outside the EU database);
- Names of the Member States experts (outside the EU database);
- Personal information identifying sponsor staff (protection personal data);
- Personal information identifying MAH/applicant (protection personal data);
- Direct contacts of clinical investigators, sponsors or MAH personnel (protection personal data);
- Agreements between the sponsor and the investigator site;
- SUSARs and Annual Safety Reports (outside the EU database- in EV).



Conclusions

- **Harmonisation:** One single submission for authorisation of a clinical trial to National Competent Authority & Ethics Committee and for public registration (primary register of clinical trials);
- **Member state collaboration:** Facilitate cooperation among MSCs in assessing a request for authorisation of a clinical trial;
- **One single decision** per Member States;
- **IT maintenance:** EMA in charge maintain and update the IT platforms;
- **Public data** and information about medicines, their development
 - To generate trust – information is available
 - To build confidence – I understand what is happening
 - To empower – knowledge enables decision-making





Thank you for your attention

Further information

laura.pioppo@ema.europa.eu

European Medicines Agency

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom

Telephone +44 (0)20 3660 8449 **Facsimile** +44 (0)20 3660 5555

Send a question via our website www.ema.europa.eu/contact

Follow us on  **@EMA_News**