CTR & CTIS

Key Aspects for users to consider when preparing for CTIS

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Clinical Trials Regulation 536/2014 (CTR)

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27.5.2014 EN Official Journal of the European Union L 158/1

I

(Legislative acts)

REGULATIONS

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 April 2014

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

(Text with EEA relevance)

TBD:
- Implementing and Delegated Acts
- Guidelines

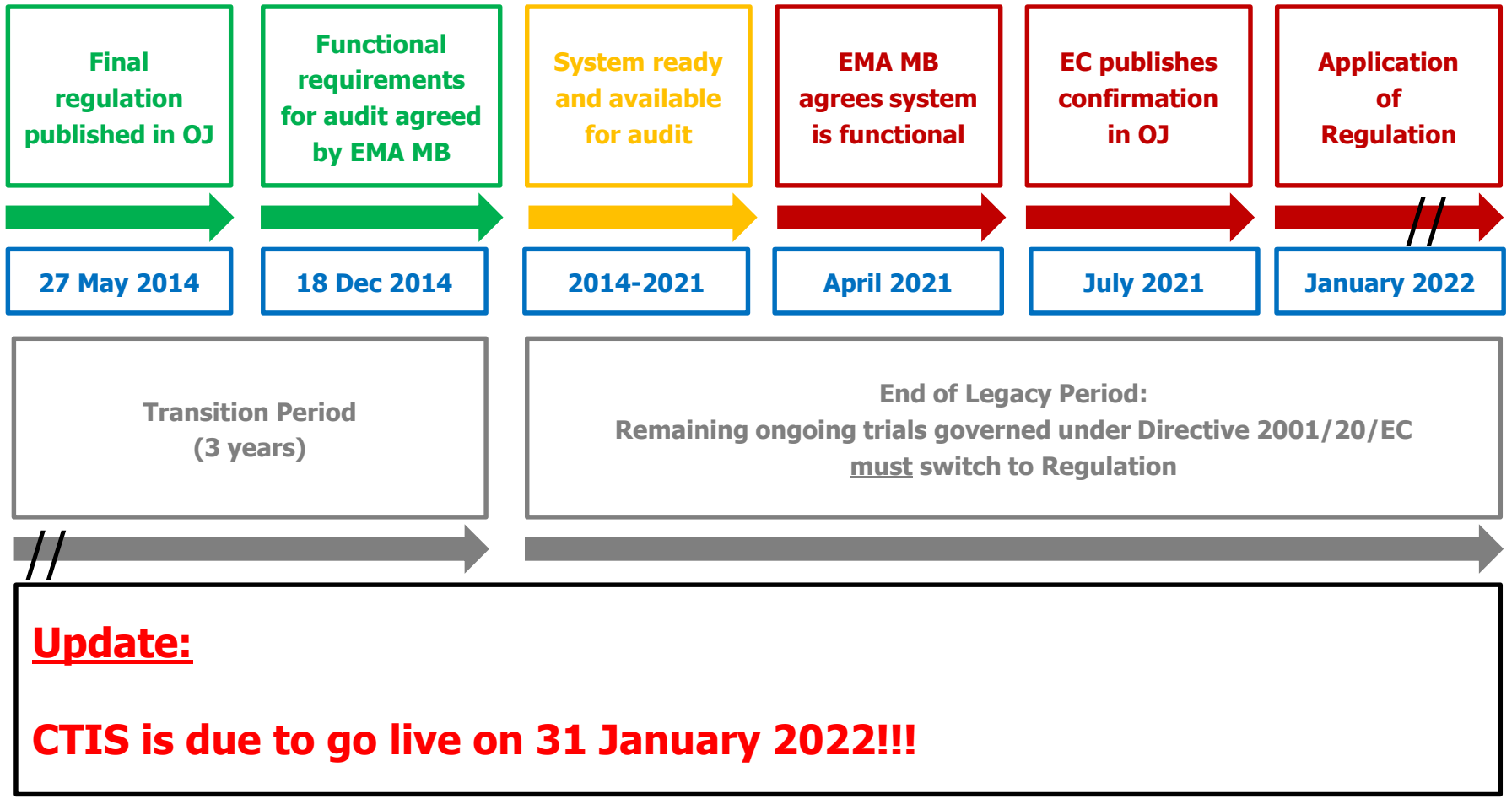
http://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=OJ:JOL_2014_158_R_0001&from=EN

http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_158_R_0001&from=EN

CTR in a nutshell

- **New definitions**
- **Harmonised dossier - "Part I" (global) and "Part II" (national)**
- **Centralised system** for submission (managed by EMA)
- **Competitive timelines** (transparent, reliable, short)
- Worksharing between **"Reporting Member State (RMS)"** and **"Member States Concerned"**
- Process for **"single decision"** is within the remit of the MSC (NCA & EC)
- Fully electronic process via **EU Portal & EU Database**
- Documents and information **public by default**

Milestones of the CTR



https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

CTIS High Level Structure

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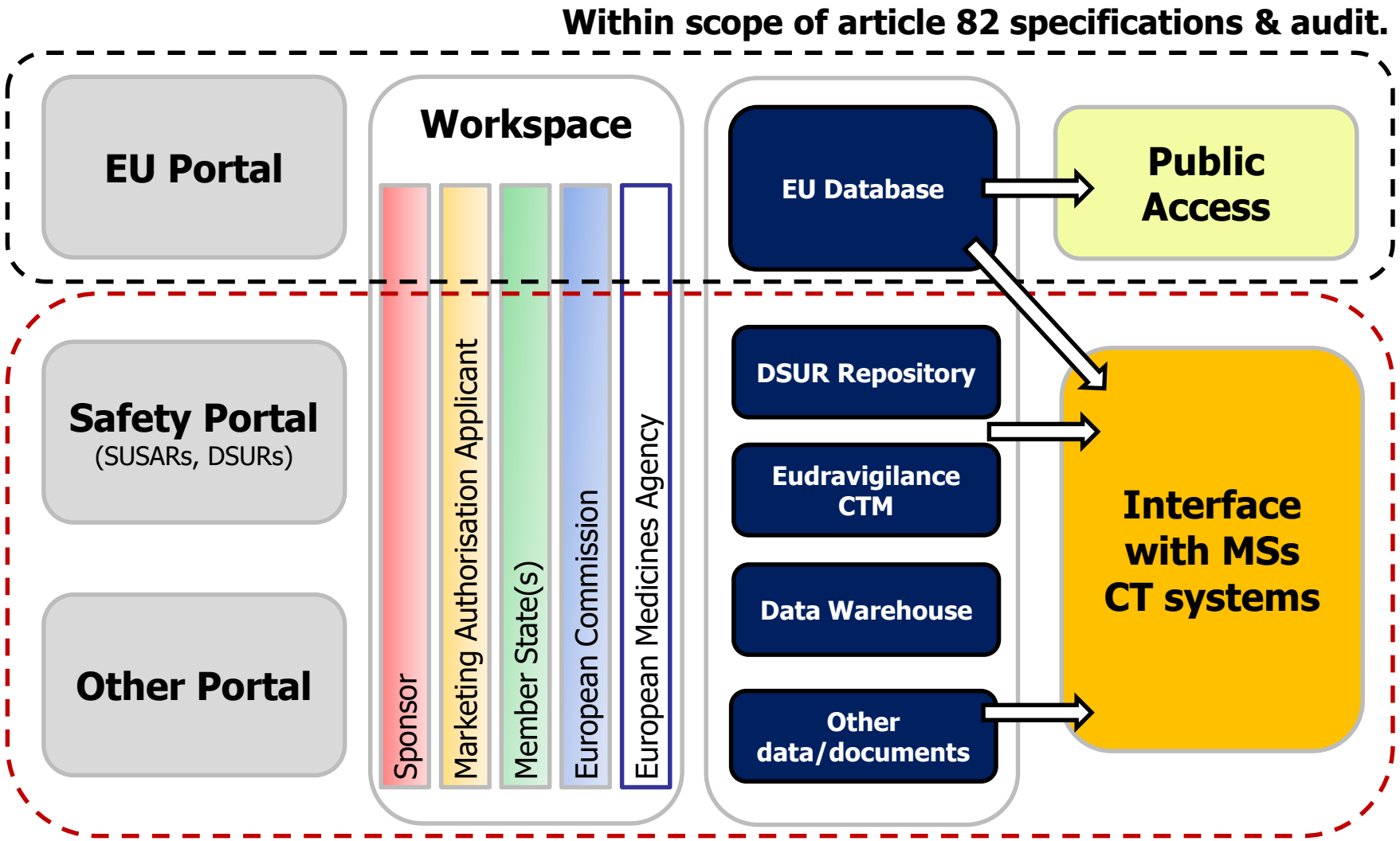

SUSAR = Suspect. Unexp. Adverse Event
ASR = Annual Safety Report

CTIS Roles & Actions

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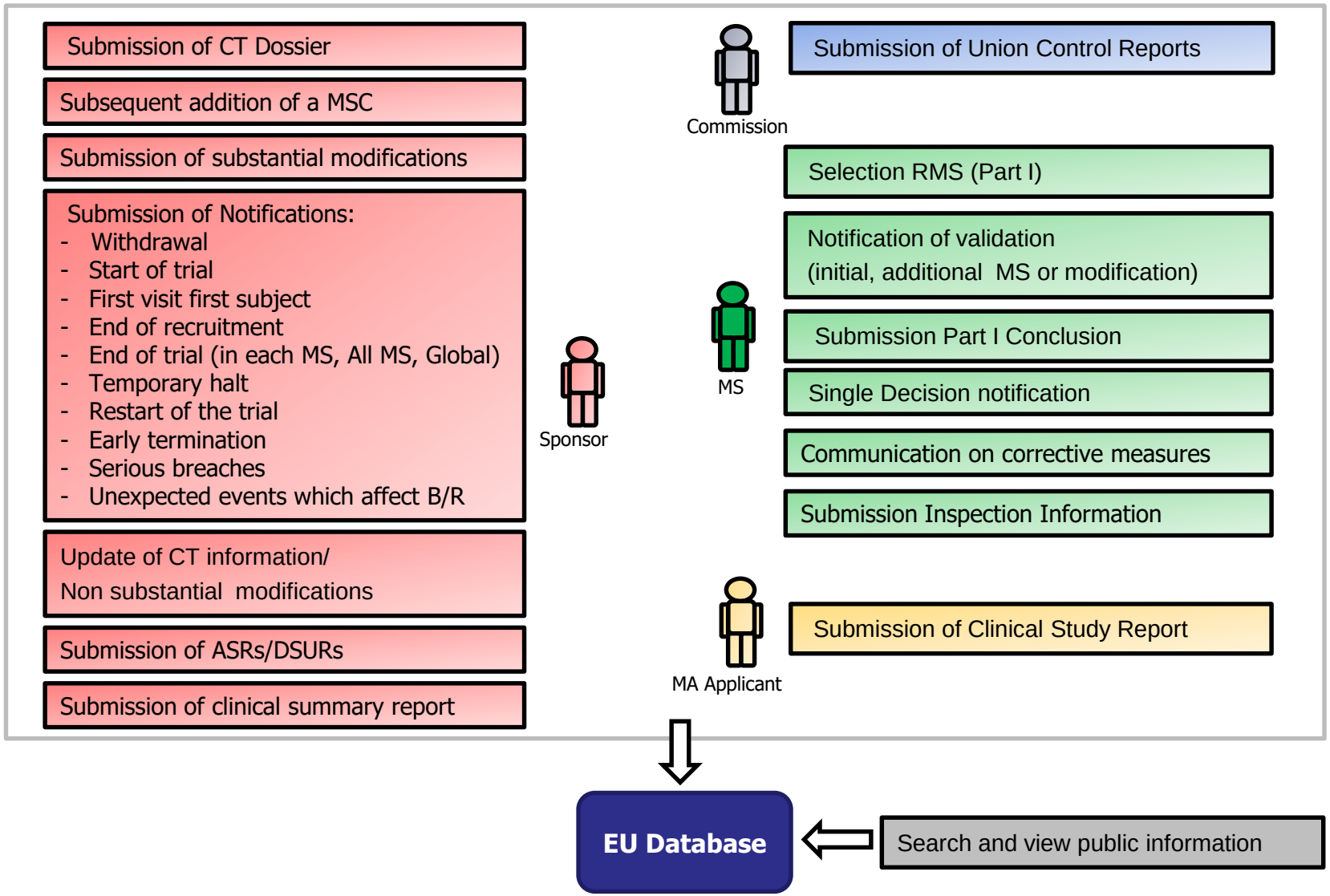

Define your role…

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CTIS is a **role-based system**

It enables users to perform different actions depending on the **permissions** attached to the **roles** assigned to them by a user from their organisation or Member State with administrator permissions.

→ Permissions:

Predefined levels of actions that users can perform on data and documents stored in CTIS.

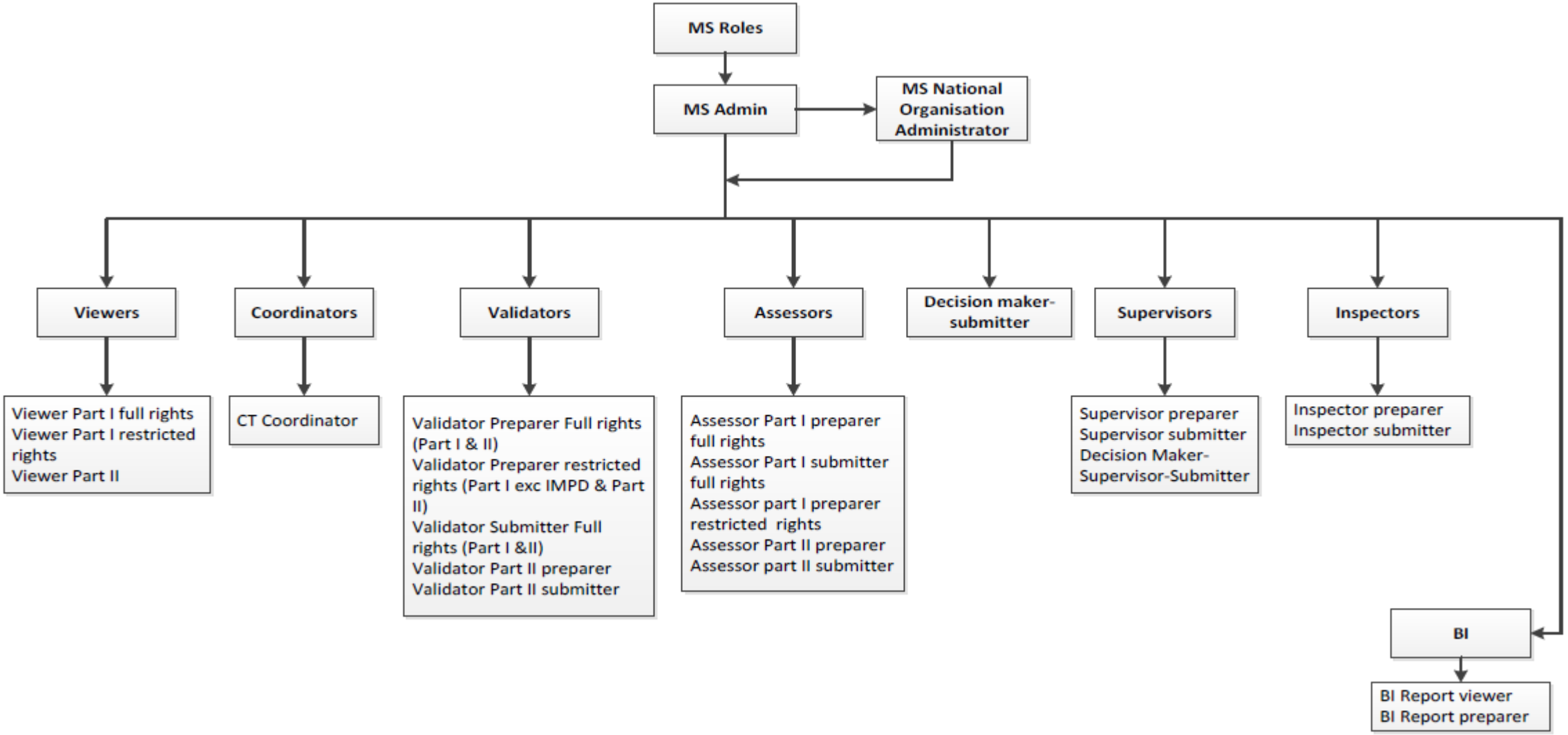
- *Business permissions*
- *Access level permissions (View, Prepare and Submit)*
- *Other permissions*

→ Roles:

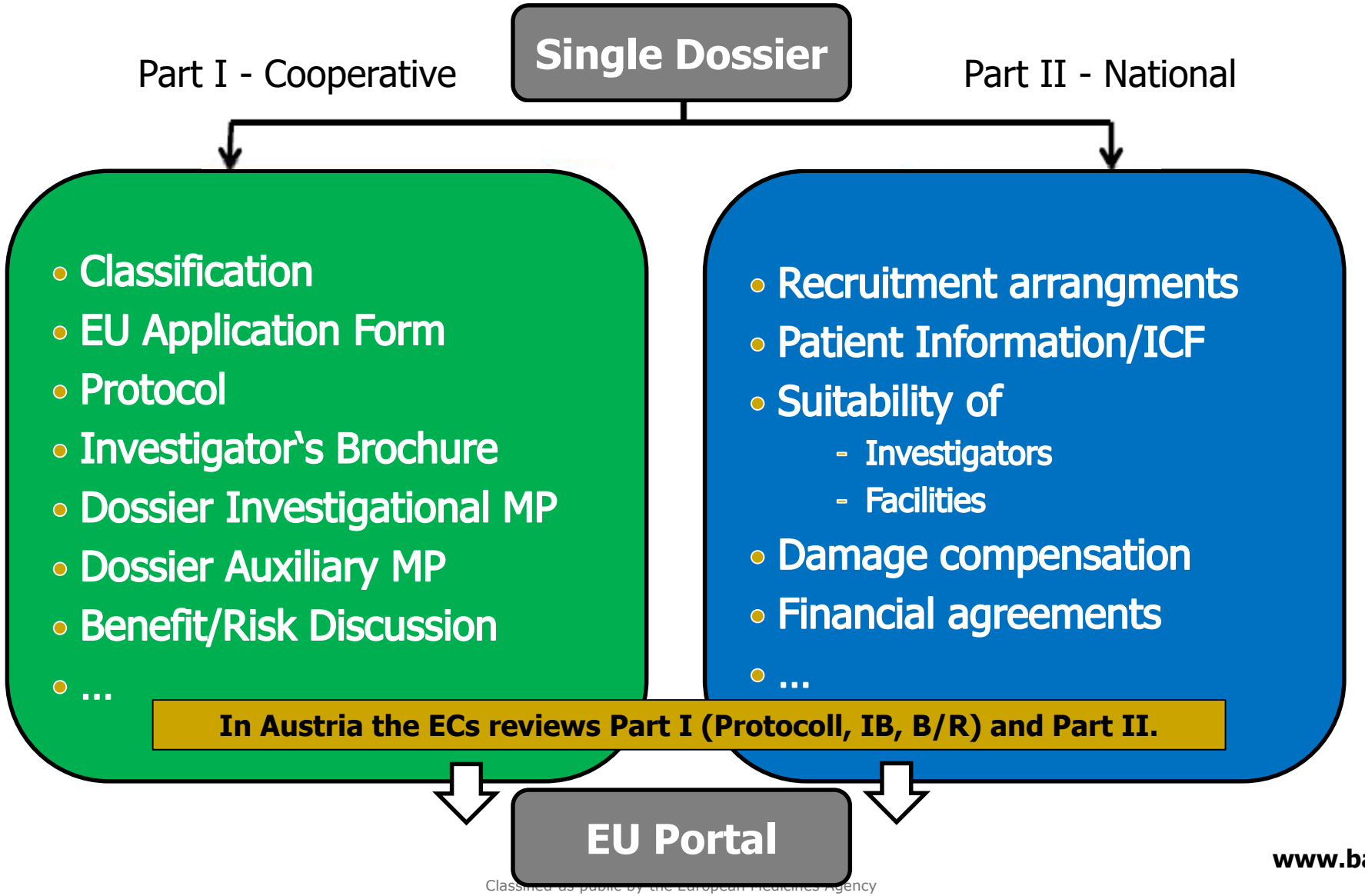
Predefined **group of actions** that users are able to perform in CTIS regarding a clinical trial application, or regarding data and documents submitted during the trial life cycle, in accordance with their responsibilities.

- ***Administrator roles*** *which are able to assign roles to other users*
- ***Business roles****, reflecting the responsibilities of users during the life-cycle of a clinical trial. They are assigned by administrator users and are attached to the permissions described above.*

… for your permissions!



The Harmonised Dossier



CTR Assessment Process

Part I – Global Aspects
Lead:
Reporting Member State (RMS)

Dossier (Part I & II) Submission to CTIS

Part II – National Aspects
Lead:
Member State Concerned (MSC)

Confirmation of RMS and Validation

Part I (Draft) Assessment by RMS
Discussion with CMS & Consolidation
List of Questions to applicant
Response Assessment & Discussion
Part I (Final) and Conclusion

Acceptable w/wo conditions

Not acceptable

MSC accepts RMS conclusion
or
opts-out
1) Inferior Rx compared to clinical practice in MSC
2) Infringement of national legislation
3) Concerns for patient safety or data reliability

Part II Assessment by MSC
List of Questions to applicant
Response Assessment by MSC
Conclusion

MSC combines Part I and Part II conclusion into the National decision.

Single Decision per Member State – Notification via EU Portal

„Where the MSC has not notified the sponsor […] the conclusion on Part I shall be […] the decision of the MS for authorisation of the clinical trial.

Timelines

Validation	Part I assessment	Part II assessment	Decision	Total
Initial CTA				
10 days (+10/+5)	**45 days** (+12/+19)	Same as Part I	**5 days**	**60 days** (max. 106 days)
Additional MS				
N/A	**52 days** (+12/+19)	Same as Part I	N/A	**52 days** (max. 83 days)
Substantial Modification				
6 days (+10/+5)	**38 days** (+12/+19)	Same as Part I	**5 days** (Pt I) **N/A** (Pt II)	**49/44 days** (max. 95/90 days)

Time for the sponsor to respond to questions
Time for the RMS and CMS to assess and discuss responses

Changes during the lifecycle

- **Subsequent addition of another MSC (Art. 14)**

- **Substantial modification for Part I (Art. 17-19)**
  e.g. protocol, IB, IMPD

- **Substantial modification for Part II (Art. 20)**
  e.g. patient information, insurance, trial site, investigator

- **Substantial modification for Part I and II combined (Art. 21-23)**
  e.g. protocol and patient information

When can a SM/new MSC be submitted?

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- The definition of a SM in the Clinical Trials Regulation (article 2(2)13) implies that a SM request can be considered **only after a decision is taken** on
  - an initial application or
  - an application for substantial modification or
  - an addition of a Member State concern

„You can only change the course when the water is calm."

- This implies that **no SM request can be assessed while any assessment is on-going** (be it an assessment of an initial application, a request to add a Member State concerned (MSC) or a request for another SM).
- Therefore, the **SM can be assessed only after the decision on the previously submitted application is issued or authorized by tacit approval**.

Attention!

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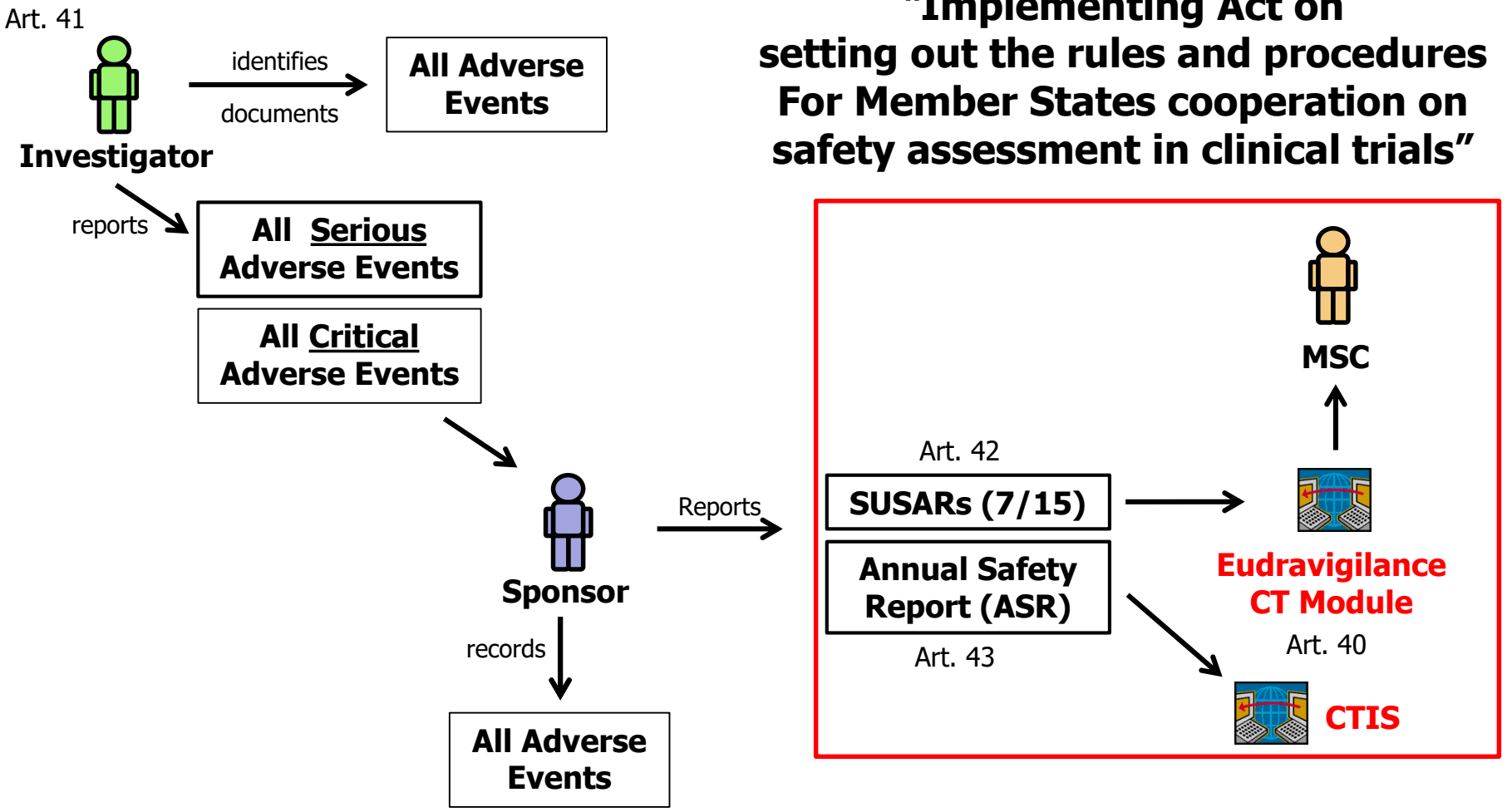
- Substantial modifications are a critical process in the life-cycle of a trial.
  - Changes for reasons of patient safety
  - Changes for reasons of validity and reproducibility of trial results
- There can only be one SM within the same scope at one time
  → might lead to more combined SM (protocol/IB, protocol/IMPD etc.)

- **There is no partial approval of a combined SM!**
- **RMS and MSC have to make sure that via the RFI either all questions are resolved or unacceptable changes are removed.**
- **Otherwise it will lead to withdrawal or rejection.**

Safety Reporting



EMA plans to develop a web-based reporting tool.

Notifications

- **Start of the CT in each MS**
- **Inclusion of first patient in each MS**
- **End of recruitment in each MS**
- **National end of CT in each MS**

- Temporary halt and reasons to each cMS (max. 2 years)
- Restart after temporary halt to each cMS (SM when halt was due to safety)
- Early termination to each cMS

- **End of CT in EEA to all MSC**
- Global end of CT (including 3rd countries) to all MSC

Summary & Full Study Report

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- **Within 1 year from the end of the CT** in all MSC or longer, if previously justified in the protocol
- **Summary of results** according to Annex IIIa
- **Summary for lay persons** according to Annex IIIb

- CT used for marketing authorisation (MA) → submit clinical study report within 30d of
    - MA granted
    - decision-making process on MA completed, or
    - application for MA withdrawn

Transparency in the CTR

Article 81 (4), Regulation (EG) Nr. 536/2014

The EU database shall be **publicly accessible unless**, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:

(a) protecting **personal data** in accordance with Regulation (EC) No 45/2001;

(b) protecting **commercially confidential information**, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure;

(c) protecting **confidential communication between Member States** in relation to the preparation of the assessment report;

(d) ensuring effective **supervision of the conduct** of a clinical trial by Member States.

Recitals 67 und 68

Summary of rules

- All information is **public by default** unless and only if an exception applies.
- Publication at the **earliest possible time**
- All trials publicly **registered at the start**
- All **summary reports available**
- Some exceptions/restrictions for **Category 1** trials
- Publication can be **deferred by the sponsor (optional)**
- Use of deferral will be **monitored by the commission**

Example (IMPD)

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	Category One	Category Two	Category 3
IMPD S and E sections Investigator Brochure	Default – time of decision on the trial. Sponsor may defer **up to** maximum of 7 years after the end of the trial or the time of MA using this trial if earlier Versions used at time of CT decision made public	Default – time of decision on the trial. Sponsor may defer **up to** maximum of 5 years after the end of the trial or the time of MA using this trial if earlier Versions used at time of CT decision made public	Default – time of decision on the trial. Sponsor may defer **up to** time when summary of results is made public (Justification required of which summary made public immediately)
IMPD Q section, and related assessment reports, request for additional information…	IMPD Q section will not be made public.	IMPD Q section will not be made public.	IMPD Q section will not be made public.
Assessments reports List of questions Sponsor responses	Default – time of decision on the trial. Member State will decide when to make public taking into account the exceptions of the legislation and the time proposed by the sponsor	Default – time of decision on the trial. Member State will decide when to make public taking into account the exceptions of the legislation and the time proposed by the sponsor	Time of decision on trial

Appendix, on disclosure rules, to the 'Functional specifications for the EU portal and EU database to be audited
http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500195084

Overr

NATURE | BREAKING NEWS

Scientists in the dark after French clinical trial proves fatal

Knowledge about the drug's structure would help researchers understand what happened.

Declan Butler & Ewen Callaway

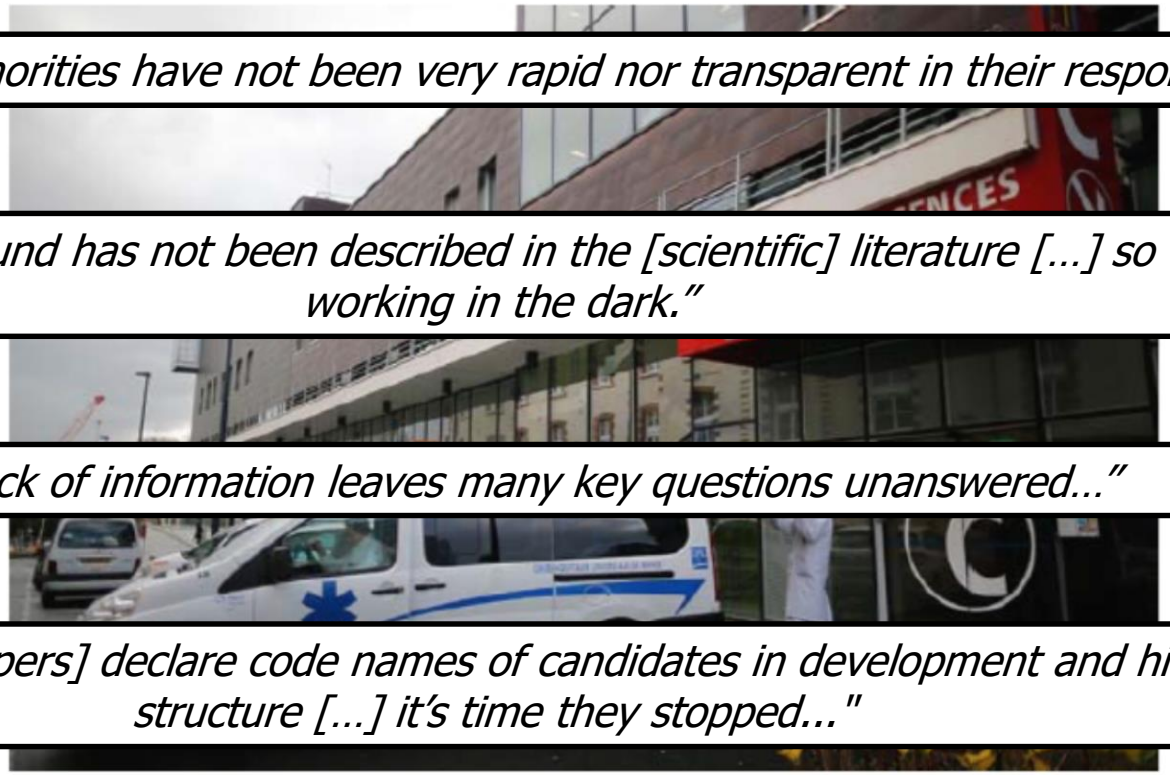
18 January 2016

"… French authorities have not been very rapid nor transparent in their response..."

"…this compound has not been described in the [scientific] literature […] so we're working in the dark."

"…a lack of information leaves many key questions unanswered…"

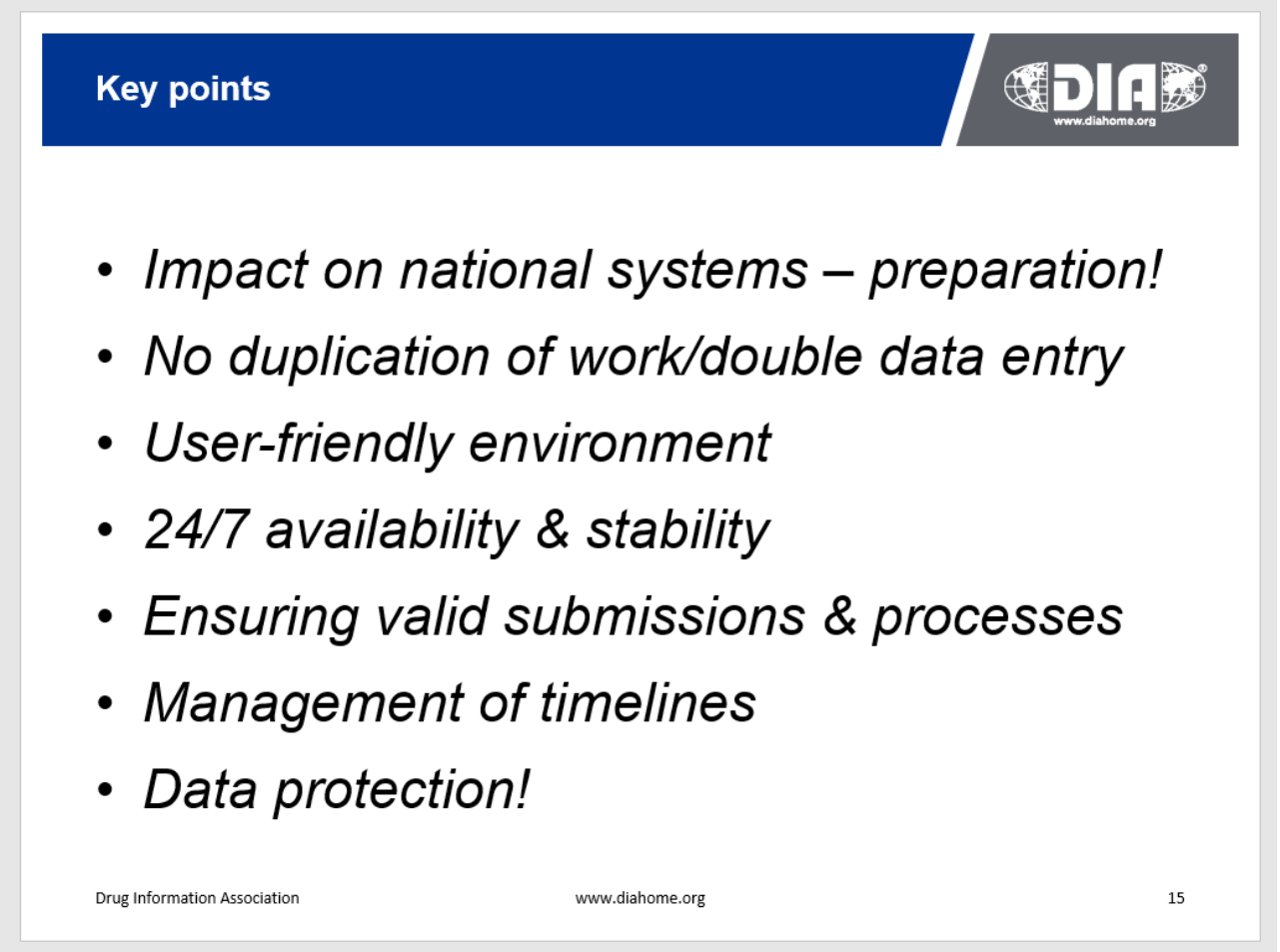
"…[drug developers] declare code names of candidates in development and hide the structure […] it's time they stopped..."



Stephane Mahe/Reuters

The hospital in Rennes where six people were taken after taking part in a Phase 1 clinical trial.

Once upon a time – in 2014!



Do you want to know more?

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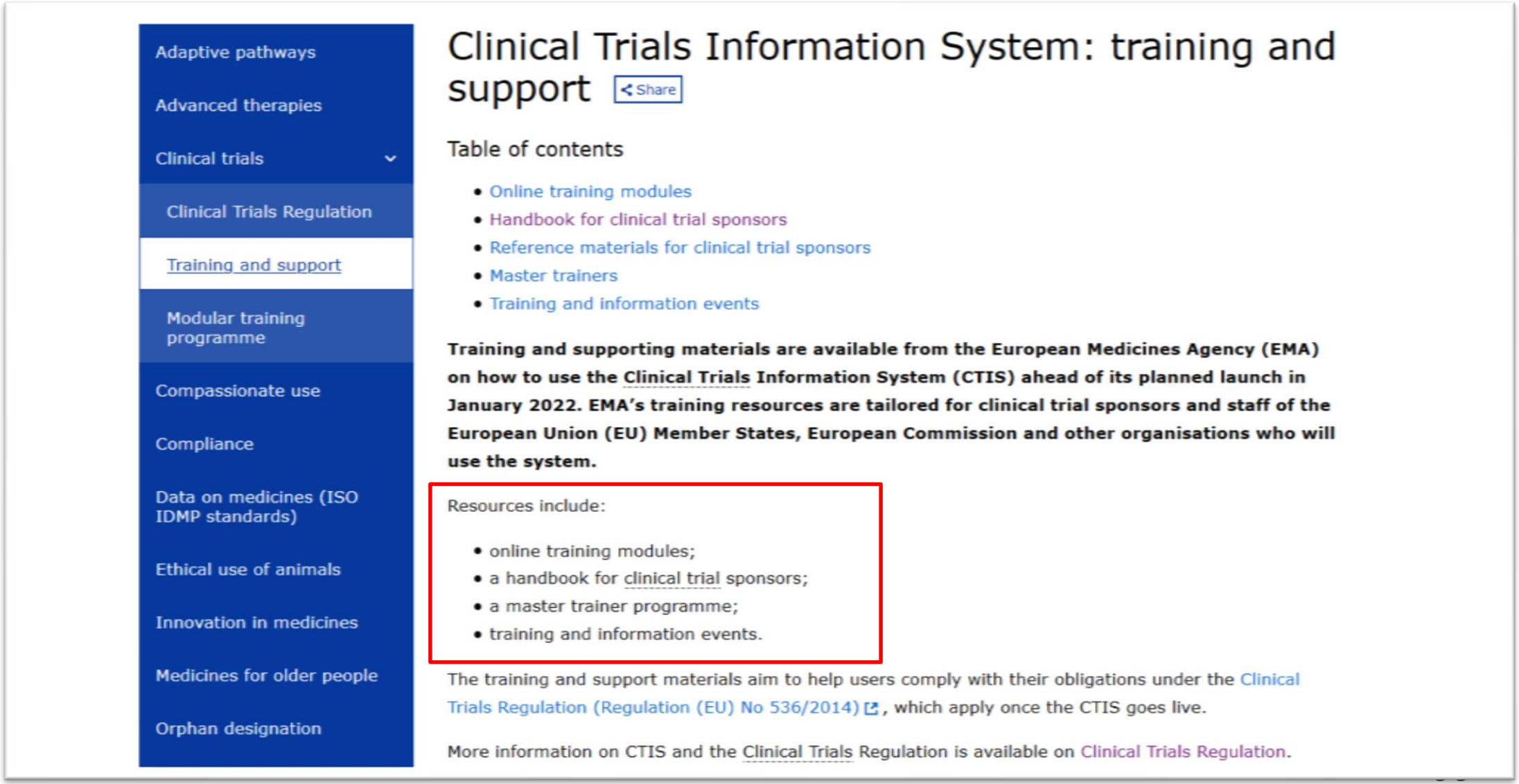
https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-



Adaptive pathways
Advanced therapies
Clinical trials
Clinical Trials Regulation
Training and support
Modular training programme
Compassionate use
Compliance
Data on medicines (ISO IDMP standards)
Ethical use of animals
Innovation in medicines
Medicines for older people
Orphan designation

Clinical Trials Information System: training and support

Share

Table of contents

- Online training modules
- Handbook for clinical trial sponsors
- Reference materials for clinical trial sponsors
- Master trainers
- Training and information events

Training and supporting materials are available from the European Medicines Agency (EMA) on how to use the Clinical Trials Information System (CTIS) ahead of its planned launch in January 2022. EMA's training resources are tailored for clinical trial sponsors and staff of the European Union (EU) Member States, European Commission and other organisations who will use the system.

Resources include:

- online training modules;
- a handbook for clinical trial sponsors;
- a master trainer programme;
- training and information events.

The training and support materials aim to help users comply with their obligations under the Clinical Trials Regulation (Regulation (EU) No 536/2014), which apply once the CTIS goes live.

More information on CTIS and the Clinical Trials Regulation is available on Clinical Trials Regulation.