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Clinical Trials Regulation – An Update

Thomas Sudhop, BfArM

Clinical Trials in the EU – A long journey

Before May 2004

National rules only, no harmonisation within the EU

- Paper based submission
- CT authorisation mainly by ethics committees (favourable opinion)
- National competent authorities (NCA) not in all Member States (MS) involved

Directive 2001/20/EC

(since May 2004)

First harmonisation step, but still many national specificities

- Electronic application form but otherwise paper based submission
- Both, NCA + ethics committee (EC) involved, but work independently of each other and issue own decisions

Regulation (EU) No 536/2014 (CTR)

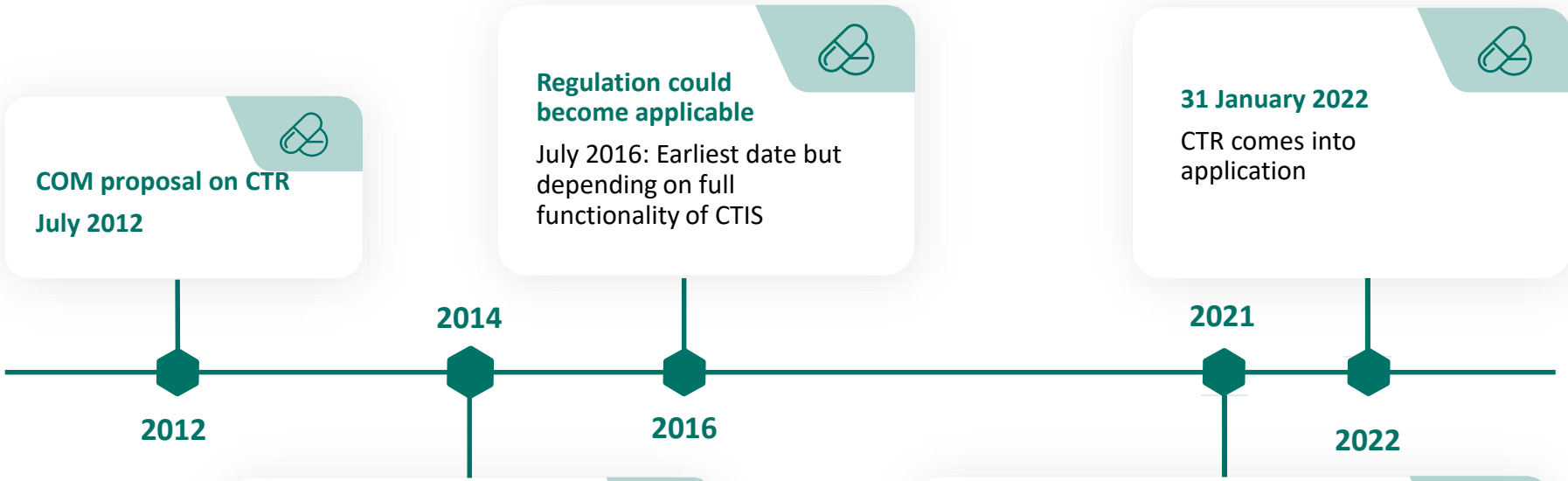
(May 2014 + January 2022)

Full harmonisation and joint assessment of multi-state trials

- E-submission through EU portal (CTIS) for all MS
- Joint assessment of all Member States concerned (MSC)

The CTR

10 years path from proposal to coming into application



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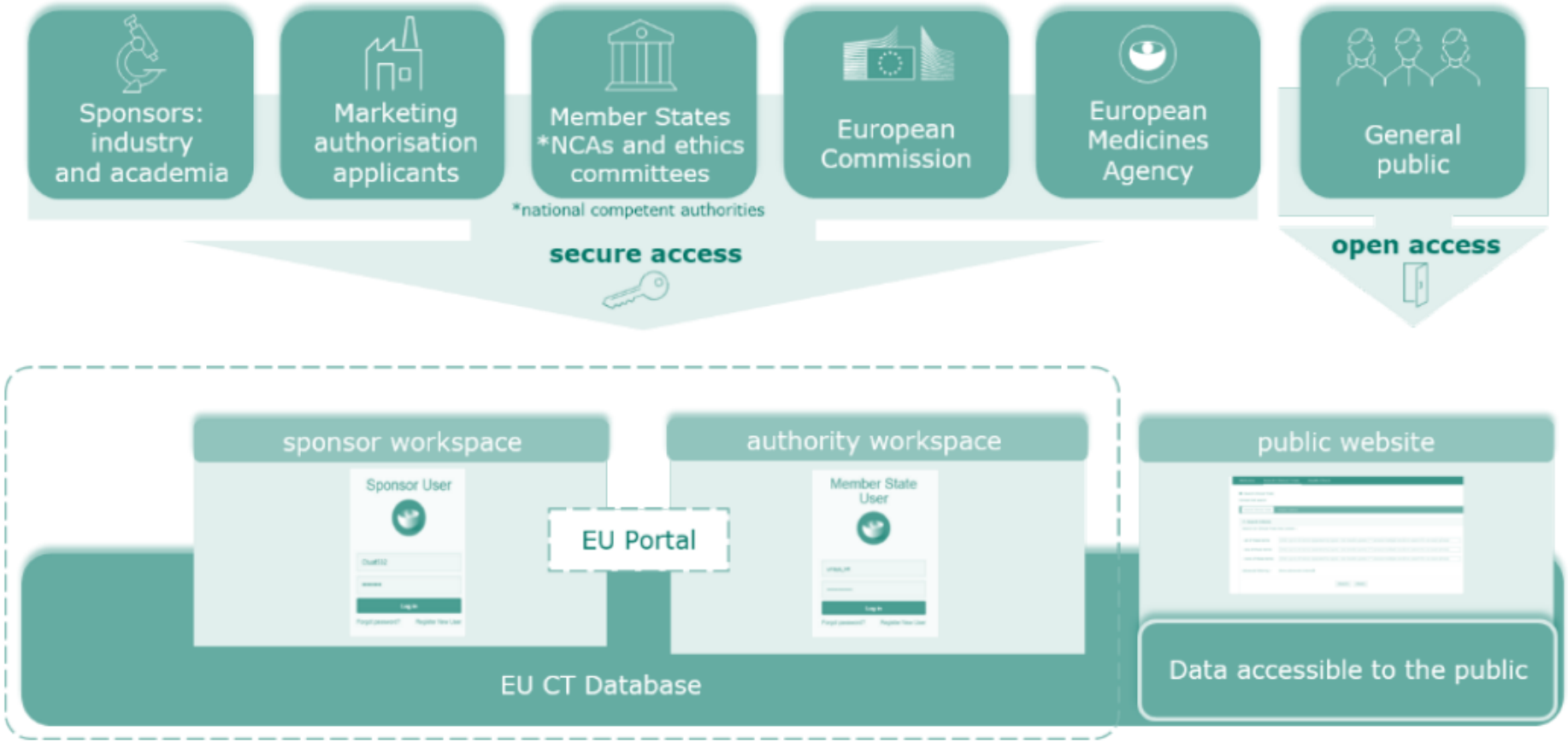
Clinical Trials Information System (CTIS)

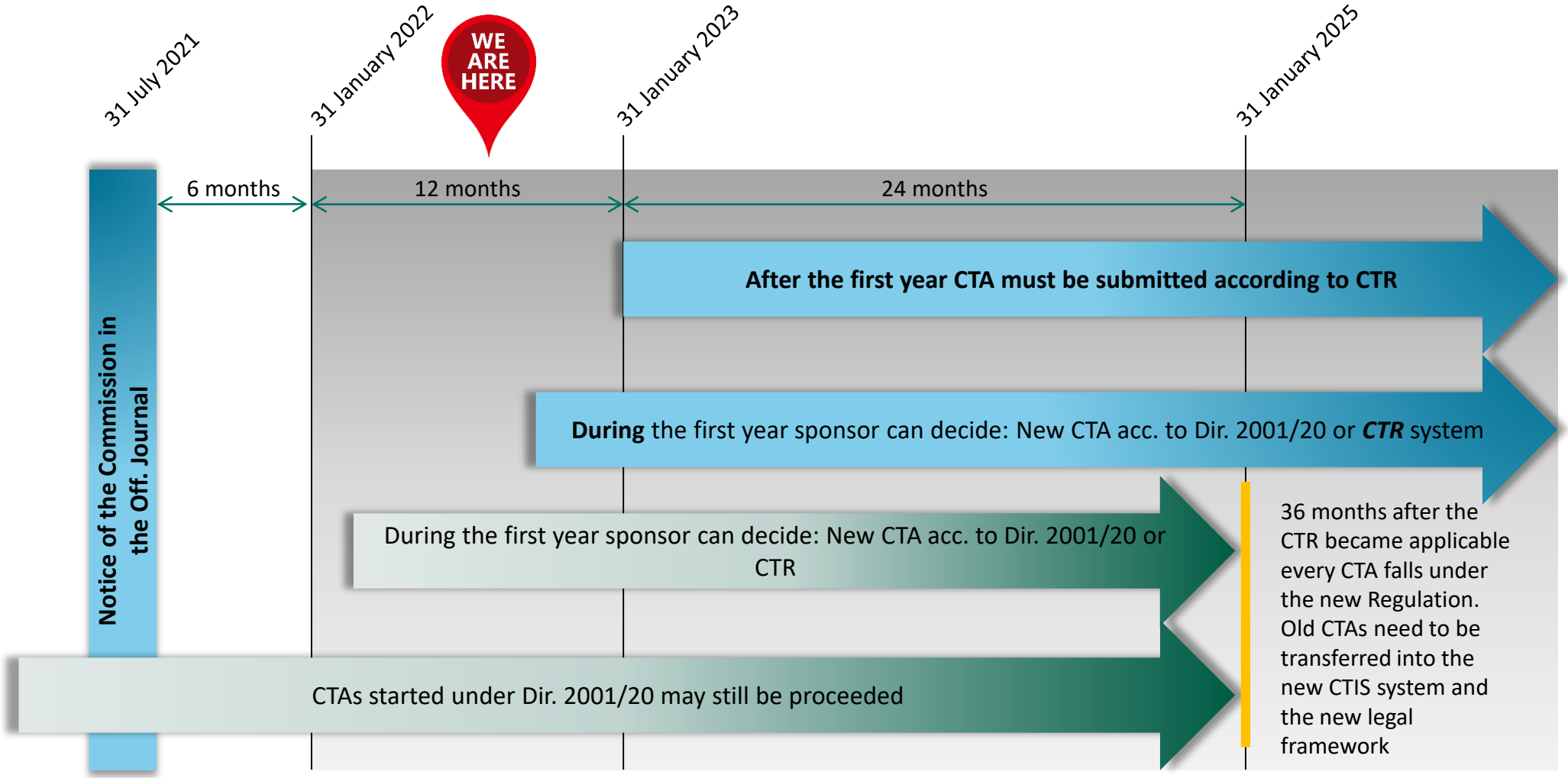


https://www.ema.europa.eu/en/documents/other/quick-guide-overview-ctis-workspaces-common-system-functionalities-ctis-training-programme-module-02_en.pdf

CTR and CTIS

- The EU portal and EU database (CTIS) are the central submission and collaboration platform and are therefore crucial for the functioning of the CTR processes
- Therefore, the start of the CTR had been linked to the functionality of CTIS (Article 82)

Transition period of the CTR



The CTR
Primary Objectives

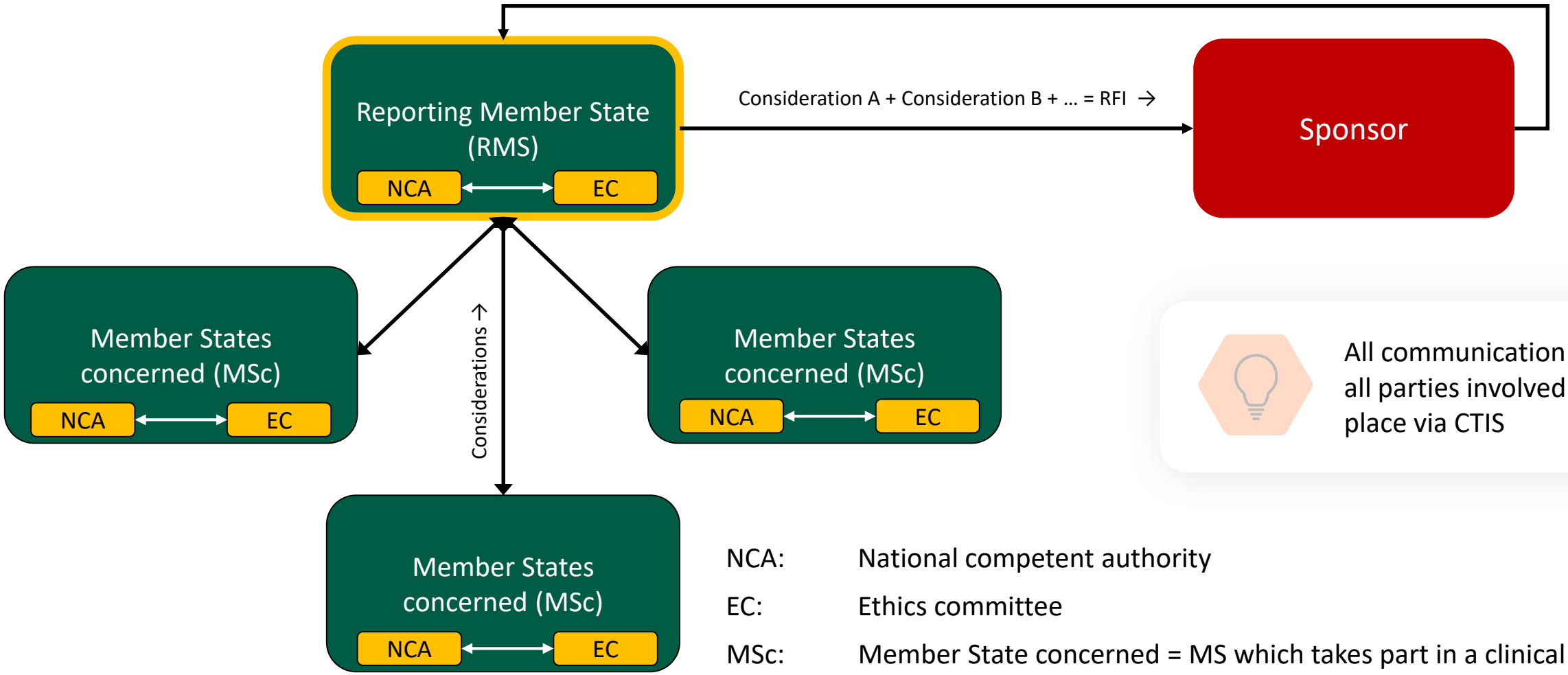
- Risk based approach to reduce unnecessary bureaucratic burden
- Full harmonisation by directly applicable EU Regulation rather than a Directive
- Full electronic submission and communication process
- Joint/coordinated review for multi-state trials under coordination of one Member State (MS)
- Enhanced transparency on each aspect of a clinical trial

- Overarching goal: To foster innovation and keep the EU attractive for international R&D

Key changes and principles of the CTR

- Segmentation of the CTA dossier and the assessment report into **two parts**
  - **Part I** identical for all Member States concerned (MSc): protocol, IMP dossiers, investigator's brochures …
  - **Part II** covers the **national concerns** in each MSc: informed consent, damage compensation …
- **Joint assessment** of **Part I** by all MSc under coordination of a **Reporting Member State (RMS)**
  - RMS manages communication and drafts the initial assessment report for the joint assessment by all MSc
  - RMS consolidates final assessment report and concludes **decision on Part I** (binding for all MSc)
- Development of an EU clinical trial information system (CTIS) for
  - Electronic submission of the CTA and related documents to all MSc without need of (electronic) signatures
- Secure communication between sponsor, RMS and MSc
- Content of CTIS is publicly accessible except some confidential information
  - Information become publicly accessible after CTA authorisation (deferral possible)

Roles and Communication during Part I Assessment



All communication between all parties involved takes place via CTIS

NCA:	National competent authority
EC:	Ethics committee
MSc:	Member State concerned = MS which takes part in a clinical trial
RMS:	Reporting Member State = Selected MSc which coordinates assessment
RFI:	Request for information

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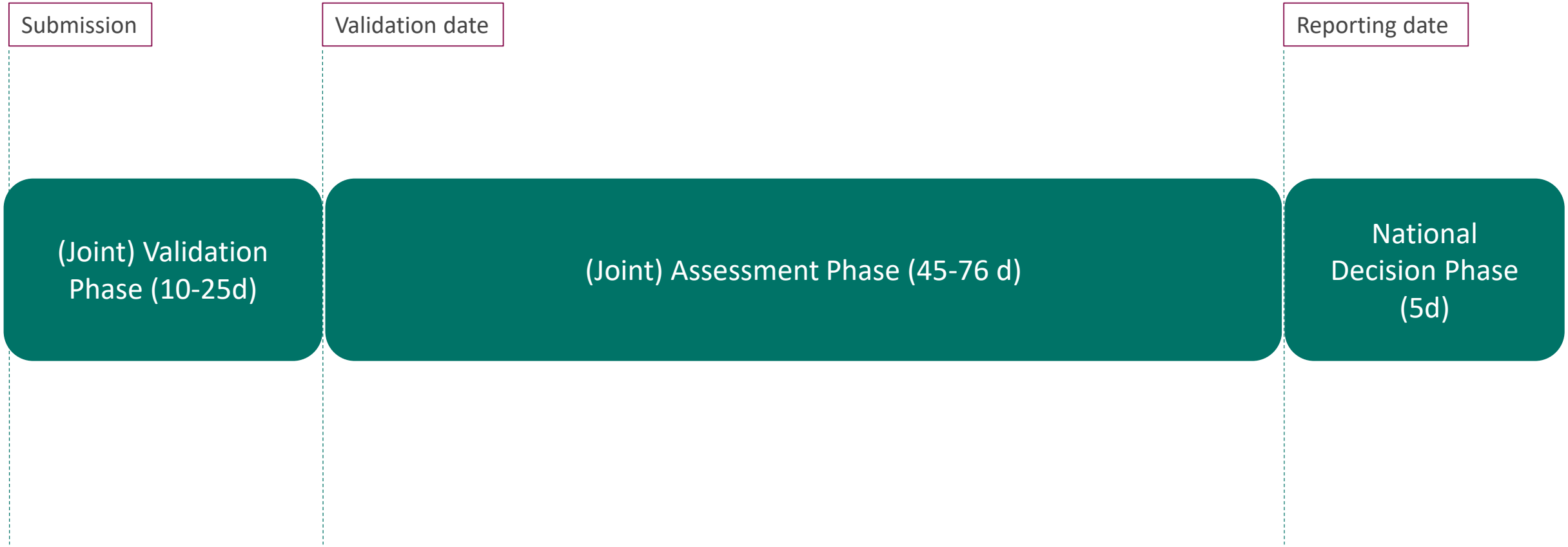
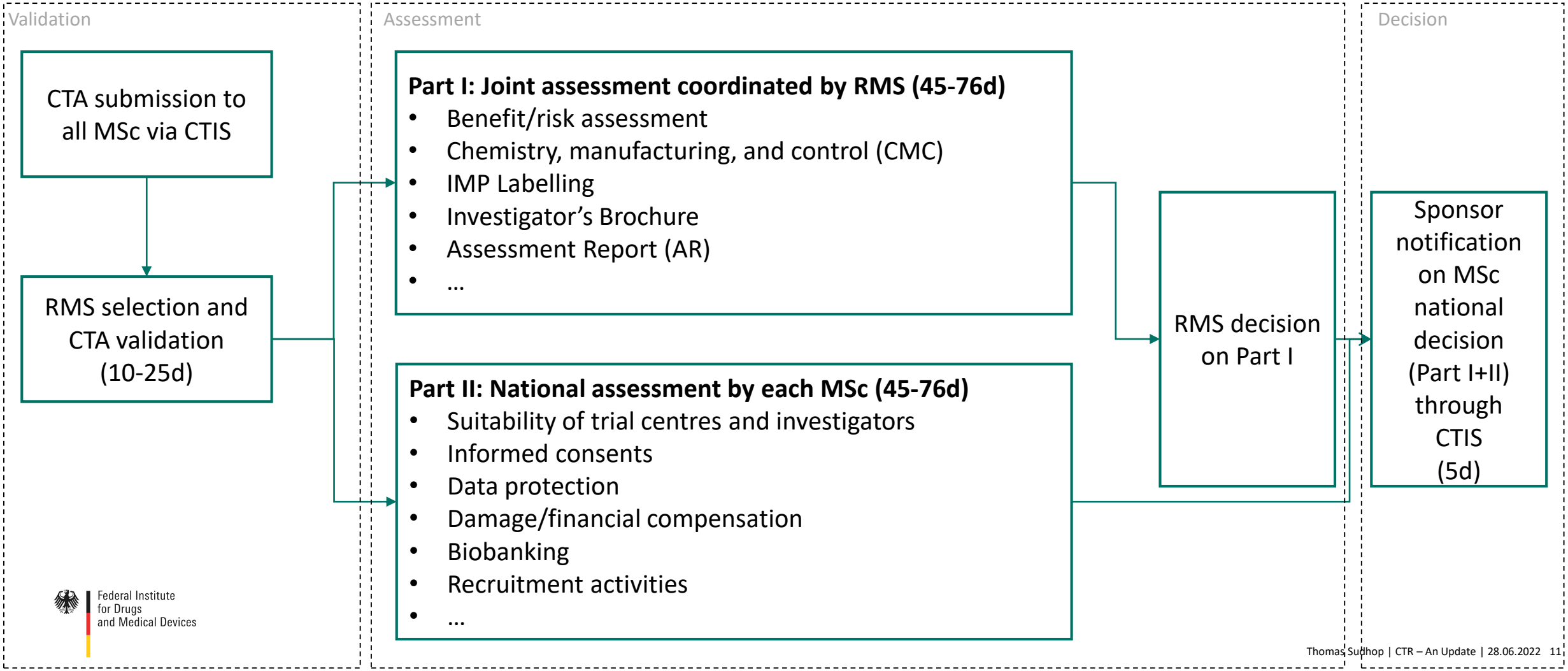
3-phase authorisation process



CTA authorisation process



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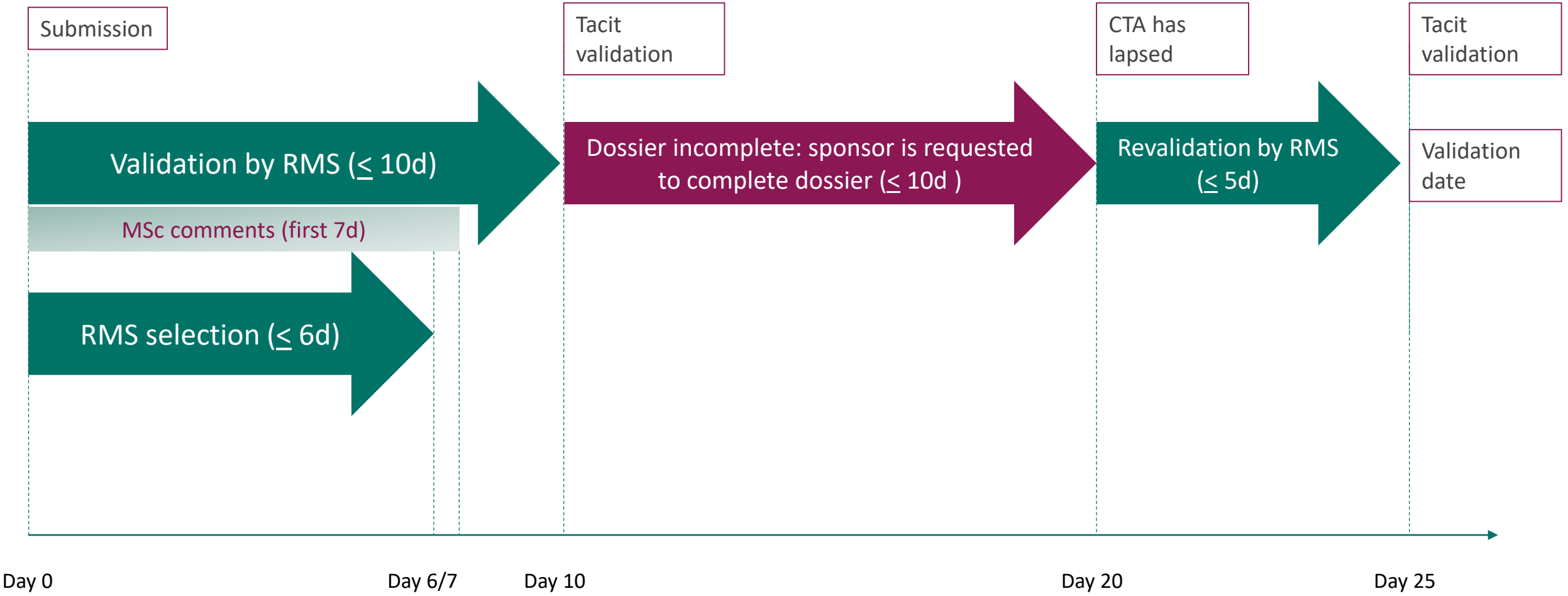
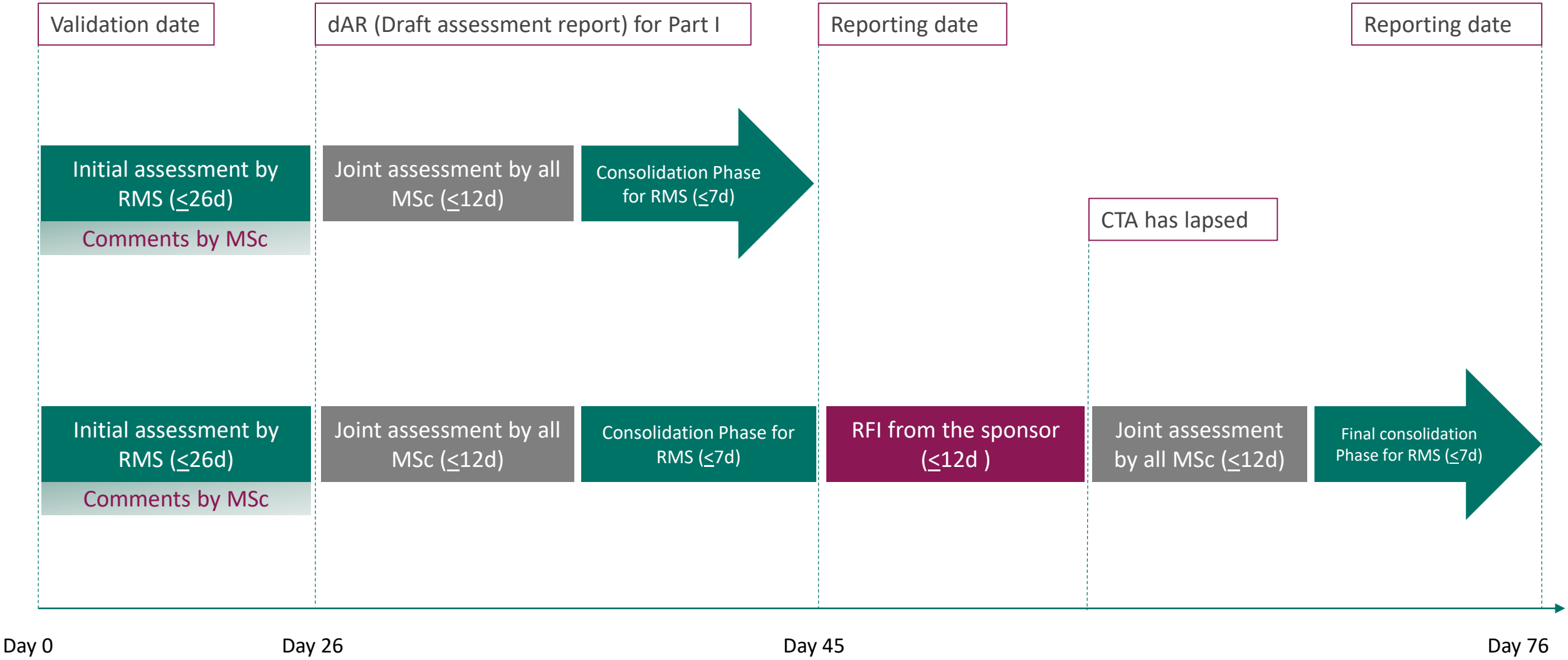
Part I: Validation

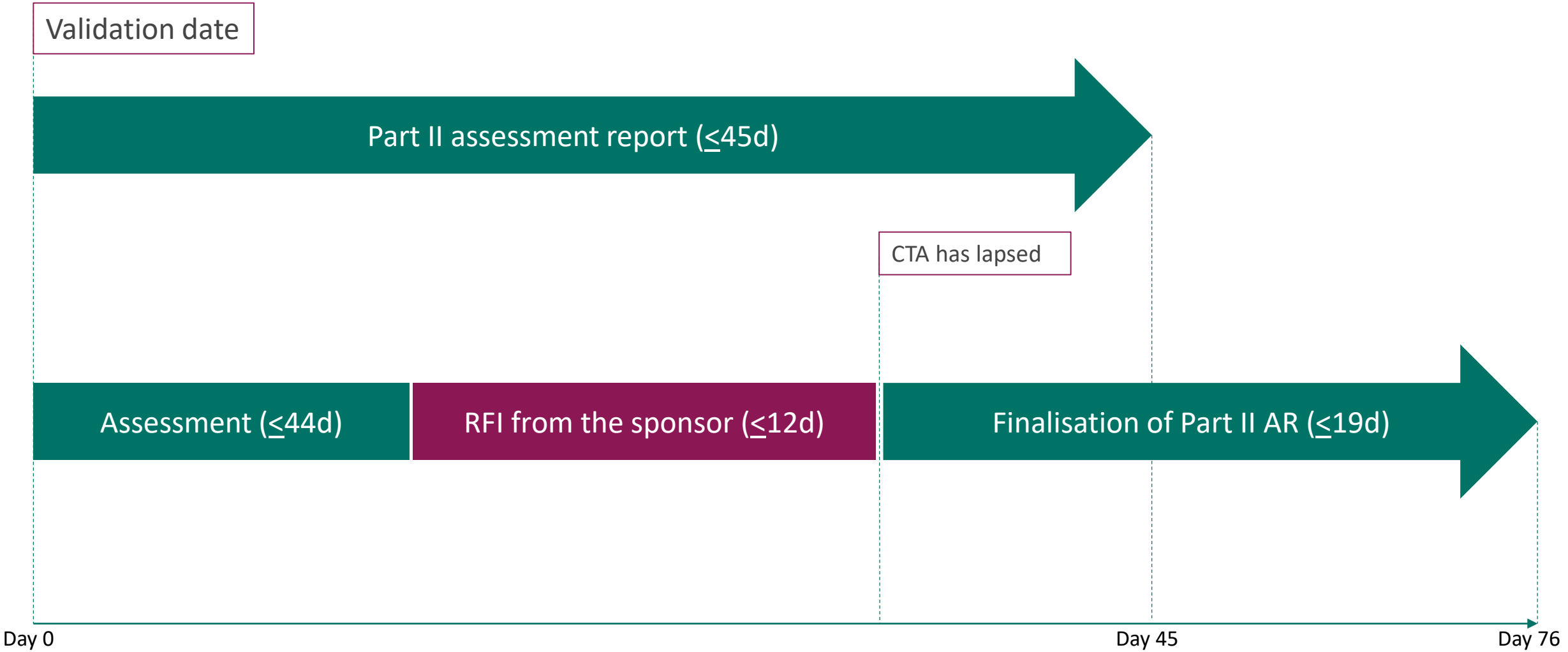
Validation objectives:
a) Study falls under CTR
b) CTS is complete (valid)



Part I Assessment



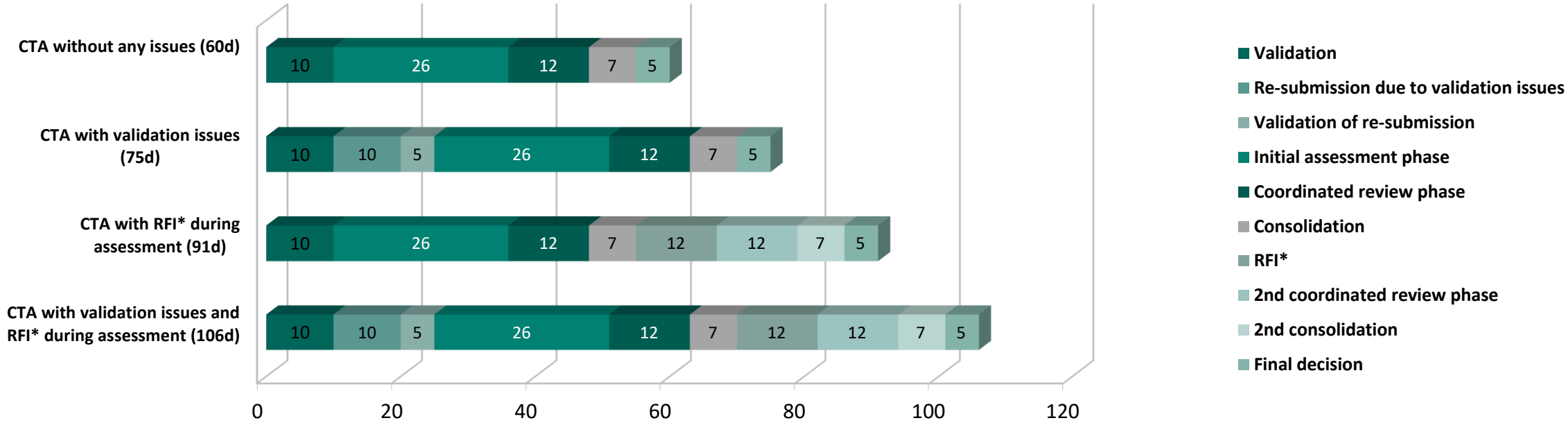
Part II Assessment



Deadlines for sponsors and authorities

*RFI: Request for (additional) information

Part I



Deadlines for Part II comparable to Part I

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Additional 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

- Commission Implementing Regulation (EU) 2017/556 of 24 March 2017 on **detailed arrangements for the good clinical practice inspection procedures** pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council

- Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) 536/2014 of the European Parliament and of the Council by **specifying principles and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections**

- Commission Implementing Regulation (EU) 2022/20 of 7 January 2022 laying down rules for the application of Regulation (EU) No 536/2014 of the European Parliament and of the Council as regards **setting up the rules and procedures for the cooperation of the Member States in safety assessment of clinical trials**

Current Status and Transitional Measures

Current Status

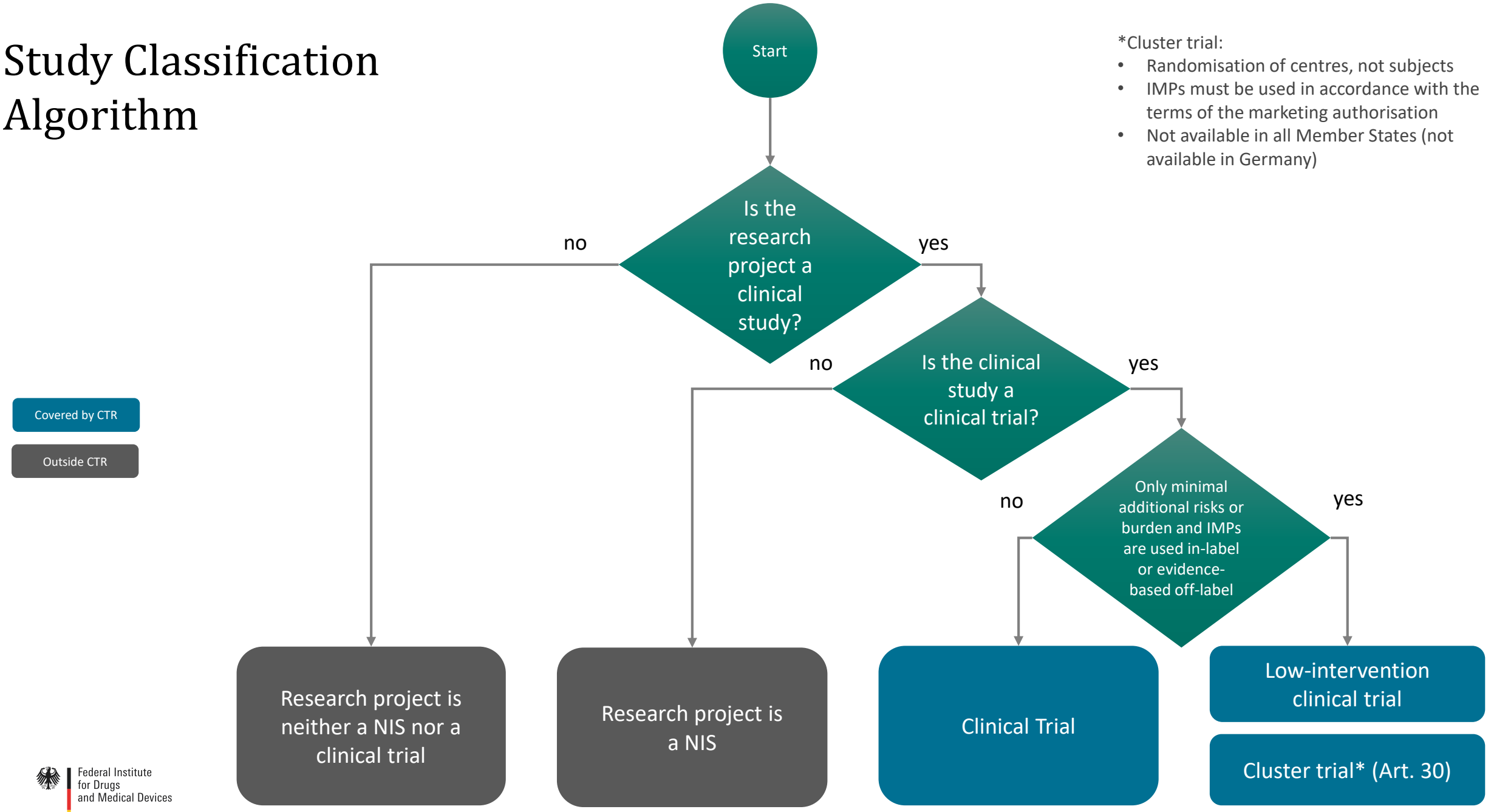
- CTR became applicable on 31 January 2022
  - Since that sponsors may apply for a clinical trial authorisation either according CTR or CTD (Clincial Trials Directive 2001/20/EC)
  - The new definitions of the CTR on clinical study, clinical trial and noninterventional trial became applicable
- From 31 January 2023, new applications for CTA authorisation can only be submitted in accordance with the CTR
- Authorised CTAs running under the CTD can be continued under the CTD framework until 31 January 2025
- After 31 January 2025 all active clinical trials hat to be transferred into the CTR framework and all required documents had to be uploaded to CTIS

CTR applicable

New definitions on clinical investigations since 31 January 2022

- **Clinical study:** Investigation on medicinal products with regard to efficacy, safety or pharmacokinetics to ascertain their safety and/or efficacy
- **Clinical trial:** A clinical study where treatment assignment is decided in advance and is in contrast to the normal clinical practise, prescription and study inclusion is taken together, or diagnostic or monitoring in addition to normal clinical practise are applied
- **Low-intervention trial:** A clinical trial where
  - All IMPs (except placebo) are authorised and used in-label or in an evidence-based off-label use
  - The additional procedures have only minimal additional risks and burden compared to normal clinical practise
- **Cluster trial:** A low-intervention clinical trial that randomizes trials sites rather than individual trial subjects (not foreseen in all Member States)
- **Non-interventional study (NIS):** A clinical study other than a clinical trial

Study Classification Algorithm



*Cluster trial:

- Randomisation of centres, not subjects
- IMPs must be used in accordance with the terms of the marketing authorisation
- Not available in all Member States (not available in Germany)

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Transition of CTD clinical trials – fundamental principles

- Refer to Section 11 of the QA document of the Commission!
  - https://ec.europa.eu/health/system/files/2022-05/regulation5362014_qa_en.pdf
- A CT transition is not a new authorisation
  - CTD trials had already been authorised under the CTD and to not require a new authorisation
  - Transitioned CTD trials receive a (tacit) approval by the transition process
  - But, transferred CTD trials need to be compliant with the CTR
- Therefore, CTAs under CTD should be first “face lifted” according to the requirements of the CTR by **substantial amendments** according CTD **and then** transferred to the CTR
  - Only fully authorised and active trials could be transferred (no pending SAs, no temporary hold …)
- New CTA form (part I+II) based on the existing and in all MS authorised dossier submitted to CTIS
  - Multi-state trials need to be fully harmonised across all MSc in advance (cf. CTFG BP-Guide)

Transition of CTD clinical trials – Part I of the CTA

- New cover letter + new application form (part I+II)
- Latest approved version of the (harmonised) protocol, IB, IMPD and other GMP relevant documents
- If applicable documents related to non IMPs (NIMPs)
  - NIMPs under CTD are considered as auxiliary MPs (AxMPs: background treatment, challenge agents, rescue medication, MPs required to assess endpoints) under the CTR and need to be compliant with the prerequisites
  - Usually only authorised AxMPs should be used (simplified SmPC)
- Remember: Most documents become publicly available. Therefore, redacted versions are (additionally) required
- In case of a multi-state trial: one MSc needs to be nominated as RMS by the sponsor
  - In case of a VHP trial the Ref-NCA should be nominated as RMS

Transition of CTD clinical trials – Part II of the CTA

- Latest approved version of the subjects' information sheet and informed consent form
- Cover letter identify the EC which issued the positive opinion according CTD and its EudraCT number
- Usually the former EC remains responsible for CTR
  - Situation in Germany: Only 37 of 50 ECs operating under CTD are also registered acc. CTR
  - Therefore, a special business plan has been issued for those CTs which “lost” their initial EC
- In case that the sponsor cannot provide certain documents listed in Annex I of the CTR, which **were not required under the CTD**, the sponsor should upload a blank document clarifying that this aspect was already assessed by NCA or EC

Consequences of a transition of a CT

- A transitioned CT will be governed by the CTR **from the moment of its (tacit) authorisation** under the CTR
- From this time point onwards, all requirements of the CTR will apply, e.g.
  - Obligations of notifications
  - Safety reporting rules
  - Archiving requirements
  - Rules on substantial modifications
  - Addition of further Member States …
- **MS are obliged to enforce corrective actions under Article 77 if a transitioned CT is found not to be CTR compliant!**
- **Therefore, CTD trials should be very carefully updated under the CTD to guarantee CTR compliance!**

CTD/CTR applications at BfArM in 2022

- In 2022 BfArM receives approx. 300 applications under CTD
- From 31 January – 24 June 2022 Germany receives 31 clinical trial applications under CTR (21 BfArM/10 PEI)
  - In 13 of 21 applications BfArM has been selected as RMS!
  - 3 CTAs approved
  - 3 CTAs withdrawn
  - 1 rejection pending (due to unresolved CMC issues)

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Points to consider when working under the CTR

Transparency

Balancing business interests and interests of the public

Article 81(4)

The EU database [CTIS] **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.

Transparency rules
acc. to the functional specification of CTIS

- CTAs with a final decision in a MSc will be made public available
- The default is: Public availability at the first opportunity, but sponsors may apply for a deferral on the timing of publication
- Deferral rules and maximum timelines depend on trial category

Category 1: phase I trials (FIH, BE/BA, PK/PD, bio similarity trials)
Most information up to **7 years after end of trial (EOT)** in the EU/EEA
Trial results 12 months after interim analysis or 30 months after EOT

Category 2: phase II and III
Most information up to **5 years after EOT** in the EU/EEA

Category 3: phase IV trials
Most information with **final summary of results** (12 month of EOT)

Aspects <u>not</u> be made public

- Quality related information that include:
  - The IMPD quality part
  - Quality related RFIs
  - Quality Assessment reports
- Draft assessment reports
- Personal information identifying Member States experts, sponsor staff, MAH/applicant staff
- Financial agreements between the sponsor and the investigator site


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2 October 2015
EMA/228383/2015 Endorsed

Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014"

DOI: EMA/228383/2015

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https://www.ema.europa.eu/en/documents/presentation/presentation-transparency-publication-clinical-trial-information-contained-ctis-laura-pioppo_en.pdf

CT Registration prior start

Article 25 (6)

- CTR requires that all clinical data from previous clinical trials in the dossier (IB) are from clinical trials that **have been registered prior to its start in a public register, if that trial had been started after 31 January 2022**

- Data from clinical trials started before 31 January 2022 could also be submitted **if the results of that clinical trial had been published in an independent peer-reviewed scientific publication**

- Compliance statement with Article 25 (6) is required with the CTA (Annex I, No 47)

Serious GCP breaches

Article 52

*"1. The **sponsor shall notify** the **Member States concerned** about **a serious breach** of this Regulation or of the version of the protocol applicable at the time of the breach **through the EU portal without undue delay** but not later than **seven days of becoming aware of that breach.***

*2. For the purposes of this Article, a 'serious breach' means a breach **likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data** generated in the clinical trial."*

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SCIENCE MEDICINES HEALTH

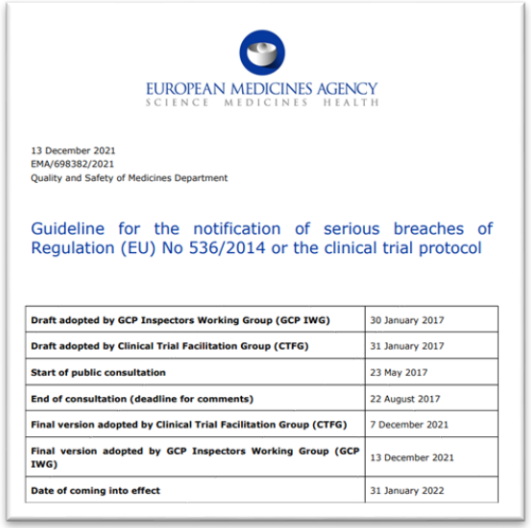
13 December 2021
EMA/698382/2021
Quality and Safety of Medicines Department

Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol

Draft adopted by GCP Inspectors Working Group (GCP IWG)	30 January 2017
Draft adopted by Clinical Trial Facilitation Group (CTFG)	31 January 2017
Start of public consultation	23 May 2017
End of consultation (deadline for comments)	22 August 2017
Final version adopted by Clinical Trial Facilitation Group (CTFG)	7 December 2021
Final version adopted by GCP Inspectors Working Group (GCP IWG)	13 December 2021
Date of coming into effect	31 January 2022

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf

Serious GCP breaches



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- Suspected serious GCP breaches should be promptly reported to the sponsor by investigators and by service providers in order to perform further investigation and assess if the breach qualifies as serious
  - Management of the serious breaches should be part of the sponsor's quality system or described in the trial protocol
- The sponsor assess each GCP breach report to identify whether it is "serious"
  - For serious breaches the sponsor performs a root cause analysis and identifies CAPAs
  - Reporting of the serious breach through CTIS should be done within 7 calendar days of the sponsor becoming aware of a serious breach

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf

Union Controls

- Article 79 requires Union Controls by the European Commission in order to verify, that
  - Member States correctly supervise compliance with the CTR, and that
  - The regulatory system applicable to clinical trials outside the EU/EEA ensures that general principles of the Annex I to Dir. 2001/83/EC or Article 25 (5) of the CTR is complied with (ICH fundamentals)

Union controls plan

- A Union control by the European Commission targeting Member States

Union controls programme

- A Union control by the European Commission targeting third countries

- For each Union control a **Union control report** is uploaded to CTIS and published on the public website of CTIS

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German specialities

Trial site suitability / investigator qualification

- Currently most Member States require the submission of a description of qualification **only** for the **principal investigator**

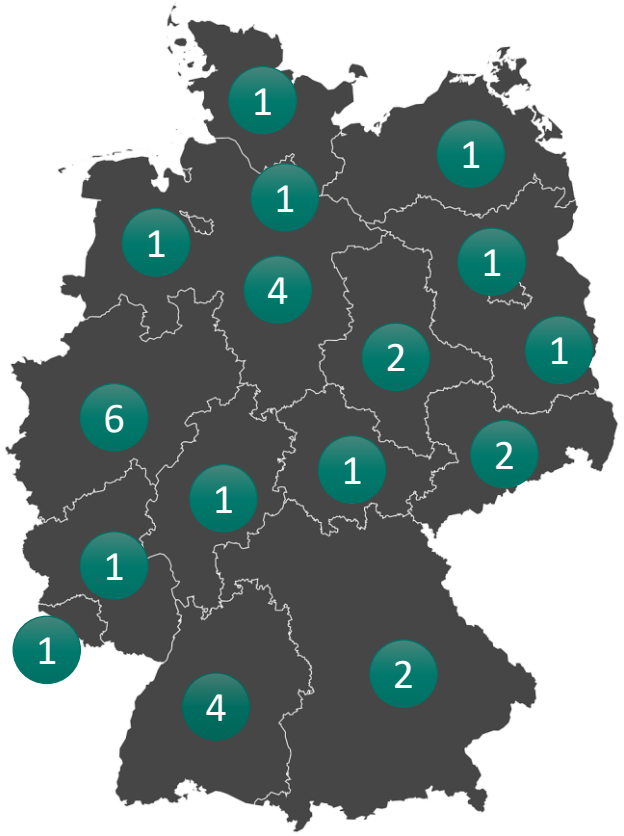
- CTR requires in Annex I, Section M, No 65 the submission of a description of the qualification of **the investigators**

- Based on this German ECs ask for qualification documents for the **principal investigator and the deputy principal investigator**
  - At least for long lasting trials with complex trial related procedures in order to ensure that a qualified investigator is always present
  - German ECs seek discussion with other European ECs on this topic to harmonise the requirements

Legal Situation in Germany since 31 January 2022

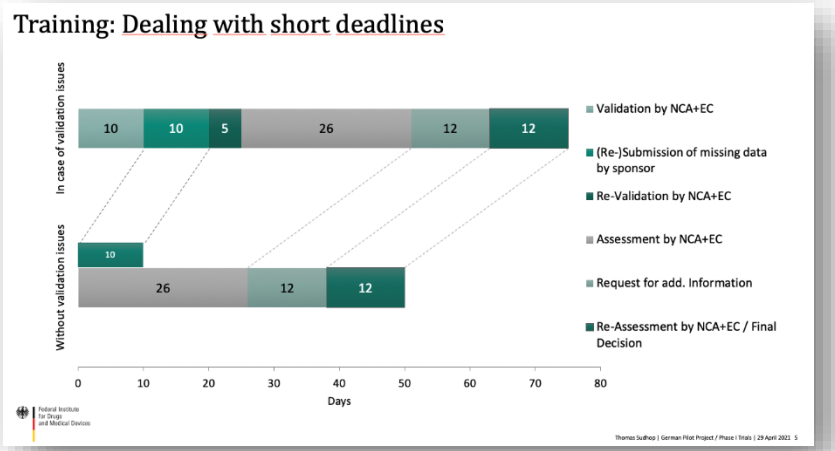
- CTR in force and applicable
- Two NCAs for CTA authorisation (BfArM, PEI)
  - National Contact Point according Art. 83 (1): BfArM (ctr@bfarm.de)
- 30 local authorities in 16 federal states (”Länder”)
- 37 registered ethics committees (EC) at medical faculties and state medical associations

- German Medicines Act (AMG) amended on 27 January 2022
  - to comply with CTR
  - to regulate the aspects that the CTR has left to the Member States (MS), i.e. informed consent in incapable subjects, damage comp.
  - to establish collaboration between ethics committees (EC) and NCAs (additional Ordinance)
  - to regulate competence between NCAs and local authorities
  - to establish standards and processes for ECs registration at BfArM
  - ...



Number of local authorities per federal state

Pilot project: National training on cooperation betweeen NCA and EC

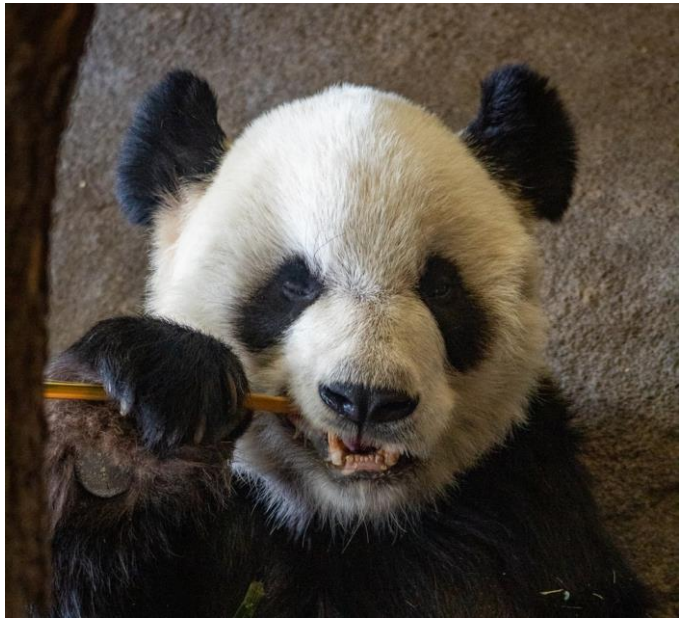


- Launched in 2015
- Only open for mono-national CTAs
- 36 of 50 Ethics Committees took part
- To take part in the Pilot Project the sponsor had to choose a principle investigator in the competence of one of the 36 participating ECs
- Participating NCAs: BfArM (PEI)

IT tool for collaboration between NCAs, ECs and local authorities: PANDA

PANDA: **Pa**rallel **N**ational **Da**tabase

- National Database/SharePoint/Workflow-System to facilitate cooperation between
  - NCAs (BfArM/PEI), ECs (n=37), local (state) authorities (30)
- Cloud based IT solution on MS SharePoint and MS Dynamics 365
- Data link to CTIS via CTIS-API
- Currently API not fully functional, sometimes data provided by API and CTIS web interface differ



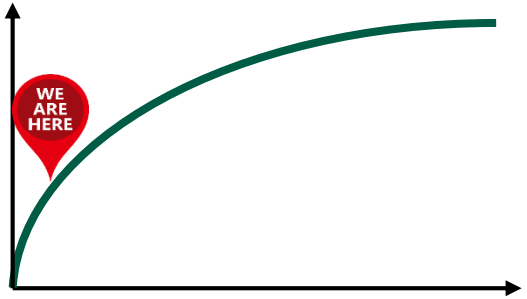
5 Months Experience with the CTR

How did Europe start?

First Experiences: Bumpy start

- Not all Member States seem to be CTR ready (reports from sponsors)
- Some issues with the EMA OMS for certain types of trial centres (doctor's practises)
- Newly identified issues with CTIS (deadline calculation, dead lock situation)
- Some procedures are still unclear (because not yet used)
- Applicants from pharmaceutical industry currently rather wait-and-see
- Transitions trials require too much efforts at present
- *First impression: Administrative burden increased significantly for both, Member States and applicants!*

But: Steep learning curve: "We will get used to it!"

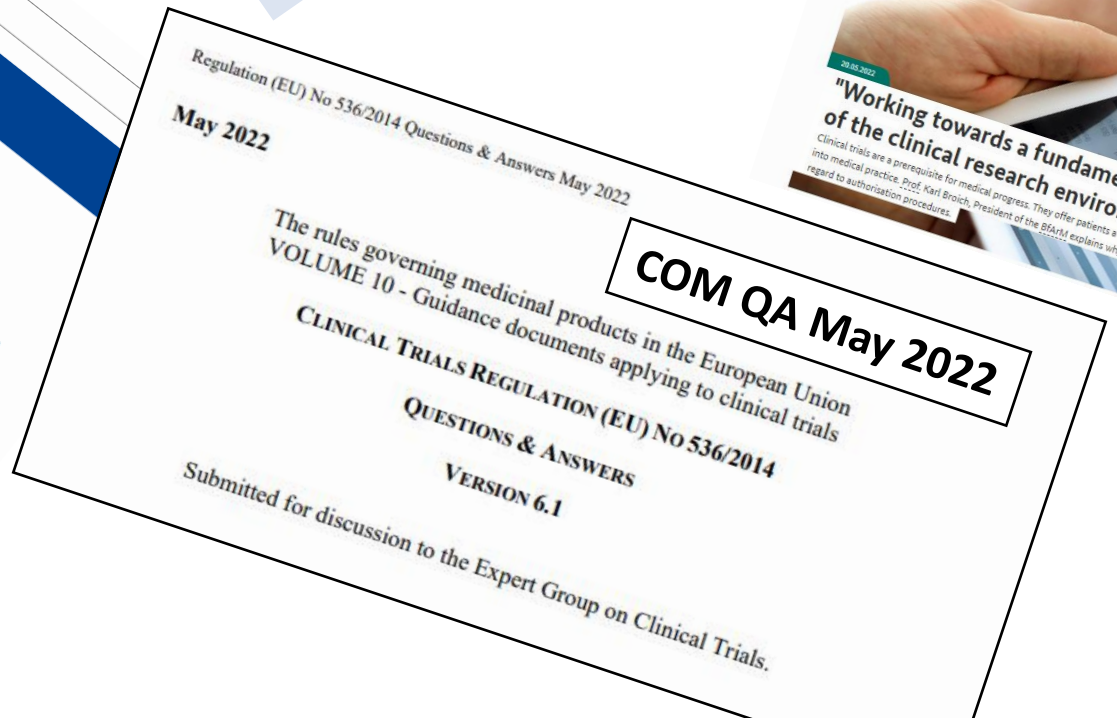


Further information…

#EudraLex10

euclinicaltrials.eu

#BfArM4Health



COM QA May 2022

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Thank you very much for your attention!

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