AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Clinical Trials Regulation overview objectives and why the replacement of EU directive is needed

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22/10/2019

Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	☐	☐	☐	X optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	☐	☐	☐	X optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Massimiliano Sarra, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. I am not receiving any compensation

Before May 2004

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.

Directive 2001/20/EC

First step to harmonise **processes and requirements** for clinical trial authorisations.

Implementation **1 May 2004**.

Concerns expressed soon after its implementation.

Regulation (EU) 536/2014

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 2001/20/CE

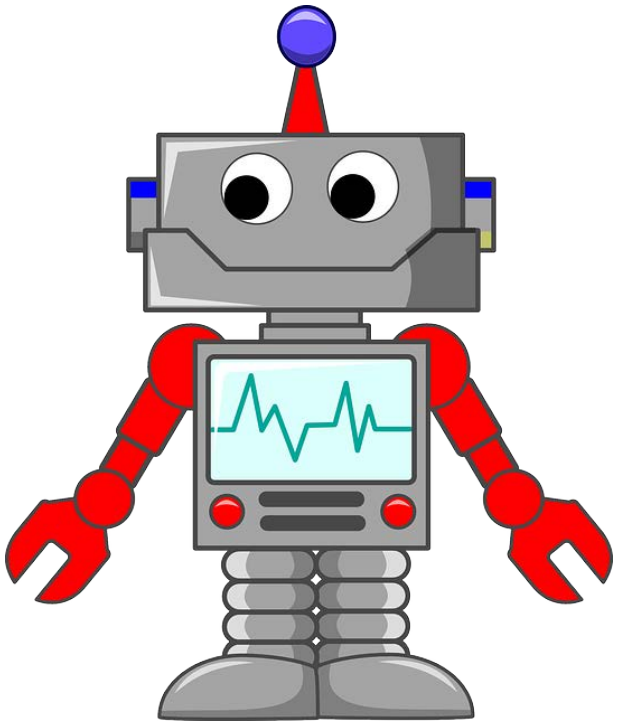
Directive 2001/20/CE

- Different Assessments
- Different Timelines
- Different Outcomes/Decisions

Need to consolidate documents by submission of Substantial Amendments

Regulation 536/2014/CE

Regulation 536/2014/CE



- Consolidated Assessments
- Clear Timeline
- Documents harmonized

Rationalization of resources for National Competent Authorities (NCA) and cost reduction for the Companies

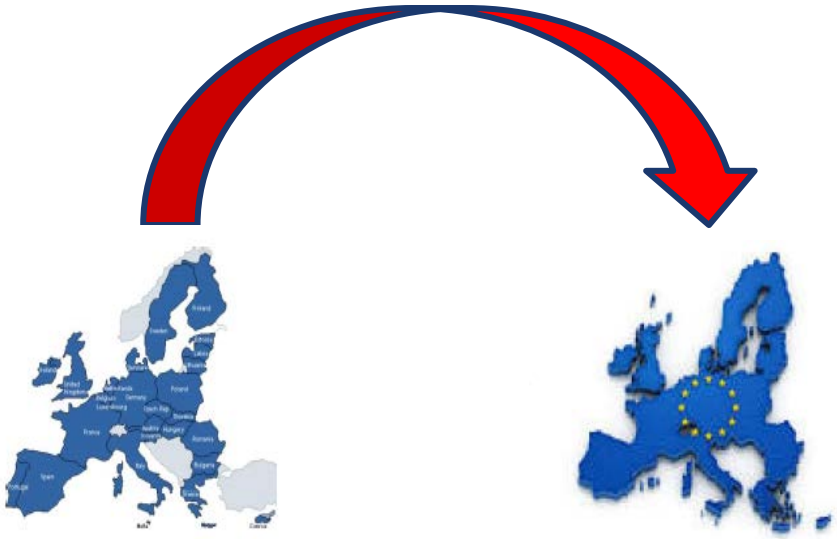
When will the Regulation come into Force?

Article 99 shall apply “no earlier than 28th May 2016” (6 months after successful audit of IT system).

Transitional aspects

Date of publication of Regulation	Date of application of Regulation
April 16th 2014	2016 – 2018 – 2019 - 2020

Transition Period



2001/20/CE 536/2014/CE

3-year transition period

- Starts when Regulation becomes applicable
- CT can be submitted under old (Dir.) or new (Reg.) systems,
- Trials authorized under old system remain under that system.

End of legacy

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

Scope and Definitions

Article 1

Scope

This Regulation applies to all clinical trials conducted in the Union.

It does not apply to non-interventional studies.

(2) 'Clinical trial' means a clinical study which fulfils any of the following conditions:

(a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;

(b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or

(c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

(3) 'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions:

(a) the investigational medicinal products, excluding placebos, are authorised;

(b) according to the protocol of the clinical trial,

(i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or

(ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and

(c) 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;

This Regulation applies to all clinical trials conducted in the Union.
It does not apply to non-interventional studies.

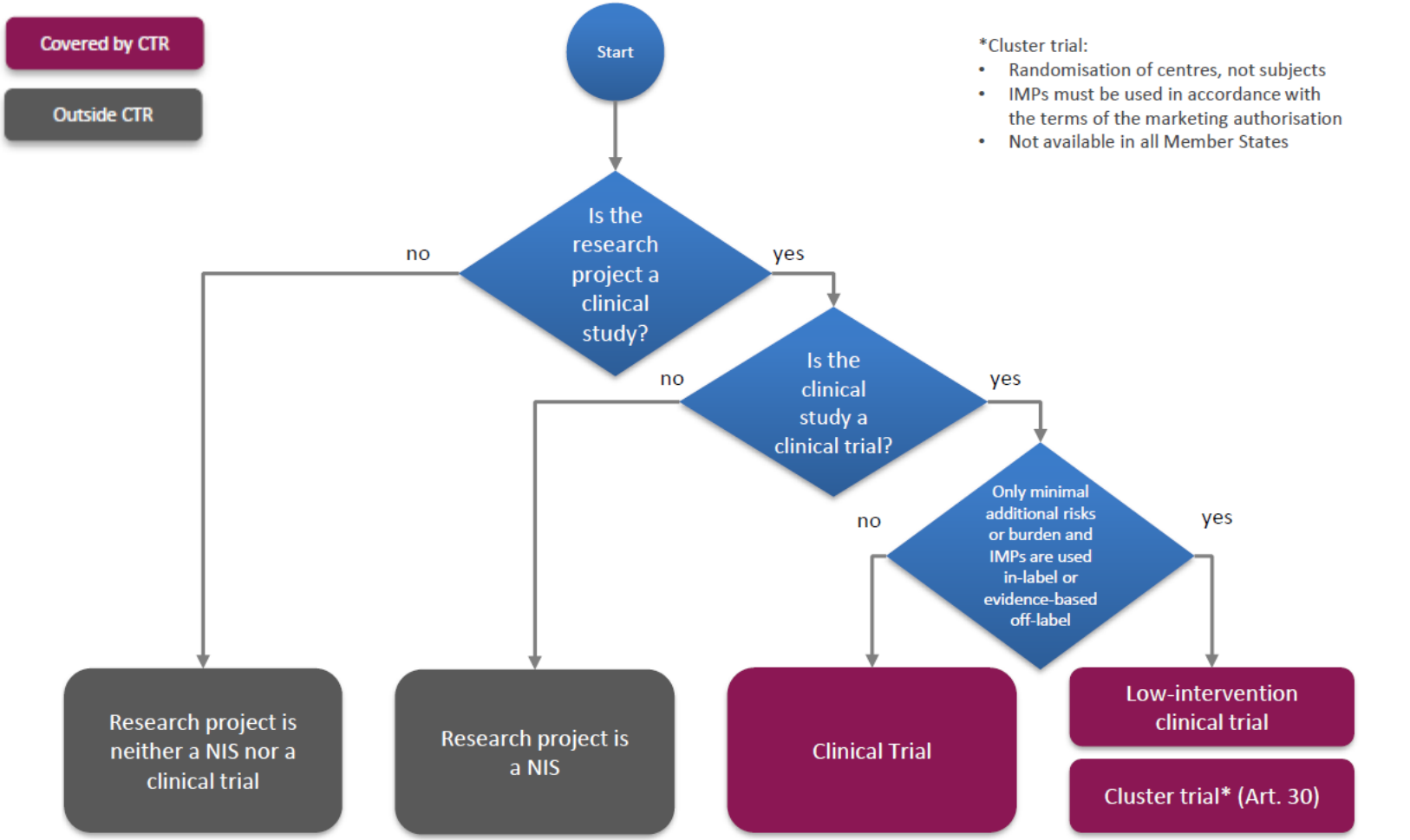
Non- Vs. Low-Interventional Clinical trials

Unchanged scope: Interventional clinical trials with medicinal products for human use

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).

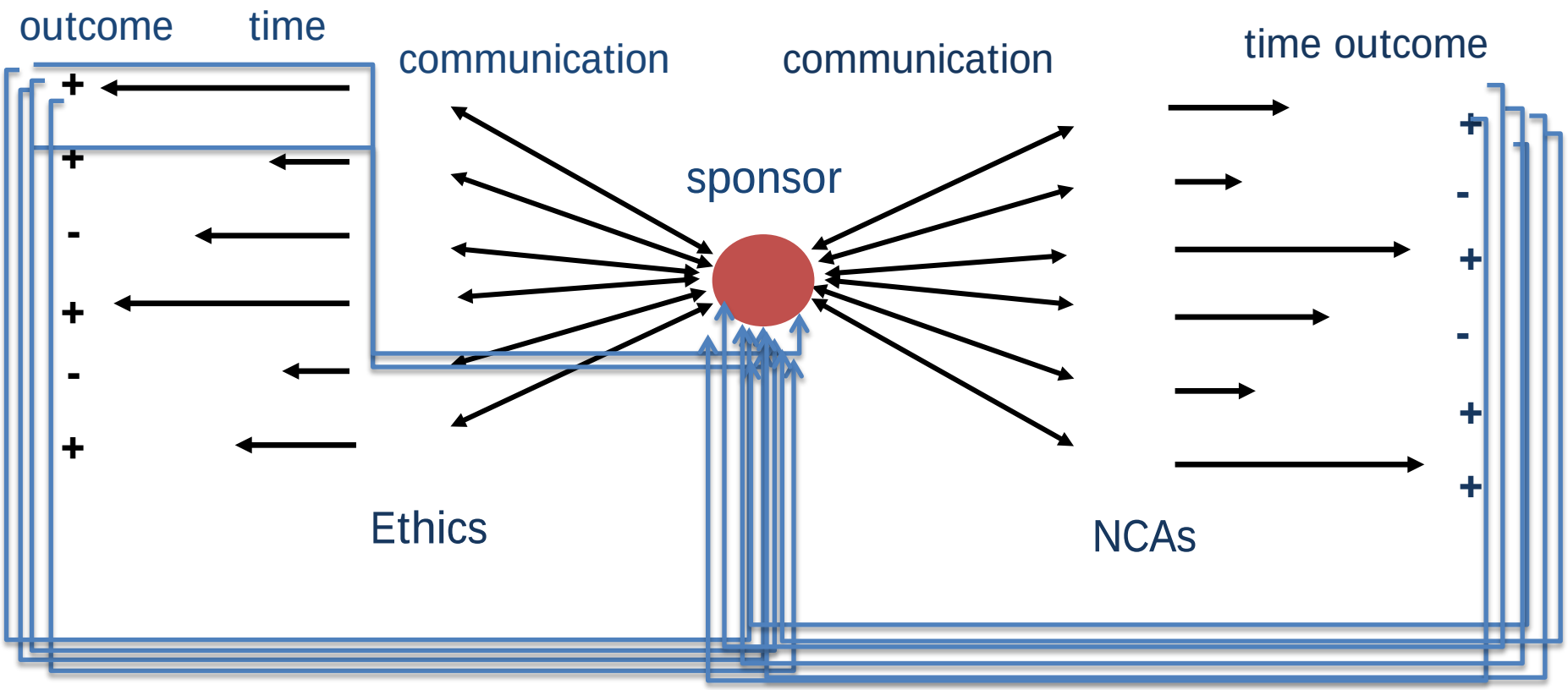
Classification Algorithm



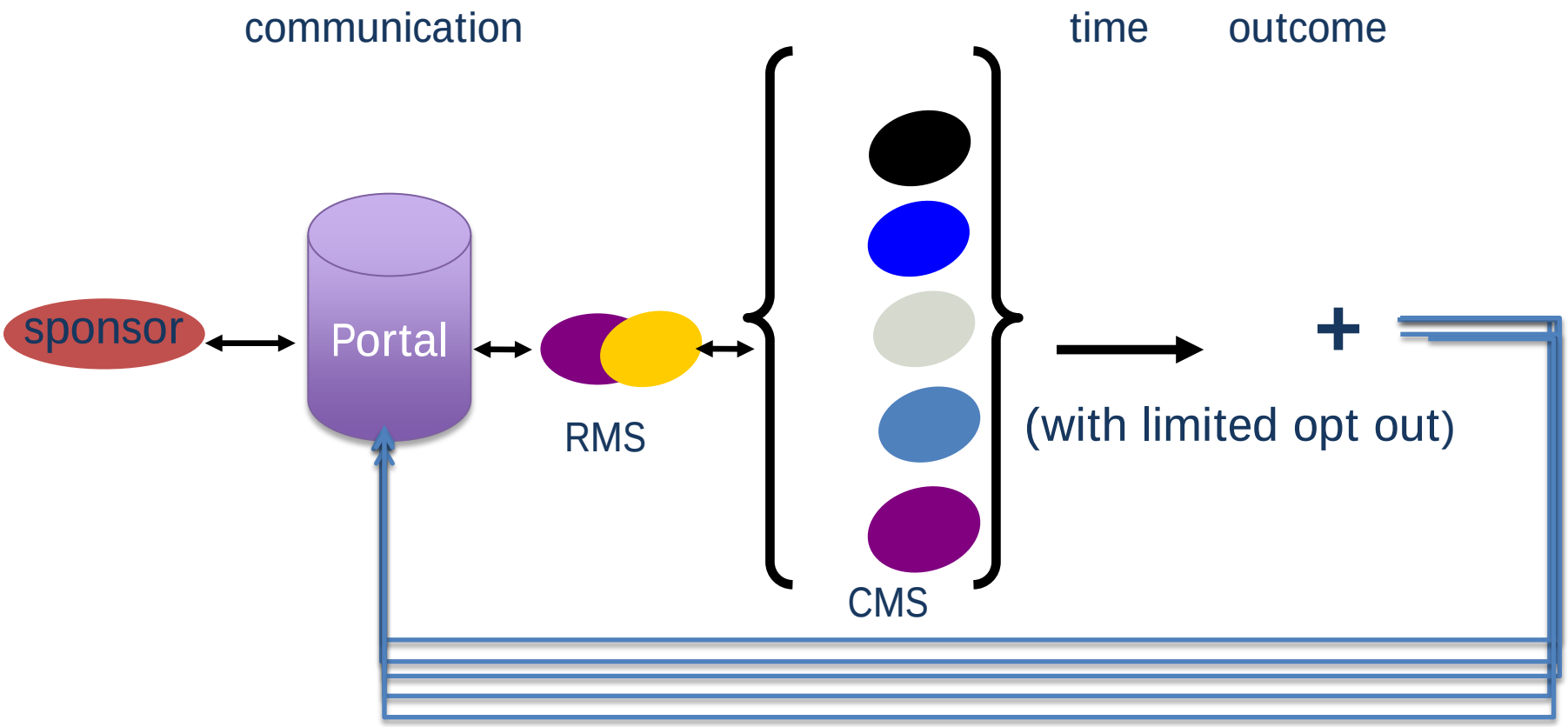
New simplified approval procedure

- Single EU Portal & Database
- Single dossier and single submission
- Sponsor can propose Reporting MS
- Coordinated assessment for multi-state clinical trials
  - Part I – joint assessment by all concerned MS (NCA+EC), led by RMS
  - Part II – National assessment only (R&D offices and Ethics Committee)
- Clear timelines (extended compared with Directive), concept of tacit approval

EU Multi-national clinical trials: current situation



EU Multi-national clinical trials: under new Regulation



Mononational CT

RMS assesses the aspects of part I, generates an assessment report (AR), and formulates a conclusion (acceptable, acceptable with conditions, not acceptable) between the validation date and the reporting date.

Multinational CT

For multinational trials, this happens in 3 phases :

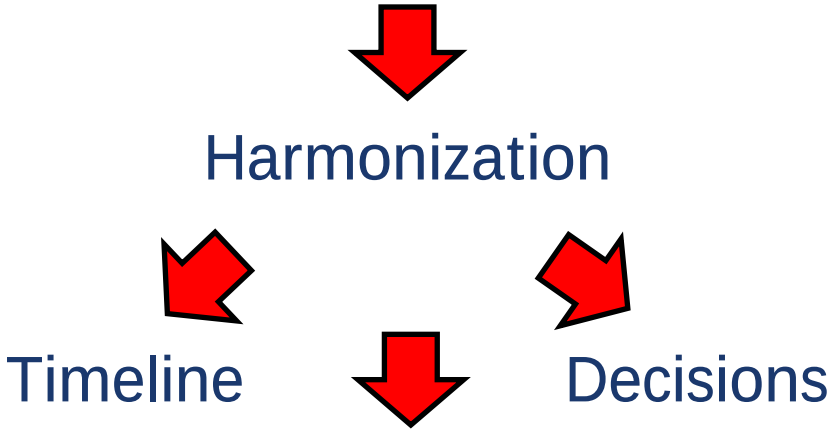
- Initial assessment phase (drafting of the AR by the RMS)
- Coordinated review phase (all member states review the draft AR and share their considerations)
- Consolidation phase (consolidation of the considerations in a final part I AR)

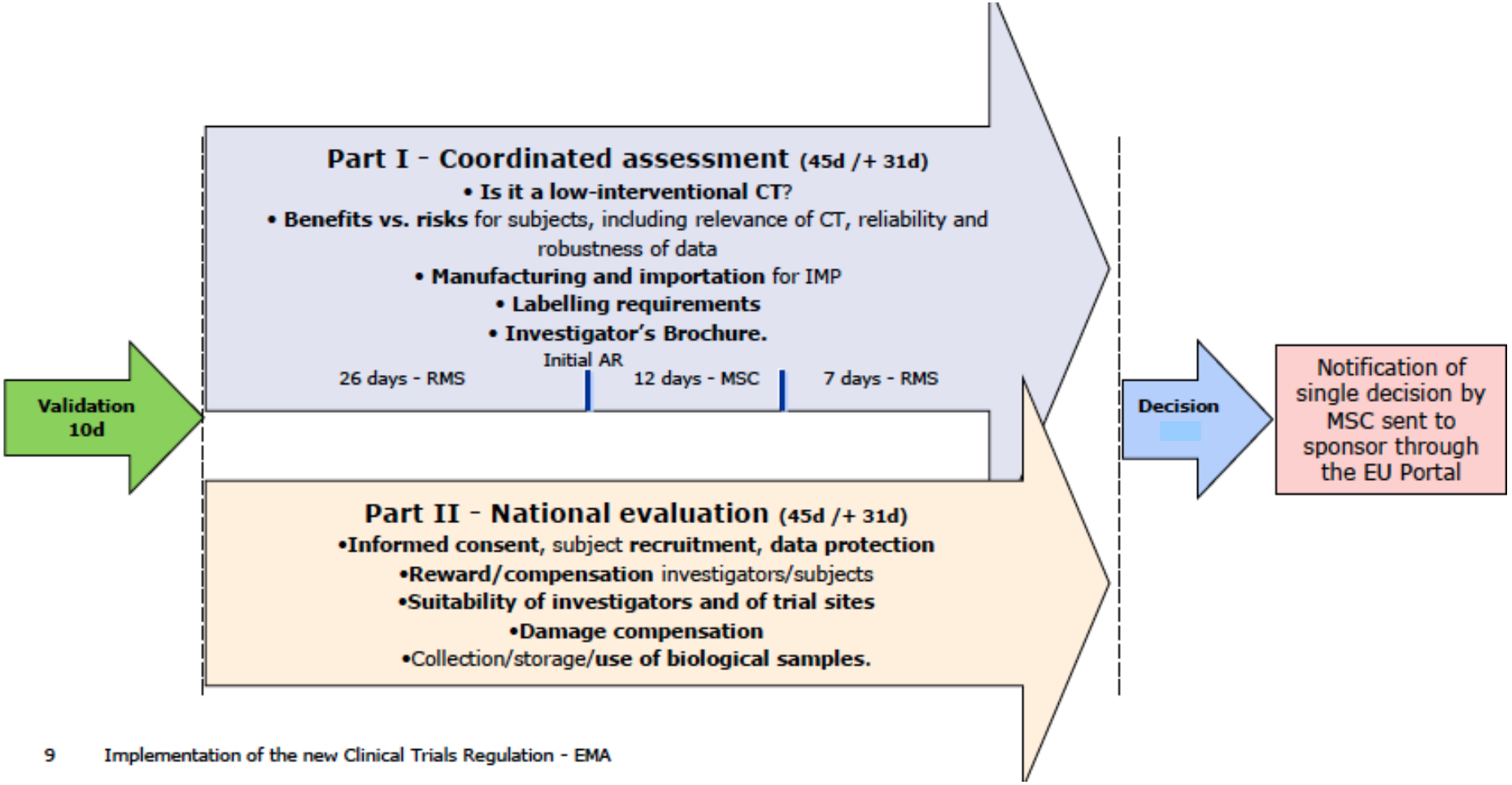
ARTICLE 6

New Evaluation Process

Worksharing

(Election of a rMS)




Validation
10d
Part I - Coordinated assessment (45d /+ 31d)
• Is it a low-interventional CT?
• Benefits vs. risks for subjects, including relevance of CT, reliability and robustness of data
• Manufacturing and importation for IMP
• Labelling requirements
• Investigator's Brochure.
Initial AR
26 days - RMS
12 days - MSC
7 days - RMS
Part II - National evaluation (45d /+ 31d)
•Informed consent, subject recruitment, data protection
•Reward/compensation investigators/subjects
•Suitability of investigators and of trial sites
•Damage compensation
•Collection/storage/use of biological samples.
Decision
Notification of single decision by MSC sent to sponsor through the EU Portal

Validation of an initial submission

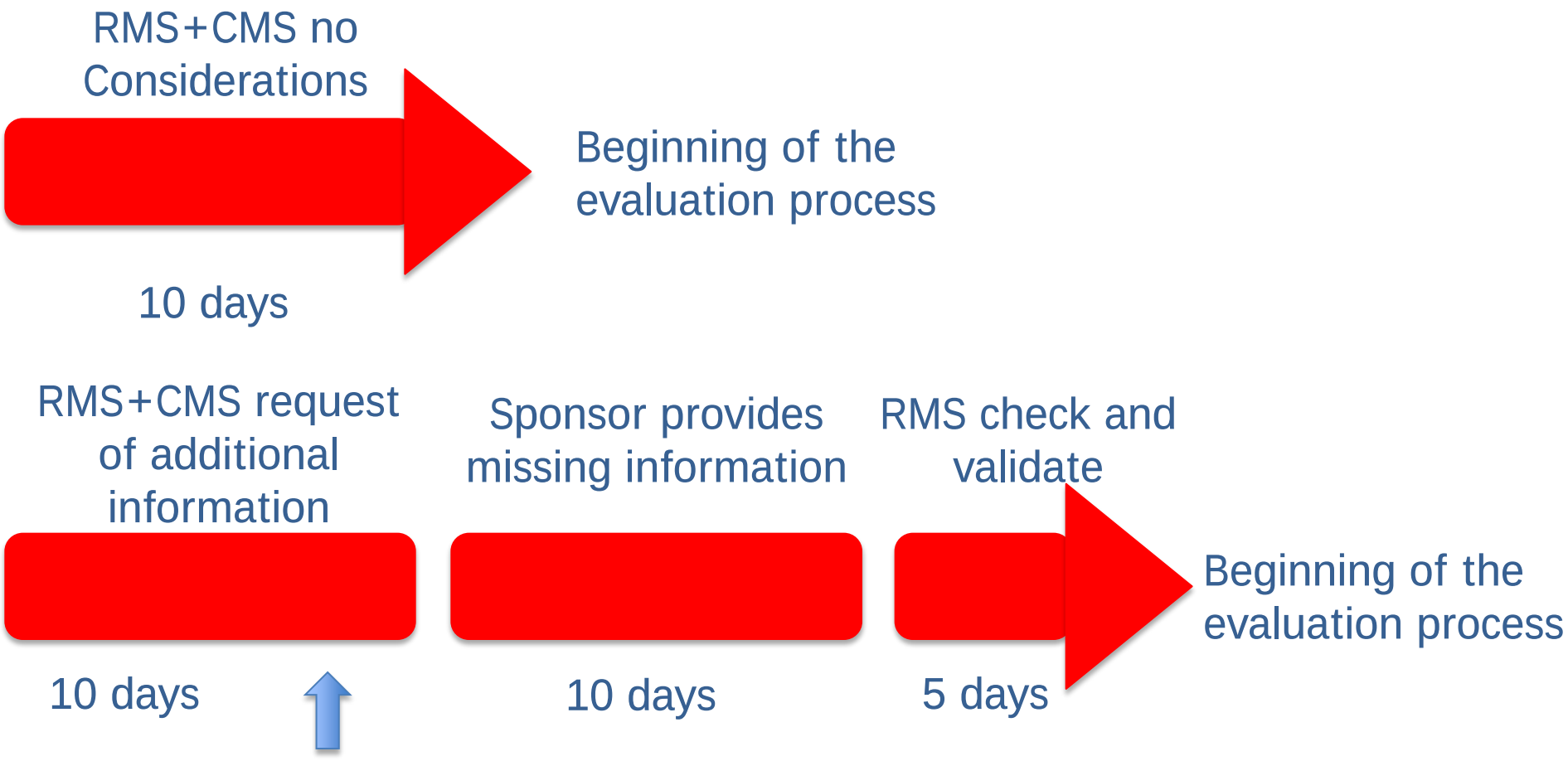
- Does the CT falls within the Scope of CTR?

- Is the CTA complete in accordance with Annex I (APPLICATION DOSSIER FOR THE INITIAL APPLICATION)

- rMS shall validate the CTA
  - if no considerations → Evaluation process starts
  - in case of request of additinal information from the MS → Sponsor should provide missing information to allow the evaluation process start

ARTICLE 5

Validation process timelines



ARTICLE 5

Assessment Part I

(a) Low-intervention clinical trial or not

(b) Compliance to chapter V with regard to the benefits (IMP, relevance, reliability of the data) and the risks (IMP, AMP, comparison with normal clinical practice, safety measures, risk of the medical condition) of the trial

(c) Manufacturing & import of IMP & AMP (chapter IX)

(d) Labelling requirements (chapter X)

(e) Completeness & adequateness of the Investigators Brochure

ARTICLE 6

Assessment procedure (Multinational CT)

- D0: validation date of the application
- D26: draft Part I AR made available by the RMS (initial assessment phase)
- D38 (+12): all CMS can share considerations (coordinated review phase)
- D45 (+7): RMS finalizes the Part I AR (consolidation phase); the final assessment report from the RMS submitted to the EU Portal (reporting date)

ARTICLE 6

Request of Additional information by the RMS

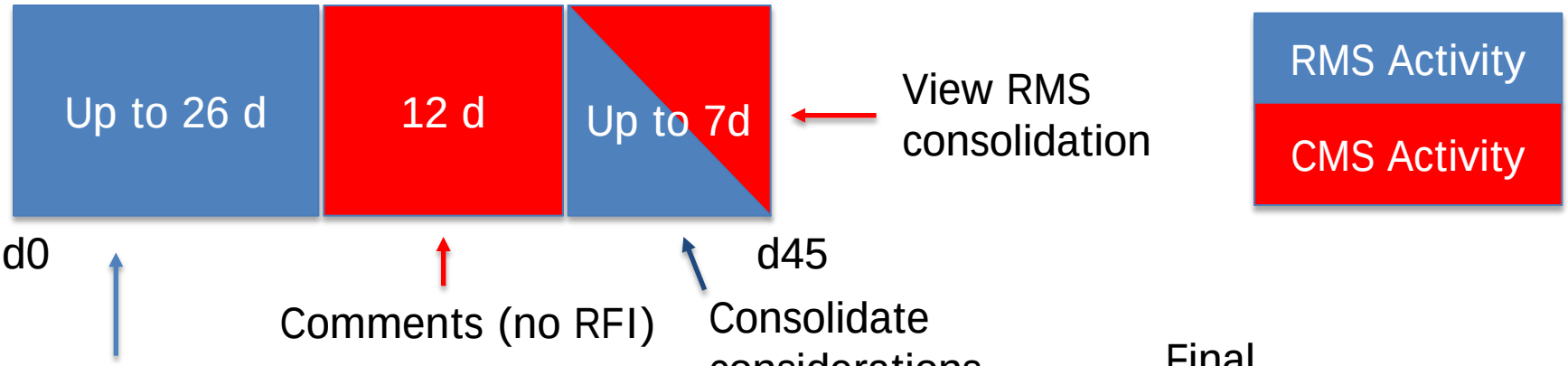
The RMS can request additional information from the sponsor between validation date and reporting date – timeline is extended (31 days):

- ✓ Sponsor submits the additional information within 12 days
- ✓ The answer is jointly reviewed by all CMS, considerations are shared within 12 days
- ✓ Final consolidation by the RMS within 7 days.

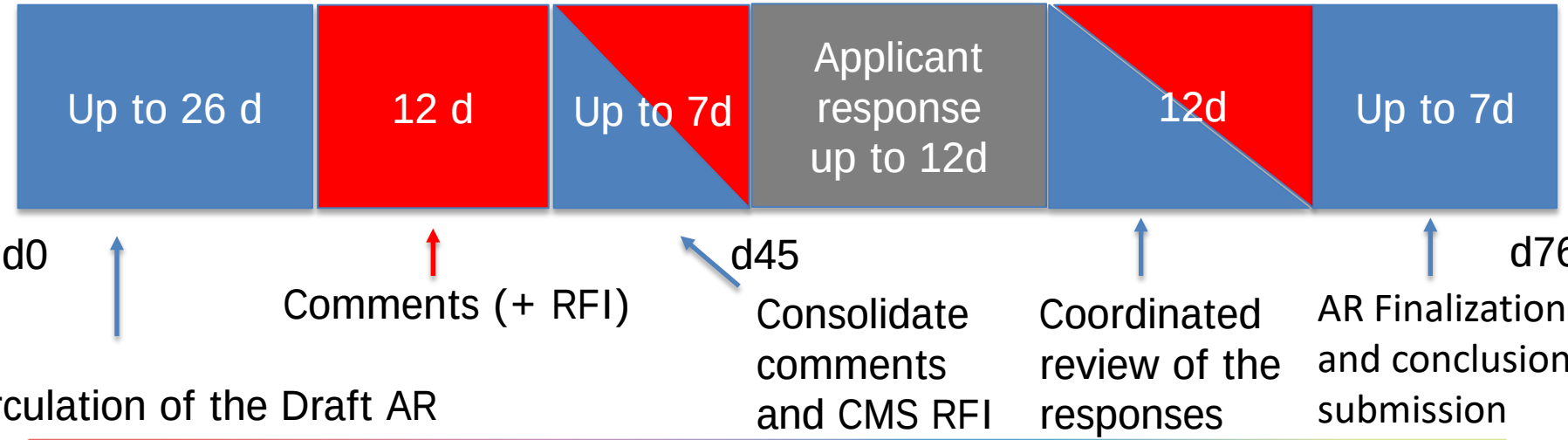
ARTICLE 6

Schematic overview of timelines for an initial application

(A) NO request of further information (RFI)

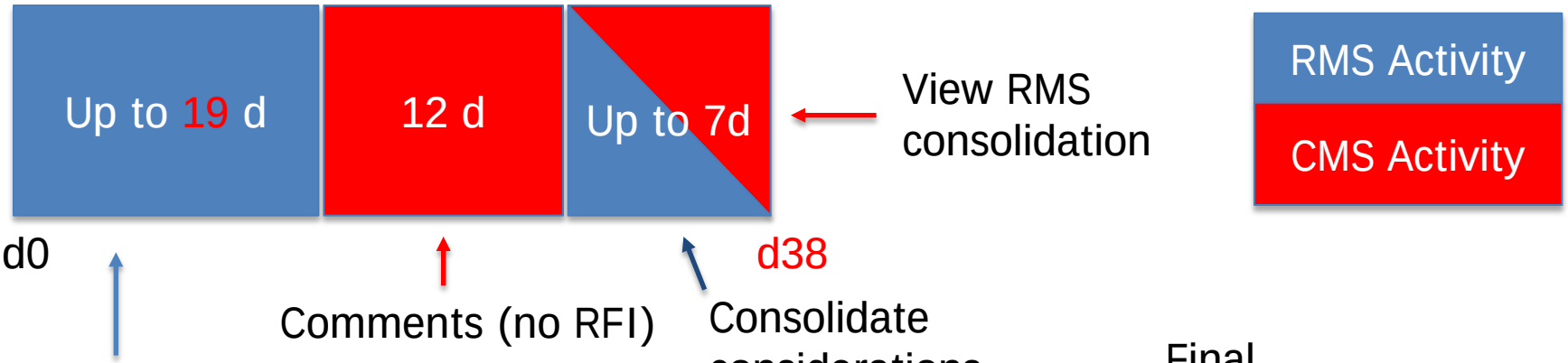


(B) Request of further information (RFI)

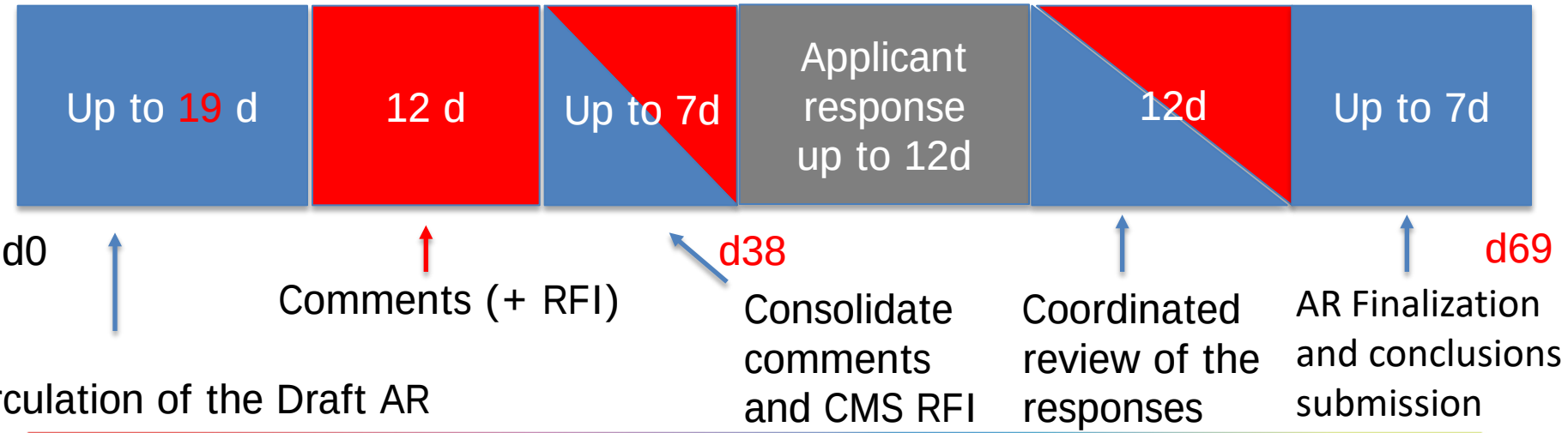


Schematic overview of timelines for a substantial modification application

(A) NO request of further information (RFI)



(B) Request of further information (RFI)



Outcome of the assessment

- The CT is authorized: The trial can start in the MS who have authorized the CT
- The Authorization of the CT is refused: The trial cannot start
- The CT is authorized subject to specific conditions. Conditions should not impact on the B/R profile and should be requirments that by their nature cannot be fulfilled at the time of the authorisation.

The trial can start

Assessment Part II

- All MSC assess (for their own territory), the aspects of part II, generate a part II AR, and formulate a conclusion
- Aspects of part II :

(a) Requirements for informed consent (chapter V)

(b) Compensation of subjects and investigators

(c) Recruitment arrangements

(d) Compliance with the rules on data protection

(e) Suitability of individuals involved in the conduct of the trial

(f) Suitability of the clinical trial sites

(g) Damage compensation

(h) Collection, storage and future use of biological samples

Timeline for Assessment of part II

- D0: validation date of the application
- D+45 : final assessment report from each MSC submitted
- All MSC can request additional information from the sponsor between validation date and reporting date – timeline is extended with 31 days
- Sponsor submits the additional information within 12 days
- Final assessment by the MSC shall be performed within 19 days.

Persons assessing the application

1. Member States shall ensure that assessors:
   - have no conflicts of interest (financial or personal),
   - are independent,
   - are free of any other undue influence.

2. Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience.

3. At least one lay-person shall participate in the assessment.

ARTICLE 9

The Clinical Trial Information System

- Article 80: “The Agency shall, in collaboration with the Member States and the Commission, draw up the functional specifications for the EU portal and the EU database, together with the time frame for their implementation.”

- The Regulation 536/2014 (Art. 82) provides the legal basis for the development of the EUPD and EMA collaborates with MS, EC and the stakeholders for the development.

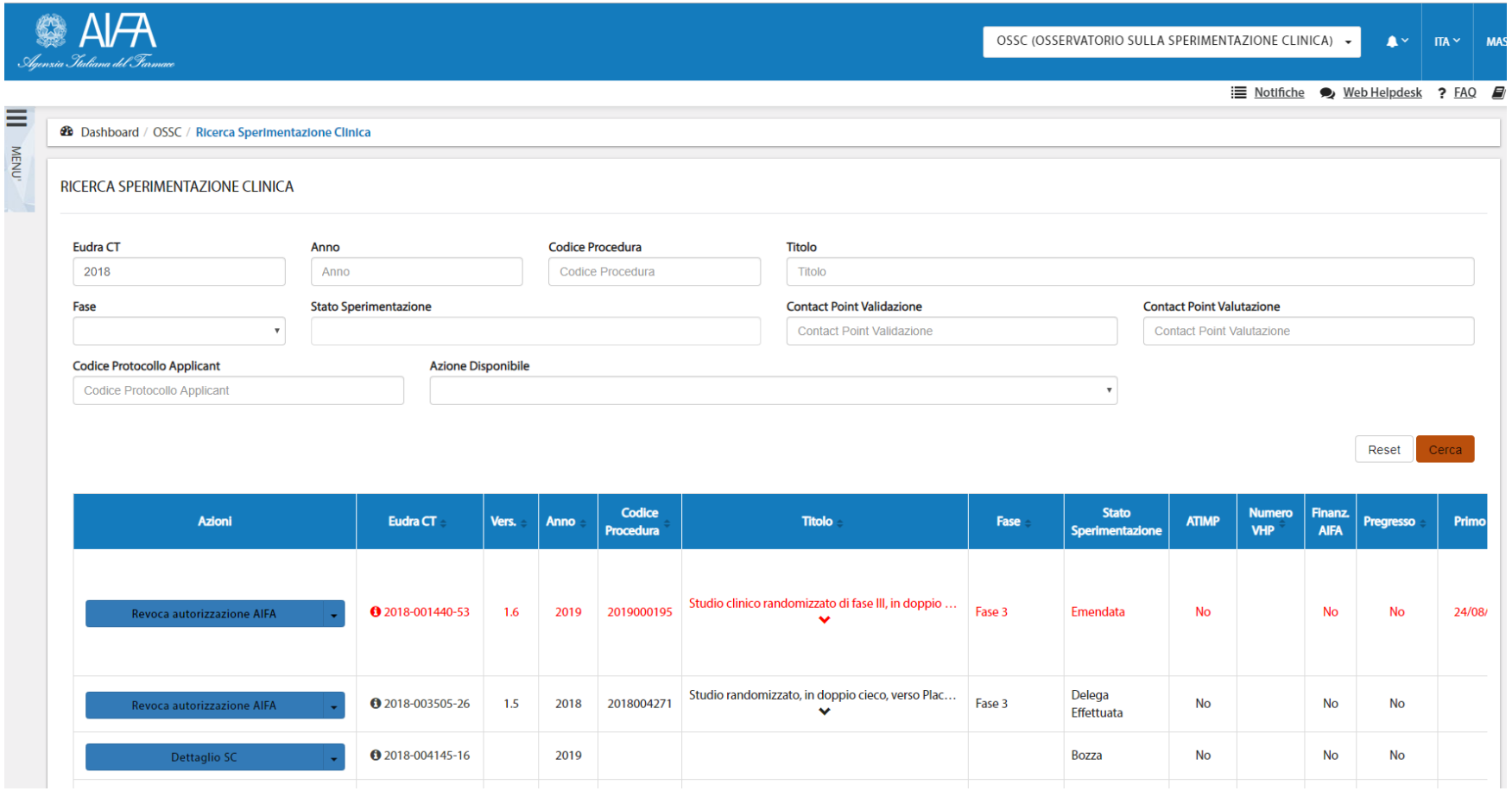
The Clinical Trial Information System

- EMA should provide, handle and update the informatic systems in collaboration with MS and EC
  - EU Portal e database (Art. 80, 81, 82 e 84)
  - Safety Reporting (Art. 40 e 44)
  - EudraCT e fase transitoria (Art. 98)
- The database should have a public access that assure the data protection as well as the confidentiality of the communications among the MS.
- The EUPD should be the only access for clinical trial application

Revised Timelines

September 2015	• V.1 Go live Oct. 2017 • Regulation applicable Dec. 2017
March 2016	• V.1 Go live Sep. 2018 • Regulation applicable Oct. 2018
October 2017	• V.1 Go live Jul. 2019? • Regulation applicable Jul. 2019?
2018	• V.1 Go live 2020? • Regulation applicable 2020?

National IT system: OsSC



Transparency

- The Regulation requires that information contained in the clinical trial database shall be publicly available unless one or more of the following exceptions apply:
- protection of personal data;
- protection of commercially confidential information, in particular taking into account the marketing authorisation status of the medicinal product, unless there is an overriding public interest;
- protection of confidential communication between Member States in the preparation of their assessment;
- protection of the supervision of clinical trials by Member States

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
- *Provides balance between encouraging innovation and providing extensive public information on clinical trials conducted in EU.*

Safety reporting in the context of a clinical trial

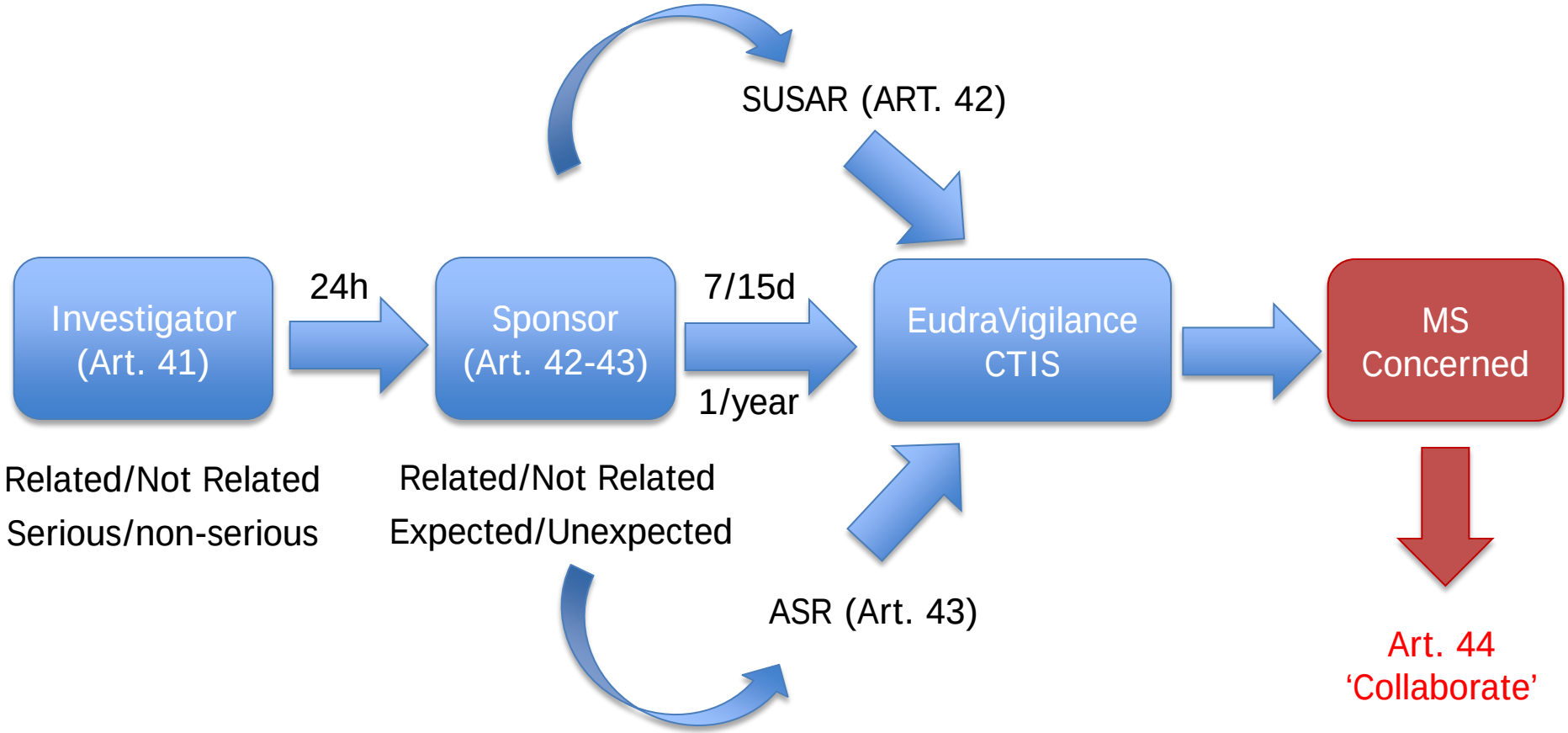
- EMA shall set up and maintain an electronic database for the safety reporting (ASR).

- The database shall be a module of the Eudravigilance database (SUSAR).

- The safety reporting should be made through a specific web-based structured form developed by EMA in collaboration with the MS.

Article 40

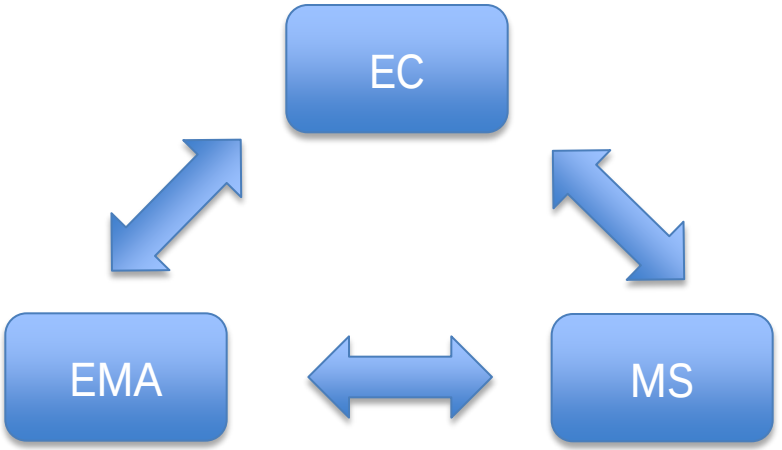
Safety Reporting under Reg. 536/2014



Safety Reporting under Reg. 536/2014

- The Agency shall, by electronic means, forward to the Member States concerned the information reported in accordance with Article 42 and 43.

- Member States shall cooperate in assessing the information reported in accordance with Articles 42 and 43.



- The Commission may, by means of implementing acts, set up and modify the rules on such cooperation.
- The Commission assigned CTFG task to develop cooperation procedure

Article 44

Safety Reporting under Reg. 536/2014: The Sponsor Role

Submission of the safety information to the portal is a Sponsor's responsibility.

Submission of one single ASR in the format on a DSUR (ICH E2F) is strongly recommended if the same IMP (or combination) is used in several CTs. However, the MS concerned can accept (as an exception) a trial-specific ASR if this is justified.

Safety reporting during the transition period

Nationally if the CT is under the 2001/20

Through the Portal if the CT is under the 536/2014

Safety reporting during the transition period

Same IMP in different CTs submitted under the 536/2014 or the 2001/20

The ASR should be submitted to the database specified in the regulation, thus leading to the coordinated assessment.

Sponsors are still obliged as of CT-3 to submit ASRs to Ethics Committees according to national legislations in MSs with ongoing clinical trials within Directive 2001/20/EC and inform investigators of any new safety data or change in benefit-risk evaluation.

Sponsors are strongly encouraged to name all MSs concerned for all ongoing CTs in EU/EEA (i.e. in the cover letter) within Directive as well as Clinical Trials Regulation (EU) 536/2014 and the CTs, respectively.

DSUR – Reg. 536/2014 Art.44

"Member states shall cooperate in assessing the information reported in accordance with articles 42 and 43."

No details in the new regulation on:

- How to do it
- Roles and responsibilities
- Involvement of different regulatory bodies

Safety Reporting under Reg. 536/2014: The MS/CTFG Activity and the worksharing process

- To harmonize safety assessment of an Investigational Medicinal Product (IMP) and get common opinion on an IMP used in a CT.
- To improve transparency on (potential) safety issues among MS.
- To avoid duplicity of assessment, save resources and improve supervision of safety of CT participants.
- To trigger expedite actions, in order to facilitate harmonized corrective measures in clinical trials when appropriate and needed.

Safety Assessing Member State (saMS)

- Leading MS in coordinating all the activities related to the safety of an IMP (assessment of safety reports and upcoming safety issues)

- Is expert and communication hub for all MS concerned with a particular IMP/API

- Might be different from the RMS (IMP-based selection), and not for lifetime of CT/IMP

SaMS selection

First CT submitted with an IMP in EU/EEA

- The selection of the saMS is based on hierarchic approach:

1. All MSC can volunteer for the saMS role/task
2. In case of no volunteer or more than 1 volunteers a fair Work-share algorithm that takes into account the MS workload will be used
3. Random selection in case of the same priority given by the algorithm.

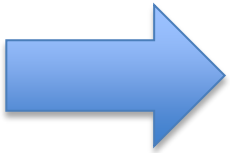
Re-selection

After the finalization of the ASR assessment a re-selection of saMS can be initiated in specific cases where the saMS is no longer able to carry on the task (i.e. the CTs has been completed in the MS). The re-selection follows the same hierarchic rules.

“Leading saMS” and “AdHoc Assessment”

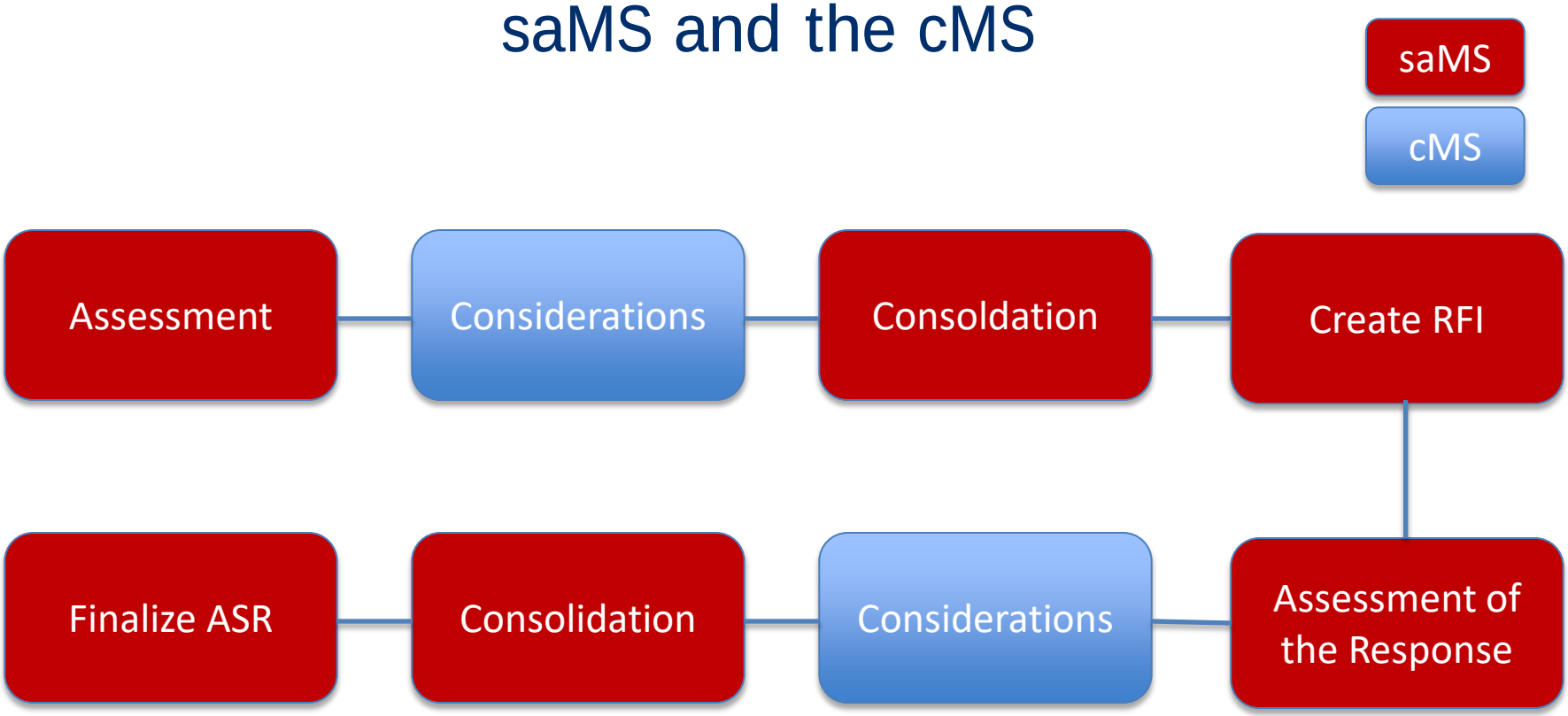
Safety issues concerning different IMPs (i.e. class effects AR) – More than one saMS/RMS involved – one will coordinate.

Need to take action following serious breach, unexpected event, urgent safety measure, temporary halt notification submitted by the sponsor or other information received from different/other sources.



- Selection of a “leading” saMS who lead and coordinate the ad hoc assessment activity involving exchange with the other saMSs, while these involve all MSCs (RMS, CMS).
- Need of tight collaboration and harmonization among all the parties involved.
- If not ASR assessment it is called ‘AdHoc Assessment’ in CTIS

MS Assessment Workflow: roles of the saMS and the cMS



Clinical Trials Facilitation and Coordination Group CTFG

ASR Worksharing CTFG Project

- The project is coordinated by CZ and currently 19 NCA join the work-sharing activity

- MS collaborate in assessing ASR submitted by the Sponsors nationally on a voluntary-based project aimed at providing a coordinate review of the safety information

- MS who takes the lead of the assessment process is selected per IMP

- Almost 300 DSUR/ASR have been assessed from 2015 involved more than 230 IMPs

Challenges of the safety assessment

- ASR incl. reference safety information
  - Amount of information
  - Number of reports received

- SUSARs
  - Amount of signals received every day
  - Need to prioritize reactions
  - Need to assess the *'real potential risks'*

- Others e.g. urgent safety measures, halted CT, other sources
  - Need to coordinate rapid assessment, coordinated common responses and activity involving all the parties involved.

Aims of Directive 2001/20 EC

- The protection of the health and safety of clinical trial participants
- The ethical soundness of the clinical trial
- The reliability and robustness of data generated in clinical trials
- Simplification and harmonisation of the administrative provisions governing clinical trials in order to allow for cost-efficient clinical research

- *This "should be achieved while promoting high-quality research in the EU and the competitiveness of the European pharmaceutical industry."*

- Did the Directive met its objectives?

Conclusions: Why change from the Directive?

- *Improvements in the safety and ethical soundness of clinical trials in the EU and in the reliability of clinical trials data. Also increased cooperation between MS; however….*
  - Decrease in EU CTAs (2007-2011)
  - Increase in costs
  - Increase in delay to trial initiation
  - Different requirements in different MS

- Not all because of Directive 2001/20/EC but it is *"Arguably the most heavily criticised piece of EU-legislation in the area of pharmaceuticals."* (European Commission)

Conclusions: 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.

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