EUROPEAN MEDICAL WRITERS ASSOCIATION

All about CTIS and what's in it for medical writers

(CTIS = Clinical Trial Management System in EU/EEA)

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Agenda

What is CTIS?

Who are the players?

Basics: Other databases OMS & XEVMPD, Data formats, Initial Clinical Trial Application, Substantial Modifications, Requests for Information

CTIS look & key content requirement for CTIS

Maintaining clinical trial approval: Notifications

Transparency requirements in CTIS

What's in it for medical writers?

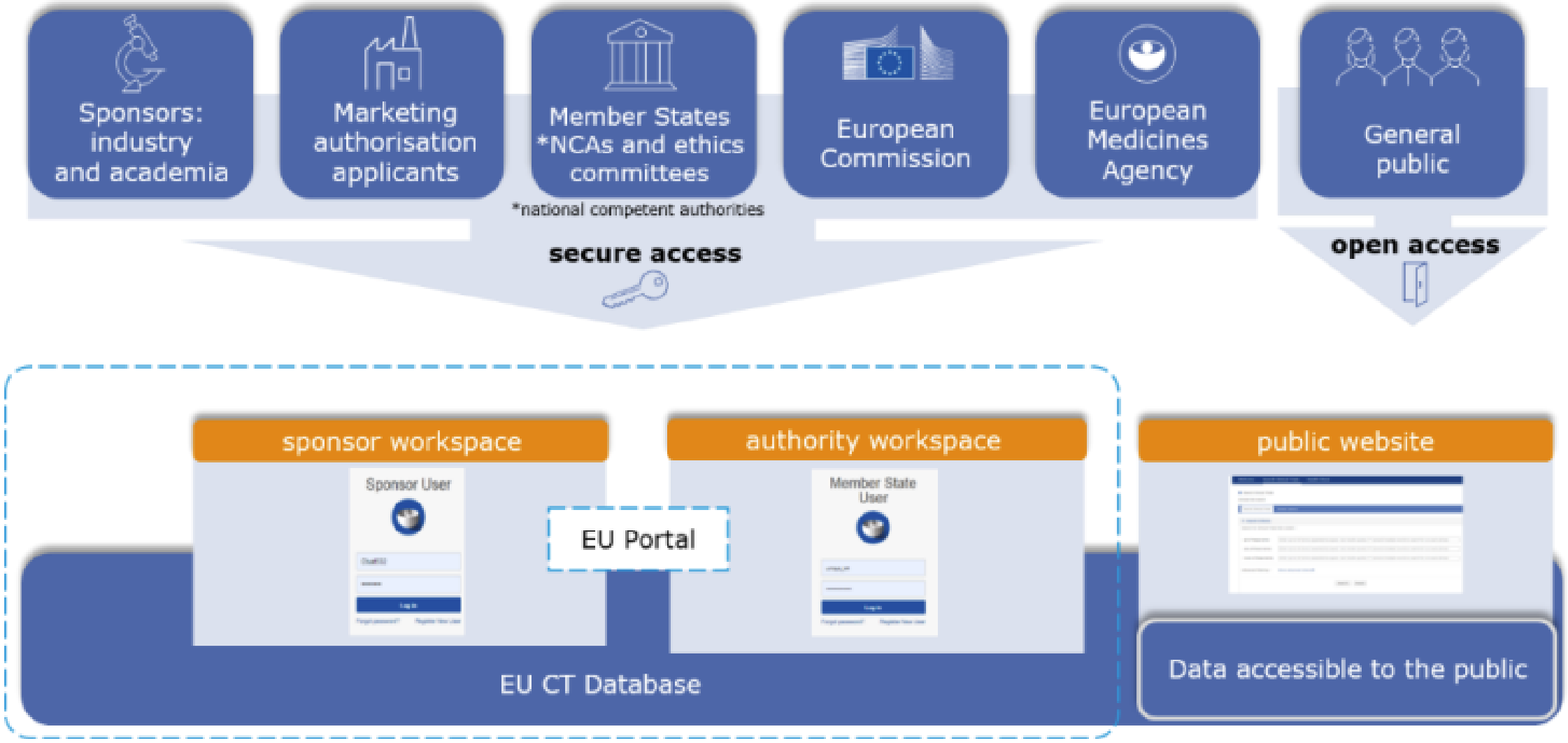
CTIS as an information source: CTIS is an international clinical trial registry

Self-training opportunities and starting points

What is the Clinical Trial Information System - CTIS?

- It is a common workspace for all aspects of clinical trial approval, maintenance, and results reporting in the EU/EEA. The use of CTIS is mandatory for all clinical trials with a trial site in the European Union and the European Economic Area (EU/EEA).
- It enables implementation of the European Clinical Trials Regulation 536/2014 (EU CTR).
- Is mandatory for all aspects of clinical trials including:
  - Initial application
  - Management and oversight of a clinical trial during conduct
  - Reporting of important events during a clinical trial: Notifications
  - Reporting of clinical trial results
- Is an international clinical trial registry and fulfils the transparency requirements of the EU CTR
- Is a resource for researchers and patients: the public portal

Who are the major players in CTIS?



Source: Quick guide Overview of CTIS workspaces and common system functionalities CTIS Training Programme – Module 2

Who are the major players in CTIS?

- Sponsors: submit study applications, modify study conduct, maintain authorization through notifications, submit Annual Safety Reports, Study Results, and Clinical Study Reports
- Competent Authorities and Ethics Committees: assess applications, assess modifications, maintain oversight, receive notifications, invoke corrective measures
- EMA: maintains the CTIS workspace infrastructure including a Help Desk; European Commission, Heads of Medicines Agencies (HMA) / Clinical Trial Coordination Group (CTCG): provide guidance on CTIS processes
- General public: has rapid access to clinical trial data in Europe

Basics: CTIS relies on 2 other databases

XEVMPD =
EudraVigilance Medicinal Product Dictionary
→ pre-registration of all IMPs and AuxMPs used in trial

OMS =
Organisation Management System
→ pre-registration of all investigators and sites used in trial

CTIS =
Clinical trial information system
Sponsor and authority workspace
→ Data fields need to be completed, and documents need to be uploaded
→ Decisions communicated

Public view on almost all sponsor documents and regulatory decisions

Basics: Data formats in CTIS

- Structured data:
  - data that needs to be provided either as text or by selecting items of drop-down menus
  - Manual entry (→ QC)
- Documents:
  - clinical and quality documents for Part I,
  - Investigator, site suitability, insurance, informed consent for Part II,
  - CTIS process specific documents: Cover Letter, Modification Description, Declarations of Compliance

Basics: Separation of Part I and Part II

Simplification !

- **Part I → trial specific information**
  - Clinical Trial Protocol
  - Committee Charters
  - Scientific advice and Paediatric Investigation Plan (PIP) summary
  - IB / SmPC
  - IMPD-Quality
  - IMP Labels

Jointly assessed by the competent authorities of the Reporting Member State (RMS) and the Member State(s) MSC(s) concerned & Ethics committees

- **Part II → site specific information**
  - Site suitability
  - Investigator suitability, CV
  - ICF, also in translations
  - Insurance
  - Financial arrangements
  - Biological samples and data protection compliance statements (according to national law)

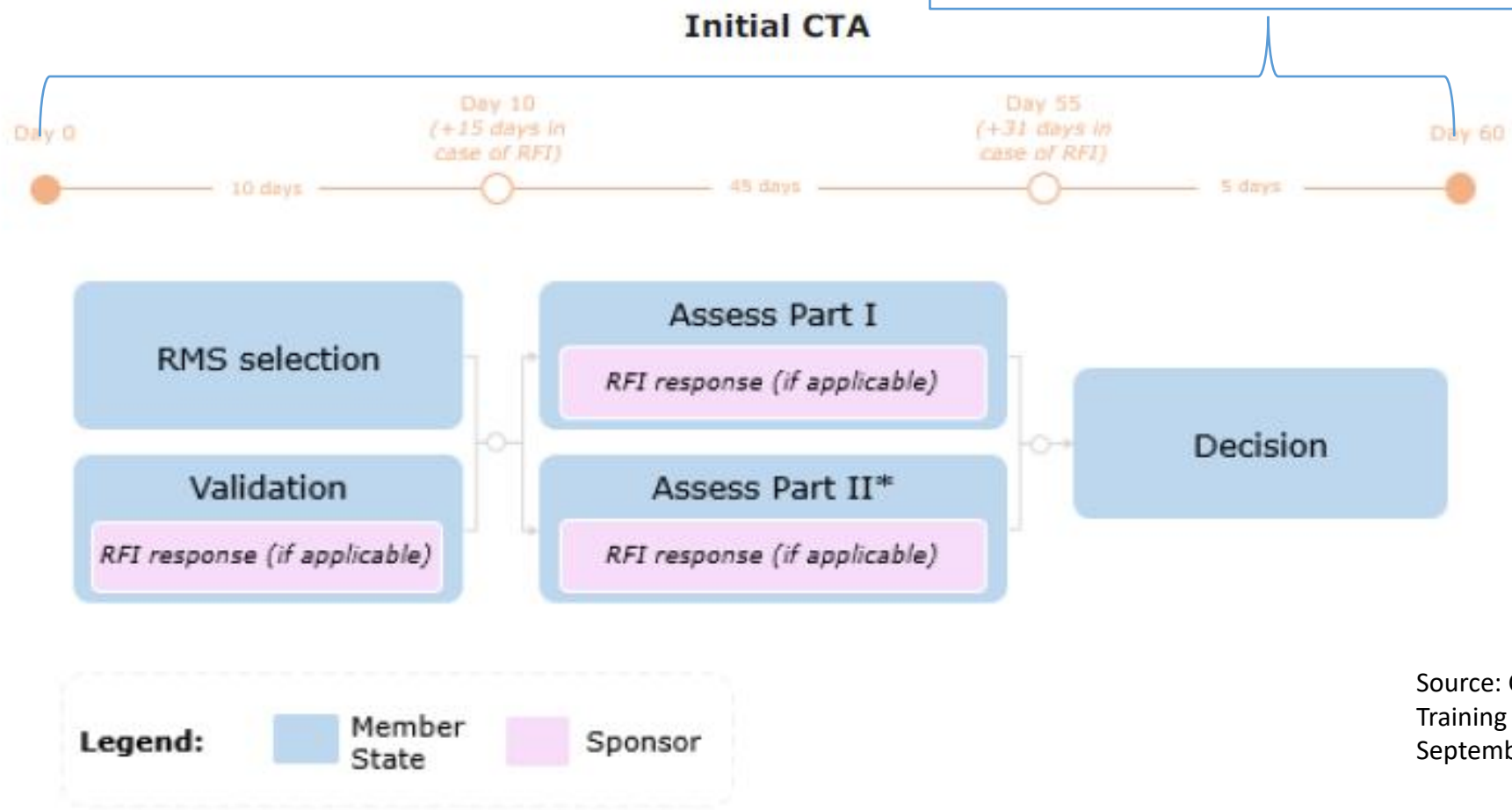
Jointly assessed by the ethic committees of the Reporting Member State (RMS) and the Member State(s) MSC(s) concerned & competent authorities

Basics: Assessment of an initial Clinical Trial Application (CTA)

Ideal: 60 days

Real: 91 days (60+31, 1 RFI)

ATMP: 141 days (60+50+31, 1 RFI)



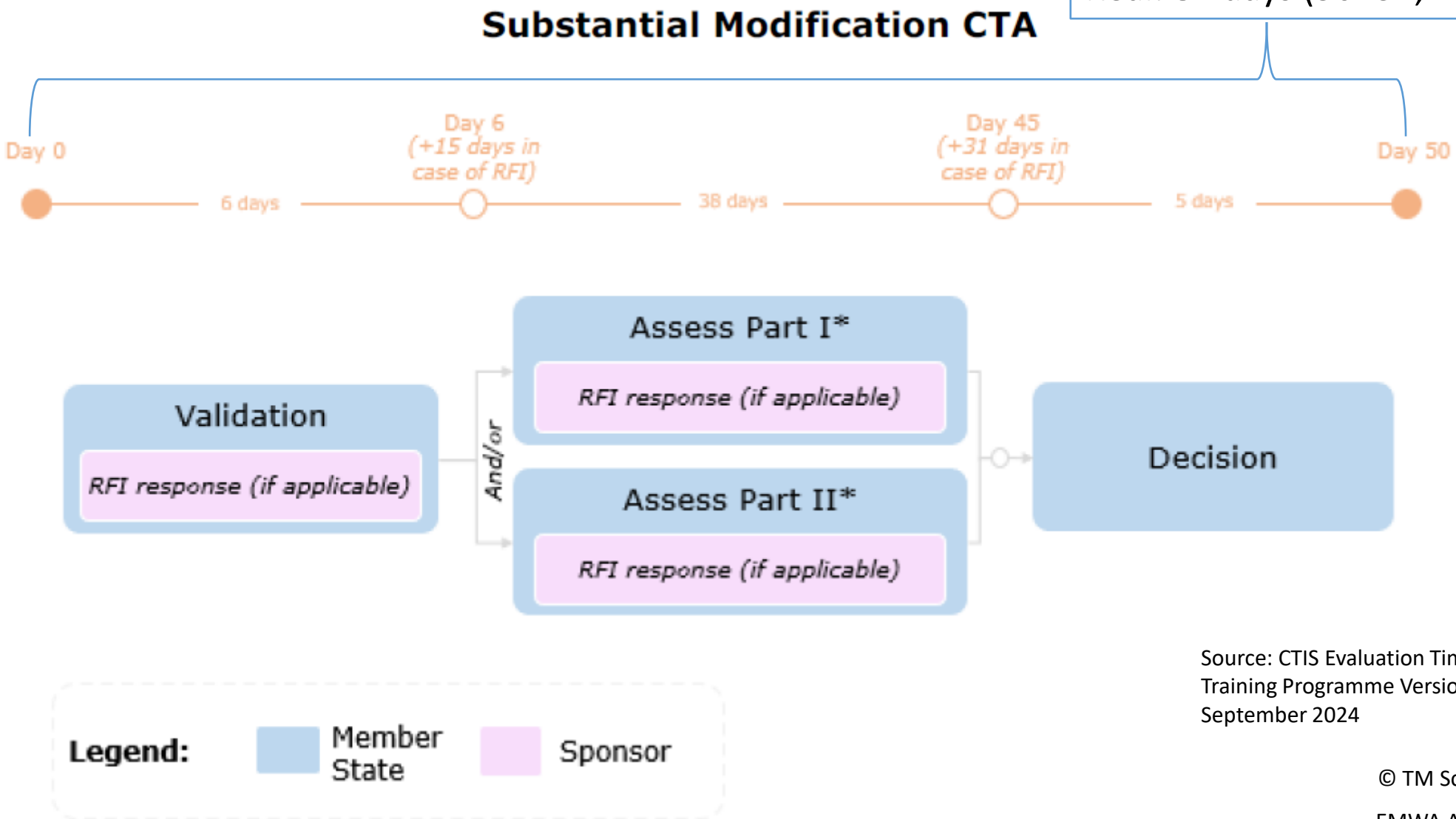
RFI = Request for Information
ATMP = Advanced Therapy Medicinal Product

Source: CTIS Evaluation Timelines CTIS Training Programme Version 2.1 – September 2024

Basics: Assessment of a Substantial Modification

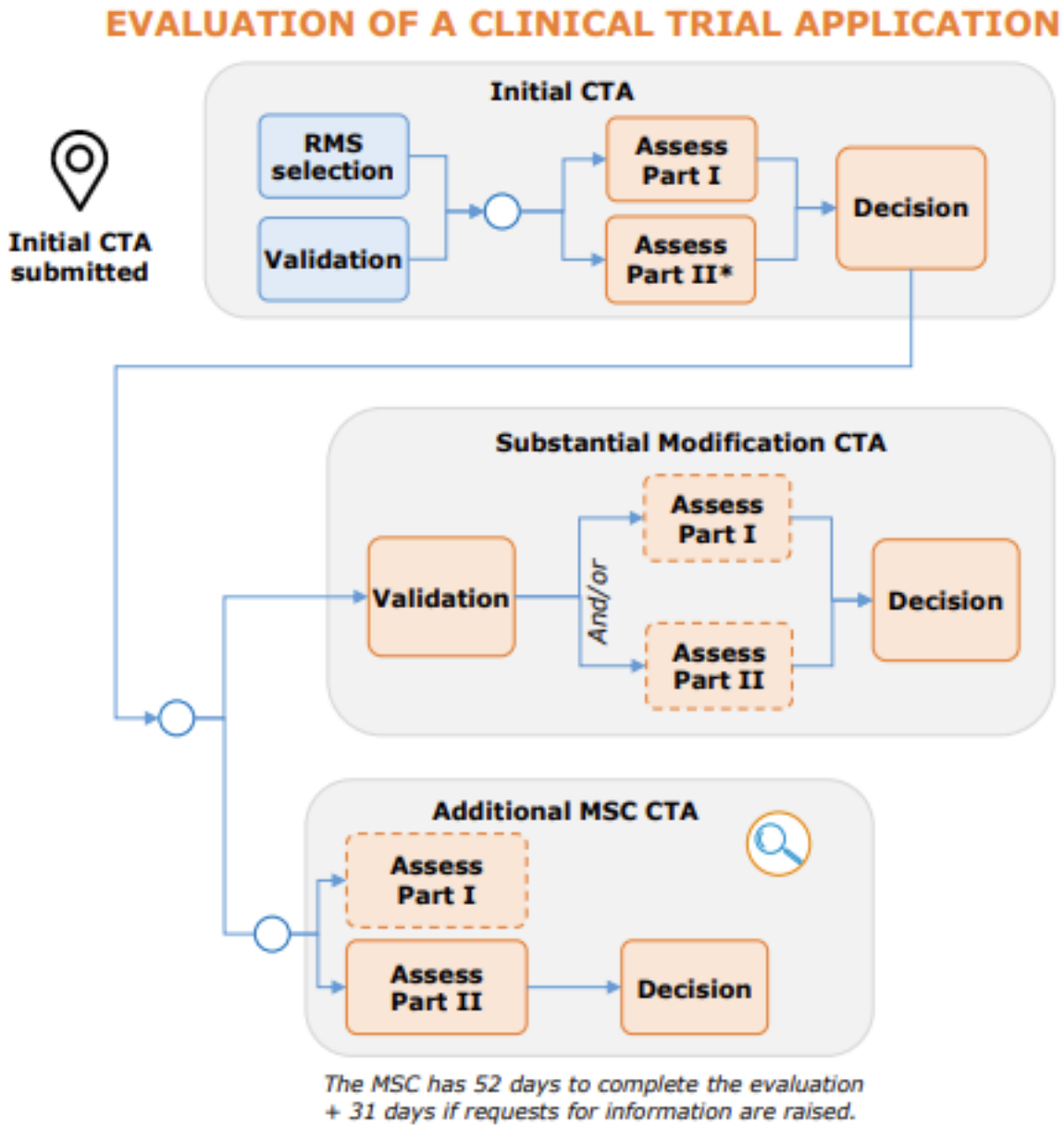
Ideal: 50 days

Real: 81 days (50+31, 1 RFI)



Source: CTIS Evaluation Timelines CTIS Training Programme Version 2.1 – September 2024

Basics: Sequential Assessment of procedures



Processes are sequential: While an initial CTA is assessed no changes to the study can be made.

What is a CTA RFI?

Clinical Trial Application (CTA) RFIs

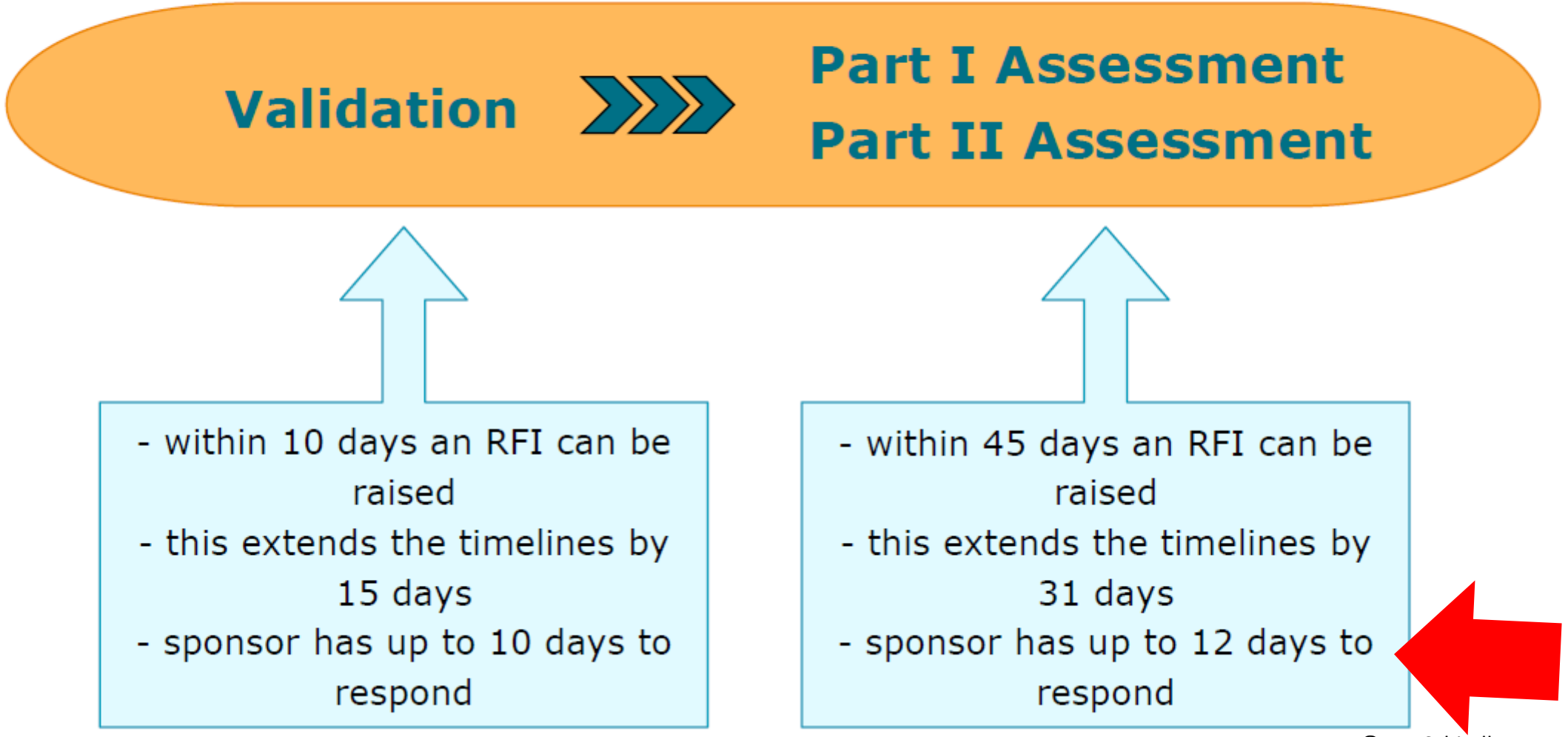
A CTA RFI is a request for additional information raised optionally by the RMS/MSC during the evaluation of an application

Evaluation

Validation | Part I | Part II

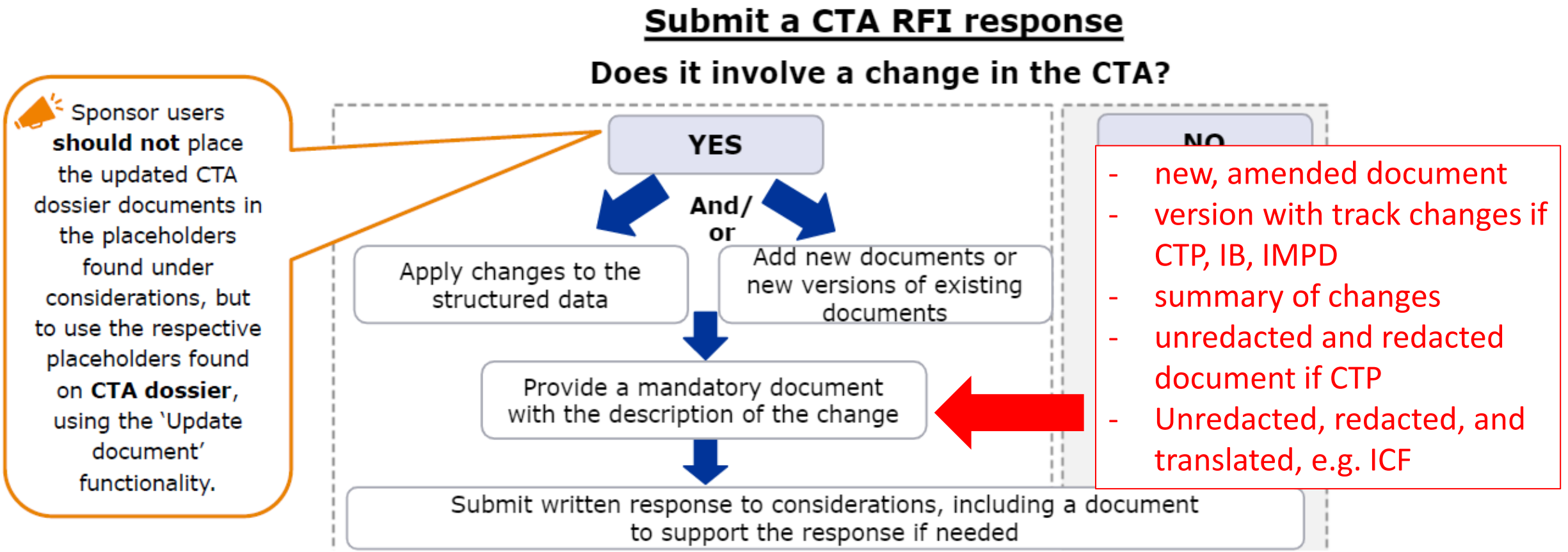
Sponsors must respond to CTA RFIs in order for the assessment of the CTAs to move forward. In case the sponsor does not respond to the individual RFI within the period set for it, **the CTA will lapse**, i.e. it will come to an end and no decision will be provided

CTA evaluation and RFIs timelines

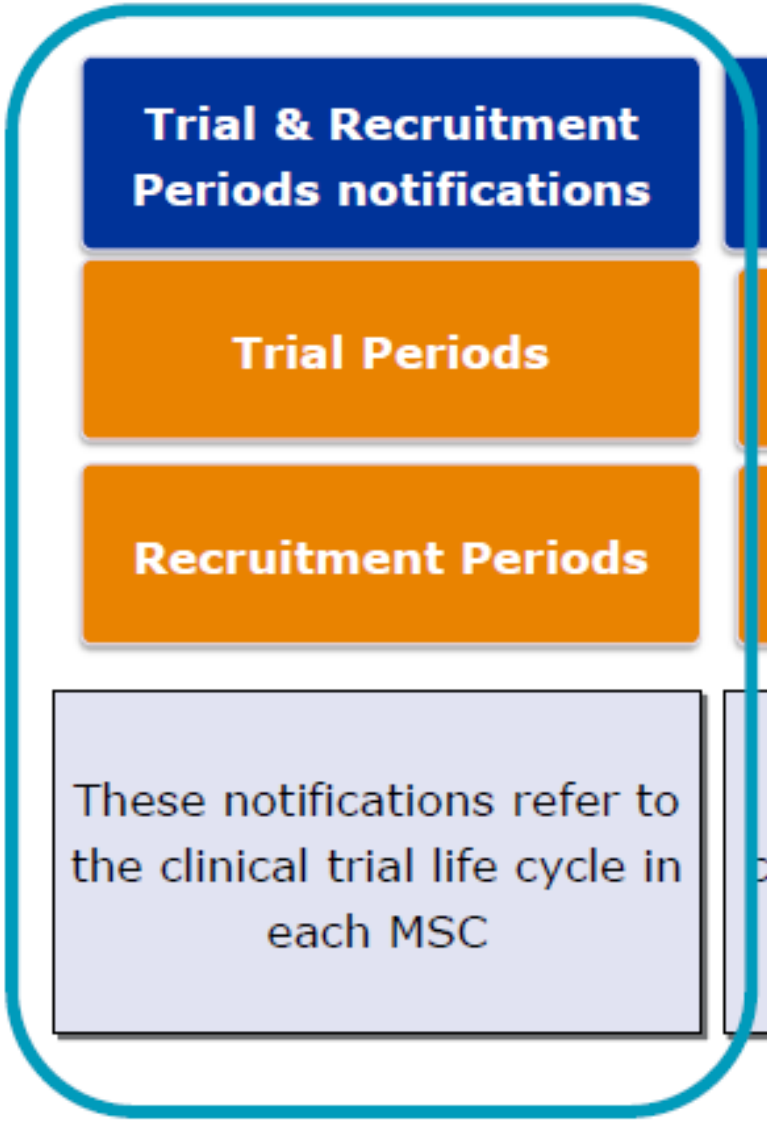


Sponsors' responses to RFI and CTA changes

The response to a CTA RFI involve the following actions: respond to the considerations in writing (mandatory); change the CTA structured data; and update or add documents.



Maintenance of clinical trial approval: notifications

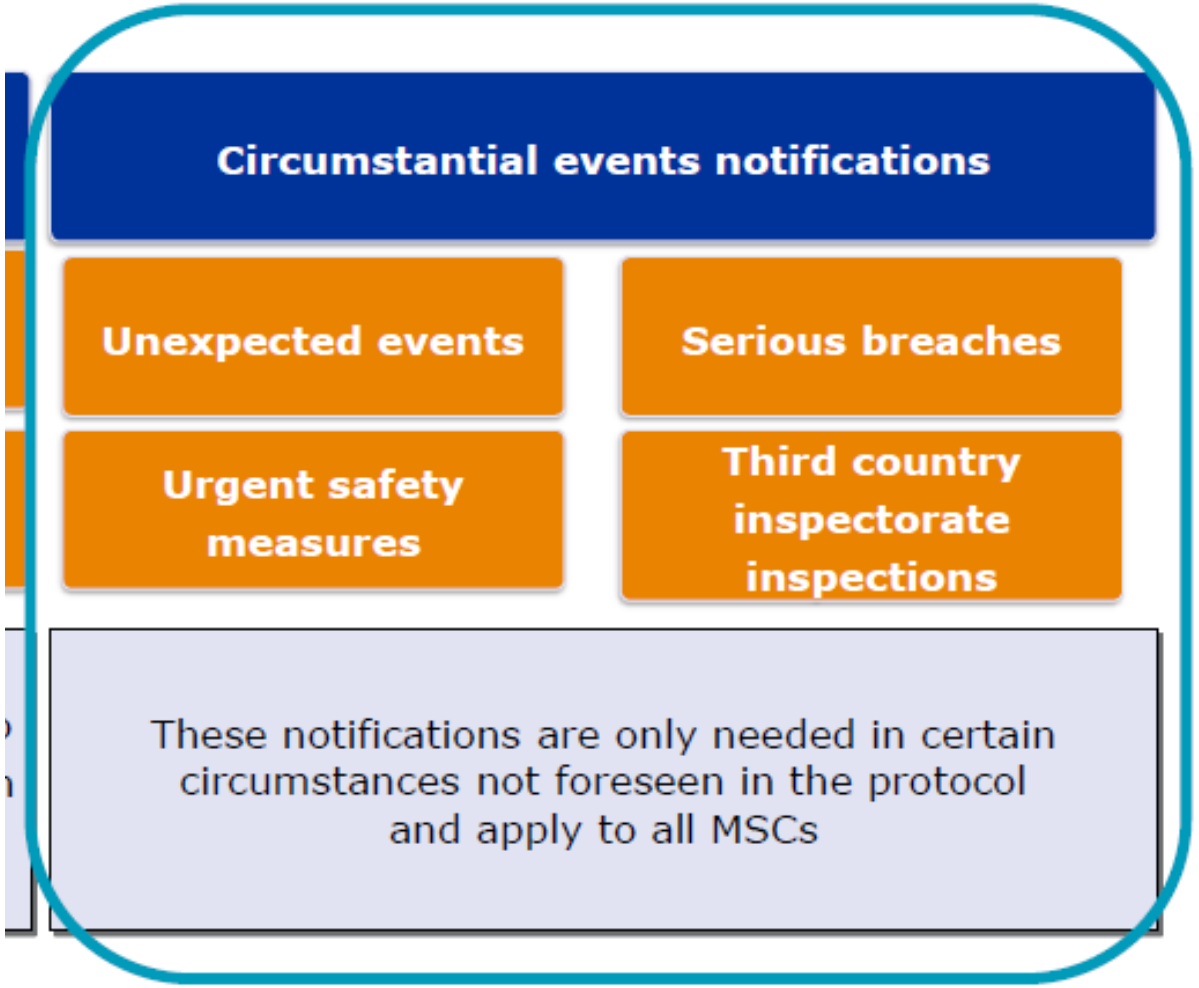


- Start of trial
- Start of recruitment
- End of recruitment
- End of trial
- Temporary halt
- Restart of trial
- Restart of recruitment

To be reported within 15 days

Maintenance of clinical trial approval: notifications

Notifications for unplanned events



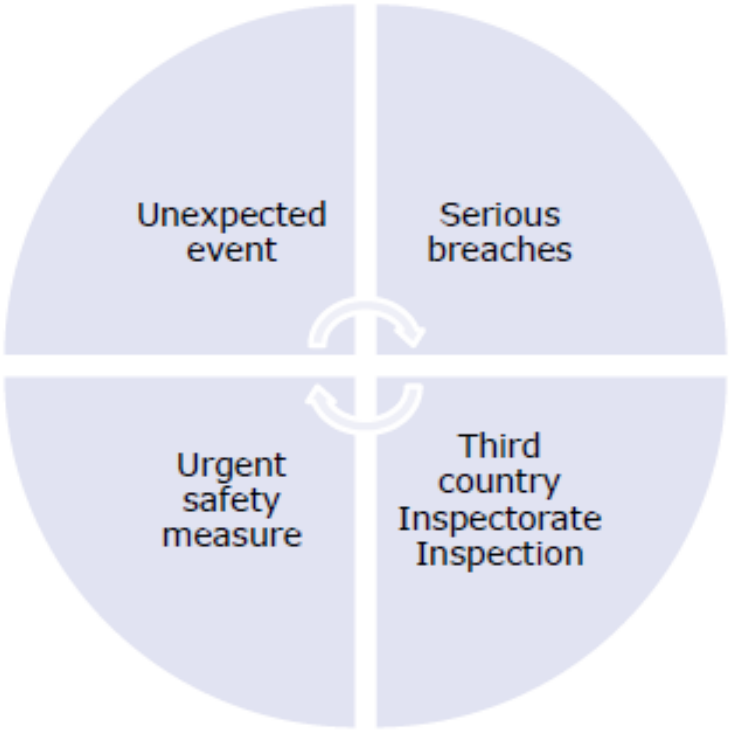
Maintenance of clinical trial approval: notifications

- *Primarily independent of each other*
- *Can only be submitted after a clinical trial has been decided*

UE (unexpected event)
- might influence the **benefit-risk assessment** of the medicinal product
- or that would lead to changes in the administration of a medicinal product or in overall conduct of a CT

Notifications no later than **15 days** from the date of sponsor awareness
Art. 53 (1) of the CT Regulation

USMs (urgent safety measures) taken to protect the subjects when an UE is likely to seriously affect the benefit-risk balance
Notifications no later than **7 days** from the date USMs were taken
Art. 54 of the CT Regulation

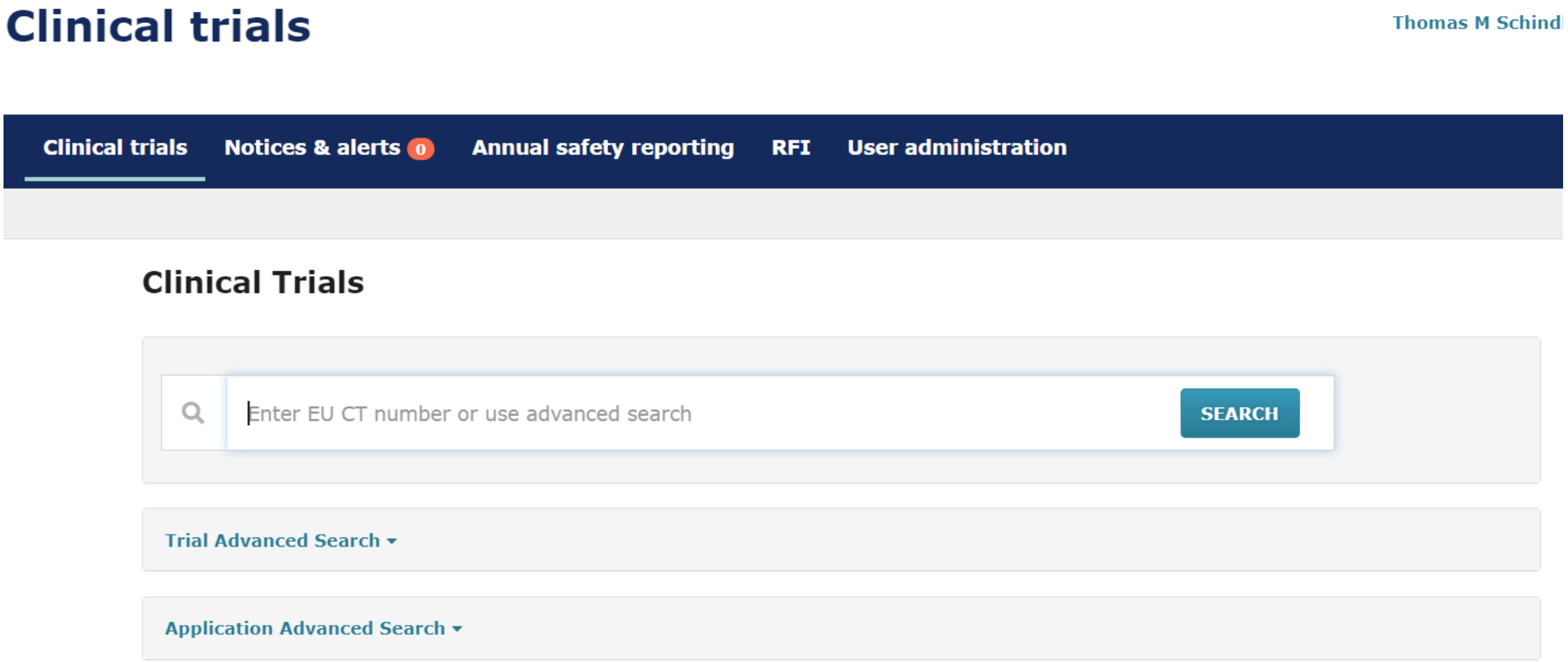


SB (serious breach) is likely to affect
- safety and rights of subject, or
- reliability and robustness of the data generated in the CT

Notifications no later than **7 days** from the date of sponsor awareness.
Art. 52 of the CT Regulation

Sponsor submits all inspection reports of third countries' authorities concerning a CT
Art. 53 (2) of the CT Regulation

CTIS – Landing Page



https://euclinicaltrials.eu/ct-sponsor-services/index.html#!/trials

CTIS – Part I – Entry page

CTIS – Part II Entry page

CTIS – Information requirements – Part I

Part I section	Sub-sections		Required fields
Trial details	**Trial identifiers**		• Full title • Public title
		Trial category	• If Low intervention trial (check box) / Justification for the low intervention trial • Trial phase
	Trial information	***Medical condition***	• Add condition (button) / Medical condition(s) • Therapeutic area
		Main objective	• Trial scope • Main objective
		Eligibility criteria	• Add inclusion criteria (button) • Add exclusion criteria (button)
		End points	• Add primary endpoint (button)
		Trial duration	• Estimated recruitment start date in EEA • Estimated end of trial date in EEA
		Individual Participant Data (IPD) Sharing Statement	• 'Plan to share IPD', is mandatory • Selection from a drop-down list of pre-defined values
		Population of trial subjects	• Age range • Gender • Clinical trial group • (if check box 'Vulnerable group' is clicked) Recruitment population group
	Protocol information	***Clinical trial protocol***	• Protocol
Sponsors	**Contact point for Union**		• Add contact point for Union (button) • Scientific Contact Point • Public Contact Point
Products	**Products**		• +Add (button)
	Role: Test (example)		• +Add (button) / Authorised product (example)
	Dosage and administration details		• Route of administration • Maximum duration of treatment • Maximum daily dose allowed • Total dose unit of measure
	Information about the modification of the medicinal product		• Has the medicinal product been modified in relation to its Marketing Authorisation? (check box)
	Investigator brochure for the medicinal product		• Investigator brochure • Summary of product characteristics (SmPC)
	IMPD Quality*		• IMPD-Q • Simplified IMPD-Q • Justification for no IMPD upload
	IMPD - Safety and efficacy*		• IMPD - Safety and Efficacy • Simplified IMPD - Safety and Efficacy • Justification for no IMPD upload
	Content labelling		• Content labelling of the IMP's

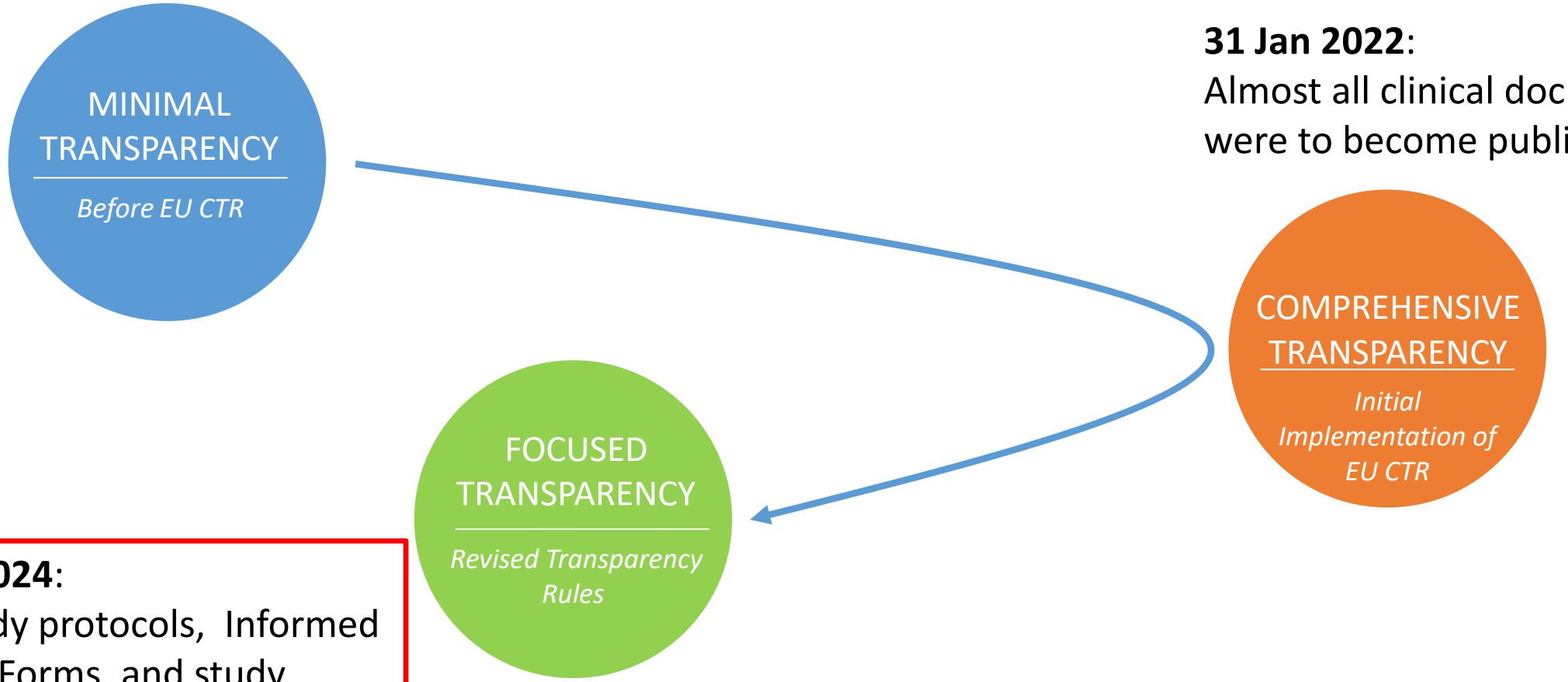
Checklist of required fields per application type: How to create, submit and withdraw a CTA CTIS Training Programme – Module 10 Version 1.2 – June 2024

CTIS – Information requirements – Part II

Part II section	Sub-sections	Required fields
Country specific details	**Trial sites**	• +Add sites (button) • Search organisation (or create an organisation) • Edit information (pencil) • First name / last name / department / phone / email
	Documents	• Recruitment arrangements • Subject information and informed consent form • Investigator CV • Suitability of the facilities • Proof of insurance cover or indemnification • Financial and other arrangements

Checklist of required fields per application type: How to create, submit and withdraw a CTA CTIS Training Programme – Module 10 Version 1.2 – June 2024

CTIS – Transparency



31 Jan 2022:
Almost all clinical documents were to become public.

18 Jun 2024:
Only study protocols, Informed Consent Forms, and study results become public.

EU CTR = EU Clinical Trial Regulation 536/2014

CTIS – Transparency of documents

Documents – what will be published & when

	Category 1 (First in human)		Category 2 and 3 *including integrated ph1&2* (Phase I/II, II, III)
Documents type	**Paediatrics and/or PIP**	**Adults**	
Protocol, synopsis, patients facing documents	Upon results' submission	30 months after EU/EEA End of Trial	**60 - 100 days after submission**
SmPC, if available	Never		
Subject information and informed consent form			That MSC decision
Recruitment arrangements, *including procedures for inclusion and copy of advertising material*			
Final summary of results, Lay person summary of results	As soon as submitted	30 months after EU/EEA End of Trial	As soon as submitted
Clinical study report, *if available*	As soon as submitted		
All other documents, including any MS document	Never		

Revised CTIS transparency rules, historical trials and interim period: quick guide for users
V. 1.3, https://www.ema.europa.eu/en/documents/other/revised-ctis-transparency-rules_en.pdf

CTIS - What's in it for medical writers?

- Potential contributions of medical writers:
  - Ensure that clinical documents (IB, CTP, ICF) are "CTR-ready", comply with rules set out in Clinical Trial Regulation including transparency requirements
  - Ensure that the content of structured data fields is in line with transparency requirements and internal policies
  - Manage the multi-stakeholder process in the run-up of a clinical trial application
  - Lead/manage the writing of Responses to Requests for Information (RFI)
  - Write/Review the Cover Letter and Modification Description
  - Support the writing of response documents to ensure completeness, adequacy of structure, style and tone
  - Perform quality control checks

Working with CTIS will suit medical writers who:

- Have a profound interest for the regulatory processes for clinical trial approval, maintenance, and trial results reporting
- Have a knack for technical challenges → there are a numerous technical inconsistencies in CTIS
- Have a strong collaborative attitude and are good team players → collaboration with many functions: RA, CMC/quality, medicine/clinical, CRO, drug supply, labelling
- Are prepared to invest considerable time to stay up to date → CTIS processes keep changing
- Can instantaneously create alternative expressions for a given content → responses to RFIs
- Appreciate the complexities around transparency and lay language content → various levels of documentation: CTIS fields & documents
- Have a good sense of document aesthetics → Cover Letter, Response documents

CTIS - What's in it for medical writers? - Example 0

The no-brainer:

Ensure that:

- the Clinical trial protocol,
- the Investigator's brochure,
- Investigational Medicinal Product Dossier Quality and Safety & Efficacy

are compliant with the requirements of the EU Clinical Trial Regulation.

- Be cognizant of the transparency requirements of CTIS and ensure that the clinical documents do not need redaction (are free of commercially sensitive information) and free of signatures and personal information

CTIS - What's in it for medical writers? - Example 1

Cover letter

- All types of Clinical Trial Applications (CTAs) need a cover letter
- Cover letter needs to convey certain information → EMA templates
- Needs to be clearly structured and clearly written as it is the sole place for discussions and elaborations, and nuances
    - Simple and clear language, often translations are required
- Needs to be short and succinct, often requires cross-functional input and alignment
- Is usually produced last minute under pressure of a looming deadline
- Is the little brother/sister of the Clinical Overview in a Marketing Authorisation Application

CTIS - What's in it for medical writers? - Example 2

Responses to RFIs

- RFIs may be received during validation and during assessment
- Completion of responses to RFIs are extremely important and time-critical
- MW can serve as facilitator for multi-stakeholder group needed to create the replies
- MW can be writing the response document, ensure adequate structure and reference, ensure clear and understandable replies
  - Need to adequately summarize available data
  - Need for clear and understandable language
- MW will need to be able to work under considerable pressure: 12 days from receipt to submission

CTIS - What's in it for medical writers? - Example 3

Lay language documents

- EU CTR mandates 3 lay language documents:
  - Informed Consent Form – information about the study as information to potential study participants
  - Layperson protocol synopsis –summary of the study protocol synopsis in lay language following certain content requirements, also in all national languages
  - Lay summary of study results – results of a clinical trial with certain content requirements as per Good Lay Summary Practice guidance
- MW needs to ensure that these documents are indeed understandable to members of the public
- Write and coordinate review and approval of these documents, perform QC-checks

CTIS – public portal

Searching for clinical trials

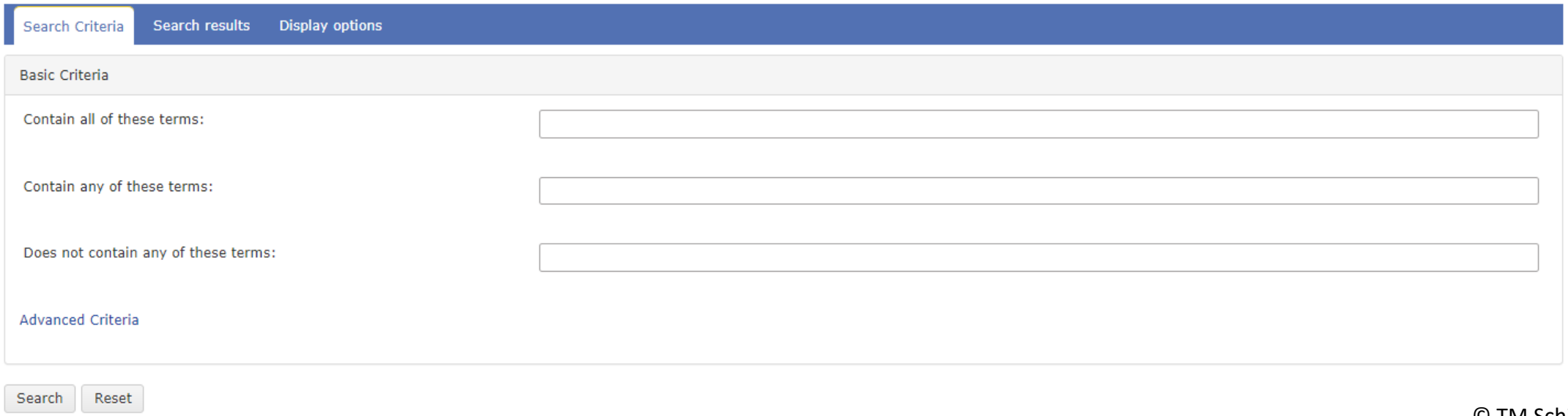
This website provides information on individual clinical trials in the European Union and European Economic Area since its launch on 31 January 2022. It will gradually contain more information as clinical trial sponsors and EU/EEA regulators use it to initiate and oversee clinical trials in the EU and EEA.

Search clinical trials →

> 7100 trials in CTIS (Nov 2024)

Information on individual clinical trials initiated in the European Union and the European Economic Area before 31 January 2022 can be found in the European Union Clinical Trials Register.

Search in the EU Clinical Trials Register

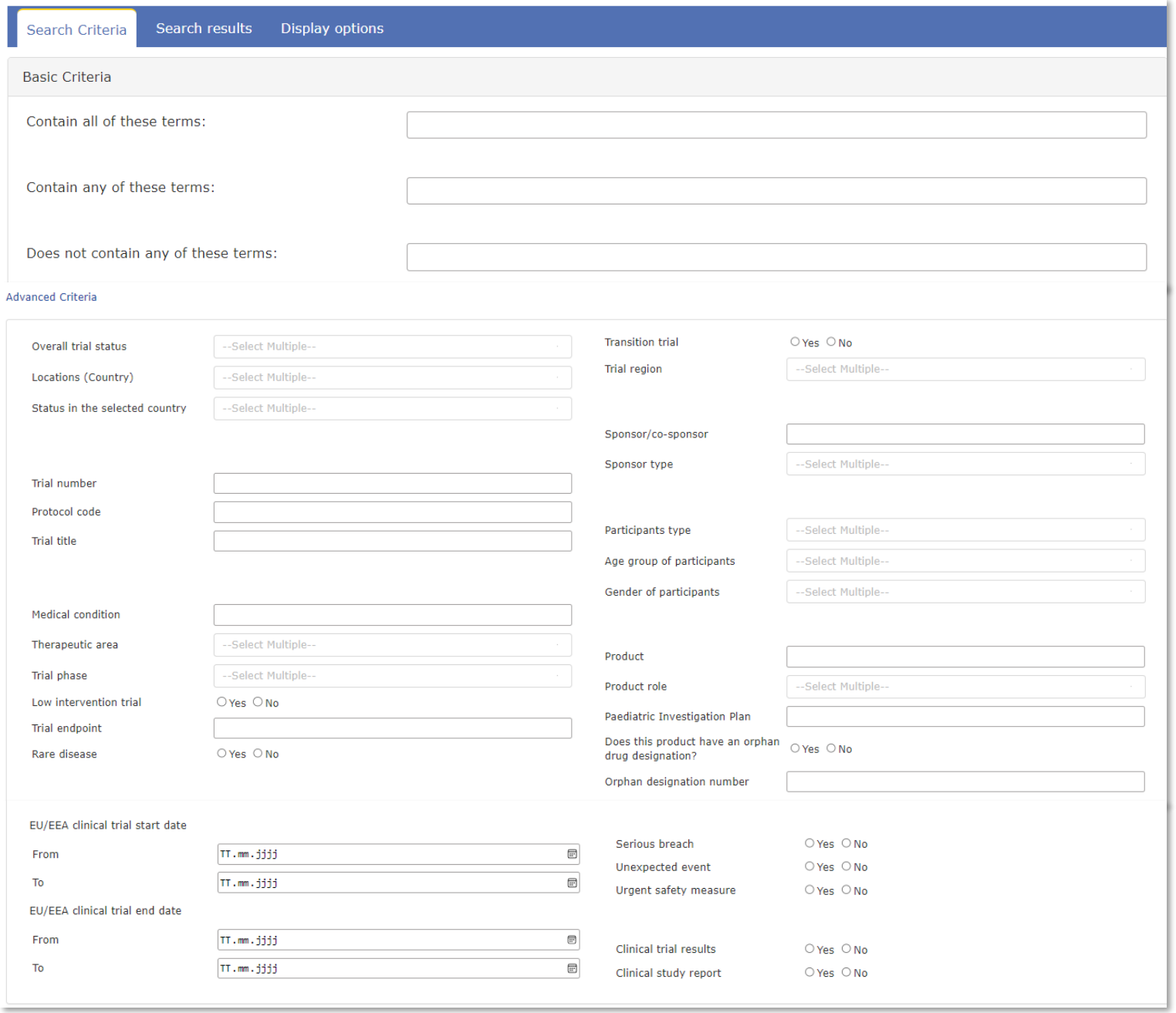


CTIS – public portal

https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en

New functionalities:

- Expanded Trial Summary information
- Comprehensive details in Full Trial Information
- Easy access to trial documents
- Easy access to trial locations & contacts
- Direct access to trial results
- Storing of searches
- Subscribe to RSS feeds



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CTIS - Training and support

Clinical Trials Information System: training and support

Share

Training and supporting materials are available from the European Medicines Agency (EMA) to help users of the Clinical Trials Information System (CTIS) comply with their legal obligations.

Human | Clinical trials

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

Clinical Trials Information System (CTIS): online training modules

Share

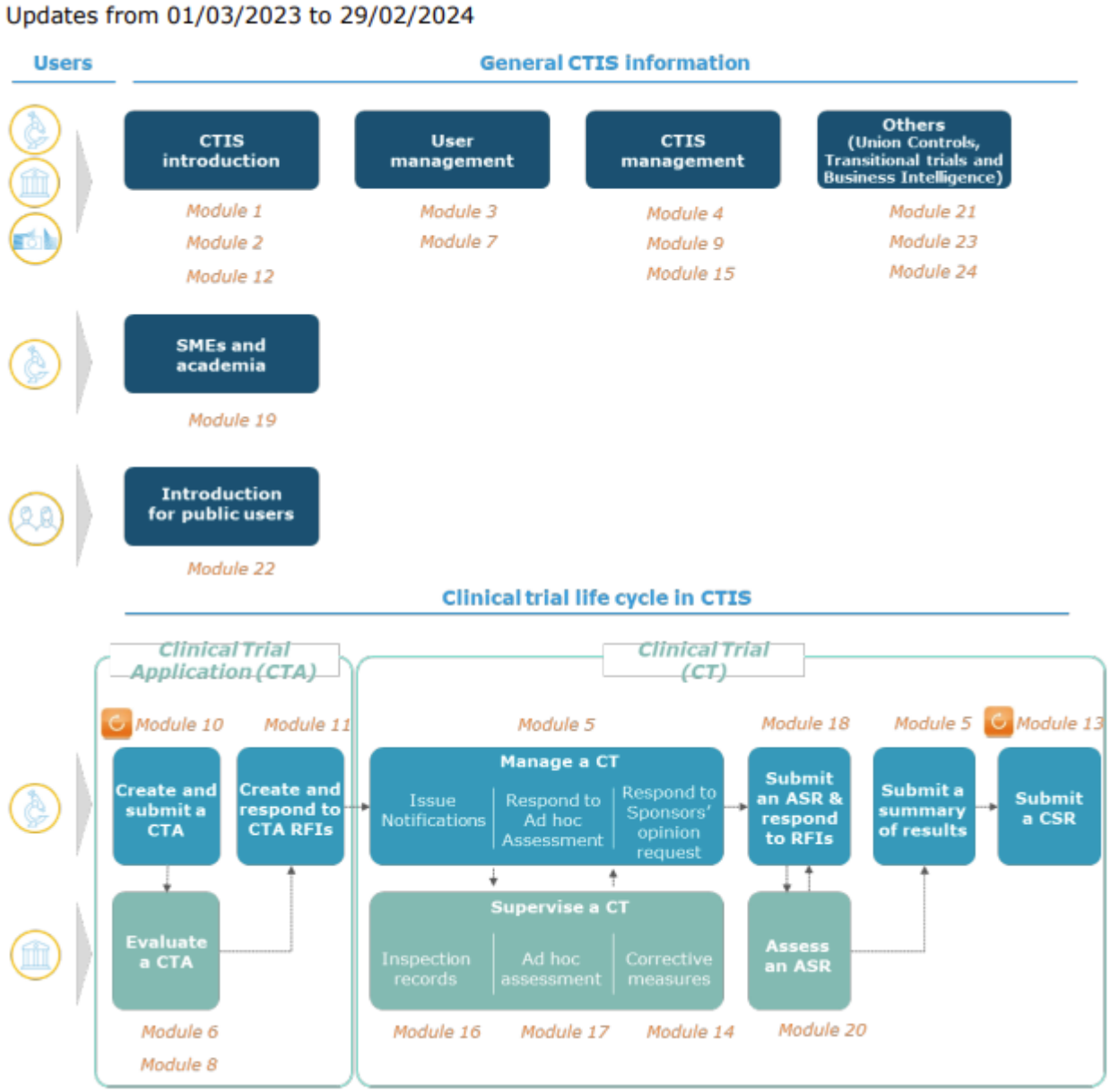
EMA provides an online modular training programme to help clinical trial sponsors, national competent authorities, ethics committees, European Commission and EMA staff use the Clinical Trials Information System (CTIS). The programme contains modules and audience-targeted materials covering all clinical trial lifecycle stages, from submission through authorisation to supervision.

Human | Clinical trials

https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines/clinical-trials-information-system-training-support/clinical-trials-information-system-ctis-online-training-modules

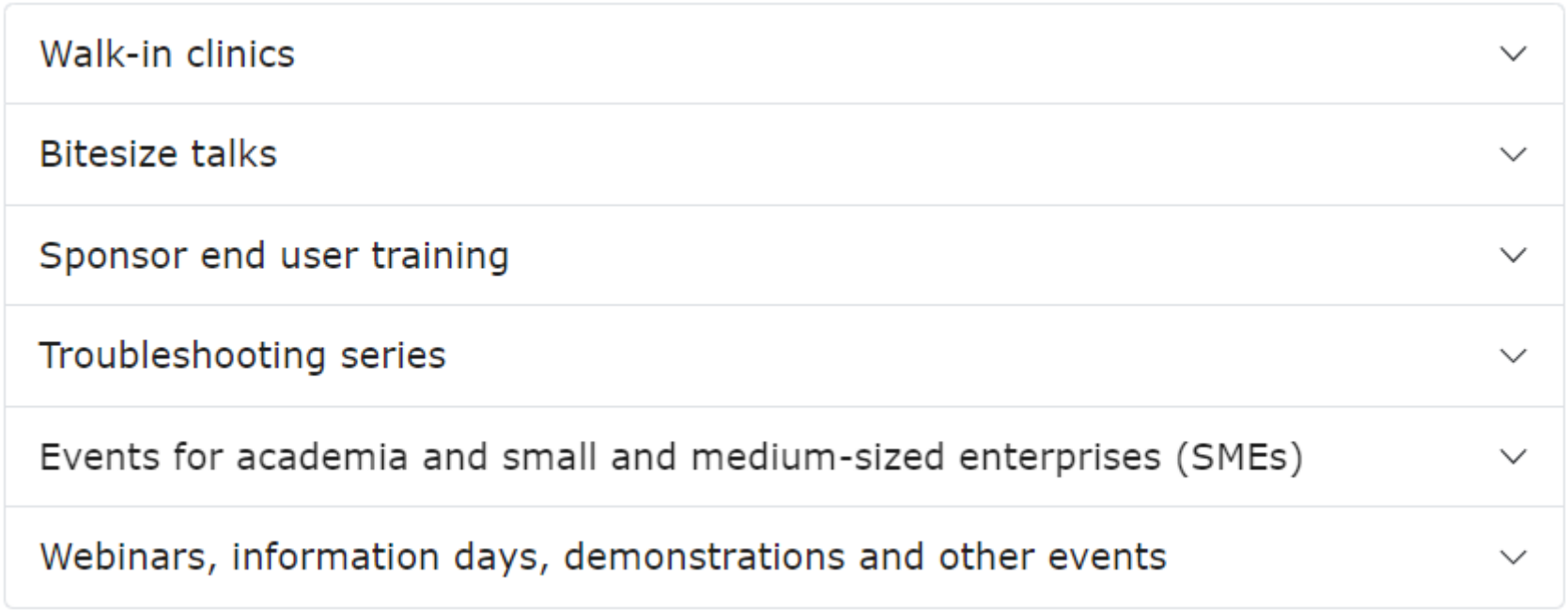
CTIS Training catalogue

24 Training modules with Quick Guides, Instructor guides, FAQs, videos, and Q&As



Source: CTIS Training materials – Latest updates Version 1.3 – February 2024

CTIS - Additional training and support



Source: CTIS Training materials – Latest updates Version 1.3 – February 2024

Thank you!

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