New clinical trials regulation targeted for early phase trials

SPARK Europe Webinar Series 2023

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Content

- Current in legislative regulations regulating changes in clinical evaluations
- Regulation N. 536/2014 and portal CTIS
- Registration in OMS
- Documentation for PART I and PART II

https://stock.adobe.com/cz/search?k=regulation&asset_id=52734917

European legislation valid until the turn of 31st of January 2022 (?)

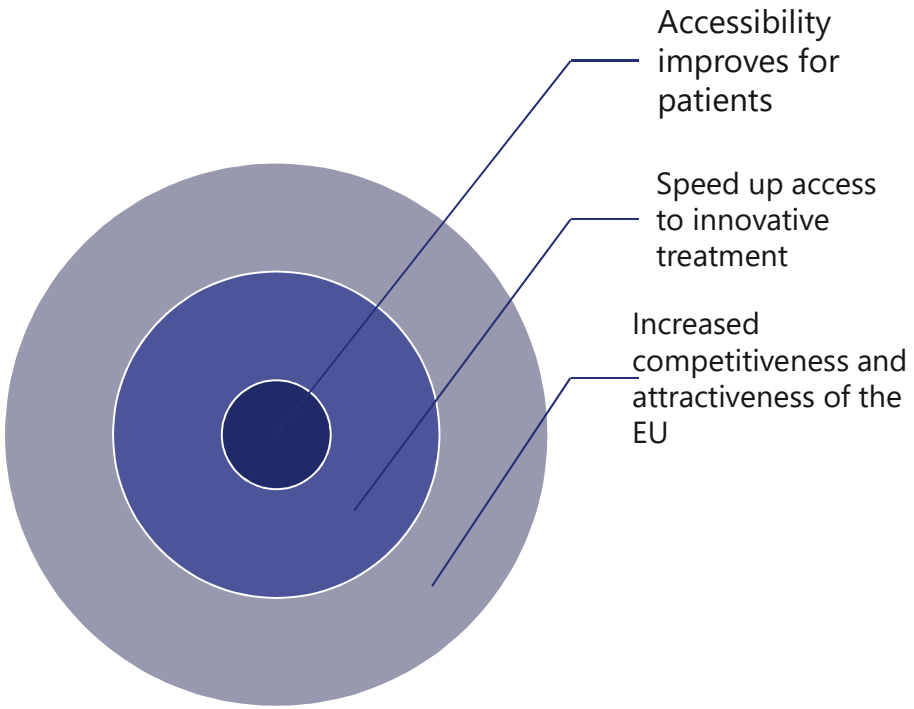
- Declaration of Helsinki of the World Medical Association (1964, last update 2013)
- Commission **Directive 2005/28/EC (GCP Directive)**
- European Parliament and Commission **Directive 2001/20/EC (CT Directive)**

- https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0020
- https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32005L0028

Why more regulations and amendments?

Directive 2001/20/EC

- the effort to harmonize the approval of CTs in the EU was not successful (25% decrease in applications for new CTs in the EU in the years 2007-2011)
- the change was prompted by the European Commission's proposal for a new Regulation in 2012 (Regulation x Directive), approved in 2014, effective from 31.1. 2022, the launch of the key CTIS portal, which replaces EudraCT, was expected



New European legislation valid from 31.01.2022

- Declaration of Helsinki of the World Medical Association
- Commission **Directive 2005/28/EC (GCP Directive)**
- Clinical Trial **Regulation No. 536/2014** on clinical trials on medicial products for human use (**CT Regulation**)

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 -

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Transitional period – legislative perspective

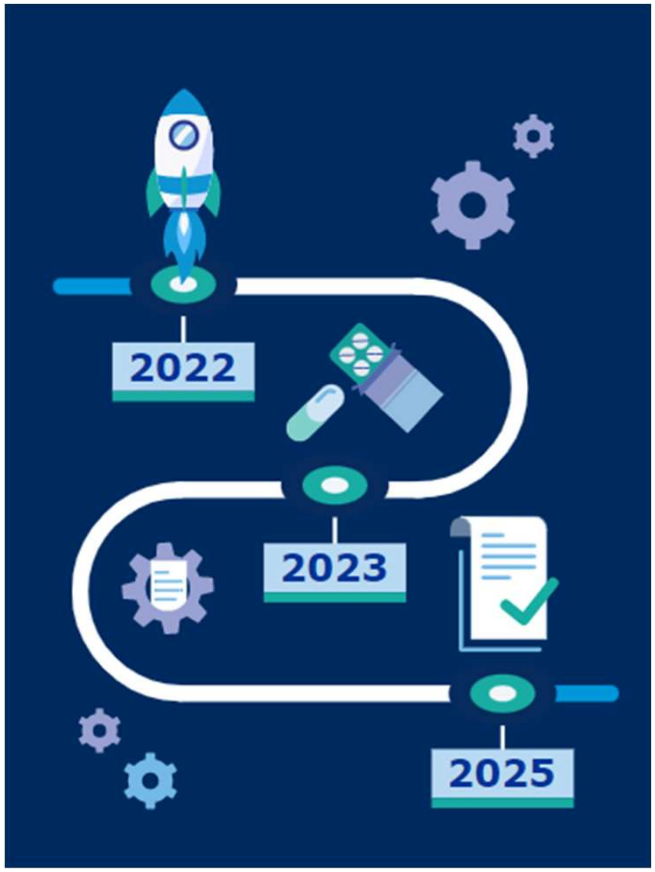
30rd January 2022	31st January 2022- 30rd January 2025	31st January 2025
Directive 2005/28/EC **Directive 2001/20/EC** **CTA portal**	**Directive 2005/28/EC** **Directive 2001/20/EC** **EUDRA CT only for approved trial before 31st Jan 2022** **/** **Directive 2005/28/EC** **Regulation No. 536/2014** **All new applications via CTIS**	**Directive 2005/28/EC** **Regulation No. 536/2014** **CTIS**

! for a transitional period of 3 years

(**February 1, 2022 – January 31, 2025**),

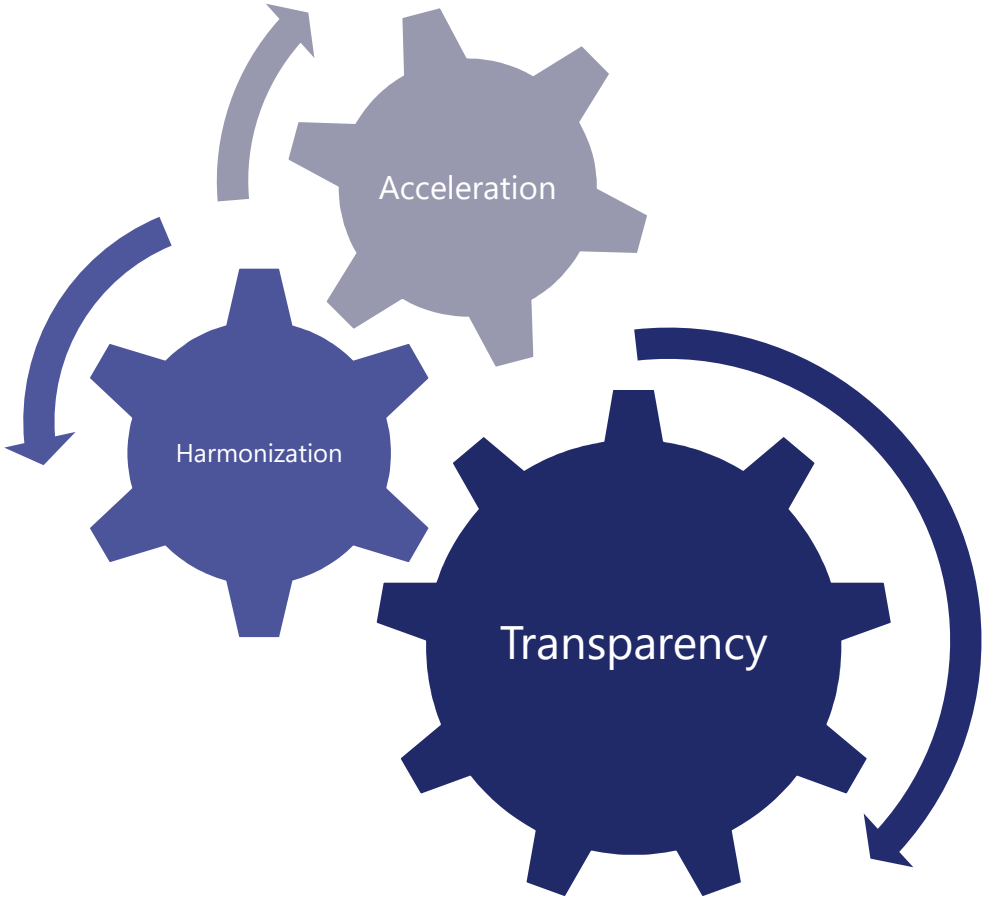
both the old and new legislation apply **!**

- For CTs submitted via the "national" route and approved before 31/01/2023, the old Directive applies
- If the CT is not completed (including the final report) by 31.01.2025, it will have to be transferred to CTIS
- From 01.02.2023 it can only be submitted via CTIS (for new CTs, the new legislation is valid)
- By 31 January 2025, any ongoing trials approved under the Clinical Trials Directive will fall under the Clinical Trials Regulation.



Scope and benefits of the Regulation

- Single CTA for multiple member states
- Harmonize clinical trials/studies across the EU
- Faster evaluation/authorisation of trials/studies
- Increased transparency and data sharing



Regulation of the European Parliament and of the Council (EU) No. 536/2014

- Effective immediately in full
- Simplification of administration for contracting authorities, acceleration and efficiency of the assessment process
- Creation of a unified EU portal **Clinical Trials Information System (CTIS)** with a new EU CTs database (not linked to the EudraCT database) → **https://euclinicaltrials.eu/search-for-clinical-trials**
- Easy search, publicly available data, transparency
- Each EU Member State has one point of contact (National regulatory authority), submission of documentation only electronically via the portal, the portal is the only means of communication with the contracting authority

Regulation No. 536/2014 (99 articles, 19 chapters, 7 annexes)

- Main sections for investigators and study centers:
- Art. 2: Definitions (new terms)
- Art. 29-30: Informed consent
- Art. 41: Report of AE/SAE to examining sponsor
- Articles 49-50: Suitability of persons (and places) participating in the implementation of CT
- Art. 57: Basic document CT
- Art. 58: Archiving of the CT essential document (newly 25 years, carriers?)
- Art. 73: Principal investigator
- Annex 3: Safety reporting

Regulation No. 536/2014 – definitions:

It applies only to interventional studies.

- Clinical study
- Clinical trial
- ‘Low-intervention clinical trial’

It doesn´t apply to non-interventional studies and trials without medicinal products.

Clinical study – definition:

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

(b) to identify any adverse reactions to one or more medicinal products; or

(c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;

Clinical trial – definition:

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

- 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;
- the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or
- diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

Low-intervention clinical trial - definition:

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

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

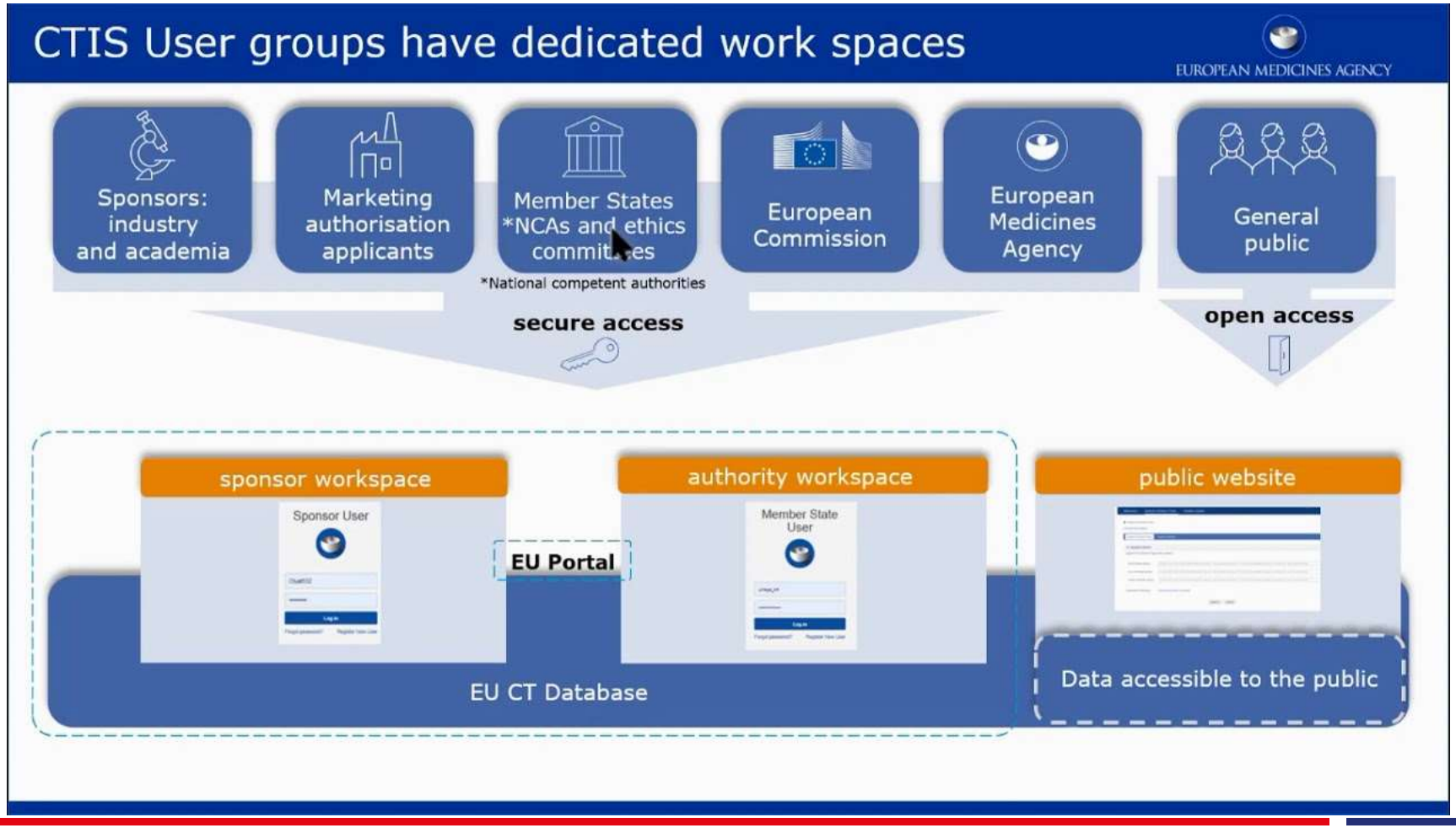
(i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or

(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

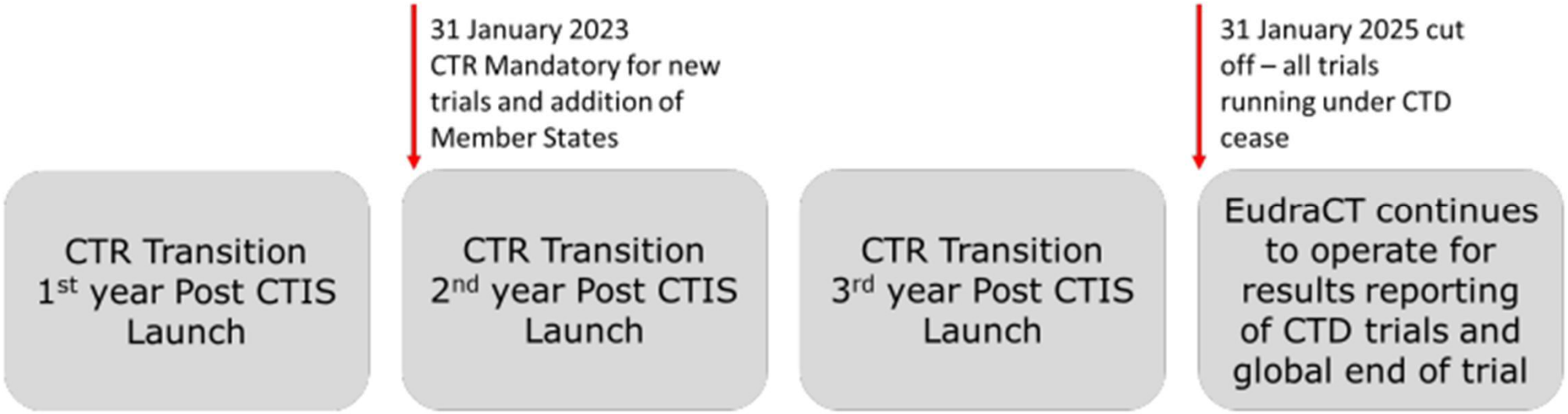
(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;

CTIS

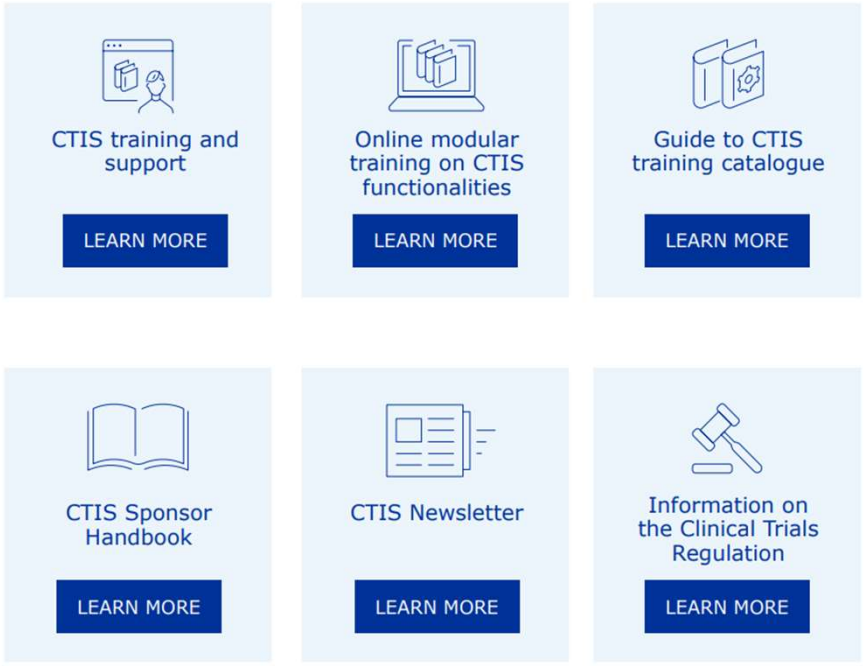
Data provider for WHO



The transition period – CTIS perspective



Clinical Trials Information System - CTIS

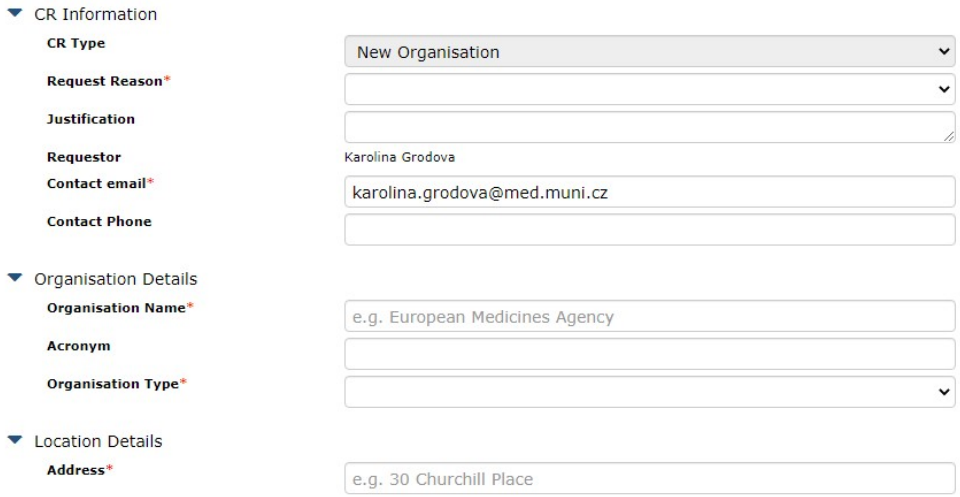


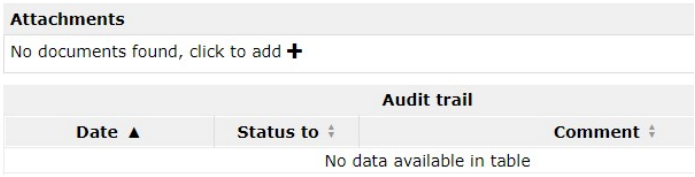
clinical-trials-information-system-key-information-sponsors-ctis_en.pdf (europa.eu)

Registration in Organisation Management System (OMS)

Fill out the application form. The applicant will be listed as the person who applied via the EMA account.

Insert the document according to the EMA instructions in the attachment E - OMS Change Requests)





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Registration in Organisation Management System (OMS)

When you find your organisation, check that the name and address are correct. If the Organization ID is assigned you don't need to do anything else.

⏮ ◀◀ Page 1 of 1 ▶▶ ⏭

Organisation ID	Organisation Name ▲	Country	Location ID	City	Address	Postcode	Location status	Mo
ORG-100029481	Masaryk Memorial Cancer Institute	Czechia	LOC-100046793	Brno-Stred	Zluty Kopec 543/7	602 00	ACTIVE	2022-07
ORG-100036390	Masarykova Nemocnice Rakovnik s.r.o.	Czechia	LOC-100064015	Rakovnik	Dukel Hrdinu 200	269 01	ACTIVE	2021-12
ORG-100036390	Masarykova Nemocnice Rakovnik s.r.o.	Czechia	LOC-100057546	Plzen	Kotikovska 927/19	323 00	ACTIVE	2021-09
ORG-100021184	Masarykova Univerzita	Czechia	LOC-100036186	Brno	Zerotinovo Namesti 617/9	602 00	ACTIVE	2021-09
ORG-100021184	Masarykova Univerzita	Czechia	LOC-100042785	Brno	Kamenice 753/5	625 00	ACTIVE	2020-07
ORG-100021184	Masarykova Univerzita	Czechia	LOC-100045467	Brno	Research Center For Environmental Chemistry And Ecotoxicology	625 00	ACTIVE	2020-10
ORG-100021184	Masarykova Univerzita	Czechia	LOC-100045465	Brno	Cernopolni 9	625 00	ACTIVE	2020-10
ORG-100021184	Masarykova Univerzita	Czechia	LOC-100046432	Brno	Kamenice 126/3	625 00	ACTIVE	2020-10

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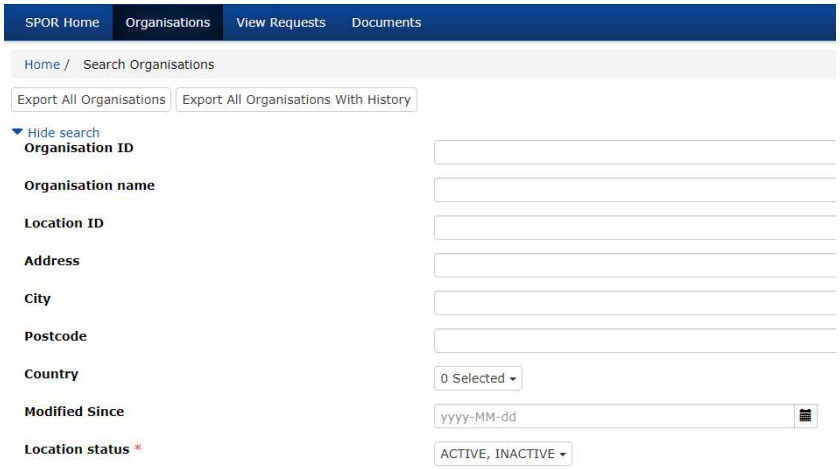
Request New Organisation | Export Results

If you can't find your institution, click on **Request New Organisation** - bottom right bellow.

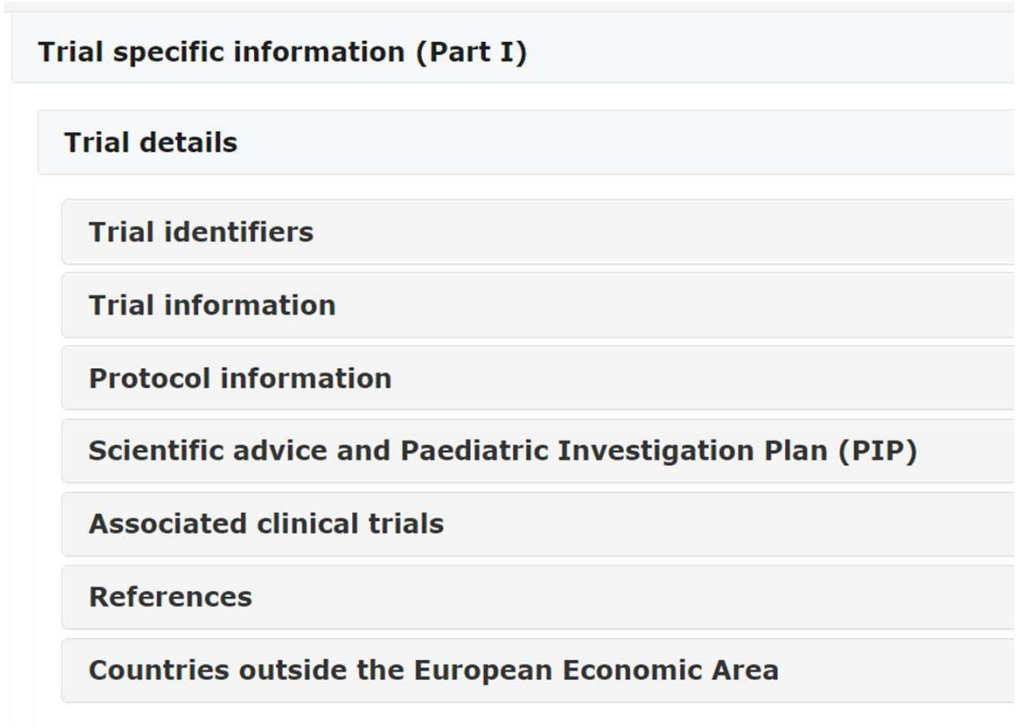
Getting access to CTIS

1. Select your user management approach: the best user management approach for you in CTIS depends on how many trials your organisation expects to run
2. Ensure you have an EMA account: username and account details for CTIS are provided via EMA Account Management
3. Register your organisation/trial sites in OMS https://register.ema.europa.eu/identityiq/external/registration.jsf#/register
4. Ensure your medicinal products are registered in xEVMPD



Documents needed in a **PART I**

- Cover Letter
- Information about a clinical study
- Protocol
- Pharmaceutical documentation
- Investigator´s Brochure
- PIP
- Scientific Advice
- Payment
- Sponsor/s



Documents needed in a **PART II**

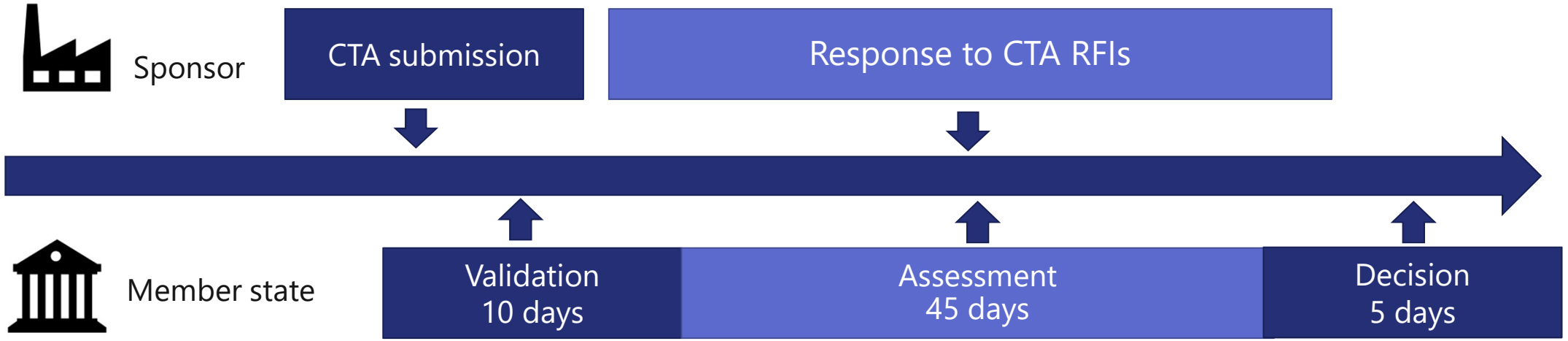
- Necessary cooperation of all centres
- In the case of comments – 12 calendar days for a correction/addition
- It is possible to add/correct only once, after which the entire clinical study must be submitted again

Workplace in CTIS

- Access to CTIS via **EMA´s** account
- Lock – always lock to work on the given section→ will ensure that no more people work on the CTA at the same time

- Role PART II preparer = access to PART II **of all MSC**, documents can also be uploaded here.

Timeline



No automatic notifications to sponsor.

Past vs. present

	Directive 20/2001/ES	**Regulation 536/2014**
Submission	National – Regulatory authority (RA) and Ethics committees (EC) (multicentric/local) ⇒ **2 decisions in each involved EU state**	CTIS • PART I = same for all MS • PART II = specific for each MS (evaluated by EC esthablished by RA) => **1 decision by MS**
Deadlines Validation Assessment Decision	**Total 10 + 60 calendar days** 10 30/60/60 + 30 (+90)	**Total 60 calendar days*** 10 (+10 addition by sponsor+5 verification by MS) 45 (+12 addition by sponsor+19 verification by MS) 5 (decision)
Interruption	**repeatedly - time duration as needed**	**Only 1x** – 31 days (12 days for sponsor, 19 days MS)

* Non-compliance with deadlines by MS = application is considered complete/approved = tacit consent

Ethics committee

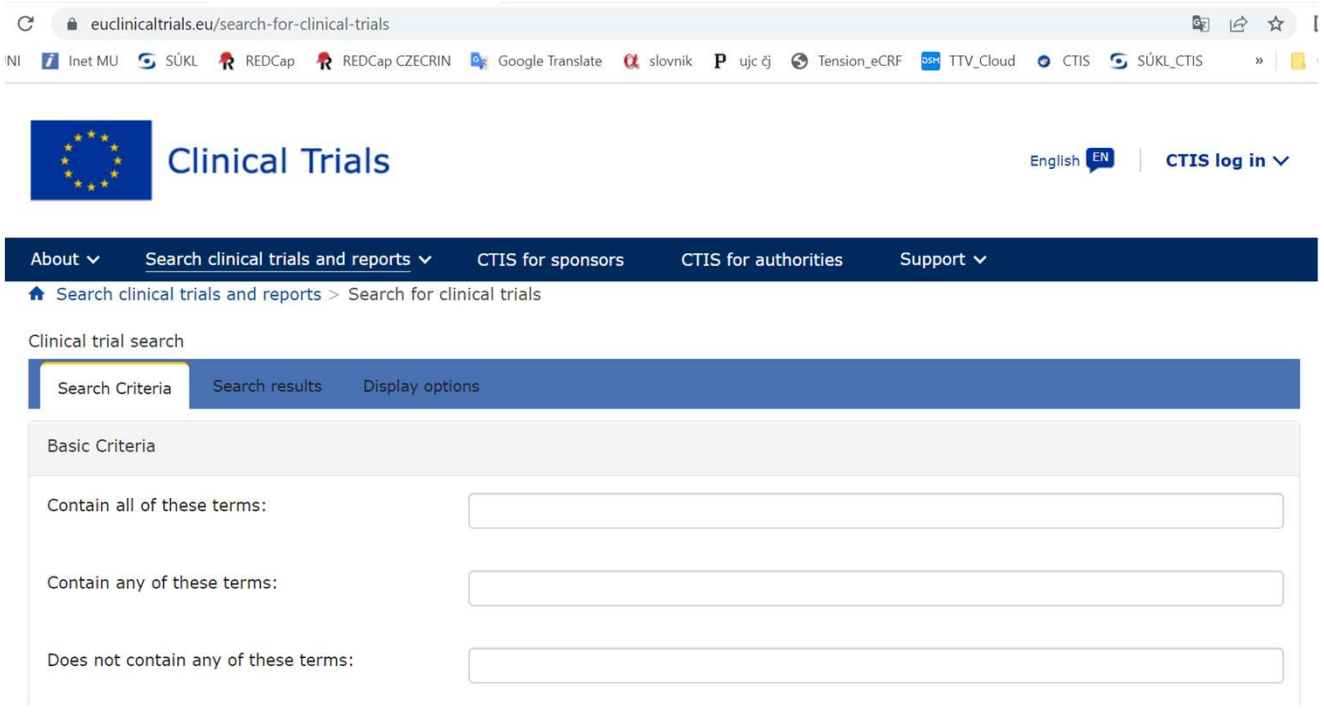
- Ethics committee' means an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients' organisations;
- A clinical trial shall be subject to scientific and ethical review and shall be authorised in accordance with this Regulation.

- The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7 as appropriate for each Member State concerned.

- Member States shall ensure that the timelines and procedures for the review by the ethics committees are compatible with the timelines and procedures set out in this Regulation for the assessment of the application for authorisation of a clinical trial.

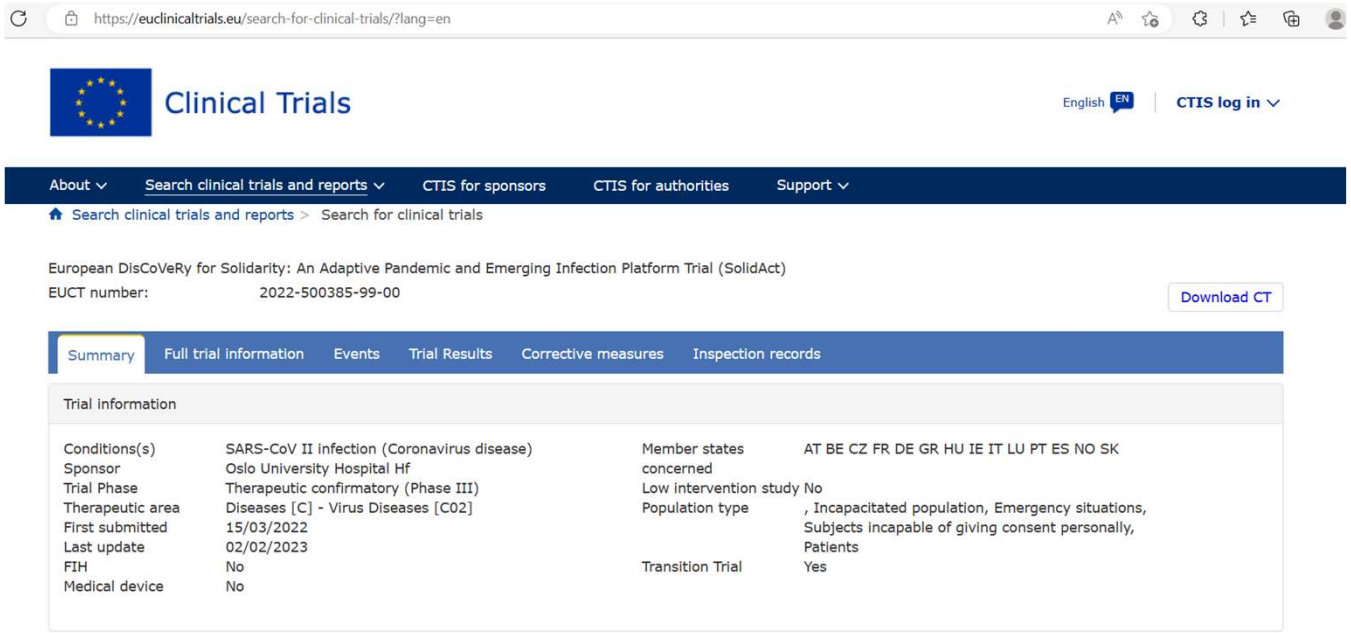
Publicly accessible CTs database

→ https://euclinicaltrials.eu/search-for-clinical-trials



Publicly accessible CTs database

- Publicly available information about CTs
- Possibility to download published documents - currently not possible to download individually



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Thank you for attention.