Applications under CTR

-Overview
-Experiences from NOMA
-And some pitfalls adressed..

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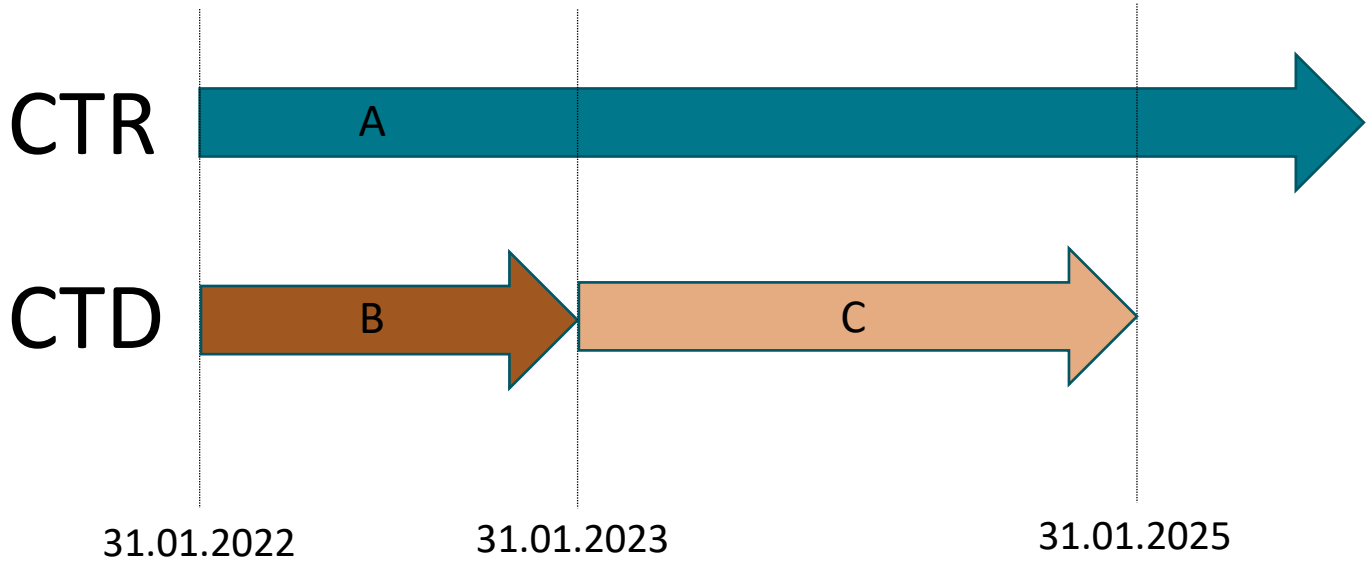
Topics

- Transition applications
- Transperency rules under the regulation
- New applications
- Low-intervention clinical trials

Transitioning applications

Transition period



A CTs may be submitted and started under CTR = «CTR studies»

B CTs may be submitted and started under CTD = «CTD studies»

C CTs submitted under B, may be continued under CTD

31.01.2025 CTs approved under the CTD must have been transitioned to the CTR

CTR Clinical Trial Regulation
CTD Clinical trial Directive
CT clinical trial

Status for CTD studies following implementation of the CTR

- CTD studies projected to be completed before 31.01.2025
  - End of study definition: lat patient - last visit (LPLV)
  - Not obliged to be transitioned to the CTR
  - CTD will apply for these studies

- CTD studies that have active sites in EU on the 31.01.2025 **must** be transitioned
  - Transition application in Clinical Trial Information system (CTIS)
  - Administrative handling, no new assessment
  - Process time may approach 90 days
  - If country-specific protocol versions apply, the protocol must be consolidated/harmonized before transition

Which CTD studies may be transitioned?

- The CTD study may be transitioned **as approved** under CTD
  - No modifications introduced
  - No MSC added
- No ongoing procedures/assessment in any MSC
- Include declaration in cover letter

MSC Member states concerned

Requirement for the transition application

- New cover letter and all application data (Part I and II) to be completed in CTIS
- Minimum requirements for the application:

Part I, the latest authorised versions as a minimum :

- Protocol (as authorised)
- Investigator's brochure (IB)
- Good manufacturing Process (GMP) relevant documents
- Investigational medicinal product dossier (IMPD)

Part II, the latest authorised versions of the:

- Subjects' information sheet
- Informed consent form
- Information on which Ethics committee that approved the trial

- First substantial modification: Application dossier updated to CTR requirements
- Please note that transparency rules apply

Requirement for the transition application

- Transition application dossier must comply with CTR
- Sponsor's responsibility that the clinical trial is in line with the requirements for transitioning from CTD to CTR
  - Declaration in cover letter

- CTFG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No 536/2014: 2018_05_CTFG_Best_Practice_Guide_for_sponsors_of_transition_multinational_clinical_trials.pdf (hma.eu)

Harmonised vs consolidated protocol

Harmonised protocol:

- Identical protocol document that includes identical trial procedures across all EU Member States
- If necessary, by a substantial modification under the CTD before transitioning

Consolidated protocol: differences in procedures in different Member States, but the "core" protocol document is identical:

- EudraCT number
- Trial Title
- Protocol version number
- Primary objective and endpoint
- Definition of end of trial
- Main inclusion and exclusion criteria

Requirements for transitioned trials

- From the time of authorization:
  - Transparency requirements (including deferrals)
  - Archiving requirements
  - Obligations of notifications via CTIS
  - Safety reporting rules
  - Procedural rules of the Regulation
    - Substantial modifications
    - Addition of a Member State
- At the end of the trial:
  - Publication of summary of results
  - Clinical Study Report (CSR)

Transition period QnA

- Section 11 of the CLINICAL TRIALS REGULATION (EU) NO 536/2014 QUESTIONS & ANSWERS: regulation5362014_qa_en (3).pdf


Transparency rules

Transparency under CTR

- CTR aims to increase transparency and availability of information on clinical trials
  - Supports public scrutiny
  - Improves research efficiency
  - Provides public with the necessary information to identify ongoing trials for their participation
- All documents will be made public available
  - Documents in the application dossier
  - Assessment reports
  - Communication between competent authority and the sponsor/applicant

Transparency rules

- For the purpose of the transparency rules, trials approved under CTR are categorized in 3 categories that determine deferral of publication

Category	Type of trial	Phase	Deferral of publication may be requested
1	Pharmaceutical development clinical trials	1	Up to the time of MA using this trial or up to 7 years after the end of the trial
2	Therapeutic exploratory and confirmatory clinical trials	2 and 3	Up to the time of MA using this trial or up to 5 years after the end of the trial
3	Therapeutic use clinical trials	4 and low intervention	Up to the time when the summary of results is made public usually 12 months after the end of the trial

Transparency rules

- Redaction is preferred over deferral of publication
- Appendix, on disclosure rules, to the “Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014”

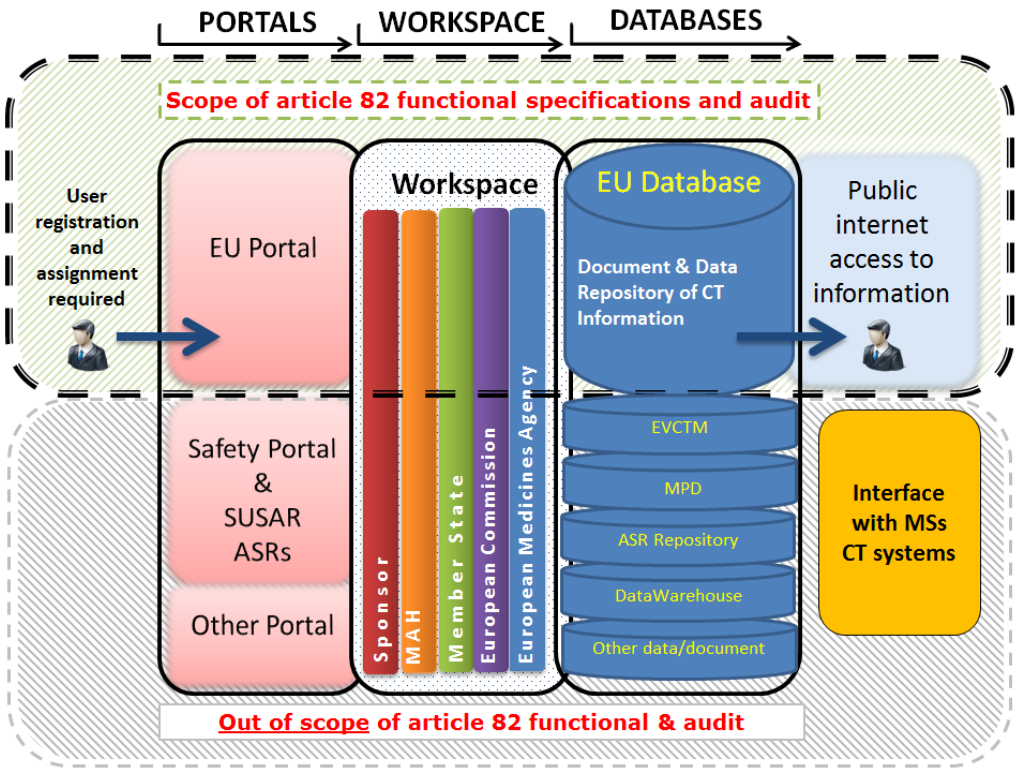

New applications under CTR

CTR benefits

- Intention of the CTR to harmonise the processes for assessment and supervision of clinical trials throughout the EU
- One single application
  - Up to 30 EU/EEA member states
  - Per member state: joint assessment by the medicine agency and the ethics committee

Clinical trial information system (CTIS)

- Enables sponsors to apply for clinical trial authorisation in up to 30 European countries with a single online application
- Allows national regulators to collaboratively process clinical trial applications
- Facilitates the expansion of trials to other EEA countries
- Enables transparency and access to information for any party interested in clinical trials



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The clinical trial application

Application dossier

Submission in CTIS

Part I

- Is the CT «low-intervention»?
- Benefit/risk
- Manufacturing and import
- Labelling
- IB/protocol

Part II

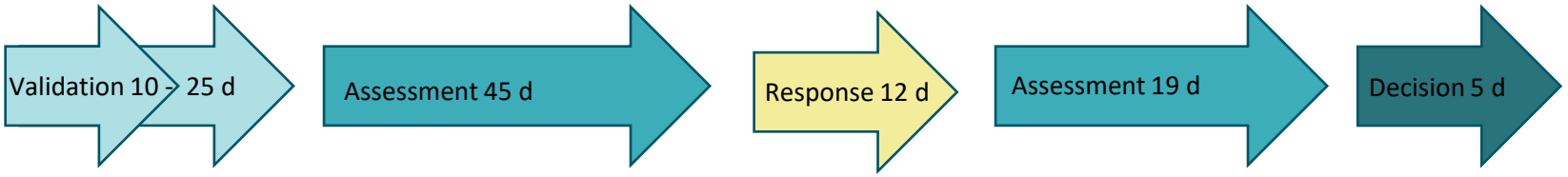
- ICF, recruitment and data integrity
- Insurance
- Rewarding or compensating
- Collection, storage and future use of biological samples

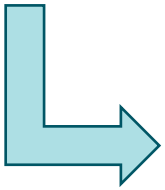
Assessment by NCA + EC

Assessment by EC

Application processing time

Part I submission: Includes all MSC = 1 application



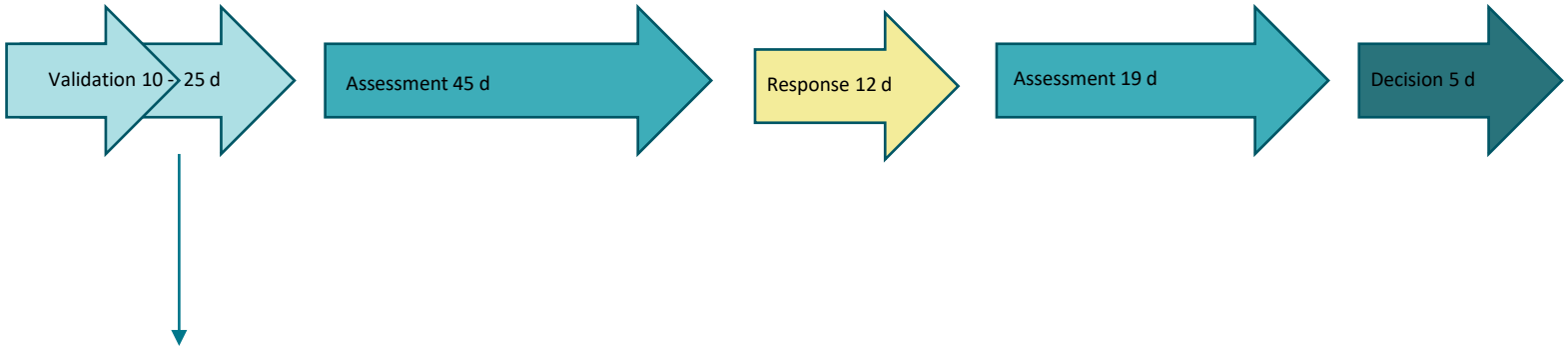


Submission of part II to individual MSC = several applications
May be submitted at any time (not before part I)
Final deadline 2 years post-approval of part I

Submission of the clinical trial application

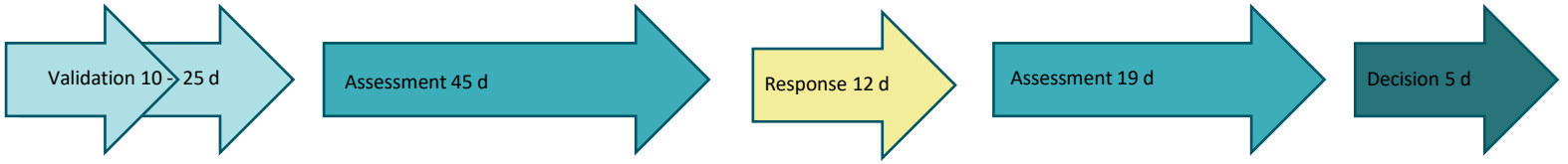
- Dossier requirements: Annexes of the Regulation
  - Annex 1: Initial application
  - Annex 2: Substantial modification
- Language requirements for part I documents
  - Annex II of the QnA document
- Acceptability of Part II templates in the Member States
  - Under development: Annex III of the QnA document
- Please note that non-substantial modifications is not possible for core documents of the dossier

Please note



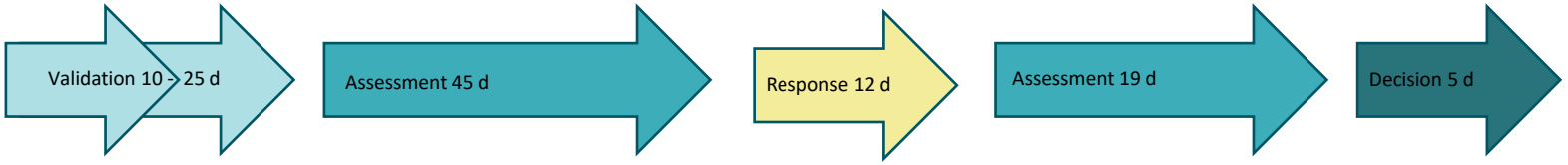
- Questions/RFIs on validation
  - NCA/EC may have questions/request updates of the submitted documentation following validation
  - A request for information (RFI) may be submitted at day 10(-ish) following submission
  - Respond within 5 days

Please note



- Part I and part II may run at different time schedules
- MS may not use maximum timelines (best practice for multinational trials)
- Multiple RFIs may be issued (part I and part II)

Please note



- Notices is NOT issued
- Applicant/sponsor must log in to view list of notices
- Pay attention during ongoing assessments

Useful links: CTR, CTIS and guidelines

- Clinical Trials Regulation: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation
- Clinical Trials Information System: training and support: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-training-support
- Clinical Trials Information System (CTIS): online modular training programme : https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-ctis-online-modular-training-programme
- Handbook for clinical trial sponsors: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-training-support#handbook-for-clinical-trial-sponsors-section
- CTIS Newsletters: https://www.ema.europa.eu/en/news-events/publications/newsletters#clinical-trials-information-system-(ctis)-highlights-section
- Clinical trials guidelines: EudraLex - Volume 10 - Clinical trials guidelines | Public Health (europa.eu) and Draft - Questions and Answers Document - Regulation (EU) 536/2014 – Version 4.1 (September 2021)


Low intervention clinical trial

Low intervention clinical trials (LICT) – New category under CTR

- The definition of LICTs (per CTR, Article 2(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
- Note that comparators are IMPs are required to fulfil the above definition when used in LICT

Exemptions for LICT

Area	Regards	Practical consequences
Safety reporting	- Safety profile of the IMP - Validity of data	- **selective recording and reporting** of adverse events, - **adaptations to immediate reporting** from the investigator to the sponsor, for certain serious adverse events - Any such adaptation should be clearly stated and justified in the **protocol**
Handling of investigational medicinal product (IMP)	Tracebility and accountability	**routinely maintained pharmacy documentation** on receipt, storage and handling may be sufficient, if: a) normal prescribing practice and documentation applies and b) specific documentation of prescribed amounts and doses taken is available in the patient's medical records or other source documents, e.g. the patient's diary. - if a marketed product is re-labelled or repackaged for blinding purposes or distributed outside of normal supply chains, **sufficient traceability and documentation** should be available to allow for a recall of the IMP or its inclusion in a more general recall of a marketed product, to the extent that recall applies.
Conduct of the study	Monitoring	«Risk proportionate approach»
Documentation	Trial master file (TMF)	- **combining of documents:** one document serves multiple purposes (screening logs and recruitment logs, signature and delegation logs, site assessment and site initiation etc.) - **absence of documents,** as a result of implementation of other risk proportionate measures (SmPC I stedet for IB, lab-akkreditering og sertifikat når data fra disse ikke er kritisk for resultatene)

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