EU CTR implementation Opportunities and Challenges

Siard Houtzager (Johnson & Johnson) - Christopher Price (Merck Healthcare KGaA)

Contributors:

M. Rychter (AstraZeneca); L. Baschirotto (Lilly); C. Popp (Roche);

Ch. Le Floch (Seagen / Pfizer); S.Frauenschuh (Bayer); S. Wissink and B. García-Ochoa (MSD)

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Clinical Trials Regulation (EU 536/2014)

(entry into application 31 Jan 2022)

EU CTR's main goal is to make Europe more **attractive for clinical research** by **simplifying** and **harmonizing** requirements and assessment of clinical trial applications across Europe.

Directive 2001/20/EC	Regulation No 536/2014
Multiple application to each MSC	**Single application submission** via an online platform called **CTIS,** harmonized for NCAs and ECs
Individual assessment by each MSC	**Joint assessment** of part I of the application (part II assessed by individual countries)
No single MSC decision (NCAs and ECs)	**Single decision**

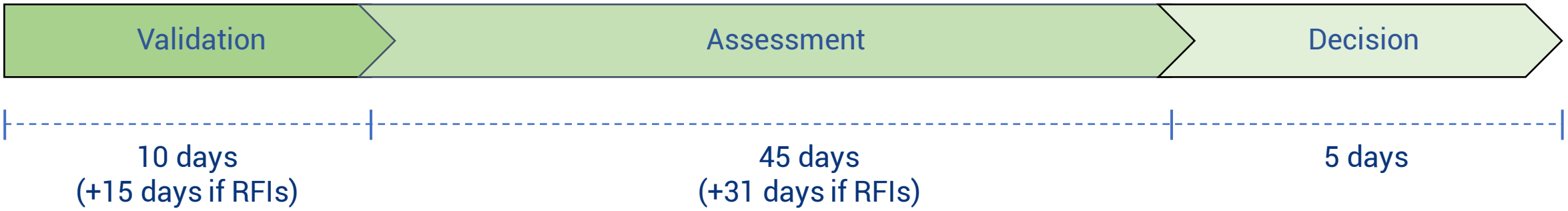
EU CTR has changed the EU country-level CTA model to a **single application dossier**

MSC: Member State Concerned, CTIS: Clinical Trials Information System, NCA: National Competent Authority, EC: Ethics Committee

Predictable timelines dictated by CTIS

Harmonized Regulatory CTA (Part I) and Ethics Committee (Part II) review timeline across all Member States:

60 days for approval, up to **106 days** in case of Request For Information (RFI)



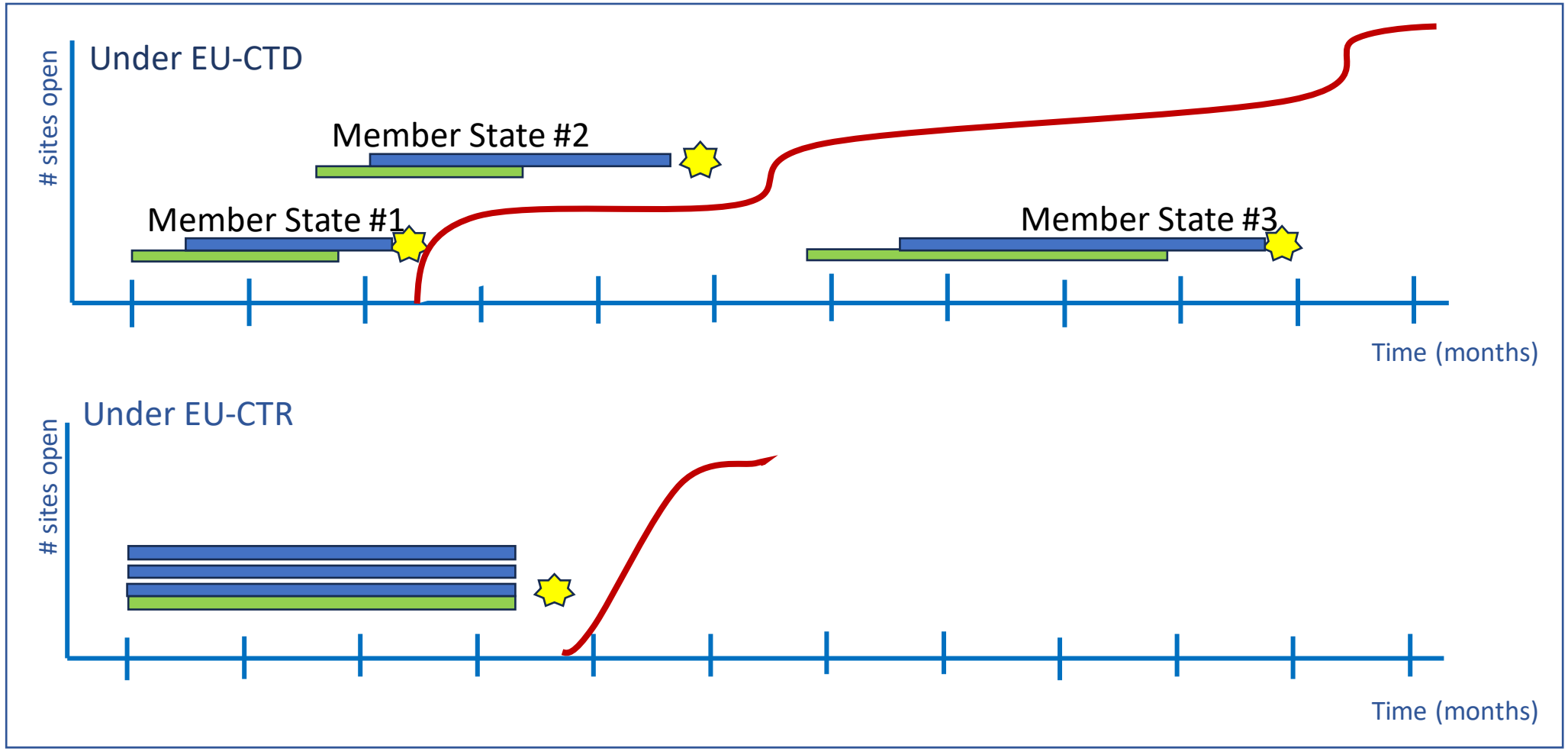
Release of Part I RFI is scheduled in the CTIS system

RFIs for Part II can be issued *anytime* during the assessment

Article 6, 7 and 8 of EU-CTR (No 536/2014)

Predictable timelines – Faster Study Execution under EUCTR

compressed timelines can shorten the study start up time.



A dynamic regulatory EU-CTR landscape

CTCG and EMA actively driving the debate and improvements:

- New and revised Transition Best Practice Guide@
- Revised EUCTR Q&A documents#
- Revised Transparency guidance*
- Q-IMPD confidentiality to support Academic trials and trials with partners

@ https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTCG/2023_11_CTCG_Best_Practice_Guide_for_sponsors.pdf
# https://health.ec.europa.eu/system/files/2023-12/regulation5362014_qa_en_0.pdf
*https://www.ema.europa.eu/en/documents/other/revised-ctis-transparency-rules_en.pdf

After this slide Christopher Price will address Sponsor experiences with EUCTR

Sponsor Experiences of EU-CTR

Practical Benefits

- Harmonization of Part I requirements
  - ➢ *Greater consistency on core Part I documentation requirements*
- Clarity and predictability of assessment timelines
  - ➢ *Centralised system with automated timeline governance*
- Structured data requirements in CTIS
  - ➢ *Single harmonised EU wide application platform*
- Pan-European approvals
  - ➢ *Approvals issued on predictable timeline for each Member State (covering EC and RA) in CTIS*

EC : Ethics Committee, RA: Regulatory Authority

Sponsor Experiences in 2023

Practical Challenges and Improvements in Preparation

Current Challenge	Improvements Underway
'Fragile' CTIS system, low user-friendliness, bugs lead to work-arounds	Additional capabilities anticipated to make CTIS more stable and usable.
Timing of RFIs not aligned - variability of receiving RFIs for Part I vs Part II (example of the ICFs / protocol)	Further harmonise authority and EC review at MS level. Some initiatives have been started under ACT-EU.
Substantial modifications (SMs) – long and complex process to introduce changes in the trial. Not possible to submit SMs in parallel, blocking additional MSC applications Currently no distinction between study- and program-level document submissions	Updates to CTIS could allow parallel review. Under discussion. Distinction of study / program level submissions would drive higher compliance (eg more timely IB submissions)

CTIS: Clinical Trials Information System, RFI: Request For Information, MS : Member State, MSC: Member State Concerned

Sponsor Experiences in 2023

Practical Challenges and Sponsor Proposed Improvements

Current Challenge	Potential Solution for Improvement
Transitioning of trials from CTD to CTR (deadline 30 Jan 2025). Potential 'bottleneck' of applications in 2Q/3Q 2024 due to the high number of trials still to be transitioned vs system capacity / MS resource.	Simplify and streamline : - **MSs:** follow principle of transition guideline[1], ie no additional content review of already approved documentation under CTD should be necessary. -**Sponsors:** plan submissions in timely manner in 2024
Member State variability of document requirements and assessments, especially in Part 2	Further harmonisation. Some initiatives have been started under ACT-EU.
12 day window for RFI response can be challenging to meet if substantial dossier updates required.	Allow further flexibility in utilising conditional approvals with commitments
In multinational submissions, RFIs can lack consolidation by rMS and include high number of questions.	Need to reinforce the role of the rMS and streamline the review process to allow time for consolidation.

CTD: Clinical Trial Directive, CTR: Clinical Trial Regulation, MS : Member State, RFI: Request For Information, rMS: reporting Member State

Sponsor view on 2024 and beyond

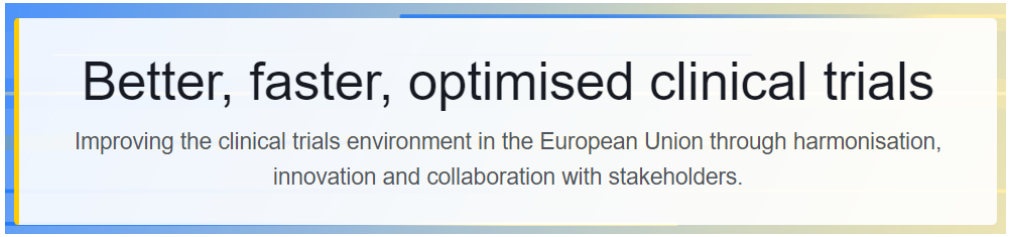
Improving CTR Process

Accelerating clinical trials in the EU – **ACT EU**:

Initiative aims to develop the European Union further as a competitive centre for innovative clinical research.

Updated workplan (2023-2026) →updated priority areas including "*CTR implementation*":

- **CTR Collaborate initiative** - led by CTCG, to support optimised MS and NCA/ethics collaboration on clinical trial authorisation under CTR
- Transition trials
- Reinforcement of CTIS improvements



CTR: Clinical Trial Regulation, CTCG: Clinical Trials Coordination Group, MS : Member State, NCA: National Competent Authority

Sponsor view on 2024 and beyond

Improving Combination Trial Applications

COMBINE ('IVDR/MDR/CTR Interface') project :

- Seeks to resolve procedural challenges encountered by sponsors in conducting combined trials of a medicinal product together with a performance study of an IVD or a clinical investigation of a medical device.
- Anchored to ACT EU through the activity of the multistakeholder platform.

Scope and Project phases:

Issue :

- The interaction of IVDR/MDR/CTR procedures is posing a challenge and leading to significant delays in clinical trial initiation.
- Lack of guidance and infrastructure to execute new requirements are the main cause.

IVDR: In-Vitro Diagnostic Regulation, MDR : Medical Device Regulation, CTR: Clinical Trial Regulation

Summarizing & Conclusion

EU-CTR provides a harmonised authorization process of clinical trials, through a coordinate assessment by the Member states

- Further enhancements are needed (CTIS, further harmonization of the assessments, more flexibility of submission pathways), driven by ACT-EU

- One smooth pan-European submission and approval process of clinical trials is needed to make Europe a competitive place for clinical research.