



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clinical Trial Information System (CTIS) Webinar Second Year of Transition





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Etiquette for CTIS Webinar: Second Year of Transition



**Microphones
are muted**



**Recorded
Event**



**Questions
were /can
be
submitted in
Slido**

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Agenda

13:00-13:20

Welcome and Introduction / Welcome and Opening remarks

13:20-13:30

Session 1: CTR Implementation

13:30-14:00

Session 1: Member States' Experience and Perspective on Transitional Trials

14:00-14:30

Session 1: Sponsors' Experience and Perspective on Transitional Trials

14:30-15:20

Session 1: Question and Answers – Panel Discussion

15:20-15:40

Coffee break

15:40-16:10

Session 2: Member States' Best Practices for Transitional Trials

16:10-16:35

Session 2: CTIS looking forward

16:35-17:25

Session 2: Question and Answers – Panel Discussion

17:25-17:30

Closing remarks



Welcome and Introduction



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Peter Arlett

Head Data Analytics and
Methods Task Force
EMA



Marianne Lunzer

CTCG Chair

AGES



Opening remarks

Björn Eriksson
Director General
Swedish Medical Products
Agency



Emer Cooke
Executive Director
European Medicines
Agency





Session 1

CTR Implementation



Christophe Didion
Policy Officer, DG Sante
European Commission



Transition of clinical trials trials

From the Directive to the Regulation



EMA 4 July 2023

CTR provisions

- (79) Directive 2001/20/EC should be repealed to ensure that only one set of rules applies to the conduct of clinical trials in the Union. In order to facilitate the transition to the rules set out in this Regulation, sponsors should be allowed to start and conduct a clinical trial in accordance with Directive 2001/20/EC during a transitional period.

Article 98

Transitional provision

1. By way of derogation from Article 96(1) of this Regulation, where the request for authorisation of a clinical trial has been submitted before the date referred to in the second paragraph of Article 99 of this Regulation pursuant to Directive 2001/20/EC, that clinical trial shall continue to be governed by that Directive until three years from that date.

2. By way of derogation from Article 96(1) of this Regulation, where the request for authorisation of a clinical trial is submitted between six months after the date of publication of the notice referred to in Article 82(3) of this Regulation and 18 months after the date of publication of that notice, or, if the publication of that notice occurs earlier than 28 November 2015, where that request is submitted between 28 May 2016 and 28 May 2017, that clinical trial may be started in accordance with Articles 6, 7 and 9 of Directive 2001/20/EC. That clinical trial shall continue to be governed by that Directive until 42 months after the date of publication of the notice referred to in Article 82(3) of this Regulation, or, if that publication occurs earlier than 28 November 2015, until 28 May 2019.

9. The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States concerned.

CTR compliance

new clinical trial

- Application
- Assessment

- Decision
- Request for SM
- SM assessment
- SM decision

ongoing / pending clinical trials

- Authorisation under CTD

- Application for transition
- Assessment

- Decision
- Request for SM
- SM assessment
- SM decision

CTR compliance



Thank you



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Slide xx: **element concerned**, source: **e.g. Fotolia.com**; Slide xx: **element concerned**, source: **e.g. iStock.com**





Session 1

Member States' Experience and Perspective on Transitional Trials



Maria Elgaard Sørensen
Special Advisor
Danish Medicines Agency



LÆGEMIDDELSTYRELSEN

Clinical Trials Regulation Implementation

Member States' Experience and Perspective



Coordinated assessment and shared responsibilities between authorities

– DK example

Roles and responsibilities

➤ National Contact Point - Danish Medicines Agency (DKMA)

- Facilitator of the procedures in the regulation, chapter II og III
- Member of Clinical Trial Advisory Group (CTAG)
- DKMA assesses if a trial falls under the scope of the regulation

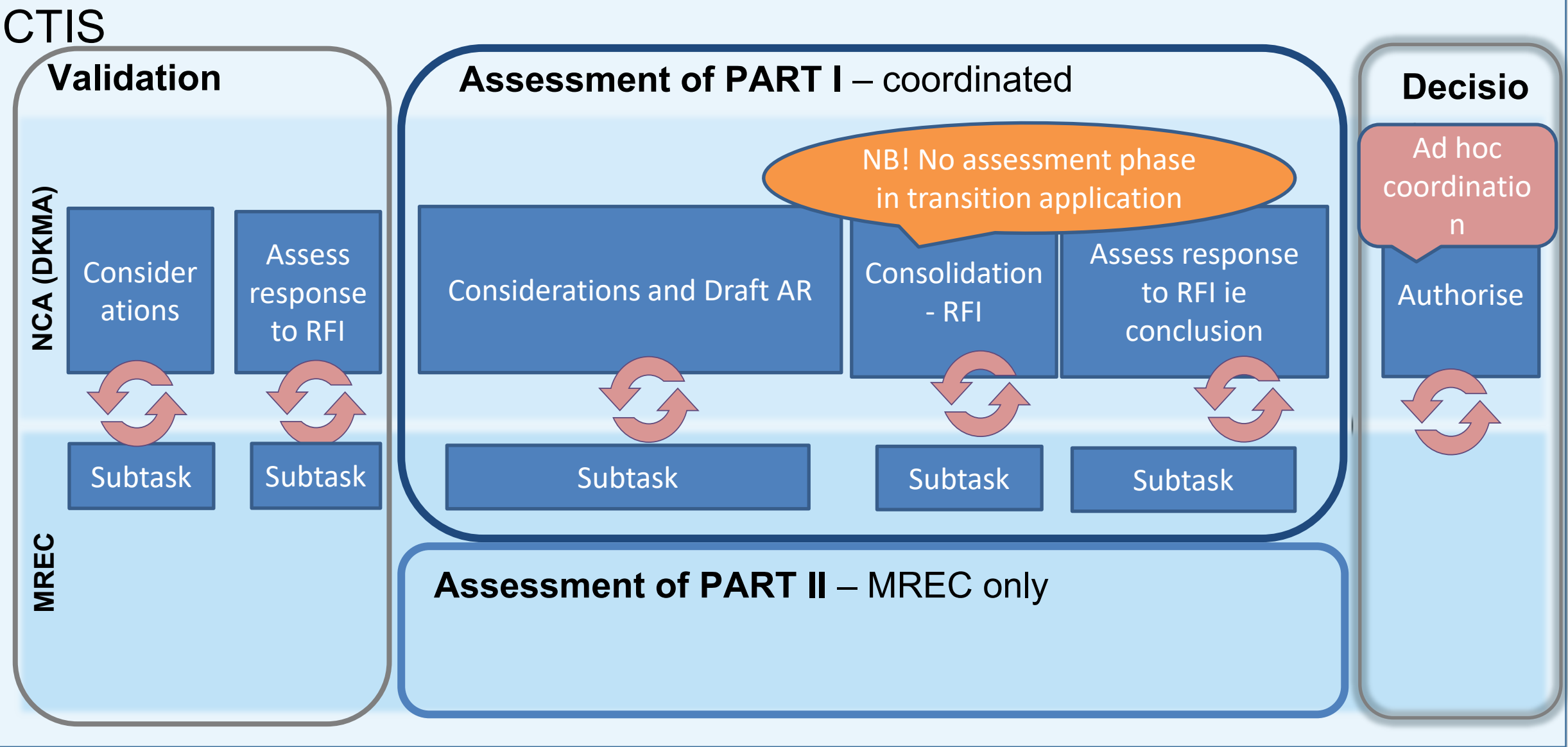
➤ Obligation for Medicinal Research Ethics Committee (MREC) and DKMA to cooperate on the assessment of applications and notifications

- DKMA assesses part I (scientific and health related aspects)
- Ethic Committee assesses part I (research ethical aspects) and part II

➤ Independent authorities

- If either DKMA or MREC finds the part I not acceptable or disagrees with the conclusion of the RMS or concerning AR for part I, the clinical trial will be rejected in DK
- Disagreement shall be based on reasons for opt out (art. 81, 2, a-c)

Coordinated assessment procedure in CTIS – national perspective





LÆGEMIDDELSTYRELSEN

Thank you for the attention

Follow us



@laegemiddelstyrelsen



Session 1

Member States' Experience and Perspective on Transitional Trials



Marie Mi Bonde Hansen
Special Consultant
Danish National Center
for Ethics

Smooth transition

Perspective on transitioning part II from
the Danish Medical Research Ethics Committees (MRECs)

Marie Mi Bonde Hansen, PhD

National Center for Ethics, Science and Ethics, Research Ethical Assessment, Denmark



DANISH NATIONAL
CENTER FOR ETHICS



3 COMMITTEES

Secretariat



SECTION HEADS



20+ ASSESSORS



3 ADMINISTRATIVE ASSOCIATES

The MREC assesses clinical trials under the CTR and MDR/IVDR

The assessors have various backgrounds, including bioethical, legal, health and science



Proces overview



Q&A chapter 11

- Transfer of clinical trials authorised under the CTD.
- Sponsor must declare in the coverletter that requirements are met.
- No re-assessment upon transitional application.
- CTR rules apply once transitioned.
- Dossier must be completed upon first substantial modification.



Validation of part II

Coverletter

- The specific name of the ethics committee who has given a favorable opinion on the clinical trial under CTD.
- Declaration that all documents submitted under part II for Denmark have received a favorable opinion by the mentioned ethics committee.



Validation of part II

Part II dossier

- Only the currently approved versions of the participant information sheet and informed consent form are required.
- Placeholder documents (e.g. insurance, financial arrangements), which must contain a statement that this aspect was assessed and approved by ethics committee who approved the trial under the CTD.



Assessment of part II

Part II dossier

- No re-assessment of documents.
- No RFI in the assessment phase
 - Exception: in case of unresolved issues during validation, administrative RFI to prevent rejection of the trial.
- Assessment report part II Denmark:
 - This trial is a transition trial and the dossier is in line with existing dossier already assessed and authorised by the Member States, why no further assessment is done in accordance with section 11 on the Q&A in volume 10.



Exception:

Clinical trials in emergency situations

Trials under CTR Art. 35

- Difference in rules for informed consent process between CTR and CTD in Denmark.
- RFI asking sponsor to commit substantial modification following transition.
- Assessment report part II Denmark:
 - Acceptable with condition:
 - Sponsor has confirmed via RFI in CTIS that application for a substantial modification will be made as soon as possible following transition into CTIS. This will ensure that the trial adheres to article 35 in CTR, as it is not possible to conduct a trial under CTR using the regulatory framework of the CTD.



Typical issues/considerations raised

- Please state in the coverletter the specific ethics committee that assessed the application.
- Please confirm that the documents submitted under part II for Denmark are the versions approved by the XXX Ethics Committee.
- The blank documents in the sections "Recruitment arrangements", "Financial arrangements" and "Proof of insurance" must all be updated with a description/confirmation that this aspect was assessed and approved by the XXX Ethics Committee that assessed the application.
- Please confirm/make sure that all documents submitted in this section have already been approved under the CTD in these versions by the XXX Ethics Committee, otherwise you need to remove the documents from the application. (The Transition in CTIS is an administrative procedure, and the documents will not be assessed. Therefore it is important that NO new documents are added to the application. With the next substantial amendment, you can submit documents missing according to Annex I).



Practical tips

Recommendations/for information

- We encourage you to upload the Danish addendum to the protocol that was approved under the Clinical Trials Directive by the original authorising ethics committee if possible.
- Please note that you should inform the original authorising ethics committee that your clinical trial has been transitioned into CTIS and is therefore now regulated by the rules of CTR.



Thank you for your attention

Danish National Center for Ethics

Danish Medical Research Ethics Committees

kontakt@dvmk.dk

<https://en.nationaltcenterforetik.dk/>



DANISH NATIONAL
CENTER FOR ETHICS



Session 1

Member States' Experience and Perspective on Transitional Trials



Elena Garcia Méndez

**Hospital Universitario La Paz
Spain**



Clinical Trials Information System Webinar:

Second Year of Transition

TRANSITIONAL TRIALS:

THE SPANISH EXPERIENCE AND
THE ETHICS COMMITTEE
PERSPECTIVE

Elena García Méndez



Hospital Universitario La Paz

Hospital de Cantoblanco
Hospital Carlos III



Agenda



Background



Our role



Our data



Our perspective



REGULATIONS

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
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

EU CTR (2014)



BOLETÍN OFICIAL DEL ESTADO



Núm. 307

Jueves 24 de diciembre de 2015

Sec. I. Pág. 121923

I. DISPOSICIONES GENERALES

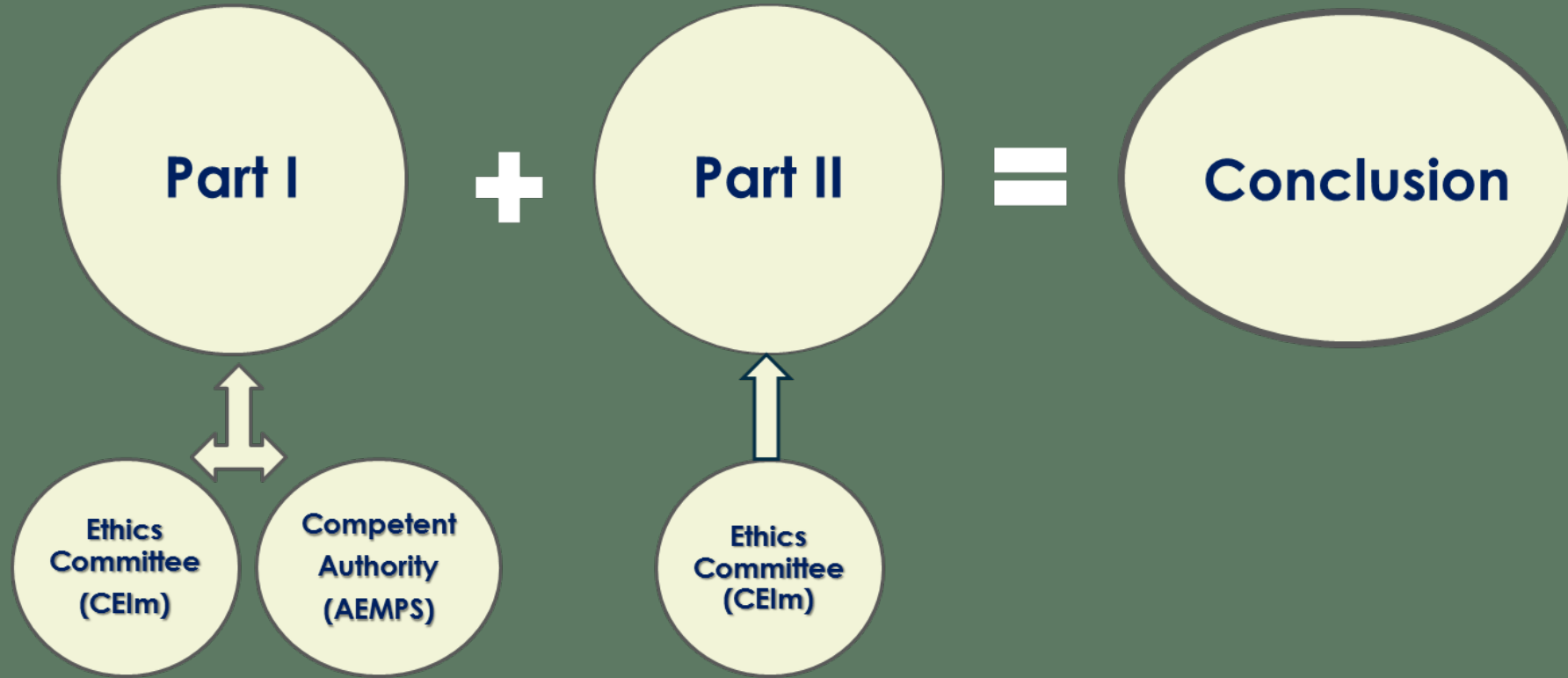
MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

14082 *Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos.*

NATIONAL
REGULATION
(2015)

Royal Decree 1090/2015

BACKGROUND:
where we come
from





Memorandum on Collaboration and Exchange of Information between the Spanish Agency and Ethics Committees. Version: 21/Jun/2016



Memorandum on Collaboration and Exchange of Information between the Spanish Agency of Medicinal Products and Medical Devices and Ethics Committees for investigation with medicinal products

VERSION: 21st June 2016

Instruction document of the Spanish Agency for conducting clinical trials in Spain.
Last version: 31Jan23



DEPARTMENT OF MEDICINAL
PRODUCTS FOR HUMAN USE

Instruction document of the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain

Version 16, dated 31st January 2022 (all versions can be reviewed at the end of the document)

English Version publication: 06th June 2022



Clinical Trial
Coordination
Group (GCEC)

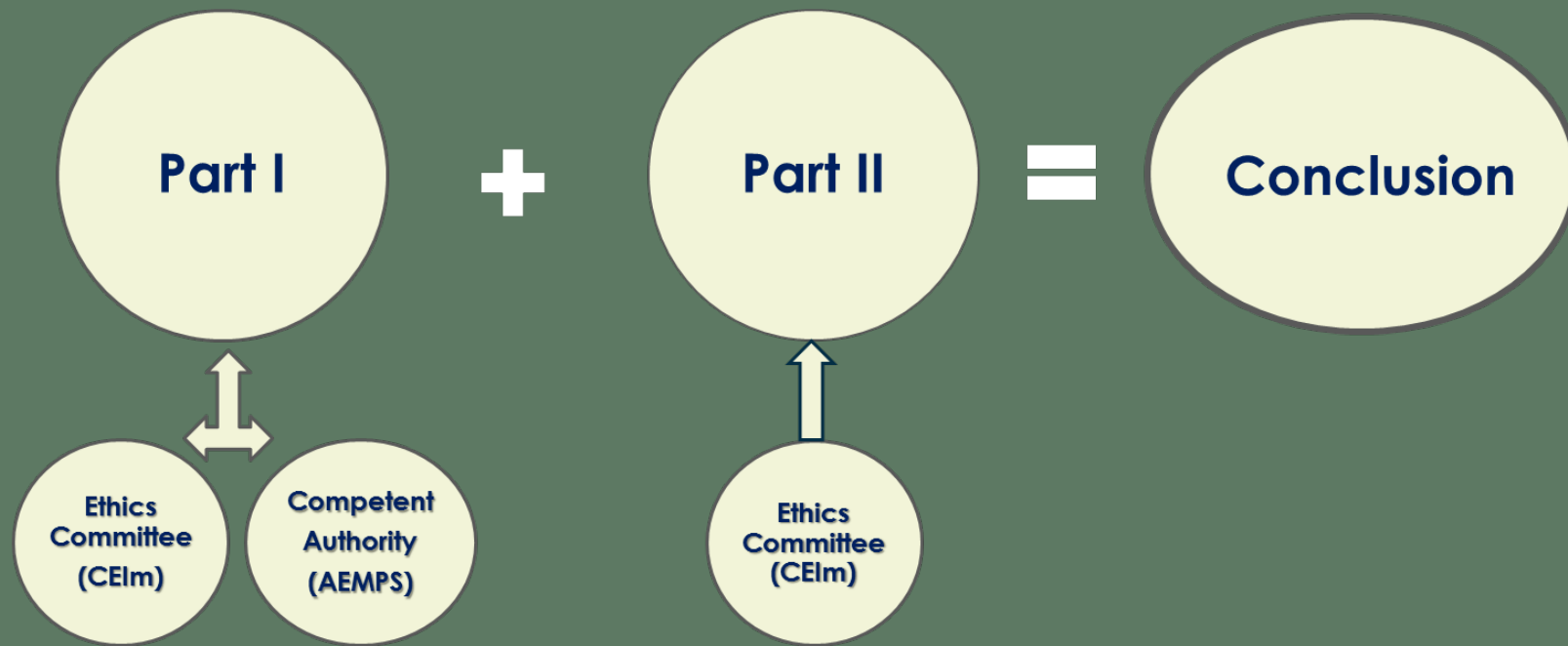


CEIm

Sponsors
farmaindustria

CROs





2016

Part I documents (both AEMPS/ CEIm)

- Cover letter
- Application form
- Protocol and summary
- Investigator Brochure / SPC (for both IMP and auxiliary MP)
- Scientific Advice / PIP

Part I documents (AEMPS)

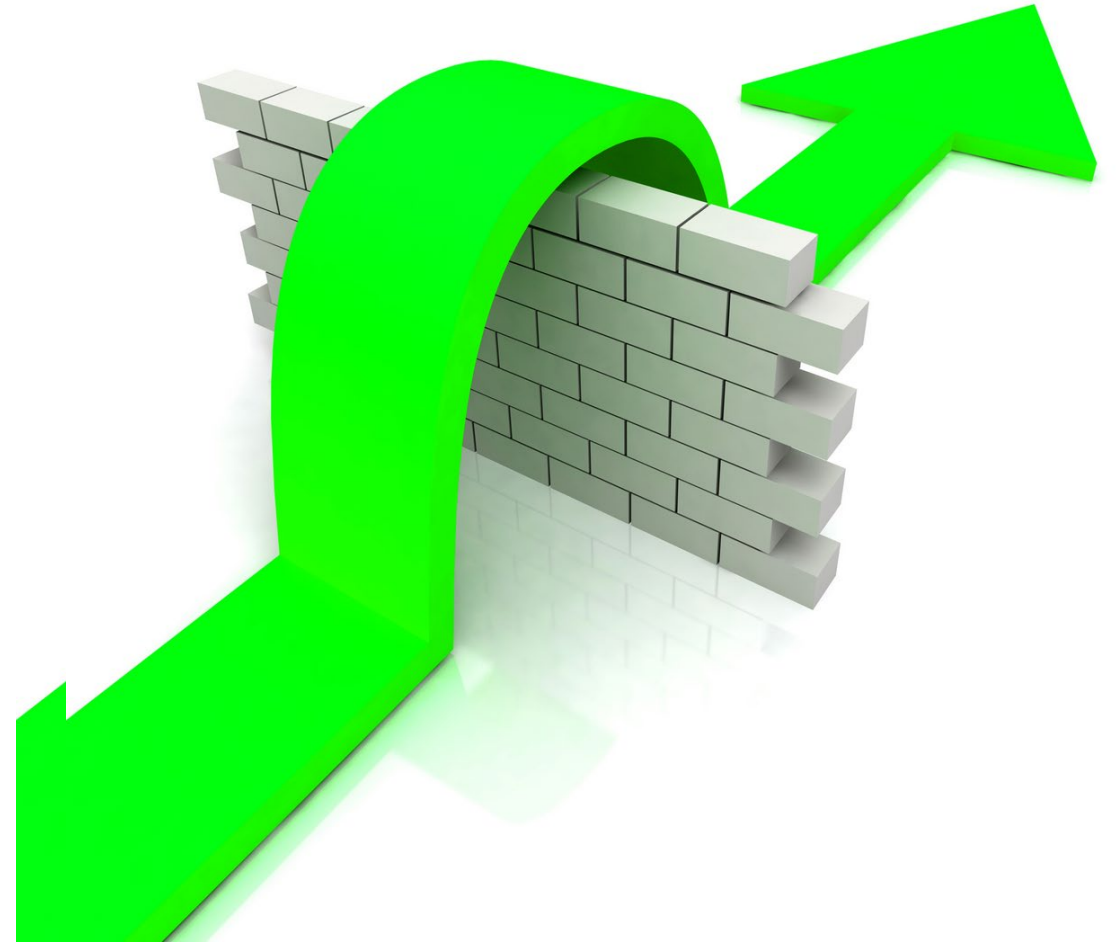
- GMP
- IMPD
- Labelling

Part II documents (CEIm)

- Recruitment arrangements
- Subject information sheet
- Suitability of the investigator
- Suitability of the facilities
- Proof of insurance cover or financial guarantee
- Financial schedule
- Management of biological samples
- Compliance with national legislation on data protection

WHAT DID WE LEARN?

- To harmonise and simplify processes and criteria
- To standardise documents (templates)
- To work on mutual trust and recognition





BOLETÍN OFICIAL DEL ESTADO



Núm. 307Jueves 24 de diciembre de 2015Sec. I. Pág. 121923

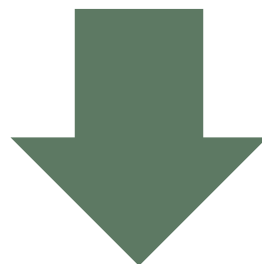
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MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

14082 *Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos.*

NATIONAL REGULATION (2015)

Royal Decree 1090/2015





EUROPEAN
MEDICINES
AGENCY

REGULATIONS

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
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

CTIS (2022)



BACKGROUND:
where we are



Memorandum on Collaboration and Exchange of Information between the Spanish Agency and Ethics Committees. Last version: 21/Feb/2023



Memorando de Colaboración e Intercambio de Información entre la Agencia Española de Medicamentos y Productos Sanitarios y los Comités de Ética de la Investigación con medicamentos

VERSIÓN: 21 de febrero de 2023

Fecha de publicación: 27 de abril de 2023

Instruction document of the Spanish Agency for conducting clinical trials in Spain.
Last version: 31Jan22



DEPARTMENT OF MEDICINAL
PRODUCTS FOR HUMAN USE

Instruction document of the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain

Version 16, dated 31st January 2022 (all versions can be reviewed at the end of the document)

English Version publication: 06th June 2022

SOPs on Validation, assessment of initial application and Substantial Modification

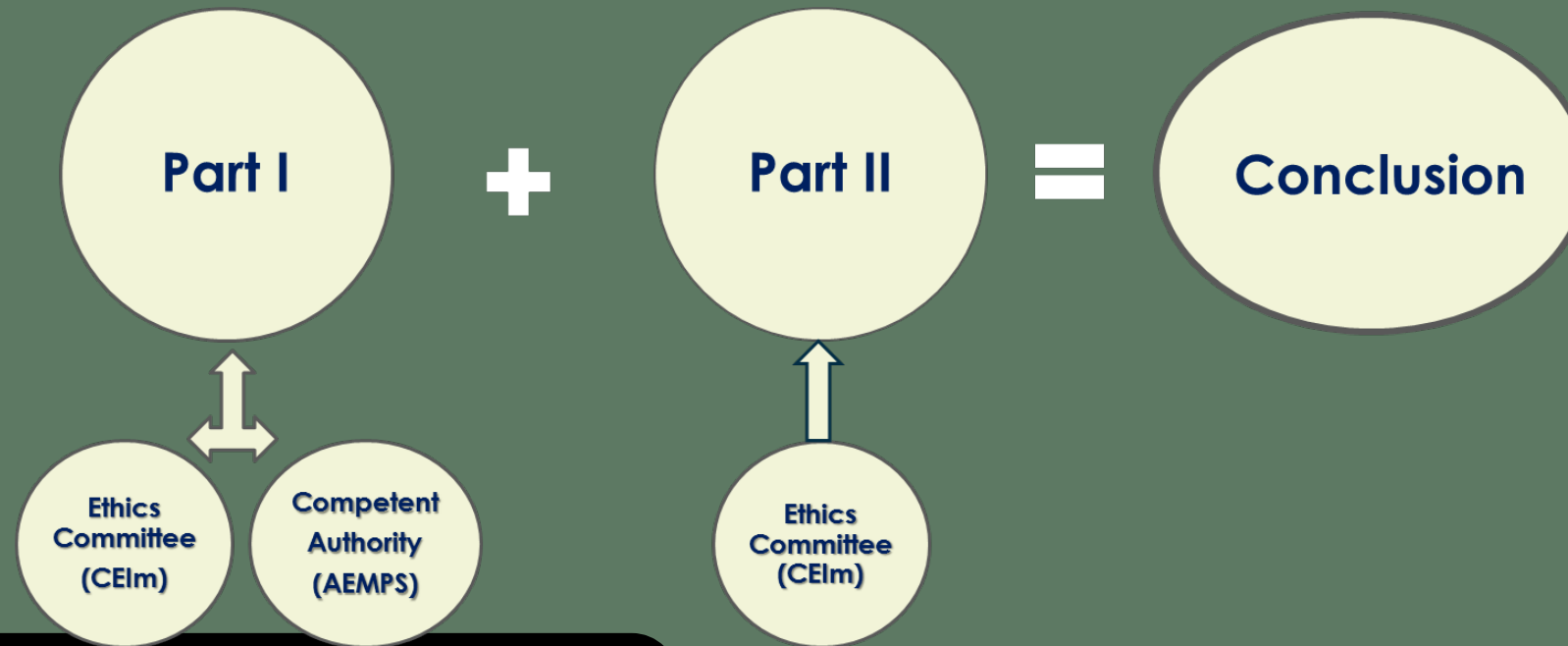


Clinical Trial
Coordination
Group (GCEC)



**CTIS GUIDANCE
FOR SPONSORS
- SPAIN -**

Version 1
March 2023



2022

Part I documents (both AEMPS/ CEIm)

- Cover letter
- Application form
- Protocol and summary
- Investigator Brochure / SPC (for both IMP and auxiliary MP)
- Scientific Advice / PIP
- **Compliance with EU legislation on data protection**

Part I documents (AEMPS)

- GMP
- IMPD
- Labelling

Part II documents (CEIm)

- Recruitment arrangements
- Subject information sheet
- Suitability of the investigator
- Suitability of the facilities
- Proof of insurance cover or financial guarantee
- Financial schedule
- **Management of biological samples**
- **Compliance with national legislation on data protection**

Our role as EC in transition trials

So far, we have been the
Ethics Committee (CTD) of
the trials transitioning

Validation of Part II (7)

- Applying min requirements (2): to check that the subjects' information sheet/ICF uploaded on CTIS are the latest approved versions
 - Rest of documentation to be submitted as part of first SM
- Validating all Part II documentation when uploaded (5)
 - Documentation not meeting CTR to be submitted as part of first SM

Our experience

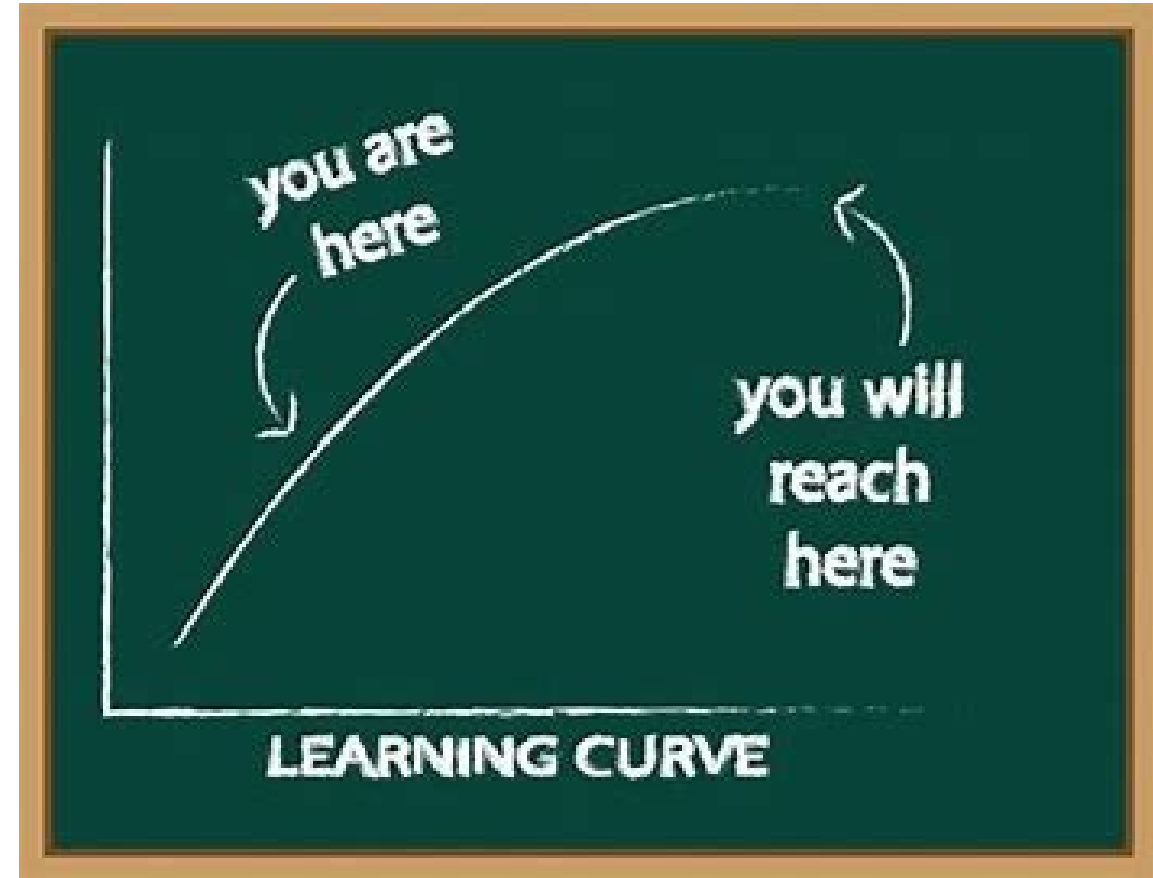
Minor issues



- Missing documents:
 - When multiple Subject Information Sheet/ICF have been authorised, some may be missing
 - Some of the sites documents may be missing
- Difficulties in confirming that the documents uploaded are the ones reviewed/approved by EC (the original document - the one approved by EC- was not appropriately versioned; most recent versions of CV uploaded)

TO APPLY LEARNINGS

- To harmonise and simplify processes and criteria
- To standardise documents (templates)
- To work on mutual trust and recognition
- Feel free to contact



IMPORTANT MESSAGE TO TAKE HOME

DO NOT EXHAUST TIMELINES:
TRANSITION TAKES TIME AND LAST-MINUTE UNEXPECTED
SHOWSTOPPERS MAY ARISE



Remember the two-week
winter clock stop



THANK YOU!





Session 1

Member States' Experience and Perspective on Transitional Trials

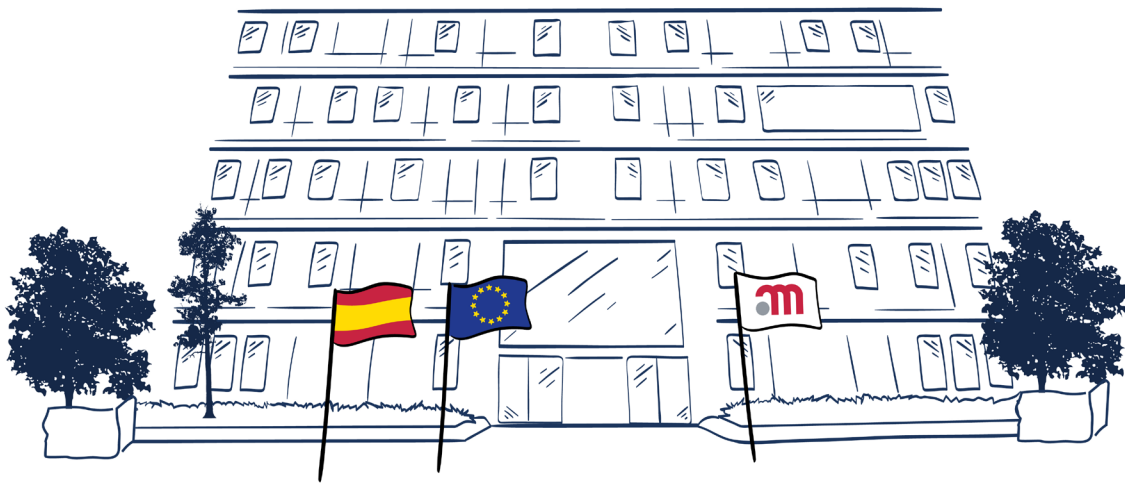


Laura Lavín de Juan
Clinical Trial Division
AEMPS

CTIS WEBINAR: SECOND YEAR OF TRANSITION

Spanish Experience and Perspective on Transitional Trials

July 4th 2023



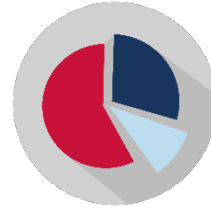
Laura Lavín de Juan

Spanish Agency for Medicines and
Medical Devices (AEMPS)



Validation

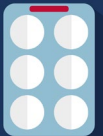
**Assessment
and decision**



**Substantial
Modification**

Conclusion





1 Validation

Validator notices it
is a Transitional CT



- Summary → **Transitioned Trial: Yes**
- Form → **Transition trial section & EudraCT Number**

1. Validation of Part II

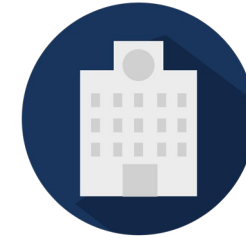
AEMPS involves the Ethics Committee in validation phase with a **subtask**.

EC checks the ICF and information sheet version.



Document Considerations for Validation Completed 2023-	RMS: SPAIN	Application and Non-SM type: Initial	Sponsor/Co-sponsors: 	Evaluation process: Validation	Created: 16/06/2023	Due: 26/06/2023	Completed date: 22/06/2023	Assignee: mencia_r
IMP1: Efzofitimod · EFZOFITIMOD								
(RME) CEIm (hgugm_c) – Validation part II Transition for Document Considerations for Validation Completed	EC				Created: 16/06/2023	Due: 23/06/2023	Completed: 21/06/2023	Assignee: hgugm_c
(RME) AEMPS – Review part I Transition for Document Considerations for Validation Completed	AEMPS				Created: 16/06/2023	Due: 23/06/2023	Completed: 19/06/2023	Assignee: mencia_r

If EC does not work in CTIS environment, **the validation of part II will be performed by AEMPS:** check last versions of ICF in the most recent part II authorization letter.



Ask the EC for confirmation if necessary.

**Authorised with
condition**



Sponsor must select another Ethics Committee for Spain for further substantial modifications for this clinical trial since selected Ethics Committee does not work in CTIS environment anymore. Sponsor must also notify the previous Committee the new selection.

Spanish EC working in CTIS environment published in [AEMPS website](#)



2. Validation of part I

AEMPS' validator creates another **subtask** for himself → check that version of the documents of questions 11.6 and 11.7 are the ones approved under the CTD:

- **Protocol**
- **IB**
- **GMP documents**
- **IMPD**
- **AxMP documents if applicable**

Consolidated
protocol

Take SM into
account!



AEMPS checks Trial category during validation phase → RFI if incorrect



Assessment and decision

**After validation, AEMPS validator assigns himself all the assessment tasks.
No EC involved in assessment phase of Transitional Trials.**



MSC assessment

- **Document Considerations Assess Part I**
Complete it quickly: deficiencies solved in validation phase.
- **Document Consideration Assess Part II**
Complete it quickly.
- **Submit Part II Conclusion**
Upload FAR part II, using a standardised template.



**We usually complete these tasks on the first or second day after validation.
When DAR is circulated by RMS, we review it.**

RMS assessment



- **Circulate Draft Assessment Part I Report**

Preparation of DAR part I downloading **Section 1 – Introduction template** and completing it with a model text. Upload it in **Section 7- conclusion** and share if multinational.

- **Document Considerations Assess Part I**

Once MSCs have completed Document Cons Assess Part I, validator also completes it and does the task Submit Part I Conclusion.

- **Submit Part I Conclusion**

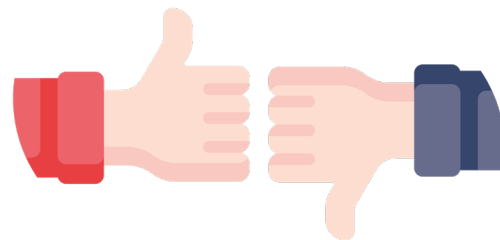
Upload FAR part I (quality and except quality): DAR in PDF.
FAR quality and except quality are the same document.

Document Cons Assess Part II and Submit Part II Conclusion: the same as in MSC assessment.

Decision

After assessment phase, once conclusion of part I and part II have been submitted, AEMPS validator complete the task **Authorise**.

Condition if EC who approved the CT under CTD does not work in CTIS → sponsor needs to select another EC when submitting the first SM.





Substantial Modification

First SM

EC is involved both in validation and assessment phases:

- Validation of part II
- Assessment of part I (with AEMPS) and part II

AEMPS (part I) and EC (part II) check if dossier has been completed and fulfills CTR requirements.

Assessment phase: same procedure than SM for non-transitional CTs.





Conclusion

Transitional Tials Applications in Spain



90 Transitional CTAs in ES until June 22nd:

- 18 RMS
- 8 National
- 64 MSC



Final conclusions

- ✓ Assessment of new applications must be the priority for MSCs.
- ✓ Transition process should be **simplified as much as possible** → only administrative. Quick and smooth.
- ✓ Use of simplified DAR and FAR in transition applications.



¡Thank you for your attention!

Clinical Trials Division – AEMPS

aecaem@aemps.es



Session 1

Sponsors' Experience and Perspective on Transitional Trials



Tatjana Djerkovic
Global Submission Manager
Pfizer

CTIS: Second Year of Transition

Pfizer Experience and Perspective
on Transitional Trials

Tatjana Djerkovic
Global Submission Manager
Global Regulatory Sciences

4 July 2023



Pfizer CTIS Experience

Overall aim and Objectives of this session:

**To provide perspective
on Year 1**

**To share initial
application
experience**

**To share transition
experience**



31 January 2023

The use of the Clinical Trials Information System (CTIS) is now mandatory for all new clinical trial applications (CTAs) in the European Union (EU) and will serve as the single-entry point for submission by sponsors and for regulatory assessment.

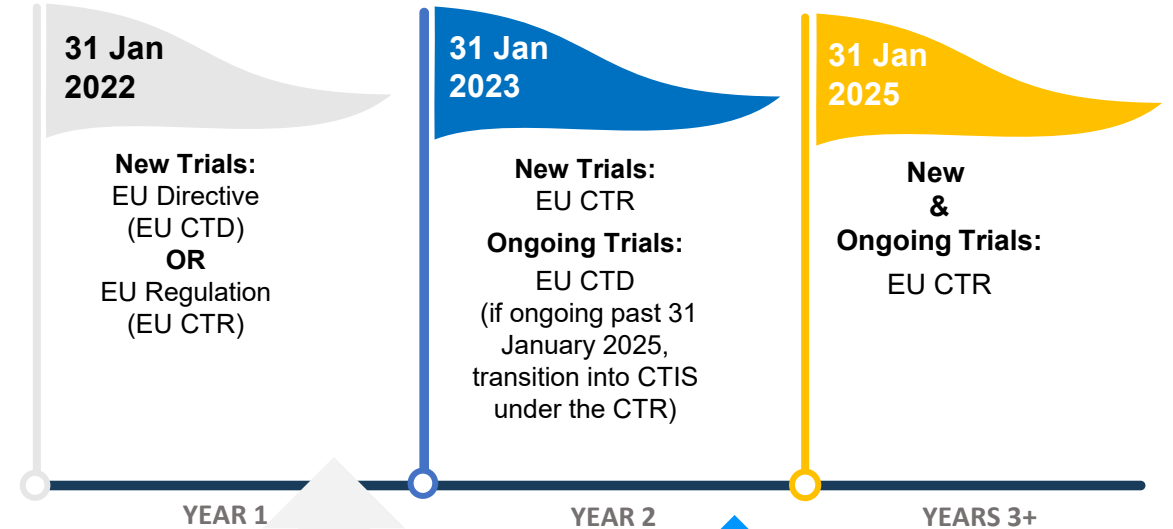
Objective of Today's Session:

Give overview of experience so far

- **CTIS system and overall process**

Give an update on transition planning

- Snapshot view on here through to 31st Jan 2025



Full Programme Management Office

Cross function team of experts are along for the ride

Start of Epic Journey

Reaching the start Line – with learnings

In preparation

WE ARE ALL HERE!

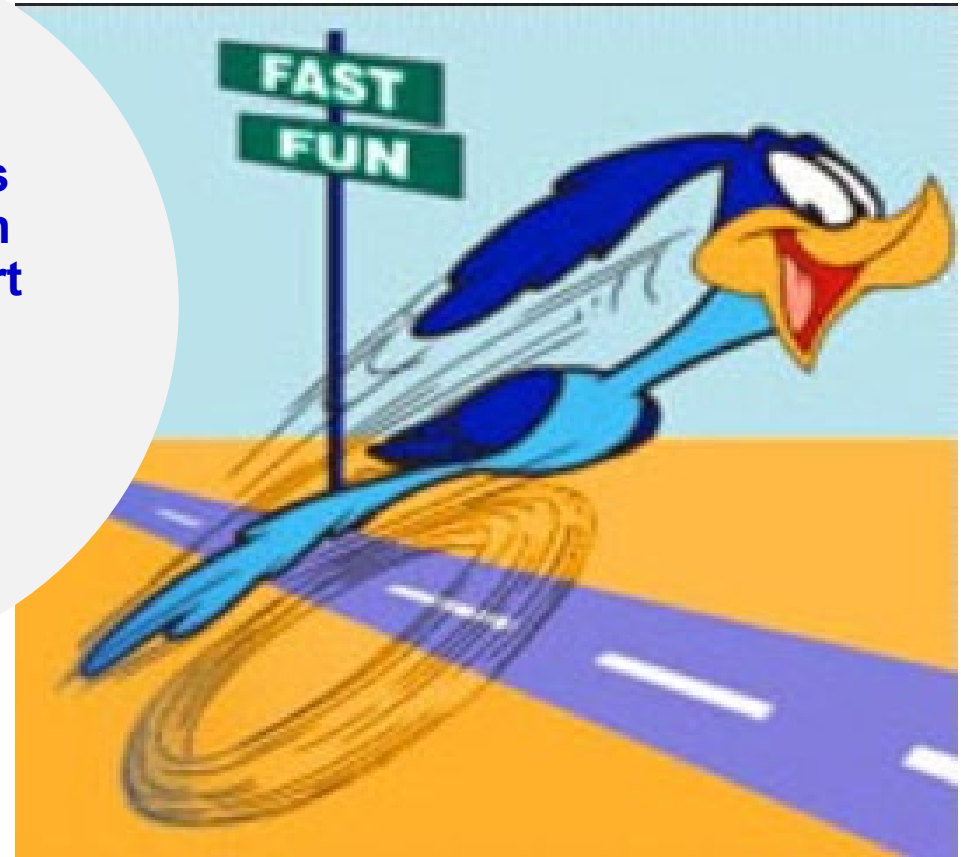
With years in the planning we were prepared, but there was so much to learn

This is how we wanted EUCTR to arrive....

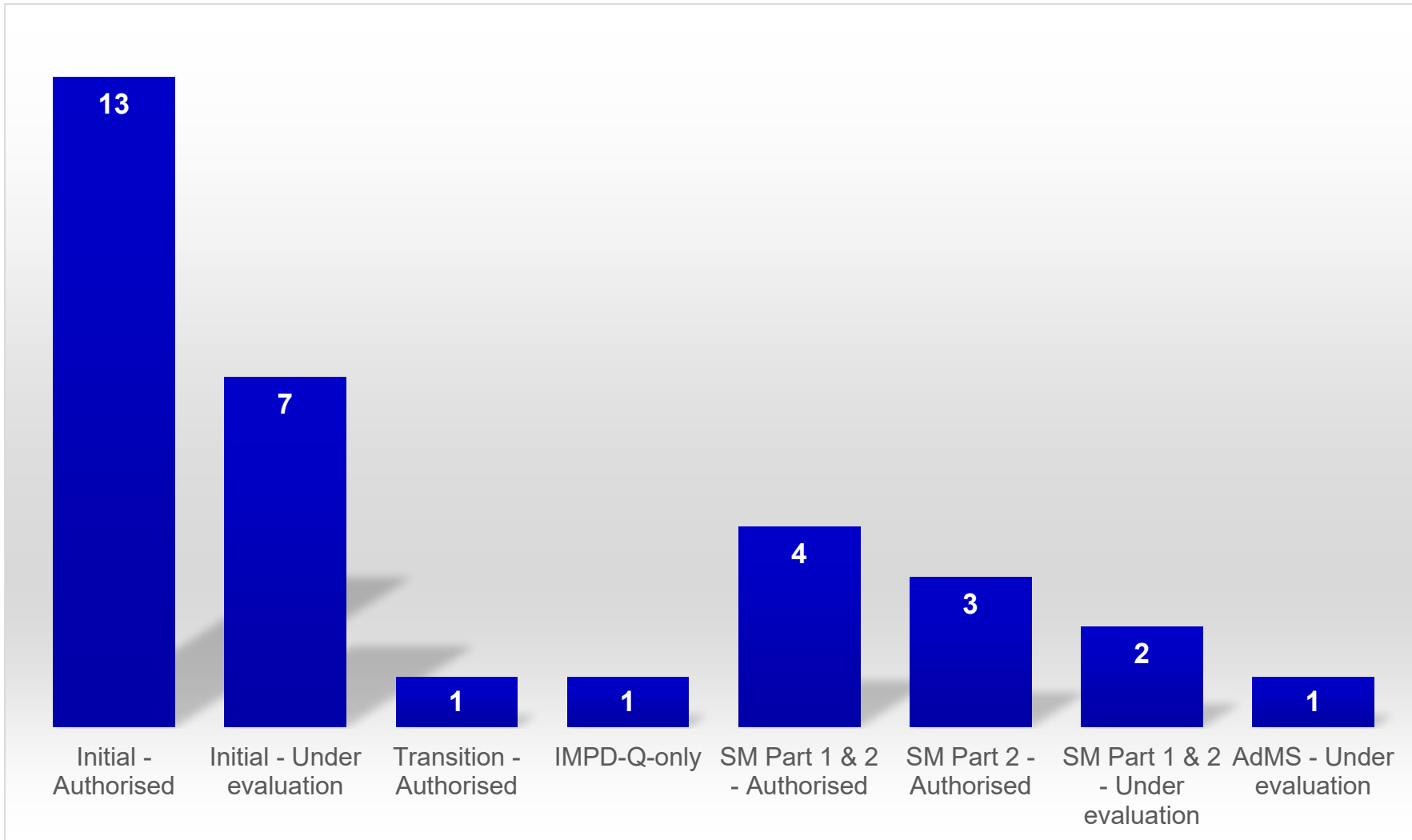


What has helped is close collaboration with EMA & Support of Many industry forums Sharing information

THIS IS REALLY EUCTR...



Pfizer metrics CTIS so Far



¹ Sample source formatting.
² Sample source formatting.

What have we learned so far?

Submission process

Clear Planning to make appropriate Submissions for Part I and/or all Part II

Q&As delivered by EMA vital to success and reduction in validation issues

Automation supports upload of documents

Some CTIS bugs still present

RFI and Response

Some RFIs are still present in validation

12 Day response timelines does support acceleration of overall timelines but are challenging

Part II RFIs coming post Part I: there is an improvement in overall process

On occasion multiple rounds of queries received

Opinion

Countries decision come on average on the same 10-day window

Allowing predictability to Study Start up

Average approval time:

Initial sub.: 125 D (winter clock stop and holidays calculated)

SM: 75 D

Our target for approval: 91 days

Each submission is providing new lesson learned and enabling streamlining of processes to align with CTIS.

What do we need from EMA & EC:

- Stable CTIS
- MSC alignment on Part II for reviewing process and required documents,
- To align with IVDR and BfS submission

Learning curve

EU CTR requirements different from CTD

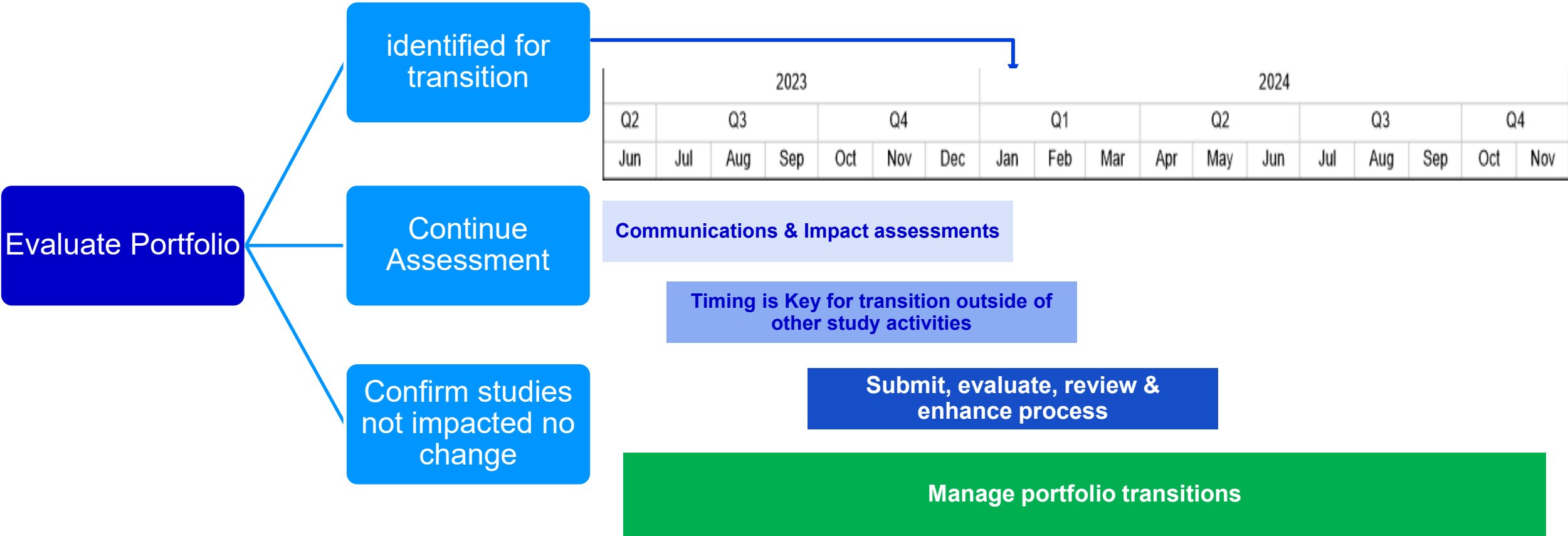
Part I documents
are mostly
aligned on CTD

- Big difference with AxMPD (medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product – not required under CTD)
- Patient facing documents that are related to endpoints to be submitted along with Protocol within Part I
- Different language requirements among countries for Part I documents
- Data Protection statement is now a specific document
- Deferrals and Transparency are giving headaches to sponsors
- CCI and PPD redaction is additional work

Part II
requirements

- Simplification intended by EU CTR is the biggest change (very positive !)
- Not all ECs are yet aligned with CTR requirements
- Not always clear to all sponsors that EU CTR is aligned with ICH GCP
- PPD (sometimes CCI) redaction is adding to workload

EU CTR Transition: Decisions and Planning; Staged Approach



Pfizer Transitioning plan – current experience

Over the next 12
Month a stage
approach to transition

Complexities are
evident when
transitioning on-going
trials in study conduct

Impact assessments
are continually being
completed



Snapshot view on here through to 31st Jan
2025 will finalize under the Clinical Trial
Directive (CTD)

Some CECs asked
for CTR-specific
document during
validation

Timelines & efficiencies are created where markets have
allowed CTR-specific documents will have to be
submitted during first SM

Pfizer: In Summary

This is still a learning Curve – across all areas, internally, industry and through assessment

Pfizer is committed to supporting this change & have full confidence in time EUCTR will harmonise the processes for **assessment and supervision of clinical trials** throughout the EU.



Planning & Execution becoming easier

Request for CTD documents has started to reduce – but we are still seeing some requests for documentation not required as part of EUCTR

Training our teams on the disclosure requirements and how to amend their protocols and IBs to make them disclosure ready.



System Improvements

- Max file size 10MB→50MB
- Improved CTIS stability
- Several users working together in CTIS



Request for Consideration

- Addition clarifications through Q&A on transition documentation
- Review of Calendar days for RFI
- Increased focus on system bugs
- Clear guidance on what will trigger technical summary disclosure of intermediate analysis for a transitional trial
- Support to ensure Member States do not request documents/public versions be created that were not required under the Directive

EMA support

Responsiveness of Service Desk

Walk-in clinics and Bitesize talks

Both allow to ask detailed questions to EMA and MSC representatives

- Allows for pragmatic approach when there is unclarity
- Allows to share suggestions when there is room for interpretation

Thank You



Breakthroughs that change patients' lives



Session 1

Sponsors' Experience and Perspective on Transitional Trials



Natalia Ayas Montero
EU Regional Submission Lead
MSD



MSD Experience and Perspective on Transitional Trials

Natalia Ayas Montero

4-07-2023

Agenda



Transition Strategy @MSD



MSD experience so far



Lessons Learnt & Recommendations

Transition Strategy @MSD



Ongoing Studies Transition

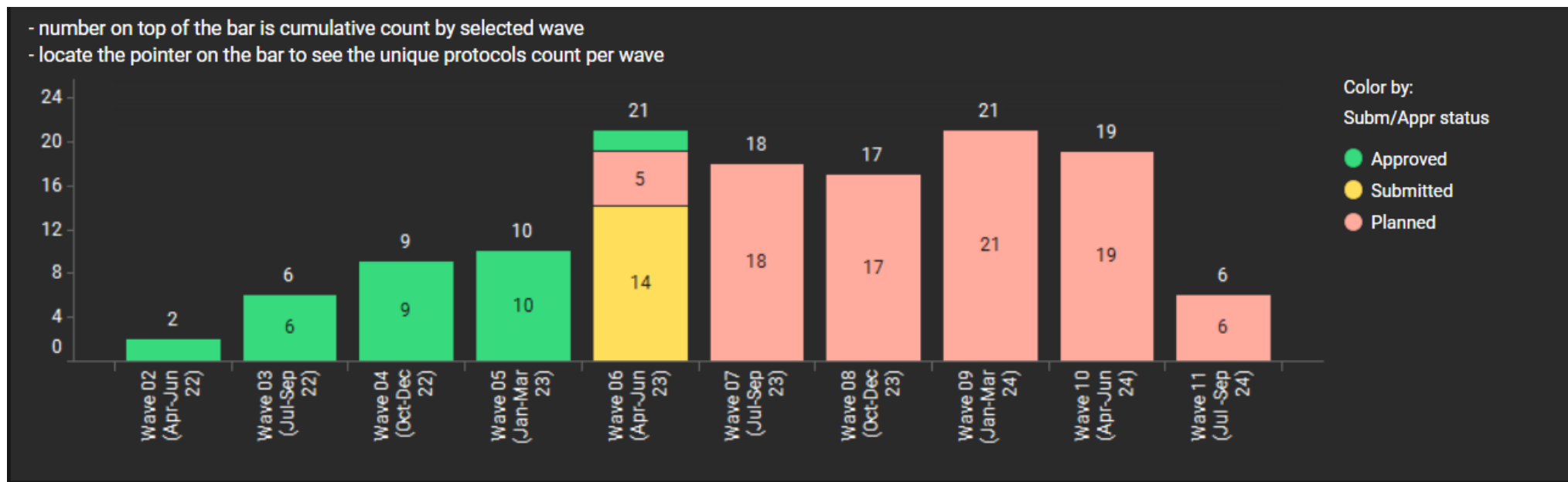
During 2022, transition of 18 ongoing studies completed

During 2023-2024, the rest (> 100) will be transitioned

By the end of 2024, all ongoing studies with Last Patient Last Visit (LPLV) post Year 3 should be transitioned to EU CTR.

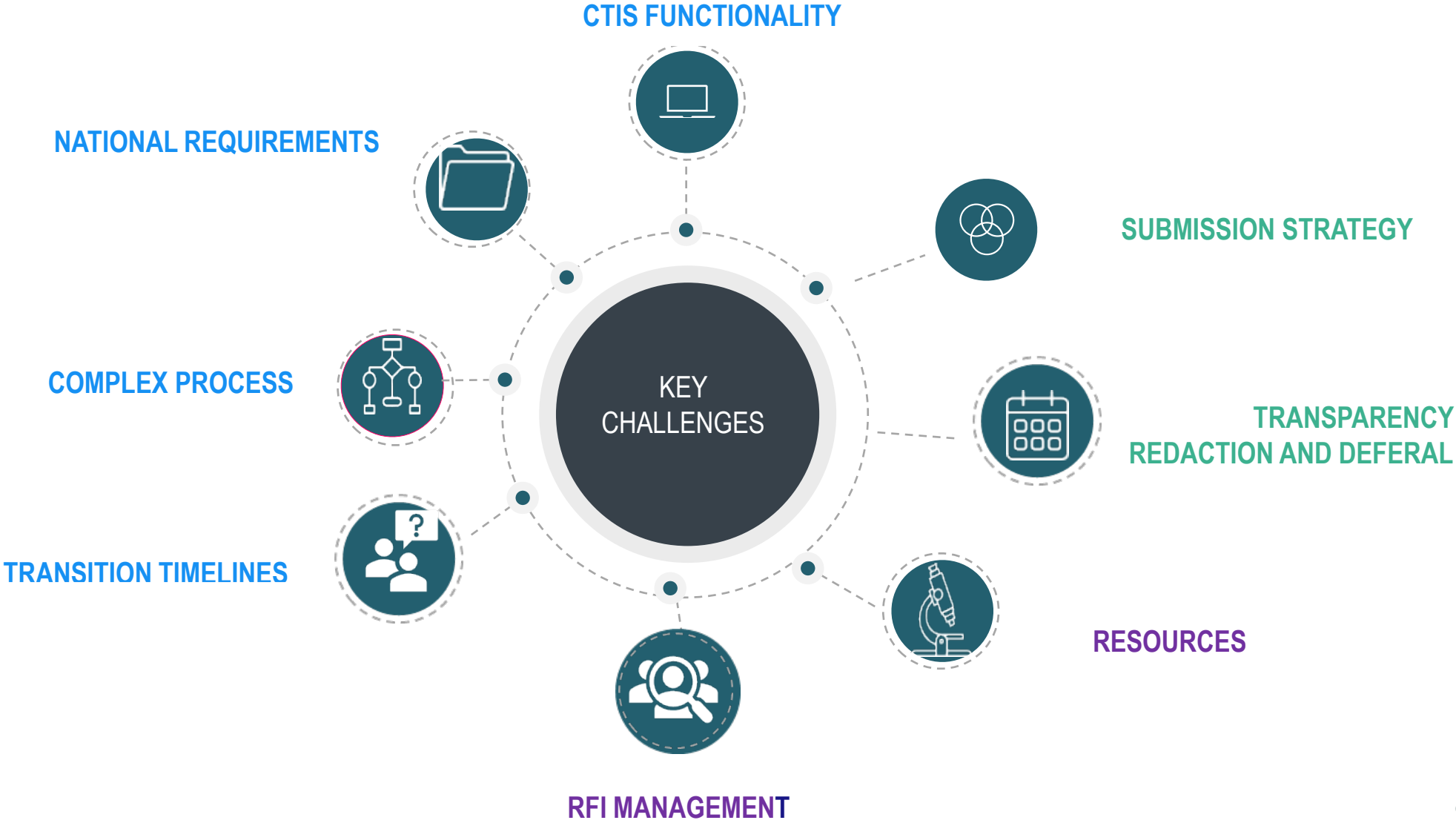


Transition Strategy @MSD



- Intense internal negotiations with all functional areas for Transition Plan
- Initial Review of Last Patient last Visit for Studies categorized as Out of Scope for Transition
- Going Forward: Quarterly Review of LPLV for Out of Scope Studies

Our Experience



Key Internal Challenges – How to tackle them?

- **Submission Strategy for Transition**

- Part I documents harmonization across all MS might be required. New amendment to be handled under CTD before transition
- Long HA/ EC approvals for ongoing amendments under CTD in some countries
- Studies with multiple IMPs. Many amendments to be managed, difficult to find free window for transition

- **Transparency: Redaction and Deferral**

- Internal process adaptation to achieve alignment on CCI and PPD redaction
- Time delay for preparation of CTA application dossier

Key Internal & External Challenges – How to tackle them?

- **Resources**

- Team evolution and adaptation to cope with all the new requirements
- New requirements in Q&A for immediate implementation
- Unexpected issues which are resource demanding to resolve in short time

- **RFI Management**

- During transition application assessment RFIs are received for already approved documents under CTD.
- Tight timelines to respond RFIs and assess responses

Key External Challenges – How to tackle them?

- **Transition timelines**

- May vary up to 106 days, MSD average is 59 days for first MS approval
- No substantial amendments can be submitted for other important changes
- Some MS best practice approval only 2 weeks after the submission (e.g. ES, DK, NL)

- **Complex Process**

- Requires 2-month preparation to collect Part 2 documentation for SM after transition
- Prevents submission of other important SMs (e.g. add a rescue country, new principal investigator)
- Not possible to submit parallel amendments: e.g. addition of Member state in parallel with IB update or protocol amendment. Potential impact on patient safety and/or delay broad patient access to innovative treatments in the new countries.

- **National Requirements**

- MS continue to require specific national documentation (e.g. patient card, EC approval letter, FDs...)

- **CTIS functionality**

- Unstable, multiple technical issues
- Application lapsed because of technical issues of the system
- CTIS portal does not allow a communication with EC/MSD sometimes needed to understand the needs

Lessons Learnt & Recommendations

Industry

- Call to Action:
Start now – there is no time to waste - plan your transitions
- Resources adaptation to cope with EUCTR requirements
- Close collaboration across functional areas is a must
- Learning curve continues

Regulators

- Simplify transition requirements
- Reduce timelines for approval of transition applications
 - Only validation should be required, no assessment
- Increased flexibility for SMs
 - Allow submission to assess additional docs after 31 Jan 2025
 - Allow transition, document updates and other changes within one SM procedure to speed up and focus resources
- Improve CTIS functionality in collaboration with stakeholders





Session 1



Questions & Answers – Panel Discussion



Coffee break

Back at 15:50(CET)

Coming up next...
Session 2

For questions, go on www.sli.do
#InfoJul2023 or scan the QR-code





Session 2

Member States' Best Practices for Transitional Trials



Monique Al
Vice-chair CTCG

CTCG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under the Directive 2001/20/EC that will transition to the Regulation (EU) No. 536/2014

Clinical Trials Information System Webinar: Second Year of Transition

CTIS webinar, 4 July 2023

Monique Al, vice-chair CTCG

Introduction

Active sites

Documentation

Procedures

Addition of MS in a transition trial

Some introductory notes

- Chapter 11 of the COM Q&A about transition trials (Eudralex volume 10):
https://health.ec.europa.eu/system/files/2023-04/regulation5362014_qa_en.pdf
- Update of CTCG best practice transition multinational clinical trials: to be published soon at key document list CTCG website: <https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html>
- Principles of CTCG best practice transition multinational clinical trials also apply for mononational clinical trials

Concept of active sites

- Trials that can be transitioned: Only trials authorised under the CTD and likely to be ongoing beyond 30 January 2025 need to be transitioned if they meet these criteria:
 - are interventional clinical trials in humans;
 - involve **at least one active site** in the EU/EEA where the trial is still ongoing;
 - there are no substantial amendments ongoing in any Member State Concerned (MSC) under CTD.
- **Active site***: the concept active site implies that if the last visit last subject (LVLS) or any other trial specific intervention with the subject as specified in the protocol took place before this date, the trial does not have to be transitioned.
- If there are **no active sites in EU/EEA** but the EoT has not yet been notified, the trial should **not be transitioned**
- EudraCT remains active beyond the end of the transition period for sponsors:
 - to notify global end of the trial and submission of summary results of trials completed under the Directive.
 - to keep registering in EudraCT trials conducted exclusively outside of the EU/EEA that are part of a Paediatric Investigation Plan (PIP) and/or in scope of Article 46 of the Paediatric Regulation (EC) 1901/2006, until a relevant functionality is delivered in CTIS.

*expected to be clarified in next version of COM Q&A on Eudralex volume 10

Documentation – minimum set of documents

Sponsor needs to submit an initial application relying on the existing CTD dossier, already assessed and authorised. The following minimum set of documentation is required:

- All mandatory application structured data fields in CTIS need to be completed.
- Statement on GDPR compliance (*new, required for users CTIS*)
- Cover Letter. The cover letter should follow the format of the CTCG template cover letter for transition trials (annex to CTCG best practice on transition multinational trials)
- Protocol: a harmonised or consolidated protocol (Part I)
- Investigator's Brochure (Part I)
- GMP relevant documents (Part I)
- IMPD (Part I)
- Documents related to auxiliary medicinal products (non-IMPs under CTD) (Part I)
- Subject information sheet and informed consent form (Part II)

Documentation – minimum set of documents



Retrospective documents do not need to be submitted to CTIS.

Only the **latest approved versions** should be included in the transition application.

Documentation – on top of minimum set of documents Part I

- The sponsor may choose to include additional **part I documents** (not listed in previous slide) as outlined in CTR annex I, **provided that these have been authorised** under CTD
- It is acceptable that for all **other part I documents** (not listed in the previous slide), the sponsor **replace them with a document clarifying “Assessed by National Competent Authority (NCA) and/or ethics committee** who has given a positive opinion on the clinical trial **under the CTD** and therefore **covered by the conclusion of the assessment under the CTD**.
- **Additional documents Part I documents approved in some, but not all MSCs** (e.g. the DSMB Charter for Part I or layperson summary in national language) can be included as well, provided that these have been **authorised under the CTD** and they are **clearly indicated in the cover letter** as applicable for those MSs only.

Documentation – on top of minimum set of documents Part II

- The sponsor may choose to include **additional part II documents** (not listed in previous slide) as outlined in CTR annex I, **provided that these have been authorised** under CTD
- It is acceptable that for all **other part II documents** (not listed in the previous slide), the sponsor **replace them with a document clarifying “Assessed by ethics committee** who has given a positive opinion on the clinical trial **under the CTD** and therefore **covered by the conclusion of the assessment under the CTD.**”
- A MSC may raise a **validation consideration** requiring the sponsor to submit additional, earlier approved part II documents (limited to those described in CTR annex I)
- *To be updated in COM Q&A Chapter 11 (Eudralex volume 10)*

Multinational protocol: harmonised or consolidated (1)

To transition a multinational clinical trial protocol, **only one protocol per clinical trial** should be uploaded in CTIS. It should be either a **harmonised** or a **consolidated protocol**.

- A **harmonised protocol** is one where an identical protocol that **includes the same trial procedures in all countries** has been approved across all EU Member States under the CTD.
- A **consolidated protocol** is one in which there are a **few differences in procedures in different Member States, but the protocol document itself is identical**, i.e. Member State-specific issues are outlined within the protocol or in an appendix to the protocol. The consolidated protocol does not need prior CTD approval before the transition.
- If there are **significant differences across Member States**, authorisation of a harmonised protocol under the CTD is required prior transition. This requires a **substantial modification application approval under the CTD to harmonise protocol**.
- If there are only **a few substantial** (e.g. subject population age groups) **and/or non-substantial differences** (e.g. administrative differences, in line with Annex IV of the COM Q&A on Eudralex volume 10) **across Member States** concerned in the authorised versions of the protocol, **a consolidated version may be transitioned as a single new version without prior approval under the CTD**.

Multinational protocol: harmonised or consolidated (2)

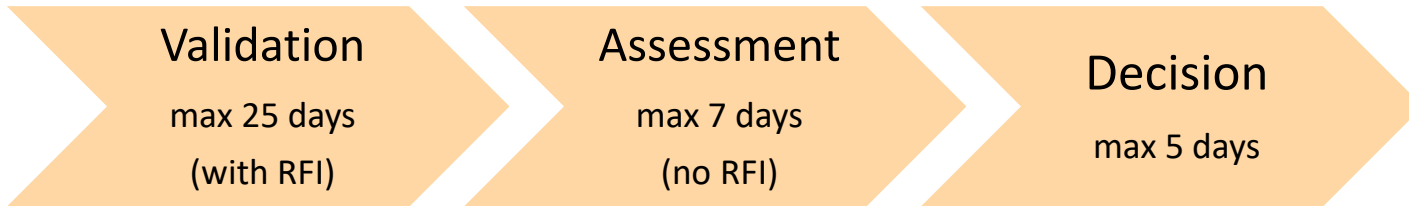
The following aspects of the protocol must be the same across all MSCs:

- EudraCT number
- Trial Title
- Protocol version number (for a consolidated protocol a new version number is acceptable, when the cover letter clearly indicates the authorised version number per MSC used as a basis for the new consolidated version)
- Primary objective
- Primary endpoint
- Definition of end of trial
- In addition, the main inclusion and exclusion criteria should be the same, while accepting limited national restrictions in e.g. trial population age groups for a particular Member State

Documentation – some specifications

- IB and IMPD should be harmonised between the different MSC of the clinical trial. A consolidated version will not be accepted
- The approved IMPD can be uploaded in the Clinical Trials Information System (CTIS) slot for IMPD-Q, providing a reference to this document or to the IB/SmPC in the CTIS slot for IMPD S&E.
- Documentation labelled with EudraCT trial number (=approved under CTD) is acceptable and does not have to be updated with EU CT number before transition (e.g. protocol, QP declaration or IMP labels)
- Mandatory use of format cover letter indicating approved versions of submitted documents, overview of non-SM (according to annex IV of COM Q&A, if applicable), the name of the ethics committee and a declaration that all submitted documents are approved under CTD (CTCG template cover letter → annex to CTCG best practice guidance for sponsors).

Procedure – expedited administrative procedure



- Validation phase in line with article 5 CTR (no RFI max 10 days; with RFI max 25 days)
- Assessment phase max 7 days – no re-assessment of clinical trial
- If there are errors in trial category/deferrals as proposed by sponsor → RFI → timelines for assessment phase fall back on max timelines article 6 CTR (max 76 days)
- No tacit conclusion part II – assessment phase also max 7 days (*under discussion, tbd*)
- Decision phase in line with article 8 CTR (max 5 days)
- During transition, the clinical trial can continue

After approval transition trial

- Sponsor should comply with CTR regulation, e.g. notifications of serious breaches, urgent safety measures and unexpected events even if protocol in minimum transition dossier restricted to documents approved under CTD do not specify such obligations.
- The clinical trial dossier can be updated in line with annex I CTR with the next substantial modification:
 - SM part I → update dossier part I in line with annex I and II CTR
 - SM part II → update dossier part II in line with annex I and II CTR
- Start of trial in CTIS – retrospective first subject inclusion date
- Additional MS in a transition trial only after approval of the SM aligning the dossier with CTR requirements

Additional MS procedure in a transition dossier

- **For the first MS to be added**

- Sponsor should submit a substantial modification part I to complete dossier Part I dossier and to announce in the cover letter the intention to add a new MS to this clinical trial
- After approval of this substantial modification part I, an additional MS procedure can be initiated by sponsor
- This 2-step approach is needed to complete the Part I dossier for the additional MS since this MS has not assessed the clinical trial before, and to allow the RMS to complete a draft assessment report part I for the additional MS.

- **Second, third, additional MS in a transition trial**

- Sponsor can start additional MS procedure if no other assessments part I are ongoing.

Transition in time

To transition ongoing trials to CTR, sponsors will need to submit them in time and before the end of the transition period, **considering the time needed for assessment** and the two-week winter clock stop.



QUESTIONS?



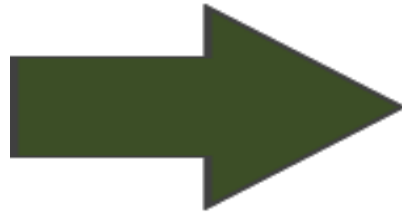
Session 2

CTIS Looking forward



Noemie Manent
Principal Scientific
Administrator
EMA

The European Clinical Trials Regulation



Before the Clinical Trials Regulation

Clinical trial applications were submitted separately to regulators and ethics committees in each EU Member State

After the Clinical Trials Regulation

Single clinical trial application covering regulatory and ethics submission in up to 27 Member States

Applies as of **31 January 2022**

CTIS is the business tool of the Clinical Trials Regulation

The Clinical Trials Information System (CTIS) is the single submission portal which **harmonises the submission, assessment and supervision of clinical trials** in the EU/EEA.



Public health

Facilitates multinational trials to address key health issues, increase transparency & enables patient enrolment



Research and innovation

Enables medical innovation through collaboration and access to clinical research data.

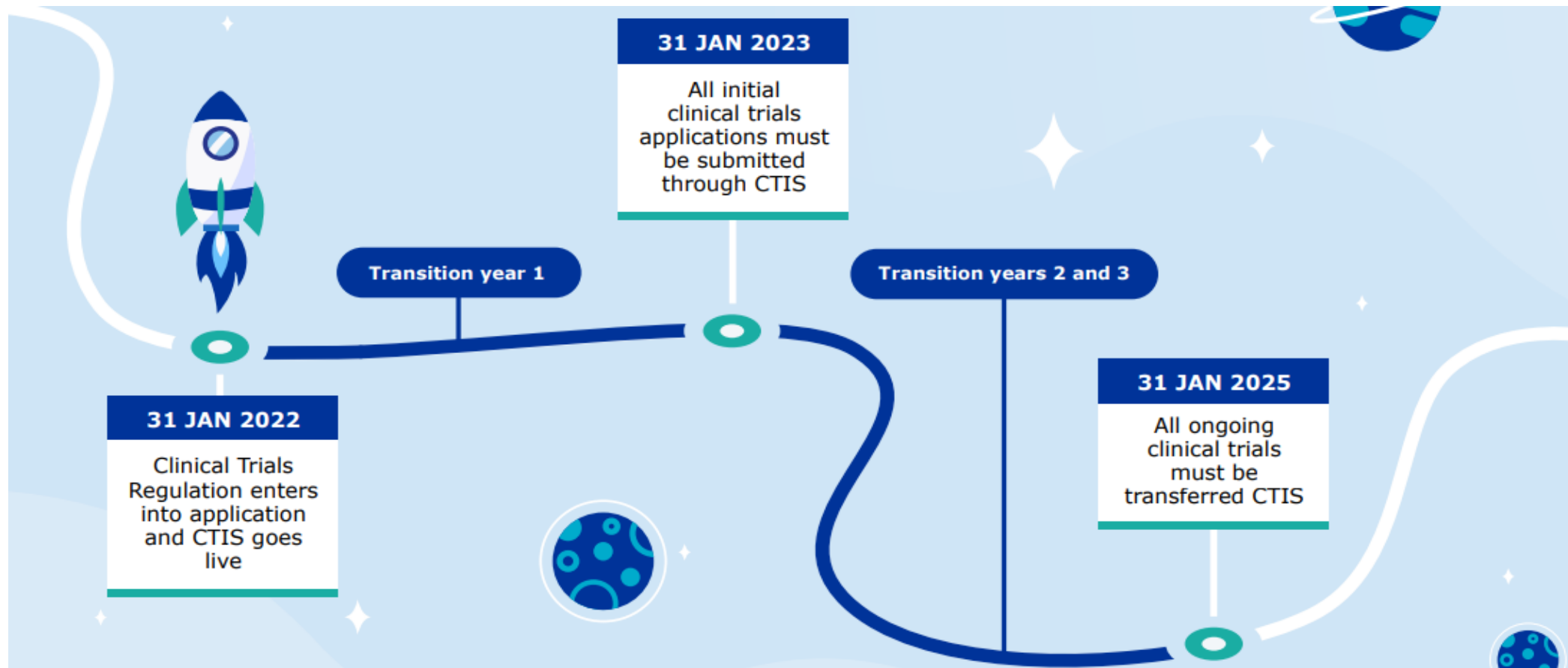


Global hub for clinical trials

Ensures the EU/EEA remains an attractive clinical research hub globally.

A 3-year transition period

The Clinical Trials Regulation foresees a 3-year transition period to CTIS:



Transition period for trials authorised before the CTR

How to manage trials authorised under the previous legislative framework:



CTCG will publish updated guidance for sponsors on transition of multinational trials at the HMA website beginning of July (<https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html>, under key documents)

CTR/CTIS benefits for Sponsor, assessors, patients, researchers

On <https://euclinicaltrials.eu>

- Apply for a clinical trial in up to 30 EU/EEA countries with a **single application**
- Facilitate involvement of trial participants by allowing **easy expansion of trials to other EU/EEA countries**
- **Collaborate across borders** for better results and knowledge sharing
- Ensure the EU/EEA remains an attractive location for **clinical research investment**
- Fulfil all **clinical trial publication requirements** with no additional effort

CTIS public website & secure domains

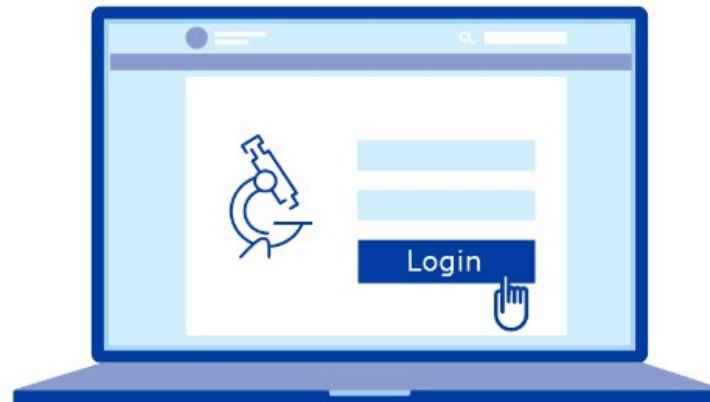


A **public website** where anyone can search for information on clinical trials

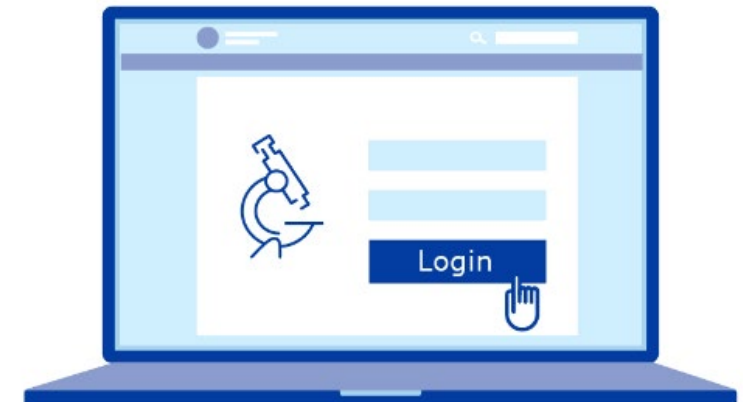
<https://euclinicaltrials.eu>



Open access



A **Sponsor workspace** where clinical trial sponsors and the organisations that work with them can apply for and manage a clinical trial in up to 30 EU/EEA countries

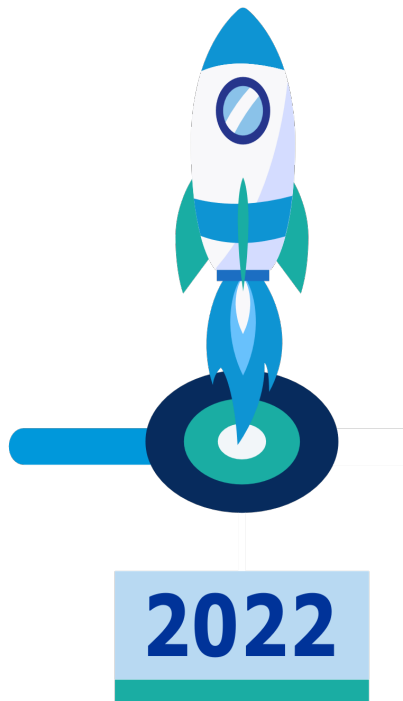


An **Authority workspace** for EU Member States, EEA countries and the European Commission to assess, authorise and oversee clinical trials



Secure access

CTIS Overview: 2022 - now



- CTIS went live on **31 January 2022**, kicking off the 1st year of transition of the Clinical Trials Regulation (CTR)
- A total of **1,589*** initial clinical trial applications, **621** Substantial Modification, **130** additional MSC submitted since 31 January 2022 with **731 clinical trials with a decision**
- More than **200** transitional trials have been submitted to CTIS, **116** have been authorised
- Intensive collaboration with Sponsors, MS to resolve challenges with a small number of trials

*Status as of 27/06/2023

Accelerating Clinical Trials in the EU (ACT EU)

ACT EU is business change initiative to **transform the EU clinical research environment** in support of medical innovation and better patient outcomes.

- Builds on the momentum of the Clinical Trials Regulation and CTIS
- Driven by the Network Strategy to 2025 and the EU Pharmaceutical Strategy
- Launched 13 January 2022
- 10 priority actions with a focus on:
 - **enabling clinical trials** (in particular multinational trials)
 - **innovative trial methods**
 - **GCP modernisation**
 - **engaging all stakeholders**



Read the [press release](#) and [paper](#)

ACT EU, CTR and CTIS – Sponsors, Regulators, Patients and R&D

➤ ACT EU:

- **Ensures the voice of patients is heard** on clinical trials modernisation
- Builds engagement with all stakeholders to improve EU as a **global centre for bigger and faster clinical trials**
- Addresses health needs **by facilitating innovation in CT methods, data insights and multinational trials**



➤ The Clinical Trial Regulation and CTIS:

- Find clinical trials
- Trial results in lay language
- Medical innovation and support patient safety

Organisation name	Site location	Site street address	Site city	Site post code	Site country	Title First name	Last name	Department name	number	email
Centre Hospitalier Régional Universitaire De Tours	Avenue De La République	Avenue De La République	Chambray Les Tours	37170	France	Jean-Baptiste	VALENTIN	Service d'Immunologie Hépatite	+33247477635	jean-baptiste.valentin@chu-tours.fr
University Hospital Of Clermont-Ferrand	1 Place Lucie Et Raymond Aubrac	1 Place Lucie Et Raymond Aubrac	Clermont-Ferrand	63100	France	Aurélien	LEBRETON	Service d'Immunologie Hépatite	+33473750200	alexis@chu-clermontferrand.fr
Centre Hospitalier Universitaire De Rennes	2 Rue Henri Le Guilloux	2 Rue Henri Le Guilloux	Rennes Cedex 9	35033	France	Sophie	BAYART	Service d'Immunologie Hépatite	+33299268935	sophie.bayart@chu-rennes.fr
Centre Hospitalier Universitaire De Bordeaux	Place Amélie Raba Léon	Place Amélie Raba Léon	Bordeaux	33000	France	Sabine-Marie	CASTET	Service d'Immunologie Hépatite	+33556795878	sabine.marie.castet@chu-bordeaux.fr

CTIS 2024 roadmap

Progress update on system improvements

- Overall performance has been improved and the system is stable
- Enhanced security by implementing multi-factor authentication – deployment on 8 June 2023 and prior communication to users
- Performance challenges remain on certain transactions for clinical trials with 20+ member states and thousands of documents – technical solution in development
- In May, 90% of CTAs with a decision have gone through the system with no manual intervention required (up from 64% in April)
- Transition of CTIS user support to EMA service desk is in motion
- Transition to high availability infrastructure was performed in June 2023

CTIS 2024 Road Map



CTIS backlog and priorities will continue to evolve based on multiple factors (end user feedback, need for simplification and future proofing, etc..)



EMA team in collaboration with the Product Owners and Stakeholders will assess the situation and put together a view how the backlog should be addressed



Independent assessment and recommendation on future proofing and simplification of the technology landscape



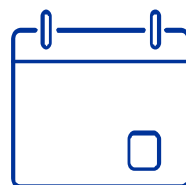
Timeframe: Goal to have a 2024 roadmap by end of October 2023

Support to CTIS Users



Regular Communications

- Clinical trials KPI reports are published as part of the ACT EU programme ([link](#))
- Bi-weekly Newsflash to all users - [link](#)
- Clinical Trials Highlights Newsletter – [link](#) - *next in July 2023*



Regular Events

- CTIS Walk-in Clinics - [link](#)
- Bitesize talks - [link](#)
- Quarterly CTIS Forum with Stakeholders – *next on 14 September 2023*
- DIA CTIS Info event - *next on 17 October 2023*



Trainings & related materials

- Sponsor end user trainings - *next in September 2023*
- CTIS Training environment – survey [link](#) to request access
- Q&A on protection of personal data & CCI in CTIS – [link](#)
- Query Management Working Group Q&A on CTR and CTIS – [link](#)
- Step by step guide on registering organisations locally in CTIS - [link](#)

Support to CTIS Users

- Strengthening collaboration with COM and MS via CTCG, aiming towards harmonisation in the EU
 - Support to weekly CTCG Assessors Round Table
- Survey of CTIS sponsor users on system usability and CTR implementation (as part of the ACT EU initiative)
- Hands-on support from EMA to sponsor users
- Publication of MS calendars to [EMA corporate website](#)
- 23 online training modules published
- Sponsor Handbook available with link to training, guidance and Q&A documentation



CTIS Release Communication

- June 2023 release notes and List of known issues documents available on the [Website outages and system releases](#) page on the Clinical Trials website
- Provides details on:
 - ✓ Maintenance windows for CTIS (**updated starting 24 April 2023**) and related systems updates
 - ✓ Release notes describing updates made
 - ✓ Known issues and workarounds



CTIS Training Environment update

The CTIS Training environment survey (Survey 4.0) is reopened:

<https://ec.europa.eu/eusurvey/runner/2abb5ba8-0ec4-9979-b692-0c63f4508b9b>

This survey collects expressions of interest in accessing the CTIS training environment ('CTIS Sandbox'), information and contact details of representative individuals, the organisations that they represent and the planning for use of CTIS of these organisations is reopened.

All details will serve to proactively identify the needs and intention of use of CTIS and grant access accordingly.

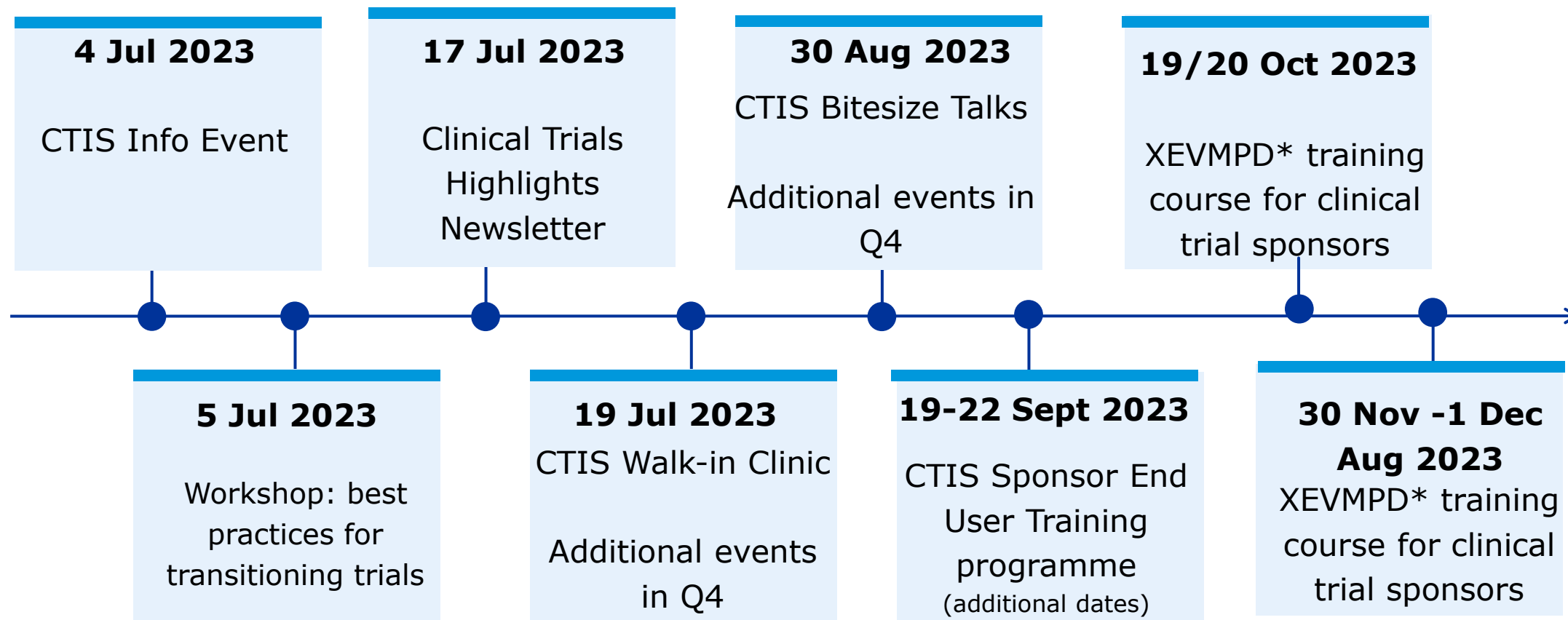


CTIS Service Desk move to ServiceNow from 31 July 2023

- CTIS User Support Service to move from Jira to ServiceNow:
 - Industry best practice
 - More user-oriented service
- ServiceNow will be accessible via a [link](#) (starting 31 July) and via a mobile app
- Training material and information for end-users available [here](#)
- More details in upcoming communications in CTIS Newsflash, CT Highlights Newsletter, CTIS website support page



Upcoming Meetings, Events, Communications



*Extended EudraVigilance medicinal product dictionary

Thank you for your attention

Further information

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Follow us on  **@EMA_News**

XEVMPD training course for clinical trial sponsors – 2023 Q2 – Q4

Event Name	Event date(s)	Time of event (CET)
Extended EudraVigilance medicinal product dictionary (XEVMPD) training course for clinical trial sponsors	19-20 October	09:00 – 13:00
	30 Nov – 1 Dec	09:00 – 13:00

CTIS Walk-in Clinic – 2023 Q3 – Q4

Event Name	Event date(s)	Time of event (CET)
CTIS Walk-in Clinic	19-Jul	16:00 - 17:00
CTIS Walk-in Clinic	20-Sep	16:00 - 17:00
CTIS Walk-in Clinic	10-Oct	16:00 - 17:00
CTIS Walk-in Clinic	15-Nov	16:00 - 17:00
CTIS Walk-in Clinic	13-Dec	16:00 - 17:00

CTIS Bitesize Talks – 2023 Q2 – Q4

Event Name	Event date(s)	Time of event (CET)
CTIS Bitesize talk: IMPD-Q workaround as a part I only submission	10-May	15:30 - 17:00
CTIS Bitesize talk: How to submit a transitional trial in CTIS	21-Jun	15:30 - 17:00
CTIS Bitesize talk: Partial application (part I only) and how to satisfy the part II requirements in CTIS	30-Aug	15:30 - 17:00
CTIS Bitesize talk – theme to be confirmed	4-Oct	15:30 - 17:00
CTIS Bitesize talk – theme to be confirmed	29-Nov	15:30 - 17:00

CTIS Sponsor End User Training programme

Event Name	Event date(s)	Time of event (CET)
CTIS Sponsor End User Training	19 – 22 Sep	09:00 – 13:30
	6 – 9 Nov	14:00 – 18:30
	11 – 14 Dec	09:00 – 13:30



Session 2



Questions & Answers – Panel Discussion



Closing remarks



Thank you for attending today's event

Please provide your feedback
for this event in our **Slido**
survey



Further information

For the [CTIS Newsletter](https://ec.europa.eu/newsroom/ema/user-subscriptions/3201/create) sign up at <https://ec.europa.eu/newsroom/ema/user-subscriptions/3201/create>

Latest CTIS Newsflash can be consulted [here](#)

For upcoming CTIS events, visit the [EMA event page](#).

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