Mastering the EU CTR:
How to Adapt & Succeed Under the New Framework

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DISCLAIMER

The views and opinions expressed in this presentation are solely my own, and do not represent those of Invivyd, The Conjugate Group, Northeastern University, or ClinOps Solutions.

Agenda

01 Background

- EU CTR Directive
- Part I & Part II

02 Deep Dive

- Preparing for submission
- Parallel vs. Sequential Submissions
- Redactions
- Selection of coordinating country
- RFIs

03 Case Study

- Review lessons learned from recent phase 2 study – initial submission, amendments, and early study termination

04 Conclusion

- Recommendations & Key Takeaways

05 Q&A

A One Size Fits None Presentation

EU Clinical Trial Regulation 536/2014 (EU CTR) Overview

Regulation (EU) No 536/2014 (the Clinical Trials Regulation) governs conduct of clinical trials (CT) in the EU and EEA. It replaced EU Directive 2001/20/EC (EU CTD)

Main objectives of EU CTR include single submission in one system (CTIS) with one dossier for all member states to harmonized and streamline clinical trial approvals while increasing transparency and efficiency.

Changes Introduced

- Single electronic combined CA (part I) and ethics (part II) submissions via the CTIS portal
- Harmonized timelines and communication rules for all EU Member States
- Increased transparency – more information is published once trial is initially approved
  - Documentation, decisions, safety information, milestones, study results
  - Increased milestone reporting
- Increased labelling requirements (expiry date of primary packaging)
- TMF retention periods extended to 25 years (from 15yrs)

When

- Came into force on 31Jan2022, with 3-year transition period
- All new studies must follow EU CTR as of Jan 2023
- Existing studies did not have to move over if completed by Dec 2024

System

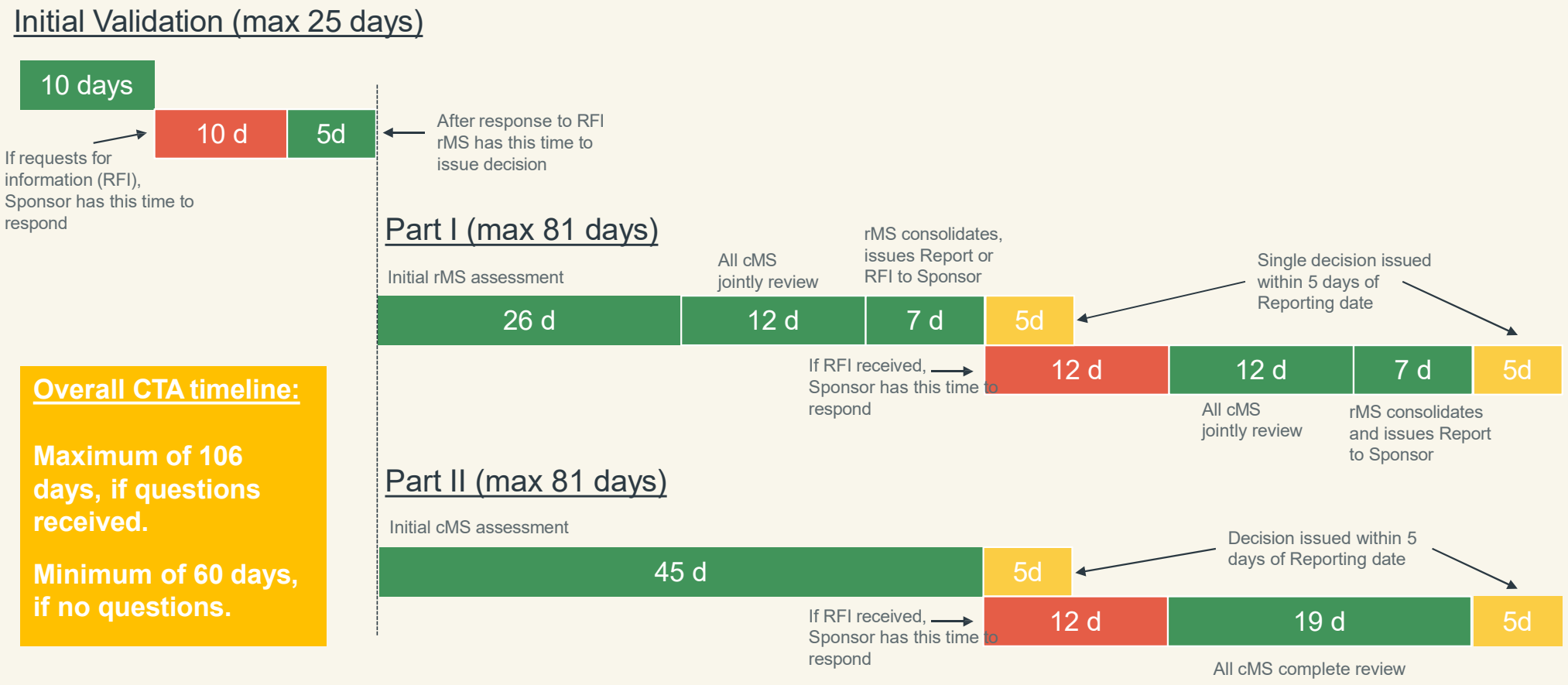
- Central portal – Clinical Trial Information System (CTIS)
- Sponsor, CRO, and authority workspaces
- Publicly accessible

27 Member States make up the EU plus 3 European Economic Area (EEA)

Austria
Belgium
Bulgaria
Croatia
Cyprus
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Ireland
Italy
Latvia
Lithuania
Luxembourg
Malta
Netherlands
Poland
Portugal
Romania
Slovakia
Slovenia
Spain
Sweden

Iceland (EEA)
Lichtenstein (EEA)
Norway (EEA)

CTA Timelines (all timeframes represent maximum timelines)

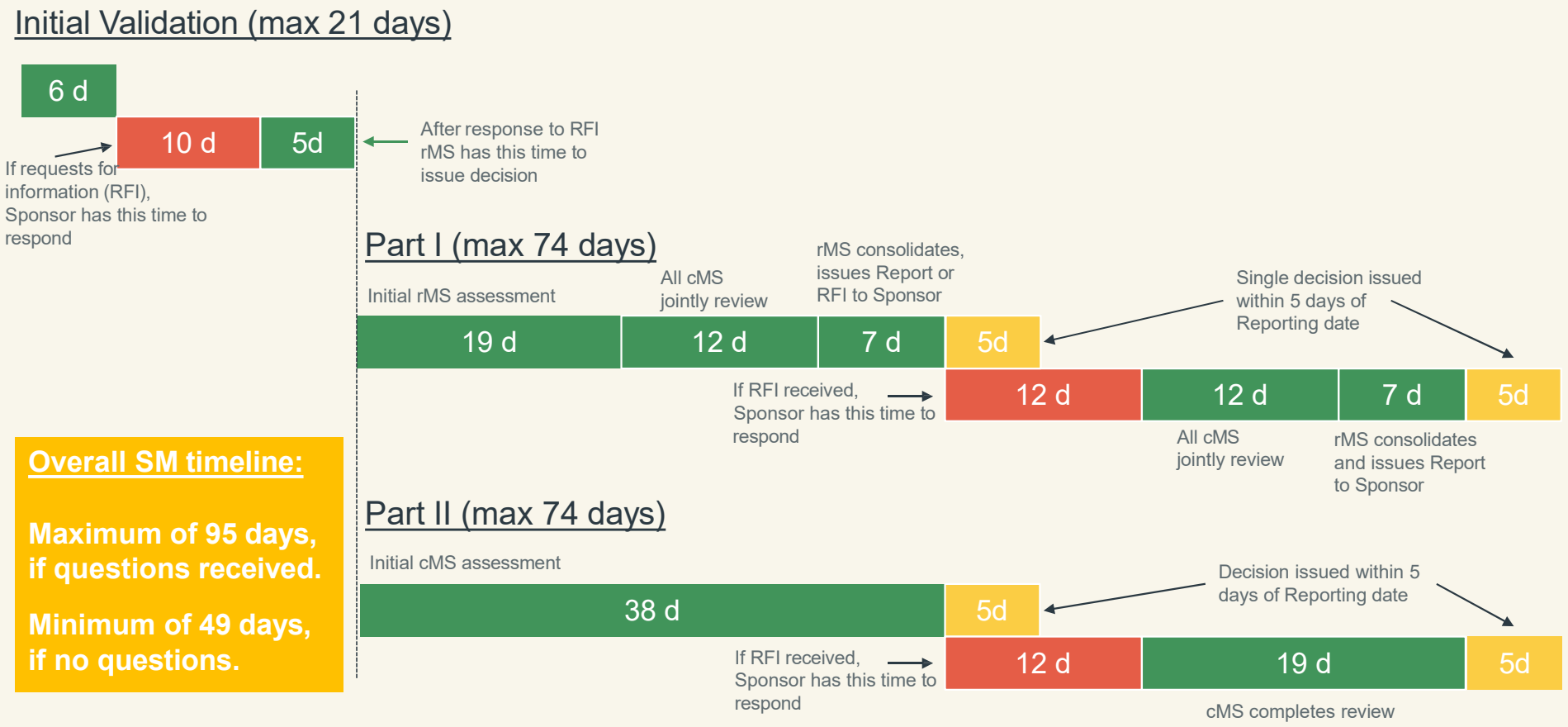


Overall CTA timeline:

Maximum of 106 days, if questions received.

Minimum of 60 days, if no questions.

Substantial Modification (aka Protocol Amendment) Timelines within the Regulation



Overall SM timeline:

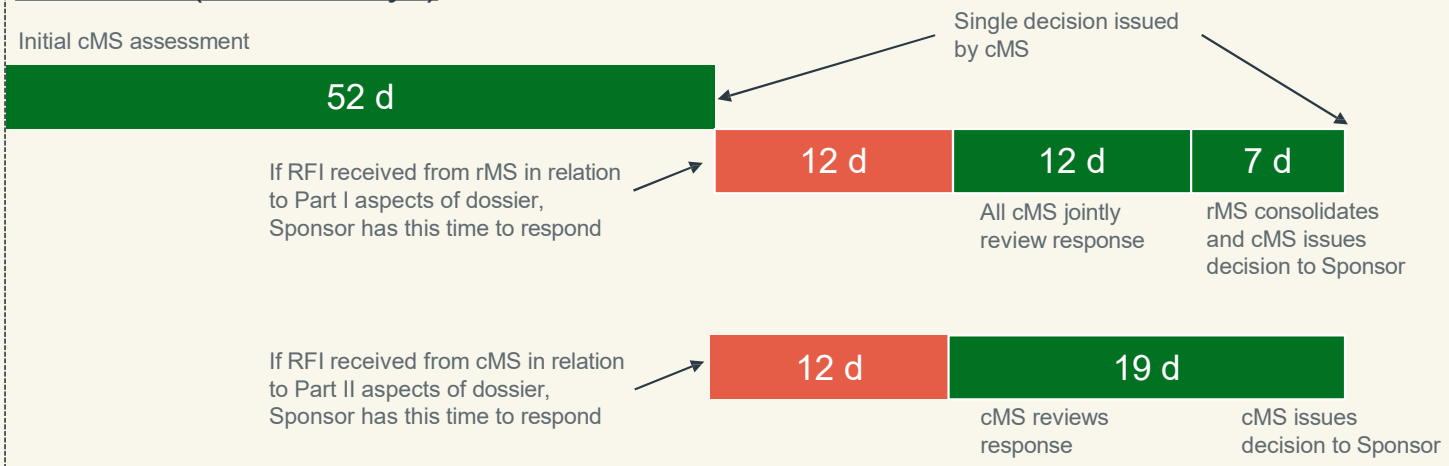
Maximum of 95 days, if questions received.

Minimum of 49 days, if no questions.

Additional Member State Submission Timelines

No Validation Step

Part I & II (max 83 days)



Overall AMS timeline:

Maximum of 83 days, if questions received.

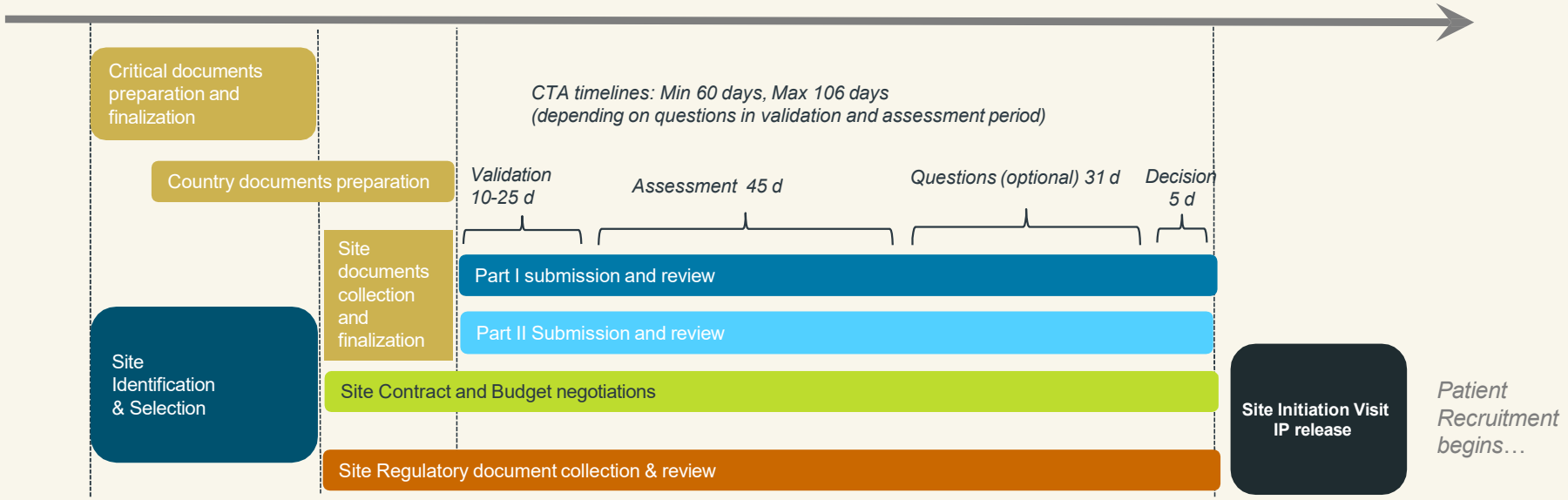
Minimum of 52 days, if no questions.

Part I & II Strategy

Breaking down submission strategy

- Parallel Part I & II – require all countries/sites being selected and documents ready all at once
- Sequential Part I → Part II – more time to select sites and collect local documents
- Hybrid approach – consider splitting countries

PARALLEL Submission process for Part I and Part II

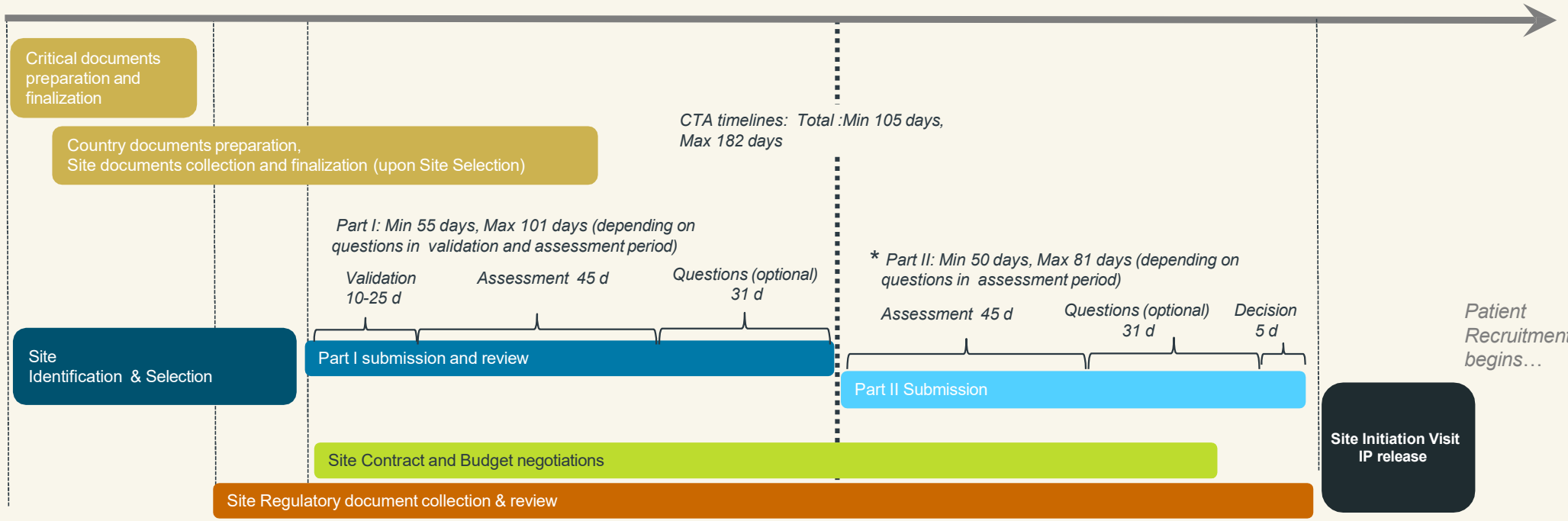


- Considerations for Part I & II in parallel
  - Countries identified proactively to accelerate final country and site selection
  - Accelerated country and site document preparation required for submissions
  - Agreement on potential timing of submission and subsequent approval

Longer preparation time due to need for all Part II docs, but shorter overall CTA review and approval. Requires early agreement and acceleration of site selection. Allows Part II to be submitted asap, rather than needing to await decision on Part I.

Incentivize sites with bonus payments for prompt document turnaround

SEQUENTIAL Submission process for Part I & Part II

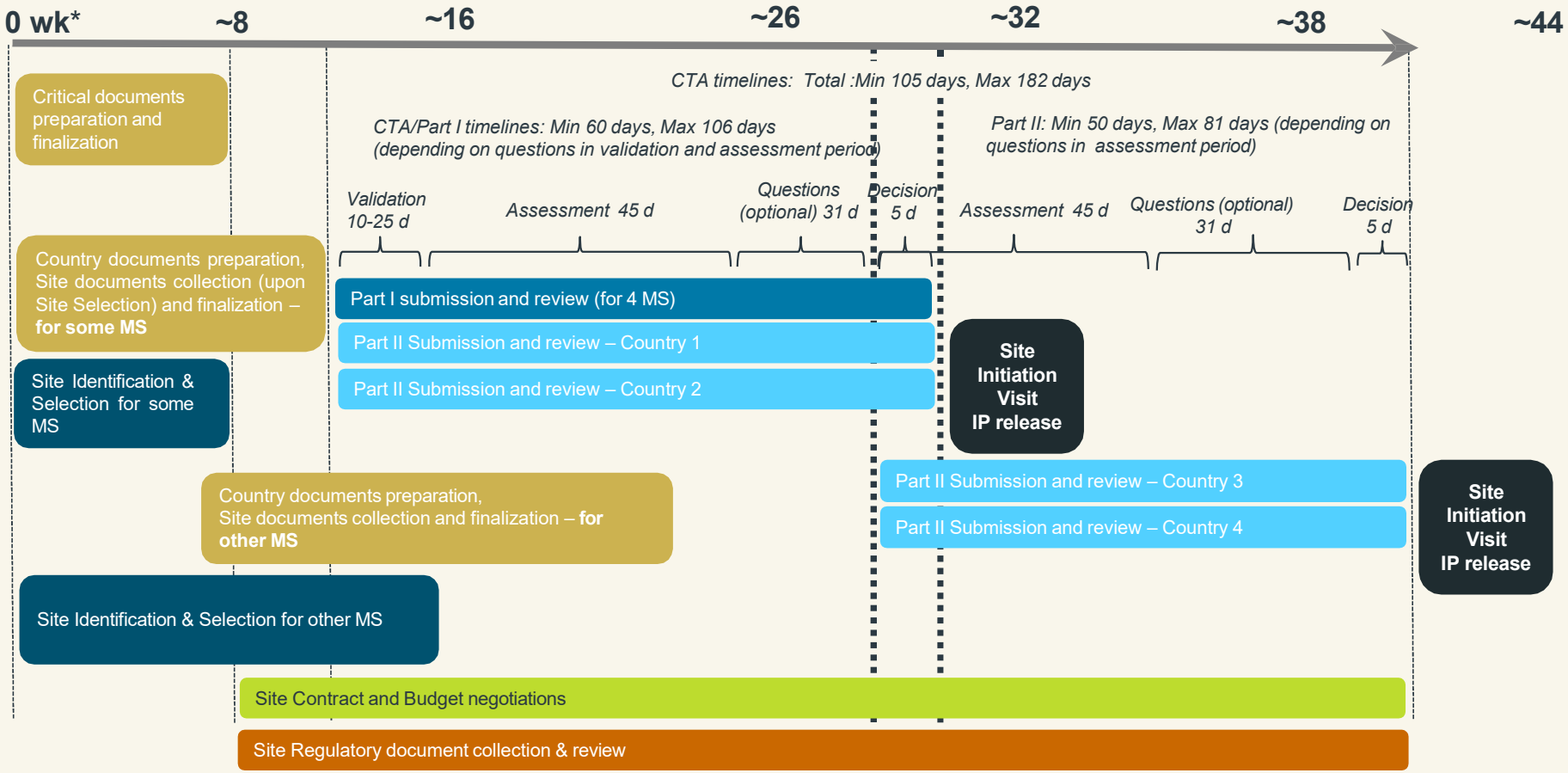


- Considerations for Part I & Part II in sequence:
  - Countries identified, but site selection is not yet in final stages which will delay document availability for Part II submission;
  - Submission strategy foresees countries submission in tiers

More time for country & site documents finalization, but longer overall CTA review and approval. Flexibility with country/site list finalisation, but no flexibility with Modifications submission – Modification can be submitted only upon Part II approval by all MSs. Other option – a MS can be added as 'Additional MS' instead of as sequential Part II, if expected to be delayed relative to other countries.

**Although there will be no validation period, if any documents are missing or incorrect, the National Contact Point could request corrections or to provide the documents with quick RFI*

Submit Part I & Part II in parallel for some MS, sequentially for the other MS



* Illustrative timelines, to visualise comparison of different options – in reality these will be impacted by many other factors

Preparation Considerations

Selection of Reporting Member State (rMS)

One key feature of EU CTR is selecting the reporting Member State (rMS). This is a strategic decision made by the sponsor company.

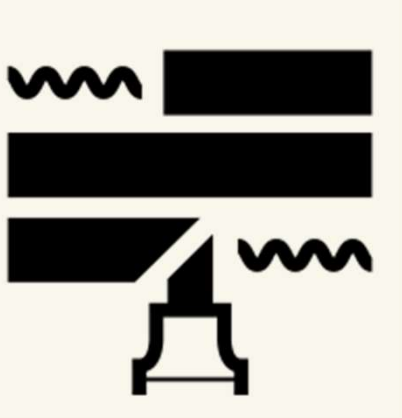
Part I (core scientific dossier) – Assessment report by rMS with contributions by each MS
Part II (country-specific ethics) – Assessment report by each MS

Consider prior experience with your company, molecule, technology, platform, etc.

Consider country specific preferences

Redactions

- The EU CTR mandates that documents submitted via the CTIS are made public
- Article 81(4) of CTR outlines justifications for confidentiality
  - Personal data
  - Commercially confidential information (CCI)
  - Confidential communication among/between member states

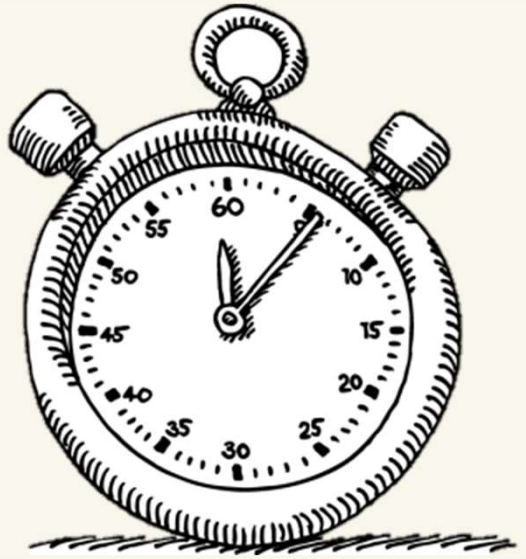


- Determine who will perform redaction – sponsor, CRO, or third party
- Allow for extra time to perform and review
- Over redaction can cause delays in approval or non-approval so careful consideration is needed to determine what should be considered CCI
- Refer to deferral policy

They pay attention!
CRO missed redaction of name on email correspondence with CTIS help desk causing RFI and unhappy reviewers.

Not all responses to RFIs are considered public and thus may not require the same level of redaction.

RFIs & Clock Stops



RFI Turnaround Times

During Validation – 10 days for sponsor and 5days for rMS
Assessment phase – 12 days for sponsor

This is inclusive of translations if applicable.

These are max timeframes; MS could request shorter response times!
No extensions granted!

So… how do you do it???

Utilization of checklists to ensure complete submissions with all required documents

Assemble RFI response team – cross-functional representation who are on standby including identification of subject matter experts to streamline reviews

Prepare response to areas of identified risks to approval prior to submission

Track RFIs – apply lessons learned and ensure RFI responses are consistent

If you have a double-blind study, how do you submit potentially unblinding information when blinded members have access to CTIS?

Case Study

Phase 2 Study in Rare Disease

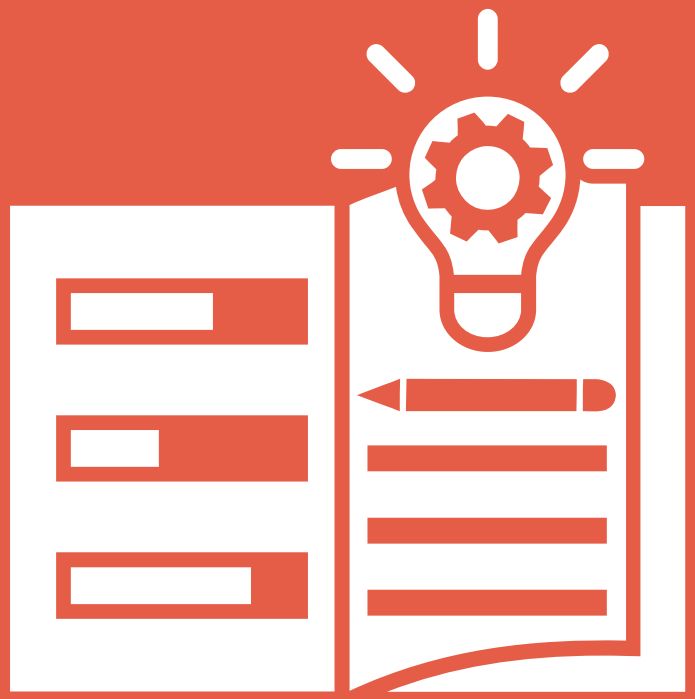
- Selected 5 countries – Spain (rMS), Germany, France, Portugal, Poland
  - Spain selected as rMS at recommendation of CRO for being efficient and generally easy to work with
- Delegated responsibility of submissions to CRO team however as sponsor still had access to CTIS

- During part I RFIs, different MS required different protocol-specific language
  - To maintain a single harmonized protocol, we created country specific sections/sub-sections to add the required country specific language
  - e.g. Compliance with French laws, not recruiting protected citizens

- Part II considerations – country/local specifics needed to be "submission ready"
  - French CNIL (GDPR Compliance) certificate required
  - Germany requires GCP certification
  - Some countries require proof of payment, others do not

Ensure local expertise is available to ensure initial submission has all local required documents

- Inability to submit updates during handling of urgent safety measure and early termination of study
  - Due to only one submission being able to be active at a time, a swiftly evolving situation cause a backlog in submission of protocol updates and eventual study termination resulting in submission of amended ICFs long after participant visits were completed



Final Takeaways

01

Harmonization-ish

One of the main goals of EU CTR is to increase harmonization however individual MS are still able to require country-specific adaptations

02

Timelines

The EU CTR sets clear timelines for review, RFI, and approvals that allow you to better plan however strategy is still needed determining how to submit Part I, II, and addition of MS. Also ensuring team readiness for prompt handling of RFIs.

03

Transparency

Understand the policies and guidelines regarding redaction and have a plan in place on what information will be redacted and how will the redaction be completed.

04

Collaboration

Identify internal and external team with CTIS experience; local expertise to ensure compliance with different requirements

Questions?

Thank you!

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