



# SA07 Programming pooled safety data for ongoing oncology submissions.

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November 2021



# We will cover

- Background
- Keys to success
- Challenges
- Conclusion



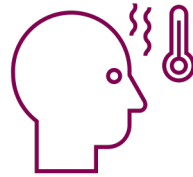
What is safety  
pooling?

# What is safety pooling?

- Safety profile of an investigational product



- On study level, risks vs benefit



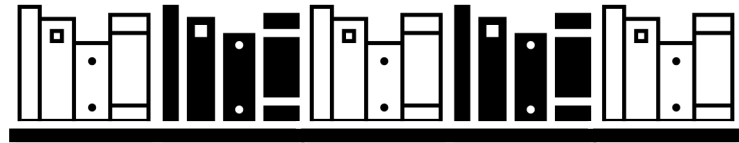
- Pooled

- DSUR/PBRER
- Submission – clinical summary of safety/integrated summary of safety
- RMP



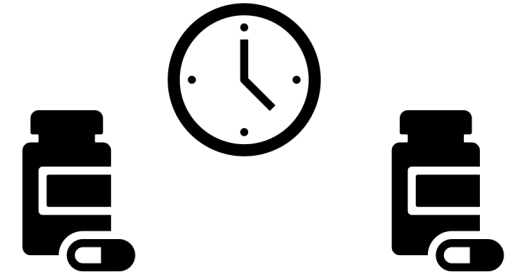
# What do I want?

- Outputs to support the safety profile in submissions for dose level of interest\*
- Repeated submissions,
  - minimise duplicated work
  - Maintain consistency



## \*dose level of interest

“Monotherapy studies, with continuous twice daily dosing”



For some studies this is the full treatment period,

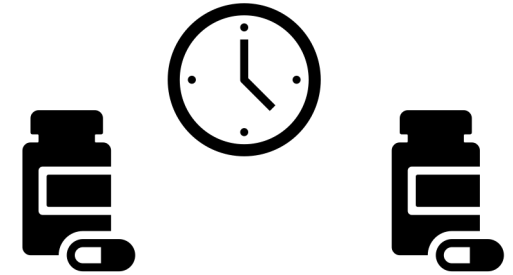
For others it isn't:

|          | Period 1  | Period 2  |
|----------|-----------|-----------|
| Cohort 1 | 200 MG OD | 200 MG BD |
| Cohort 2 | 300 MG OD | 300 MG BD |



## \*dose level of interest

“Monotherapy studies, with continuous twice daily dosing”



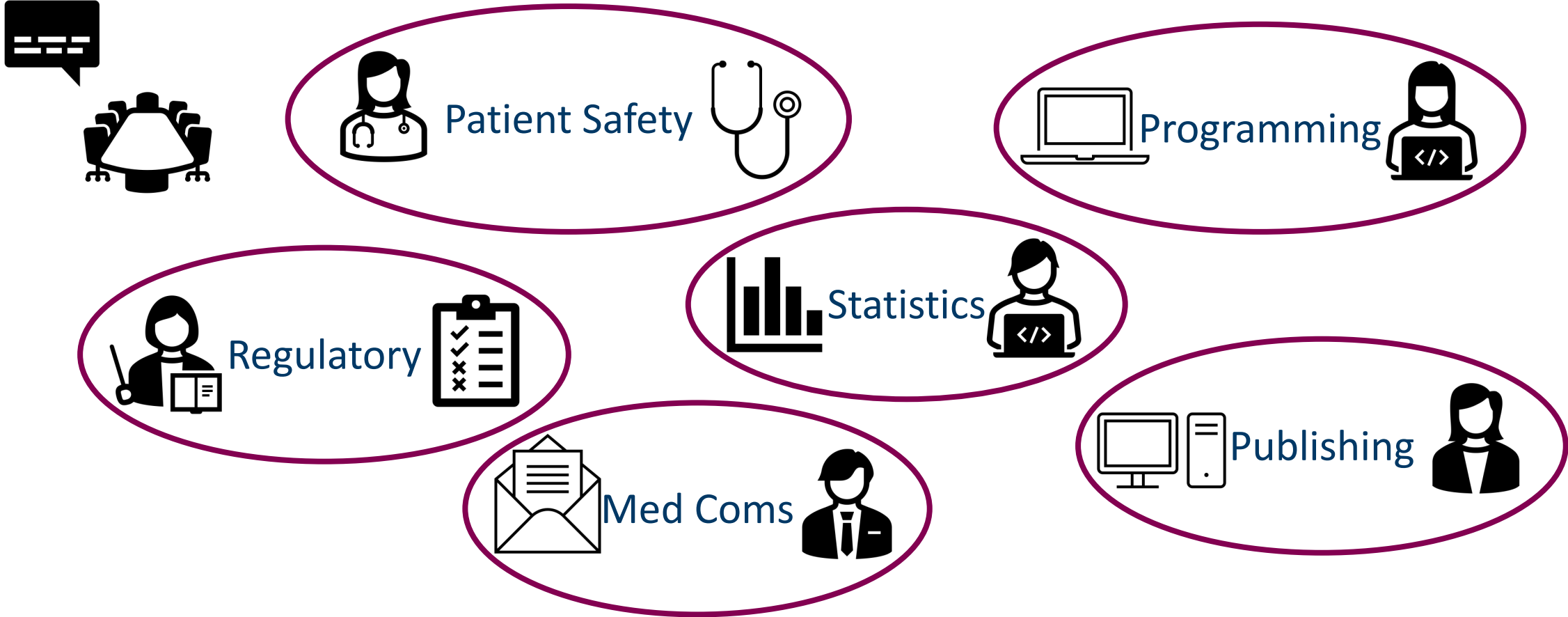
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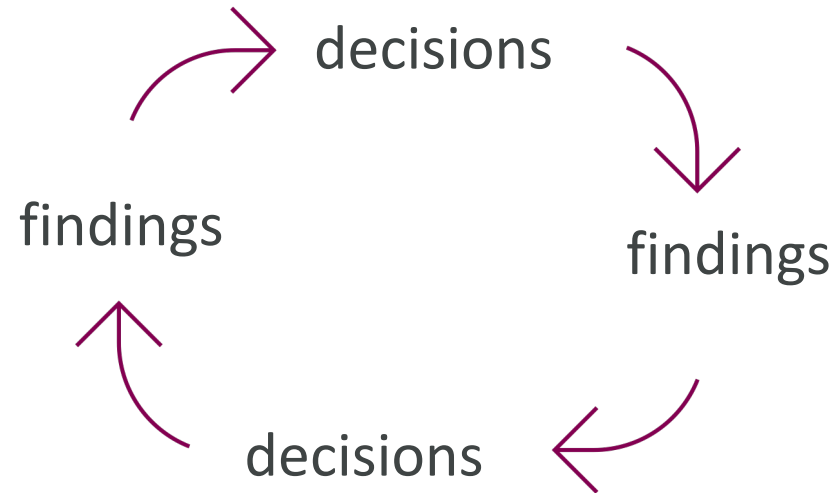


# Who is involved?



# What needs to happen?

- Pooled outputs to tight timeline following pivotal study **P**lanned **S**stats **C**omplete
- Study work, pooled data, pooled outputs, eCRT package, validation (and documentation)



# Keys to success



# Slice structure



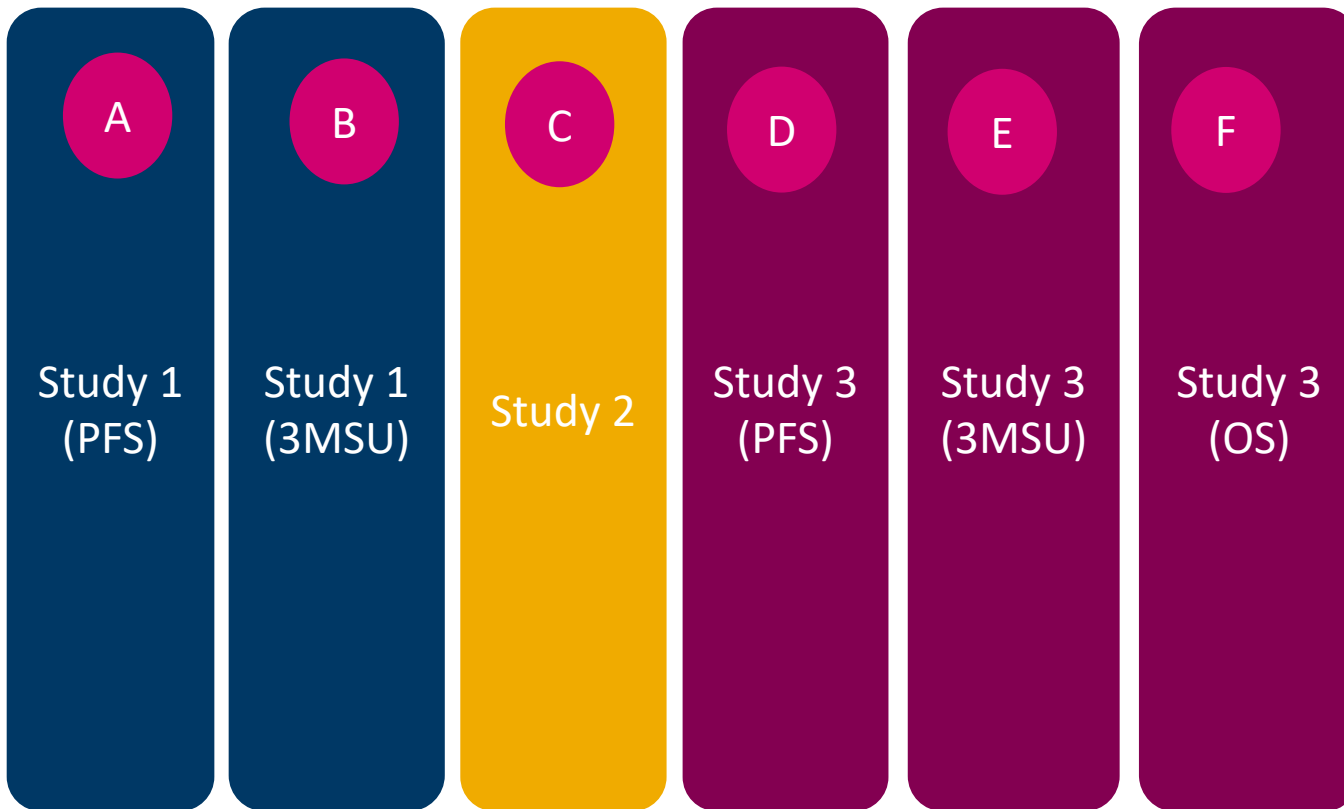
Fix work and documentation for completed studies.



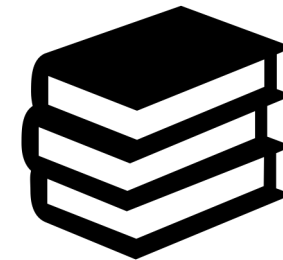
Process for new Data Cut Off for ongoing studies.



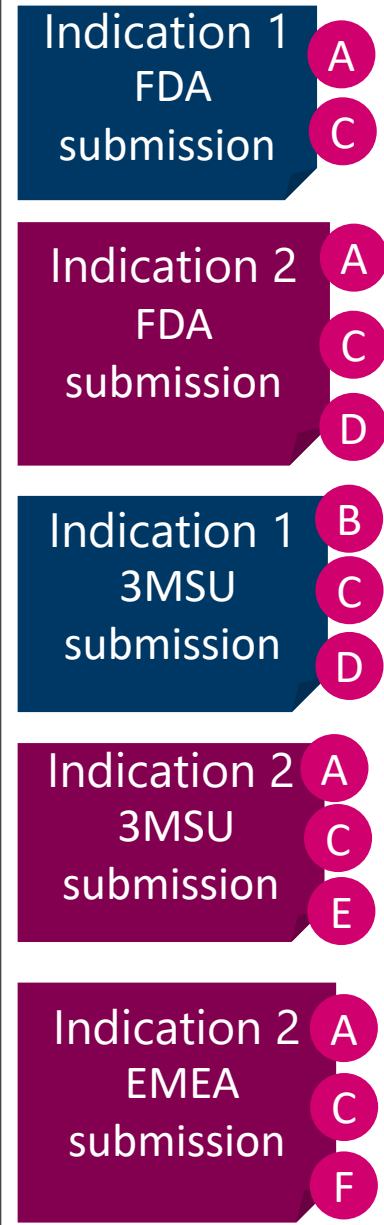
# Modular structure



Slices are taken off the shelf and submission specific derivations are added.



Chronological time



# Modular structure

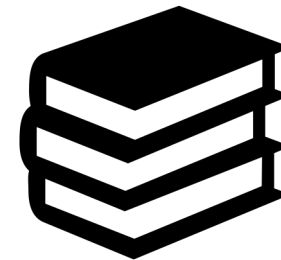
A

Study 1  
(PFS)

C

Study 2

Slices are taken off  
the shelf and  
submission specific  
derivations are  
added.



Chronological  
time

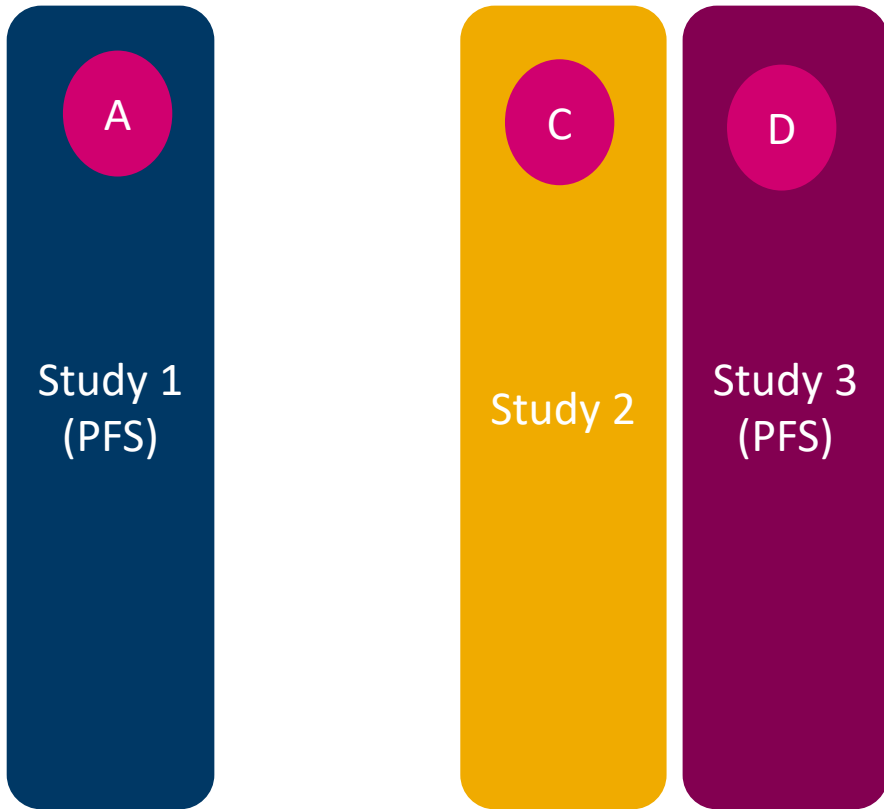
Indication 1  
FDA  
submission

A

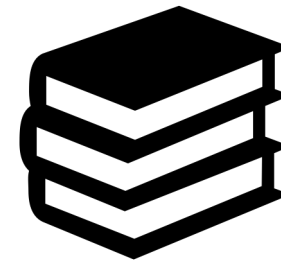
C



# Modular structure



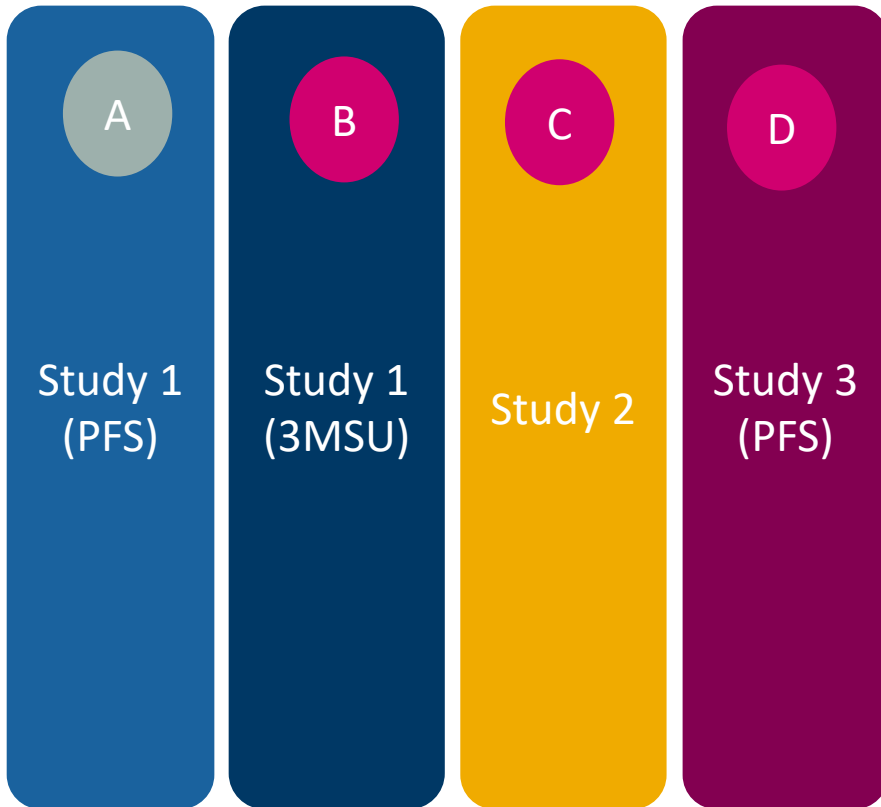
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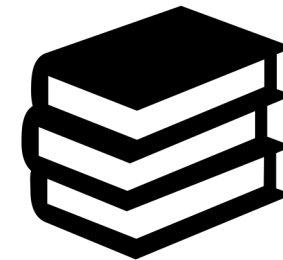
Chronological time



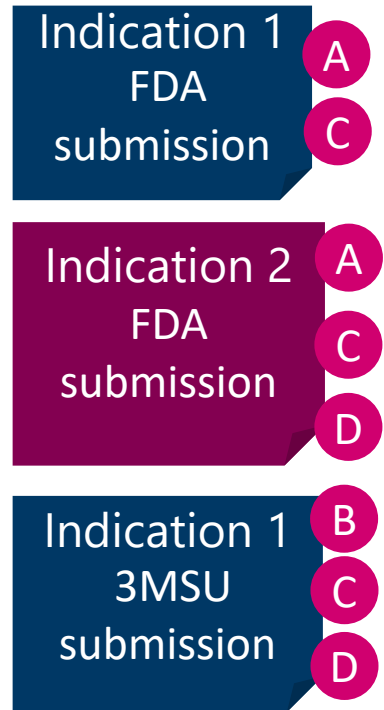
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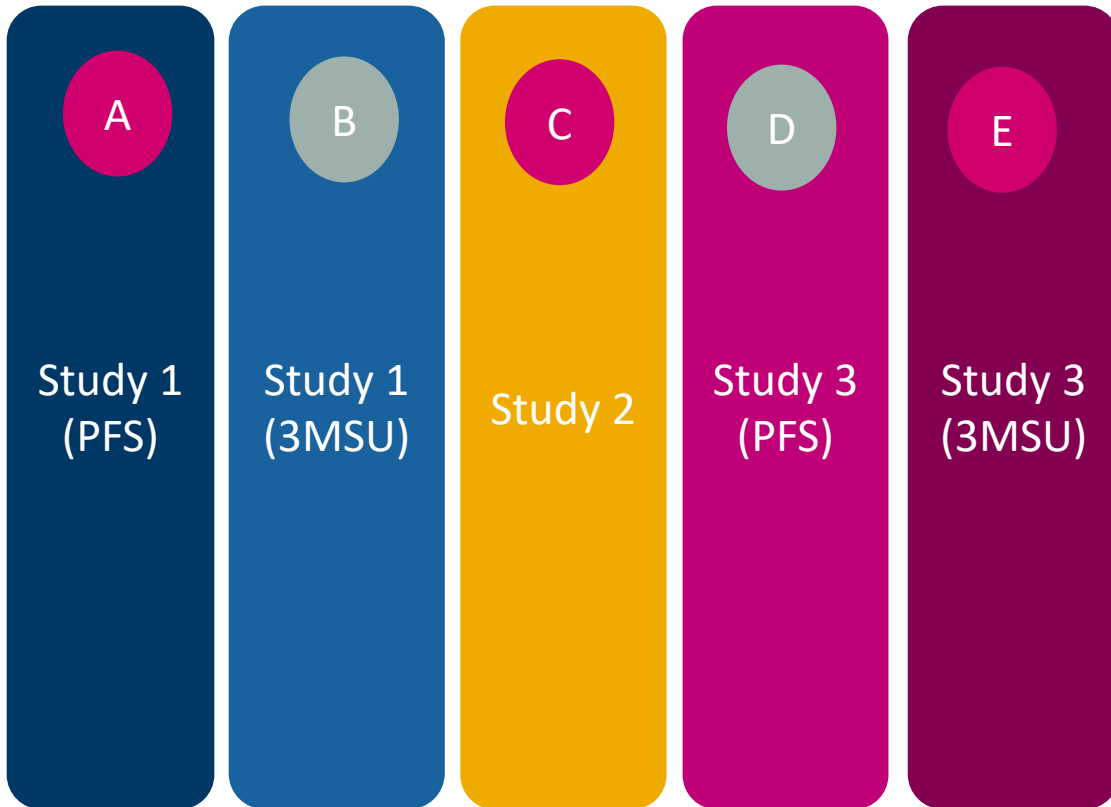
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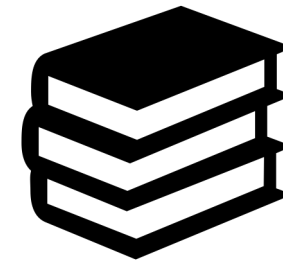
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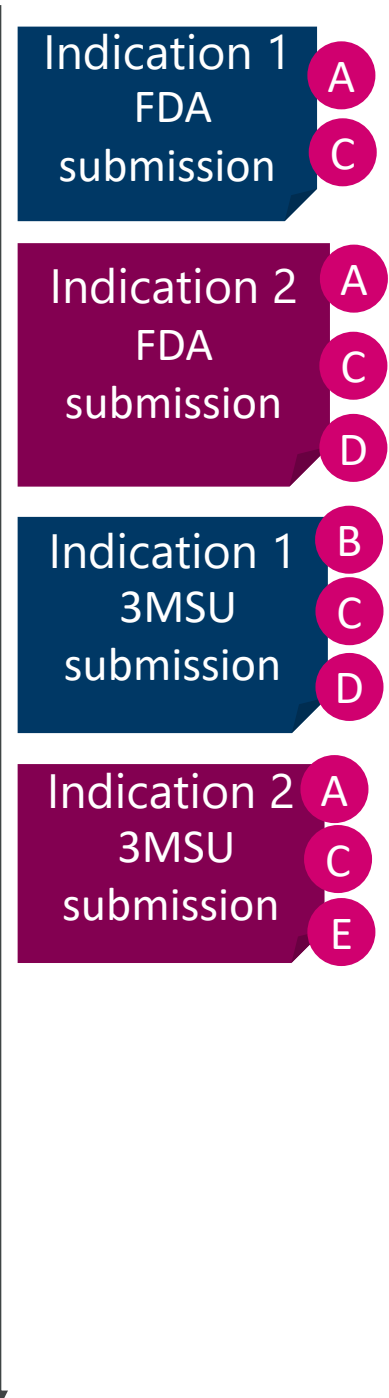
# Modular structure



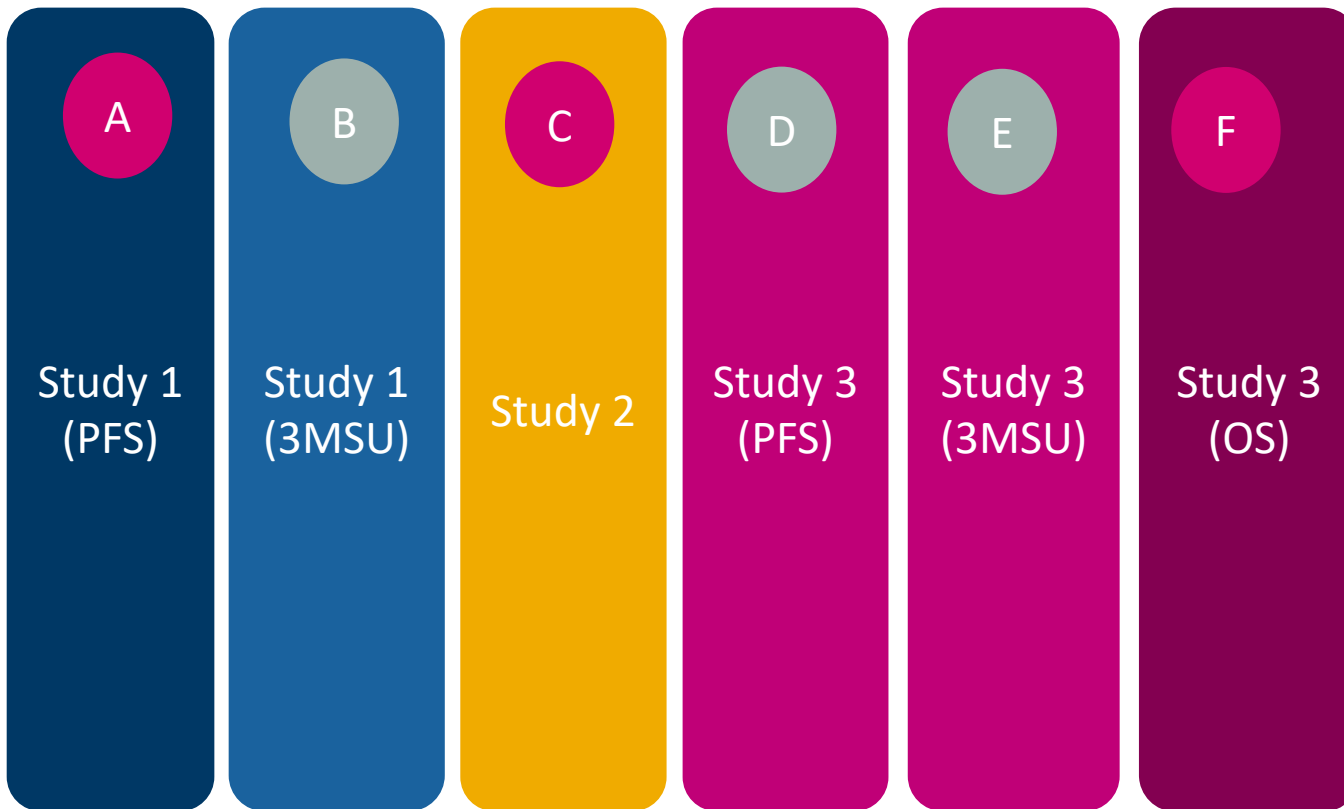
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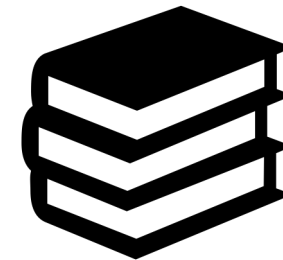
Chronological time



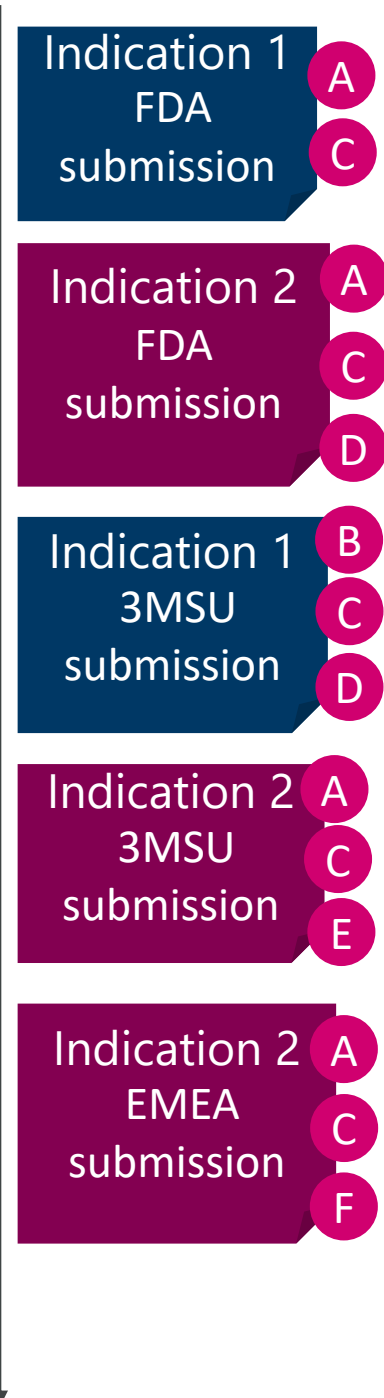
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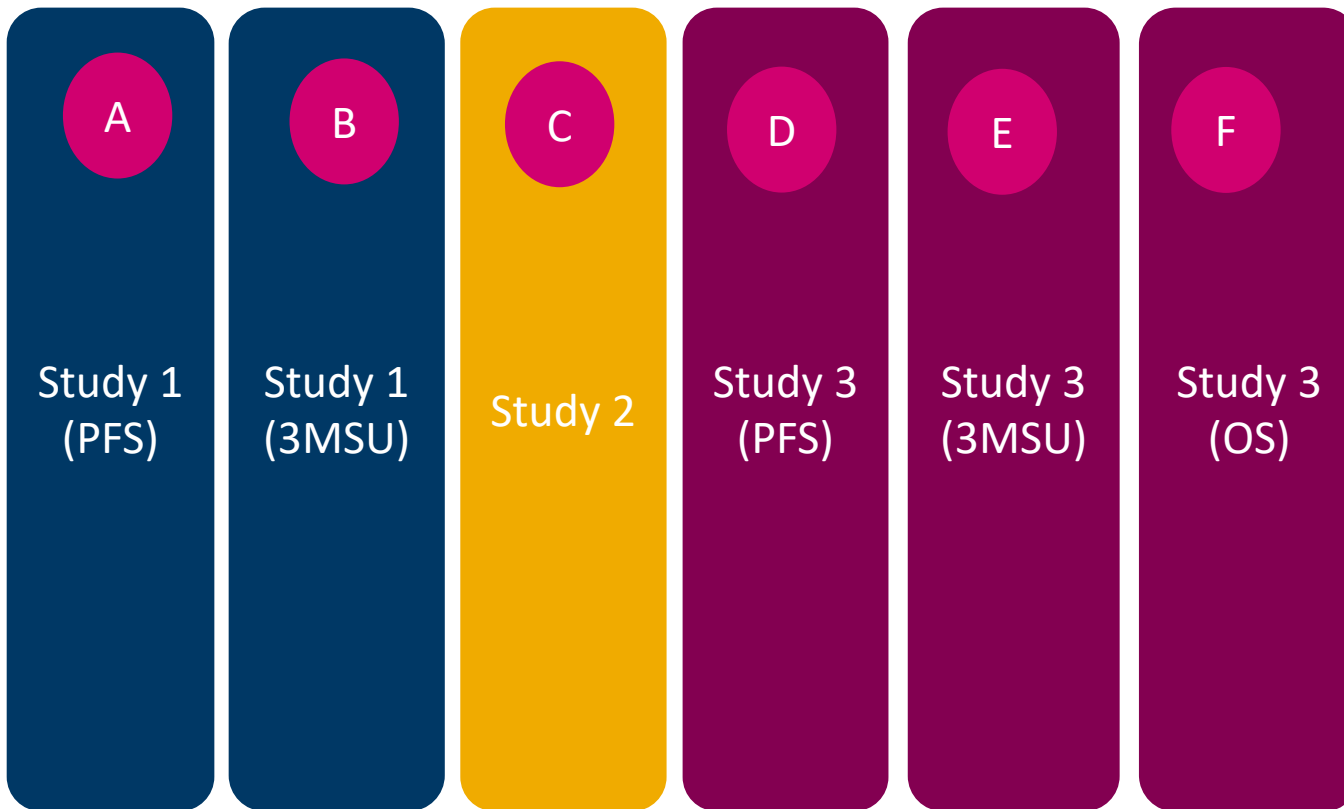
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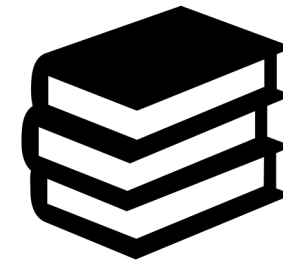
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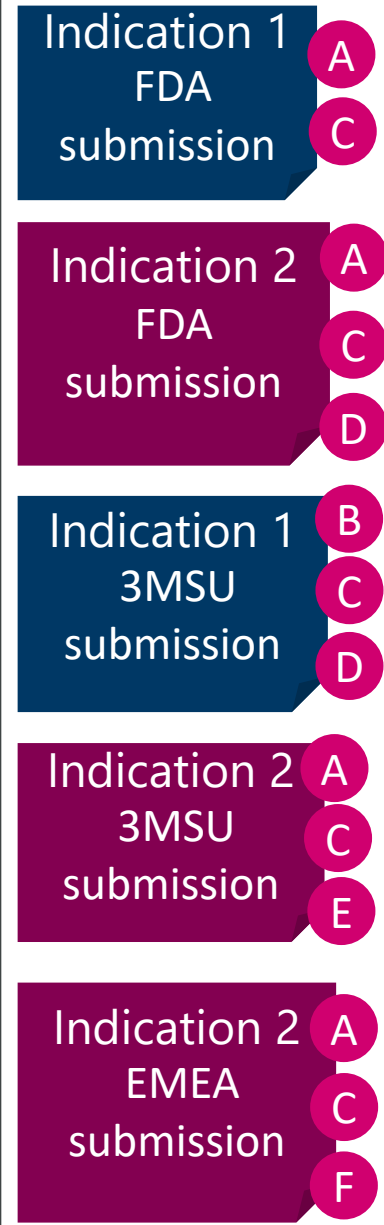
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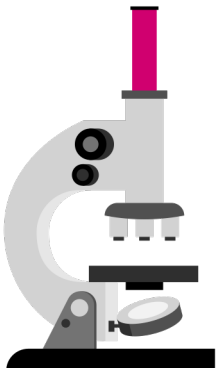


Chronological time



# AE planning and reporting

- Pre defined Adverse Drug Reactions
- Prepare for safety profile updates
- Prepare for MedDRA updates



# AE planning and reporting

## MedDRA v19.0

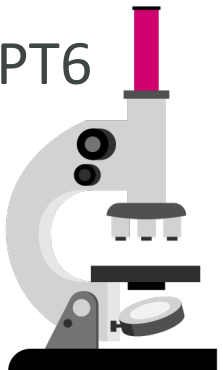
### ADR1

- PT1
- PT2
- PT3



### ADR2

- PT4
- PT5
- PT6



# AE planning and reporting

## MedDRA v19.0

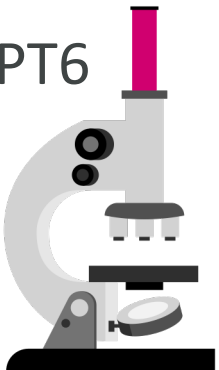
### ADR1

- PT1
- PT2
- PT3



### ADR2

- PT4
- PT5
- PT6



## MedDRA v22.1

### ADR1

- PT1<sup>a</sup>
- PT2
- PT3



### ADR2

- PT4
- PT5<sup>a</sup>
- PT6
- PT7



# AE planning and reporting

## MedDRA v19.0

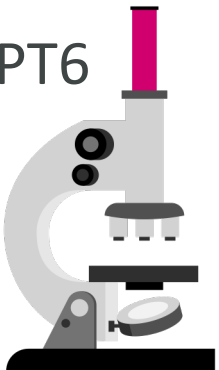
### ADR1

- PT1
- PT2
- PT3



### ADR2

- PT4
- PT5
- PT6



## MedDRA v22.1

### ADR1

- PT1<sup>a</sup>
- PT2
- PT3



### ADR2

- PT4
- PT5<sup>a</sup>
- PT6
- PT7



## MedDRA v24.0

### ADR1

- PT1<sup>b</sup>
- PT2
- PT3

### ADR2

- PT4
- PT5<sup>a</sup>
- PT6
- PT7



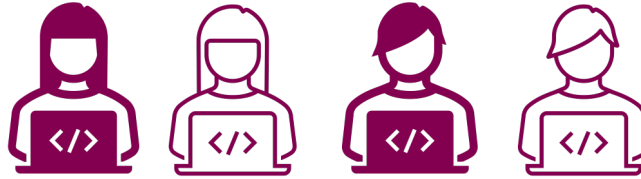
### ADR3

- PT8
- PT9



# Fixed programming team

- Full time pooling programmers
  - Familiar with pooling requirements
    - What works
    - What is likely to have errors



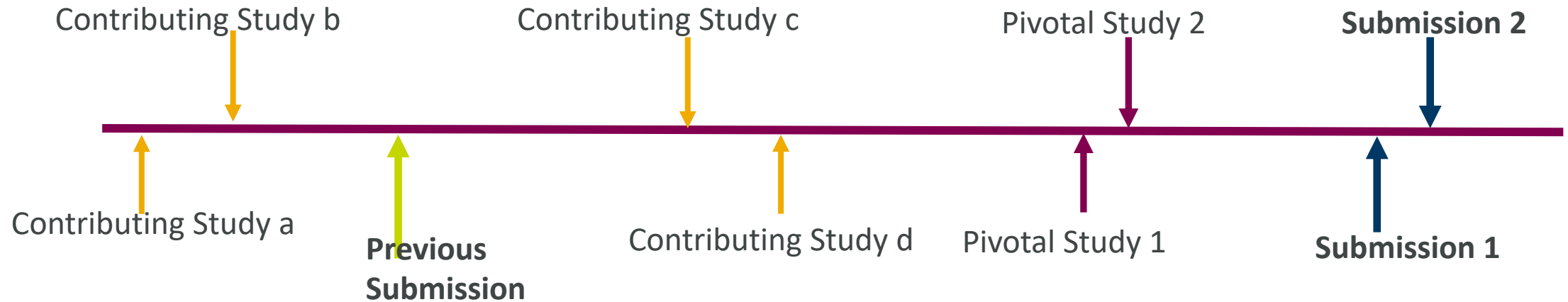
# Challenges



# Changing timelines (1)

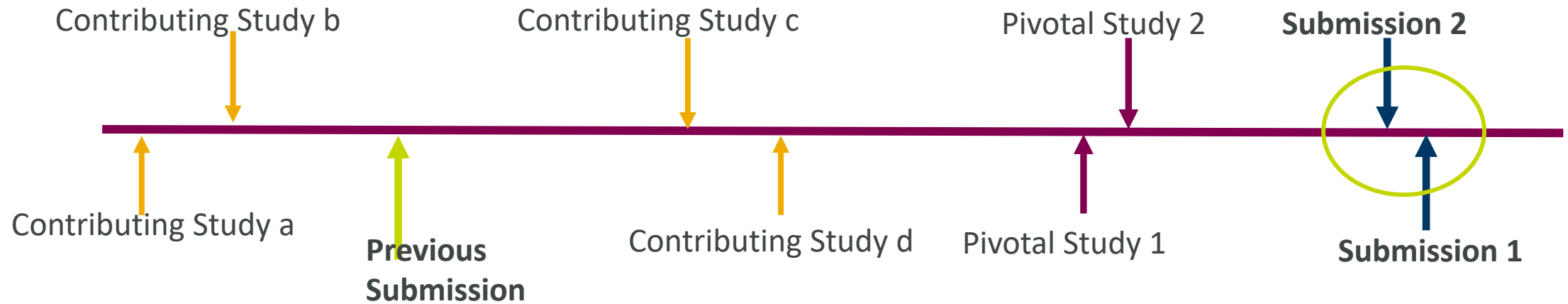
- Prepare expecting particular order:

## The Plan



# Changing timelines (2)

## What happened



# Dose interruptions and reductions (1)

- What is a dose interruption?

- Investigator flag?



- Programmatic derivation?

- 1 day?

- 3 days?



if... then... ;

- With twice daily dosing, consider 2 missed doses.

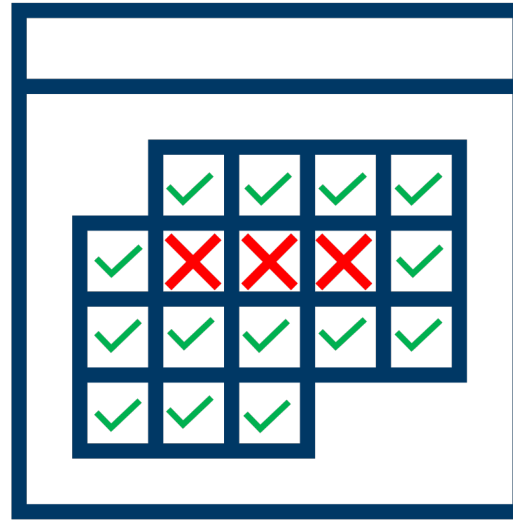
- Evening, morning, 2 day reduction?

- Morning, evening, 1 day interruption?



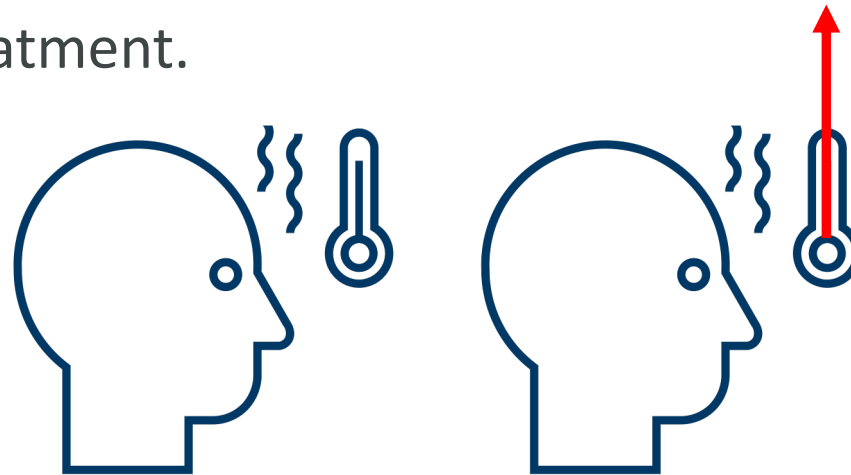
# Dose interruptions and reductions (2)

- Pool level definition
- 3 days with no dosing



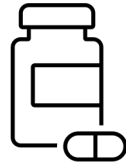
# Treatment emergent AEs (1)

- Updated definition to be more in line with CDISC.
  - From: AE starting on treatment.
  - To: AEs starting or **worsening** on treatment.



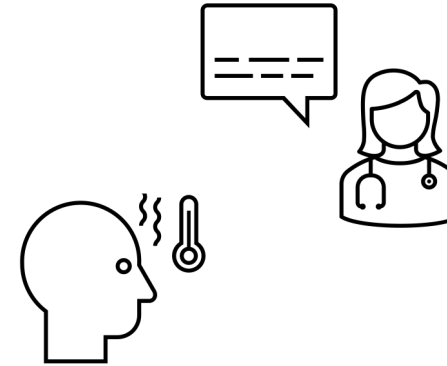
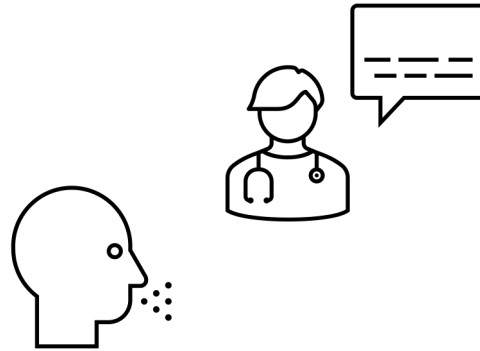
# Treatment emergent AEs (2)

- Study level definition



- Match the study

- Report to standards at time of collection.



# MedDRA up-versioning

- Many studies over time, mean many MedDRA versions.
- This doesn't change safety profile.
- Up-versioned for consistency.

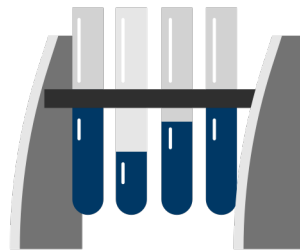


# Reconciliations

- Compare pooled outputs to study outputs.
- Find and investigate differences.
  - Fix or explain



`trtedt-trtsdt+1`



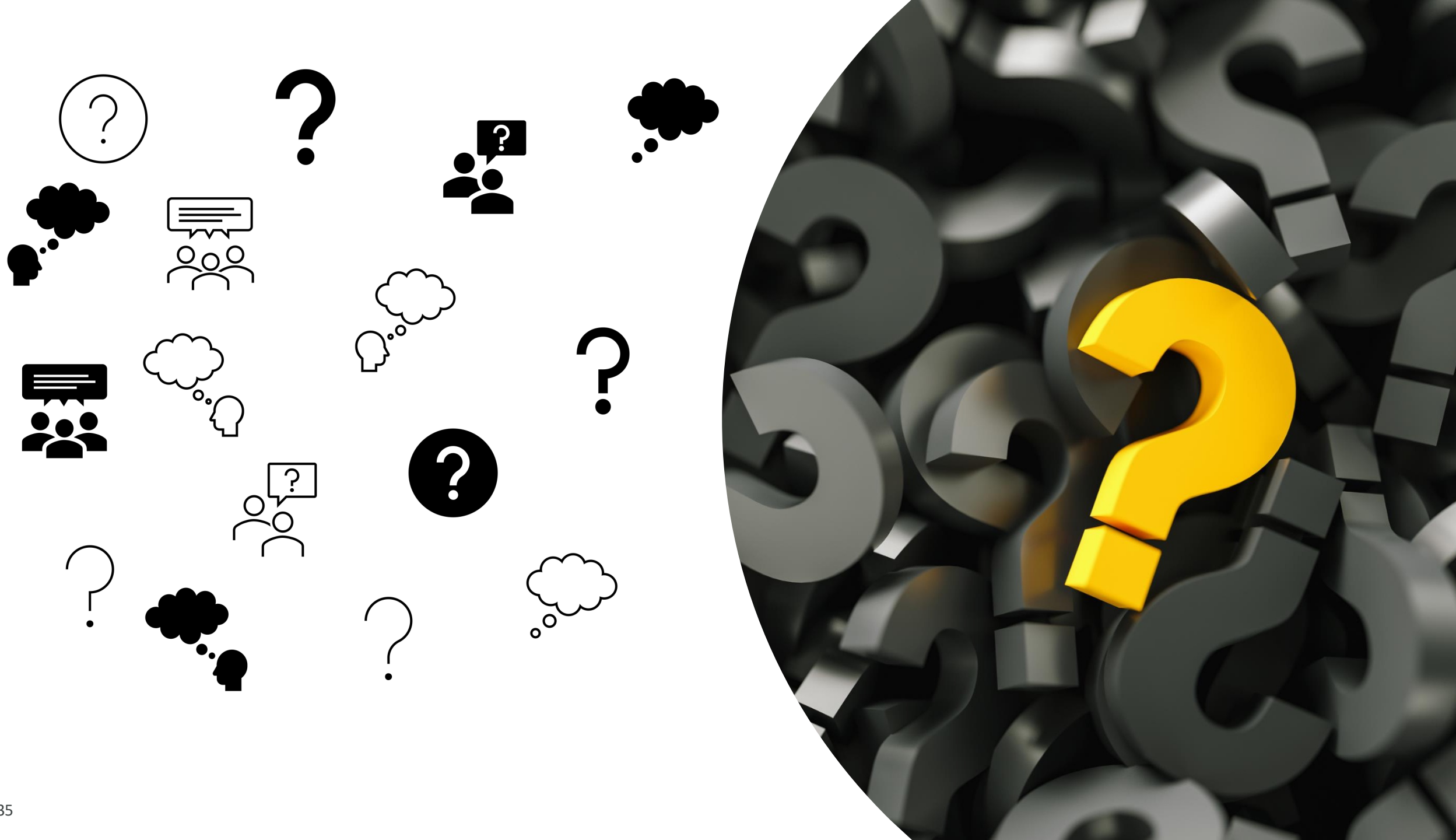
# Conclusions



# Conclusion

- Be prepared for changes to timelines.
- Expect differences between studies.
- Have a process for decision making.





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