



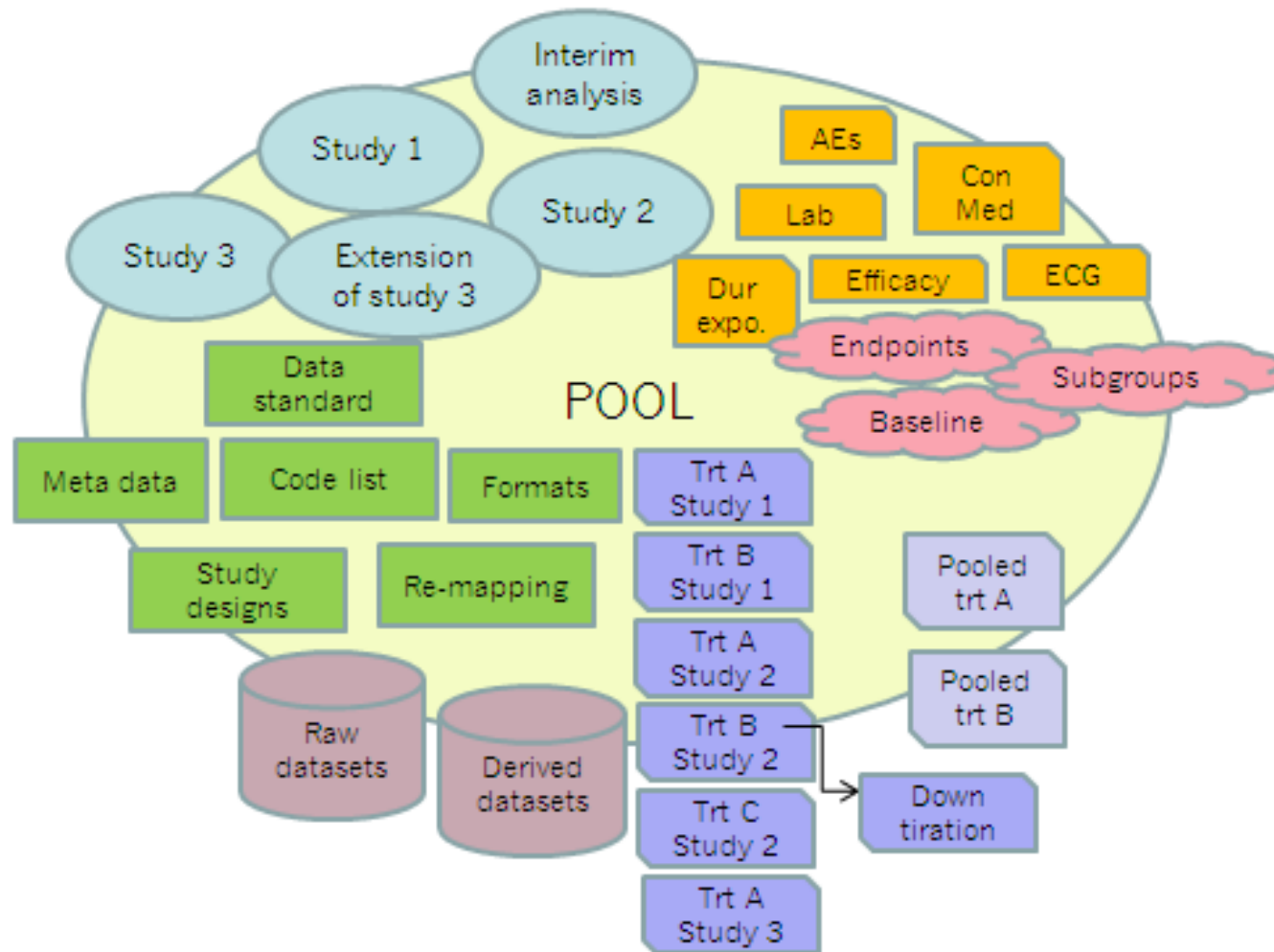
Pooling Clinical Data: Key points and Pitfalls

October 16, 2012 – Phuse 2012 conference, Budapest
Florence Buchheit

Introduction

- Are there any pre-defined **rules** to pool clinical data ?
- Are there any pre-defined **steps** to pool clinical data ?
- What is **the right way** to pool clinical data?

Agenda



- Purpose of the pool
- Planning
- Execution
- Possible pitfalls

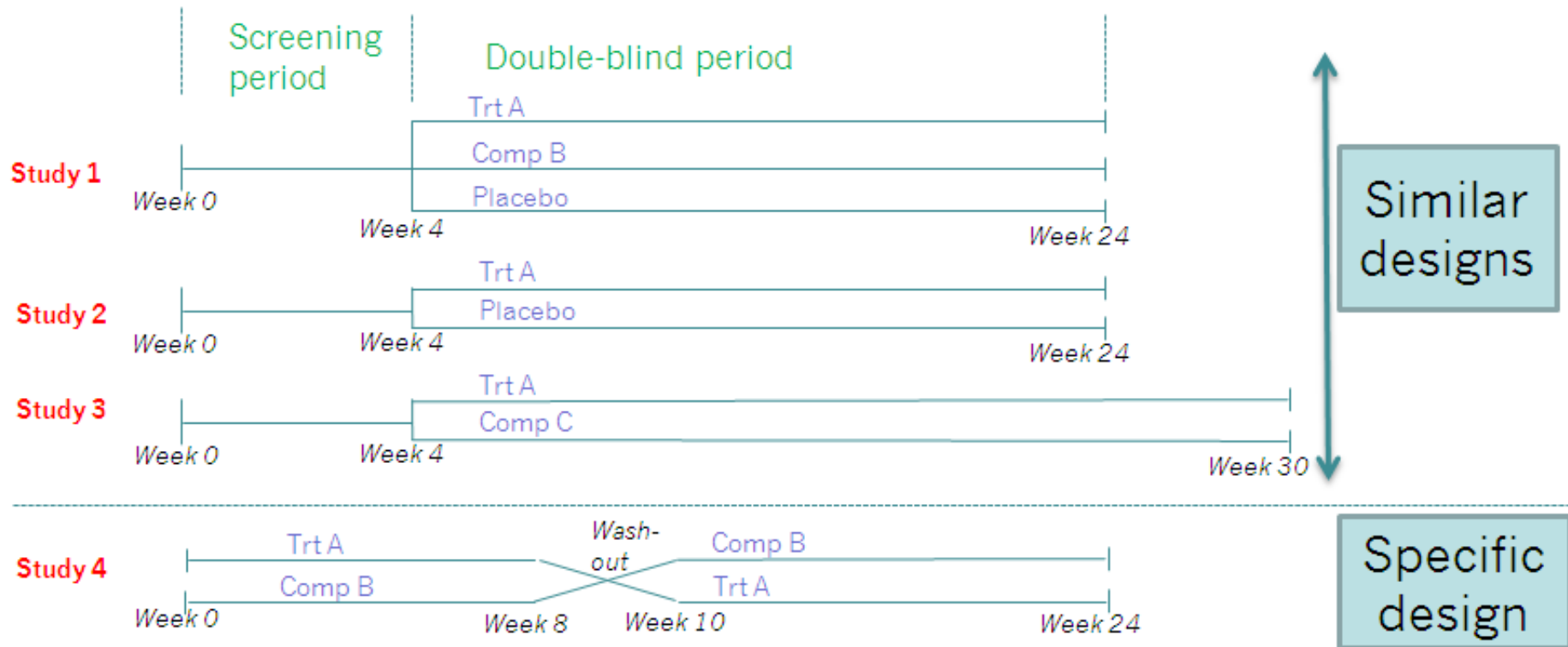
Purpose of the pool

- showing safety profile across whole program
- improving the precision of incidence estimate for main efficacy analysis
- identifying rare safety signals
- exploration of possible drug-demographic, drug-disease or drug-drug interactions in subgroups of populations.

But

The quality of the pool is dependent on the individual trials used

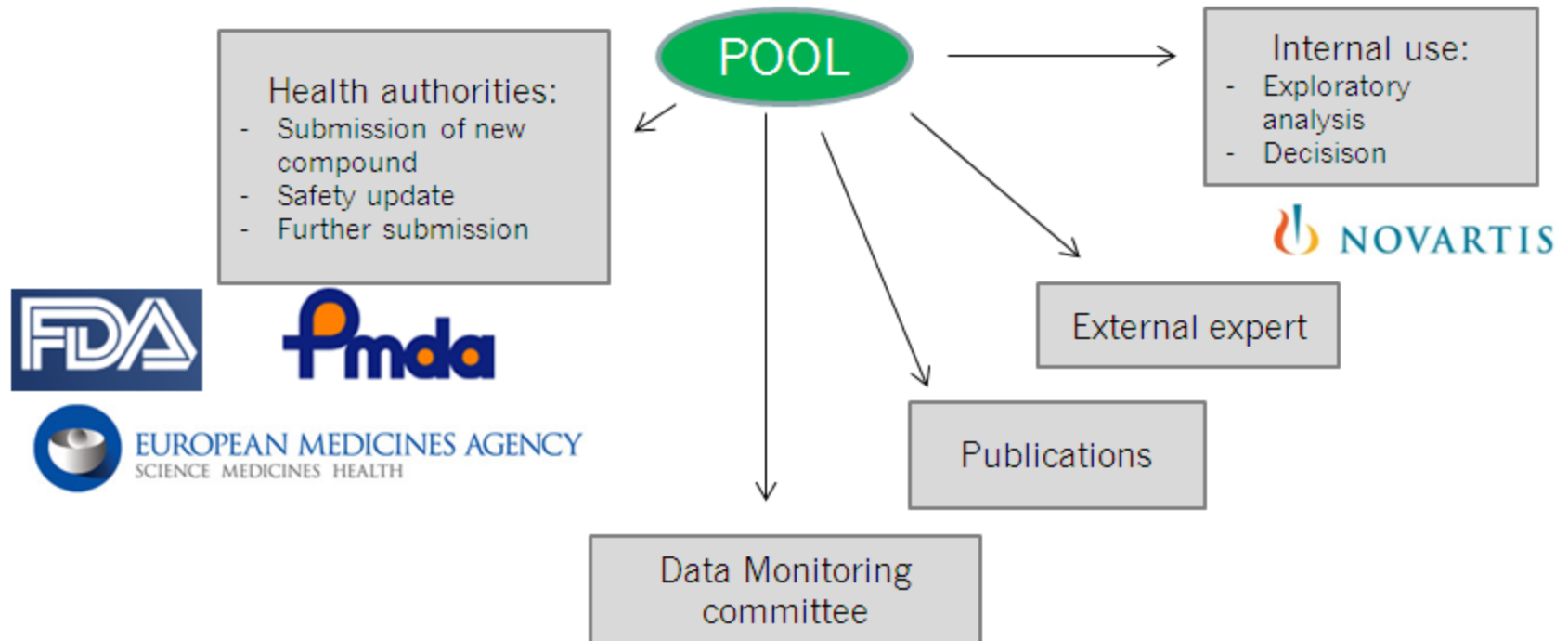
Purpose of the pool



- It is often most appropriate to combine data from studies that are of similar design (dose, duration, control and population)

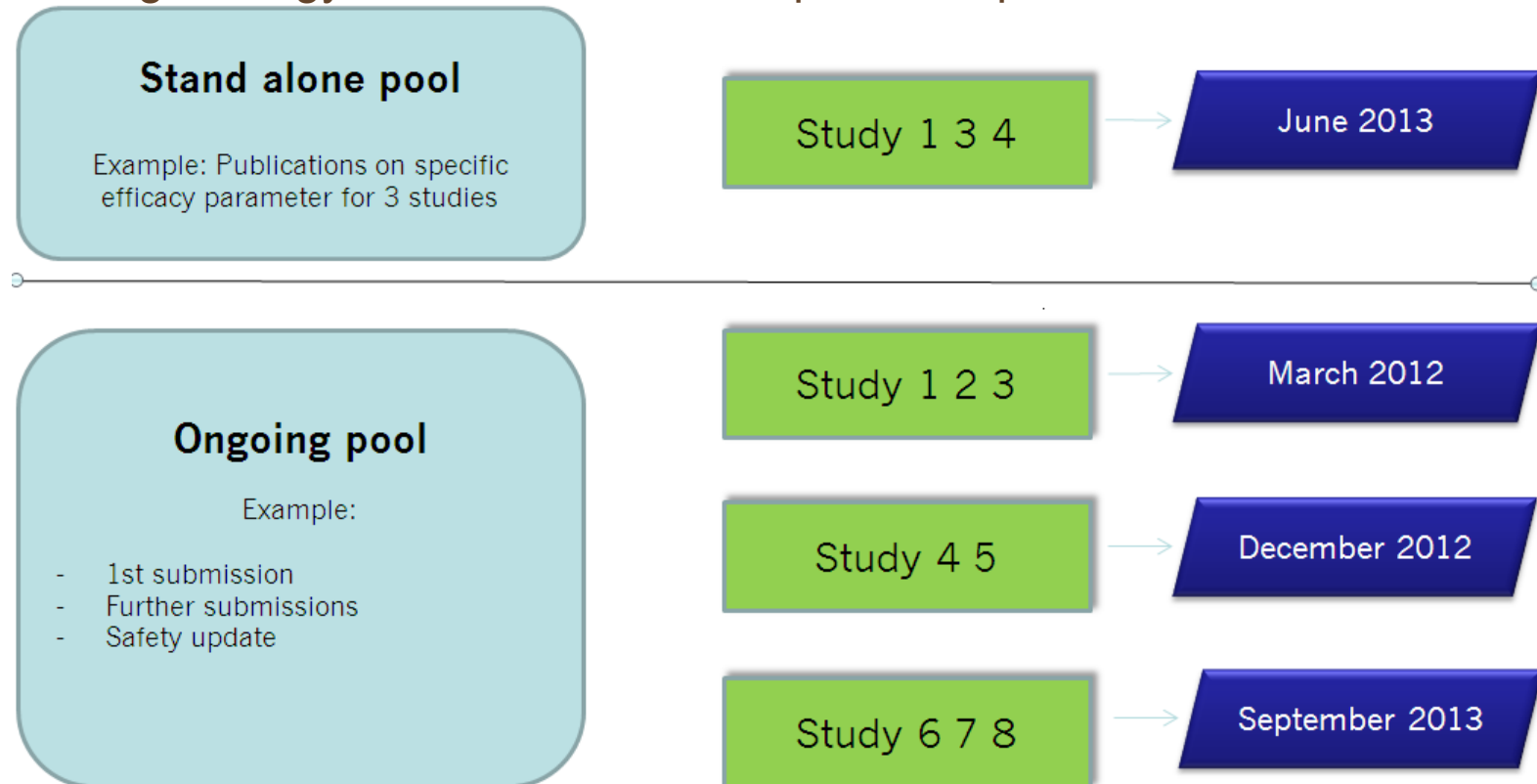
Purpose of the pool

■ Business reasons:

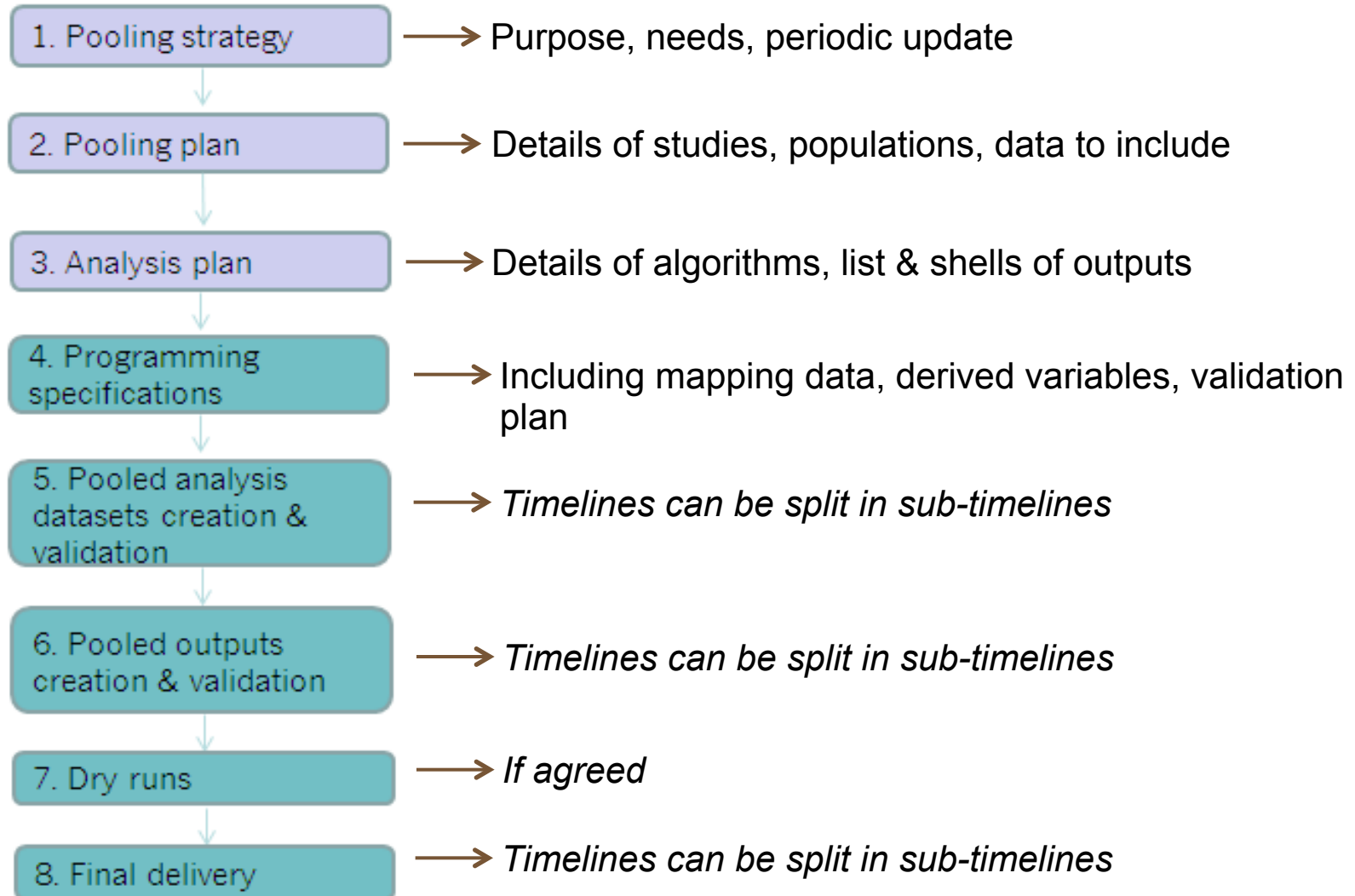


Planning

- Earlier the better
- Consideration of health authorities, medical expert input
- Pooling strategy : stand-alone versus periodic update



Planning



Planning

■ Pooling content - safety:

- Duration of treatment exposure
- Adverse events, SAEs (including deaths) and ADRs
- Specific defined risks of interest
- Lab values
- Further areas of potential interest : Vital signs, specifically solicited events captured outside of standard panels (e.g. immunogenicity problems), ECG...

■ Pooling content - efficacy:

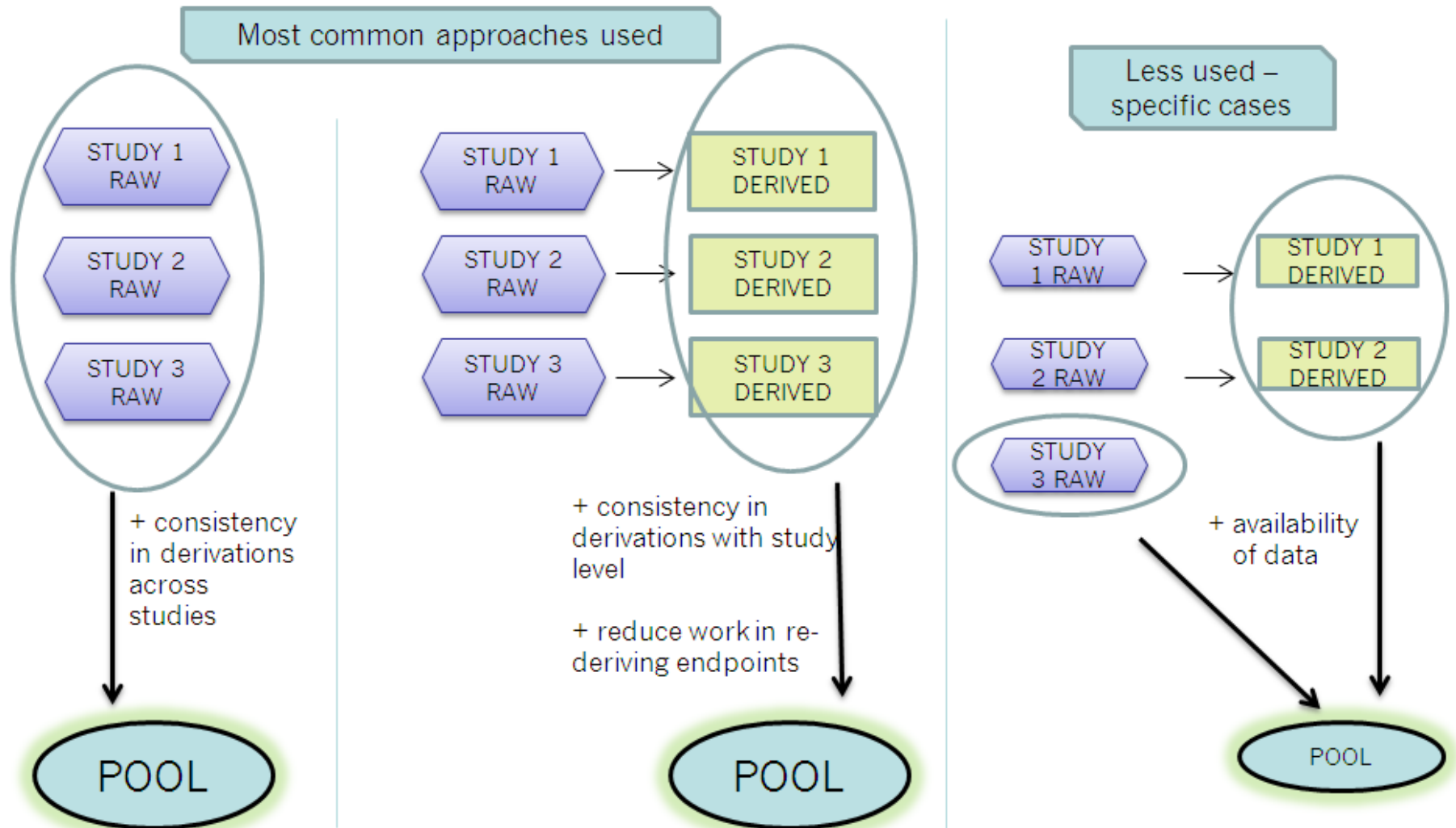
- Depends on the compound
- Focus on key endpoint
- Analysis of subgroup

Execution

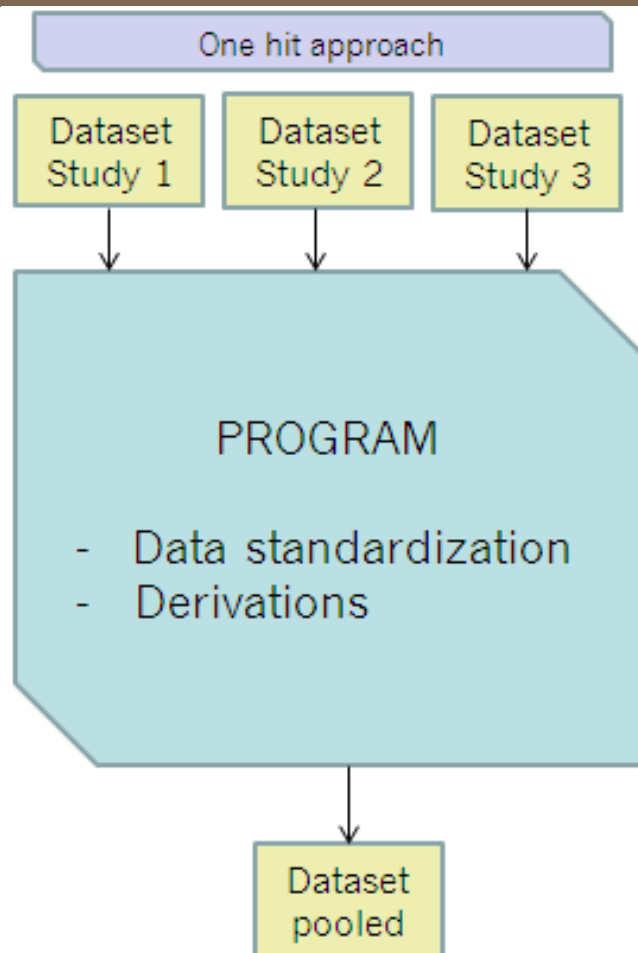
- Mapping study level data to pool level:
 - Mapping process: comparison of
 - Meta data
 - Code lists
 - Endpoints
 - Algorithms
 - Increase of mapping work if legacy data, outsourced studies or locally run studies
 - Creation of reports to compare raw and analysis data and meta data for a given study with the final pooled dataset



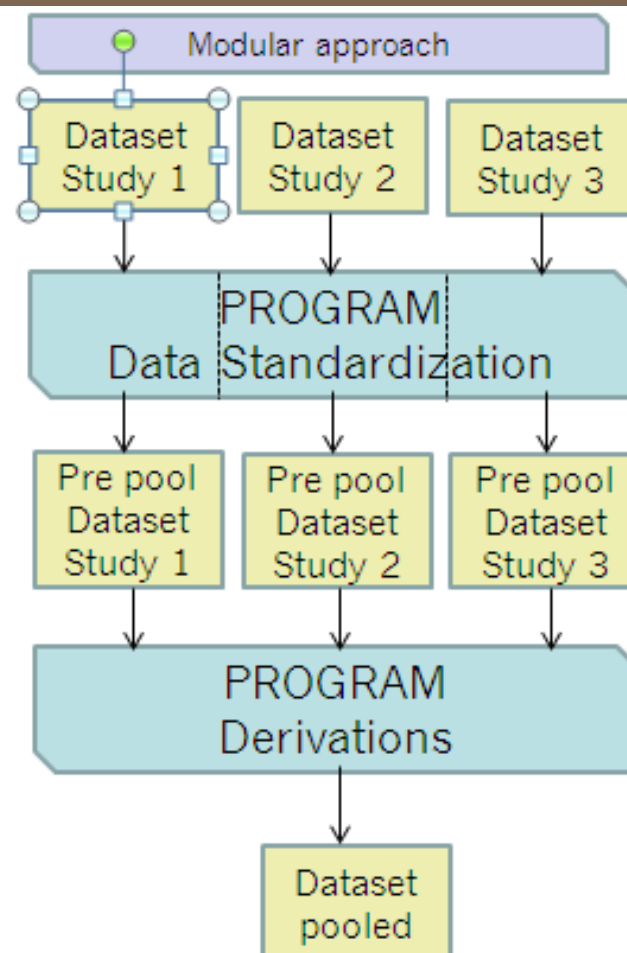
Execution: raw versus derived



Execution: programs strategy



- + fewer programs
- + common code to process data across studies



- + more flexible for resources studies and derivations
- + allows preparing studies as they are available

Documentation and validation consideration

■ Documentation:

Tracking information regarding data pools centrally to provide an easy reference in cases where multiple requests come

Project Data Pool Tracking Sheet				
Project:	CABC123X			
Description of data pool	Type of data pooled	Used to support (E.g. 2010 submission, HAQ, HE &OR) etc.	Studies Pooled	Description of data included (e.g. all Safety parameters, All efficacy to 6 months of treatment)

■ Validation:

- Risks assessment
- Validation strategy
- Review data is mapped as required
- Cross check between pooled and study level data

Possible pitfalls

■ Mapping of treatments:

- Treatments are presented differently in pooled outputs compared to study level
- Special care for studies with multiple periods, down-up titrations, add-on therapies

In derived dataset

Pooled Trt var	Trt description	STUDIES						
		Study 1	Study 2	Study 3	Ext Study 3	Study 4	Study 5	Study 6
T1	Treatment A	A		A	A	B		B
T2	Treatment B		C	B	B, C	A	A	
T3	Comparator C		A			C		A
T4	Comparator D	C					B	
T5	Placebo	B	B	C		D		C

In outputs

Output type 1	
Output Trt	Pooled trt var
All Trt	T1, T2
All Active Comp	T3, T4
Placebo	T5

Output type 2	
Output Trt	Pooled trt var
Treatment A	T1
Treatment B	T2
All Comp	T3, T4, T5

Possible pitfalls

- Mapping of visit window and timepoints:
 - Are pre-dose assessments in all pooled studies consistent?
 - Are key reporting visits consistent across trials?

- Extension studies:
 - On which treatment should patients who switch treatment from core to extension be considered ?
 - Should we consider baseline as core baseline or end of core study ?
 - How to handle of duplicate records (events starting in a core study and continuing to its extension)

Possible pitfalls

- Interim analysis

- How to determine the cut-off point for interim analysis (include all data up to a specific date? a specific visit? include only patients who completed the study? etc.)

- Coding

- Studies coded using different versions of a coding dictionary (MedDRA and WHO DRL dictionaries).
- Re-code using the latest version available



Conclusion

- No obvious right or wrong way to pool data
but they are many points that need to be well thought in advance.
- Early planning
- Clear pooling strategy
- Programming strategies: raw versus derived / one hit approach versus modular approach should be considered depending on the pool objectives, update, data availability...
- Pooling will be facilitating if adherence to standards

Questions ?

