Pooling Clinical Data: Key Points and Pitfalls

—— PhUSE Single Day Event

Presenter: Kate Gao (高艳)

Author: Florence Buchheit

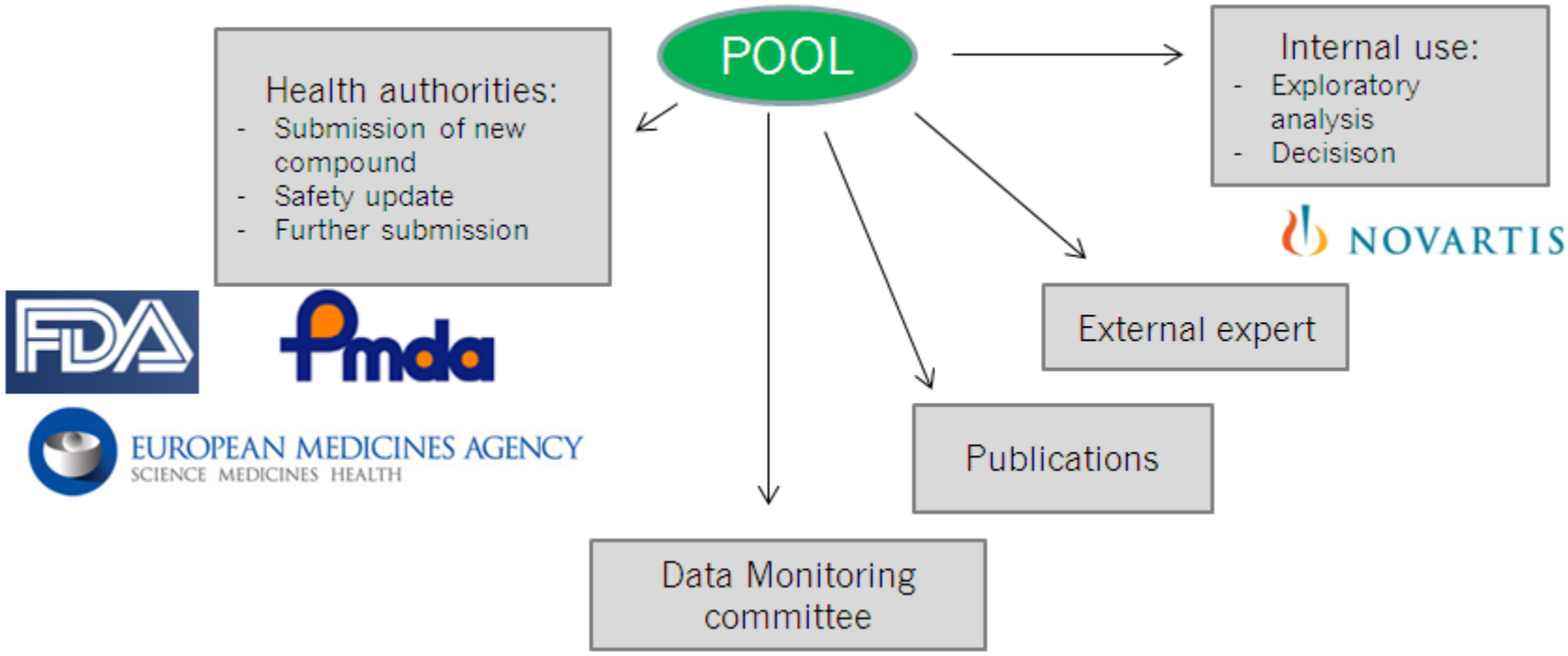
Shanghai, May 24th, 2013

NOVARTIS

Content

- Purpose
- Planning
- Execution
- Documentation
- Possible Pitfalls

Purpose - Business Reasons

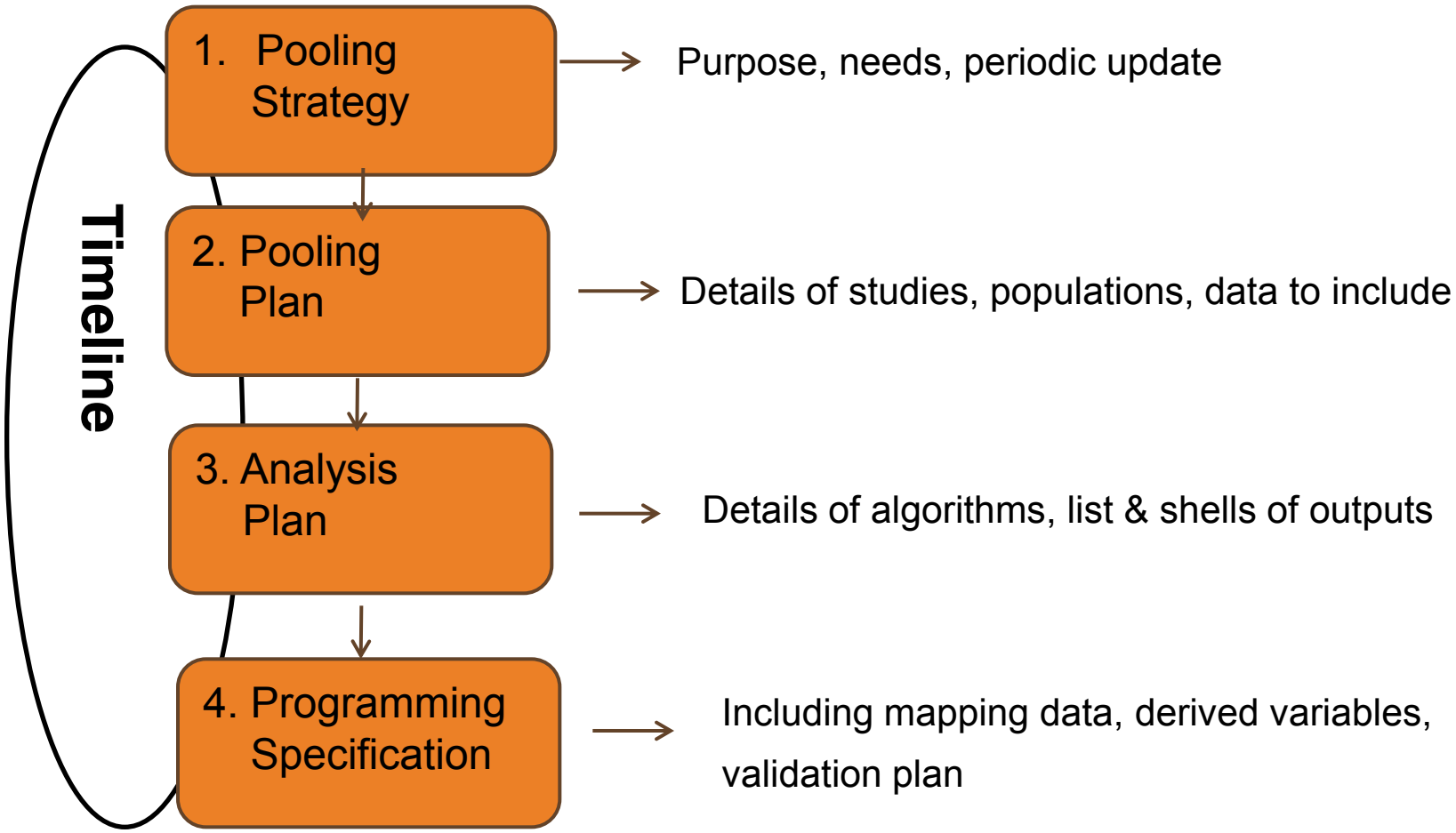


Purpose - Safety Reasons

- **Safety profile**
  - Rare safety signals
  - Analyses for support of Data Monitoring Committee (DMC) review
  - Development Safety Update Report (DSUR) for drugs under development
  - Periodic Safety Update Report (PSUR) for marketed products

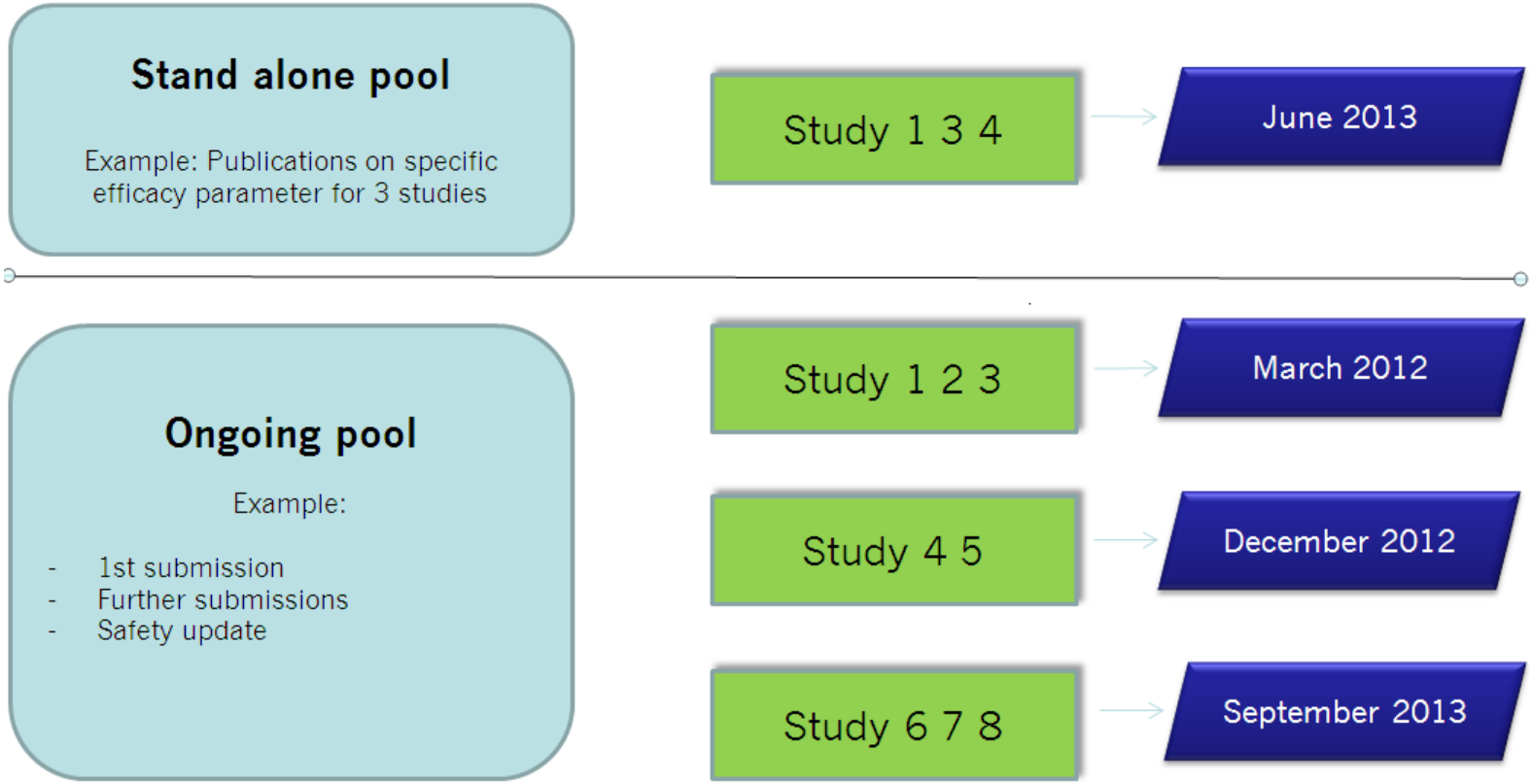
    (submitted once a year)
  - Risk Management Plan (RMP)

Planning



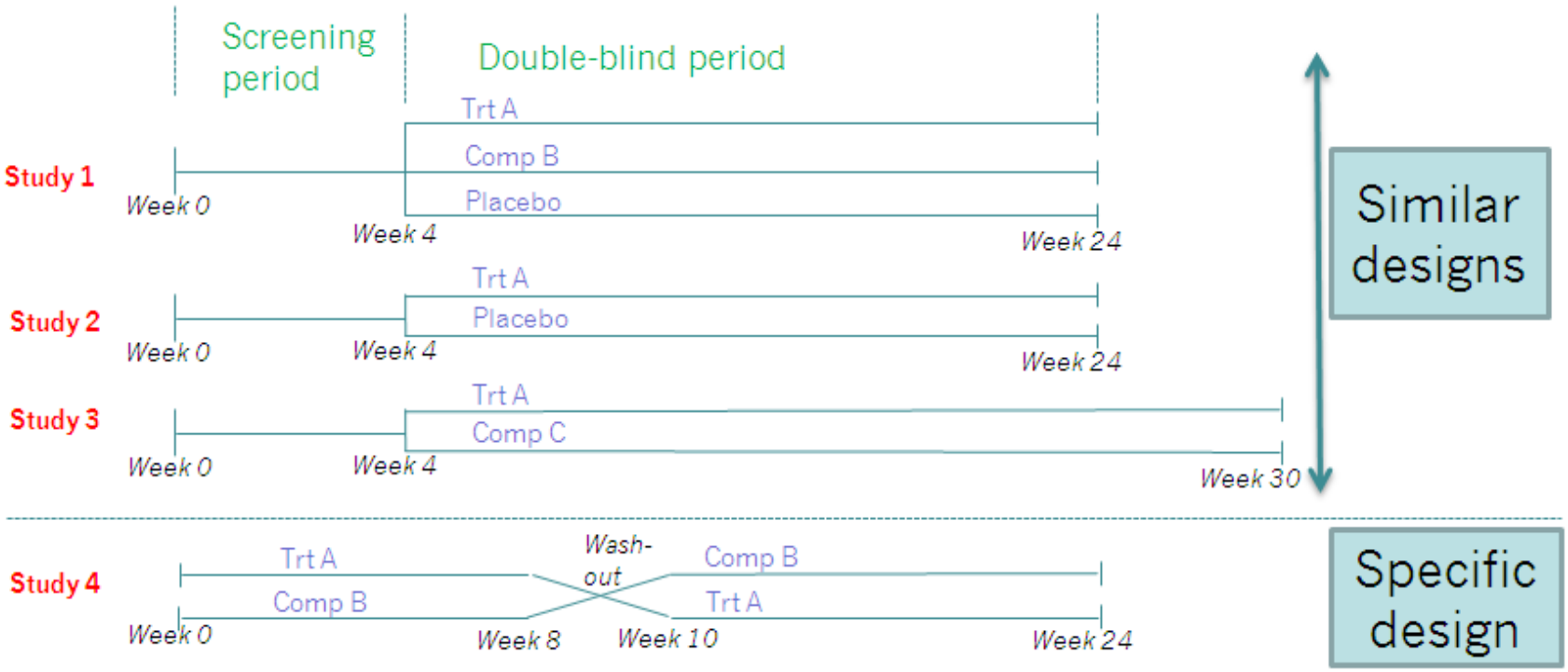
Planning - Pooling Strategy

- The earlier, the better
- Consideration of health autorities, medical expert, key team members, etc.
- Stand-alone versus periodic update



NOVARTIS

Planning - Pooling Plan



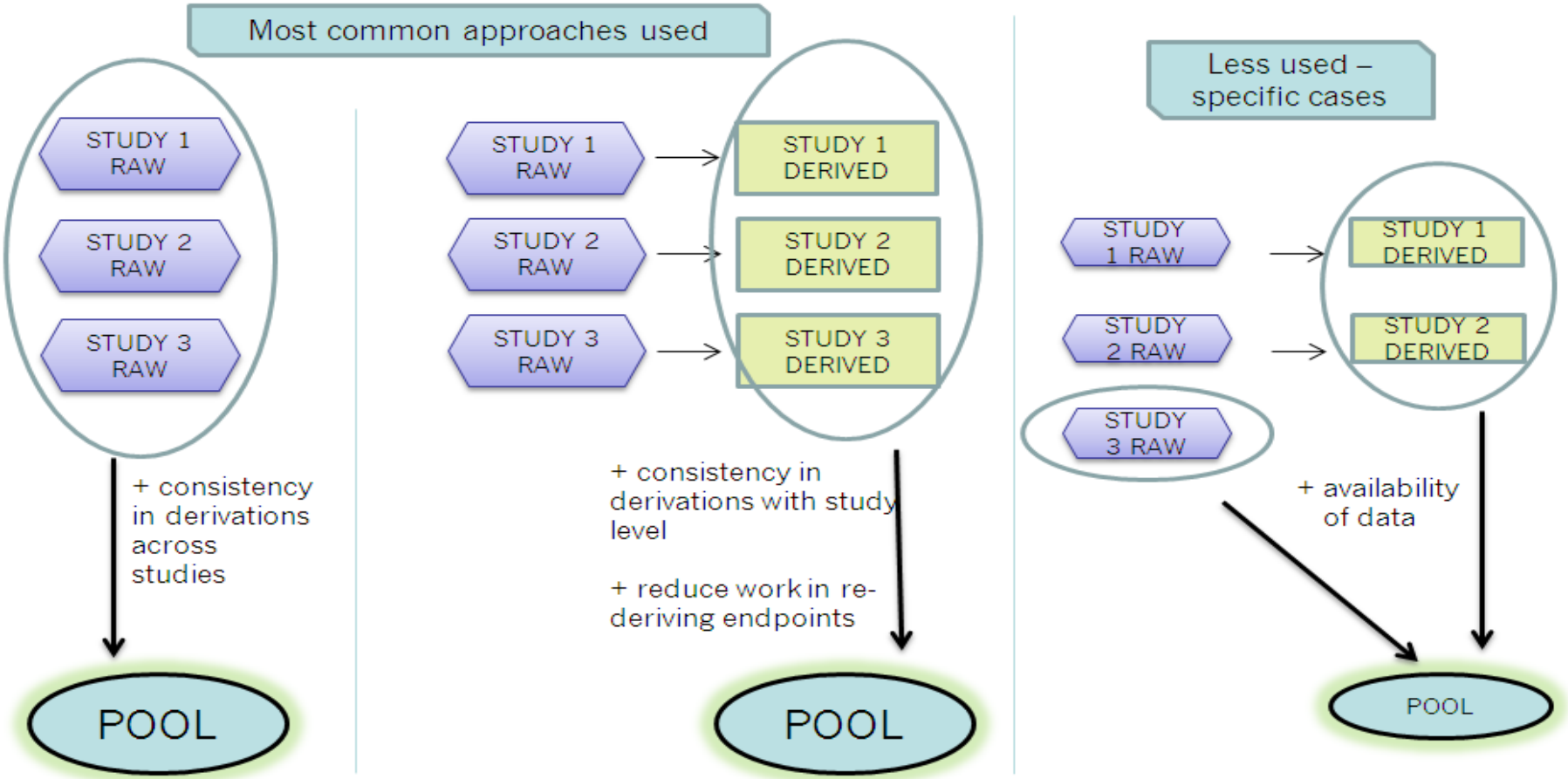
- It is often most appropriate to combine data from studies that are of similar design (dose, duration, control and population)

Planning - Analysis Plan

- **Safety**
  - Duration of treatment exposure
  - Adverse events, SAEs (including deaths) and ADRs
  - Specific defined risks of interest
  - Lab values
  - Potential interest : Vital signs, specifically solicited events captured outside of standard panels (e.g. immunogenicity problems), ECG...
- **Efficacy**
  - Depends on the compound
  - Focus on key endpoint
  - Analysis of subgroup

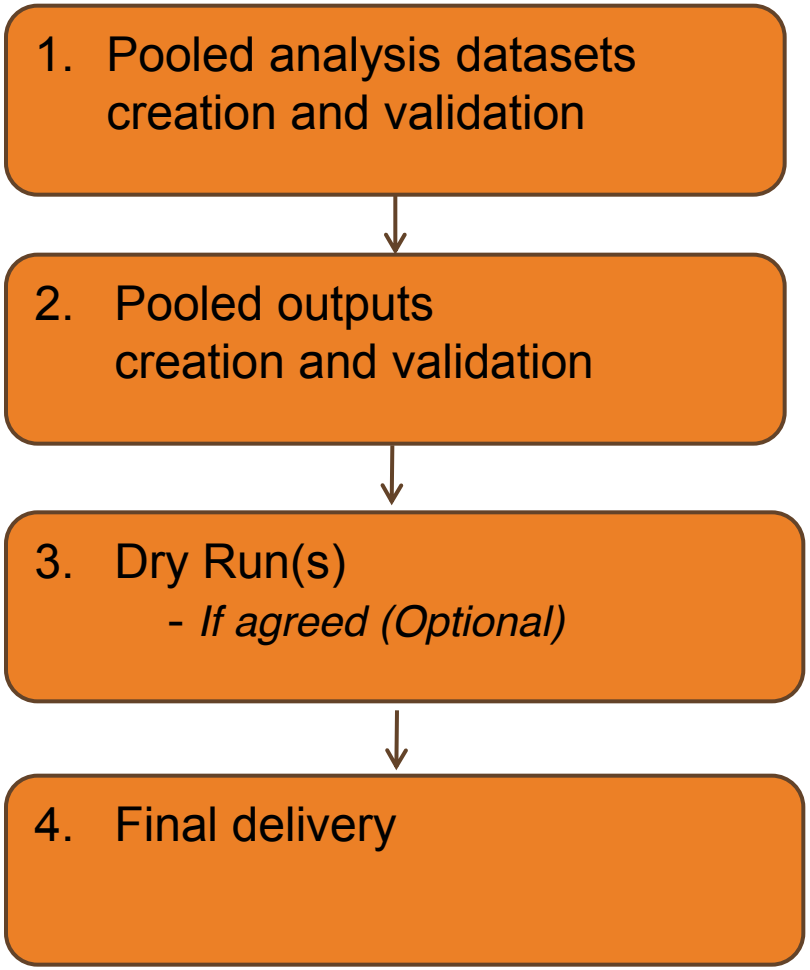
Planning – Programming Specification

Raw datasets vs. Derived datasets

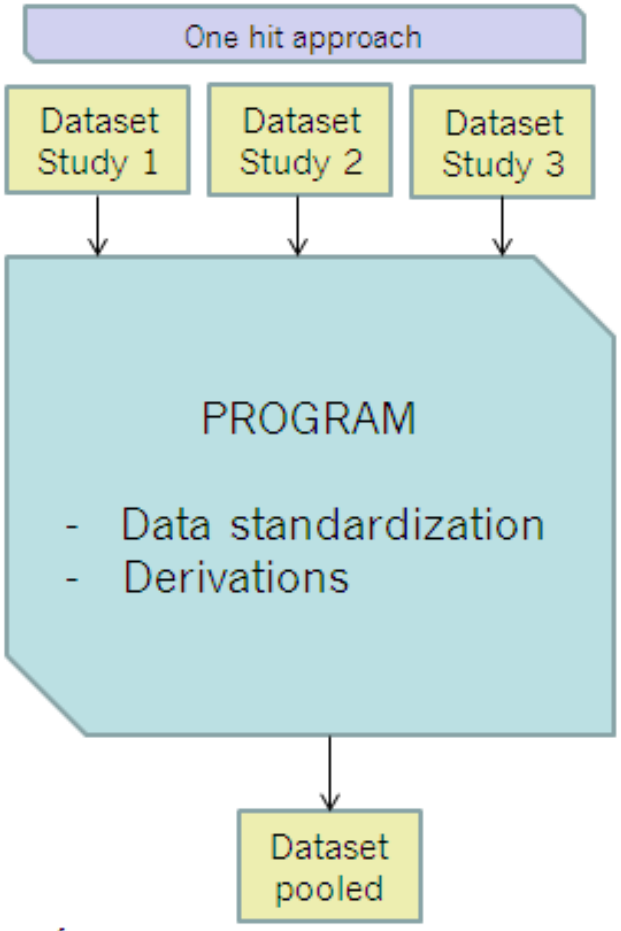


NOVARTIS

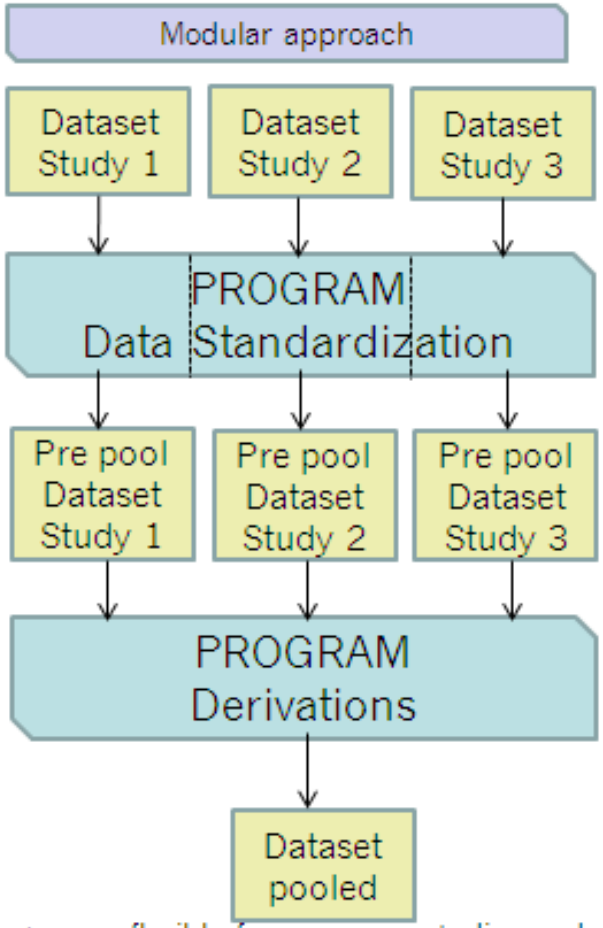
Execution



Execution - Pooled Analysis Datasets



+ fewer programs
+ common code to process data across studies



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

Execution

- Mapping study level data to pool level:
  - 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 - Validation

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

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)

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 Time Points

- Are pre-dose assessments in all pooled studies consistent?
- Consistent key reporting visits across trials?

Possible Pitfalls - Extension Studies

- Whether the patients maintained the same treatment in the extension studies compared to the core studies?
- If patients switch to another treatment group in the extension studies, which treatments should they belong to?
- How to calculate the baseline in the pool:
  - Baseline in core baseline
  - 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:

- Include all data up to a specific date?
- A specific visit?
- Include only patients who completed the study?

Possible Pitfalls - Coding

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

Summary

- No unique way, to find a more efficient way to pool data
- Early planning and 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 facilitated if individual studies adhere to standards

Questions ?