



S109

Choosing the right path to follow when integrating ADaM

Magalie Gallet, Geneva, Switzerland

Laura Phelan, Cytel, Paris, France

PhUSE EU Connect 2019, Amsterdam

November 11, 2019

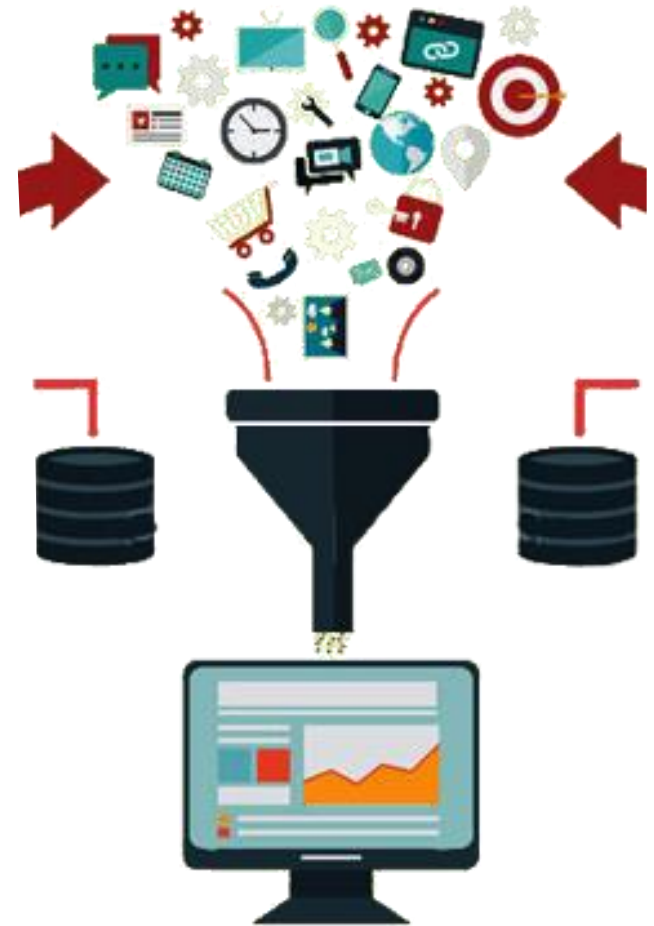
- Introduction
- ISS Design
- How to Structure ADaMs?
- Future/Not released Guidelines
- Conclusion

DISCLAIMER

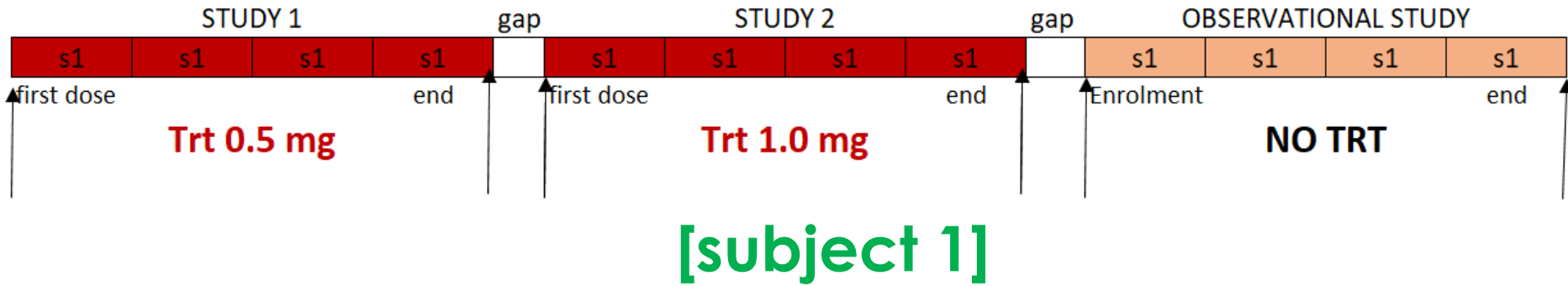
What you are about to see in the following slides is an interpretation of the fundamental principles of the ADaM model and IG.

Some terminology may be harmful to a more sensitive audience, notably with regards to the use of “integration” vs “pooling”.

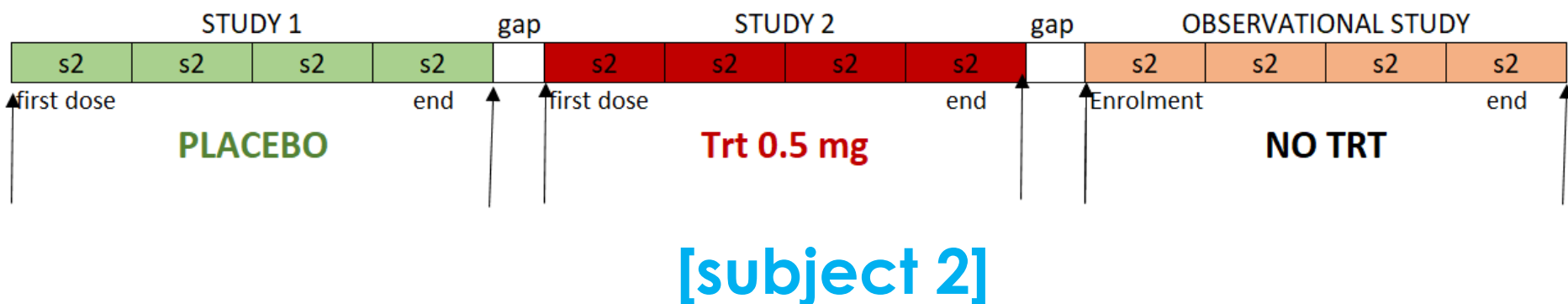
- ISS of 10 Studies
- Several analysis “Cohorts”
- 2017, ADaM IG 1.1



Introduction: Study design

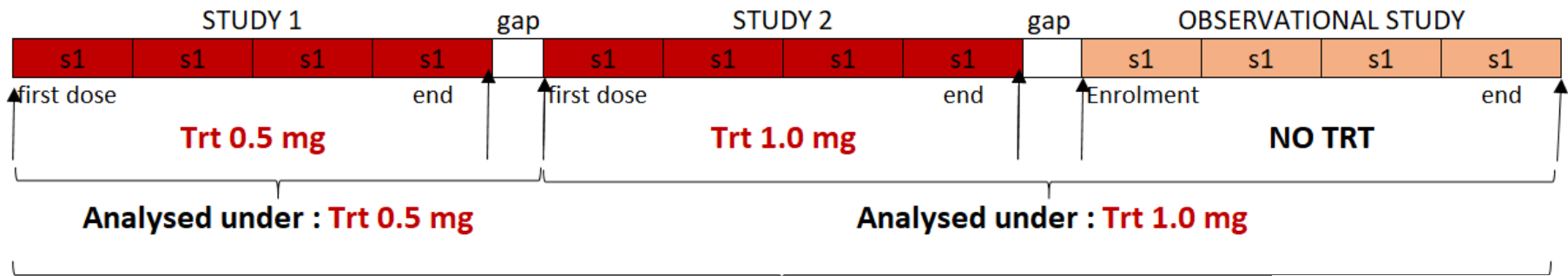


[subject 1]



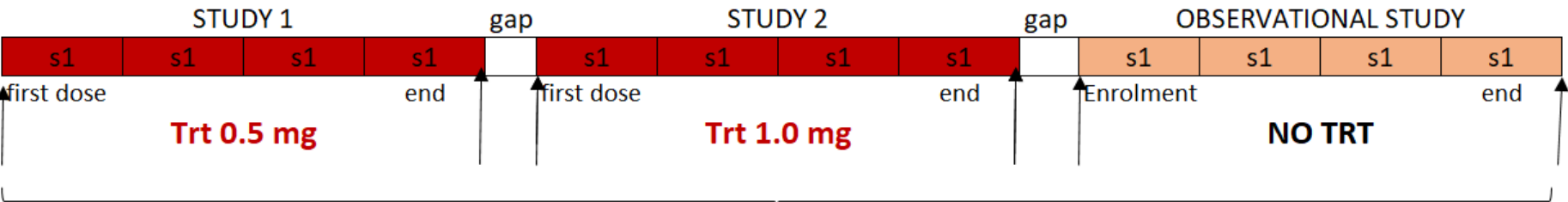
[subject 2]

Introduction: Subject 1



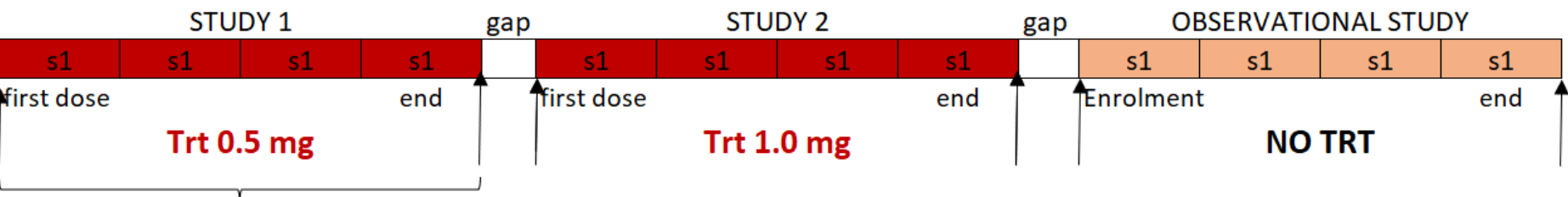
Analyzed under : Trt 0.5 & 1.0 mg = 1.5 mg

[cohort 1]



Analyzed under : Trt

[cohort 2]



Analyzed under : Trt

[cohort 3]

Introduction: ideally...

ROW	USUBJID	COHORT	TREATMENT VARIABLE	START DATE	STOP DATE
1	Subject 1	Cohort 1	Trt 0.5 mg	Start 1	Stop 1
2	Subject 1	Cohort 1	Trt 1.5 mg	Start 1	Stop 2
3	Subject 1	Cohort 1	Trt 1.0 mg	Start 2	Stop 2
4	Subject 1	Cohort 2	Trt	Start 1	Stop 2
5	Subject 1	Cohort 3	Trt	Start 1	Stop 3
7	Subject 2	Cohort 1	PLACEBO	Start 1	Stop 1
8	Subject 2	Cohort 1	Trt 0.5 mg	Start 2	Stop 2
9	Subject 2	Cohort 2	PLACEBO	Start 1	Stop 1
10	Subject 2	Cohort 2	Trt	Start 2	Stop 2
11	Subject 2	Cohort 3	PLACEBO	Start 1	Stop 3



- Treatment variables in ADSL?
- All cohorts in one BDS/OCCDS?
- TLFs “one proc away”?
- Traceability




Current ADaM IG options


- ✓ **TRxxPGy** IG says *“Planned pooled treatment y for period xx. Useful when planned treatments (TRTxxP) in the specified period xx are pooled together for analysis according to pooling algorithm y. Each value of TRTxxP is pooled within at most one value of TRxxPGy.”*
- ✓ **APHASE: PHxxSDT/EDT** IG says *“categorization of timing within a study”*
- ✓ **TRTxxP/APERIOD: APxxSDT/EDT** IG says *“record-level timing variable that represents the analysis period within the study associated with the record for analysis purposes.”*
- ✓ **Sub-period ASPER: PxxSwSDT/EDT** IG says *“sublevel within APERIOD to which the record belongs”*

HOW TO STRUCTURE ADaMs?

➤ TRxxAGy

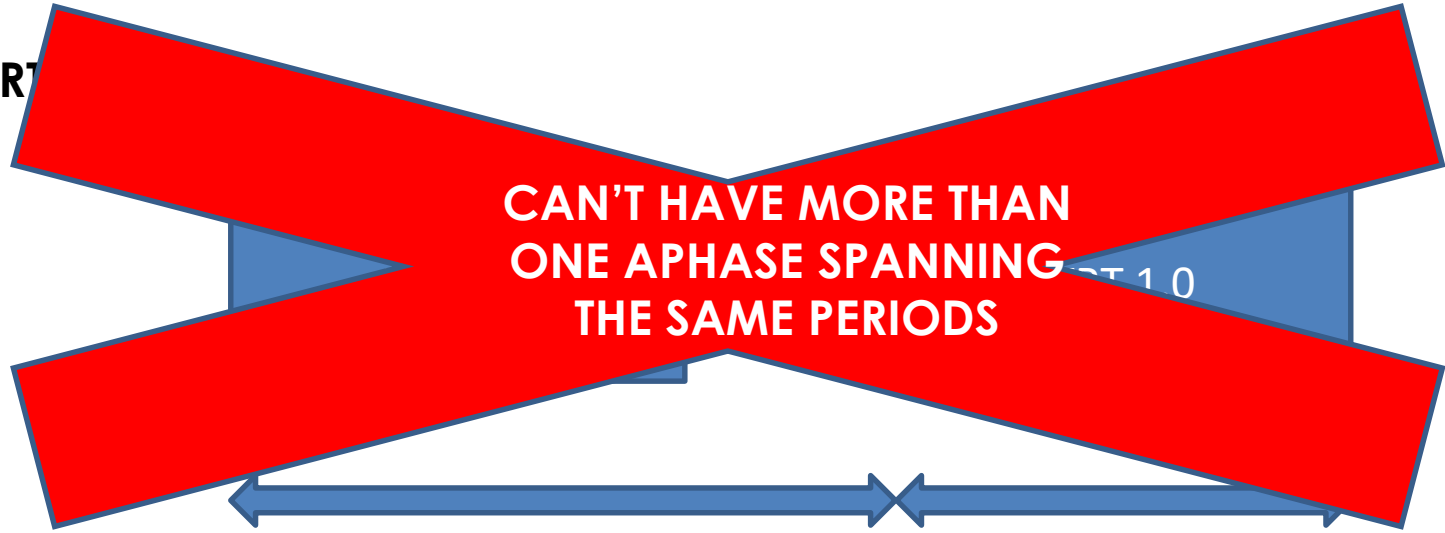


ROW	STUDYID***	USUBJID	TRT01A	TRT02A	TR01AG1 (Actual pooled treatment 1 based on period 01 TRT01A)	TR02AG1 (Actual pooled treatment 1 based on period 02 TRT02A)
1	which to use?	s1	Trt 0.5 mg	Trt 1.0 mg	Trt	Trt
2	which to use?	s2	PLACEBO	Trt 0.5 mg	PLACEBO	Trt
3	which to use?	s3	Trt 0.5 mg		Trt	



**CAN GROUP SAME
TREATMENT WITH DIFFERENT
DOSES BUT NOT FROM
DIFFERENT PERIODS**

COHORT



CAN'T HAVE MORE THAN ONE APHASE SPANNING THE SAME PERIODS

PERIOD 1

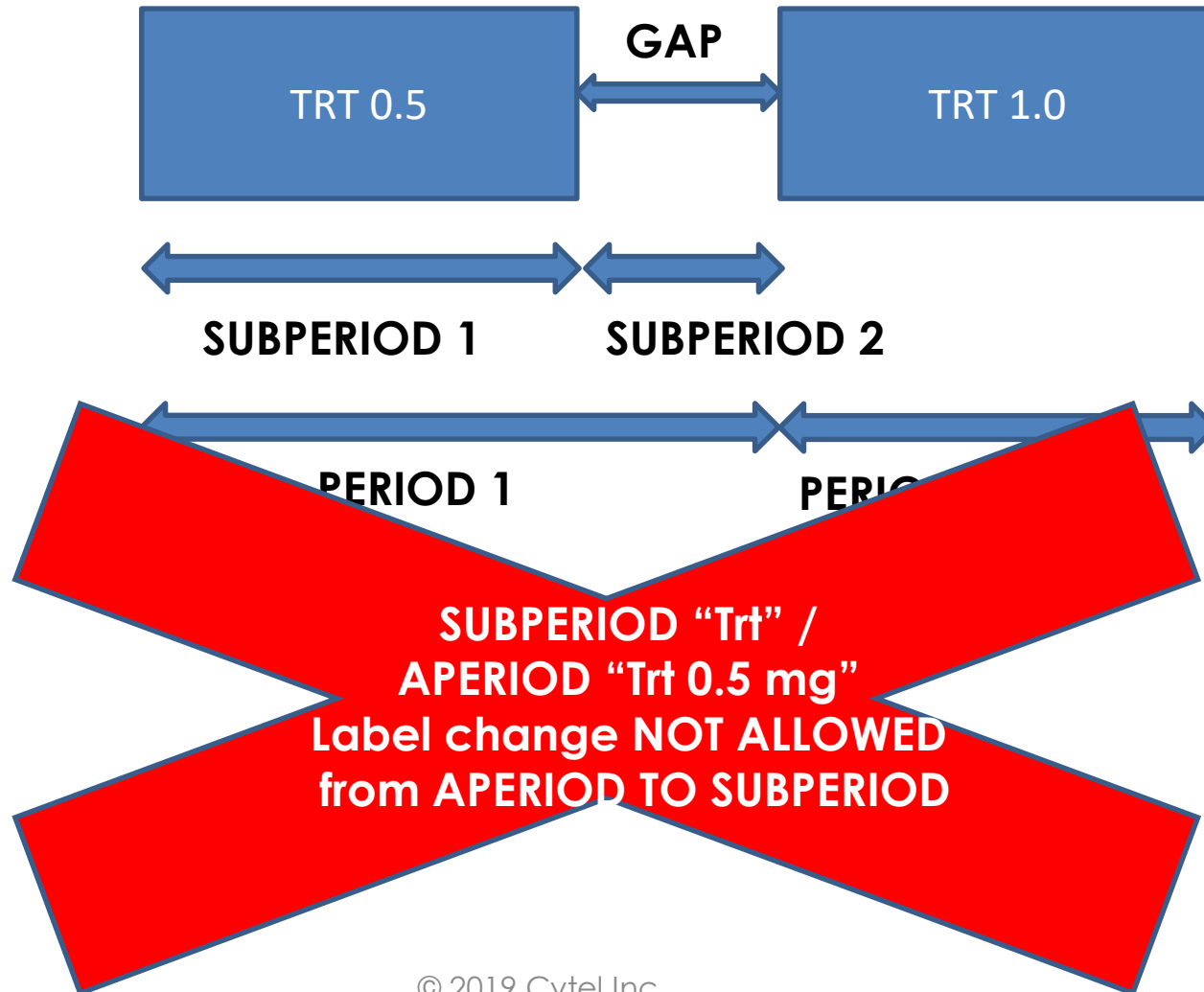
PERIOD 2

$$\text{APHASE1} = \text{TRT } 0.5 + 1.0$$

COHORT 2

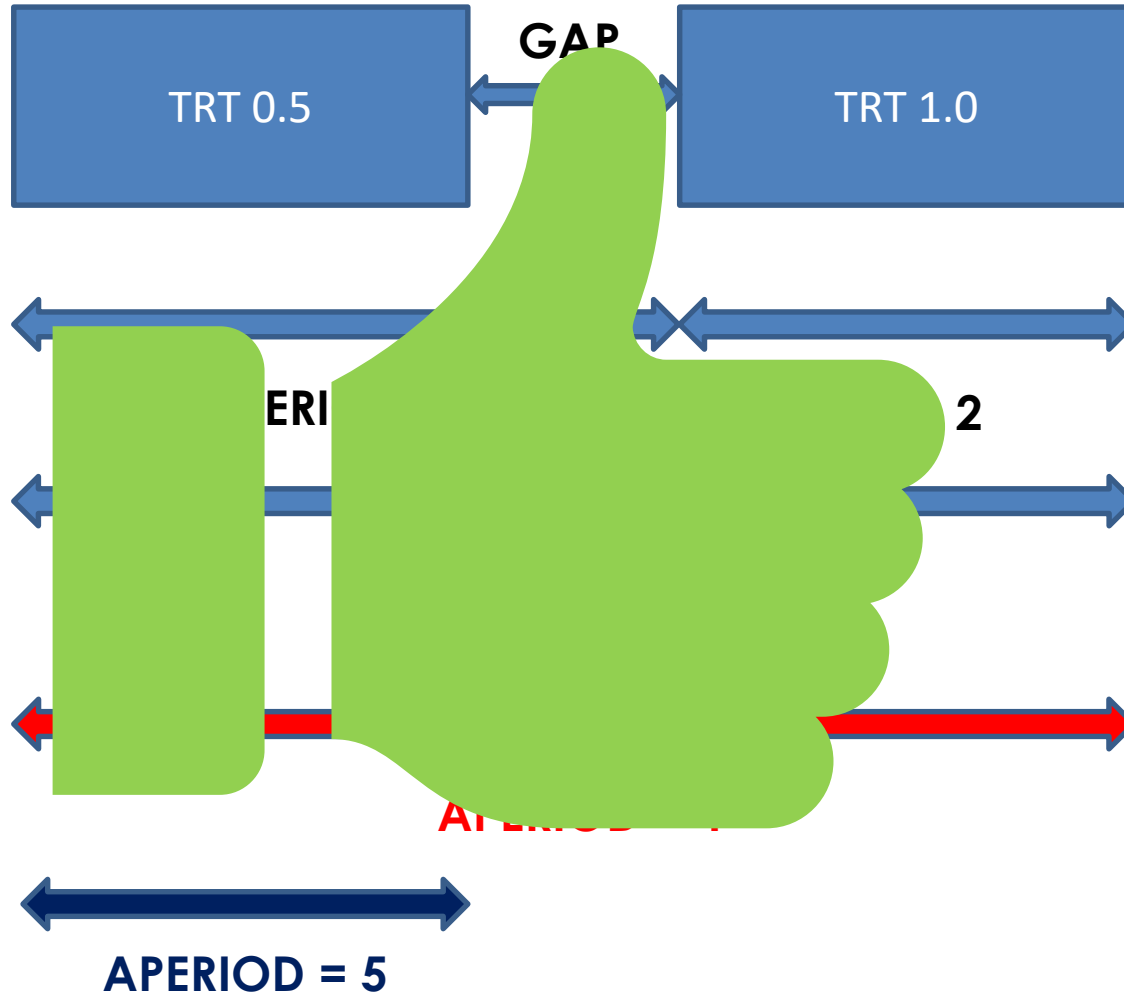
$$\text{APHASE2} = \text{TRT}$$

COHORT 3 – Need of Subperiod to get only STUDY 1



TRTxxP and APERIOD

COHORT 1

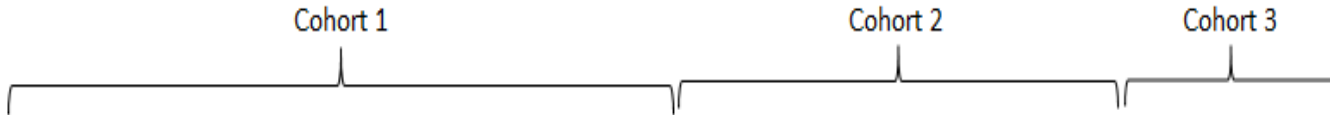


COHORT 2

COHORT 3

APERIOD = 5

ADSL STRUCTURE



ROW	STUDYID	USUBJID	TRT01A	TRT02A	TRT03A	TRT04A	TRT05A	TRT06A
1	which to use?	s1	Trt 0.5 mg	Trt 1.5 mg	Trt 1.0 mg	Trt	null	Trt
2	which to use?	s2	PLACEBO	Trt 0.5 mg	null	PLACEBO	Trt	PLACEBO

➤ BDS/OCCDS Datasets

- ❖ Use of a Baseline dataset structured as “*one row per subject per cohort per treatment group/period*”

ROW	USUBJID	COHORT	TREATMENT VARIABLE	START DATE	STOP DATE
1	Subject 1	Cohort 1	Trt 0.5 mg	Start 1	Stop 1
2	Subject 1	Cohort 1	Trt 1.5 mg	Start 1	Stop 2
3	Subject 1	Cohort 1	Trt 1.0 mg	Start 2	Stop 2
4	Subject 1	Cohort 2	Trt	Start 1	Stop 2
5	Subject 1	Cohort 3	Trt	Start 1	Stop 3
7	Subject 2	Cohort 1	PLACEBO	Start 1	Stop 1
8	Subject 2	Cohort 1	Trt 0.5 mg	Start 2	Stop 2
9	Subject 2	Cohort 2	PLACEBO	Start 1	Stop 1
10	Subject 2	Cohort 2	Trt	Start 2	Stop 2
11	Subject 2	Cohort 3	PLACEBO	Start 1	Stop 3

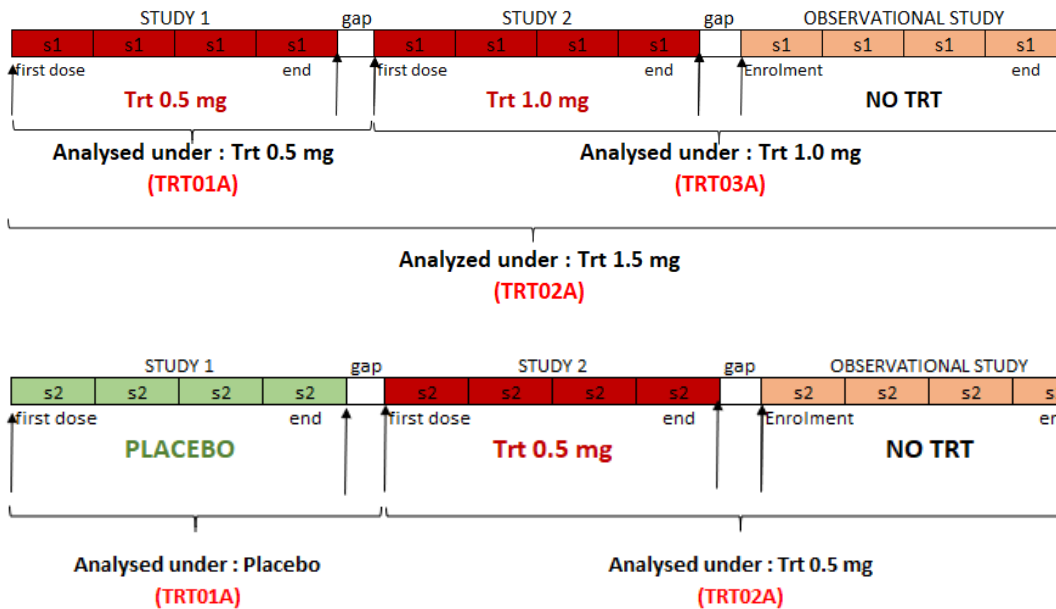
- ❖ All cohorts in one or split by cohort

HOW TO STRUCTURE ADaMs - TRACEABILITY

✓ STUDYID/ASTUDYID

STUDYID	ASTUDYID	USUBJID	AETERM	AESTDTC	AEENDTC
STUDY 1	STUDY 1	Subject 1	Urinary tract infection	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 1	Subject 1	head cold	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 2	Subject 1	headache	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 2	Subject 1	unusual feeling in gut	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 2	Subject 1	head cold	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 1	Subject 2	Urinary tract infection	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 1	Subject 2	Urinary Tract Infection	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 1	Subject 2	Urinary tract infection	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 1	Subject 2	Gastric Reflux	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 1	Subject 2	right rib pain	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 1	Subject 2	Right Knee Pain	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 2	Subject 2	Common Cold	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 2	Subject 2	Depression	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 2	Subject 2	Insomnia	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	STUDY 2	Subject 2	Elevated liver enzymes	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	OBS	Subject 2	Fall onto right shoulder	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	OBS	Subject 2	Herpes Simplex rash	yyyy-mm-dd	yyyy-mm-dd
STUDY 1	OBS	Subject 2	Falls	yyyy-mm-dd	yyyy-mm-dd

➤ ADaMs Reviewers Guide



Cohorts	Treatment variable	Treatment group
COHORT 1	TRT01A	Placebo <u>Trt</u> 0.5 mg
	TRT02A	<u>Trt</u> 0.5 mg <u>Trt</u> 1.5 mg
	TRT03A	<u>Trt</u> 1.0 mg
COHORT 2	TRT04A	Placebo <u>Trt</u>
	TRT05A	<u>Trt</u>
COHORT 3	TRT06A	Placebo <u>Trt</u>

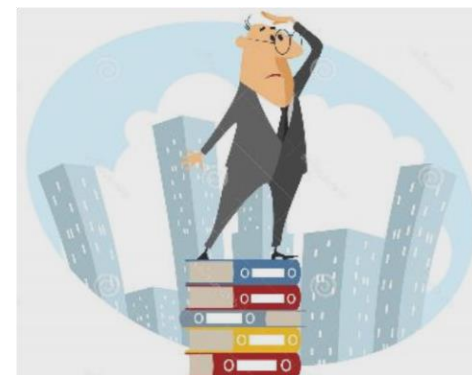
Study	Indication	Type of control/blinding/design	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
STUDY 1	Indication xx	Randomized, placebo-controlled, double-blind.....	✓	✓	✓	✓	✓
STUDY 2	Indication x1	Randomized, placebo-controlled, double blind.....	✓	✓ (only subjects from Study 1 and 3)			
STUDY 3	Indication xx with...	Randomized, placebo-controlled, double blind.....	✓		✓ (only first sequence)		
OBS	Indication x...	Ongoing, prospective observational long-term	✓	✓ (only subjects from Study 2 and 3)			

IADSL

“one record per subject per pool”

or

“one record per subject per pool per subject identifier for the pool”.



ROW	USUBJID	STUDIES	POOL	PSUBJID	PSREAS	NUMSTUDY	TRT01A
1	s1	STUDY 1	COHORT 1	s11	Cohort 1 Treatment 1 definition	1	Trt 0.5 mg
2	s1	STUDY 1 + STUDY 2 + OBS	COHORT 1	s12	Cohort 1 Treatment 2 definition	3	Trt 1.5 mg
3	s1	STUDY 2 + OBS	COHORT 1	s13	Cohort 1 Treatment 3 definition	2	Trt 1.0 mg
4	s1	STUDY 1 + STUDY 2 + OBS	COHORT 2			3	Trt
5	s1	STUDY 1	COHORT 3			1	Trt
6	s1	STUDY 1 + STUDY 2 + OBS	OVERALL			3	
7	s2	STUDY 1	COHORT 1	s21	Cohort 1 Treatment 1 definition	1	PLACEBO
8	s2	STUDY 2 + OBS	COHORT 1	s22	Cohort 1 Treatment 2 definition	2	Trt 0.5 mg
9	s2	STUDY 1	COHORT 2	s21	Cohort 2 Treatment 1 definition	1	PLACEBO
10	s2	STUDY 2 + OBS	COHORT 2	s22	Cohort 2 Treatment 2 definition	2	Trt
11	s2	STUDY 1	COHORT 3			1	PLACEBO
12	s2	STUDY 1 + STUDY 2 + OBS	OVERALL			3	

IBDS/IOCCDS Structure

- ✓ Similar structure
- ✓ Only pools needed from ADSL are copied
- ✓ STUDYID variable can only contain a value present in IADSL.STUDIES

- Many interpretations possible
- Future IG - anticipated !!



Magalie Gallet

Email: Magalie.Gallet@cytel.com

Laura Phelan

Email: Laura.Phelan@cytel.com

Web: www.Cytel.com

Latest CDISC ADaM guidelines available used for this analysis:

- ✓ ADaM Implementation Guideline v1.1
- ✓ ADaM Structure for Occurrence Data (OCCDS) v1.0
- ✓ ADaM Time-to-Event Analyses v1.0
- ✓ Sponsor ADaM Guideline

Pinnacle conformance was run using Pinnacle 21 Community version 2.2.0.

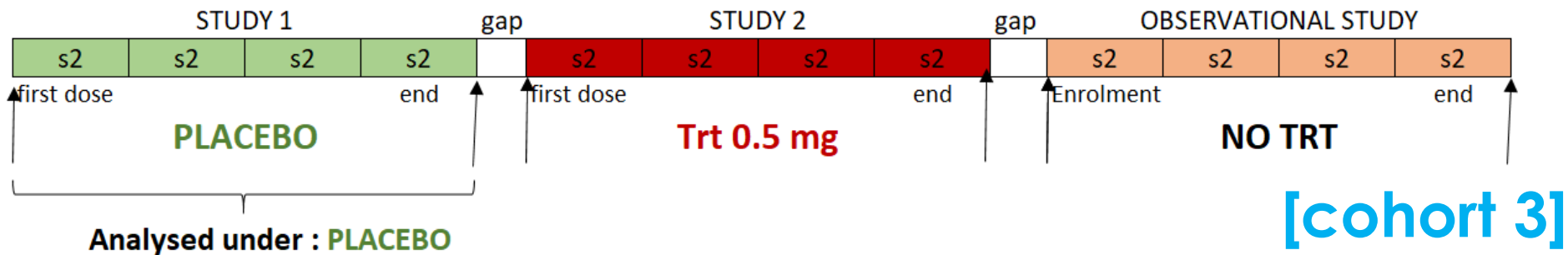
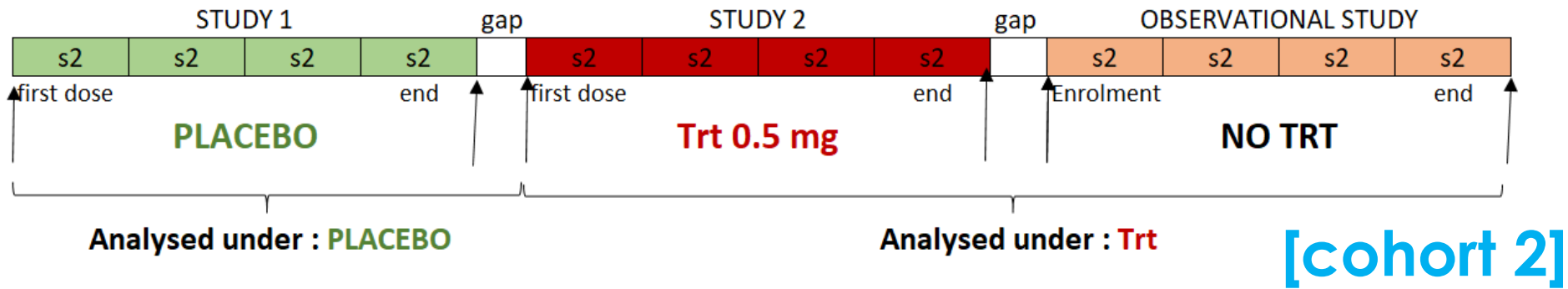
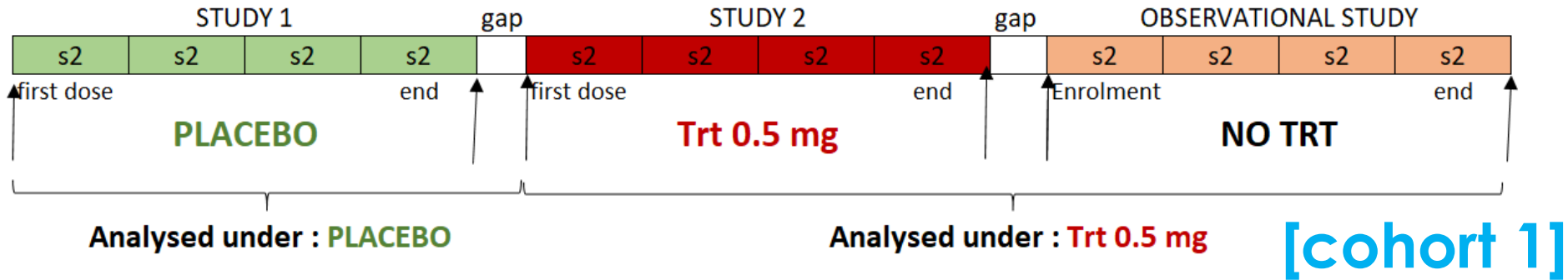
➤ References:

- ✓ Analysis Data Model Implementation Guide – version 1.1 prepared by CDISC Analysis Data Model Team
- ✓ CDISC ADaM Occurrence Data Structure (OCCDS) (Version 1.0)
- ✓ STUDY DATA TECHNICAL CONFORMANCE GUIDE - Technical Specifications Document – From U.S. Department of Health and Human Services Food and Drug Administration (Dated March 2018)
- ✓ ADAMINT-ADaMDataStructuresforIntegration-Compiled-180919-1017-730 – Version 1.0 Draft (Dated February 2018)

➤ Other discussed approaches:

- ✓ <https://www.lexjansen.com/pharmasug/2018/BB/PharmaSUG-2018-BB06.pdf>
- ✓ <https://www.pharmasug.org/proceedings/2019/AD/PharmaSUG-2019-AD-299.pdf>

Introduction: Subject 2



✓ Managing data from different sources:

❖ AE, ZA, CE.... → Axxx variables

✓ Managing different dictionaries

Table 3.2.10.1 Original or Prior MedDRA Coding Variables

Variable Name	Variable Label	Type	Codelist / Controlled Terms	Core	CDISC Notes
DECDORGw	PT in Original Dictionary w	Char	MedDRAw*	Perm	Original preferred term coding of XX.--TERM using MedDRA or other dictionary version X.X.
BDSYORGw	SOC in Original Dictionary w	Char	MedDRAw*	Perm	Original body system coding of XX.--TERM using MedDRA or other dictionary version X.X.
HLGTORGw	HLGT in Original Dictionary w	Char	MedDRAw*	Perm	Original HLGT coding of XX.--TERM using MedDRA or other dictionary version X.X.