



The Ultimate Integration Challenge

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Topics

- **Overview**
 - Provides high level overview of CDISC compliant data warehouse
- **Integration Challenges**
 - Data Variation and Harmonization
 - Derivations
- **Conclusion**
- **Questions**

Overview

This Presentation

- **Data challenges while CDISC compliant data warehouse was built for submission to FDA & EMA**
- **Challenges are limited on integration data associated with safety analyses**
- **High level overview of approach in dealing with large and complex data integration**
 - **Key data variation & harmonisation issues, how they were being dealt with**
 - **Some examples of derivations, how we overcame difficulties**
- **Best enhancement solutions for data displays**
 - **Consistency across phases**

Overview (Cont.)

More About the Integration

- 30 + Phases I – III studies
- 162 SDTMs, 226 ADaMs and 6,747 patients
- | By | Study | Patients |
|-----------|-------|----------|
| Phase III | 12% | 41% |
| Phase II | 15% | 40% |
| Phase I | 73% | 19% |
- Two phase III studies with > 12 months long-term data
- 70% of Phase I are clinical pharmacology PK & PD studies in healthy volunteers
- Special concerns and special populations

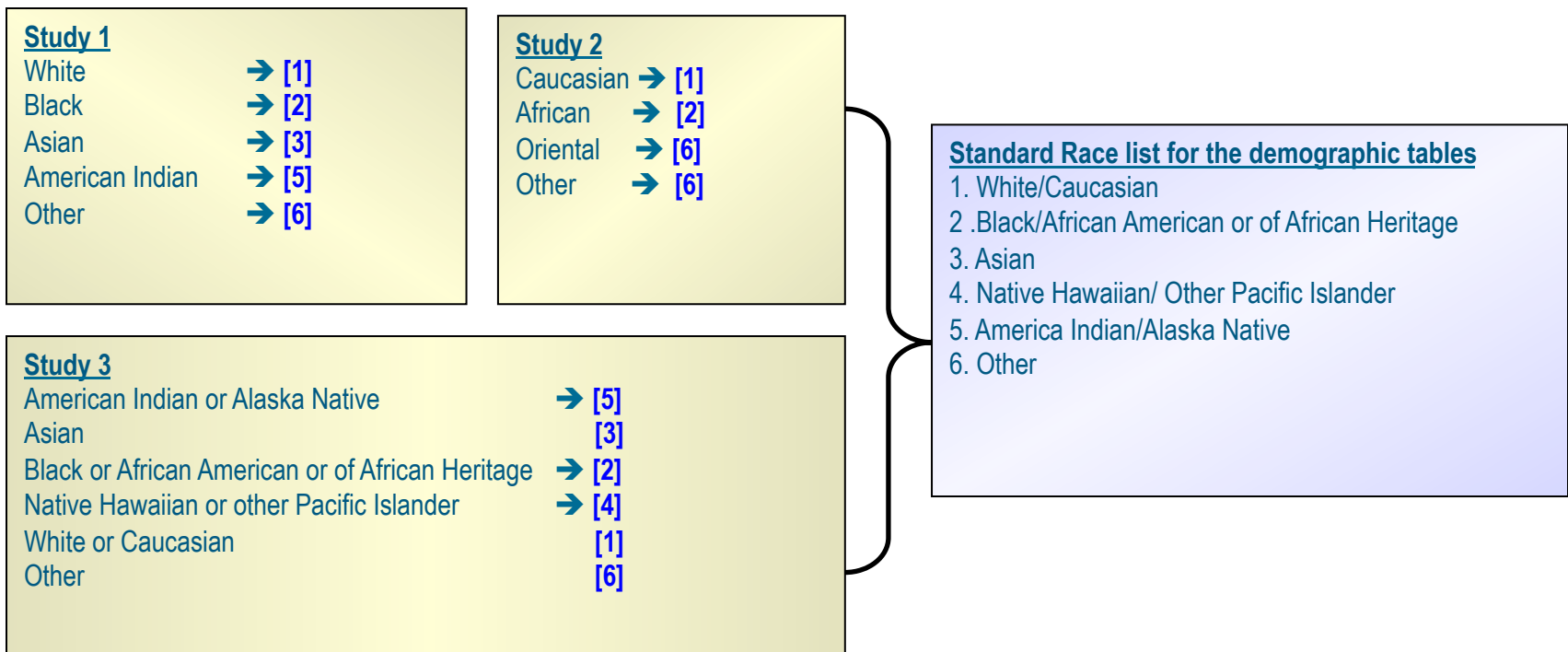
Data Variation and Harmonization

Data Variation and Harmonization

Race

Studies with SDTM, two step approach: Raw → SDTM → ADaM

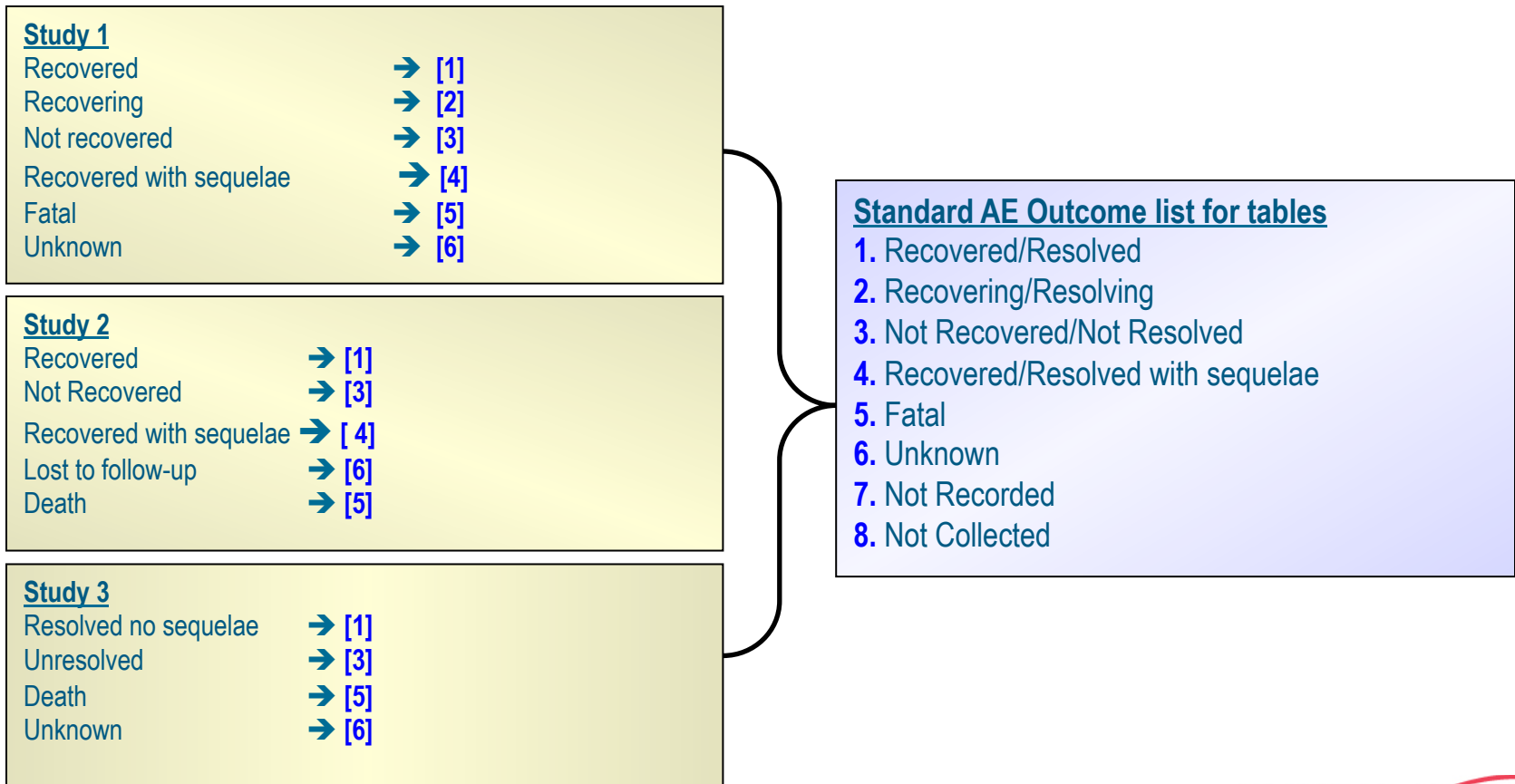
Studies with No SDTM: Raw → ADaM



Data Variation and Harmonization (Cont.)

AE outcome

The following illustrates the variations in recording AE outcome across studies and the mapping from individual study to a standard list.

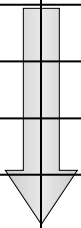


Data Variation and Harmonization (Cont.)

Vital Signs

Assessment numbers corresponding to each visit denoted the vital signs recording positions and the time interval between multiple tests

	Day 1	Day 2	Day 3	Week 1		Assmt No.	Description
Visit	2	2.5	3	4		-10	Given to all measurements at screening visit (visit 1)
Before dose	-1	71	71	71		-1	Given to all measurements taken before first IP dose at visit 2
1h after	72	72	72			71	Given to extra safety monitoring measurements taken before dose at visits 2.5, 3, 4
2h after	73	73	73			72	Given to extra safety monitoring measurements taken 1 hour after dose at visits 2, 2.5, 3
2-3h after				75		73	Given to extra safety monitoring measurements taken 2 hour after dose at visits 2, 2.5, 3
3h after	74	74	74			74	Given to extra safety monitoring measurements taken 3 hour after dose at visits 2, 2.5, 3
4h after	76	76	76			75	Given to extra safety monitoring measurements taken 2-3 hour after dose at visit 4
5h after	77	77	77			76	Given to extra safety monitoring measurements taken 4 hour after dose at visits 2, 2.5, 3
6h after	78	78	78			77	Given to extra safety monitoring measurements taken 5 hour after dose at visits 2, 2.5, 3
						78	Given to extra safety monitoring measurements taken 6 hour after dose at visits 2, 2.5, 3
						xx	For all measurements of supine BP and Pulse after 15 mins of resting
						xx.10	For all measurements of standing BP and Pulse after 2 mins of standing
						xx.20	For all measurements of standing BP and Pulse after 5 mins of standing
						xx = Assessment Number	



Data Variation and Harmonization (Cont.)

Variables in the Dataset

VSPOS	VISIT	VSTPT1	VSTPT2
Supine	2	Before intake of IP	After 15 mins of Resting
Standing	2.5	1 hour after administration of IP	After 2 mins of Standing
	3	2 hours after administration of IP	After 5 mins of Standing
	4	3 hours after administration of IP	
		4 hours after administration of IP	
		5 hours after administration of IP	
		6 hours after administration of IP	

No format is available to decode the assessment numbers in order to identify the position and the time interval between two readings of the same BP test. Format had to be created using the study flow chart.

Data Variation and Harmonization (Cont.)

Laboratory Data

- Phase II lab data had most inconsistencies and variations
 - test code values
 - non standard units
 - PCS criteria differed

1	LAB CATEGOR	RAW LAB TEST SHORT NAME	RAW LAB TEST NAME	NEW LAB SHORT TEST NAM	NEW LAB TEST NAME
2	CHEMISTRY	XGP	ALAT (SGPT)	ALT	ALANINE AMINOTRANSFERASE
3	CHEMISTRY	ALAT		ALT	ALANINE AMINOTRANSFERASE
4	CHEMISTRY	XAL	ALBUMIN	ALB	ALBUMIN
5	CHEMISTRY	Alb		ALB	ALBUMIN
6	CHEMISTRY	XLK	ALKALINE PHOSPHATASE	ALP	ALKALINE PHOSPHATASE
7	CHEMISTRY	ALP		ALP	ALKALINE PHOSPHATASE
8	CHEMISTRY	XGO	ASAT (SGOT)	AST	ASPARTATE AMINOTRANSFERASE
9	CHEMISTRY	ASAT		AST	ASPARTATE AMINOTRANSFERASE
10	CHEMISTRY	StBic		C02	BICARBONATE
11	CHEMISTRY	XBT	BILIRUBIN, TOTAL	BILI	BILIRUBIN, TOTAL
12	CHEMISTRY	Bili, tot		BILI	BILIRUBIN, TOTAL
13	CHEMISTRY	UN		BUN	BLOOD UREA NITROGEN
14	CHEMISTRY	Urea		BUN	BLOOD UREA NITROGEN
15	CHEMISTRY	XUN	UREA NITROGEN	BUN	BLOOD UREA NITROGEN
16	CHEMISTRY	XAB	CALCIUM	CA	CALCIUM
17	CHEMISTRY	Ca		CA	CALCIUM
18	CHEMISTRY	Cl		CL	CHLORIDE
19	CHEMISTRY	XCH	CHOLESTEROL, TOTAL	CHOL	CHOLESTEROL, TOTAL

Derivations

Derivations

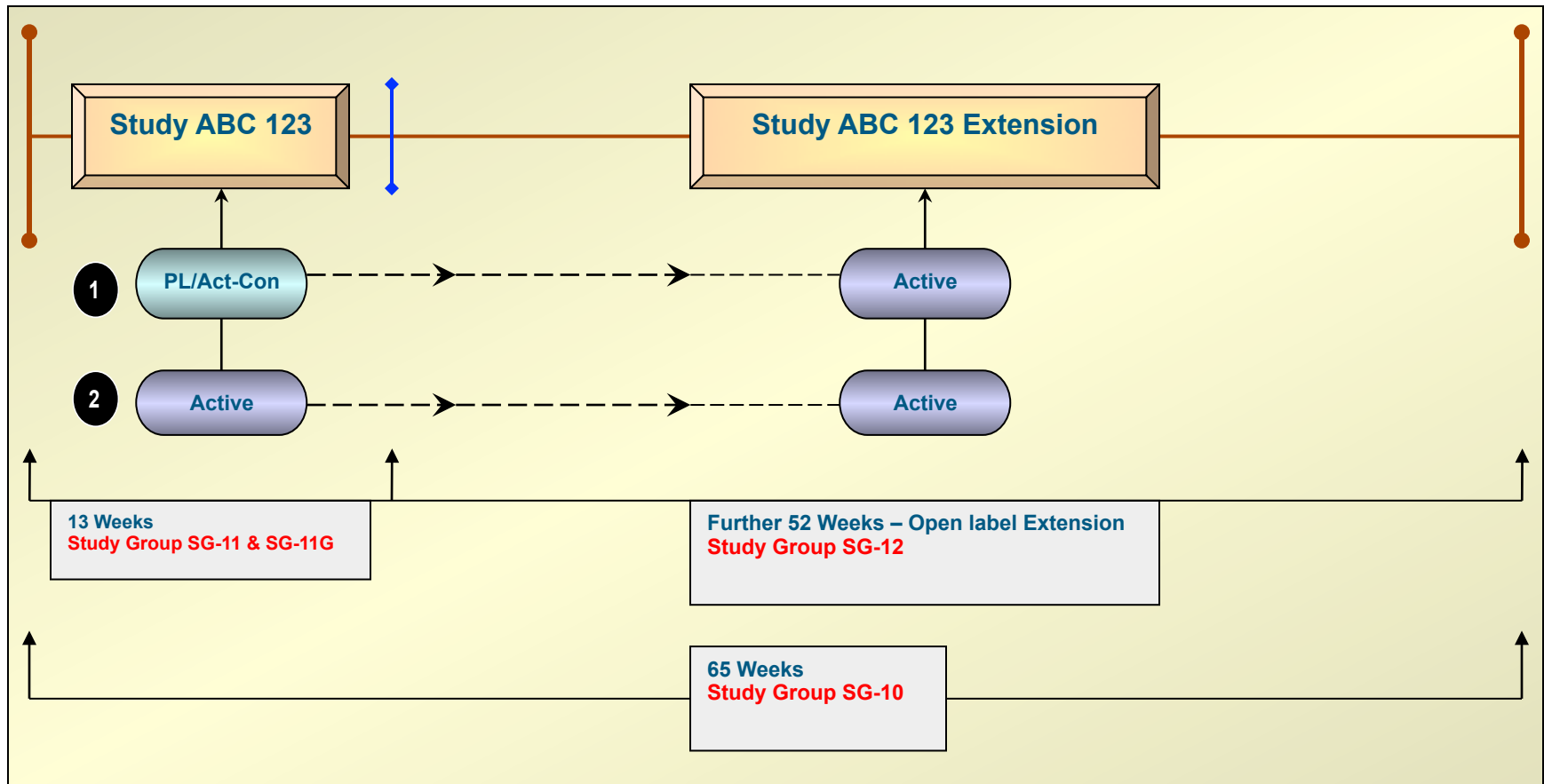
Study Group

Four study groups (Groups 1 – 4). Each group had sub-groups. Different studies contributed to different treatment groups within each study group. Multiple sub-groups were based on population studied, study design, treatment exposure and period of interest.. For example, within Group 1 (SG10, 11, 12, 13 and 14).

Sub-Group	Description
SG-10	Completed Phase 2/3 Clinical Studies
SG-11	All Placebo-Controlled Studies (all data up to 13 Weeks)
SG-11A	All Placebo-Controlled Studies (all data up to 13 Weeks) by Age, Gender, Race
SG-11B	All Placebo-Controlled Studies (all data up to 13 Weeks) by Specific Body Site
	... etc for other characteristics of interest
SG-12	Open-Label (Extension)
SG-13	Only patients with ≥ 26 weeks of treatment exposure
SG-14	Only patients with ≥ 52 weeks of treatment exposure
SG-20	Placebo-Controlled Studies in Healthy Subjects
SG-31	Single-Dose Studies in Healthy Subjects
SG-32	Multiple-Dose Studies in Healthy Subjects
SG-41	Blood Pressure Monitoring Studies
SG-42	Special Populations

Derivations (Cont.)

Example



Derivations (Cont.)

1

A patient randomized and treated with different IMPs in both studies. As displayed in the previous slide

- For study group SG-11 and SG-11G, the exposure will only include either Placebo (PL) or Active Control (Act-Con) Treatment
- For study group SG-12, the exposure will only include Active Treatment
- For study group SG-10, the exposure will include both Placebo and Active Treatment. Here, the patient was counted in more than one treatment group

2

A patient randomized and treated with the same IMP in both studies. As displayed in previous slide

- For study group SG-11 and SG-11G, the exposure will only include the first study i.e first 13 weeks of Active Treatment
- For study group SG-12, the exposure will only include the extension period i.e 52 weeks of Active Treatment
- For study group SG-10, the exposure will include the whole Active Treatment Period across both studies (13 + 52 weeks). Here, the patient was counted just once under the Active Treatment group

Derivations (Cont.)

Adverse Events

- MedDRA version 11.0
- AEs were categorized by System Organ Class (SOC) and Preferred terms (PT).
- Only treatment emergent AEs were reported
- Most complex derivations were from phase 1 cross-over studies
- Onset of event associated to the start of individual treatment phase and not the start of the first dose
- AE can be associated with more than one treatment if it increased in severity/seriousness/relationship
- Placebo run-in: any AEs that started during the placebo run-in were not treatment emergent
- AEs that became treatment-emergent during placebo wash out were assigned to the last active treatment received.
- The study day of the start of the AEs was created to validate derivations

Derivations (Cont.)

Baseline and Endpoints (Lab, ECG and Vital Signs)

- Baseline
 - Initially baseline definitions as per CSR
 - Discrepancies found where time for tests collected after time of first IMP
 - Revision of baseline definition for some patients
 - New flag for baseline
- Endpoint
 - Initially applied global endpoint definition
 - Last post-baseline visit before the follow-up visit.
 - Exclusion of some endpoint values
 - Revision was necessary to follow endpoint definition for pivotal studies
 - For each Vital Signs test it was the last non-missing post-baseline visit for each test
 - For ECG and Laboratory test it was using the last non-missing on-treatment post-baseline visit

Conclusion

- ☐ **Good opportunity**
- ☐ **Steep learning curve**
- ☐ **Team is more CDISC aware, more knowledgeable and experience**
- ☐ **For the next integration, we will –**
 - ☐ **be able to identify ALL data variations in different studies across all phases and harmonise it before programming commences**
 - ☐ **identify data issues to be addressed to conform with CDISC requirements**

Questions

