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24-25 APRIL: CONFERENCE & EXPO | 22, 23, 26 APRIL: TRAININGS

Visualizing ADaM: A Practical Guide Through Examples

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Meet the Speakers

Silvia Faini, Principal Statistical Programmer, Project Based Service (PBS), Cytel Inc.

Silvia Faini has a degree in Statistics, 15 years of experience in clinical trials. During her working experience she acted as Biostatistician and then as Statistical Programmer having the chance to develop standard SAS macros and implement CDISC standards. As Principal Statistical Programmer she gained wide experience in submissions, CDISC ADaM, SDTM and define-xml and in medical device. Active member of Italian CDISC UN, E3C and, previously, also of CDISC Medical Device team.

Angelo Tinazzi, Senior Director - Standards, Systems, CDISC Consulting, Statistical Programming, PBS, Cytel Inc.

Angelo Tinazzi, Senior Director, Statistical Programming, responsible for Clinical Data Standards and Data Submission. Angelo has about 30 years of experience.

In his role at Cytel, Angelo lead data standards initiatives as well supporting applications development and automation initiatives.

Angelo is a CDISC ADaM Authorized Instructor and member of the CDISC European Coordinating Committee where he is also leading Italian speaking User Network.
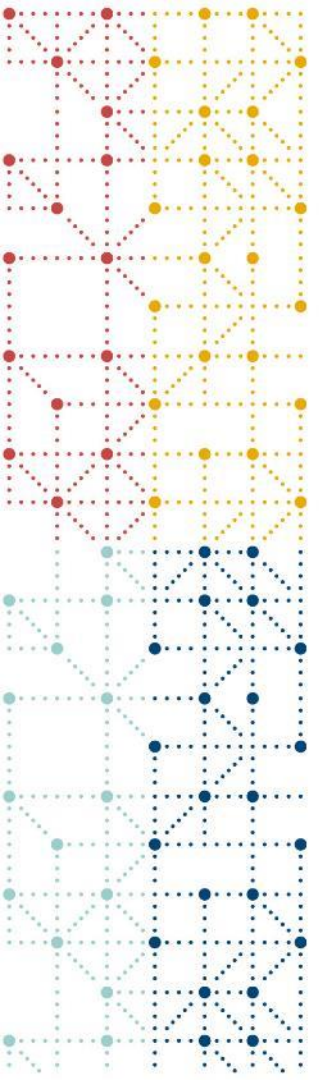
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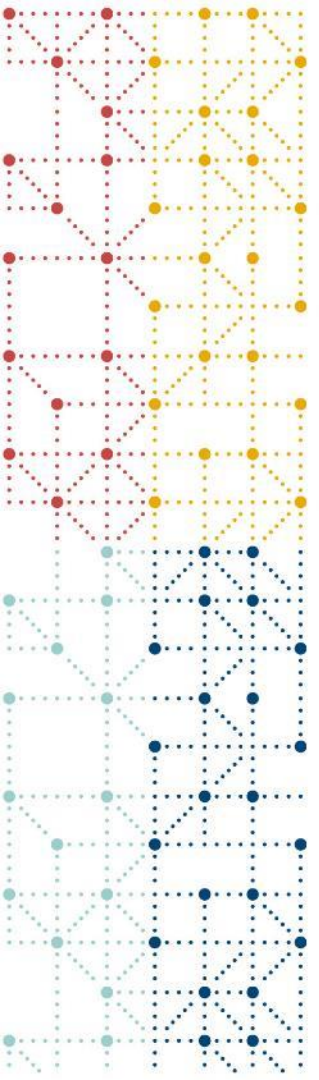
Agenda

1. Why a visual approach?
2. Visualizing ADaM Examples
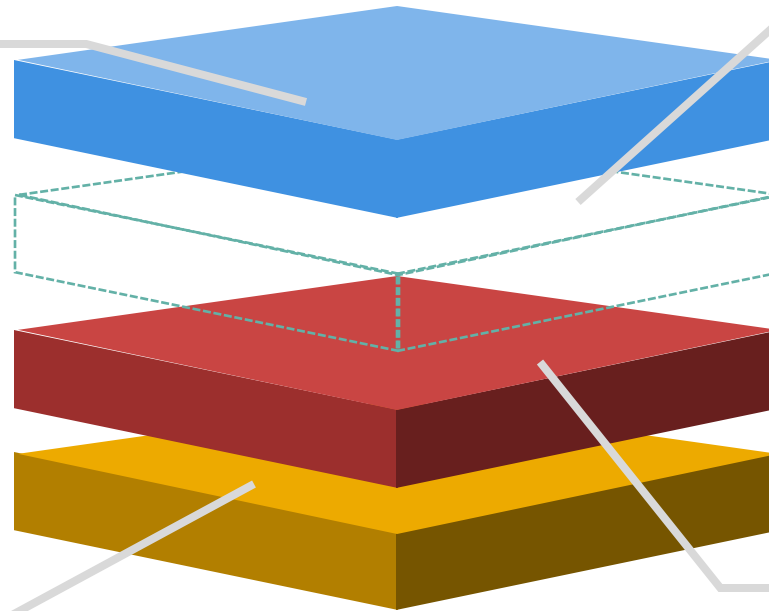3. Next steps and takeaways

Why a visual approach?

Why a visual approach?

ADaM specifications and datasets

CDISC Guidelines:

- ADaM Examples in Commonly Used Statistical Analysis Methods
- ADaM Basic Data Structure (BDS) for Time-to-Event (TTE) Analyses
- ADaM IG for Non-compartmental Analysis Input Data
- Basic Data Structure for ADaM popPK Implementation Guide
- ADaM IG for Medical Devices
- ADaM Examples of Traceability
- TAUGs

Statistical programmer expertise + Standard Governance Team

Study documents:

- Protocol
- Statistical Analysis Plan
- Mock shells

Why a visual approach?

ADaM specifications and datasets

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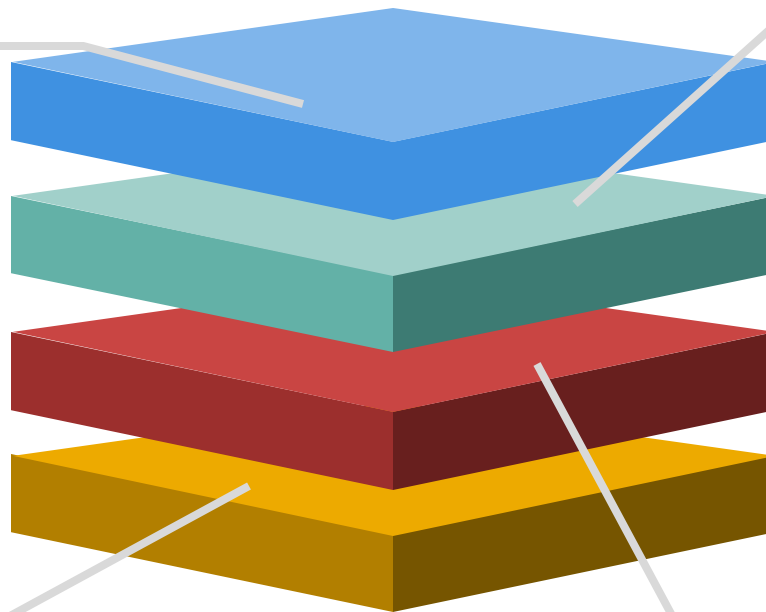
ADaM Visualization Tool:

- Annotated standard mock shells
- ADaM dataset visual sample
- In addition to Statistical programmer expertise + Standard Governance Team

Study documents:

- Protocol
- Statistical Analysis Plan
- Mock shells

Why a visual approach?

Guarantee ADaM Principles

- How to **achieve traceability** through ADaM datasets and their documentation
- How to design ADaM datasets to facilitate their '**analysis-readiness**'
- **Specific implementation** topics (e.g. which standard ADaM variable to use when grouping, classifying, or flagging observation for specific criteria)

Cytel ADaM Visual Approach

- Visual shells based on Cytel standard SAP table shells:
  - Annotated ADaM dataset and variables to be used, filters and other conditions
- ADaM datasets "Visual" sample
- Standard specs for Cytel automation-tools
- Internal training to statistical programmers
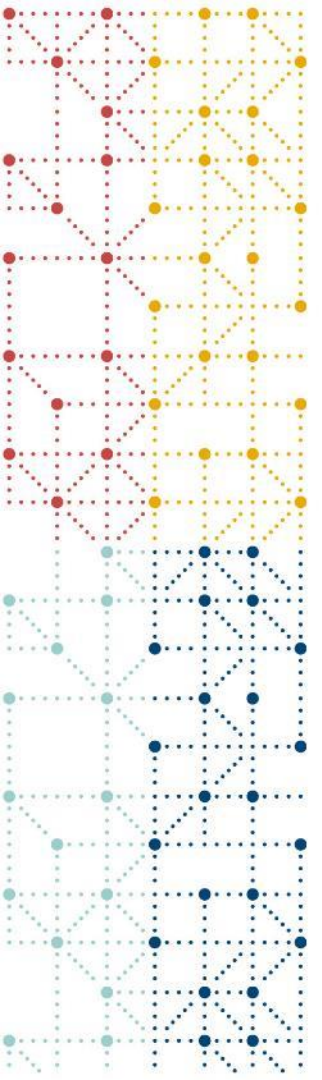
Visualizing ADaM Examples

Key Questions – Informative Answers

Questions

Filters on population flags	Check presence in ADSL
Filters on analysis flags, occurrence flags	This is one of the element which helps ADaM Class identification
Treatment Variables	Planned/actual, pooled treatment group
Statistics on continuous variables	CHG, PCHG are needed. One or more BASETYPE.
Statistics on categorical variables	Derive both numeric and character versions for sorting flexibility
Events/Medications frequencies	OCCDS class, presence of all required hierarchical levels

Answers

ADaM Visual 1: Demographics

- ADaM Class: **ADSL**

- Because the table is on the Safety Population subset (**SAFFL=Y**), the Actual Treatment Variable should be used as column group (e.g., **TRT01AN**)

- Despite numeric version of variables such as **SEX** and **RACE** are permissible, it is a good practice to also add the numeric version to facilitate tool automation and the desired sorting in the outputs (not alphabetic) e.g., **SEXN** and **RACEN**.

- In addition to **AGE** analyzed with continuous descriptive stats (copied from SDTM), the age is required to be analyzed in category, and the standard ADSL variable **AGEGR1** and its numeric version **AGEGR1N** are added to ADSL.

[ADSL] **[SAFFL = Y]** **[TRT01AN]**

Table 14.1.2: Demographics - Safety Analysis Set

	Placebo (N=XXXX)	Active Drug (N=XXXX)	All Subjects (N=XXXX)
Age (Years) **[AGE]**			
n (missing)	xxx (x)	xxx (x)	xxx (x)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x
Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
Min ; Max	xx ; xx	xx ; xx	xx ; xx
Age Categories, n(%) **[AGEGR1 / AGEGR1N]**			
n (missing)	xxx (x)	xxx (x)	xxx (x)
<25	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
25-39	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
40-49	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
50-59	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>=60	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Sex, n(%) **[SEXN / SEX]**			
n (missing)	xxx (x)	xxx (x)	xxx (x)
Male	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Female	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Race, n(%) **[RACEN / RACE]**			
n (missing)	xxx (x)	xxx (x)	xxx (x)
White	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Black or African American	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Asian	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Native Hawaiian or Other Pacific Islander	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
American Indian or Alaska Native	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Multiracial	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

ADaM Visual 2: Adverse Events Incidence

[ADAE]   **[TRTEMFL = Y]**   **[SAFFL = Y]**

Table 14.3.1.2: Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term - Safety Analysis Set

[TRT01AN]

System Organ Class Preferred Term	Placebo (N=XXXX) n (%)	Active Drug (N=XXXX) n (%)	All Subjects (N=XXXX) n (%)
[AEBODSYS] **[AEDECOD]**			
Subjects with at least one TEAE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Uncoded	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Term 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Term 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
System Organ Class 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
System Organ Class 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

A TEAE is defined as an AE whose date of onset occurs after the first dose of study drug through the follow up visit

- ADaM Class: **OCCDS** / Sub-Class: **ADVERSE EVENT**

- In addition to the Safety Population subset (**SAFFL=Y**), and the appropriate treatment variables (e.g., **TRT01AN**) to be used as column group.

- Due to ADVERSE EVENT is a sub-class of the OCCDS class, as such the variables **AEBODSYS** and **AEDECOD** became "Required".

- For this type of analysis only the treatment emergent adverse event (**TRTEMFL=Y**) should be used

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ADaM Visual 3a: Adverse Events Overview

[ADAE]   [TRTEMFL = Y]   [SAFFL = Y]

Table 14.3.1.1: Overview of Treatment-Emergent Adverse Events - Safety Analysis Set

	Placebo (N=XXXX) n (%)	Active Drug (N=XXXX) n (%)	All Subjects (N=XXXX) n (%)
[TRT01AN]			
[TRTEMFL = Y]			
Subjects with at least one TEAE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
[AESER = Y]			
Subjects with at least one Serious TEAE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
[AEACN = DRUG WITHDRAWN]			
Subjects with TEAE leading to Withdrawal of Study Drug	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
[AEACNOTH = LED TO STUDY TERMINATION]			
Subjects with TEAE leading to Withdrawal from Study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
[AEOUT = FATAL]			
Subjects with TEAE leading to death	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
[ASEVN / ASEV where AOCCIFL=Y]			
Subjects with TEAE by Worst Severity			
Mild	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Moderate	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Severe	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Option 1

- ADaM Class: **OCCDS** / Sub-Class: **ADVERSE EVENT**

- the Safety Population subset (**SAFFL=Y**), and the appropriate treatment variables (e.g., **TRT01AN**) to be used as column group

- Each condition needed for the summary output can be represented by a selection from ADAE (e.g. **AEOUT=FATAL**) or numeric/character variables **ASEVN** / **ASEV** with additional filter (**AOCCIFL=Y**).

- **TRTEMFL=Y** is needed if Treatment Emergent AEs are the target of the table, if similar output must be produced for different selection, another flag is annotated (e.g., **PREFL**, **FUPFL**, **ANLzzFL**).

ADaM Visual 3b: Adverse Events Overview

[ADAESUM]   [SAFFL = Y]

Table 14.3.1.1: Overview of Treatment-Emergent Adverse Events - Safety Analysis Set

	Placebo (N=XXXX) n (%)	Active Drug (N=XXXX) n (%)	All Subjects (N=XXXX) n (%)
[TRT01AN]			
[count AVALC = Y where PARAMCD = ANYTEAE]			
Subjects with at least one TEAE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
[count AVALC = Y where PARAMCD = ANYTESAE]			
Subjects with at least one Serious TEAE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
[count AVALC = Y where PARAMCD = EOT]			
Subjects with TEAE leading to Withdrawal of Study Drug	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
[count AVALC = Y where PARAMCD = EOS]			
Subjects with TEAE leading to Withdrawal from Study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
[count AVALC = Y where PARAMCD = DEATH]			
Subjects with TEAE leading to death	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
[AVAL / AVALC where PARAMCD = WSEV]			
Subjects with TEAE by Worst Severity			
Mild	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Moderate	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Severe	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Option 2

- ADaM Class: **BDS**

- the Safety Population subset (**SAFFL=Y**), and the appropriate treatment variables (e.g., **TRT01AN**) to be used as column group

- Each condition needed for the summary output can be represented with the count of specific **PARAMN** / **PARAMCD** / **PARAM** with **AVAL** / **AVALC**.

ADaM Visual 3b: Adverse Events Overview

#	USUBJID	PARAMN	PARAMCD	PARAM	AVAL	AVALC
1	001-001	1	ANYTEAE	Subject with at least one TEAE	1	Yes
2	001-001	2	ANYTESAE	Subject with at least one Serious TEAE	0	No
3	001-001	3	EOT	Subject with at least one TEAE …. Study Drug	1	Yes
4	001-001	4	EOS	Subject with at least one TEAE …. From Study	0	No
5	001-001	5	AESEV	Subject with TEAE by Worst Severity	2	Moderate
6	001-001	..	..	..	..	..
7	001-002	1	ANYTEAE	Subject with at least one TEAE	0	No
8	001-002	..	..	..	..	..
9	..	..	..	..	..	..

Table 1: ADAESUM Example

PROs:

- when subset of AEs to be included into table are clearly defined and no further analysis is needed: e.g. same frequencies to be presented for TEAEs, Follow-Up AEs and AESI subset

- BDS facilitates QC: doble programming at ADaM level, and a smoother outputs creation

CONs:

- additional dataset to be created and double programmed

- Complex metadata

ADaM Visual 4: Change from Baseline with Baseline derivation

```
[ADVS]                [PARAMCD = XXXXX]    [ANL01FL = Y]   [SAFFL = Y]
Table 14.3.3.1: Summary of Vital Signs Parameters and Change from Baseline by Visit - Safety Analysis Set

[AVISITN / AVISIT]

                        Observed/                      All Subjects
Analysis Visit          Change              Statistics    (N=XXX)

Baseline                Observed            n (missing)    xxx (x)
                                            Mean (SD)    xx.xx (x.xx)
                        [AVAL]              Median         xx.xx
                                            Q1 ; Q3     xx.xx ; xx.xx
                                            Min ; Max   xx.x ; xx.x

<Visit 1,Visit 2,...>   Observed            n (missing)    xxx (x)
                                            Mean (SD)    xx.xx (x.xx)
                        [AVAL]              Median         xx.xx
                                            Q1 ; Q3     xx.xx ; xx.xx
                                            Min ; Max   xx.x ; xx.x

<Visit 1,Visit 2,...>   Change from Baseline n (missing)   xxx (x)
                                            Mean (SD)    xx.xx (x.xx)
                        [CHG]               Median         xx.xx
                                            Q1 ; Q3     xx.xx ; xx.xx
                                            Min ; Max   xx.x ; xx.x

Output ID: t_vs_chg1 DDMMMYY HH:MM <PROJECT/TASK LOCATION>..\t_vs_chg1.sas
                                                          Page 1 of x
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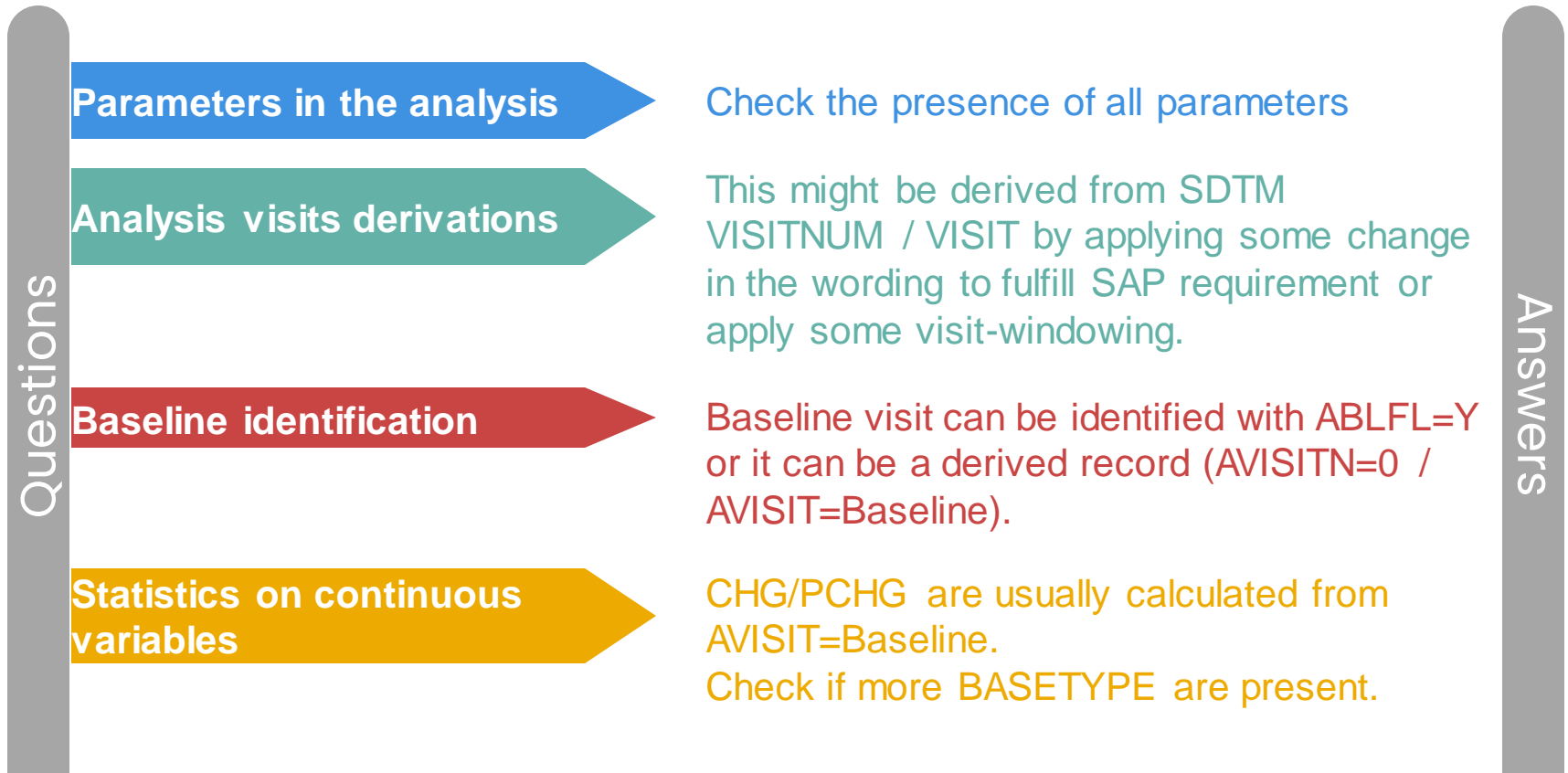
- ADaM Class: **BDS**

- the Safety Population subset (**SAFFL=Y**) and only records valid for the analysis (**ANL01FL=Y**) and for parameters specified (e.g. **PARAMCD=SYSBP**)

- The Analysis Visit is derived in ADVS (**AVISITN / AVISIT**) → details in dataset example

- **AVAL** and **CHG** are used for observed and change from baseline respectively.

# ADaM Visual 4: Change from Baseline with Baseline derivation

Questions

Parameters in the analysis	Check the presence of all parameters
Analysis visits derivations	This might be derived from SDTM VISITNUM / VISIT by applying some change in the wording to fulfill SAP requirement or apply some visit-windowing.
Baseline identification	Baseline visit can be identified with ABLFL=Y or it can be a derived record (AVISITN=0 / AVISIT=Baseline).
Statistics on continuous variables	CHG/PCHG are usually calculated from AVISIT=Baseline. Check if more BASETYPE are present.

Answers

ADaM Visual 4: Change from Baseline with Baseline derivation

#	PARAMCD	PARAM	AVAL	ABLFL	BASE	CHG	AVISITN	AVISIT	VISITNUM	VISIT	ANL01FL	DTYPE
1	SBP	Systolic Blood Pressure	123				-1	Screening	1	Screen		
2	SBP	Systolic Blood Pressure	127				-2	Day-0	2	D0		
3	SBP	Systolic Blood Pressure	125	Y			0	Baseline	.		Y	AVERAGE
4	SBP	Systolic Blood Pressure	127		125	2	1	Week 1	3	Wk 1	Y	
5	SBP	Systolic Blood Pressure	135		125	10	1.1	Unsch	3.1	Unsch Wk 1		
6	SBP	Systolic Blood Pressure	..		..		..		..		Y	
7	DBP	Diastolic Blood Pressure	88				-1	Screening	1	Screen		
8	DBP	Diastolic Blood Pressure	84				-2	Day-0	2	D0		
9	DBP	Diastolic Blood Pressure	86	Y			0	Baseline	.		Y	AVERAGE
10	DBP	Diastolic Blood Pressure	84		86	-2	1	Week 1	3	Wk 1	Y	
11	DBP	Diastolic Blood Pressure	88		86	2	1.1	Unsch	3.1	Unsch Wk 1		
12	DBP	Diastolic Blood Pressure	88		86	2	2	Week 2	4	Wk 2	Y	
13	..	..	..		..		..		..			

Table 2: ADVS example with Baseline phantom visit (USUBJID, PARAMN and traceability variables such VSSEQ omitted from the example)

Table shows the ADaM dataset:

- lines 3 and 9 show the derive baseline visit with DTYPE variable which identifies it and the method used for the derivation (AVERAGE). ABLFL is set to 'Y'

- lines 1, 2, 7 and 8 will be not used in the analysis (ANL01FL=Null) because they occurred before the phantom derived "Baseline" visit, but kept in the ADaM dataset showing traceability e.g., from which the Baseline visit was derived

- lines 5 and 11 will not be used in the analysis (ANL01FL=Null) because they were unscheduled visits. However, the records are kept in the ADaM dataset showing traceability so that reviewer is aware which information were not used in the analysis. Eventually, if AVISIT/AVISTN are derived using some windowing.

- all records post baseline have the change from baseline (CHG) derived, including the unscheduled visits
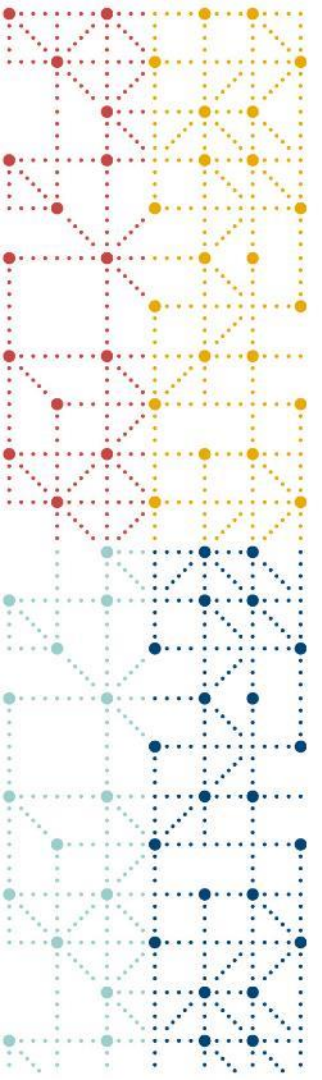
Takeaways and Next steps

Takeaways

PROs – Speed up

- Beneficial to ADaM newcomers
- Speed up ADaM specifications and programming
- Speed up standard outputs production
  - More time to focus on non-standard outputs which are usually more challenging than standard ones

PROs - Automation

- Integration with other Cytel automation tools
  - Lighthouse
  - ALPS
  - PRISM

Next steps

New layouts

- Programmers can internally share the challenges found in ADaM creation / output programming
- Evaluate if this can trigger a new mock shell annotation
- Speed up of production of the same layout in the future

Integration and Automation

- More background integration of Cytel automation tools
- R-Shiny

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Thank You!

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References

- PHUSE EU Connect 2023, AD16 "Leveraging the Analysis Results Standard (ARS): The Cytel PRISM Experience" S. Barceló, N. Rouillé, A. Tinazzi, Cytel Inc.

- PHUSE EU Connect 2022, DS04 "From Artifact to Metadata: A Divergent Approach to Automation through Standardization" N. Rouillé, C. Britton, A. Tinazzi, Cytel Inc.

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Abstract

With this presentation we would like to present ADaM in a unique and innovative perspective, by guiding through practical examples the audience, "catering" both novice and advanced users. The presentation begins with a straightforward illustration, visually walking the audience through hypothetical Statistical Analysis Plan (SAP) outputs, assist with the identification of the most suitable ADaM class/structure and selecting the right derived variables for analysis-ready and traceable ADaM datasets.

Building upon this foundation, the session delves into more complex scenarios, showcasing techniques such as the creation of phantom records for intricate baseline identification and handling complex study endpoints. We'll also explore approaches for identifying analysis periods in studies with complex designs, such as cross-over and multi-treatment therapy.

Novice users will gain a structured introduction to ADaM principles, understanding fundamental concepts and best practices. Concurrently, advanced users will delve into optimizing ADaM implementation for varied study designs, gaining valuable insights.

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