Cytel
Shaping the Future of Drug Development

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Real World Evidence
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Pitfalls with an Observational long-term safety registry : A practical Experience

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CONTENTS

To complete the long-term safety profile of a compound for one of our sponsor, an **observational long-term safety registry was conducted**. **Subjects participated in one of the clinical trials (“mother” studies) of the same compound / program, were allowed to be enrolled into the study**.

Cytel was responsible for the SDTM mapping and analysis of the study; moreover, for analysis purposes, the **data from the “mother” studies had to be used**. The study was finally part of the FDA submission package for the final approval of the drug in 2018.

With our presentation we want to share our experience and the issues we encountered mainly during the **SDTM mapping** and the analysis of this study, including the creation of the **ADaM datasets**.

Examples of issues or special situations we had to handle are but not limited to:

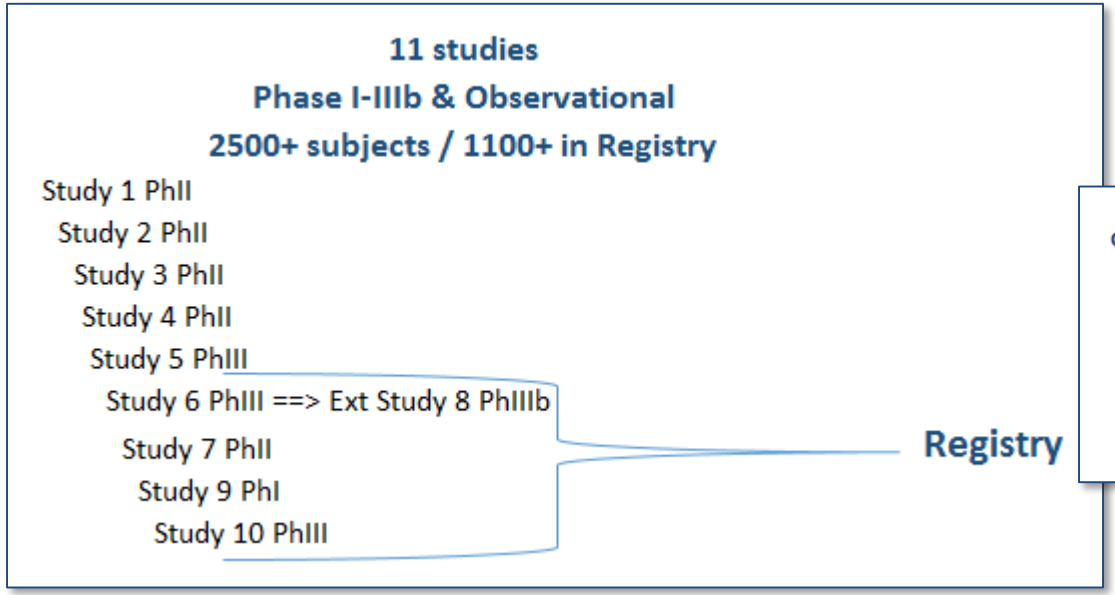
- Data Management / Data-Quality Issues
- Conformance / Compliance with data collected in the “mother” studies
- Handling of Associated Person Data in SDTM and in the analysis
- Pooling information from “mother” studies in ADaM

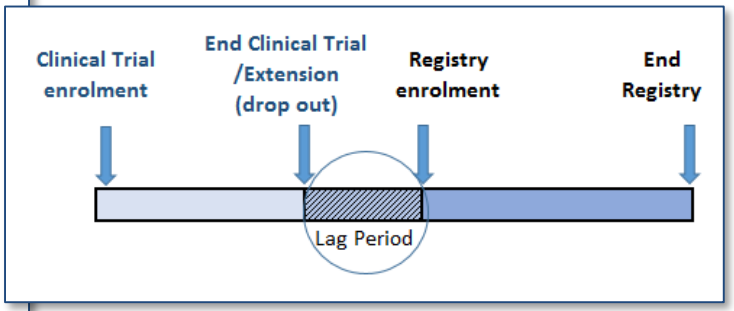
Introduction

How this presentation fits in the « Real Word »

Study characteristics

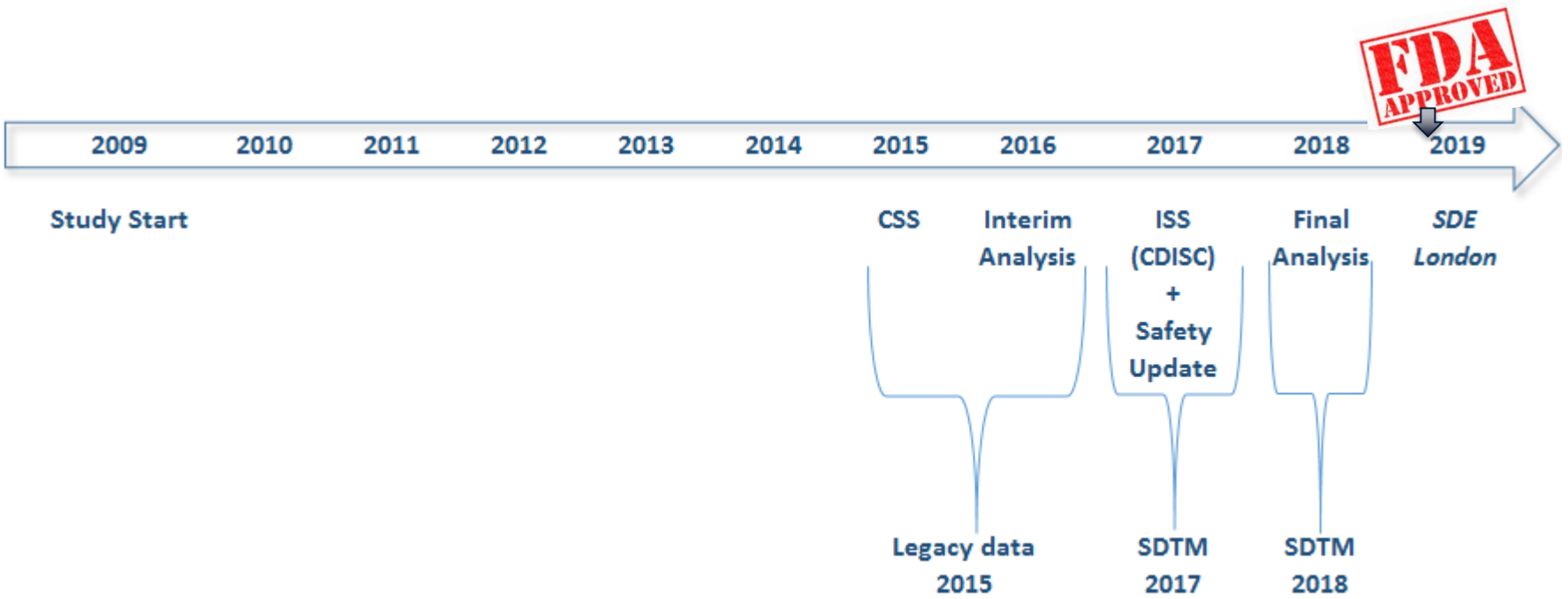
How this presentation fits in the « Real Word »





- **Prospective** overall – some **retrospective** data collection
- 8 years duration – routine visits, phone interviews….

Study Characteristics

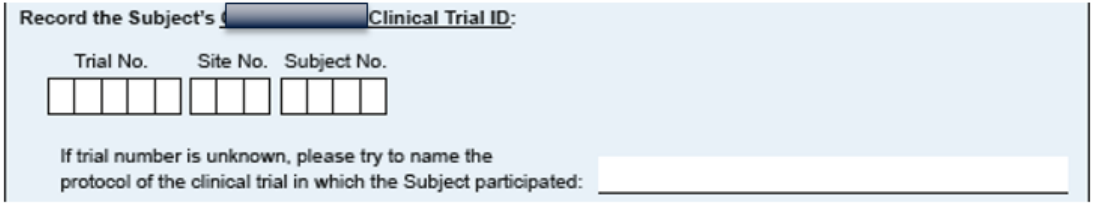


Data-Management Issues

Mapping USUBJID to the “Mother” Studies

Comparison with data mapped in the “Mother” Studies

Mapping USUBJID to the "Mother" Studies



	Clinical Trial ID	Clinical Trial Site	Clinical Trial Subject Identifier	Subject Identifier
1	11111	000	1234	000009990001
2	11111	000	1234	000009990002

Subject "00000999001", Birth Date = 02-Dec-1940, Sex= Female

Subject "00000999002", Birth Date = 09-Feb-1963, Sex= Male

- Core study ➔ select subject with same Birth Date & Sex
- Ignored **all** data from remaining subject

== PREVSTUD=Clinical Trial study id – no standard for this..(yet) ==

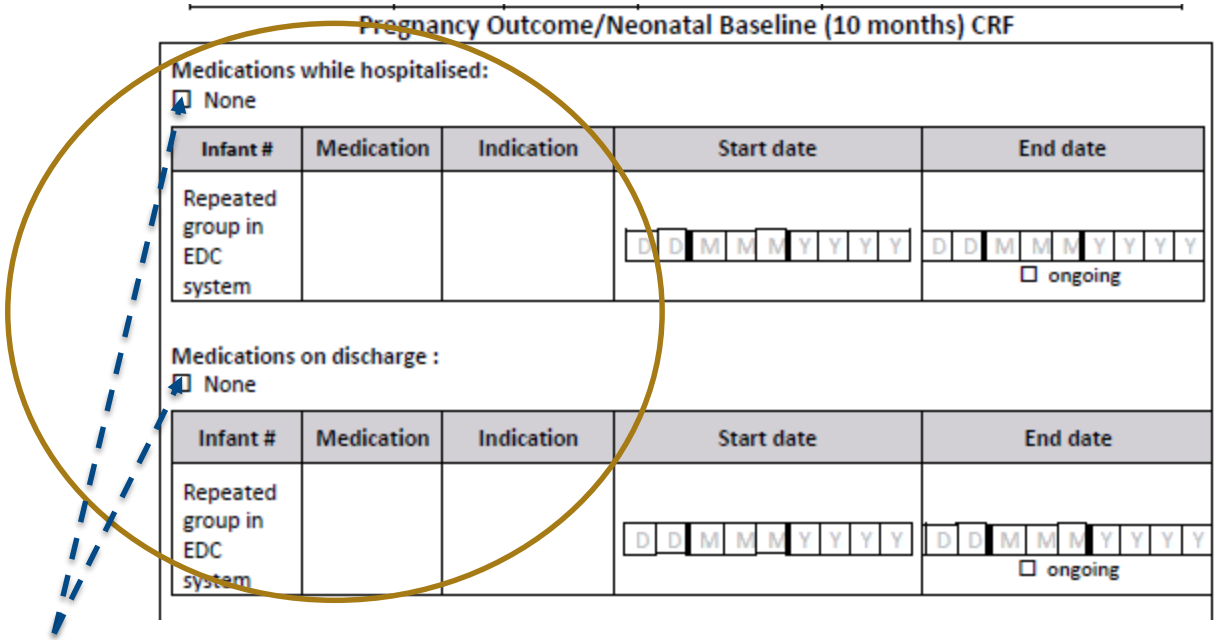
Mapping USUBJID to the "Mother" Studies

- Ran a few frequency counts on characteristics just for information:
  - 89% with same DOB
    - 5% DOB missing (at the time), 6% with different DOBs
  - 94% same SEX
    - 6% missing, .4% different
  - 77% same Initials
    - 6% missing, 17% differences

! All other Trial/site/subject number mismatches excluded from analyses !

Big Challenge in RWD to correctly map subject

Comparison with data mapped in the "Mother" Studies



Pregnancy Outcome/Neonatal Baseline (10 months) CRF

Medications while hospitalised:

☐ None

Infant #	Medication	Indication	Start date	End date
Repeated group in EDC system			D D M M M Y Y Y Y	D D M M M Y Y Y Y ☐ ongoing

Medications on discharge :

☐ None

Infant #	Medication	Indication	Start date	End date
Repeated group in EDC system			D D M M M Y Y Y Y	D D M M M Y Y Y Y ☐ ongoing

Coded with WHODrug

Comparison with data mapped in the "Mother" Studies

Has the infant/child been hospitalised for any reason? ☐ Yes ☐ No ☐ Unknown

↳ If yes, do you know the reason for the hospitalisation ☐ Yes ☐ No

↳ If yes, please provide all reasons for hospitalisation and the duration:

	Reason for hospitalisation	Duration of hospitalisation (days)
1		
2		

Pregnancy Outcome/Neonatal Baseline (10 months) CRF

Were any congenital malformations/anomalies diagnosed in the neonatal period?	☐ Yes, describe: _____ ☐ No ☐ Unknown

NEW DIAGNOSES

New diagnoses/conditions since completing or discontinuing the [redacted] trial:

☐ None ☐ Already captured on the subject lag-interval CRF

Diagnosis/Condition	Date of diagnosis		
☐ Cancer	D D M M M Y Y Y Y ☐ unknown	☐ Recovered ☐ Not yet recovered	Cancer type: _____ ☐ Incident ☐ Recurrent Metastatic? ☐ Yes ☐ No ☐ Unknown ☐ Secondary ☐ Unknown

Coded in MedDRA

Analysis

Combining data from Registry with “mother” studies

Period Definition and Multiple Baseline Definition

Combining data from Registry with "mother" studies

- Primary endpoint: "resolution of Lymphopenia"
- Definition: grade 3/4 resolves to grade 0/1

Absolute Lymphocyte Count (ALC) will be tabulated by grade using the NCI CTCAE version v3.0, and lymphopenia grades are defined as follows:

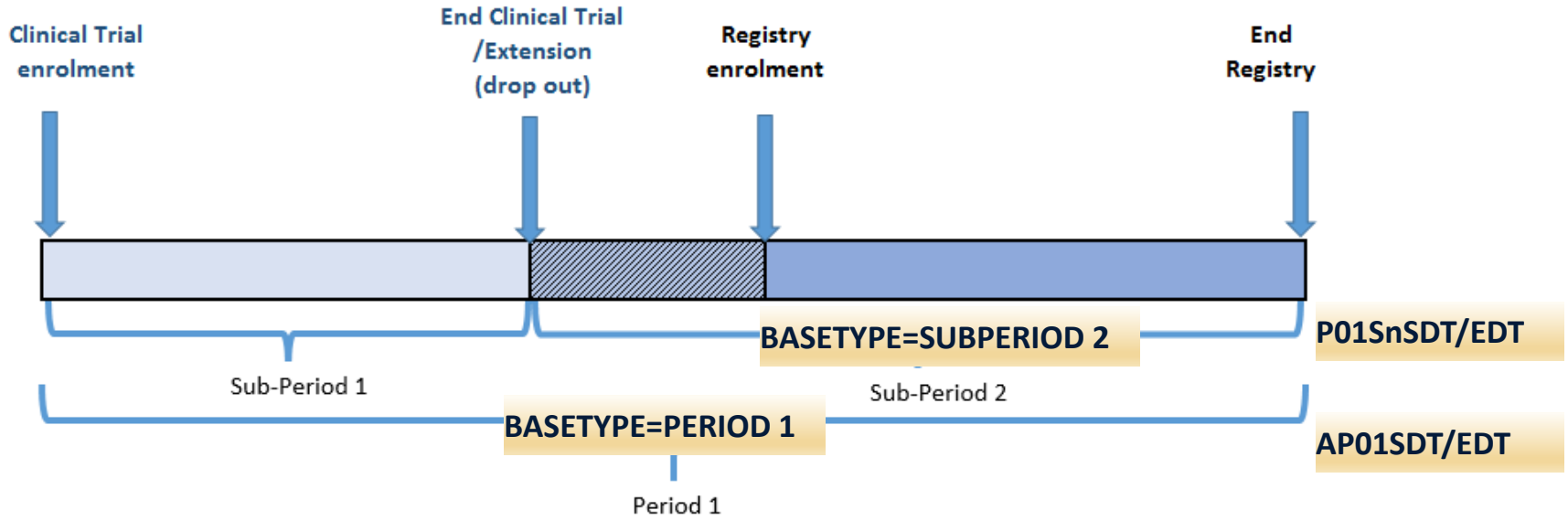
Table 9 NCI CTCAE Lymphopenia Grade

Laboratory Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
ALC Decreased	<LLN – 800/mm^3 <LLN – 0.8 x 10^9/L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9/L	<500 - 200/mm^3 <0.5 – 0.2 x 10^9/L	<200/mm^3 < 0.2 x 10^9/L

- Need LLN – no ranges captured in the registry DB
  - Used last available ANRLO/ANRHI from CT

- Duplicate management: CT EOS date/result = Registry SD1

Period Definition and Multiple Baseline Definition



- Period 1 & Sub-Period 2 – Lymphocyte analysis
- Sub-Period 2 – Adverse Events & Con Meds

Non-Interventional Studies and CDISC

A non-legalized (yet) “couple”

Conformance and data validation concerns

- Historically, CDISC standards were **primarily designed for use in studies of regulated medical products**
- Recent expansion of CDISC standards in therapeutic area development, and the recognition of the value in using CDISC standards has led to increased interest in **using standards in other areas of medical research**

"Challenges and Opportunities: Using CDISC standards for non-interventional studies", Jon Neville, 2018 International Interchange

- Many SDTM required domains and variables are not applicable / relevant
  E.g. EX domain
- Arm is not applicable

  E.g. ARM/ARMCD in DM

ARMCD	ARM
OBS	Observational (No Treatment)

- The concept of VISIT may not be as rigid as we think of in SDTM

  E.g. Visits Windowing needed in ADaM

AVISIT	ADY	LBDTC	AWRANGE	AWTARGET	AWTDIFF	AWLO	AWHI	AWU
Last Value from last Clinical trial	-168	2011-11-16T11:15						
Day 1 Registry	1	2012-05-02	1-1 Days	1	0	1	1	Days
Week 36	211	2012-11-28	183-266 Days	183	28	183	266	Days
Week 60	421	2013-06-26	351-423 Days	351	70	351	423	Days
Week 60	423	2013-06-28	351-423 Days	351	72	351	423	Days

- Perfectly appropriate non-interventional data will result in validation errors

Data Standards for Non-Interventional Studies:
Collaboration on common goals

Yuliia Bahatska, Syneos Health
Vladlen Ivanushkin, DataFocus
Jon Neville, CDISC

https://www.surveymonkey.co.uk/r/ZM6JBWK

Currently, there are no strict standards and guidelines for observational studies. This project studies the challenges that programmers face during creation of the analysis datasets and handling of the data for the observational studies. The plan is to network with the programmers who have experience in observational studies and summarise the most frequent issues they have faced. The next step will be to discuss and optimise the ways they can be resolved from programming and data handling perspectives. Data transparency should be taken into account in the discussion of dataset creation. If possible, CDISC experts should be involved in the project in order to provide guidance. The results are to be presented in the form of a white paper.

Handling of Associated Person (AP) Data

AP who?

Intro to SDTM AP Ig

What about ADaM for AP?

Issues with AP data collection / mapping

Validate SDTM AP data

FDA Initial Feedback on the use of AP

- Associated Persons (AP)
  - *Non-Subject* specific data
  - Intended for Human Data → ?? Can be a Foetus considerd « Human » data ??
  - Example of AP Use
    - New born in Fertility Studies
    - Accidental Exposure to Study Drug
    - Donor → Kidney Transplant TAUG
    - Document family history → Breast Cancer TAUG
- In our Study
  - Pregnant Female Partner of a male Subject
  - Male Partner of a Female Pregnant Subject
  - Infant

- Introduced with **SDTM standards v1.4** (2013-11-26) and **SDTM AP Ig** (2013-12-12), supported by **Ig 3.2** (2013-11-26)

  !!!! But our sponsor was still using SDTM Ig 3.1.3 !!!

- AP Datasets created based on SDTM Observational Classes
  - Use of AP prefix e.g. APDM
  - SQAP-- prefix for supplemental qualifiers e.g. SQAPDM
  - Variables Names same as standard SDTM domains e.g. SEX and not APSEX

- Three non-standard SDTM variables for AP
  - APID Associated Person Identifier
  - RSUBJID Related Subject (USUBJID of « related » subject in the parent domains)
  - SREL Subject, Device or Study Relationship (it has a standard CT) e.g.
    - CHILD, BIOLOGICAL
    - HUSBAND
    - MOTHER, BIOLOGICAL e.g. for pediatric studies
- Structure of SQAP– same as SUPP– except for APID instead of USUBJID

DOMAIN	APID	RSUBJID	SREL	BRTHDTC	…….
APDM	A-01929-001-01-01-01	XXX-01929-001	CHILD, BIOLOGICAL	2014-12-25	……..
APDM	A-01929-001-01-02-01	XXX-01929-001	CHILD, BIOLOGICAL	2017-01-15	……..

Children of …

DOMAIN	USUBJID	BRTHDTC	……
DM	XXX-01929-001	1974-03-04	……

- Make it informative

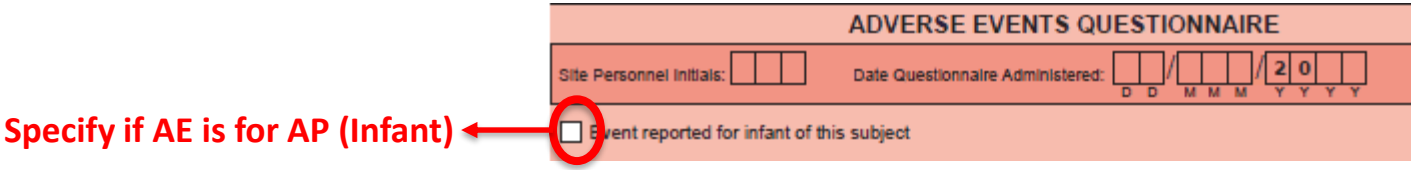
  e.g. include a part to reference the subject id

- In our study
  - Concatenation of ‘pre-trial prefix’ + ‘subject id’ + ‘AP Id’
  - AP ID
    - For partner: partner number
    - For child: concatenation of partner number (if available) + pregnancy number + child number
  - Examples A-01929-001-01-01-01
    - **A**-01929-001-01-01-01: Study A (what is study A in cSDRG)
    - A-**01929-001**-01-01-01 : Related Subject Id e.g. mother
    - A-01929-001-**01**-01-01 : Partner nr 1
    - A-01929-001-01-**01**-01 : Pregnancy nr 1
    - A-01929-001-01-01-**01** : Child nr 1

- No specific guidance
- ADAPxx?
- Not an issue in our study
  - AP datasets/records analyzed together with subject data

  e.g. AE occurred to AP pooled with AE occurred to Subjects
  - This is analysis-driven

- Make sure CRF is designed for AP
  - Ad-hoc demographics page (if applicable)
  - Same page to allow data collection for subject and AP can be used



  - Sometime in our CRF not always straightforward to understand when collected data were about AP vs Subject

- SDTM Mapping
  - One program to map both subject and AP domain e.g. AE.sas for both AE and APAE dataset
  - Same CRF page but multiple annotations for dataset names

If reported for infant then APAE = Associated Persons Adverse Events;
else AE = Adverse Events

If reported for subject's partner then APVS = Associated Persons Vital Signs;
APXT = Associated Persons Subject Pregnancy; APXU = Associated Persons Prenatal Testing;
APMH = Associated Persons Medical History; APSU=Associated Persons Substance Use;
APLB = Associated Persons Laboratory Tests; APCM = Associated Persons Concomitant Meds;
APRP = Associated Persons Reproductive Systems
else VS = Vital Signs; XT = Subject Pregnancy; XU = Prenatal Testing; MH = Medical History;
SU=Substance Use; RP = Reproductive Systems; LB = Laboratory Test Results;
CM = Concomitant Medications

  - But only one set of variables annotations

- Checks available in SDTM Conformance Rules v1 (Ig 3.2)
- Key AP checks not yet implemented in P21c (v3.0.0) and P21e
- AP-- Datasets not recognized

APCM					
	SD9999	CG0320, CG0321, CG0463, CG0464	Dataset APCM class not recognized	Error	1
APCO					
	SD9999	CG0320, CG0321, CG0463, CG0464	Dataset APCO class not recognized	Error	1

- SQAP-- Datasets partially validated

SQAPCM					
	SD0058	CG0013	Variable appears in dataset, but is not in SDTM model	Error	1
	SD0057	FDAB027, CG0016	SDTM Expected variable USUBJID not found	Warning	1

Validate SDTM AP Data – Possible Work Around

- Make APs subject datasets
  - Rename Datasets: APDM → DM, SQAPDM → SUPPDM
  - Rename Variables → APID → USUBJID
  - Validate with P21 only modified AP datasets together with Trial Design Datasets
- Additional Ad-hoc checks
  - e.g. all subjects referenced in the AP datasets (i.e. RSUBJID) exist in DM (i.e. USUBJID)
- Documented in the « Data Conformance Summary » section of the cSDRG

- FDA Consulted (e-data team)

We recommend to stick to the model (Ig 3.1.3), i.e. not use AP domains, and submit infant and partner data in a sponsor domain

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Ok keep AP

Conclusions

Final Remarks / References

We Need better Standards to support RWE/RDW

- *Challenges and Opportunities: Using CDISC standards for non-interventional studies"* - Jon Neville, CDISC International Interchange 2018
- *Associated Persons Domains – Who? What? Where? When? Why? How?* – A. Wittle, PA M Stackhouse, PharmaSUG 2016, DS10