CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

The CDISC Vision is to Inform Patient Care & Safety Through Higher Quality Medical Research

Strength *through Collaboration*

Overview of Handling of PK Data in CDISC Standards

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Agenda

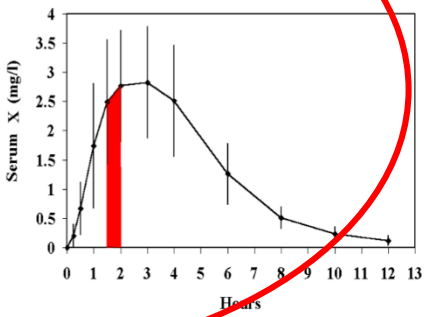
- Some PK Terminology and Concepts
- PK Data and CDISC
- Specific Considerations
  - Relationship Records
- What's next?

Some of my Sources

- Considerations in Submitting PK Data in an SDTM-Compliant Format
  - F. Wood, P. Schaefer, R. Lewis, PharmaSUG 2012
- Considerations in the Use of Timing Variables in Submitting SDTM-Compliant Datasets
  - J. Salyers, R. Lewis, F. Wood, PharmaSUG 2013
- Implementation of CDISC ADaM in the Pharmacokinetics Department
  - J. Magielse, CDISC Interchange 2014
- Phoenix Connect Users Guide, 2014
- … and of course the various standards documents

Some PK Terminology

Pharmacokinetics
Referred to as "PK" - in short: "What the body does to the drug". Often means "individual PK" in contrast to pop PK

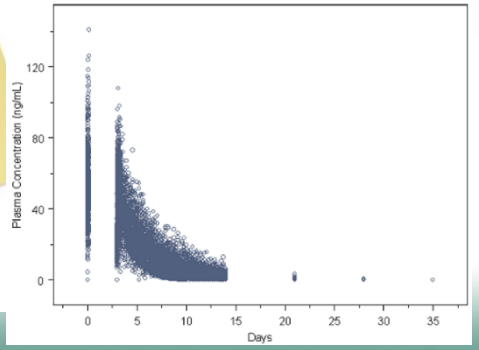


ADME
Absorption,
Distribution,
Metabolism,
Excretion
– what happens to a drug in the body

Pharmacodynamics
Referred to as "PD" - in short: "What the drug does to the body"

PBPK
Physiologically-based PK, i.e. mechanistic models for ADME using mathematics to represent physiological components

Population PK
Analysis of data from a whole population using a unified model



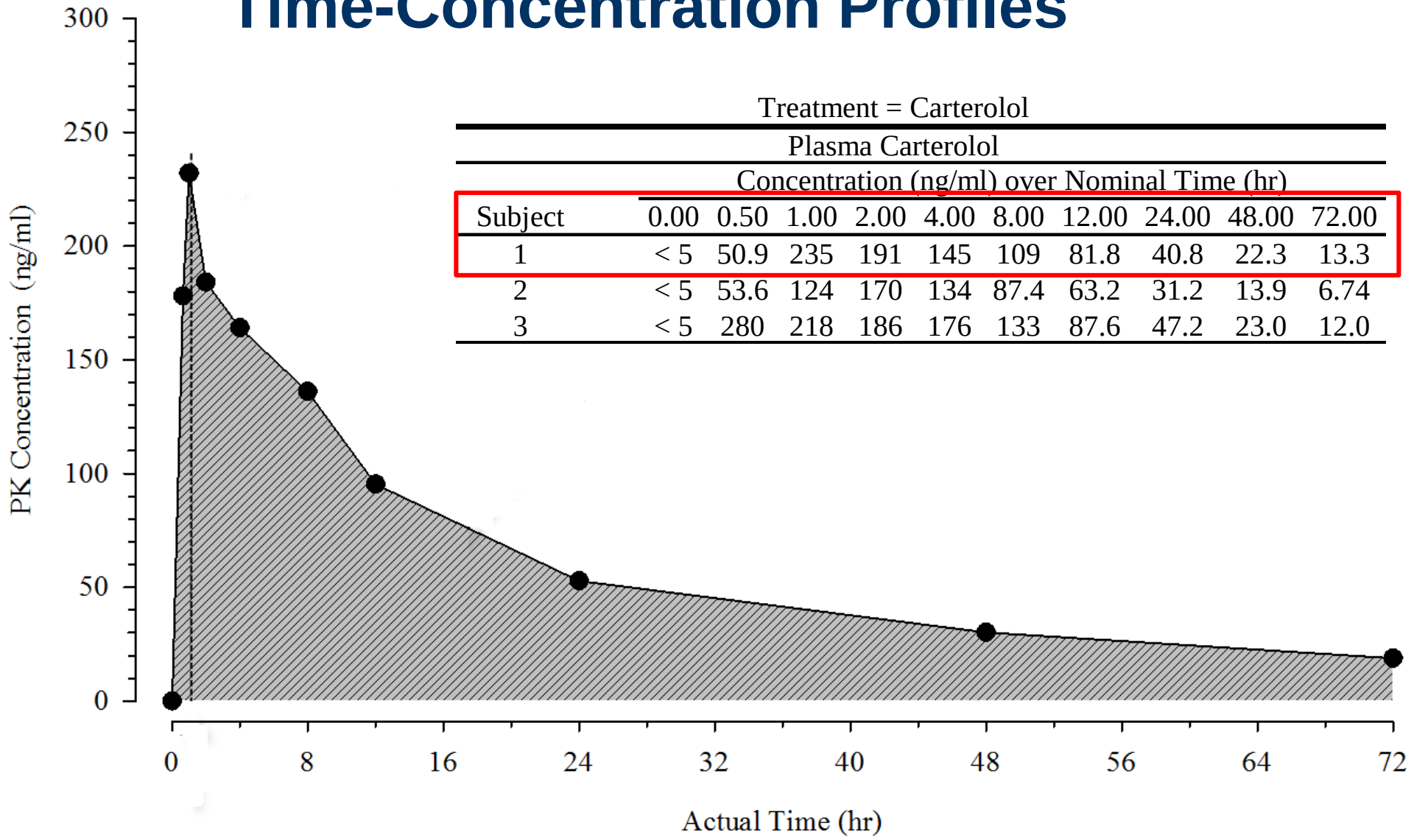
PK Analysis – NCA: Time-Concentration Profiles

Treatment = Carterolol

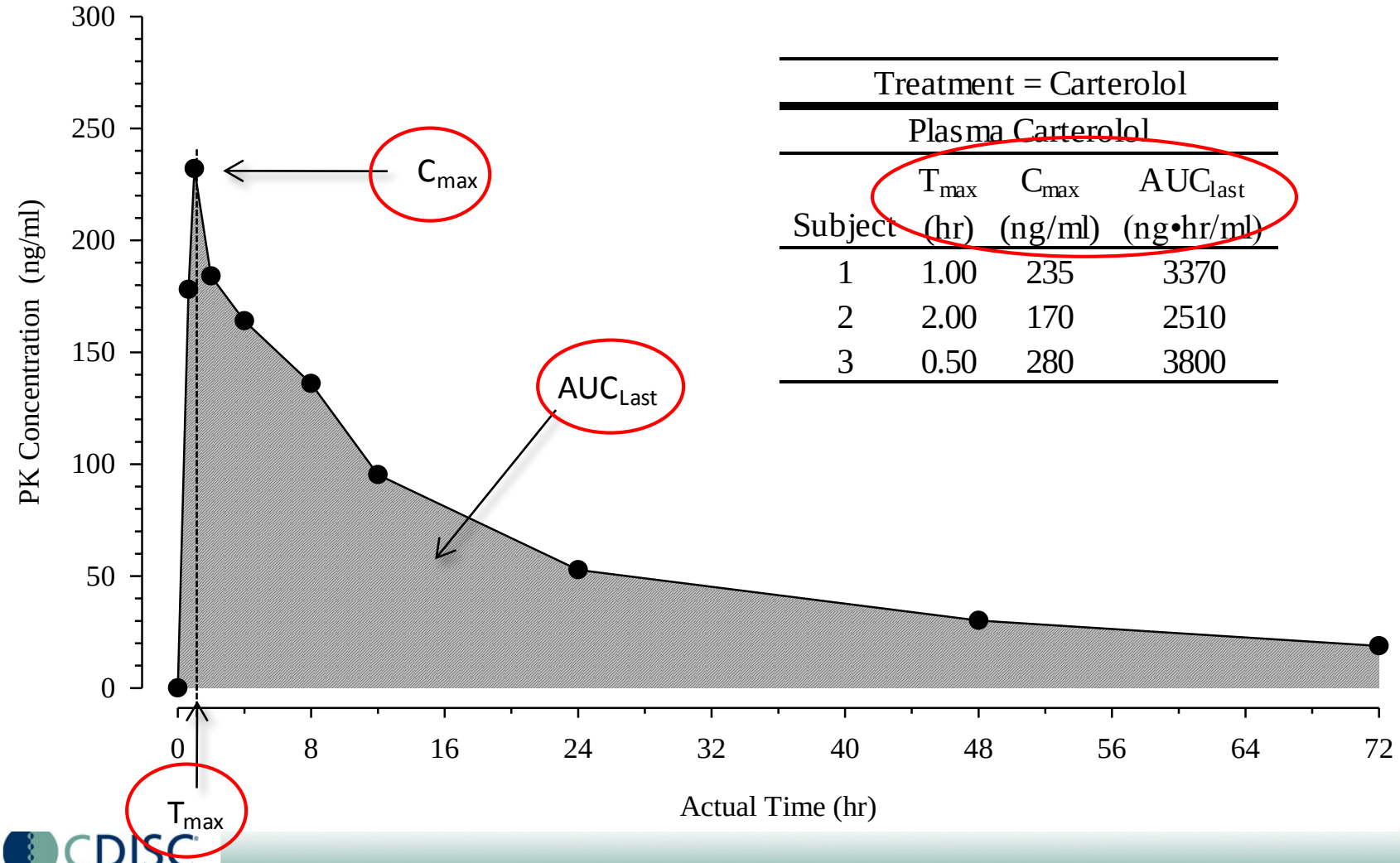
Plasma Carterolol

Concentration (ng/ml) over Nominal Time (hr)

Subject	0.00	0.50	1.00	2.00	4.00	8.00	12.00	24.00	48.00	72.00
1	< 5	50.9	235	191	145	109	81.8	40.8	22.3	13.3
2	< 5	53.6	124	170	134	87.4	63.2	31.2	13.9	6.74
3	< 5	280	218	186	176	133	87.6	47.2	23.0	12.0



PK Analysis Results: Some PK Parameters

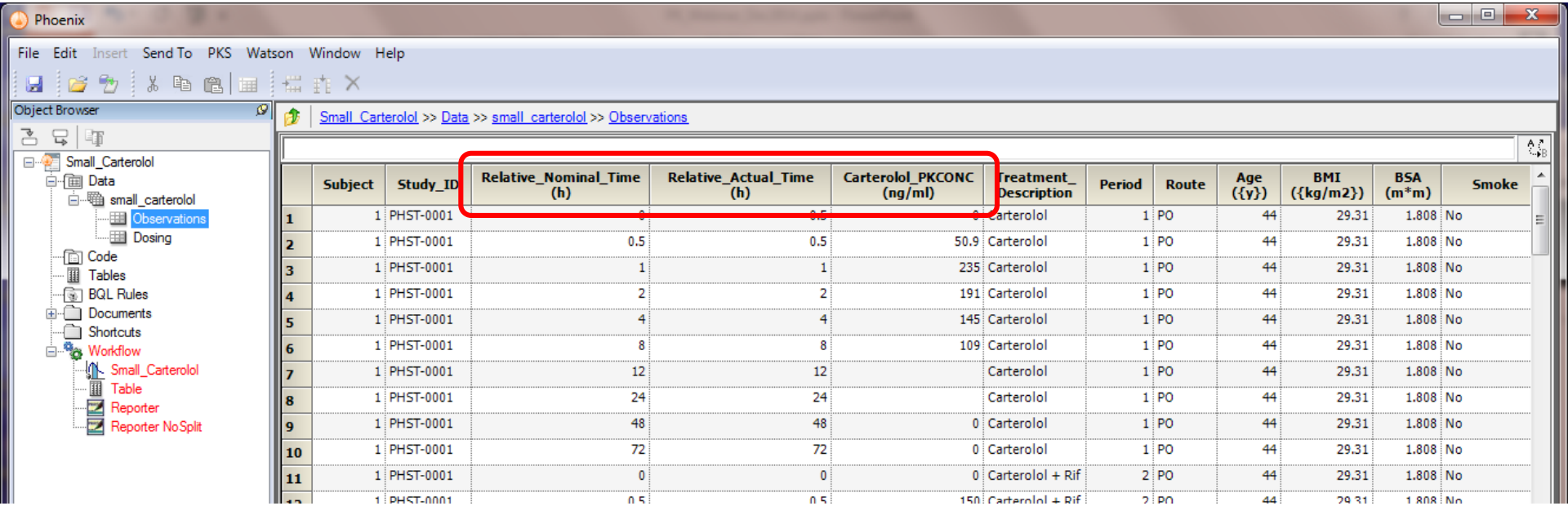


Treatment = Carterolol			
Plasma Carterolol			
Subject	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)
1	1.00	235	3370
2	2.00	170	2510
3	0.50	280	3800

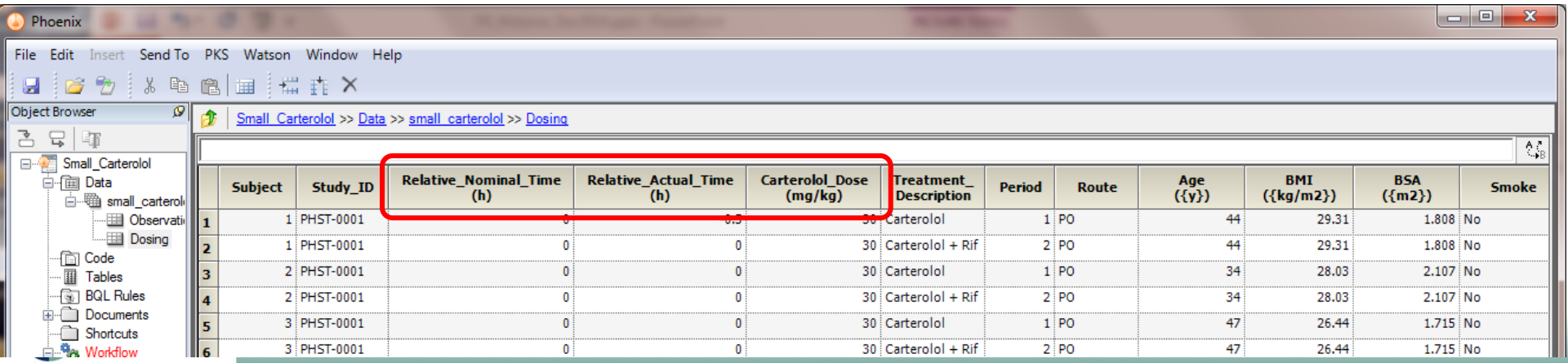
Variables for PK Analysis

- Observations: Set of variables to identify **unique time-concentration profiles** (‘key’ variables such as subject, treatment, study id, …).
- Dosing: Same ‘key’ variables + dose value and time point
- Additional subject data: Per subject demographics (such as age, race, etc.) and additional findings (such as weight, alcohol usage, smoking habits, etc.)
- Depending on the analysis program the data can be in one dataset or in separate datasets, like observation and dosing worksheets

Example for PK Analysis Datasets – Observation and Dosing Worksheet



	Subject	Study_ID	Relative_Nominal_Time (h)	Relative_Actual_Time (h)	Carterolol_PKCONC (ng/ml)	Treatment_ Description	Period	Route	Age ({y})	BMI ({kg/m2})	BSA (m*m)	Smoke
1	1	PHST-0001	0	0.5	0	Carterolol	1	PO	44	29.31	1.808	No
2	1	PHST-0001	0.5	0.5	50.9	Carterolol	1	PO	44	29.31	1.808	No
3	1	PHST-0001	1	1	235	Carterolol	1	PO	44	29.31	1.808	No
4	1	PHST-0001	2	2	191	Carterolol	1	PO	44	29.31	1.808	No
5	1	PHST-0001	4	4	145	Carterolol	1	PO	44	29.31	1.808	No
6	1	PHST-0001	8	8	109	Carterolol	1	PO	44	29.31	1.808	No
7	1	PHST-0001	12	12		Carterolol	1	PO	44	29.31	1.808	No
8	1	PHST-0001	24	24		Carterolol	1	PO	44	29.31	1.808	No
9	1	PHST-0001	48	48	0	Carterolol	1	PO	44	29.31	1.808	No
10	1	PHST-0001	72	72	0	Carterolol	1	PO	44	29.31	1.808	No
11	1	PHST-0001	0	0	0	Carterolol + Rif	2	PO	44	29.31	1.808	No
12	1	PHST-0001	0.5	0.5	150	Carterolol + Rif	2	PO	44	29.31	1.808	No



	Subject	Study_ID	Relative_Nominal_Time (h)	Relative_Actual_Time (h)	Carterolol_Dose (mg/kg)	Treatment_ Description	Period	Route	Age ({y})	BMI ({kg/m2})	BSA ({m2})	Smoke
1	1	PHST-0001	0	0.5	30	Carterolol	1	PO	44	29.31	1.808	No
2	1	PHST-0001	0	0	30	Carterolol + Rif	2	PO	44	29.31	1.808	No
3	2	PHST-0001	0	0	30	Carterolol	1	PO	34	28.03	2.107	No
4	2	PHST-0001	0	0	30	Carterolol + Rif	2	PO	34	28.03	2.107	No
5	3	PHST-0001	0	0	30	Carterolol	1	PO	47	26.44	1.715	No
6	3	PHST-0001	0	0	30	Carterolol + Rif	2	PO	47	26.44	1.715	No

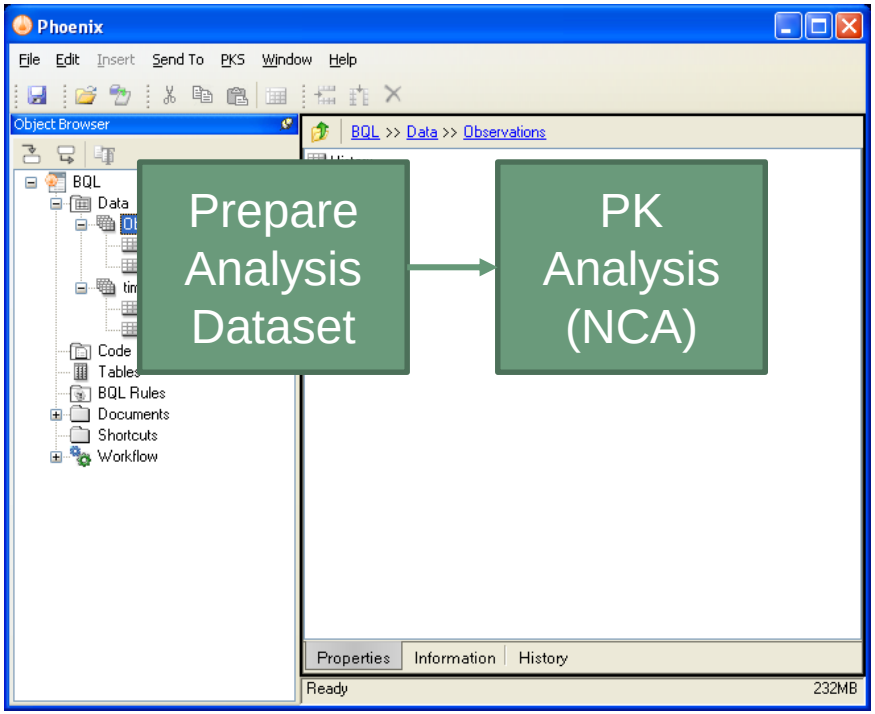
PK Data in SDTM

- Specific pharmacokinetics domains based on General Observation class were introduced in SDTMIG v. 3.1.2
  - PC – Pharmacokinetics Concentration – for time-concentration profiles
  - PP – Pharmacokinetics Parameters – for PK results
- Dosing information, like treatment and dose amount are in EX domain
- Some subject data (like AGE, SEX, RACE) are in DM domain
- Additional subject data (like weight, height, smoking, …) are in SC, VS, and maybe other finding domains. For PK analysis typically baseline values are relevant.

The PK Analysis Workflow based on CDISC Data

SDTM Datasets

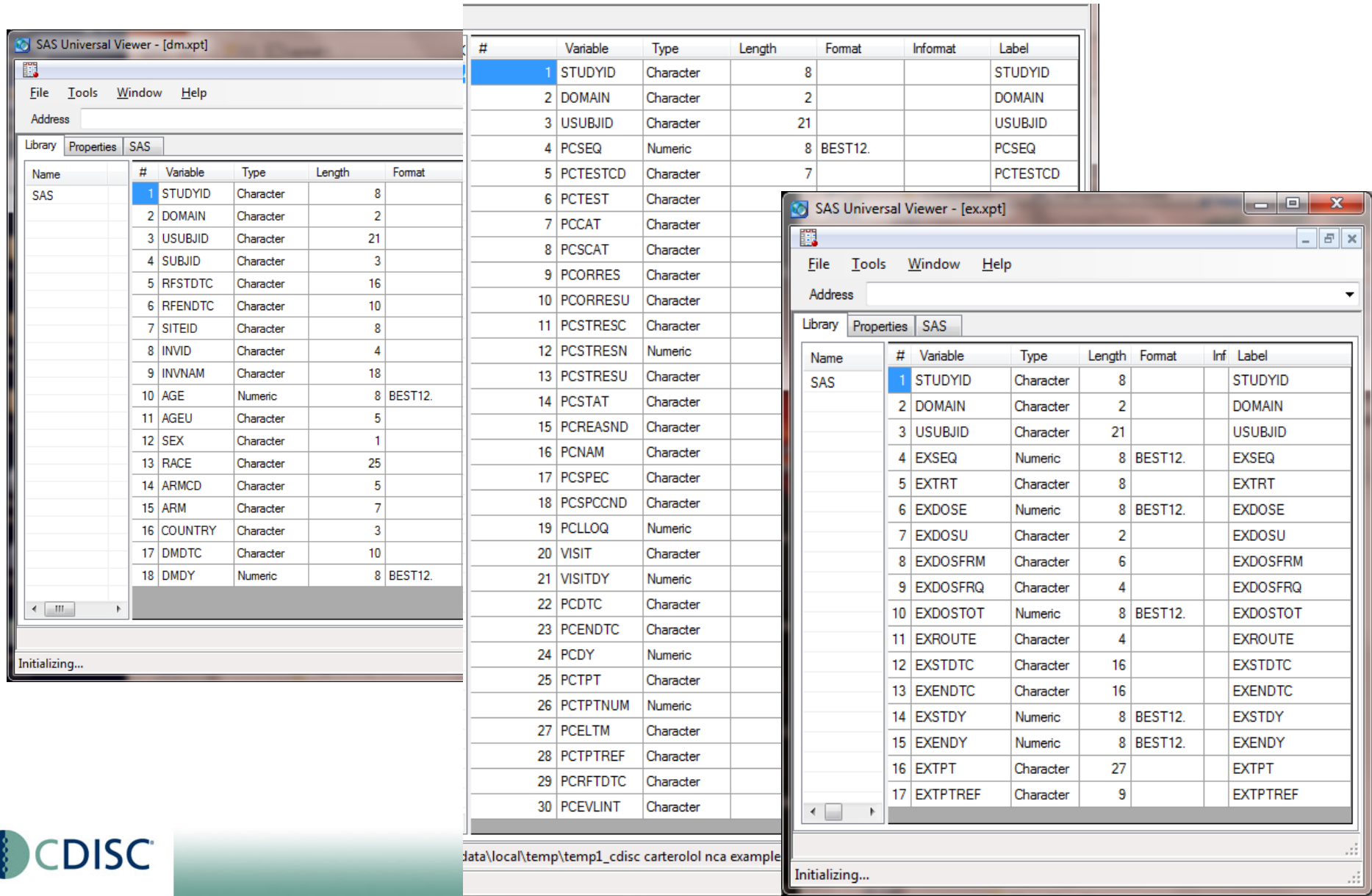
PC
EX
DM
others …



PP Dataset

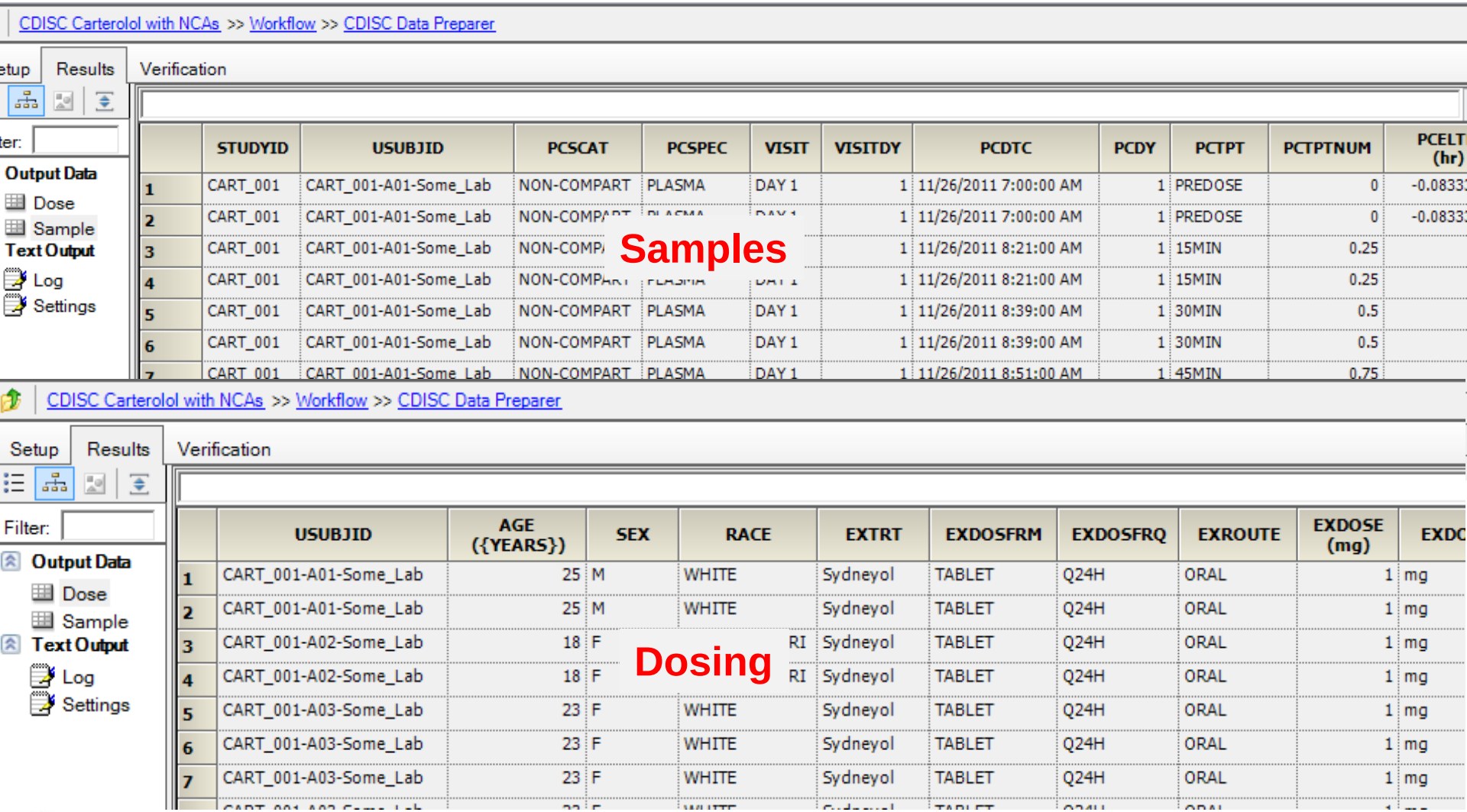
What if your tool does not create an analysis-ready dataset?

From Here …



CDISC

… to Here:
Merged PK Analysis Datasets



	STUDYID	USUBJID	PCSCAT	PCSPEC	VISIT	VISITDY	PCDTC	PCDY	PCTPT	PCTPTNUM	PCELT (hr)
1	CART_001	CART_001-A01-Some_Lab	NON-COMPART	PLASMA	DAY 1	1	11/26/2011 7:00:00 AM	1	PREDOSE	0	-0.0833
2	CART_001	CART_001-A01-Some_Lab	NON-COMPART	PLASMA	DAY 1	1	11/26/2011 7:00:00 AM	1	PREDOSE	0	-0.0833
3	CART_001	CART_001-A01-Some_Lab	NON-COMPART	PLASMA	DAY 1	1	11/26/2011 8:21:00 AM	1	15MIN	0.25	
4	CART_001	CART_001-A01-Some_Lab	NON-COMPART	PLASMA	DAY 1	1	11/26/2011 8:21:00 AM	1	15MIN	0.25	
5	CART_001	CART_001-A01-Some_Lab	NON-COMPART	PLASMA	DAY 1	1	11/26/2011 8:39:00 AM	1	30MIN	0.5	
6	CART_001	CART_001-A01-Some_Lab	NON-COMPART	PLASMA	DAY 1	1	11/26/2011 8:39:00 AM	1	30MIN	0.5	
7	CART_001	CART_001-A01-Some_Lab	NON-COMPART	PLASMA	DAY 1	1	11/26/2011 8:51:00 AM	1	45MIN	0.75	

	USUBJID	AGE ({YEARS})	SEX	RACE	EXTRT	EXDOSFRM	EXDOSFRQ	EXROUTE	EXDOSE (mg)	EXDO
1	CART_001-A01-Some_Lab	25	M	WHITE	Sydneyol	TABLET	Q24H	ORAL	1	mg
2	CART_001-A01-Some_Lab	25	M	WHITE	Sydneyol	TABLET	Q24H	ORAL	1	mg
3	CART_001-A02-Some_Lab	18	F	RI	Sydneyol	TABLET	Q24H	ORAL	1	mg
4	CART_001-A02-Some_Lab	18	F	RI	Sydneyol	TABLET	Q24H	ORAL	1	mg
5	CART_001-A03-Some_Lab	23	F	WHITE	Sydneyol	TABLET	Q24H	ORAL	1	mg
6	CART_001-A03-Some_Lab	23	F	WHITE	Sydneyol	TABLET	Q24H	ORAL	1	mg
7	CART_001-A03-Some_Lab	23	F	WHITE	Sydneyol	TABLET	Q24H	ORAL	1	mg

Steps for Merging SDTM Datasets into PK Analysis Datasets

- The list of all subjects is derived from the DM domain. Carry STUDYID in case there are multiple studies in the dataset.
- The samples per subject are derived from the PC domain.
  - Typically, the reference time point (PCRFDTC) is matched to the dosing start time (EXSTDTC). Time variables (PCELTM, PCDTC, PCENDTC) are used to calculate nominal and actual sample times.
  - For distinct values of PCTESTCD decide whether data are stacked (narrow dataset) or pivoted (wide dataset).
  - Need to decide which result value to use (typically, PSTRESN, but consider PCSTRESC and PCORRES as well). Add unit to column header or keep in separate column.
  - Urine volume observations (PCTESTCD=VOLUME) will typically go on the same row as the corresponding concentration observation.
- Get unique treatment from EX domain (typically, subset of EXTRT, EXDOSFRM, EXROUTE, and EXDOSFRQ) and extract dosing time and amount.
  - If creating separate datasets for samples and dosing, add treatment information also to the sample dataset

Observation Worksheet

Name	derived from		Name	derived from
STUDYID	DM		EXTRT	EX
USUBJID	DM		EXDOSFRM	EX
PCSCAT	PC		EXDOSFRQ	EX
PCSPEC	PC		EXROUTE	EX
PCSPCCND	PC		EXSTDY	EX
VISIT	DM		EXENDY	EX
VISITDY	DM		EXTPT	EX
PCDTC	PC		EXTPTREF	EX
PCDY	PC		PCORRES	PC
PCTPT	PC		PCORRESU	PC
PCTPTNUM	PC		PCSTRESC	PC
PCELTM	PC		PCSTRESN	PC
PCTPTREF	PC		PCSTRESU	PC
PCENDTC	PC		PCLLOQ	PC
PCRFTDTC	PC		PCSEQ	PC
PCTESTCD	PC		VOLUME_PCORRES	PC
AGE	DM		VOLUME_PCSTRESC	PC
SEX	DM		VOLUME_PCSTRESN	PC
RACE	DM		VOLUME_PCLLOQ	PC
			VOLUME_PCSEQ	PC
			Relative_Actual_Time	Derived from PCRFDTC and PCDTC
			Relative_Nominal_Time	PCELTM
			Relative_Actual_End_Time	Derived from PCRFDTC and PCDTC
			Relative_Nominal_End_Time	PCELTM

Dosing Worksheet

Name	derived from
STUDYID	DM
USUBJID	DM
AGE	DM
SEX	DM
RACE	DM
EXTRT	EX
EXDOSFRM	EX
EXDOSFRQ	EX
EXROUTE	EX
EXDOSE	EX
EXDOSU	EX
EXSTDY	EX
EXENDY	EX
EXTPT	EX
EXTPTREF	EX
EXENDTC	EX
EXSTDTC	EX
Relative_Actual_Time	Derived from PCRFDTC and PCDTC
Relative_Nominal_Time	PCELTM

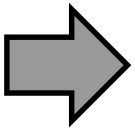
Some Specific Aspects

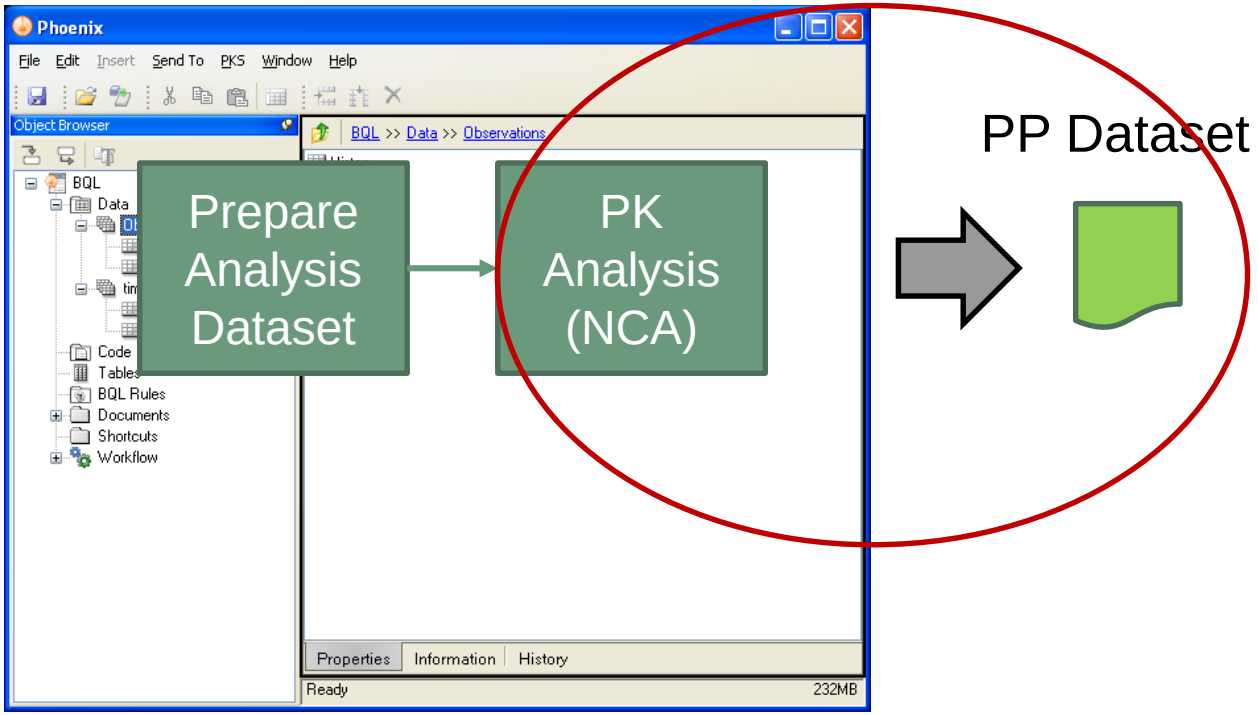
- For volume sampling (urine samples) need to create start and end time of sampling interval
- For volume sampling need to place volume and concentration in one row for PK analysis
- Harmonize units and add units as properties to columns
  - If there are multiple units in one column, create multiple ("pivoted" not stacked) columns
- Handling of LOQ values for analysis and summary statistics
- Negative pre-dose sampling times are typically set to zero for PK analysis

The PK Analysis Workflow based on CDISC Data

SDTM Datasets

PC
EX
DM
others …



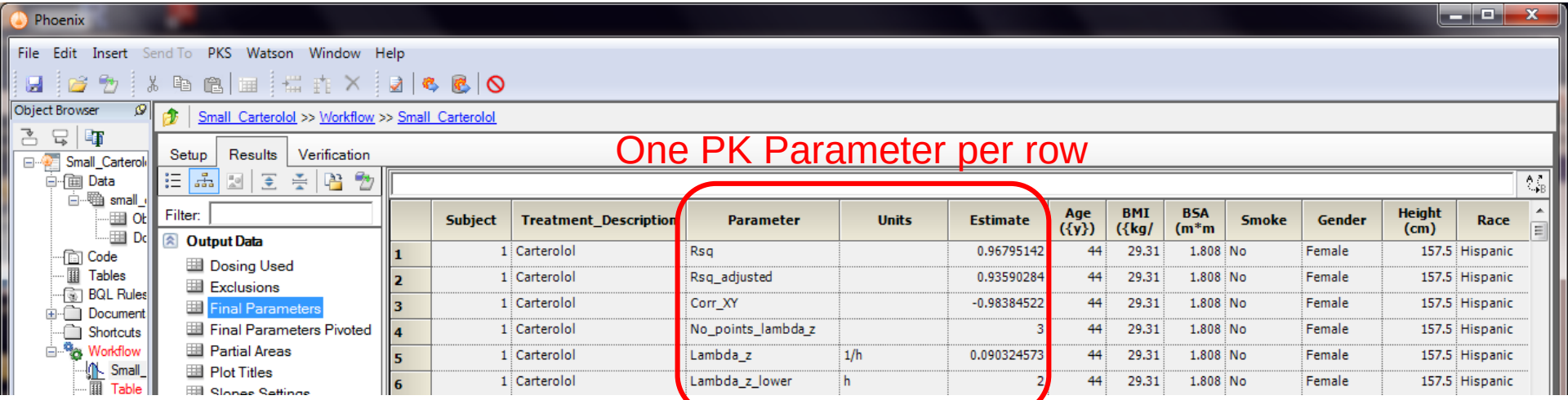


PP Dataset

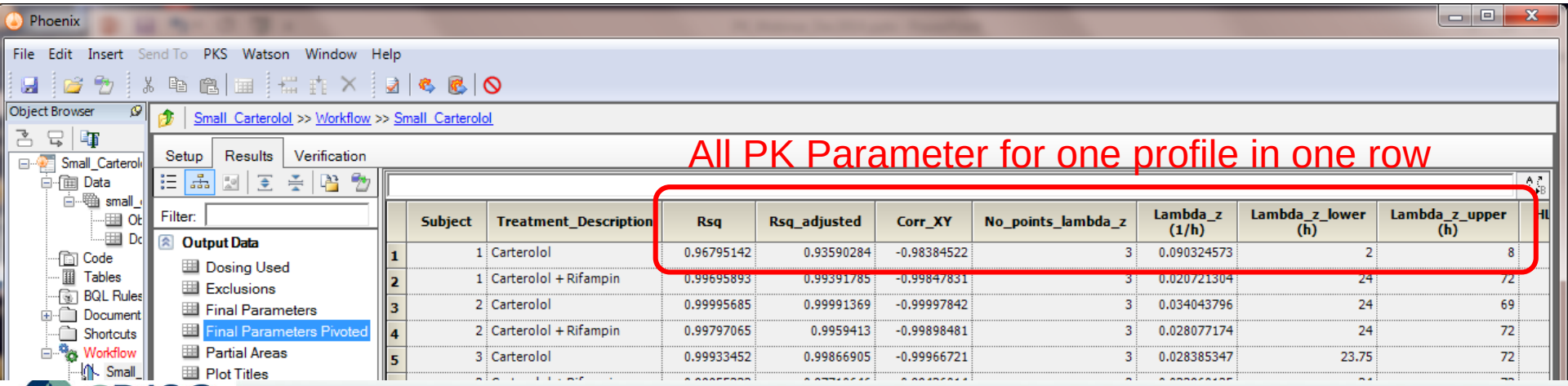
PK Analysis Results Dataset

- A set of PK parameter values for each unique time-concentration profile (i.e. per subject, per treatment, …)
- Organization of data can be
  - ‘narrow’ (aka ‘CDISC-like’ i.e. PK Parameter / Value pair per row)
  - or ‘wide’ (aka ‘pivoted’, i.e. there is a column for each PK Parameter and one row per profile)

Example for PK Results – Narrow and Wide Data Format

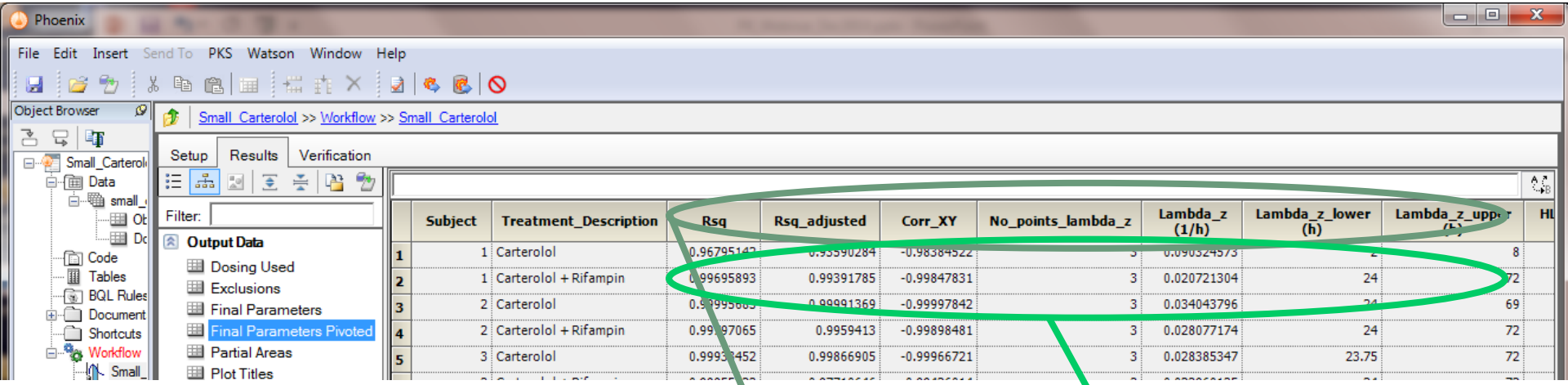


	Subject	Treatment_Description	Parameter	Units	Estimate	Age ({y})	BMI ({kg/	BSA (m*m	Smoke	Gender	Height (cm)	Race
1	1	Carterolol	Rsq		0.96795142	44	29.31	1.808	No	Female	157.5	Hispanic
2	1	Carterolol	Rsq_adjusted		0.93590284	44	29.31	1.808	No	Female	157.5	Hispanic
3	1	Carterolol	Corr_XY		-0.98384522	44	29.31	1.808	No	Female	157.5	Hispanic
4	1	Carterolol	No_points_lambda_z		3	44	29.31	1.808	No	Female	157.5	Hispanic
5	1	Carterolol	Lambda_z	1/h	0.090324573	44	29.31	1.808	No	Female	157.5	Hispanic
6	1	Carterolol	Lambda_z_lower	h	2	44	29.31	1.808	No	Female	157.5	Hispanic



	Subject	Treatment_Description	Rsq	Rsq_adjusted	Corr_XY	No_points_lambda_z	Lambda_z (1/h)	Lambda_z_lower (h)	Lambda_z_upper (h)
1	1	Carterolol	0.96795142	0.93590284	-0.98384522	3	0.090324573	2	8
2	1	Carterolol + Rifampin	0.99695893	0.99391785	-0.99847831	3	0.020721304	24	72
3	2	Carterolol	0.99995685	0.99991369	-0.99997842	3	0.034043796	24	69
4	2	Carterolol + Rifampin	0.99797065	0.9959413	-0.99898481	3	0.028077174	24	72
5	3	Carterolol	0.99933452	0.99866905	-0.99966721	3	0.028385347	23.75	72

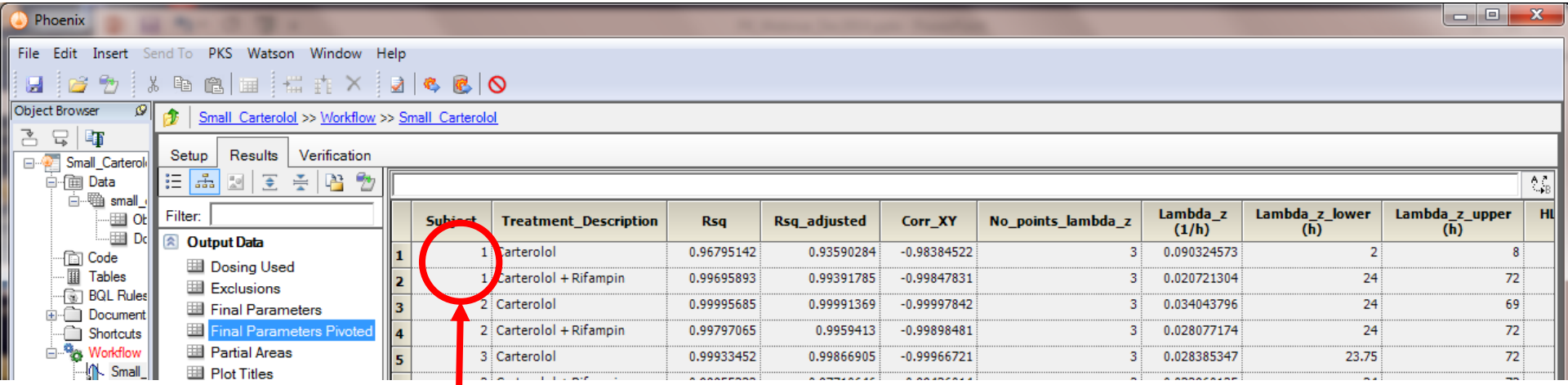
Mapping of PK Results to PP Domain



STUDYID	USUBJID	PPGRPID	PPSEQ	PPTESTCD	PPTEST	PPORRES	PPORRESU	…
…	…	…	…	…	…	…	…	
…	…	…	…	…	…	…	…	…
…	…	…						…

PK Parameter names and units are subject to Controlled Terminology, so appropriate mapping might be required

Mapping of PK Results to PP Domain



	Subject	Treatment_Description	Rsq	Rsq_adjusted	Corr_XY	No_points_lambda_z	Lambda_z (1/h)	Lambda_z_lower (h)	Lambda_z_upper (h)	Hl
1	1	Carterolol	0.96795142	0.93590284	-0.98384522	3	0.090324573	2	8	
2	1	Carterolol + Rifampin	0.99695893	0.99391785	-0.99847831	3	0.020721304	24	72	
3	2	Carterolol	0.99995685	0.99991369	-0.99997842	3	0.034043796	24	69	
4	2	Carterolol + Rifampin	0.99797065	0.9959413	-0.99898481	3	0.028077174	24	72	
5	3	Carterolol	0.99933452	0.99866905	-0.99966721	3	0.028385347	23.75	72	

STUDYID	USUBJID	PPGRPID	PPSEQ	PPTESTCD	PPTEST	PPORRES	PPORRESU	…
…	…	…	…	…	…	…	…	
…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…

But there are 2 rows per subject because there were 2 profiles per subject …

Connect PP & PC Records

- Very often, there is more than one time-concentration profile per subject, so the set of PK parameters (rows in PP) must be connected to the right profile (rows in PC).
- A straight forward way is to making sure that the PCRFTDTC for the set of PC records matches the PPRFTDTC in the PP records
- In some cases (exclusions of specific observations, multiple analytes per profile) this won't be powerful enough:
  - Then use RELREC records

Relationship Records – RELREC

- RELREC is a special-purpose dataset that is used to describe relationships between records for a subject or relationships between datasets
- How relationships are recorded:
  - Each RELREC record points to one or more records in another dataset or domain
  - The relationship is expressed by the same relationship ID in the related RELREC records
- This can be used to connect the PP records to the corresponding PC records, i.e. to indicate which rows from PC (in other words which time-concentration profile) was used to calculate the PK parameter in a specific row in PP (see example on next slide)

RELREC Structure

Variable Name	Variable Label	What it means …
STUDYID	Study Identifier	
RDOMAIN	Related Domain Abbreviation	Identifies the domain of the record
USUBJID	Unique Subject Identifier	
IDVAR	Identifying Variable	Defines which variable in the domain is used to identify the record
IDVARVAL	Identifying Variable Value	Defines which value of the variable IDVAR is used
RELTYPE	Relationship Type	Ignore for relating subjects
RELID	Relationship Identifier	Unique value to mark the RELREC records that define a relationship

RELREC for Dataset to Dataset Relationships

- All the records in MB domain are being related to all of the records in MS domain, so both USUBJID and IDVARVAL are null.
- Variables with sponsor-defined values (like - -GRPID, --SPID, - -REFID) are good candidates for identifying related records: Same value -> The records are related.
  - Note that - -SEQ can't be used (has not meaning across datasets)
- Meaning of RELTYPE
  - ONE / ONE: only one record from each dataset
  - ONE / MANY: One record from one dataset is related to multiple records of the other dataset
  - MANY / MANY: Multiple records from one dataset are related to multiple records in the other dataset.

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
EFC1234	MB		MBGRPID		ONE	A
EFC1234	MS		MSGRPID		MANY	A

RELREC for PP and PC Relationship

- Each PP record is related to all PC records of the profile by a number of RELREC records

STUDYID	USUBJID	…	PPSEQ	PPGRPID	…	PPTEST	PPORRES	…
TST_ST-2A	SUBJ-002	…	10	…	…	AUCLST	…	…

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
TST_ST_2A	PP	SUBJ-002	PPSEQ	10		REL_1
TST_ST_2A	PC	SUBJ-002	PCSEQ	20		REL_1
TST_ST_2A	PC	SUBJ-002	PCSEQ	21		REL_1
TST_ST_2A	PC	SUBJ-002	PCSEQ	23		REL_1

STUDYID	USUBJID	PCSEQ	PCTESTCD	PCTEST	PCCAT	PCORRES	…
TST_ST_2A	SUB-002	20	SYDN	Sydneyol	ANALYTE	13.54	…
TST_ST_2A	SUB-002	21	SYDN	Sydneyol	ANALYTE	11.365	
TST_ST_2A	SUB-002	22	SYDN	Sydneyol	ANALYTE	HEM	
TST_ST_2A	SUB-002	23	SYDN	Sydneyol	ANALYTE	6.48	

Some Final Remarks

- The described approach does not use ADaM datasets (like ADSL) instead transforms SDTM directly into an analysis-ready dataset.
- Note that a subgroup of the ADaM team is working on a data structure for a PK analysis dataset – this will provide a standard supporting individual PK analysis
- Some users are discussing what would be required for population PK datasets and results
- The PK Controlled Terminology team is constantly updating PK parameter terms and units. Keep watching …

You can contact me at Peter.Schaefer@nc.rr.com