Capture and Use of Meaningful Data for Population PK/PD Analysis with Non-Linear Mixed Effects Modeling

by Rebecca Humphrey and Mitali Gaurav

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Introduction to PK / PD Analysis Dataset

- Datasets intended for PopPK/PD analysis are complex arrangements of information
  - Assembled in a format compatible by the software used for analysis
- Time-ordered datasets
  - Records representing time course of events
  - Pertaining to drug administration and resulting concentrations and/or PD responses
  - Longitudinal
- Capturing meaningful data is essential for modeling because:
  - Critical component of modeling
  - Data determines the modeling results

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Introduction to PK / PD Analysis Dataset

- Can be tedious when working with complex data
  - Multiple studies (number of studies, different phases, etc.)
  - Multiple dosing (dosing diaries, missed doses, etc.)
  - Covariates (time varying, different units, etc.)
  - Subjects enrolled (patients versus healthy volunteers, pediatrics, etc.)
  - Concomitant medications etc.
- Dataset discussions are important
  - Should be had before modeling begins
  - Model goal
- Model is informed by the data that is fed in – *your model is only as good as your data*

Owen JS and Fiedler-Kelly J. Introduction to Population Pharmacokinetic / Pharmacodynamic Analysis with Nonlinear Mixed Effects Models. Hoboken, NJ: John Wiley & Sons, Inc.; 2014.

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PK / PD Analysis Dataset

PK/PD example

- Separate records for
  - Doses
  - PK concentration
  - PD endpoint measures
- Also includes covariates as columns or variables

USUBJID	AFRLT	AMT	DOSEA	DV	DVID	EVDTC	AVISIT	ATPT
WOW-001-101-1001	-0.1	.	100	15.0434962	2	2005-01-15T07:59	Day 1	PREDOSE
WOW-001-101-1001	-0.08333333	.	100	0.05	1	2005-01-15T08:00	Day 1	PREDOSE
WOW-001-101-1001	0	100	100	.	0	2005-01-15T08:05	Day 1	
WOW-001-101-1001	1.016666667	.	100	40.788	1	2005-01-15T09:06	Day 1	1 HR
WOW-001-101-1001	1.95	.	100	61.182	1	2005-01-15T10:02	Day 1	2 HR
WOW-001-101-1001	4.066666667	.	100	15.2955	1	2005-01-15T12:09	Day 1	4 HR
WOW-001-101-1001	8.083333333	.	100	2.4926	1	2005-01-15T16:10	Day 1	8 HR
WOW-001-101-1001	11.93333333	.	100	0.3399	1	2005-01-15T20:01	Day 1	12 HR
WOW-001-101-1001	23.95	.	100	0.05	1	2005-01-16T08:02	Day 1	24 HR
WOW-001-101-1001	24.06666667	.	100	15.2946355	2	2005-01-16T08:09	Day 2	PREDOSE
WOW-001-101-1001	24.16666667	100	100	.	0	2005-01-16T08:15	Day 2	
WOW-001-101-1001	48.06666667	.	100	16.7369319	2	2005-01-17T08:09	Day 3	PREDOSE
WOW-001-101-1001	48.08333333	.	100	0.05	1	2005-01-17T08:10	Day 3	PREDOSE
WOW-001-101-1001	48.16666667	100	100	.	0	2005-01-17T08:15	Day 3	
WOW-001-101-1001	72.06666667	.	100	14.7353095	2	2005-01-18T08:09	Day 4	PREDOSE
WOW-001-101-1001	72.16666667	100	100	.	0	2005-01-18T08:15	Day 4	
WOW-001-101-1001	96.06666667	.	100	15.2376866	2	2005-01-19T08:09	Day 5	PREDOSE
WOW-001-101-1001	96.08333333	.	100	0.05	1	2005-01-19T08:10	Day 5	PREDOSE
WOW-001-101-1001	96.16666667	100	100	.	0	2005-01-19T08:15	Day 5	
WOW-001-101-1001	120.2333333	.	100	13.4195038	2	2005-01-20T08:19	Day 6	PREDOSE
WOW-001-101-1001	120.25	.	100	0.05	1	2005-01-20T08:20	Day 6	PREDOSE
WOW-001-101-1001	120.3333333	100	100	.	0	2005-01-20T08:25	Day 6	
WOW-001-101-1001	144.3166667	.	100	16.4078954	2	2005-01-21T08:24	Day 7	PREDOSE
WOW-001-101-1001	144.3333333	.	100	0.05	1	2005-01-21T08:25	Day 7	PREDOSE
WOW-001-101-1001	144.4166667	100	100	.	0	2005-01-21T08:30	Day 7	
WOW-001-101-1001	145.4333333	.	100	62.8641	1	2005-01-21T09:31	Day 7	1 HR

PARAM	DVID
WOW Dose (mg)	0
WOW (ng/ml)	1
Hemoglobin (g/dL)	2

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Dosing Data Collection

SDTM Guidance

- https://www.cdisc.org/standards/foundational/sdtmig/sdtmig-v3-4

The focus of this webinar is dosing data

- Dose date/time as well as amount recorded in either EC or EX
  - EC – Exposures as Collected
  - EX – Exposures
- Date/time for doses relative to PK samples recorded
  - PC – Pharmacokinetics Concentration
  - dose amount not recorded in PC

Dosing Data Collection (con't)

Dose Amount

- Vital to a successful model
  - Amount administered needs to be collected and recorded as well as units

First Dose Date/Time

- PKPD analysis datasets are time ordered in relation to the first dose.
  - Sorted by a time variable
    - Actual Relative Time From First Dose (AFRLT)
    - Time Since First Dose (TSFD)
    - PKPD can be sorted from the first event time (PD measure),
      - Time Since First Event
  - The order of the events/records in an analysis dataset inform the model

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Dosing Data Collection (con't)

- Record dose times in EC/EX or PC?
  - EC & EX have date time fields. Doses can be recorded as individual dose records with the start date/time = end date/time.
  - EC example

DOMAIN	USUBJID	ECTRT	ECOCCUR	ECDOSE	ECDOSU	ECDOSFRQ	EPOCH	ECSTDTC	ECENDTC	ECSTDY	ECENDY
EC	56798001	BOTTLE 1	Y	1	TABLET	QD	TREATMENT 1	2002-07-01T07:30	2002-07-01T07:30	1	1
EC	56798001	BOTTLE 2	Y	1	CAPSULE	QD	TREATMENT 1	2002-07-01T07:30	2002-07-01T07:30	1	1
EC	56798001	BOTTLE 1	Y	1	TABLET	QD	TREATMENT 1	2002-07-02T07:33	2002-07-02T07:33	2	2
EC	56798001	BOTTLE 2	Y	1	CAPSULE	QD	TREATMENT 1	2002-07-02T07:33	2002-07-02T07:33	2	2
EC	56798001	BOTTLE 1	Y	1	TABLET	QD	TREATMENT 1	2002-07-03T07:30	2002-07-03T07:30	3	3
EC	56798001	BOTTLE 2	Y	1	CAPSULE	QD	TREATMENT 1	2002-07-03T07:30	2002-07-03T07:30	3	3
EC	56798001	BOTTLE 1	Y	1	TABLET	QD	TREATMENT 2	2002-07-09T07:35	2002-07-10T07:30	9	10
EC	56798001	BOTTLE 2	Y	1	CAPSULE	QD	TREATMENT 2	2002-07-09T07:35	2002-07-10T07:30	9	10
EC	56798001	BOTTLE 1	Y	1	TABLET	QD	TREATMENT 2	2002-07-11T07:34	2002-07-11T07:34	11	11
EC	56798001	BOTTLE 2	Y	1	CAPSULE	QD	TREATMENT 2	2002-07-11T07:34	2002-07-11T07:34	11	11

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Dosing Data Collection (con't)

- EX versus EC
  - EX can be a detailed version of EC

DOMAIN	USUBJID	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXDOSFRQ	EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
EX	56798001	DRUG X	10	mg	TABLET	QD	TREATMENT 1	2002-07-01T07:30	2002-07-01T07:30	1	3
EX	56798001	PLACEBO	0	mg	CAPSULE	QD	TREATMENT 1	2002-07-01T07:30	2002-07-01T07:30	1	3
EX	56798001	DRUG X	10	mg	TABLET	QD	TREATMENT 1	2002-07-02T07:33	2002-07-02T07:33	2	2
EX	56798001	PLACEBO	0	mg	CAPSULE	QD	TREATMENT 1	2002-07-02T07:33	2002-07-02T07:33	2	2
EX	56798001	DRUG X	10	mg	TABLET	QD	TREATMENT 1	2002-07-03T07:30	2002-07-03T07:30	3	3
EX	56798001	PLACEBO	0	mg	CAPSULE	QD	TREATMENT 1	2002-07-03T07:30	2002-07-03T07:30	3	3
EX	56798001	DRUG X	20	mg	TABLET	QD	TREATMENT 2	2002-07-09T07:35	2002-07-10T07:30	9	10
EX	56798001	PLACEBO	0	mg	CAPSULE	QD	TREATMENT 2	2002-07-09T07:35	2002-07-10T07:30	9	10
EX	56798001	DRUG X	20	mg	TABLET	QD	TREATMENT 2	2002-07-11T07:34	2002-07-11T07:34	11	11
EX	56798001	PLACEBO	0	mg	CAPSULE	QD	TREATMENT 2	2002-07-11T07:34	2002-07-11T07:34	11	11

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Dosing Data Collection (con't)

- PC also has a variable for relative dose date/time, PCRFTDTC, Date/Time of Reference Point.

- PC would only have the dose time point relevant to PK collection.

- By only including time of dose in the PC domain, dose timing (if collected) data can be lost.

DOMAIN	USUBJID	VISIT	PCTPT	PCDTC	PCTPTREF	PCRFTDTC
PC	56798001	Day 1	PREDOSE	2002-07-01T07:25	NEXT DOSE	2002-07-01T07:30
PC	56798001	Day 1	1 HR	2002-07-01T08:30	PRIOR DOSE	2002-07-01T07:30
PC	56798001	Day 1	2 HR	2002-07-01T09:33	PRIOR DOSE	2002-07-01T07:30
PC	56798001	Day 1	4 HR	2002-07-01T11:30	PRIOR DOSE	2002-07-01T07:30
PC	56798001	Day 1	6 HR	2002-07-01T13:29	PRIOR DOSE	2002-07-01T07:30
PC	56798001	Day 1	12 HR	2002-07-01T19:35	PRIOR DOSE	2002-07-01T07:30
PC	56798001	Day 1	24 HR	2002-07-02T07:20	PRIOR DOSE	2002-07-01T07:30
PC	56798001	Day 9	PREDOSE	2002-07-09T07:15	NEXT DOSE	2002-07-09T07:35

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Dosing Data Collection (con't)

- EX versus EC (con't)
  - EX can be over simplified and granular information can be lost
  - Dose data can be represented as a date range during which the drug was taken using start and end dates.

DOMAIN	USUBJID	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXDOSFRQ	EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
EX	56798001	DRUG X	10	mg	TABLET	QD	TREATMENT 1	2002-07-01	2002-07-03	1	3
EX	56798001	PLACEBO	0	mg	CAPSULE	QD	TREATMENT 1	2002-07-01	2002-07-03	1	3
EX	56798001	DRUG X	20	mg	TABLET	QD	TREATMENT 2	2002-07-09	2002-07-11	9	11
EX	56798001	PLACEBO	0	mg	CAPSULE	QD	TREATMENT 2	2002-07-09	2002-07-11	9	11

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Dosing Data Collection (con't)

- Dose records for PKPD analysis dataset created from a range of dates from EX are expanded into individual dose records and dose times from PC

- Time from PC carried backward then forward to fill in missing time
  - PC only had times recorded on day 1 and 9

USUBJID	TRT	DTTM	AMT	EVID	DAY
56798001	DRUG X 10 mg	2002-07-01T07:30	10	1	1
56798002	DRUG X 10 mg	2002-07-02T07:35	10	1	2
56798001	DRUG X 10 mg	2002-07-03T07:35	10	1	3
56798001	DRUG X 20 mg	2002-07-09T07:35	20	1	9
56798001	DRUG X 20 mg	2002-07-10T07:35	20	1	10
56798001	DRUG X 20 mg	2002-07-11T07:35	20	1	11

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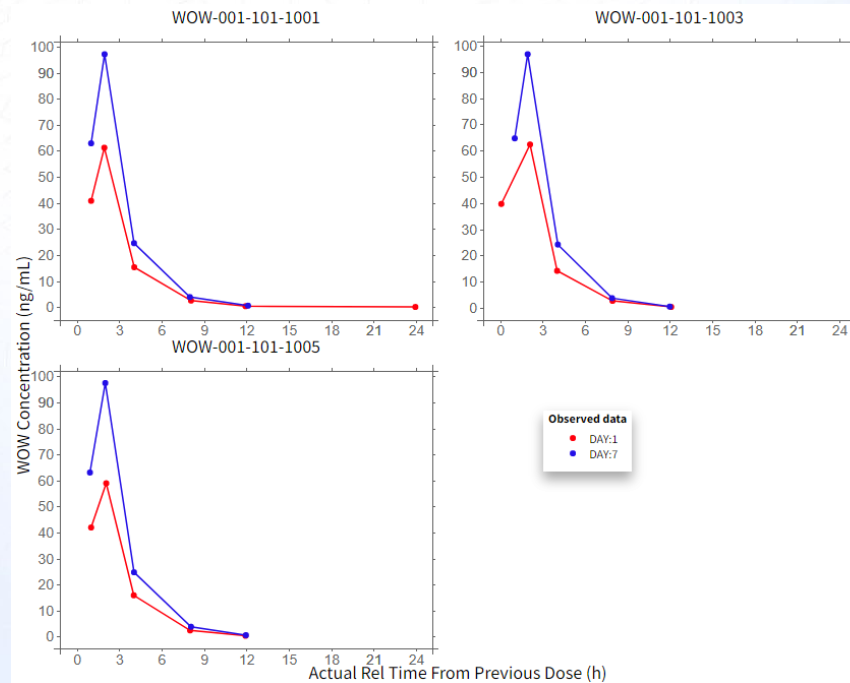# Dosing Data Collection (con't)

- Compared to dose records from well recorded date/time from EX

USUBJID	TRT	DTTM	AMT	EVID	DAY
56798001	DRUG X 10 mg	2002-07-01T07:30	10	1	1
56798002	DRUG X 10 mg	2002-07-02T07:33	10	1	2
56798001	DRUG X 10 mg	2002-07-03T07:30	10	1	3
56798001	DRUG X 20 mg	2002-07-09T07:35	20	1	9
56798001	DRUG X 20 mg	2002-07-10T07:30	20	1	10
56798001	DRUG X 20 mg	2002-07-11T07:34	20	1	11

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Dosing Data Collection (con't)

- Example of how time since previous dose is used graphically

Dosing Data Collection (con't)

Importance of collecting actual date/time

- What if the first dose date/time was not collected and recorded?

- How would the analysis data be affected?

USUBJID	AFRLT	AMT	DOSEA	DV	DVID	EVDTC	AVISIT	ATPT
WOW-001-101-1001	-0.1	.	100	15.0434962	2	2005-01-15T07:59	Day 1	PREDOSE
WOW-001-101-1001	-0.08333333	.	100	0.05	1	2005-01-15T08:00	Day 1	PREDOSE
WOW-001-101-1001	0	100	100	.	0	2005-01-15T08:05	Day 1	
WOW-001-101-1001	1.016666667	.	100	40.788	1	2005-01-15T09:06	Day 1	1 HR
WOW-001-101-1001	1.95	.	100	61.182	1	2005-01-15T10:02	Day 1	2 HR
WOW-001-101-1001	4.066666667	.	100	15.2955	1	2005-01-15T12:09	Day 1	4 HR
WOW-001-101-1001	8.083333333	.	100	2.4926	1	2005-01-15T16:10	Day 1	8 HR
WOW-001-101-1001	11.93333333	.	100	0.3399	1	2005-01-15T20:01	Day 1	12 HR
WOW-001-101-1001	23.95	.	100	0.05	1	2005-01-16T08:02	Day 1	24 HR
WOW-001-101-1001	24.06666667	.	100	15.2946355	2	2005-01-16T08:09	Day 2	PREDOSE
WOW-001-101-1001	24.16666667	100	100	.	0	2005-01-16T08:15	Day 2	
WOW-001-101-1001	48.06666667	.	100	16.7369319	2	2005-01-17T08:09	Day 3	PREDOSE
WOW-001-101-1001	48.08333333	.	100	0.05	1	2005-01-17T08:10	Day 3	PREDOSE
WOW-001-101-1001	48.16666667	100	100	.	0	2005-01-17T08:15	Day 3	
WOW-001-101-1001	72.06666667	.	100	14.7353095	2	2005-01-18T08:09	Day 4	PREDOSE
WOW-001-101-1001	72.16666667	100	100	.	0	2005-01-18T08:15	Day 4	
WOW-001-101-1001	96.06666667	.	100	15.2376866	2	2005-01-19T08:09	Day 5	PREDOSE
WOW-001-101-1001	96.08333333	.	100	0.05	1	2005-01-19T08:10	Day 5	PREDOSE
WOW-001-101-1001	96.16666667	100	100	.	0	2005-01-19T08:15	Day 5	
WOW-001-101-1001	120.2333333	.	100	13.4195038	2	2005-01-20T08:19	Day 6	PREDOSE
WOW-001-101-1001	120.25	.	100	0.05	1	2005-01-20T08:20	Day 6	PREDOSE
WOW-001-101-1001	120.3333333	100	100	.	0	2005-01-20T08:25	Day 6	
WOW-001-101-1001	144.3166667	.	100	16.4078954	2	2005-01-21T08:24	Day 7	PREDOSE
WOW-001-101-1001	144.3333333	.	100	0.05	1	2005-01-21T08:25	Day 7	PREDOSE
WOW-001-101-1001	144.4166667	100	100	.	0	2005-01-21T08:30	Day 7	
WOW-001-101-1001	145.4333333	.	100	62.8641	1	2005-01-21T09:31	Day 7	1 HR

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Dosing Data Collection (con't)

- Times would be carried back from last recorded time to impute time other dose records
- Typical to collect dose date/time in relation to PK sampling.
- Notice the Pre-dose hemoglobin sample would shift to be post dose using 'actual' date / time.

USUBJID	AFRLT	AMT	DOSEA	DV	DVID	EVDTC	AVISIT	ATPT
WOW-001-101-1003	0	100	100	.	0	2005-01-15T08:35	Day 1	
WOW-001-101-1003	0.06666667	.	100	13.7936115	2	2005-01-15T08:39	Day 1	PREDOSE
WOW-001-101-1003	23.7333333	.	100	17.0556086	2	2005-01-16T08:19	Day 2	PREDOSE
WOW-001-101-1003	24	100	100	.	0	2005-01-16T08:35	Day 2	
WOW-001-101-1003	47.7333333	.	100	16.1262527	2	2005-01-17T08:19	Day 3	PREDOSE
WOW-001-101-1003	48	100	100	.	0	2005-01-17T08:35	Day 3	
WOW-001-101-1003	71.7333333	.	100	17.9639663	2	2005-01-18T08:19	Day 4	PREDOSE
WOW-001-101-1003	72	100	100	.	0	2005-01-18T08:35	Day 4	
WOW-001-101-1003	95.7333333	.	100	16.9158141	2	2005-01-19T08:19	Day 5	PREDOSE
WOW-001-101-1003	96	100	100	.	0	2005-01-19T08:35	Day 5	
WOW-001-101-1003	119.9	.	100	17.4911633	2	2005-01-20T08:29	Day 6	PREDOSE
WOW-001-101-1003	120	100	100	.	0	2005-01-20T08:35	Day 6	
WOW-001-101-1003	144.483333	.	100	13.5690272	2	2005-01-21T09:04	Day 7	PREDOSE
WOW-001-101-1003	144.5	.	100	0.05	1	2005-01-21T09:05	Day 7	PREDOSE
WOW-001-101-1003	144.583333	100	100	.	0	2005-01-21T09:10	Day 7	
WOW-001-101-1003	145.616667	.	100	64.6551	1	2005-01-21T10:12	Day 7	1 HR
WOW-001-101-1003	146.533333	.	100	96.714	1	2005-01-21T11:07	Day 7	2 HR
WOW-001-101-1003	148.666667	.	100	24.1785	1	2005-01-21T13:15	Day 7	4 HR

collected 2 doses, day prior and day of PK

imputed by carrying time backward

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Dosing Data Collection (con't)

Accurate Dose Amount

- PKPD analysis dataset needs accurate dose amounts per dose administration
- Example of EXDOSE with summarized amounts
  - Refer to EXDOSFRQ

DOMAIN	USUBJID	EXTRT	EXDOSE	EXDOSU	EXDOSFRQ	EXSTDTC	EXENDTC	EXSTDY	EXENDY
EX	03-025	Comparator	20	ug	EVERY 2 WEEKS	2018-06-05	2019-06-03	449	812
EX	03-025	Comparator	60	ug	40 MCG EVERY 2 WEEKS 20 MCG EVERY 2 WEEKS	2019-06-04	2019-08-26	813	896
EX	03-025	Comparator	40	ug	EVERY 2 WEEKS	2019-08-27	2019-09-23	897	924
EX	03-025	Comparator	100	ug	EVERY 4 WEEKS	2019-09-24	2019-11-26	925	988
EX	03-025	Comparator	130	ug	100 MCG EVERY 2 WEEKS 30 MCG EVERY 2 WEEKS	2019-11-27	2019-12-16	989	1008
EX	03-025	Comparator	130	ug	40 MCG EVERY 10 DAYS, 50 MCG EVERY 10 DAYS, 40 MCG EVERY 10 DAYS	2019-12-17	2020-03-10	1009	1093

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Dosing Data Collection (con't)

Informative Dose Amount (con't)

USUBJID	EXDOSE	EXDOSU	EXSTDTC	EXENDTC	DATE	DOSE	LSTDSDUR	EXDOSFRQ	TFPD
03-025	20	ug	2018-06-05	2019-06-03	2019-05-21	20	14	EVERY 2 WEEKS	14
03-025	60	ug	2019-06-04	2019-08-26	2019-06-04	40	14	40 MCG EVERY 2 WEEKS20 MCG EVERY 2 WEEKS	14
03-025	60	ug	2019-06-04	2019-08-26	2019-06-18	20	14	40 MCG EVERY 2 WEEKS20 MCG EVERY 2 WEEKS	14
03-025	60	ug	2019-06-04	2019-08-26	2019-07-02	40	14	40 MCG EVERY 2 WEEKS20 MCG EVERY 2 WEEKS	14
03-025	60	ug	2019-06-04	2019-08-26	2019-07-16	20	14	40 MCG EVERY 2 WEEKS20 MCG EVERY 2 WEEKS	14
03-025	60	ug	2019-06-04	2019-08-26	2019-07-30	40	14	40 MCG EVERY 2 WEEKS20 MCG EVERY 2 WEEKS	14
03-025	60	ug	2019-06-04	2019-08-26	2019-08-13	20	14	40 MCG EVERY 2 WEEKS20 MCG EVERY 2 WEEKS	14
03-025	40	ug	2019-08-27	2019-09-23	2019-08-27	40	14	EVERY 2 WEEKS	14
03-025	40	ug	2019-08-27	2019-09-23	2019-09-10	40	14	EVERY 2 WEEKS	14
03-025	100	ug	2019-09-24	2019-11-26	2019-09-24	100	28	EVERY 4 WEEKS	14
03-025	100	ug	2019-09-24	2019-11-26	2019-10-22	100	28	EVERY 4 WEEKS	28
03-025	100	ug	2019-09-24	2019-11-26	2019-11-19	100	28	EVERY 4 WEEKS	28
03-025	130	ug	2019-11-27	2019-12-16	2019-11-27	100	14	100 MCG EVERY 2 WEEKS 30 MCG EVERY 2 WEEKS	8
03-025	130	ug	2019-11-27	2019-12-16	2019-12-11	30	14	100 MCG EVERY 2 WEEKS 30 MCG EVERY 2 WEEKS	14
03-025	130	ug	2019-12-17	2020-03-10	2019-12-17	40	10	40 MCG EVERY 10 DAYS, 50 MCG EVERY 10 DAYS, 40 MCG EVERY 10 DAYS	6
03-025	130	ug	2019-12-17	2020-03-10	2019-12-27	50	10	40 MCG EVERY 10 DAYS, 50 MCG EVERY 10 DAYS, 40 MCG EVERY 10 DAYS	10
03-025	130	ug	2019-12-17	2020-03-10	2020-01-06	40	10	40 MCG EVERY 10 DAYS, 50 MCG EVERY 10 DAYS, 40 MCG EVERY 10 DAYS	10
03-025	130	ug	2019-12-17	2020-03-10	2020-01-16	40	10	40 MCG EVERY 10 DAYS, 50 MCG EVERY 10 DAYS, 40 MCG EVERY 10 DAYS	10

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Dosing Data Collection (con't)

BID Doses

- Capturing AM / PM dosing in EX

USUBJID	EXSEQ	EXGRPID	EXDOSE	EXDOSU	EXDOSFRQ	EXSTDTC	EXENDTC	EXSTDY	EXENDY	EXTPT
WOW-101-001	1	WOW_LOGS_1_AM	300	mg	BID	2021-06-11	2021-06-16	1	6	AM DOSE
WOW-101-001	2	WOW_LOGS_1_PM	300	mg	BID	2021-06-11	2021-06-16	1	6	PM DOSE
WOW-101-001	3	WOW_LOGS_1_AM	300	mg	BID	2021-06-17	2021-06-17	7	7	AM DOSE
WOW-101-001	4	WOW_LOGS_1_PM	0	mg	BID	2021-06-17	2021-06-17	7	7	PM DOSE
WOW-101-001	5	WOW_LOGS_1_AM	300	mg	BID	2021-06-18	2021-06-20	8	10	AM DOSE
WOW-101-001	6	WOW_LOGS_1_PM	300	mg	BID	2021-06-18	2021-06-20	8	10	PM DOSE
WOW-101-001	7	WOW_LOGS_1_AM	0	mg	BID	2021-06-21	2021-06-21	11	11	AM DOSE
WOW-101-001	8	WOW_LOGS_1_PM	300	mg	BID	2021-06-21	2021-06-21	11	11	PM DOSE
WOW-101-001	9	WOW_LOGS_1_AM	300	mg	BID	2021-06-22	2021-06-25	12	15	AM DOSE

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Dosing Data Collection (con't)

BID Doses (con't)

- SUPPEX captured AM/PM of start and stop dates (EXSTDTC/ EXENDTC)

USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
WOW-101-001	EXSEQ	1	EXENAMPM	TIME OF STOP DATE	AM	CRF
WOW-101-001	EXSEQ	1	EXSTAMPM	TIME OF START DATE	AM	CRF
WOW-101-001	EXSEQ	2	EXENAMPM	TIME OF STOP DATE	AM	CRF
WOW-101-001	EXSEQ	2	EXSTAMPM	TIME OF START DATE	AM	CRF
WOW-101-001	EXSEQ	3	EXENAMPM	TIME OF STOP DATE	AM	CRF
WOW-101-001	EXSEQ	3	EXSTAMPM	TIME OF START DATE	AM	CRF
WOW-101-001	EXSEQ	4	EXENAMPM	TIME OF STOP DATE	AM	CRF
WOW-101-001	EXSEQ	4	EXSTAMPM	TIME OF START DATE	AM	CRF
WOW-101-001	EXSEQ	5	EXENAMPM	TIME OF STOP DATE	AM	CRF
WOW-101-001	EXSEQ	5	EXSTAMPM	TIME OF START DATE	AM	CRF
WOW-101-001	EXSEQ	6	EXENAMPM	TIME OF STOP DATE	AM	CRF
WOW-101-001	EXSEQ	6	EXSTAMPM	TIME OF START DATE	AM	CRF
WOW-101-001	EXSEQ	7	EXENAMPM	TIME OF STOP DATE	AM	CRF
WOW-101-001	EXSEQ	7	EXSTAMPM	TIME OF START DATE	AM	CRF

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Dosing Data Collection (con't)

BID Doses (con't)

- Dose times in SUPPPC only around PK sampling

USUBJID	IDVAR	QNAM	QLABEL	QVAL	QORIG
WOW-101-001	PCSEQ	DOSEDTC	DATE AND TIME OF DOSE OF WOW	2021-06-11T13:15	CRF
WOW-101-001	PCSEQ	WOWDTC	DOSE DT AFTER THE PREDOSE PK SAMPLE	2021-06-18T13:05	CRF
WOW-101-001	PCSEQ	WOWPDTC	DOSE DT PRIOR TO THE PREDOSE PK SAMPLE	2021-06-17T12:05	CRF
WOW-101-001	PCSEQ	WOWDTC	DOSE DT AFTER THE PREDOSE PK SAMPLE	2021-06-25T10:35	CRF
WOW-101-001	PCSEQ	WOWPDTC	DOSE DT PRIOR TO THE PREDOSE PK SAMPLE	2021-06-24T15:35	CRF
WOW-101-001	PCSEQ	WOWPDTC	DOSE DT PRIOR TO THE PREDOSE PK SAMPLE	2021-07-06T16:16	CRF

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Dosing Data Collection (con't)

BID Doses (con't)

- Coded for pop PK analysis

ID	EVID	DTTM	TSFD	TSPD	DOSE	AMT	DV	ACTDOSE	
10001	1	2021-06-11T13:15:00Z	0	0	300	300	.		1
10001	0	2021-06-11T13:45:00Z	0.5	0.5	300	.	20.6	.	
10001	0	2021-06-11T14:19:00Z	1.07	1.07	300	.	140	.	
10001	0	2021-06-11T14:49:00Z	1.57	1.57	300	.	161	.	
10001	0	2021-06-11T16:58:00Z	3.72	3.72	300	.	238	.	
10001	1	2021-06-11T17:13:00Z	3.97	0	300	300	.		0
10001	1	2021-06-12T03:35:00Z	14.33	0	300	300	.		0
10001	1	2021-06-12T15:35:00Z	26.33	0	300	300	.		0
10001	1	2021-06-13T03:35:00Z	38.33	0	300	300	.		0
10001	1	2021-06-13T15:35:00Z	50.33	0	300	300	.		0
10001	1	2021-06-14T03:35:00Z	62.33	0	300	300	.		0
10001	1	2021-06-14T15:35:00Z	74.33	0	300	300	.		0
10001	1	2021-06-15T03:35:00Z	86.33	0	300	300	.		0
10001	1	2021-06-15T15:35:00Z	98.33	0	300	300	.		0
10001	1	2021-06-16T03:35:00Z	110.33	0	300	300	.		0
10001	1	2021-06-16T15:35:00Z	122.33	0	300	300	.		0
10001	1	2021-06-17T12:05:00Z	142.83	0	300	300	.		1
10001	0	2021-06-18T11:55:00Z	166.67	23.83	300	.	326	.	
10001	1	2021-06-18T13:05:00Z	167.83	0	300	300	.		1
10001	1	2021-06-18T15:35:00Z	170.33	0	300	300	.		0

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Dosing Data Collection (con't)

BID Doses (con't)

- Coded for pop PK analysis
- Skipped dose in AM 2021-06-21

ID	EVID	DTTM	TSFD	TSPD	DOSE	AMT	DV	ACTDOSE
10001	1	2021-06-19T03:35:00Z	182.33	0	300	300	.	0
10001	1	2021-06-19T15:35:00Z	194.33	0	300	300	.	0
10001	1	2021-06-20T03:35:00Z	206.33	0	300	300	.	0
10001	1	2021-06-20T15:35:00Z	218.33	0	300	300	.	0
10001	1	2021-06-21T15:35:00Z	242.33	0	300	300	.	0
10001	1	2021-06-22T03:35:00Z	254.33	0	300	300	.	0
10001	1	2021-06-22T15:35:00Z	266.33	0	300	300	.	0
10001	1	2021-06-23T03:35:00Z	278.33	0	300	300	.	0
10001	1	2021-06-23T15:35:00Z	290.33	0	300	300	.	0
10001	1	2021-06-24T03:35:00Z	302.33	0	300	300	.	0
10001	1	2021-06-24T15:35:00Z	314.33	0	300	300	.	1
10001	0	2021-06-25T10:27:00Z	333.2	18.87	300	.	623	.
10001	1	2021-06-25T10:35:00Z	333.33	0	300	300	.	1
10001	0	2021-06-25T11:03:00Z	333.8	0.47	300	.	645	.
10001	0	2021-06-25T11:33:00Z	334.3	0.97	300	.	782	.
10001	0	2021-06-25T12:35:00Z	335.33	2	300	.	1140	.
10001	0	2021-06-25T14:12:00Z	336.95	3.62	300	.	801	.

Dosing Data Collection (con't)

Intravenous Doses (IV)

- Dose amount administered
- Start and stop date/ time of the infusion

USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXDOSFRQ	EXROUTE	EXSTDTC	EXENDTC
103-059	1	WOW 6.0 mg/kg	585	mg	INJECTION, SOLUTION, CONCENTRATE	ONCE	INTRAVENOUS	2019-11-11T10:00	2019-11-11T11:11
103-013	1	WOW 1.0 mg/kg	80	mg	INJECTION, SOLUTION, CONCENTRATE	ONCE	INTRAVENOUS	2019-06-12T10:05	2019-06-12T11:07
103-094	1	WOW 20.0 mg/kg	1790	mg	INJECTION, SOLUTION, CONCENTRATE	ONCE	INTRAVENOUS	2020-01-22T10:20	2020-01-22T11:20

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Dosing Data Collection (con't)

Intravenous Doses (IV) (con't)

- Dose interruption recorded in SUPPEX

USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
103-059	EXSEQ	1	EXCOMP	If Interrupted, was Infusion Complete?	Y	CRF
103-059	EXSEQ	1	EXENTIM2	Infusion Restart Stop Time	11:11	CRF
103-059	EXSEQ	1	EXINREAS	Reason for Interruption Adverse Event	N	CRF
103-059	EXSEQ	1	EXINT	Was Infusion Interrupted?	Y	CRF
103-059	EXSEQ	1	EXINTOTH	Reason for Interruption Other	Y	CRF
103-059	EXSEQ	1	EXINTSP	Reason for Interruption Other, specify	BULGING OBSERVED AT CATHETER SITE.	CRF
103-059	EXSEQ	1	EXREST	Was Infusion Restarted?	Y	CRF
103-059	EXSEQ	1	EXSTTIM2	Infusion Restart Time	10:12	CRF
103-013	EXSEQ	1	EXINREAS	Reason for Interruption Adverse Event	N	CRF
103-013	EXSEQ	1	EXINT	Was Infusion Interrupted?	N	CRF
103-013	EXSEQ	1	EXINTOTH	Reason for Interruption Other	N	CRF
103-094	EXSEQ	1	EXINREAS	Reason for Interruption Adverse Event	N	CRF
103-094	EXSEQ	1	EXINT	Was Infusion Interrupted?	N	CRF
103-094	EXSEQ	1	EXINTOTH	Reason for Interruption Other	N	CRF

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Dosing Data Collection (con't)

Intravenous Doses (IV) (con't)

- Treatment arm and volume administered also recorded in SUPPEX
  - Units not specified

USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
103-059	EXSEQ	1	EXDOSLVL	Dose Level	6	CRF
103-059	EXSEQ	1	EXTOTDOS	Total Volume Infused	50	CRF
103-013	EXSEQ	1	EXDOSLVL	Dose Level	1	CRF
103-013	EXSEQ	1	EXTOTDOS	Total Volume Infused	10	CRF
103-094	EXSEQ	1	EXDOSLVL	Dose Level	20	CRF
103-094	EXSEQ	1	EXTOTDOS	Total Volume Infused	105	CRF

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Data Collection (con't)

Intravenous Doses (IV) (con't)

- To facilitate understanding of the data provided, checks can be performed
- Treatment arm compared to provided or calculated dose
  - Treatment (mg/kg) x weight (kg) = Amount (mg)

Subject	Treatment	Baseline Weight (kg)	Amount (mg)	Calculated Dose(mg)
103-059	6 mg/kg	97.5	585	585
103-013	1 mg/kg	82.3	80	82.3
103-094	20 mg/kg	89.6	1790	1792

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Dosing Data Collection (con't)

Intravenous Doses (IV) (con't)

- If one value didn't make sense, further checks could be done programmatically

- Compare calculated dose to provided value

```
Differences
x = calculated from treatment and weight
y = EX$EXDOSE as DOSE

var.x    var.y    USUBJID    values.x    values.y
------   ------   --------   ---------   ---------
DOSE     DOSE     103-004    102         100
DOSE     DOSE     103-013    82.3        80
DOSE     DOSE     103-016    81.3        80
DOSE     DOSE     103-019    66.5        65
DOSE     DOSE     103-024    67.8        70
DOSE     DOSE     103-030    65.5        65
DOSE     DOSE     103-057    507         505
DOSE     DOSE     103-062    535.8       535
DOSE     DOSE     103-063    490.8       490
DOSE     DOSE     103-085    1456        1455
DOSE     DOSE     103-086    1364        1365
DOSE     DOSE     103-092    1794        1795
DOSE     DOSE     103-094    1792        1790
DOSE     DOSE     103-098    1732        1730
n = 14 of 60
```

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Dosing Data Collection (con't)

Intravenous Doses (IV) (con't)

- Dose records for IV in PK

USUBJID	EVID	DTTM	IENDTTM	RATE	DUR	AMT	WTKG	IMPDUR
		Date / Time	IV End Date/Time	mg/h	Duration (h)	Amount (mg)		DUR Imputation Flag
103-059	1	2019-11-11T10:00	2019-11-11T11:11	585	1	585	97.5	1
103-013	1	2019-06-12T10:05	2019-06-12T11:07	77.6699029	1.03	80	82.3	0
103-094	1	2020-01-22T10:20	2020-01-22T11:20	1790	1	1790	89.6	0

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Communication

- Transparent communication is key to creating successful PKPD analysis datasets
  - Programmer
    - If there are data issues, communicate them.
    - Agree on solutions with analyst / client
  - Analyst
    - Clearly communicate dataset needs for anticipated model
  - Data Provider
    - Communicate known issues / challenges
- Understand if working with interim or locked data
  - Communicate rules for working with interim data

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Communication

- Provide data specs / define documentation with data
    - Helps the end user understand what is presented in the data
- Protocol
    - Understanding the study design and assist in what to expect in the data
        - Check for expected dosing regimens
        - Check for planned sampling scheme
            - Full
            - Sparse
- Annotated CRF
    - Can assist understanding of what was captured
        - Units
        - Planned timing

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Documentation

- Clearly document any issues and solutions
  - Easily accessible
  - Supporting queries/output used to make decision
- Data specifications for the analysis dataset should be clear enough to create a summary for an end user of the analysis dataset
- Document code
  - Comments in code can assist in understanding by another user
    - May be a gap in time
    - May be another programmer / user

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Documentation

- Documentation for example BID dosing:
  - Expand EX start and stop dates to BID dosing records
  - SUPPEX to identify the am/pm for the start date and stop date of the range of dates
  - Dose time from SUPPPC. Protocol has patients hold the AM dose on in-clinic days.
  - Dose times from SUPPPC are retained backwards and forwards in 12 hr intervals for BID dose records
  - ACTDOSE flags records with provided actual date/times.
  - Remove skipped doses where dose =0.

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Documentation

- Irregular dosing frequency (QW, Q4W) example:
  - Exceptions can be shared and reviewed together
  - For this example, an output of suspicious dose frequencies and amounts was created, and review was requested. The feedback was documented in a copy of the output and stored with the programs that created the analysis dataset.

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Tips

- Check your analysis data prior to modeling the data
  - Keep track of the number of subjects in the dataset as well as the number of records
  - Check for common date/ time errors
    - Compare calculated time since previous dose to planned time points
      - Mixed up AM / PM time
      - Date not incremented past midnight
      - Year not incremented in January
  - Check calculated dose amounts compared to actual treatment
  - Check for subjects with values all below the limit of quantitation

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Tips

- Check your analysis data (con't)
  - Look at example subjects not just a few rows
  - Check for duplicate records by subject, time, record type (dose, PK analyte, PD),
  - Check that every subject has dose record(s) and no subjects have only dose records
    - Create a unique list of subjects with dose records and subjects with observations (PK or PD) and compare the lists programmatically.
  - Check time between doses
    - Compared to expected regimen (twice daily [BID], once daily [QD], etc.)
    - When expanding dose windows, extra dose records can be accidentally created

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Tips

- Check your analysis data (con't)
  - Check categorical variables by checking min and max within each level
    - AGECAT has expected min max values of AGE for each level
  - Combining multiple studies
    - Recheck categorical variables and decodes to ensure separate studies were coded the same
      - RACE, 1 numeric value should have only 1 decode value
    - Check ranges of covariates for reasonable values considering the unit
      - SCR may be in umol/L in one study and in mg/dL in another

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Tips

- Other useful data in analysis datasets
  - Self documenting dataset
    - Include decode (character) variables for categorical variables represented by numeric values
      - Numeric values may be preferred for analysis
      - Example age category, AGECAT = 1, ACECATC = < 18 yrs
  - Data needed for graphical exploration/analysis
    - Graphical exploration or EDA (exploratory data analysis) is a useful tool to understand your data prior to modeling
    - As well as a review of the analysis data build

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Conclusion

- Dosing data can be very complex as the few examples described
- Equally importance
  - Capturing useful information
  - Recording it in shared data (SDTM)
  - Utilizing it properly in the analysis dataset to inform modeling
- Awareness is key
  - What data available
  - Model goal and how the data will inform the model
- Reproduceable results

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Thank You

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