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An End User’s Perspective of Clinical Dosing Data Used for Population PK / PD Analysis with Non-Linear Mixed Effects Modeling

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BACKGROUND: Analysis Population PK/PD datasets are time-ordered datasets with records representing time course of events pertaining to drug administration and resulting concentrations and/or PD responses.

ADPPK EXAMPLE: popPK/PD analysis dataset

USUBJID	AFRLT	AMT	DV	DVID	EVDTCT	AVISIT	ATPT
WOW-001-101-1003	-0.10	.	13.79	2	2005-01-15T08:39	Day 1	PREDOSE
WOW-001-101-1003	-0.08	.	0.1	1	2005-01-15T08:40	Day 1	PREDOSE
WOW-001-101-1003	0.00	100	.	0	2005-01-15T08:45	Day 1	
WOW-001-101-1003	0.08	.	39.7	1	2005-01-15T08:50	Day 1	1 HR
WOW-001-101-1003	2.12	.	62.3	1	2005-01-15T10:52	Day 1	2 HR
WOW-001-101-1003	4.03	.	14.2	1	2005-01-15T12:47	Day 1	4 HR
WOW-001-101-1003	7.95	.	2.7	1	2005-01-15T16:42	Day 1	8 HR
WOW-001-101-1003	12.10	.	0.4	1	2005-01-15T20:51	Day 1	12 HR
WOW-001-101-1003	23.57	.	17.1	2	2005-01-16T08:19	Day 2	PREDOSE
WOW-001-101-1003	23.67	100	.	0	2005-01-16T08:25	Day 2	
WOW-001-101-1003	24.08	.	0.1	1	2005-01-16T08:50	Day 2	PREDOSE
WOW-001-101-1003	47.57	.	16.1	2	2005-01-17T08:19	Day 3	PREDOSE
WOW-001-101-1003	47.58	.	0.1	1	2005-01-17T08:20	Day 3	PREDOSE
WOW-001-101-1003	47.67	100	.	0	2005-01-17T08:25	Day 3	
WOW-001-101-1003	71.57	.	18.0	2	2005-01-18T08:19	Day 4	PREDOSE
WOW-001-101-1003	71.58	.	0.1	1	2005-01-18T08:20	Day 4	PREDOSE
WOW-001-101-1003	71.67	100	.	0	2005-01-18T08:25	Day 4	
WOW-001-101-1003	95.57	.	16.9	2	2005-01-19T08:19	Day 5	PREDOSE
WOW-001-101-1003	95.58	.	0.1	1	2005-01-19T08:20	Day 5	PREDOSE
WOW-001-101-1003	95.67	100	.	0	2005-01-19T08:25	Day 5	
WOW-001-101-1003	119.73	.	17.5	2	2005-01-20T08:29	Day 6	PREDOSE
WOW-001-101-1003	119.75	.	0.1	1	2005-01-20T08:30	Day 6	PREDOSE
WOW-001-101-1003	119.83	100	.	0	2005-01-20T08:35	Day 6	
WOW-001-101-1003	144.32	.	13.6	2	2005-01-21T09:04	Day 7	PREDOSE
WOW-001-101-1003	144.33	.	0.1	1	2005-01-21T09:05	Day 7	PREDOSE
WOW-001-101-1003	144.42	100	.	0	2005-01-21T09:10	Day 7	
WOW-001-101-1003	145.45	.	64.7	1	2005-01-21T10:12	Day 7	1 HR
WOW-001-101-1003	146.37	.	96.7	1	2005-01-21T11:07	Day 7	2 HR

AFRLT - Actual Rel Time from First Dose

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

- ACCURATE DOSE DATA:
- What if a dose date/time was not collected and recorded?
- How would the analysis data be affected?
- Dose amount and frequency
- How does partial information impact the analysis dataset?

A population PK/PD model is only as good as the data.

Capturing and sharing good data is key to accurate modeling.

Observing how clinical dosing data are used in population PK/PD modeling will lead to a more comprehensive collection and representation of clinical data.



DOSE DATE / TIME EXAMPLE: Scenario: No PK collected on Day 1. Dose administration date/time is typically collected in relation to PK sampling. Time would be carried backwards from the next collected time (Day 6). Notice the Pre-dose hemoglobin sample would shift to be post dose using ‘actual’ date / time.

USUBJID	AFRLT	AMT	DV	DVID	EVDTCT	AVISIT	ATPT
WOW-001-101-1003	0.00	100	.	0	2005-01-15T08:35	Day 1	
WOW-001-101-1003	0.07	.	13.8	2	2005-01-15T08:39	Day 1	PREDOSE
WOW-001-101-1003	23.73	.	17.1	2	2005-01-16T08:19	Day 2	PREDOSE
WOW-001-101-1003	24.00	100	.	0	2005-01-16T08:35	Day 2	
WOW-001-101-1003	47.73	.	16.1	2	2005-01-17T08:19	Day 3	PREDOSE
WOW-001-101-1003	48.00	100	.	0	2005-01-17T08:35	Day 3	
WOW-001-101-1003	71.73	.	18.0	2	2005-01-18T08:19	Day 4	PREDOSE
WOW-001-101-1003	72.00	100	.	0	2005-01-18T08:35	Day 4	
WOW-001-101-1003	95.73	.	16.9	2	2005-01-19T08:19	Day 5	PREDOSE
WOW-001-101-1003	96.00	100	.	0	2005-01-19T08:35	Day 5	
WOW-001-101-1003	119.90	.	17.5	2	2005-01-20T08:29	Day 6	PREDOSE
WOW-001-101-1003	120.00	100	.	0	2005-01-20T08:35	Day 6	
WOW-001-101-1003	144.48	.	13.6	2	2005-01-21T09:04	Day 7	PREDOSE
WOW-001-101-1003	144.50	.	0.1	1	2005-01-21T09:05	Day 7	PREDOSE
WOW-001-101-1003	144.58	100	.	0	2005-01-21T09:10	Day 7	
WOW-001-101-1003	145.62	.	64.7	1	2005-01-21T10:12	Day 7	1 HR
WOW-001-101-1003	146.53	.	96.7	1	2005-01-21T11:07	Day 7	2 HR

collected 2 doses, day prior and day of PK
imputed by carrying time backward

DOSE AMOUNT EXAMPLE: Dose administration data as provided(EX)

USUBJID	EXDOSE	EXDOSU	EXSTDTC	EXENDTC	EXDOSFRQ
03-025	20 ug		2018-06-05	2019-06-03	EVERY 2 WEEKS
03-025	60 ug		2019-06-04	2019-08-26	40 MCG EVERY 2 WEEKS 20
					MCG EVERY 2 WEEKS
03-025	40 ug		2019-08-27	2019-09-23	EVERY 2 WEEKS

USUBJID	DATE	AMT
03-025	2019-05-07	20
03-025	2019-05-21	20
03-025	2019-06-04	40
03-025	2019-06-18	20
03-025	2019-07-02	40
03-025	2019-07-16	20
03-025	2019-07-30	40
03-025	2019-08-13	20
03-025	2019-08-27	40
03-025	2019-09-10	40

EXDOSE did not have the correct amount to create expanded records for the analysis dataset. The amount (AMT) was derived from the description in EXDOSFRQ

- IV DOSING: Key data to capture and share:
- Start and stop date & time
 - Actual amount administered
 - Administration interruption details