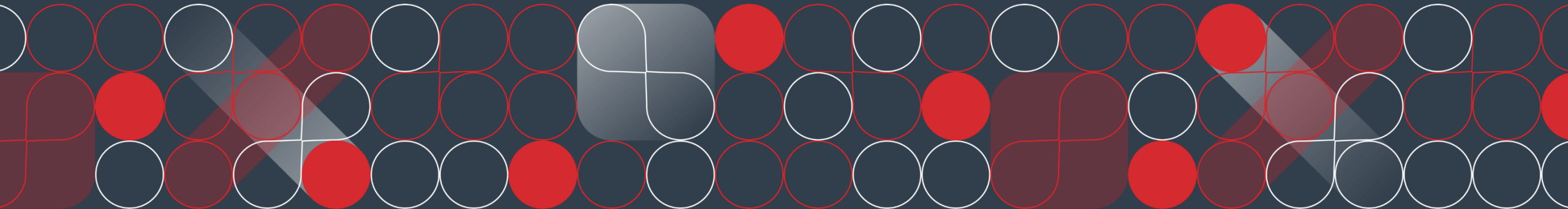


CT04: Challenges Faced When Creating Dosing Records for a Population PK Dataset

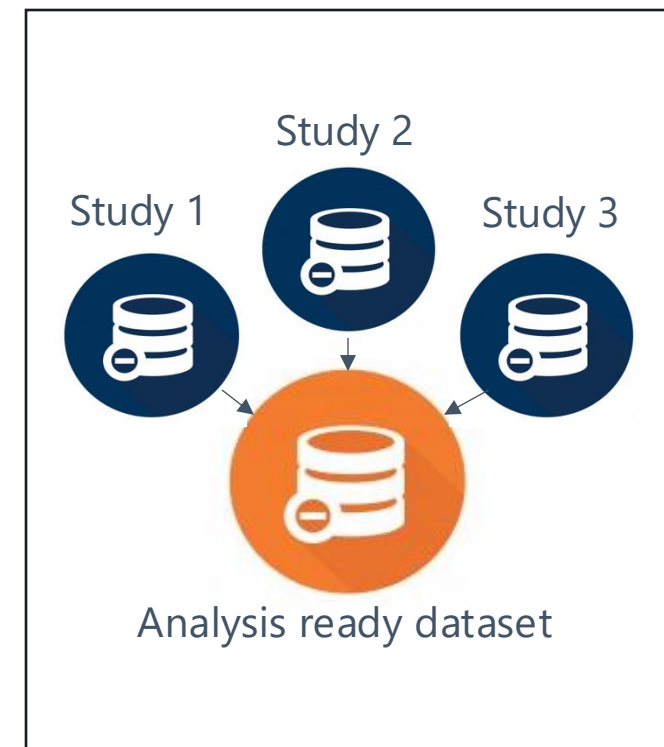
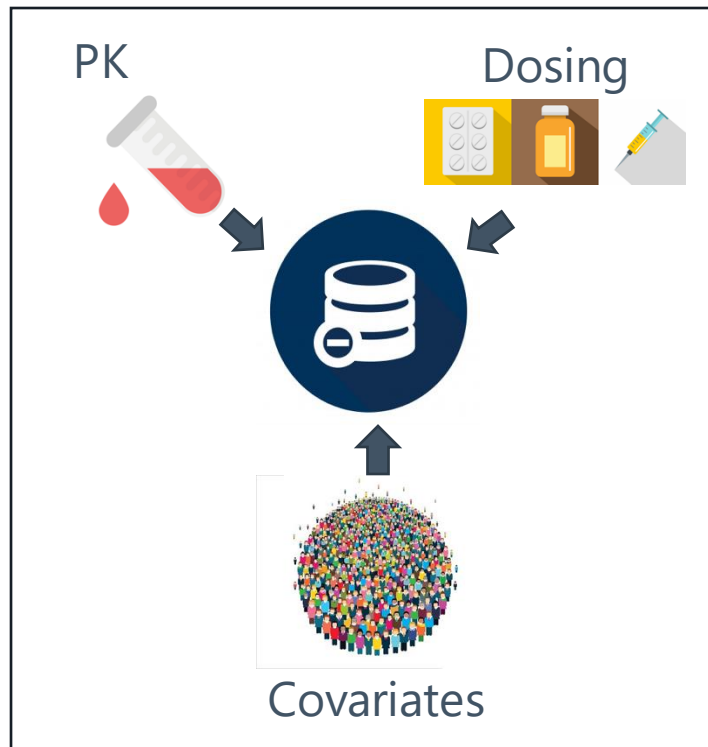
Gerly van der Vleuten and Marianne van Vugt

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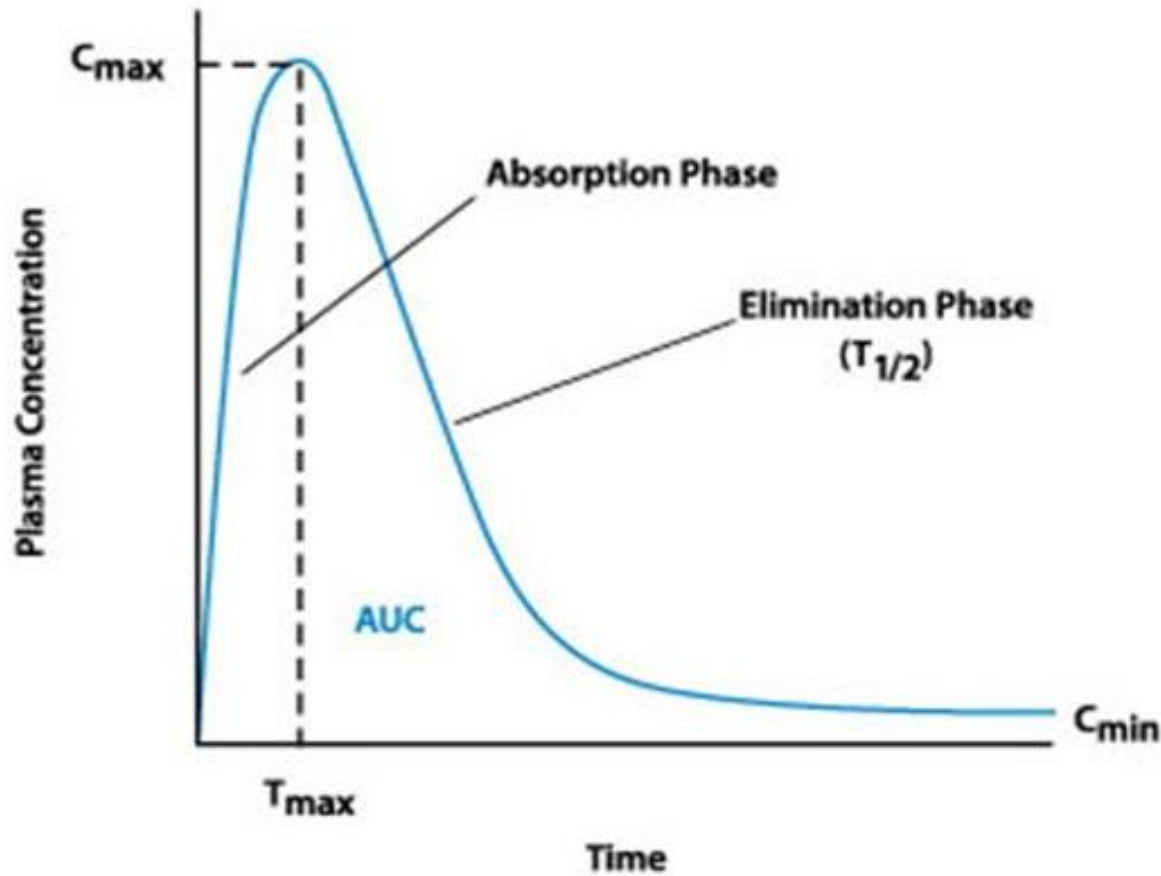
PopPK dataset

Population Pharmacokinetic dataset



Pharmacokinetic concentrations

Pharmacokinetic profile



Dosing records

One record per constant dosing interval per subject

Source data: sdtm.ex

Study Identifier	Domain Abbreviation	Unique Subject Identifier	Sequence Number	Dose	Dose Units	Route of Administration	Visit Name	Start Date/Time of Treatment	End Date/Time of Treatment	Study Day of Start of Treatment	Study Day of End of Treatment
STDY-001	EX	STDY-0011001002	1	140	mg	INTRAVENOUS	Cycle 1 Day 1	2016-12-28T11:00:00	2016-12-28T12:00:00	1	1
STDY-001	EX	STDY-0011001002	2	140	mg	INTRAVENOUS	Cycle 1 Day 15	2017-01-11T11:30:00	2017-01-11T12:30:00	15	15
STDY-001	EX	STDY-0011001002	3	140	mg	INTRAVENOUS	Cycle 2 Day 1	2017-01-25T11:00:00	2017-01-25T12:00:00	29	29
STDY-001	EX	STDY-0011001002	4	140	mg	INTRAVENOUS	Cycle 2 Day 15	2017-02-08T11:00:00	2017-02-08T12:00:00	43	43
STDY-001	EX	STDY-0011001002	5	140	mg	INTRAVENOUS	Cycle 3 Day 1	2017-02-23T11:00:00	2017-02-23T12:00:00	58	58
STDY-001	EX	STDY-0011001002	6	140	mg	INTRAVENOUS	Cycle 3 Day 15	2017-03-08T11:00:00	2017-03-08T12:00:00	71	71

Output dataset: ppk

STUDYN	SUBJID	ID	DOSE	DUR	RATE	DAY	NTIME	TIME	ADTM	USUBJID
1	11001002	1	140	1	140	1	0	0	2016-12-28T11:00:00	STDY-0011001002
1	11001002	1	140	1	140	15	336	336.5	2017-01-11T11:30:00	STDY-0011001002
1	11001002	1	140	1	140	29	672	672	2017-01-25T11:00:00	STDY-0011001002
1	11001002	1	140	1	140	43	1008	1008	2017-02-08T11:00:00	STDY-0011001002
1	11001002	1	140	1	140	58	1368	1368	2017-02-23T11:00:00	STDY-0011001002
1	11001002	1	140	1	140	71	1680	1680	2017-03-08T11:00:00	STDY-0011001002

Dosing records

Dosing data provided in intervals

Source data: sdtm.ex

Study Identifier	Domain Abbreviation	Unique Subject Identifier	Sequence Number	Dose	Dose Units	Dose Form	Intended Dosing Regimen	Start Date/Time of Treatment	End Date/Time of Treatment	Study Day of Start of Treatment	Study Day of End of Treatment	End Relative to Reference Time Point	End Reference Time Point
STDY-001	EX	STDY-0011001050	1	100	mg	CAPSULE	100 mg BID	2015-04-27T08:00	2015-05-24T20:00	1	28		
STDY-001	EX	STDY-0011001050	2	50	mg	CAPSULE	100 mg BID	2015-05-25T08:00	2015-05-25T20:00	29	29		
STDY-001	EX	STDY-0011001050	3	100	mg	CAPSULE	100 mg BID	2015-05-26T09:00	2015-06-11.	30	46		
STDY-001	EX	STDY-0011001050	4	50	mg	CAPSULE	100 mg BID	2015-06-12.	2015-06-12.	47	47		
STDY-001	EX	STDY-0011001050	5	100	mg	CAPSULE	100 mg BID	2015-06-13T13:00	2015-06-22.	48	57		
STDY-001	EX	STDY-0011001050	6	50	mg	CAPSULE	100 mg BID	2015-06-23.	2015-06-23.	58	58		
STDY-001	EX	STDY-0011001050	7	25	mg	CAPSULE	100 mg BID	2015-06-24.	2015-06-24.	59	59		
STDY-001	EX	STDY-0011001050	8	100	mg	CAPSULE	100 mg BID	2015-06-25.	2015-07-09.	60	74		
STDY-001	EX	STDY-0011001050	9	50	mg	CAPSULE	100 mg BID	2015-07-10.	2015-07-10.	75	75		
STDY-001	EX	STDY-0011001050	10	75	mg	CAPSULE	100 mg BID	2015-07-11.	2015-07-11.	76	85		

STUDYN	SUBJID	ID	DOSE	DAY	NTIME	NTAD	TIME	TAD	EVID	DV	ADTM	USUBJID
1	11001033	1	200	1	0	0	0	0	1		2015-04-27T09:00	STDY-0011001033
1	11001033	1	200	2	24	0		0	1		2015-04-28.	STDY-0011001033
1	11001033	1	200	3	48	0		0	1		2015-04-29.	STDY-0011001033
1	11001033	1	200	4	72	0		0	1		2015-04-30.	STDY-0011001033
1	11001033	1	200	5	96	0		0	1		2015-05-01.	STDY-0011001033
1	11001033	1	200	28	648	0	648	0	1		2015-05-24T09:00	STDY-0011001033
1	11001033	1	150	29	672	0	671	0	1		2015-05-25T08:00	STDY-0011001033
1	11001033	1	200	30	696	0		0	1		2015-05-26.	STDY-0011001033
1	11001033	1	200	31	720	0		0	1		2015-05-27.	STDY-0011001033
1	11001033	1	200	32	744	0		0	1		2015-05-28.	STDY-0011001033

Dosing records

Dosing data provided in intervals

Source data: sdtm.pc

Study Identifier	Domain Abbreviation	Unique Subject Identifier	Sequence Number	Pharmacokinetic Test Name	Result or Finding in Original Units	Original Units	Visit Name	Planned Time Point Name	Date/Time of Specimen Collection	Time Point Reference	Date/Time of Reference Point
STDY-001	PC	STDY-0011001033	1	MADR1234	0.0203	ug/mL	DAY 7	PRE-DOSE	2015-05-03T11:00	Most recent dose	2015-05-02T09:00
STDY-001	PC	STDY-0011001033	2	MADR1234	0.0619	ug/mL	DAY 7	1 HOURS POST-DOSE	2015-05-03T12:00	Most recent dose	2015-05-03T11:00
STDY-001	PC	STDY-0011001033	3	MADR1234	0.0336	ug/mL	DAY 7	4 HOURS POST-DOSE	2015-05-03T15:00	Most recent dose	2015-05-03T11:00

Dosing records

STUDYN	SUBJID	ID	DOSE	DAY	NTIME	NTAD	TIME	TAD	EVID	DV	ADTM	USUBJID
1	11001033	1	200	1	0	0	0	0	1		2015-04-27T09:00	STDY-0011001033
1	11001033	1	200	2	24	0		0	1		2015-04-28.	STDY-0011001033
1	11001033	1	200	3	48	0		0	1		2015-04-29.	STDY-0011001033
1	11001033	1	200	4	72	0		0	1		2015-04-30.	STDY-0011001033
1	11001033	1	200	5	96	0		0	1		2015-05-01.	STDY-0011001033
1	11001033	1	200	6	120	0	120	0	1		2015-05-02T09:00	STDY-0011001033
1	11001033	1	200	7	144	0	146	0	1		2015-05-03T11:00	STDY-0011001033
1	11001033	1	200	8	168	0		0	1		2015-05-04.	STDY-0011001033
1	11001033	1	200	9	192	0		0	1		2015-05-05.	STDY-0011001033

Dosing records – PopPK dataset

Imputation rules

If dosing time is missing:

1. On a day of a pre-dose PK sample, impute as trough date/time
2. On a date when post-dose PK samples are available, use the first post-dose sample to back-impute the dosing time
3. If no PK sample associated on the same day, impute by using next or previous dosing time

Imputed date/time records should be flagged.

Dosing records – ADDL and II

One record per constant dosing interval per subject

Source data: sdtm.ex

Study Identifier	Domain Abbreviation	Unique Subject Identifier	Sequence Number	Dose	Dose Units	Dose Form	Intended Dosing Regimen	Start Date/Time of Treatment	End Date/Time of Treatment	Study Day of Start of Treatment	Study Day of End of Treatment
STDY-001	EX	STDY-0011001033	1	200	mg	CAPSULE	200 mg QD	2015-04-27T09:00	2015-05-24T09:00	1	28
STDY-001	EX	STDY-0011001033	2	150	mg	CAPSULE	200 mg QD	2015-05-25T08:00	2015-05-25T08:00	29	29
STDY-001	EX	STDY-0011001033	3	200	mg	CAPSULE	200 mg QD	2015-05-26.	2015-06-11.	30	46
STDY-001	EX	STDY-0011001033	4	150	mg	CAPSULE	200 mg QD	2015-06-12T10:00	2015-06-12.	47	47
STDY-001	EX	STDY-0011001033	5	200	mg	CAPSULE	200 mg QD	2015-06-13.	2015-06-22.	48	57
STDY-001	EX	STDY-0011001033	6	150	mg	CAPSULE	200 mg QD	2015-06-23T09:00	2015-06-23.	58	58
STDY-001	EX	STDY-0011001033	7	100	mg	CAPSULE	200 mg QD	2015-06-24.	2015-06-24.	59	59
STDY-001	EX	STDY-0011001033	8	200	mg	CAPSULE	200 mg QD	2015-06-25.	2015-07-09.	60	74
STDY-001	EX	STDY-0011001033	9	150	mg	CAPSULE	200 mg QD	2015-07-10.	2015-07-10.	75	75
STDY-001	EX	STDY-0011001033	10	200	mg	CAPSULE	200 mg QD	2015-07-11.	2015-07-11.	76	85
STDY-001	EX	STDY-0011001033	11	150	mg	CAPSULE	200 mg QD	2015-07-21.	2015-07-21.	86	102

STUDYN	SUBJID	ID	DOSE	ADDL	II	DAY	NTIME	NTAD	TIME	TAD	EVID	DV	ADTM	USUBJID
1	11001033	1	200	27	24	1	0	0	0	0	1		2015-04-27T09:00	STDY-0011001033
1	11001033	1	150	0	0	29	672	0	671	0	1		2015-05-25T08:00	STDY-0011001033
1	11001033	1	200	16	0	30	696	0		0	1		2015-05-26.	STDY-0011001033
1	11001033	1	150	0	0	47	1104	0	1105	0	1		2015-06-12T10:00	STDY-0011001033

Dosing records – ADDL and II

One record per constant dosing interval per subject

Study Identifier	Domain Abbreviation	Unique Subject Identifier	Sequence Number	Dose	Dose Units	Dose Form	Intended Dosing Regimen	Start Date/Time of Treatment	End Date/Time of Treatment	Study Day of Start of Treatment	Study Day of End of Treatment
STDY-001	EX	STDY-0011001033	1	200	mg	CAPSULE	200 mg QD	2015-04-27T09:00	2015-05-24T09:00	1	28
STDY-001	EX	STDY-0011001033	2	150	mg	CAPSULE	200 mg QD	2015-05-25T08:00	2015-05-25T08:00	29	29
STDY-001	EX	STDY-0011001033	3	200	mg	CAPSULE	200 mg QD	2015-05-26.	2015-06-11.	30	46
STDY-001	EX	STDY-0011001033	4	150	mg	CAPSULE	200 mg QD	2015-06-12T10:00	2015-06-12.	47	47
STDY-001	EX	STDY-0011001033	5	200	mg	CAPSULE	200 mg QD	2015-06-13.	2015-06-22.	48	57
STDY-001	EX	STDY-0011001033	6	150	mg	CAPSULE	200 mg QD	2015-06-23T09:00	2015-06-23.	58	58
STDY-001	EX	STDY-0011001033	7	100	mg	CAPSULE	200 mg QD	2015-06-24.	2015-06-24.	59	59
STDY-001	EX	STDY-0011001033	8	200	mg	CAPSULE	200 mg QD	2015-06-25.	2015-07-09.	60	74
STDY-001	EX	STDY-0011001033	9	150	mg	CAPSULE	200 mg QD	2015-07-10.	2015-07-10.	75	75
STDY-001	EX	STDY-0011001033	10	200	mg	CAPSULE	200 mg QD	2015-07-11.	2015-07-11.	76	85
STDY-001	EX	STDY-0011001033	11	150	mg	CAPSULE	200 mg QD	2015-07-21.	2015-07-21.	86	102

Study Identifier	Domain Abbreviation	Unique Subject Identifier	Sequence Number	Pharmacokinetic Test Name	Result or Finding in Original Units	Original Units	Visit Name	Planned Time Point Name	Date/Time of Specimen Collection	Time Point Reference	Date/Time of Reference Point
STDY-001	PC	STDY-0011001033	1	MADR1234	0.0203	ug/mL	DAY 7	PRE-DOSE	2015-05-03T11:00	Most recent dose	2015-05-02T09:00
STDY-001	PC	STDY-0011001033	2	MADR1234	0.0619	ug/mL	DAY 7	1 HOURS POST-DOSE	2015-05-03T12:00	Most recent dose	2015-05-03T11:00
STDY-001	PC	STDY-0011001033	3	MADR1234	0.0336	ug/mL	DAY 7	4 HOURS POST-DOSE	2015-05-03T15:00	Most recent dose	2015-05-03T11:00

Dosing records – PopPK dataset

One record per constant dosing interval per subject

STUDYN	SUBJID	ID	DOSE	ADDL	II	DAY	NTIME	NTAD	TIME	TAD	EVID	DV	ADTM	USUBJID
1	11001033	1	200	4	24	1	0	0	0	0	1		2015-04-27T09:00	STDY-0011001033
1	11001033	1	200	0	0	6	120	0	120	0	1		2015-05-02T09:00	STDY-0011001033
1	11001033	1	200			7	144	24	146	26	0	0.0203	2015-05-03T11:00	STDY-0011001033
1	11001033	1	200	21	24	7	144	0	146	0	1		2015-05-03T11:00	STDY-0011001033
1	11001033	1	200			7	145	1	147	1	0	0.0619	2015-05-03T12:00	STDY-0011001033
1	11001033	1	200			7	148	4	150	4	0	0.0336	2015-05-03T15:00	STDY-0011001033
1	11001033	1	150	0	0	29	672	0	671	0	1		2015-05-25T08:00	STDY-0011001033

Dosing records - Challenges

Challenges when creating dosing records:

- Missing or incorrect reference dosing times in PC
- BID or TID dosing frequency

Study Identifier	Domain Abbreviation	Unique Subject Identifier	Sequence Number	Pharmacokinetic Test Name	Result or Finding in Original Units	Original Units	Visit Name	Planned Time Point Name	Date/Time of Specimen Collection	Time Point Reference	Date/Time of Reference Point
STDY-001	PC	STDY-0011001033	1	MADR1234	0.0203	ug/mL	DAY 7	PRE-DOSE	2015-05-03T11:00	Most recent dose	2015-05-03T11:00
STDY-001	PC	STDY-0011001033	2	MADR1234	0.0619	ug/mL	DAY 7	1 HOURS POST-DOSE	2015-05-03T12:00	Most recent dose	2015-05-03T11:00
STDY-001	PC	STDY-0011001033	3	MADR1234	0.0336	ug/mL	DAY 7	4 HOURS POST-DOSE	2015-05-03T15:00	Most recent dose	2015-05-03T11:00

Study Identifier	Domain Abbreviation	Unique Subject Identifier	Sequence Number	Dose	Dose Units	Dose Form	Intended Dosing Regimen	Start Date/Time of Treatment	End Date/Time of Treatment	Study Day of Start of Treatment	Study Day of End of Treatment
STDY-001	EX	STDY-0011001050	1	100	mg	CAPSULE	100 mg BID	2015-04-27T08:00	2015-05-24T20:00	1	28
STDY-001	EX	STDY-0011001050	2	50	mg	CAPSULE	100 mg BID	2015-05-25T08:00	2015-05-25T20:00	29	29
STDY-001	EX	STDY-0011001050	3	100	mg	CAPSULE	100 mg BID	2015-05-26T09:00	2015-06-11.	30	46
STDY-001	EX	STDY-0011001050	4	50	mg	CAPSULE	100 mg BID	2015-06-12.	2015-06-12.	47	47
STDY-001	EX	STDY-0011001050	5	100	mg	CAPSULE	100 mg BID	2015-06-13T13:00	2015-06-22.	48	57
STDY-001	EX	STDY-0011001050	6	50	mg	CAPSULE	100 mg BID	2015-06-23.	2015-06-23.	58	58

Summary

The creation of dosing records for a population PK dataset is not straight forward

It becomes more challenging when data is missing and needs to be imputed

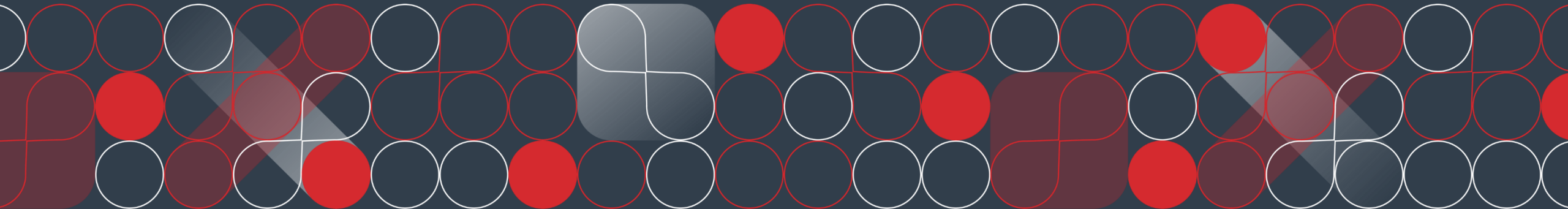
With the ADPPK guidelines, CDISC has provided great rules for imputation

BID or TID dosing remains challenging

CT04: Challenges Faced When Creating Dosing Records for a Population PK Dataset

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Dosing records - BID dosing

STUDYN	SUBJID	ID	DOSE	ADDL	II	DAY	NTIME	NTAD	TIME	TAD	EVID	DV	ADTM	USUBJID
1	11001050	1	100	10	12	1	0	0	0	0	1		2015-04-27T08:00	STDY-0011001050
1	11001050	1	100	0	0	6	132	0	134	0	1		2015-05-02T20:00	STDY-0011001050
1	11001050	1	100			7	144	12	147	14	0	0.0203	2015-05-03T11:00	STDY-0011001050
1	11001050	1	100	0	0	7	144	0	147	0	1		2015-05-03T11:00	STDY-0011001050
1	11001050	1	100			7	145	1	148	1	0	0.0619	2015-05-03T12:00	STDY-0011001050
1	11001050	1	100			7	148	4	151	4	0	0.0336	2015-05-03T15:00	STDY-0011001050
1	11001050	1	100	42	12	8	168	0	171	0	1		2015-05-03T23:00	STDY-0011001050

Study Identifier	Domain Abbreviation	Unique Subject Identifier	Sequence Number	Pharmacokinetic Test Name	Result or Finding in Original Units	Original Units	Visit Name	Planned Time Point Name	Date/Time of Specimen Collection	Time Point Reference	Date/Time of Reference Point
STDY-001	PC	STDY-0011001050	1	MADR1234	0.0203	ug/mL	DAY 7	PRE-DOSE	2015-05-03T11:00	Most recent dose	2015-05-02T20:00
STDY-001	PC	STDY-0011001050	2	MADR1234	0.0619	ug/mL	DAY 7	1 HOURS POST-DOSE	2015-05-03T12:00	Most recent dose	2015-05-03T11:00
STDY-001	PC	STDY-0011001050	3	MADR1234	0.0336	ug/mL	DAY 7	4 HOURS POST-DOSE	2015-05-03T15:00	Most recent dose	2015-05-03T11:00

STUDYN	SUBJID	ID	DOSE	DAY	NTIME	NTAD	TIME	TAD	EVID	DV	ADTM	USUBJID
1	11001068	5	100	1	0	0	0	0	1		2015-06-13T13:00	STDY-0011001068
1	11001068	5	100	2	12	0	12	0	1		2015-06-14T01:00	STDY-0011001068
1	11001068	5	100	2	24	0	19	0	1		2015-06-14T08:00	STDY-0011001068
1	11001068	5	100	2	36	0	31	0	1		2015-06-14T20:00	STDY-0011001068

Sample questions

CT04: Challenges Faced When Creating Dosing Records for a Population PK Dataset

- Question 1: You have mentioned that there are different ways of adding the dosing records to the dataset. Can you please explain how it is decided which method to use?

Answer: This depends on many factors, like what kind of analysis are planned or how the dosing regimen is and for how long subjects are being dosed and when PK samples are being taken. For example if a subject is being dosed daily for 2 years with PK samples taken only after extensively after the first dose and after that only once a month one PK sample is taken, it makes sense not to include a dosing record for every dose administered, however, to choose for the ADDL with II method. If the analysis focus more on PK at steady state, dosing records will be added as SS and II. And when you have a study with only weekly dosing for 12 weeks, you will probably decide to add all individual dosing records.

- Question 2: When data is missing, you state that data are being imputed. How can the modeler identify the records where imputations have been made for the dosing time?

Answer: That is correct, in the analysis dataset it needs to be clear if data is actually coming from the source or if dosing date and times have been imputed. To make it possible for the modeler to identify these records, we add an imputation flag variable to the dataset.