Paper CT04

Population Pharmacokinetic Datasets: Challenges in Creating Dosing Records

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ABSTRACT

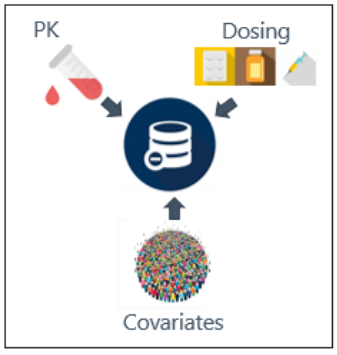
The ADaM datasets ADEX and ADPC are the two most important source datasets required for the creation of population pharmacokinetic (PopPK) datasets. The key piece of information here being the date and time at which either drug administration or PK sampling took place.
One of the primary challenges in constructing a PopPK datasets is ensuring the accuracy of dosing records, especially when dealing with missing dosing times. This paper explores the structure of PopPK datasets, methods for capturing dosing information, and the challenges faced in imputation of missing dosing data. We examine standard imputation strategies, as recommended by CDISC, and address special considerations for complex dosing regimens, such as BID (twice-daily) dosing. By applying standardized rules and thorough documentation, programmers can provide an accurate analysis dataset for population pharmacokinetic modeling.

INTRODUCTION

Population pharmacokinetic (PopPK) datasets are crucial for understanding how drugs behave in different populations by considering variability among individuals. These datasets include pharmacokinetic (PK) concentration data and dosing records for modeling drug levels and effects. One of the significant challenges in this process is creating accurate dosing records. In this paper, we will explore the nature of PopPK datasets, the sources of dosing records, and the challenges faced when constructing these datasets, with a particular focus on missing dosing times and imputation strategies.

OVERVIEW OF POPULATION PHARMACOKINETIC (POPPK) DATASETS

A PopPK dataset is used to model drug pharmacokinetics (the effect of the body on the drug) and pharmacodynamics (the effects of the drug on the body) across a population. The dataset captures variability within the population through covariates, which can be either baseline (e.g., age, weight) or time-varying (e.g., creatinine concentration throughout the study). A typical PK dataset includes PK concentration records sourced from the PC or ADPC domain and dosing records sourced from the EX or ADEX domain. Covariates are added to these records to enhance the dataset's utility for modeling purposes.



For effective modeling, it is essential to accurately capture the timing between the last dose administration and the collection of the PK sample. Understanding this interval is critical because drug concentration changes over time in a predictable pattern: it rises during absorption and falls during elimination. Knowing when a PK sample was taken (whether during absorption or elimination) is important for accurate analysis.

DOSING RECORDS IN POPPK DATASETS

Dosing records in PopPK datasets are primarily derived from the EX or ADEX domain, which captures information on the dose administered to a subject. There are two main methods of capturing dosing data:

1. **Recording each dose individually**: Each record includes details about the dose, the route of administration, the start and end date and time, and other parameters like rate of administration in case of intravenous dose administration.

Study Indentifier	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

2. **Recording one entry per constant dosing interval**: In this method, each record captures multiple doses administered within a given interval with a constant dose. This method is used when doses are given for a longer period with a high frequency (e.g., QD which stands for once daily or BID twice a day).

Study Indentifier	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		
STDY-001	EX	STDY-0011001050	11	100	mg	CAPSULE	100 mg BID	2015-07-21.	2015-07-21.	86		ONGOING	DATA CUT-OFF: 2015-08-01

Within a population PK dataset, dosing intervals are represented by 2 variables, ADDL, which value represents the number of additional doses and II, which value represents the time interval of the additional doses. For example, a dosing record on day 1 with ADDL equal to 27 and II equal to 24, indicates that this dosing record needs to be repeated for day 2 to 28 (27 times every 24 hours) in the population PK analysis.

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

In both methods, it is important to include dosing time information in the population PK dataset, such as the time since the first dose (referred to as the TIME variable) and the time since last dose (referred to as the TAD variable). This allows for calculating intervals between doses and PK samples, which are critical for understanding drug kinetics.

CHALLENGES IN CONSTRUCTING DOSING RECORDS

One of the main challenges in creating dosing records arises when dosing dates and times are missing. This is common in source data (EX or ADEX), when dosing information is captured in intervals. To resolve this issue, imputations must be made to estimate the missing data.

IMPUTATION STRATEGIES

According to guidelines from the Clinical Data Interchange Standards Consortium (CDISC), the following strategies are recommended for imputing missing dosing times:

- **Same-day imputation**: If a PK sample is taken on the same day as a missing dose, the dosing time can be estimated based on the PK sample time. For imputations you should use the pre-dose PK sample when available and only when missing, a post-dose PK sample. For example, if a pre-dose PK sample is taken at 09:00, the dosing time can be imputed to be on that same time, 9:00, or 5 minutes before, so 08:55.

- **Previous dose imputation**: If no PK sample is available for the day, the dosing time from the previous day can be carried forward to fill in the missing data. For example, if a dose was administered at 09:00 on day 1, however for the dosing on day 2, time is missing, and no PK sample was taken on day 2. In this situation the time of the previous dose (09:00) can be used for day 2.

Study Indentifier	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

These imputation rules ensure that essential data for modeling PK profiles are maintained, even when actual times are missing. However, the accuracy of the dataset depends on careful application of these rules.

SPECIAL CONSIDERATIONS FOR BID AND TID DOSING

BID (twice-daily) and TID (thrice-daily) dosing present unique challenges when constructing dosing records and imputing dosing times. In these cases, it is not always clear whether a dosing time relates to the first, second, or third dose of the day. Protocols may provide guidance on dosing schedules, such as the planned timing of the morning and evening doses for BID regimens, but discrepancies still arise.

For instance, if a reference dosing time in the PC domain indicates 08:00, it is likely the first dose of the day. However, if the reference time is 13:00, it becomes unclear whether this is a late morning dose or an early afternoon dose. In such cases, careful investigation of the protocol is required to determine the appropriate dosing time.

To handle this complexity, specific rules can be applied:

- **Morning and evening dosing logic**: For BID dosing, a time-window around the planned dosing times should be applied. When considering planned doses had to take place on 08:00 and 20:00, any dose administered between 02:00 and 14:00 should be considered the first dose, while any dose administered between 14:00 and 02:00 should be considered the second dose. This rule helps resolve ambiguity when only one dosing record is available per day.

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

Despite these strategies, BID and TID dosing schedules often lead to inconsistencies, such as cases where a subject appears to have received only one dose on one day but three doses on the next. In such situations, adhering to the protocol's instructions and using imputation techniques can help resolve or understand these discrepancies.

CONCLUSION

Creating dosing records for population PK datasets is a complex task that requires attention to detail, particularly when dealing with missing or incomplete data. The imputation rules provided by CDISC offer a standardized approach to resolving these challenges, but certain dosing regimens, like BID and TID, remain difficult to handle. Despite these challenges, by carefully documenting imputation logic and using all available information, programmers can ensure the accuracy and reliability of their PopPK datasets.

In summary, the creation of dosing records for PopPK datasets is not straightforward, but with clear rules for imputation and consistent application, most issues can be resolved. Challenges related to BID and TID dosing will persist, but thoughtful approaches and thorough documentation can mitigate their impact on analysis and modeling.

RECOMMENDED READING

Basic Data Structure for ADaM PopPK Implementation Guide V 1.0

CONTACT INFORMATION

Your comments and questions are valued and encouraged.

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