



DH07 - Mind the Gap: Imputing Missing Dosing Times in QD & BID Regimens Using ADPPK Guidelines

PHUSE EU Connect 2025 – Data Handling & Data Engineering

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CERTARA 

Introduction: Importance of Accurate Dosing Times



Fundamental Role in PK Analysis

Accurate dosing time data is fundamental for high-quality pharmacokinetic (PK) analysis.



Impact of Missing or Incorrect Data

Missing or incorrect dosing times can distort exposure calculations, misalign dosing and sampling records, and reduce dataset interpretability.



Compromise of Scientific Validity

These issues compromise scientific validity and may trigger regulatory concerns during submissions.



Support for Reliable PK Modeling

Accurate dosing time data is fundamental for high-quality pharmacokinetic (PK) analysis.



Robust Clinical Study Conclusions

Missing or incorrect dosing times can distort exposure calculations, misalign dosing and sampling records, and reduce dataset interpretability.



Common Sources of Missing Dosing Times



Variability Across Clinical Trial Sites

Differing data collection practices across sites lead to inconsistencies in dosing time records.



Patient Compliance Challenges

Incomplete or inaccurate records arise due to difficulties in patient adherence to protocols.



Operational and Logistical Factors

Delays or omissions in recording dosing times are often caused by operational and logistical issues.



Data Entry Errors

Mistakes during data entry and system limitations hinder the accurate capture of administration times.



Impact on Phase II–III Studies

Frequent gaps in dosing time data are particularly prevalent in mid- & late-phase clinical trials.



ADPPK Guidelines Overview: Standardizing Imputation



Standardized Framework for Imputation

The CDISC ADPPK guidelines provide a standardized framework to impute missing dosing times.

Preserves data integrity and traceability.



Imputation Logic Documentation

Full documentation of imputation logic is required.

Ensures reproducibility and transparency in imputation choices.



Traceability Variables

Use of Imputation Flag to mark imputed values.

Ensures clear identification of imputed data.



Compatibility with PK Modeling Tools

Datasets are formatted for direct compatibility with PK modeling tools like NONMEM.

Enhances dataset consistency and regulatory compliance.

Challenges in QD Regimens

Impact of Timing Inaccuracies

Differing data collection practices across sites lead to inconsistencies in dosing time records.

Variability in Dosing Times

Incomplete or inaccurate records arise due to difficulties in patient adherence to protocols.

Unique Challenges in QD Regimens

Delays or omissions in recording dosing times are often caused by operational and logistical issues.

Risk of Dose-PK Sampling Misalignment

Mistakes during data entry and system limitations hinder the accurate capture of administration times.

Balancing Protocol and Real-World Variability

Frequent gaps in dosing time data are particularly prevalent in mid- & late-phase clinical trials.



Challenges in BID Regimens

Complexity of BID Regimens

Twice-daily (BID) regimens introduce additional complexity.

Overlapping dosing windows (e.g., morning and evening) increase ambiguity in imputing missing times.

Impact on Derived Variables

Misalignment between dosing and sampling times can distort derived variables like time after dose (TAD).

Risk of Timing Errors

More frequent dosing raises the risk of cumulative timing errors affecting PK parameters.

Importance of Careful Imputation

Careful imputation respecting protocol windows and observed data trends is essential to avoid inconsistencies..



Interval-Based Imputation Method



Def. of Interval-Based Imputation

Interval-based imputation estimates missing dosing times using expected dosing intervals.



QD Dosing Interval Assumption

QD assumes a fixed 24-hour interval from the last known dose.



BID Dosing Interval Assumption

BID assumes a 12-hour interval between doses..



Advantages of Interval-Based Imp.

Simple and easy to implement programmatically.

Aligns with protocol dosing frequency.



Limitations of Interval-Based Imputation

Assumes strict adherence to dosing schedule, which may not reflect real-world variability.

May not capture deviations in actual administration times.



Best Application Scenario

Best applied when prior dose times are available and dosing intervals are consistent.

Protocol-Defined Window Alignment Imputation

Benefits of Protocol-Defined Window Alignment Imputation

- Benefits of Protocol-Defined Window Alignment Imputation
- Reflects study design and expected dosing times
- Minimizes guesswork and supports traceability
- Enhances transparency by grounding imputations in protocol context

Limitations of Protocol-Defined Window Alignment Imputation

- Limitations of Protocol-Defined Window Alignment Imputation
- Assumes patient dosing falls within defined windows, which may not always hold true
- Requires clear protocol dosing window definitions

PK Sampling Time–Based Imputation



Inferring Dosing Times

When dosing times are missing but PK sampling times are available, dosing times can be inferred by back-calculation..



Limitations to Consider

Dependent on strict protocol adherence and accurate sampling times.

Requires careful validation to avoid propagation of errors.



Back-Calculation Method

Uses known protocol-defined intervals between dosing and sampling.

Imputes dose time by subtracting expected post-dose sampling interval from sample collection time.



Complementary Use

Useful as a complementary approach when other dosing information is limited.



Advantages of the Approach

Leverages observed data to improve imputation accuracy.

Can reflect actual patient dosing behavior if protocol adherence is high.



Key Considerations

Ensuring protocol adherence and accurate sampling times is critical for reliable imputation.

Handling Multiple Missing Doses and Irregular Intervals



Edge Cases in Missing Doses

Multiple consecutive missing doses complicate interval-based imputation.

Irregular dosing intervals may violate assumptions of fixed schedules.



Handling Problematic Data Points

Considering exclusion or separate handling of problematic data points.

Ensuring data integrity while addressing irregularities.



Strategies for Imputation

Combining imputation methods such as interval-based, protocol window, and PK sampling.

Flagging affected records explicitly for transparency.



Importance of Documentation

Clear documentation and traceability remain critical in these scenarios.

Providing detailed records to support transparency and reproducibility.



Sensitivity Analyses

Conducting sensitivity analyses to assess impact on PK parameters.

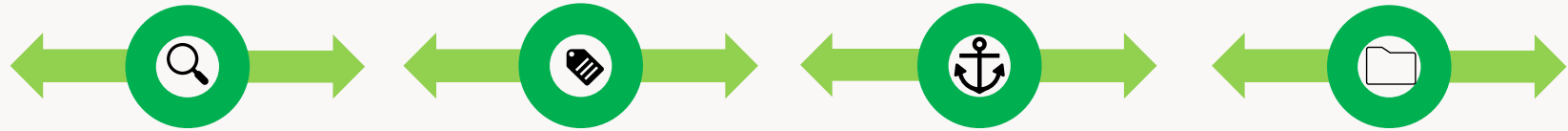
Evaluating the robustness of results under different assumptions.



Transparency in Data Handling

Ensuring protocol adherence and accurate sampling times is critical for reliable imputation.

Programming Workflow for Imputation: Data Preparation



Step 1: Scan Dosing Datasets

Identify and flag missing dosing times.
Scan dosing datasets for missing or incomplete time fields.

Step 2: Create Binary Flags

Create binary flags (e.g., `MISSING_DOSE_TIME`) to mark records needing imputation.

Step 3: Establish Reference Points

Establish baseline or anchor doses (e.g., first dose time) as reference points for imputations.

Step 4: Ensure Systematic Handling

This foundational step ensures systematic handling of missing data and supports reproducibility.

Programming Workflow: Method Selection and Application



Decision Logic for Imputation

Decision logic based on protocol details, data completeness, and dosing regimen.

Use protocol-defined window alignment if dosing windows are known.

Apply interval-based imputation relative to prior dose if available.

Use PK sampling time-based back-calculation if dosing and sampling data permit.

Programmatic Imputation Execution

Perform imputations programmatically, updating dosing time variables.

Documentation of Imputation Methods

Set ADPPK flags (EXMFL = 'Y') and explanatory variables (EXMDEF) to document methods.

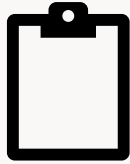
Ensuring Transparency and Traceability

This approach ensures transparent, traceable, and reproducible imputations.

Comprehensive Imputation Strategy

Combine protocol-defined alignment, interval-based imputation, and PK sampling time-based back-calculation for a robust imputation strategy.

Case Study 1 – Once-Daily (QD) Dosing: Impact of Imputation Choice



Dataset Overview

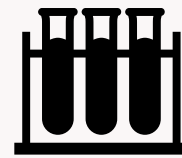
Phase III oral QD study (N = 120 subjects)

Protocol dosing window: 07:00–09:00 (target 08:00)



Missing Data Challenges

35% of dosing times missing due to delayed site entries



PK Sampling Details

PK samples at 4h and 24h post-dose



Case Study Focus

The case study focuses on the programming workflow and traceability of imputing missing dosing times.

Case Study: Raw Dosing Records (Including Outliers)

Subject ID	Recorded Dose Time	PK Sample 4h	PK Sample 24h	Notes
001	07:55	11:55	07:55 (Day 2)	Complete
002	<i>Missing</i>	12:00	08:00 (Day 2)	Missing dose time
003	08:10	12:10	08:10 (Day 2)	Complete
004	<i>Missing</i>	12:05	08:00 (Day 2)	Missing dose time
005	<i>Missing</i>	14:30	10:30 (Day 2)	PK sample suggests late dosing
006	<i>Missing</i>	14:45	10:45 (Day 2)	PK sample >5h after window

Case Study: Updated Imputed Times Table

Subject ID	Original Dose Time	Imputed Dose Time	Imputation Method
001	07:55	07:55	No imputation
002	<i>Missing</i>	08:00	Target time
003	08:10	08:10	No imputation
004	<i>Missing</i>	08:00	Target time
005	<i>Missing</i>	10:30	4h PK sample minus 4h
006	<i>Missing</i>	10:45	4h PK sample minus 4h

Case Study 1 – Twice-daily (B.I.D.) Regimen Imputation in Practice



Dataset Overview

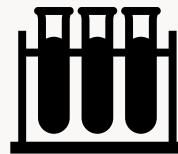
Phase III oral QD study (N = 50 subjects)

BID dosing windows:
Morning 08:00–10:00, Evening 20:00–22:00



Missing Data Challenges

20% of dosing times missing



PK Sampling Details

PK samples collected at multiple post-dose timepoints



Case Study Focus

The case study focuses on the programming workflow and traceability of imputing missing dosing times.

Case Study: Raw Dosing Records

Subject ID	Morning Dose	Evening Dose	PK Sample (2h AM)	PK Sample (2h PM)	Notes
301	08:15	20:05	10:15	22:05	Complete
302	<i>Missing</i>	20:10	10:00	22:10	Morning missing
303	09:00	<i>Missing</i>	11:00	22:30	Evening missing
304	<i>Missing</i>	<i>Missing</i>	<i>No PK</i>	<i>No PK</i>	Both missing, no PK
305	<i>Missing</i>	21:00	10:15	23:00	Morning missing

Case Study: Updated Imputed Times Table

Subject ID	Morning Dose	Evening Dose	Imputation Method
301	08:15	20:05	No imputation
302	08:00 (from PK anchor)	20:10	PK anchor for morning
303	09:00	21:00 (from PK anchor)	PK anchor for evening
304	Last known dose + 12h	Last imputed + 12h	Interval-based (no PK available)
305	08:15 (from PK anchor)	21:00	PK anchor for morning

Regulatory Considerations



Traceability

All imputations must be clearly flagged using ADPPK variables (EXMFL, EXMDEF).



Sensitivity Analyses

Recommended to evaluate how imputations influence key PK parameters and conclusions.



Justification

Detailed rationale for chosen imputation methods should be documented in submission materials.



Alignment with Standards

Adhering to CDISC ADPPK guidelines demonstrates commitment to industry best practices.



Reproducibility

Programming code, logs, and metadata must enable audit and replication of imputation steps.



Proactive Compliance

Proactive compliance reduces regulatory review delays and supports robust pharmacometric analyses.

Conclusion and Recommendations



Challenges in PK Datasets

Missing dosing times in QD and BID PK datasets challenge data integrity.



Reproducible Workflows

Implementing reproducible programming workflows that facilitate audit readiness.



Standardized Imputation

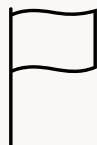
Approaches

Applying standardized imputation approaches aligned with CDISC ADPPK guidelines.



Collaborative Planning

Planning imputation strategies early in study design and fostering collaboration among programmers, pharmacometricians, and data managers.



Transparency in Imputation

Ensuring all imputations are explicitly flagged and thoroughly documented for transparency.

Questions?

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Thank you!

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