Enhancing PK Data Standardization: Insights from ADaM IG for Non-Compartmental Analysis

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Meet the Speaker

Kirana Prabeer Palangadath

Title: Enhancing PK Data Standardization: Insights from ADaM IG for Non-Compartmental Analysis

Organization: Zifo RnD Solutions

Ms. Kirana Prabeer Palangadath, Program Lead – Clinical Biometrics at Zifo RnD Solutions, has five years of professional experience in the clinical sector. Over the course of her career, she has successfully led a team of more than 10+ professionals and executed 25+ clinical studies, overseeing analysis preparation and regulatory submissions for a wide range of studies across diverse therapeutic areas. Her expertise extends to serving clients in the US, APAC, and Europe, ensuring compliance with global regulatory standards. Her proactive approach and commitment to continuous improvement have been instrumental in driving the success of the projects she oversees, ensuring efficiency, compliance, and excellence in execution.

Disclaimer and Disclosures

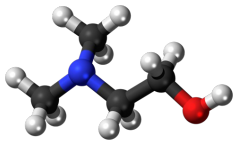
- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The author(s) have no real or apparent conflicts of interest to report.*

Agenda

1. Introduction to Pharmacokinetics data
2. What, Why and When ADNCA?
3. Difference between ADNCA and traditional ADaM IG
4. Key Components for Effective PK NCA Analysis
5. Validation Methods
6. Advantages
7. Conclusion

Introduction to Pharmacokinetics data



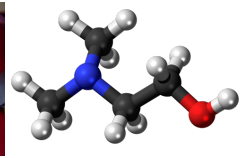
➢ **What is Pharmacokinetics (PK)?**

- The study of the effect of the body on a drug

➢ **Purpose of PK Data:**

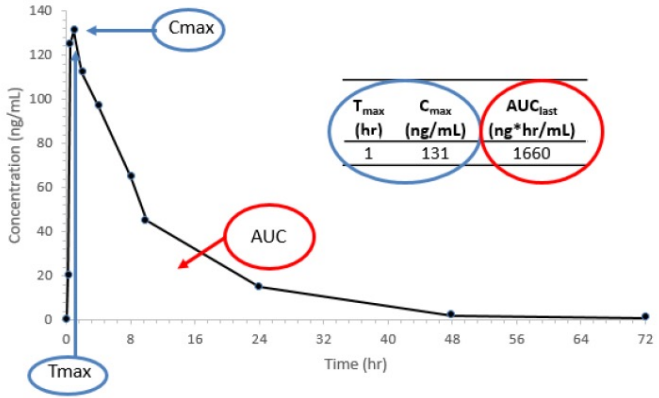
- Determines dosage, frequency, and route of administration
- Helps predict efficacy and toxicity
- Developing and monitoring drug

Introduction to Pharmacokinetics data



➢ **Key Parameters:**

- C_{max} (Maximum Concentration)
- T_{max} (Time to Maximum Concentration)
- AUC (Area Under the Curve)
- Half-life ($t_{1/2}$)
- Clearance of Distribution
- Volume of Distribution
- Bioavailability (F)



What, Why and When ADNCA?

ADaM Implementation Guide for **N**on- **C**ompartmental **A**nalysis (Version 1.0)

- Subclass of the BDS structure
- A model-independent method used to estimate pharmacokinetic parameters from drug concentration data over time
- Provides standards for creating datasets that support variables needed for calculating pharmacokinetic parameters
- Recommended for regulatory submissions because of its simplicity and reliability

What, Why and When NCA?

- **Limitations of traditional methods for PK analysis:**

- Inconsistency: Different naming conventions among organizations
- Intensive Sampling: Requires frequent sampling, impractical in clinical settings
- Computational Intensity: Complex modeling, time-consuming
- Applicability: Best for detailed studies, not initial PK assessments
- Variability: Assumptions can introduce variability

What, Why and When NCA?

- **Compartmental Analysis:**

Best for detailed mechanistic studies and when exploring variability due to intrinsic and extrinsic factors

- **Non-Compartmental Analysis:**

Ideal for initial characterizations and simpler studies where model assumptions are not necessary

Imagine you are developing a new painkiller.

NCA: For initial studies, to quickly assess basic pharmacokinetic parameters.

Compartmental: To later understand how the drug distributes in different tissues.

Difference between ADNCA and traditional ADaM IG

ADNCA (Data for Non-Compartmental Analysis)

- Purpose - built for PK NCA analysis
- Captures and analyzes concentration-time data
- Includes calculated parameters like AUC, C_{max}, etc.
- Compatible with NCA tools (e.g., WinNonlin)
- Requires dosing, timing, and interval metadata

ADPC (PK Concentration Analysis Dataset)

- Primarily used for data review and visualization
- Captures raw PK concentration data
- Does not include derived NCA parameters

Key Components for Effective PK NCA Analysis

ADNCA datasets include additional variables that are essential for handling data exclusion, identifying duplicated records, and ensuring precise timing - factors that are crucial in PK analysis.

1. Exclusion Flags:

Used to mark records that should be excluded from NCA calculations,

Reasons may include:

- Sample results below the limit of quantification (BLQ)
- Protocol deviations or data entry errors
- Statistically or visually identified outliers. Including a reason for exclusion helps to maintain transparency and facilitates QC/review
- Sample collected outside the designated visit window/period

Handling Record Level Exclusions

Row	STUDYID	USUBJID	TRTAN	ARRLT	NRRLT	RRLTU	ATPTREF	AVAL	PCSTRESU	NCAXFL	NCAXFN	NCA1XRS	NCA2XRS
1	CPW	CPW-s011	1	0	0	h	1	0	ug/L				
2	CPW	CPW-s011	1	0.4	0.25	h	1	80.3	ug/L	Y	1	Late Sample	
3	CPW	CPW-s011	1	0.5	0.5	h	1	118.8	ug/L				
4	CPW	CPW-s011	1	1	1	h	1	115	ug/L				
5	CPW	CPW-s011	1	2	2	h	1	132	ug/L				
6	CPW	CPW-s011	1	4	4	h	1	91.2	ug/L				
7	CPW	CPW-s011	1	8	8	h	1	67.6	ug/L				
8	CPW	CPW-s012	1	0	0	h	1	0	ug/L				
9	CPW	CPW-s012	1	0.4	0.25	h	1	19.8	ug/L				
10	CPW	CPW-s012	1	0.75	0.5	h	1	126	ug/L				
11	CPW	CPW-s012	1	1.33333	1	h	1	131.25	ug/L				
12	CPW	CPW-s012	1	2	2	h	1	114	ug/L				
13	CPW	CPW-s012	1	4	4	h	1	97.85	ug/L				
14	CPW	CPW-s012	1	7	8	h	1	68.25	ug/L				
15	CPW	CPW-s013	1	0	0	h	1	0	ug/L	Y	1		Incomp. Day 1 Samples
16	CPW	CPW-s013	1	0.25	0.25	h	1	19.8	ug/L	Y	1		Incomp. Day 1 Samples
17	CPW	CPW-s013	1	0.5	0.5	h	1		ug/L	Y	1		Incomp. Day 1 Samples
18	CPW	CPW-s013	1	1	1	h	1		ug/L	Y	1		Incomp. Day 1 Samples
19	CPW	CPW-s013	1	2	2	h	1		ug/L	Y	1		Incomp. Day 1 Samples
20	CPW	CPW-s013	1	4	4	h	1		ug/L	Y	1		Incomp. Day 1 Samples
21	CPW	CPW-s013	1	7	8	h	1		ug/L	Y	1		Incomp. Day 1 Samples

Key Components for Effective PK NCA Analysis

2. Duplicated Record Handling:

- In some studies, there may be instances where a single record needs to be utilized in two different ways
- This can happen when the final sample from one period (or visit) also serves as the pre-dose sample for the subsequent period (or visit) for the same subject
- In such cases, the nominal time, actual time and visit variables are altered for the duplicated record, and the DTYPE variable is populated

Duplicate record handling when 1 record needs to be used in 2 different ways

Row	USUBJID	PCRFTDTM	ADTM	ARRLT	NRRLT	MRRLT	RRLTU	ATPTREF	ATPT	AVAL	PCSTRESU	ABLFL	BASE	BASETYPE	DTYPE	CHG	PCSEQ
1	STD1-56-001	2017-04-03T08:10	2017-04-03T08:05	-0.083	0	0	h	DAY 1	Predose	0	ug/L	Y	0	DAY 1 BASELINE		0	1
2	STD1-56-001	2017-04-03T08:10	2017-04-03T08:41	0.5167	0.5	0.5167	h	DAY 1	0.5 H	383	ug/L		0	DAY 1 BASELINE		383	2
3	STD1-56-001	2017-04-03T08:10	2017-04-03T09:10	1	1	1	h	DAY 1	1 H	533	ug/L		0	DAY 1 BASELINE		533	3
4	STD1-56-001	2017-04-03T08:10	2017-04-03T10:10	2	2	2	h	DAY 1	2 H	455	ug/L		0	DAY 1 BASELINE		455	4
5	STD1-56-001	2017-04-03T08:10	2017-04-03T12:10	4	4	4	h	DAY 1	4 H	443	ug/L		0	DAY 1 BASELINE		443	5
6	STD1-56-001	2017-04-03T08:10	2017-04-03T16:15	8.083	8	8.083	h	DAY 1	8 H	356	ug/L		0	DAY 1 BASELINE		356	6
7	STD1-56-001	2017-04-03T08:10	2017-04-03T20:10	12	12	12	h	DAY 1	12 H	320	ug/L		0	DAY 1 BASELINE		320	7
8	STD1-56-001	2017-04-03T08:10	2017-04-04T08:05	23.917	24	23.917	h	DAY 1	24 H	190	ug/L		0	DAY 1 BASELINE		190	8
9	STD1-56-001	2017-04-04T08:10	2017-04-04T08:05	-0.083	0	0	h	DAY 2	Predose	190	ug/L	Y	190	DAY 2 BASELINE	COPY	0	8
10	STD1-56-001	2017-04-04T08:10	2017-04-04T08:40	0.5	0.5	0.5	h	DAY 2	0.5 H	475	ug/L		190	DAY 2 BASELINE		285	9

Key Components for Effective PK NCA Analysis

3. Timing variables:

Precise timing is crucial for PK calculations. Additional timing-related variables helps to:

- Differentiate between planned (nominal) vs. actual collection times
- Align sample times with dose times to calculate time after dose (TAD)
- Support analyses requiring time interpolation or modelling

Showing the nominal and relative times for a multiple dosing trial

Row	ATPTREF	ATPT	ADTM	PCRFTDTM	NFRLT	AFRLT	NRRLT	ARRLT	MRRLT	FRLTU	RRLTU	AVAL
1	DAY 1	Predose	15AUG15:08:30	15AUG15:09:00	0.00	-0.50	0.00	-0.50	0.00	h	h	0
2	DAY 1	0.5 H	15AUG15:09:30	15AUG15:09:00	0.50	0.50	0.50	0.50	0.50	h	h	5.168
3	DAY 1	1 H	15AUG15:10:00	15AUG15:09:00	1.00	1.00	1.00	1.00	1.00	h	h	18.020
4	DAY 1	2 H	15AUG15:11:03	15AUG15:09:00	2.00	2.05	2.00	2.05	2.05	h	h	31.580
5	DAY 1	4 H	15AUG15:13:00	15AUG15:09:00	4.00	4.00	4.00	4.00	4.00	h	h	18.500
6	DAY 1	6 H	15AUG15:15:00	15AUG15:09:00	6.00	6.00	6.00	6.00	6.00	h	h	16.700
7	DAY 1	24 H	16AUG15:08:53	15AUG15:09:00	24.00	24.88	24.00	23.88	23.88	h	h	0.656
8	DAY 6	Predose	21AUG15:08:53	21AUG15:09:00	192.00	191.88	0.00	-0.12	0.00	h	h	1.544

Nom. Rel. Time from Analyte First Dose

Act. Rel. Time from Analyte First Dose

Nominal Rel. Time from Ref. Dose

Actual Rel. Time from Ref. Dose

Modified Rel. Time from Ref. Dose

Rel. Time from First Dose Unit

Rel. Time from Ref. Dose Unit

Validation Methods

Automated Validation Tool: Pinnacle21

- The validation engine with specific rules for ADNCA, 2405.0, is already available in P21E. However, P21C does not validate the ADNCA dataset
- Validates overall data quality and integrity

Manual Review

- Check that metadata is fully described in the define.xml file

Custom Scripts

- Develop scripts to perform additional validation checks
- Tailor checks to specific study requirements and data structures

Peer Review

- Have another team or external experts review the datasets

Advantages

- Ensures data used for calculating pharmacokinetic (PK) parameters is standardized
- Aligns with CDISC standards, making it easier for regulatory authorities to review
- Enhances traceability from raw concentration data to derived PK parameters
- Consistent and accurate data supports robust pharmacokinetic analysis
- Prepares datasets for future analyses and regulatory requirements

Conclusion

- Well-prepared datasets are essential for future analyses and regulatory requirements
- Encourage the adoption of ADaM IG standards in PK data management
- Stay updated with the latest guidelines and best practices

Thank You!