PP16

Pharmacokinetic Noncompartmental Analysis (PK NCA) Using R: An Efficient Cost-Effective Alternative to Industry Standard Software

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IDDI DATA WITH PURPOSE

Abstract

Pharmacokinetic Noncompartmental Analysis (PK NCA) is often performed using extensive, proprietary software with limited flexibility. This poster presents R as a powerful, cost-effective alternative for conducting PK NCA, data manipulation, and visualization. We developed an R script that reads ADPC-like files, calculates PK parameters using packages such as pkNCA[1] and pkr[2], and generates outputs comparable to conventional tools. Results from multiple studies and administration routes (e.g., extravascular, IV infusion, and IV bolus) confirm consistency and highlight procedural differences. Our workflow enables complete analysis within R, including dataset preparation, parameter calculation, and generation of tables and figures. This approach reduces software switching, streamline processes, and supports reproducibility – making PK NCAs more accessible and efficient for teams of all sizes

The Journey

IDDI has many years of biostatistical expertise in therapeutic areas such as oncology. We have consulted with sponsors to help develop more flexible and efficient trial designs that align with sponsors' overall objectives while ensuring patient safety and optimal treatment at the lowest possible dose. Over the years, IDDI has recognized that pharmacokinetics (PK) and pharmacodynamics (PD) play an integral role in drug development and data-driven decision-making. This recognition made the inclusion of PK/PD analyses in our biometric workflow a no-brainer, allowing for a smoother and more integrated process from data receipt to final report by eliminating redundant workflows across multiple vendors. By incorporating PK/PD analyses and moving away from traditional practices, such as maximum tolerated dose, toward the FDA-preferred approach of dose optimization[3], our statistical methods have become more flexible and efficient by allowing early incorporation of clinical pharmacology data into dose-selection decisions. This enables us to identify promising dose ranges sooner, avoid exposing large numbers of patients to poorly tolerated or subtherapeutic doses, and make better informed adaptations during a trial. We have also found our dose-optimized Bayesian Optimal Interval (BOIN) design, which incorporates analyses like PK/PD driven exposure and safety assessments, makes our research more patient-centric, and reduces harm and waste. This is done by identifying the most effective dose earlier, preventing unnecessary exposure to overly toxic or ineffective doses, and enabling closer monitoring of safety-related exposure signals

Unified Workflow

- One environment for analysis, QC, and reporting.
- Fewer tool transitions, reducing manual effort and error risk.
- More productive workflows.
- Reduced handoff errors.
- High-quality & publication-ready visualizations at low cost.

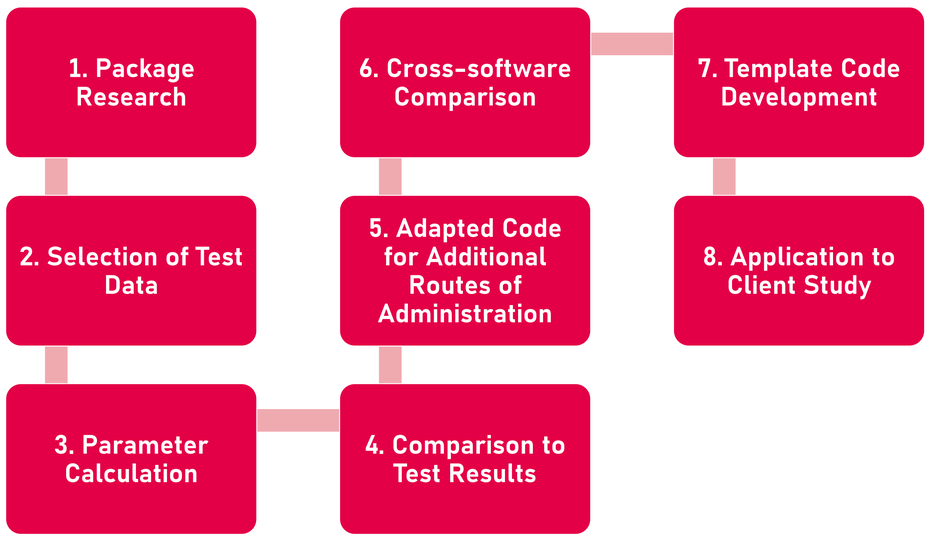
Cost-effective

- R is open-source and free.
- GitHub integrates seamlessly in R and provides traceability and version control.

Versatile & Efficient

- R scales to large and repeated analyses.
- Stable under frequent updates.
- Flexible data manipulation.
- Robust & reproducible results.

The Process



1. When researching R packages, we focused on packages with clear guidance on implementation, NCA calculated parameters, and whether routes of administration such as intravenous (IV) infusion and bolus are available. In our research, pkr and pkNCA exhibited the most promise, but the pkNCA package options were better aligned with our goals.
2. Test data containing PK concentrations along with NCA results were identified. The study contained multiple subjects who received a single IV infusion and reported key parameters we expect to routinely calculate with a similar study design, i.e. Cmax, Tmax, AUCinf, AUClast, Lambda Z, Half Life, Volume and Clearance. Data sourced from a publicly available PK dataset[4] via PK-DB[5] was selected for its PK concentration and NCA results, which enabled direct comparison with known results.
3. Using the PK concentration data[4] from PK-DB[5] and custom R code that incorporated the pkNCA package, we calculated key parameters.
4. The parameters calculated, using the custom R code, were compared against test results.
5. With the successful implementation of the custom R code for IV infusion, the code was adapted to also calculate PK NCA results for IV bolus administration.
6. Results were independently reproduced using an alternative software, calculating the same PK NCA as done in R.
7. Utilizing our well tested R code, we developed template codes for IV infusion and IV bolus NCAs.
8. The templated R codes for IV infusion and IV bolus were applied to a client study as a method to QC the PK NCA results generated in another software.

Expanding Beyond

- pkNCA was used as a foundation, with custom R code developed to support study-specific workflows and QC requirements.
- Expected numerical differences were observed across software platforms due to differing calculation methods.
- A predefined acceptance criterion of ≤10% difference was applied, reflecting inherent numerical variability rather than a target level of agreement, refer to example below.
- Differences within this range were not considered scientifically or clinically meaningful.
- Custom QC tables, like the example below, highlight subject-level parameter differences to support efficient review and issue identification.

Subject	Parameter	Main Value	QC Value	Percent Difference	Alert
I0001	Cmax	718	718	0	
I0001	Tmax	0.05	0.05	0	
I0001	AUCinf	1643.59	1649.66	0.37	
I0001	AUClast	1598.01	1596.29	-0.19	
I0001	Lambda Z	0.30	0.26	-14.6	Yes
I0001	Half Life	2.29	2.68	17.1	Yes
I0001	Volume	4019.42	4689.27	16.67	Yes
I0001	Clearance	1216.85	1212.37	-0.37	

Information

- Lessons Learned & Challenges:
  - Communication is key! This ensures a smooth workflow and facilitates faster turnaround. There were many discussions throughout this process, including the assessment of criteria for excluding data points in the determination of terminal elimination for lambda Z calculations.
  - An issue we encountered was calculating AUC parameters from one time point to another. We navigated this issue by only including concentrations based on the two time points.
  - Even though selections of concentrations for terminal elimination can be easier in other software, R is more flexible in terms of usability and overall noncompartmental analysis execution.
- Moving Forward:
  - The pkNCA package provides a strong foundation for NCA but does not support all calculations required for our workflow. We are actively researching additional methods and developing custom R code to address these gaps and better align with our workflow.
  - Create a way to calculate time point dependent AUCs in a more efficient manner.
  - Add more plots and tables tailored for PK NCA projects.

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