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

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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.

INTRODUCTION

In the spirit of entrepreneurship and innovation, many CROs and individual scientists seek low-cost, flexible solutions for conducting pharmacokinetic (PK) noncompartmental analyses (NCAs). Traditional industry-standard software, while widely used, can be expensive and limited in configurability. The growing adoption of R, within the biotechnology and pharmaceutical communities, has created new opportunities for more adaptable and cost-effective PK workflows. In this paper, we describe how we developed and customized an R-based approach for generating PK parameters, initially for QC purposes and for comparison with established tools. We also highlight how R offers efficiency, versatility, visually appealing tables, listings, and figures (TLFs), and a unified workflow without the need for multiple software programs. In addition, we summarize the key obstacles that were encountered during the process.

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.

THE PROCESS

To perform PK NCAs in R, we started by researching packages available for use. Key considerations included clarity of implementation guidance, transparency of calculated NCA parameters, and support for different routes of administration, such as IV bolus and IV infusion, are available. When researching packages, pkr[2] and pkNCA[1] exhibited the most promise. These packages were designed to generate fundamental parameters based on criteria provided. However, even though both the packages can be used to create parameters for NCA, the pkNCA package options were better aligned with our goals. Once the pkNCA[1] package was chosen, we searched for test data that contained PK NCA results with multiple subjects who received a single IV infusion and contained specific parameters we wished 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 concentrations and NCA results, which enabled direct comparison with known results, and contained our previously mentioned criteria. Using the PK concentration data[4] from PK-DB[5] and custom R code that incorporated the pkNCA[1] package, we were able to calculate the key PK parameters we desired for a single IV infusion study. Using the PK parameters calculated with the custom R code, we compared the parameters with the parameters from the sample

data[4] study.

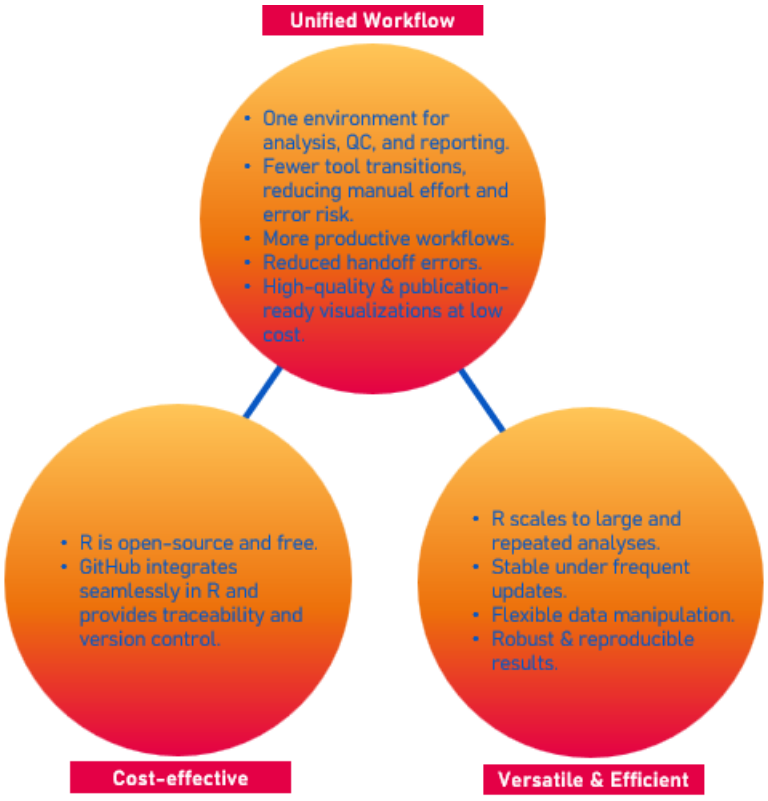
As expected, the PK parameter values generated using the pkNCA[1] R package did not match our custom R code exactly. Minor discrepancies are anticipated because different software tools and R packages implement calculations using distinct algorithms, internal defaults, and decision rules, all of which introduce inherent numerical variability. Analyst-driven choices also contribute to variation, including methods used for AUC estimation, selection of concentration-time points defining the terminal elimination phase, and criteria such as adjusted R^2 or percent AUC extrapolated.

Given these considerations, we established acceptance criteria to determine when differences between results should be considered meaningful. Based on statistical evaluation and expected computational variability, we determined that discrepancies up to 10% are acceptable. This threshold does not represent a target level of agreement but instead reflects the natural variation expected when comparing outputs from different software implementations applied to sparse or suboptimal PK data. Differences within this range were not considered scientifically or clinically meaningful and did not affect interpretation of the PK results.

We also considered the validation status of the pkNCA[1] package itself. The most recent version (0.12.1) includes author notes acknowledging that certain intravenous (IV) PK parameter calculations are still under active development, which may lead to discrepancies for IV routes of administration. Additionally, the package's development indicators[6] suggest that it is stable and moving forward in its development, while still being refined and improved.

Following the successful implementation of the custom R code for IV infusion, the code was adapted for an IV bolus route of administration. This adaptation required removing route-specific criteria, such as infusion duration that are not applicable to bolus dosing. Results were confirmed by independently reproducing the analysis in an alternative software, and calculating the same PK NCA as we produced in R. With two successful test runs we utilized the R code to develop a template code for IV infusion and IV bolus NCAs.

Serving as proof of concept, the implementation of the template code on a client study was used as a method to QC the PK NCA results generated in another software. To support this effort, we assembled a small project team responsible for running the template, troubleshooting issues, and implementing code updates as needed. This structure made communication and collaboration more efficient, which was essential given the number of technical discussions and decisions required throughout this process.



COST-EFFECTIVE

Using R for PK NCA offers several advantages, beginning with cost-effective. Because R is open-source and freely available, it reduces the financial burden associated with the commercial PK tools, which can be significant for smaller entrepreneurial and emerging companies. Beyond cost, R is a robust analytical environment that supports reproducible workflows, which is essential for regulatory work.

In addition, R integrates seamlessly with GitHub, allowing teams to implement version control and maintain full traceability of code and analyses at no cost. This is particularly valuable as FDA standards evolve and analysis templates need to be updated, especially for workflows that rely on ADaM datasets for NCA. While many commercial NCA tools offer built-in audit trails, these systems are often rigid and do not provide the same level of transparent, flexible version control that GitHub enables. Like R, GitHub is mostly free, making it an accessible, cost-effective solution for managing analytical code and documentation.

VERSATILE & EFFICIENT

Our experience with R has demonstrated substantial gains in efficiency for noncompartmental analysis, largely due to the software's flexibility and robustness. R reliably manages extensive code generation, iterative updates, and demanding execution workflows. Unlike other software that may crash after repeated runs or after making changes, such as modifying the data points used to identify the terminal elimination phase or switching to a new source data file, R maintains stability. In other tools, replacing or adding datasets can alter previously selected terminal elimination points, which can require reconstruction of prior work. When working under tight timelines, software instability is not only inconvenient but can jeopardize the reproducibility of an analysis; this has not been an issue in our use of R for dataset production, TLF generation, or NCAs.

R's infrastructure easily handles large and repeated analyses and remains stable under frequent updates. Its data manipulation capabilities are highly flexible and intuitive, enabling streamlined workflows. Because CDISC generation, TLF creation, and statistical analyses, including NCA, can all be performed within the same environment, analysts are not required to switch between multiple software packages or formats, reducing both training burdens and process inefficiencies. Additionally, tables and figures generated in R offer enhanced customization and visualization, supporting clearer interpretation for client and regulators. We have also developed tailored code to output tables and figures optimized for QC workflows. From a biostatistics perspective, R allows the method of calculation to be adjusted as needed, with all modifications fully documented in the study report.

UNIFIED WORKFLOW

To bring it all together, we chose and continue to utilize the pkNCA[1] package and R for its versatility, cost-effectiveness, and efficiency. The benefit of using R allows us to keep our projects in one environment for analysis, independent and autonomous QC, and elevated reporting of results. R also aides in having fewer tool transitions, reducing manual effort, error risk, and more productive workflows, reducing handoff errors. We can now produce high-quality NCAs & publication-ready visualizations at low cost.

EXPANDING BEYOND

pkNCA[1] was used as a foundation, but we have developed custom R code to enhance and adapt the process to our needs. The custom R code was developed to support study-specific workflows and QC requirements. As we previously mentioned, there were expected numerical differences observed across software platforms due to differing calculation methods along with analyst preferences and analysis decisions like data point selection for terminal elimination phase. A predefined acceptance criterion of ≤10% difference was applied, reflecting inherent numerical variability rather than a target level of agreement. Differences within this range were not considered scientifically or clinically meaningful. Custom QC tables, like Table 1, highlights subject-level parameter differences to support efficient review and issue identification. The purpose of the Alert column is to trigger further investigation and communication of the differences observed between the production NCA and QC NCA results that may have scientific or clinical meaning.

Table 1

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	

In Table 1, lambda Z, half-life, and volume differ by more than 10%. These parameters are highly dependent on the correct selection of data points used to characterize the terminal elimination phase. The QC analyst selected two concentration points that did not accurately represent terminal elimination, which led to the discrepancies.

The Alert column helped flag these differences and prompted a discussion between the QC analyst and me. That conversation focused on why our results differed and ultimately led to clarification around appropriate terminal elimination selection.

WE MADE IT

This is just the start of our initiative, but we regularly reflect on the challenges encountered and the lessons learned along the way, which are very beneficial to us as individuals and as a team. It takes a team to make noncompartmental pharmacokinetic analyses efficient and effective. As with any team-based activity, communication is key! This ensures a smoother 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. For example, determining how and which data points should be excluded from the terminal elimination phase for lambda Z calculations required several rounds of review. Sometimes the production analyst may view the terminal elimination phase to begin at an earlier time point, whereas the QC analyst may select a later starting point. Once analysts have independently generated the PK results and performed a comparison, strong communication is required to discuss reasoning for each difference in the data point selection. Even though selections of concentrations for terminal elimination phase can be easier in other software, R is more flexible in terms of usability and overall execution of noncompartmental analysis. You can customize data point selection to your own specifications or SOPs. Another issue we encountered was calculating AUC parameters for intervals of time. Luckily, thanks to R's flexibility we navigated this issue by only including concentrations that fall between and include the two end points of the time interval. For now, we have a crude code that does this, but we hope to build the code into a more robust solution process to not only calculate AUC for one interval, but multiple.

CONCLUSION

The pkNCA[1] 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 the analysis with our operational workflow. Our research and custom code aim to integrate our company's strong biostatistics background into PK analysis, something other software has not provided with the same level of flexibility. Because the pkNCA[1] package includes all concentrations from the dataset when calculating AUCs, moving forward we plan to create a way to calculate time point dependent AUCs using a more efficient approach that better aligns with our analytical expectations. There is also an important component our initiative to add more plots and

tables tailored for PK NCA projects. We plan to add subject- and analyte-specific PK concentration-time plots that will be generated automatically once PK concentration data is imported. We're excited to continue our progress and take it to the next level, starting with addressing some of the obstacles we have encountered.

REFERENCES

1. Denney B, Buckeridge C, Rodriquez G, Duvvuri S. pkNCA: Noncompartmental Analysis of Pharmacokinetic Data. R package version 0.95. Available at: https://cran.r-project.org/web/packages/PKNCA. Accessed 2024.
2. Bae K, Lee J. pkr: Pharmacokinetics in R. R package version 0.1.3. Available at: https://cran.r-project.org/web/packages/pkr. Accessed 2024.
3. Food and Drug Administration. Guidance for Industry: Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases. U.S. Department of Health and Human Services, Food and Drug Administration, Oncology Center of Excellence, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. August 2024. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases. Accessed 2024.
4. Singla NK, Parulan C, Samson R, et al. Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen. *Pain Pract*. 2012;12(72. doi:10.1111/j.1533-2500.2012.00556.x
5. PK-DB. Available at: https://pk-db.com/. Accessed 2024.
6. Denney W, Duvvuri S, Buckeridge C. Simple, Automatic Noncompartmental Analysis: The PKNCA R Package. *Journal of Pharmacokinetics and Pharmacodynamics*. 2015; *42*(1): 11-107, S65. doi: 10.1007/s10928-015-9432-2. Available at: https://humanpred.github.io/pknca/. Accessed 2026.

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