Harnessing GitLab, R and LaTeX to perform bespoke and robust non-compartmental analysis for patient SAD and MAD studies

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Introduction

Clinical non-compartmental analysis (NCA) is used to analyse pharmacokinetic data. NCA reports from commercial software do not always present the data in a way that allows the quality of the NCA parameters to be interrogated. In contrast to healthy volunteer studies, drug plasma concentration data from oncology dose escalation studies often comes in fragments due to inconsistent patient recruitment. In addition, individual patient profiles may be incomplete due to missing samples or be unsuitable for inclusion in summary statistics due to dose reductions, interruptions or other factors and thus require manual data modifications and exclusions. This provides challenges for the project clinical pharmacologist because if only new data is reported an overall coherent view of the data needs to be generated elsewhere. Additionally, standard NCA reports from commercial software do not always present the data in a way that allows the quality of the NCA parameters (e.g. half-life) to be interrogated.

Aims and Objectives

The aim was to create an internal validated clinical NCA tool with a workflow (Figure 1) that allows data to be “cleaned” and manipulated efficiently prior to NCA calculations and produces a coherent and reproducible report that allows full transparency of the calculations and any manipulations. The tool must also be able to be efficiently run upon receipt of new data to provide a cumulative summary of all data to date.

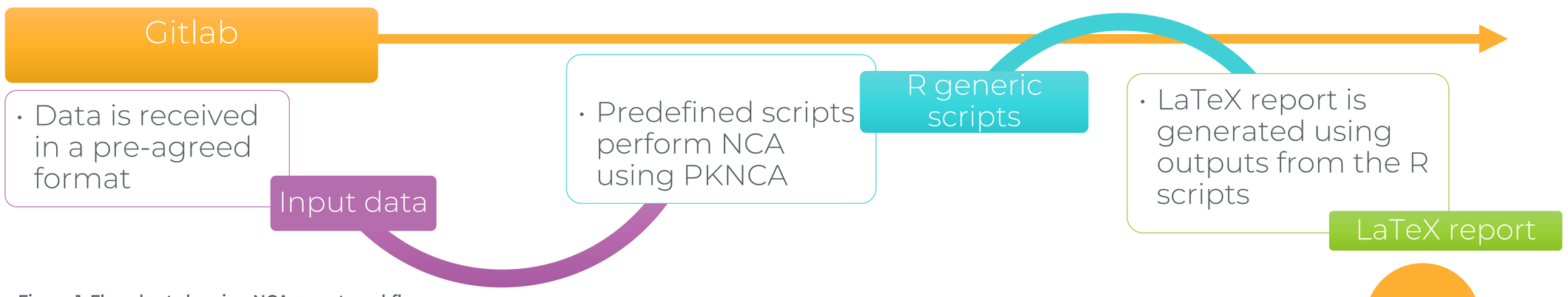


Figure 1: Flowchart showing NCA report workflow

Methods

- Three different programs, R, Gitlab and LaTeX were used in the workflow to allow for bespoke, robust and reproducible NCA (Figure 2).
- R was used to enable easy editing, tracking, and to produce tailored outputs.
- The GitLab web interface was used to save, check and track code. Gitlab also allowed specific stipulations to save and protect from any accidental changes, deletions or different users overwriting the code.
- LaTeX was used alongside R to produce a PDF report that enabled tables and figures to be imported from the R outputs minimising the risk of incorrect outputs being reported.

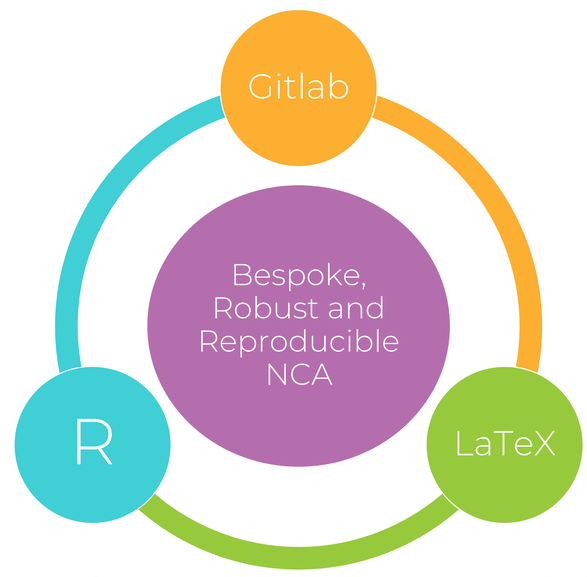
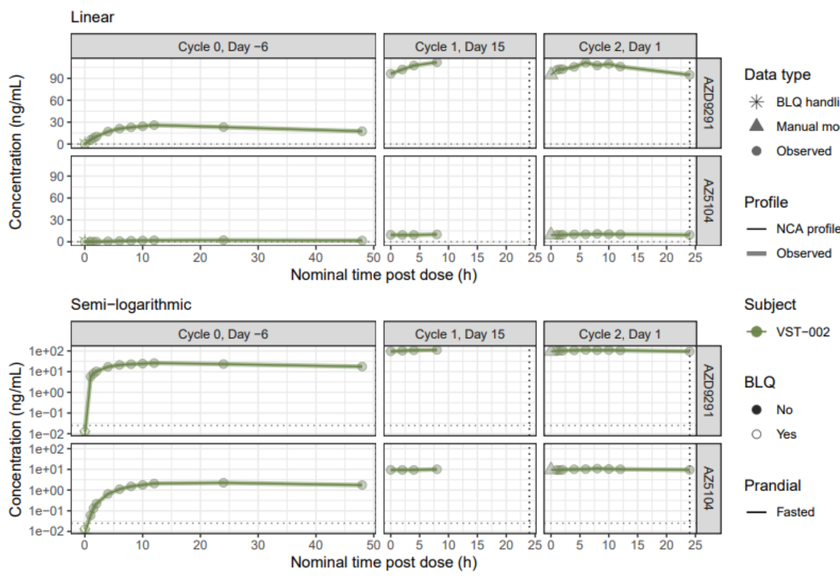


Figure 2: The use of three different components to complete our objective

A)



B)

Subject	Dose cohort	Cycle	Day	Reason for exclusion
VST-003	40 mg QD	1	15	Dose on day 15 missed
VST-005	40 mg QD	2	1	Dosing stopped after day 18
VST-007	80 mg QD	1	15	Dose amount dropped after day 14
VST-007	80 mg QD	2	1	Dose amount dropped after day 14
VST-010	80 mg QD	2	1	Dosing stopped after day 19
VST-013	160 mg QD	1	15	Dose amount dropped for 3 days between day 13-16
VST-013	160 mg QD	2	1	Dose amount dropped for 3 days between day 13-16
VST-015	160 mg QD	2	1	Wasn't dosed in cycle 2

C)

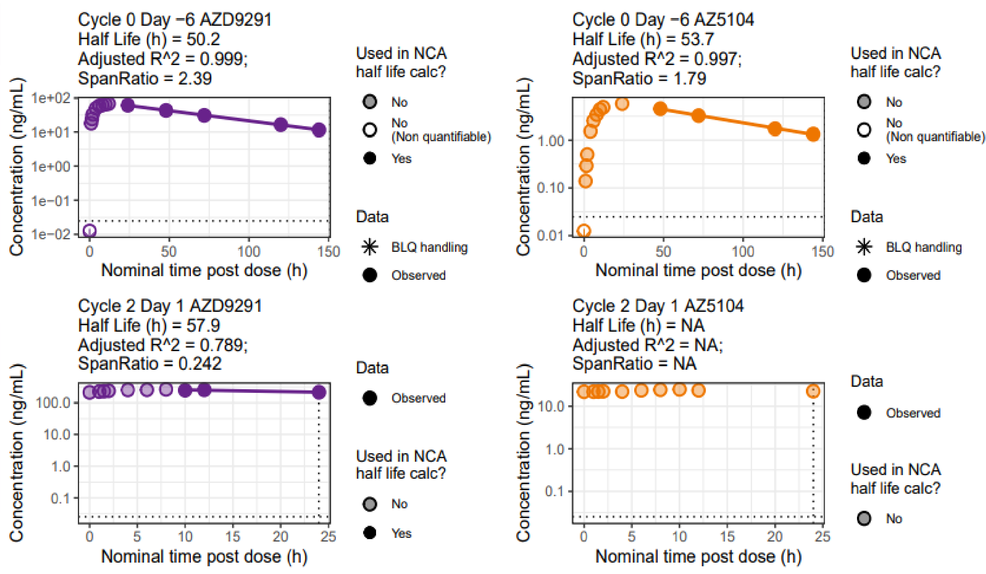


Figure 3: Examples from the NCA report where trail data was generated using the base population PK model published in both https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.13223 and the Clinical Pharmacology Review for Osimertinib published on the FDA website A) Concentration Time graph showing modifications made within the profile from the report B) manual modifications table C) half-life calculation plots

Results and Discussion

A new NCA tool was developed which allows exclusions and modifications to certain data points, with justifications tracked and recorded clearly in the report allowing full traceability. The workflow enabled good handling of sparse or incomplete data which is common in clinical oncology datasets. Figure 3 shows examples of figures and tables in the report, concentration-time graphs showing any modifications that were made, a table recording all exclusions and half-life plots indicating which points were used in the half-life calculation. All NCA parameter and summary tables were ready to be copied into an Investigators Brochure with full listing tables of all subjects allowing for a deeper understanding of the full dataset. The workflow was all linked allowing the outputs to be directly imported for the report, reducing transcription errors into the final report. This workflow provided a simple, time efficient way to produce a comprehensive report for the client, with a quick turnaround in processing the data.

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