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Background and Objective

- Pharmacometric (PMx) analyses are pivotal in streamlining clinical drug development and are key components of submission packages to regulatory agencies. These analyses involve processing large datasets from various sources and generating extensive output files in multiple formats (e.g. tables, figures, mathematical equations, and narratives).
- PMx analyses need to be properly tracked and reported in compliance with rigorous regulatory requirements, and within tight timelines, adding to the complexity of PMx reporting. Conventionally, these reports were prepared manually, in a labor-intensive fashion which is time consuming and error prone.
- To address these challenges, we developed an automated workflow integrating analysis scripts with narrative writing using R Markdown and in-house compiled R packages. The workflow seamlessly integrates different software like R Studio Server, Perl, and LaTeX within an in-house high-performance computing environment.

Concept

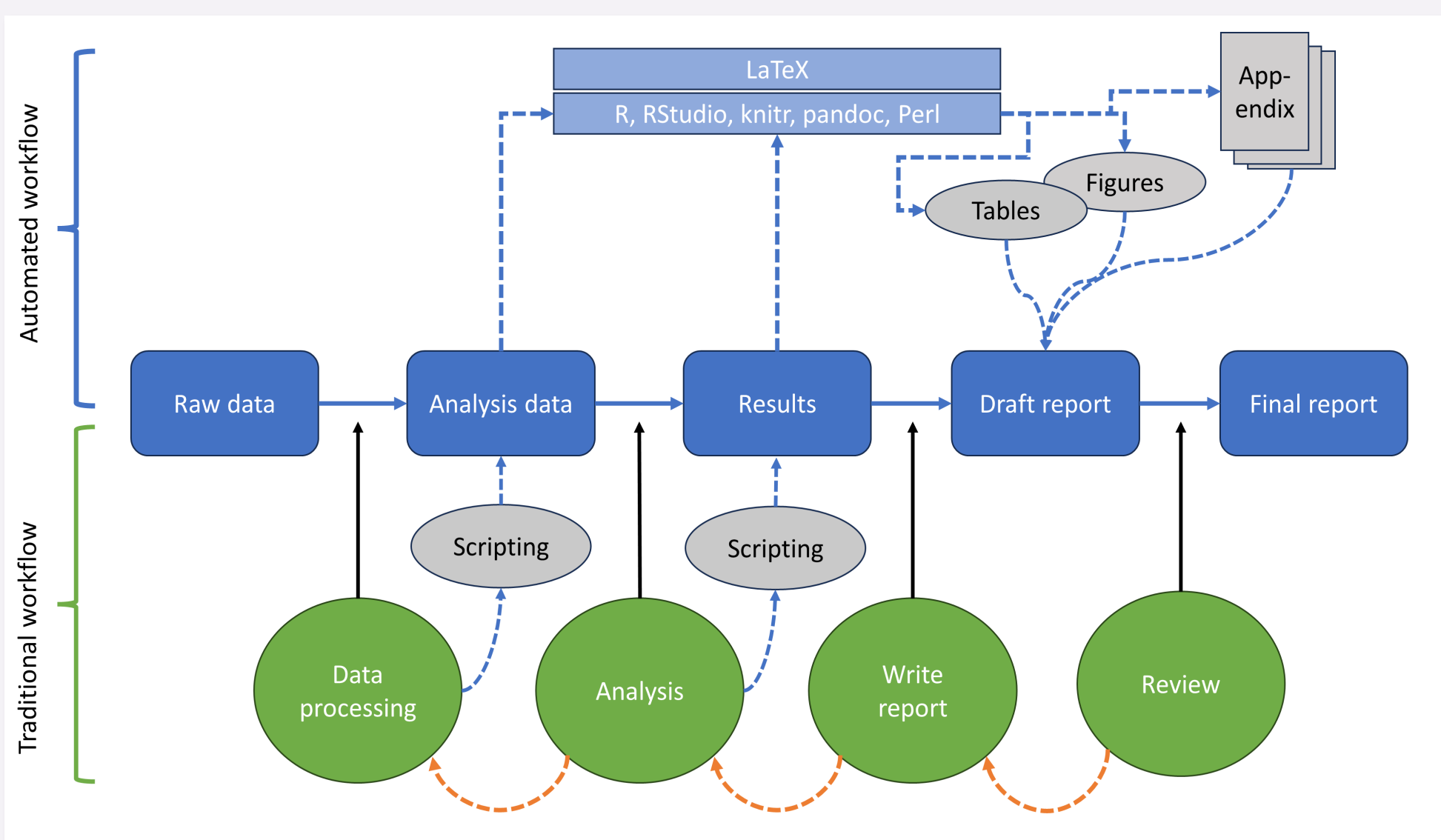


Figure 1. Workflow scheme. *Scheme adapted from [1]*

Blue boxes (central) depict the standard PMx analysis workflow, from data access to analysis reporting.

Green circles illustrate the traditional approach, with separate analysis and reporting steps requiring manual feedback implementation.

Light-blue boxes outline the tools for reproducible analysis and reporting presented in this poster.

Computational environment

- R (version 4.2.0) with ‘bookdown’ (version 0.3.4), ‘rmarkdown’ (version 2.25), ‘knitr’ (version 1.44) packages
- RStudio Server (version 2023.12.1 Build 402)
- Tex Live 2024 running under openSUSE Tumbleweed
- ‘scartcl’ document class of KOMA-Script to receive the LaTeX code generated by the pandoc converter
- Perl 5 (version 5.26.1)

Setup

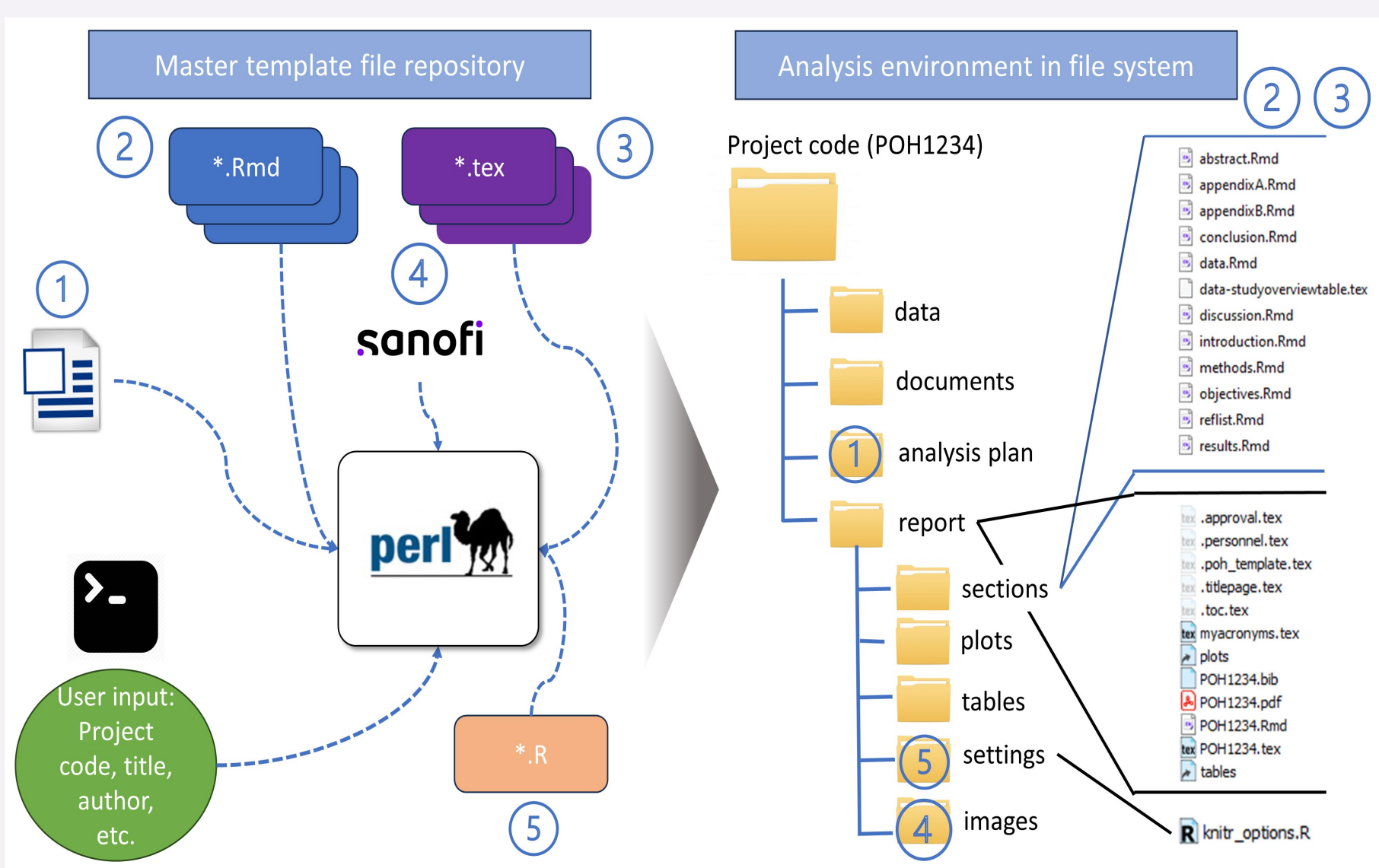


Figure 2. Automated setup of template and analysis environment

- To ensure a standardized structure for all users, a Perl script was developed to create a standard directory with all necessary templates.
- The report is prepared in a modular fashion with different child *.Rmd files corresponding to the different report sections. Each file is encodes the analyses and corresponding narrative.
- A master .Rmd file that uses a LaTeX (.tex) file in the backend is used to integrate all the report components appropriately

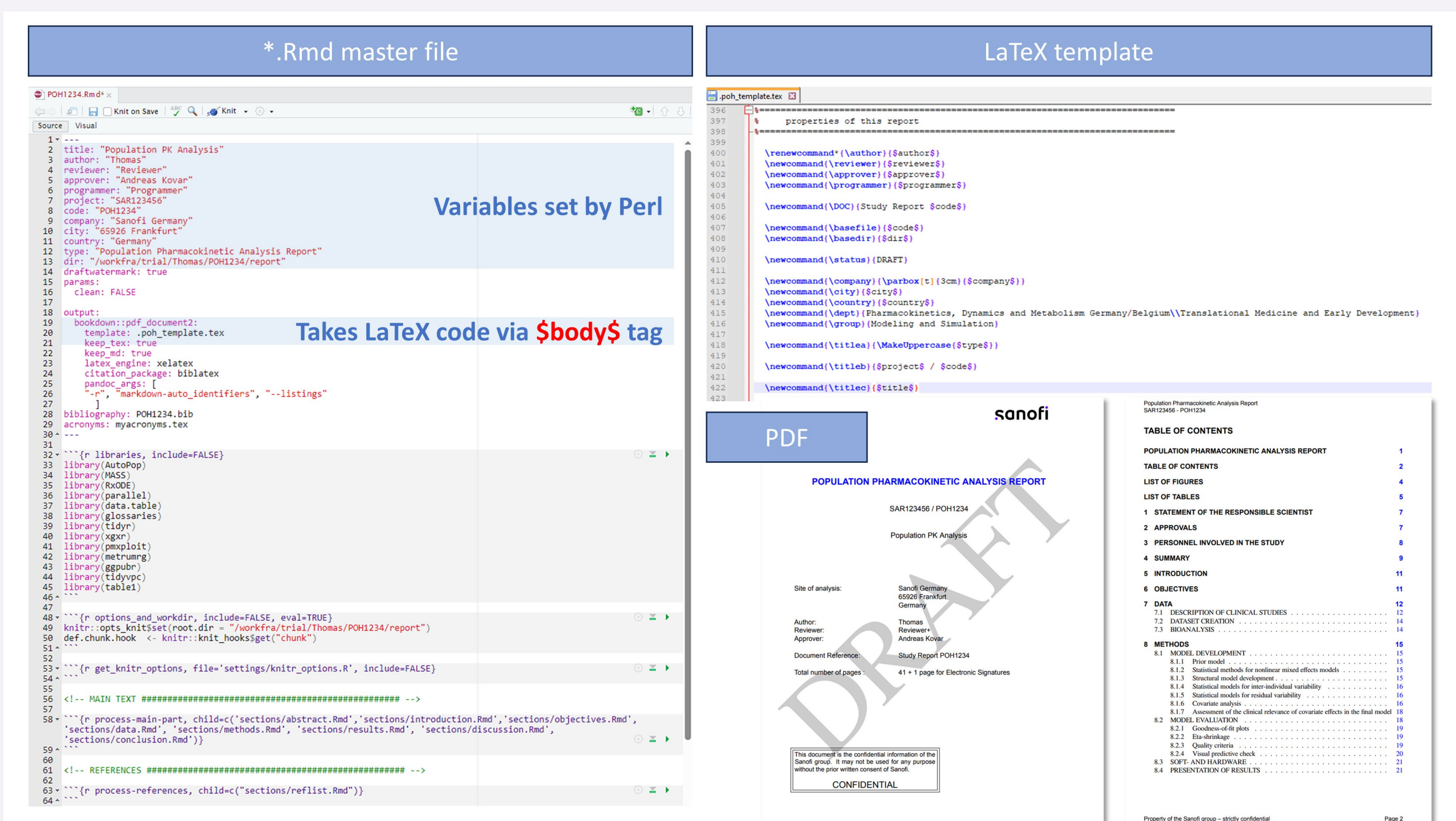


Figure 3. Self-contained *.Rmd file holds variables (meta information) that are forwarded to LaTeX template

Tailorized R functions

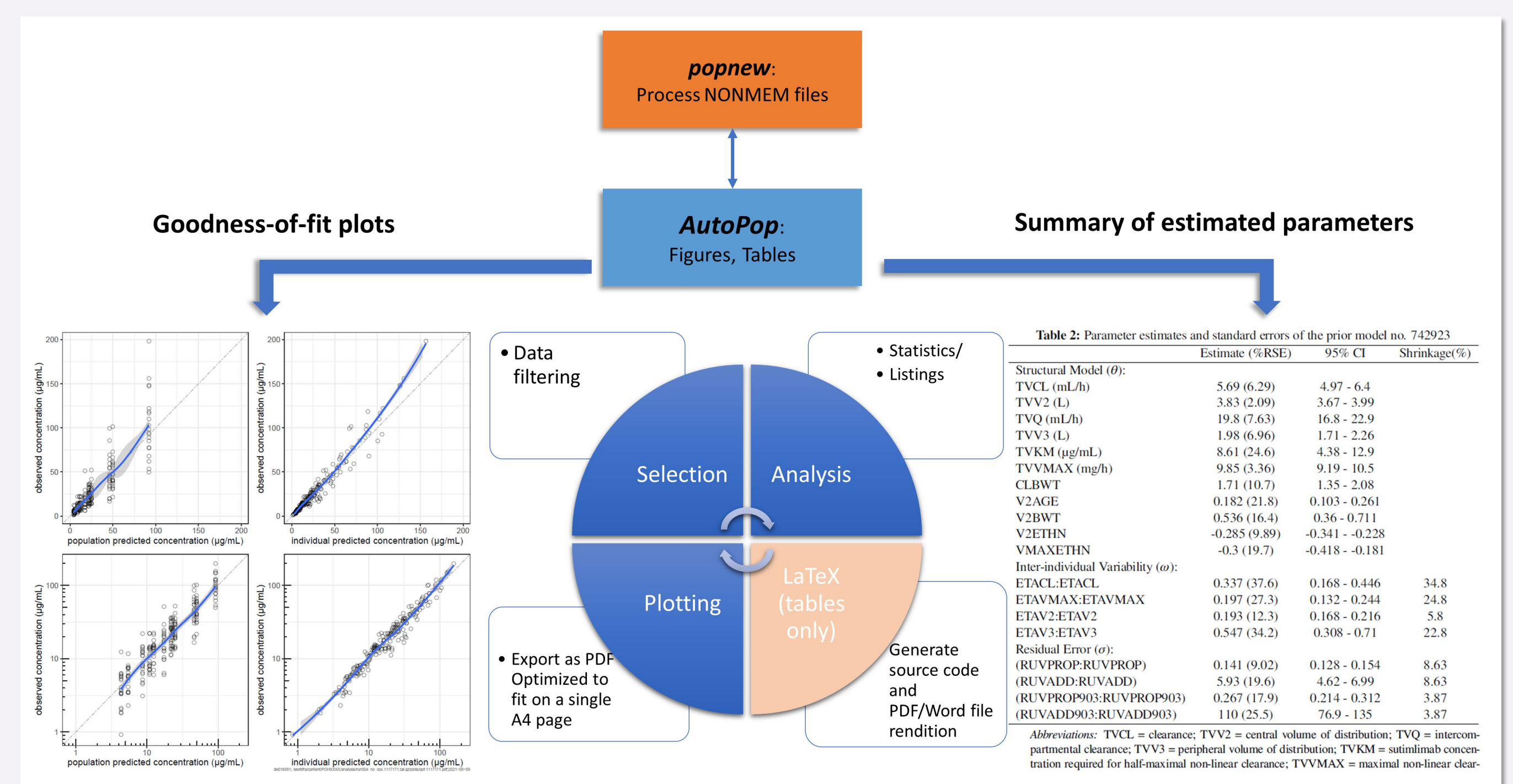


Figure 4. R packages to automate post-processing of NONMEM runs.

Internally developed R packages (Fig. 4) perform standard tasks of NONMEM post-processing (e.g., printing parameter summary, GoF plots); output is created independent from knitting the whole report enabling its usage outside of the report. The output can be integrated in R Markdown using simple commands, e.g., `knitr::include_graphics("...")` or `\input{parametersummary.tex}`.

	TDU16649	TDR16650	Overall
	(N=29)	(N=26)	(N=55)
Age (years)			
Mean (SD)	38.9 (11.3)	42.7 (9.32)	40.7 (10.5)
Median [Min, Max]	40.0 [19.0, 55.0]	44.5 [25.0, 55.0]	41.0 [19.0, 55.0]
Weight (kg)			
Mean (SD)	71.1 (16.6)	74.2 (8.20)	72.5 (10.2)
Median [Min, Max]	71.5 [53.5, 90.4]	74.1 [60.2, 89.2]	73.7 [53.5, 90.4]
Height (cm)			
Mean (SD)	169 (7.58)	169 (7.90)	169 (7.66)
Median [Min, Max]	169 [150, 185]	171 [153, 182]	169 [150, 185]
Creatinine Clearance (mL/min)			
Mean (SD)	109 (21.7)	111 (18.4)	110 (20.2)
Median [Min, Max]	112 [60.4, 153]	109 [78.4, 139]	110 [69.4, 153]
AST (U/L)			
Mean (SD)	17.2 (4.83)	18.2 (4.65)	17.9 (4.71)
Median [Min, Max]	16.0 [11.0, 31.0]	17.0 [13.0, 36.0]	17.0 [11.0, 36.0]
ALT (U/L)			
Mean (SD)	15.3 (4.88)	16.4 (9.52)	15.8 (7.39)
Median [Min, Max]	15.0 [8.00, 50.0]	14.0 [6.00, 50.0]	15.0 [6.00, 50.0]
Albumin (g/L)			
Mean (SD)	44.0 (3.01)	45.7 (3.74)	44.8 (3.31)
Median [Min, Max]	43.7 [38.1, 49.7]	45.4 [39.5, 54.3]	44.6 [38.1, 54.3]
Bilirubin (mg/dL)			
Mean (SD)	0.628 (0.230)	0.519 (0.214)	0.576 (0.227)
Median [Min, Max]	0.600 [0.300, 1.10]	0.500 [0.200, 0.900]	0.500 [0.20, 1.10]

```
618
619 ...[r.dataoverview-cont-cov-by-study, message=FALSE, echo=FALSE]
620 covtable2 <-
621   table1( ~ AGE + WT + HT + CLCR + AST + ALT + ALB + BILI |
622           STUPD,
623           data = mmcov,
624           caption = "Summary statistics of continuous covariates")
625
626 tibble(covtable2) %>%
627   kable_styling(font_size = 10)
```

Figure 5. Example of summary statistics of an analysis dataset using 'table1' R package

In the PMx report, it is customary to include a table that displays the descriptive statistics of the baseline characteristics of the study population, stratified by the study, and so on. The 'table1' package (Fig. 5) simplifies the creation of such a table in R. Using this package alongside knitr and R Markdown is advantageous for streamlined reporting.

Future Opportunities with Generative AI

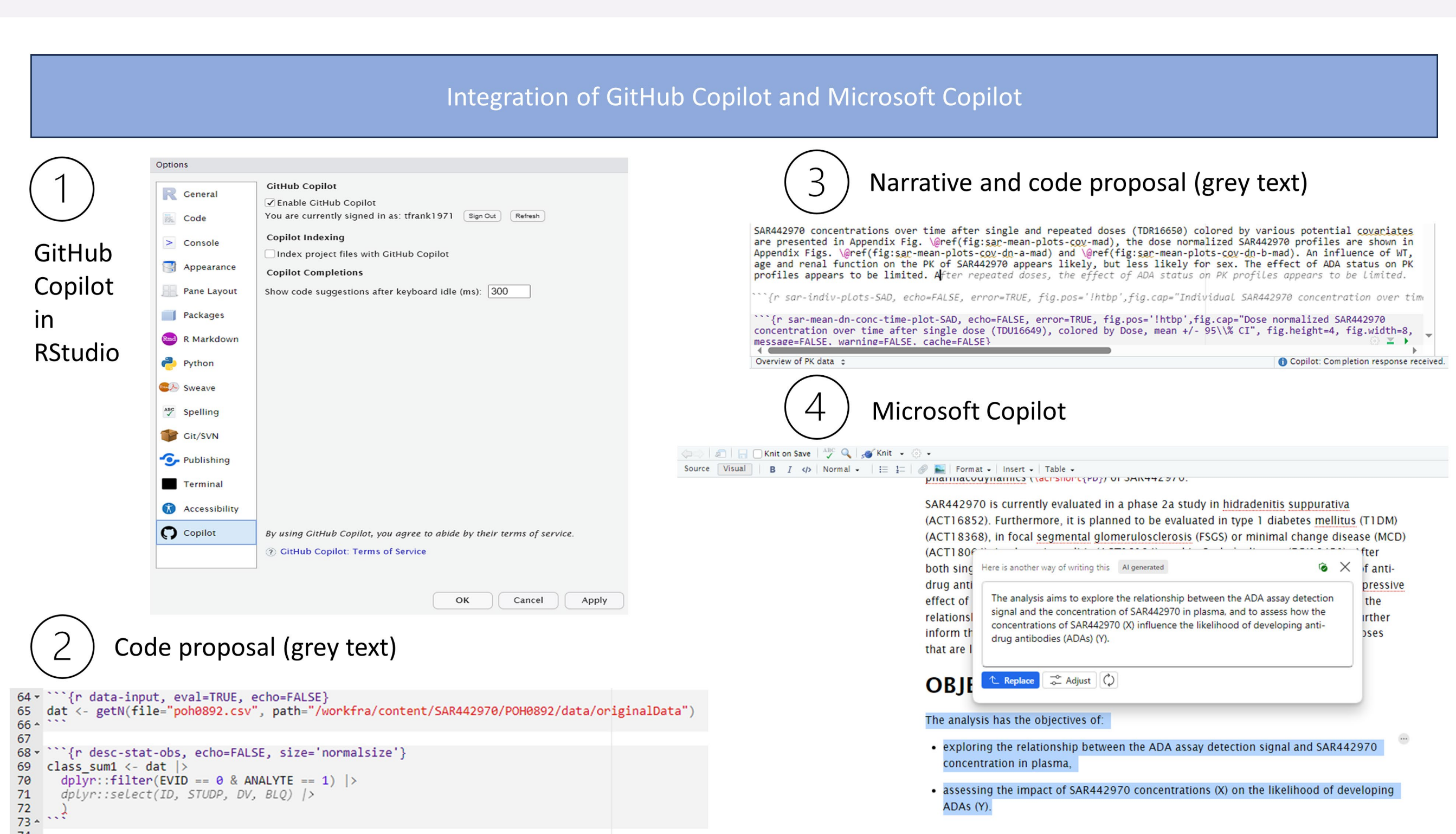


Figure 6. Copilot assisted creation of code and narratives

Activating GitHub Copilot in RStudio (1) helps to speed-up of code creation (Fig. 6): Proposals for code and/or narrative text based on the written content (2, 3) can be accepted or rejected. When running RStudio in Edge browser, Copilot (4) can provide thesaurus-like functionality and alternative text suggestions for more precise expressions, greatly assisting non-native speakers. Rapid progress in capabilities of Copilots is anticipated.

Conclusion and Outlook

- An in-house automated R Markdown-based PMX reporting workflow was developed, utilizing LaTeX in the backend to ensure compliance with electronic submission requirements.
- Integrating "analysis & results" with "reporting" in an automated fashion significantly reduced reporting time by 20-50% and enhanced traceability and reproducibility.
- The use of R Studio's interface and its visual editing mode increased the system's user friendliness.
- The AI-powered GitHub Copilot holds great potential for assisting with coding and narrative text generation.

References

- [1] Moroso V, Magnusson MO, Jonsson NE. Writing reports of modelling and simulation analysis: Our experience in the field of pharmacometrics. *Med Writina* (2023) 32 (3). 56-63.