

## INTRODUCTION

Implementation of Model-Informed Precision Dosing (MIPD) in real time at the clinical setting leverages population pharmacokinetic/pharmacodynamic (popPKPD) models to overcome limitations of traditional Therapeutic Drug Monitoring (TDM) (1). These models enable individual dose optimization first using relevant individual characteristics (covariates) for initial predictions and subsequently integrating observed concentrations and/or effects to estimate individual parameters through Bayesian updating for refined individual dosing recommendations. While popPKPD models offer significant advantages, their reliability in clinical practice requires thorough validation in the target population

This validation, also called external evaluation (2–4), should be fit-for-purpose, reporting precision and accuracy of predictions with varying amount of data. Furthermore, a proper assessment for real-time MIPD should evaluate many available models identifying the most suitable one for implementation in a specific population, adding considerable complexity to the validation process. Such comprehensive comparison involves multiple sequential steps—parameter estimation, simulation, metric calculation, and summarization—for each model under consideration, creating a workflow that is often complex, time-consuming, and prone to inconsistencies when performed manually. We aimed to develop an automated, standardized tool to streamline the external evaluation process for popPKPD models intended for real-time MIPD applications.

## EXTERNAL EVALUATION

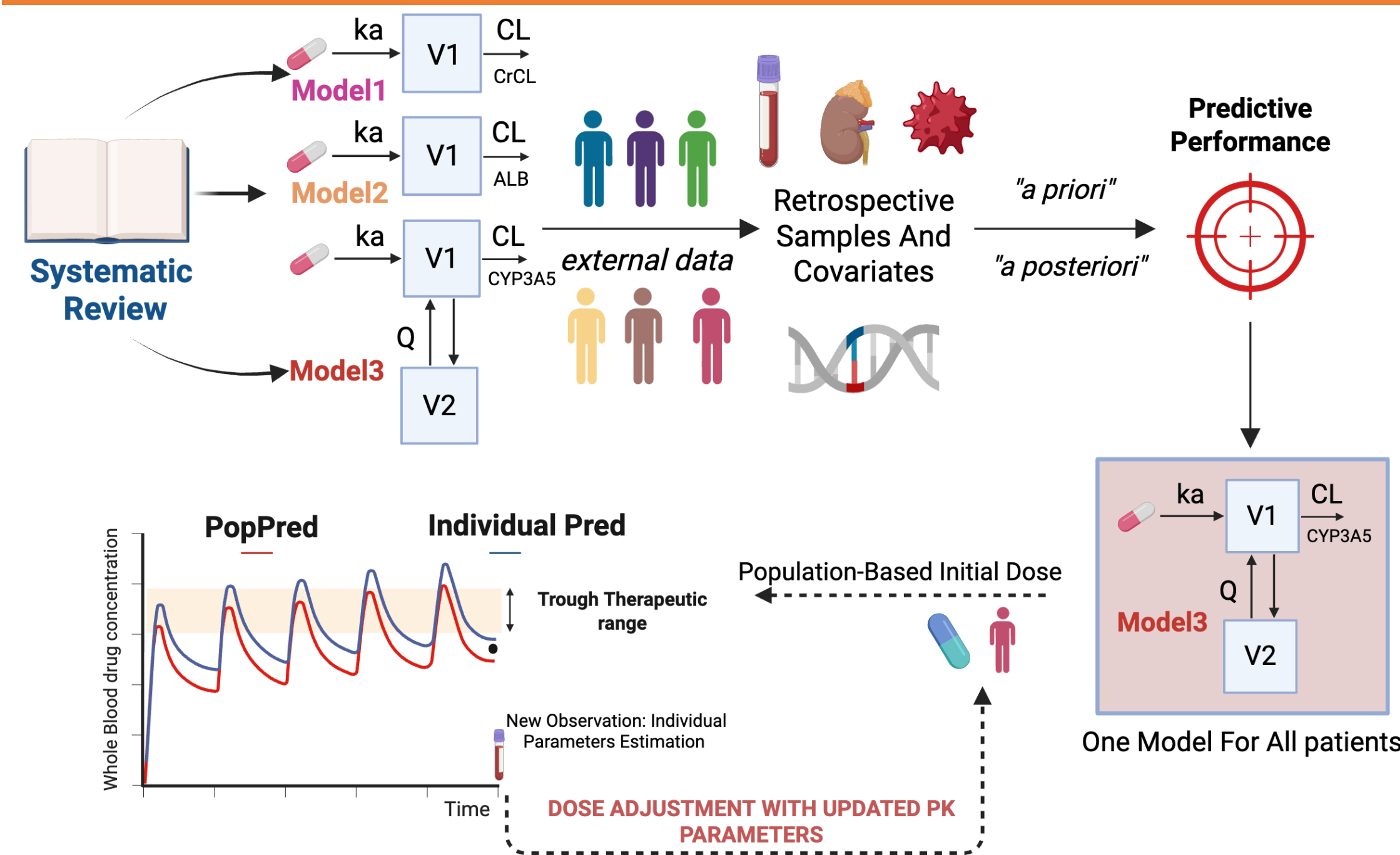


**Figure 1.** External Evaluation Process. The first step involves identifying a pool of candidate models and collecting data from a target population. This is followed by an assessment of the models' predictive performance—both *a priori* and *a posteriori*—leading to the selection of the best-performing model. The selected model can then be used for real-time MIPD.

## MATERIALS AND METHODS

The **preDose** package was developed in R 4.4.2 using the `usethis()`(5) framework. The package supports importing popPKPD models in. `mlxtran` (MonolixSuite – licence required(6)) and `mrgsolve` (7) formats alongside *external validation datasets*. To implement the first, `lixoftConnectors` package is used . For the latter, `mrgsolve` is combined with `mapbayr` (9), an open-source R package. The workflow implements a sequential evaluation process : a) A Priori evaluation: Assessment of model performance using only population parameters and individual covariates. b) A Posteriori evaluation: Sequential Bayesian updating of individual parameters using Maximum A Posteriori (MAP) estimation as observations become available across multiple occasions. An overview of the package architecture is presented in **Figure 2**.

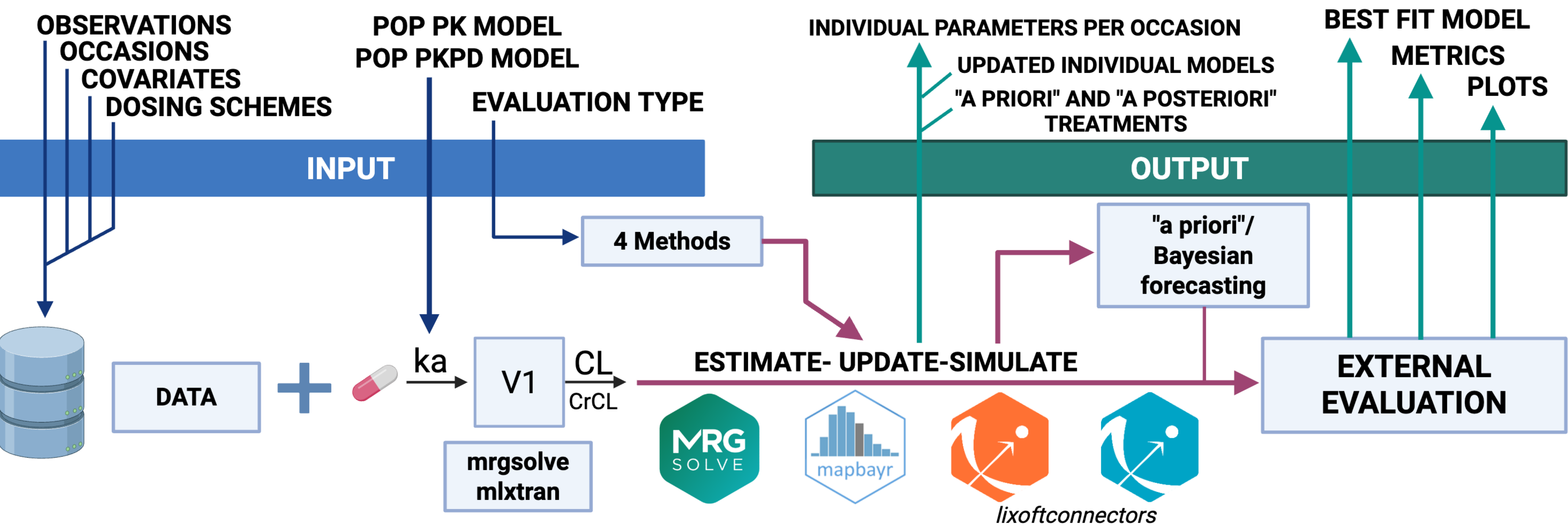


**Figure 2.** Architecture of the *preDose* package. Blue boxes and arrows indicate the required inputs for external evaluation process, including a compatible dataset in NONMEM or monolix format, a popPKPD model to be assessed, and a defined analysis strategy. Purple arrows represent internal processes such as MAP-estimations, Bayesian updating and Simulations. Green elements correspond to the outputs, including metric tables, statistical visualizations, model comparison, individual parameter estimates at each stage, treatments per occasion and an updated Individual model

preDose offers four flexible evaluation approaches: Progressive evaluation, Recent information approach, Benchmarking against a reference occasion, Proximity-based comparison: For all these, preDose automatically calculates standard predictive performance metrics (rBias, Mean Absolute Percentage Error, Root Mean Squared Error, IF20, IF30) for each sequential occasion and generates diagnostic plots using `ggplot2` for model assessment and comparison. The package was thoroughly tested and validated using several datasets, including real-world clinical data from different therapeutic contexts, to ensure robustness and reliability across various scenarios.

## RESULTS

preDose automates the external evaluation workflow for popPKPD models, systematically quantifying how predictive performance evolves as individual data accumulates across multiple occasions. The package includes several key functionalities:



Model Data and  
Integration

Perform MAP estimation

Run\_MAP\_estimation  
function

Flexible Evaluation

Allowing comprehensive assessment  
of model performance under different  
clinical scenarios.

Bayesian Update and  
Simulation

actualize\_model and  
run\_individual\_simulations  
functions

Automated Predictive Performance Assessment  
& Visual Diagnostic

metrics\_occ and metrics\_Plot function

```
Test_Model<-  
$GLOBAL  
#define CP (CENT/IV)  
SCMT @annotated  
EV : Extravascular compartment  
CENT: Central compartmenttwo compmt model with first order absorption  
SPARAM @annotated  
CL : 24.13 : Clearance  
V : 716 : central volume  
KA : 4.5 : absorption rate constant  
ETA1 : 0 : IIVCI (L/h)  
ETA2 : 0 : IIVV (L)  
SPARAM @annotated @covariate  
HCT : 0 : COV HCH  
OCC : :99 : Occasion, shall be passed by dataset imported  
$ODE  
dxdt_EV = -KA*EV;  
dxdt_CENT = IKA*EV - ICL*CP;  
$MAIN  
double CL_HCT = 1.124; ##Effect of HCT >33  
double ICL = CL * exp(ETA1) + ETA1 * pow(HCT, CL_HCT) * CL_EFFECT * CL_HCT;  
double IV = V * exp(ETA2) + ETA2 * exp (0.355 * W / 59.025);  
double IKA = KA;  
SOMEGA @name IIV  
0.248  
0.237  
SSIGMA @name SIGMA @annotated  
ADD : 0 : ADD residual error  
PROP : 0.16 : Proportional residual error  
$TABLE  
double IPRED = CENT/IV;  
double DV = IPRED * (1 + PROP);  
SCAPTURE @annotated  
CP : Plasma concentration (mass/volume)  
DV : PREDICION  
OCC: OCCASION
```



Run\_MAP\_estimation:  
Main Function  
Requires  
a) Model Name and Model Code  
b) Tool : "mapbayr" or "lixoftconnectors"  
c) Data: Full or partial analysis of lds  
d) OCC : Define number of OCCs  
e) OCC\_ref: Benchmar against one OCC  
Returns:  
a) Observed data per occasion: Includes the  
observed values for each individual in each OCC.  
b) Treatments per occasion: Contains information  
on the treatments administered in each OCC.  
c) Estimated individual parameters: Provides the  
MAP-estimated values of individual parameters for  
each subject and OCC.  
d) Eval Type: Evaluation Type used  
e) Population Model:

**EXAMPLE**  
map.est =run\_MAP\_estimations(model\_name  
= "Test\_Model", model\_code = Test\_Model,  
tool = "mapbayr", data = external\_data,  
evaluation\_type="Progressive")

1) **Progressive evaluation:** Integrating  
all prior information OCC by OCC

2) **Recent information approach:**  
Using only the most recent OCC to  
predict the next occasion

3) **Benchmarking against a reference  
occasion:** Stepwise comparison  
against a standard reference  
4) **Proximity-based comparison:**  
Using observations closest to the  
reference sample with sequential  
addition of prior information

**actualize\_model:** Updates individual model  
across OCCs  
Requires  
a)MAP estimations obtained in  
'run\_MAP\_estimations'  
b) The Evaluation Type  
Returns:  
a) A list with updated individual models  
b) The evaluation type used for the  
process.

**EXAMPLE**  
updt.md = actualize\_model(map.est,  
evaluation\_type = "Progressive")

**run\_individual simulations:** Simulates  
individual concentrations based on posterior  
estimations and treatment schedules for each  
occasion.  
Requires:  
a) Posterior estimations for every ID on each OCC.  
b)Treatment schedules for every ID in each OCC  
c) Assessment type ( " a priori " , a posteriori).  
Returns:  
a) Simulation results for each occasion and  
individual

**EXAMPLE**  
sim = run\_ind\_simulations(updt.md, map.est,  
assessment = "Bayesian\_forecasting")

**metrics\_occ:** Calculates standard accuracy and precision metrics for both "a priori"  
and "a posteriori" prediction across sequential occasions.  
Requires:  
a) Simulation results from run\_individual\_simulations  
b) Type of prediction ( "a\_priori" / "Bayesian\_forecasting" / Complete)  
Returns:  
List of individual metrics per OCC and summary of metrics per OCC

**EXAMPLE**  
Metrics<- metrics\_occ (sim, assessment = "Bayesian\_forecasting", tool="mapbayr

## CONCLUSION

The **preDose** package provides a standardized, efficient, and reproducible workflow for external evaluation of popPKPD models intended for real-time MIPD applications. By automating the sequential evaluation process across multiple candidate models, preDose enables objective model selection to inform dosing decisions in the clinical setting. The ability to quantify at which point predictions become reliable enough for clinical decision-making helps bridge the gap between model development and practical implementation. This tool addresses a critical need in the field by reducing the complexity and time investment required for comprehensive model validation, ultimately facilitating the broader adoption of model-informed precision dosing in clinical practice.

## REFERENCES

1) Keizer RJ et al. Scientific Challenges and Opportunities. Vol. 7, CPT: Pharmacometrics and Systems Pharmacology. American Society for Clinical Pharmacology and Therapeutics; 2018. p. 785–7 2) Cheng Y, et al. Vol. 60, Clinical Pharmacokinetics. Adis; 2021. p. 53–68 3) Zhao CY et al. Br J Clin Pharmacol. 2016 May 1;81(5):891–907. 4) Broecker A et al. Clinical Microbiology and Infection. 2019 Oct 1;25(10):1286.e1-1286.e7. 5) Hadley W et al. <https://CRAN.R-project.org/package=usethis>. 6) <https://monolixsuite.slp-software.com> 7) Kyle TB et al. <https://CRAN.R-project.org/package=mrgsolve>. 8) Felicien LL et al. <https://CRAN.R-project.org/package=mapbayr>.

The package is available as a development version on GitHub and can be installed using:  
`install.packages("devtools")`  
`devtools::install_github("Martin-Umpiérrez/preDose")`