Paper SD02

R you ready for Simulo: a user-friendly clinical trial simulator

Quentin Leirens, SGS Exprimo, Mechelen, Belgium
Nicolas Luyckx, SGS Exprimo, Mechelen, Belgium
Bruno Speder, SGS Exprimo, Mechelen, Belgium

ABSTRACT

Clinical trial simulation is a powerful technique for study design optimisations. However, the inclusion of all aspects of a drug model and a protocol may be complex. SGS Exprimo developed Simulo to offer a user-friendly interface and the ability to simulate and visualize the likely outcome of clinical studies or dosing scenarios. The model is described through algebraic or differential equations. Inclusion criteria, treatments, observations and study designs are easily defined. Custom R code brings total flexibility when needed. Any model may be implemented in simulation scenarios of all complexities.

Recent applications of Simulo showed how simulations help predict the effect of dose adaptation on clinical endpoints or compare study designs and data analysis approaches. As a conclusion, Simulo offers a platform for all sorts of model-based simulation activities, both for experienced and novice users. Simulo facilitates both internal and regulatory decision-making in a clear and visually attractive way.

INTRODUCTION

To perform clinical trial simulations, every scientist has his preferred language (R, S-PLUS, Python, SAS, etc.) or software (Monolix, NONMEM, Berkeley-Madonna, Pharsight TS2, etc.). However, some of these other programs require extensive and complex scripting, especially when designing clinical trials. Moreover, adequate post-processing, integration and visualization of the simulated data needed for accurate decision-making is not always a trivial task. Therefore, a user-friendly simulation platform would allow better collaboration and sharing of scripts.

Simulo [1] is a Pharmacokinetic-Pharmacodynamic-Disease model simulator which provides the ability to perform Monte Carlo simulations and subsequently to analyze clinical studies using public, published or custom-developed nonlinear mixed-effects models, in order to explore the impact of variables on outcomes.

Simulo is a Java-based application, running on an R backend with a graphical user-friendly interface. It means it is fully flexible with R and the simulation code may always be executed outside of Simulo, in any standard R environment.

Thanks to its clear framework and its user-friendly interface, Simulo offers during a project a high flexibility and consistency in the collaboration and communication between scientists.

SIMULO: KEY SOFTWARE SOLUTION IN SIMULATION PROJECTS

To demonstrate how the program can be the key tool in clinical trial simulation projects, we will detail the typical workflow of such projects and we present the associated Simulo features. We will then present a concrete case example applying those concepts.

1. DEFINE THE QUESTION

In modeling and simulation projects, spending some early time to identify and to define the main questions is often neglected even though it is extremely important. Many reasons can explain this such as lack of time, lack of tools or distance from where the actual decision is made. However, it can quickly lead to project management difficulties by putting bad priorities or by overcomplicating things. As a result, meeting deadlines may sometimes become tough, and bad decisions can conclude a period of rush. Examples of questions are: What is the endpoint for dropped-out subjects? Does my compound work? Which dose should I select? Should I continue my trial? Should I kill the compound? These simple but general investigation points must next be broken down into concrete subtasks described in a proper simulation plan. In other words, defining the question is an essential step to ensure keeping in mind the final goal throughout the whole analysis and to progress efficiently.

2. ENTER YOUR MODEL

In many cases, the previous point should allow to make the right choice of assumptions when comes the time to develop a model yourself, to choose one from the literature, to simplify an existing model or even to combine different models. Once you have a model settled, Simulo exhibits a well-structured layout on the *Drug Model* tab so that it facilitates the process of entering equations and parameters (see zone circled in purple on Figure 1). More interestingly, it eases the process of reviewing and of understanding any model implementation, even when performed by someone else. Therefore, it significantly enhances collaboration between scientists. Any model can be implemented in Simulo: simple algebraic equations; mixed effects models describing pharmacokinetics, pharmacodynamics or disease progression; survival models; count models and time-to-event models. All levels of variabilities needed for Monte-Carlo clinical trial simulations are present: residual error, inter-individual variability, population covariates, inter-occasion variability and population parameter uncertainty. Moreover, the program has a *Live Validation* checking the consistency of the items entered and avoiding typing errors.

3. EXPLORE YOUR MODEL

Starting by simulating single profiles is a good way to understand and to check the model as well as the assumptions you selected. In Simulo, a *Live Simulation* tool is available, allowing you, without having to go through all trial protocol aspects, to perform simulations of specific individuals. This useful and unique feature is shown on Figure 1 by the zone surrounded in orange.

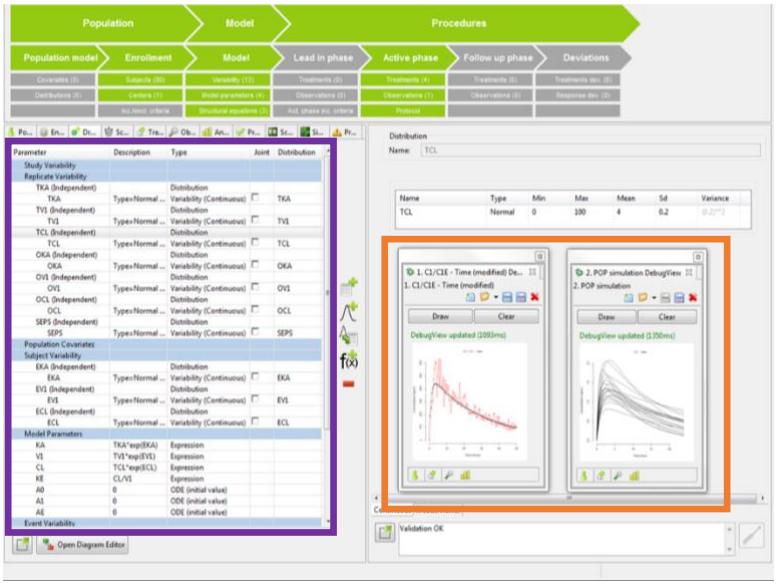

Figure 1 - Drug model tab (framed in purple) & Live simulation view (framed in orange) in Simulo user-interface

4. DESIGN YOUR CLINICAL TRIAL

Then comes the time to move on to clinical trial simulations, considering groups of virtual subjects and the trial protocol itself. Clinical trials are defined by the number of patients, the dosing and observation frequency, the treatment definition (dose amount, injection method, lag time), the parameters measured and the study design. Each

of these items corresponds to a different tab in Simulo:

- *Enrolment*: where you can define the number of subjects but also inclusion criteria. Usually, you can go for population simulations (infinite number of patients) or for proper clinical trial simulations (limited number of patients).
- *Schedules*: where you can specify the time scale of your simulations as well as treatment and observation times.
- *Treatments*: where you can create study arms (groups of one or more treatments) and implement the treatments in terms of dose, frequency (by linking to a predefined schedule), lag time, adherence (1 or 2-coin miss treatment model) and administration route (which injection compartment and whether it is a bolus or an infusion).
- *Observations*: where you can select parameters that you want to output.
- *Protocol*: where you can specify the number of periods and cohorts you need. Figure 2 shows where you put everything together to get the protocol design you wanted.

Figure 2 - Protocol design in Simulo

Optionally, complex trials can contain dose adaptation rules or interim analyses. These advanced items can be hard to code into one script. Conditional Events in Simulo are a very elegant and powerful solution to handle them. In 3 structured steps within a user-interface, you can specify when you want to monitor your population, decide which subjects require an action based on a criterion and update the dose or any other relevant parameter (see Figure 3).

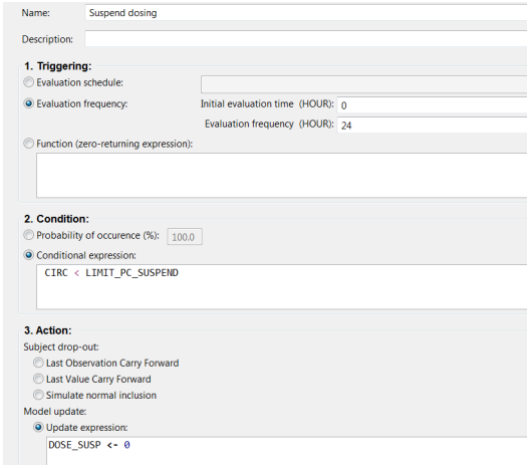

Figure 3 - Conditional event window in Simulo

5. SIMULATE

Once the model and the clinical trial protocol you want as a basis for your investigation are in place, you can start performing simulations and generating every output you need for your analysis. In Simulo, the *Scenarios* tab allows to quickly generate deviations from your base implementation. Any modification of your original protocol or any change in your model or population can be imagined and implemented through this feature. The *Analysis* tab allows you to define an automatic analysis script to be run after the simulation. It enables to only store key results, either tabularly or graphically, and not all intermediary raw results. On top of these, there is the *Simulation* tab which offers different options to easily manage your runs. There, you can determine what scenario you want to launch, how many replicates of your study you desire and what level of variability you want to enable. Reproducibility is ensured by using retrievable and fixed random seeds and any previous run can be traced back.

6. ANALYSIS FOR DECISION

Finally, the simulation outputs must be analyzed and summarized in a way that presents an answer to your question. This step is often done outside of Simulo itself, but the material required to achieve this ultimate step (simulation results of one or many replicates, already statistically summarized or not) can be more smoothly and more efficiently generated thanks to Simulo. It makes it a key software to quantitatively inform internal and regulatory decisions by facilitating clinical trial optimization and probability of success analysis.

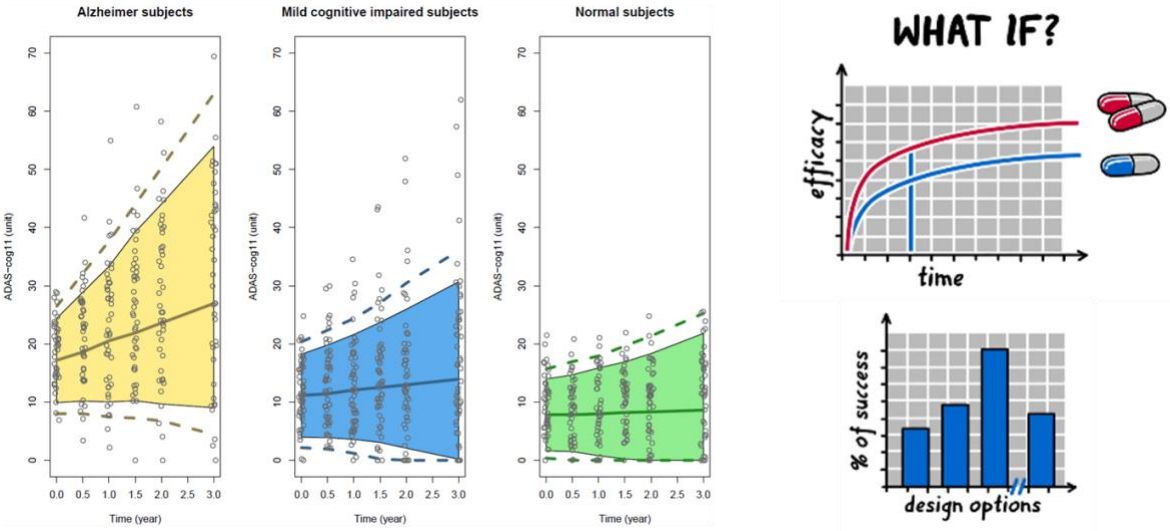

Figure 4 – Illustration of decisional output

USE CASE : EXTRAPOLATION TO PAEDIATRICS

This section will explore the workflow and the features described above in a practical example. The context will be drug development in the pediatric population. The main challenge during drug development in the pediatric population is to improve the clinical development process making it faster to have access to safer and more effective treatments. Regulatory agencies advocate the use of modelling and simulation of the available adult data to guide pediatric clinical trial designs [2]. Recently, the European Medicines Agency's (EMA) provided an overview of its position on specific issues related to modelling and simulation for pediatrics, in the form of questions and answers [3]. As an example, let's imagine a drug was successfully developed and approved for adults and we would like to scale the therapy to children. To achieve this, we plan to execute a pediatric clinical trial on a population of 16 patients aged 12 years.

1. DEFINE THE QUESTION

In this case, two major questions are asked:

- What pediatric dose should be used in the clinical trial?
- We plan to execute the trial with 16 children, is it enough?

The strategy will be to check that the drug exposure at steady-state in terms of AUC is equivalent in adults for the standard dose of 150mg and in children for the candidate dose. Moreover, we will perform an analysis of probability of success to support the proposed protocol.

2. ENTER YOUR MODEL

We choose to use the one-compartment PK model with oral absorption previously developed in adults, to link the covariates of our virtual patients to real demographics data that can be found in the NHANES database and to introduce an allometric scale. The resulted Simulo implementation is exhibited on Figure 5.

Drug Model | Enrollment | Schedules | Treatments | Observations | Analysis | Protocol | Scenarios | Simulations | Problems

Parameter	Description	Type	Distribution
Constants			
Replicate Variability			
THETAS / OMEGAS		Distribution	
THETA_KA	Type=Normal min=-Inf max=Inf mean=1.00 sd=0	Variability (Continuous)	THETAS / OMEGAS
THETA_V	Type=Normal min=-Inf max=Inf mean=70.0 sd=0	Variability (Continuous)	THETAS / OMEGAS
THETA_CL	Type=Normal min=-Inf max=Inf mean=4.00 sd=0	Variability (Continuous)	THETAS / OMEGAS
OMEGA_KA	Type=Normal min=-Inf max=Inf mean=0.3 sd=0	Variability (Continuous)	THETAS / OMEGAS
OMEGA_V	Type=Normal min=-Inf max=Inf mean=0.3 sd=0	Variability (Continuous)	THETAS / OMEGAS
OMEGA_CL	Type=Normal min=-Inf max=Inf mean=0.3 sd=0	Variability (Continuous)	THETAS / OMEGAS
Population Covariates			
NHANES BOOTSTRAP		Distribution	
AGEY	Type=Normal min=-Inf max=Inf mean=0 sd=0	Variability (Continuous)	NHANES BOOTSTRAP
AGEM	Type=Normal min=-Inf max=Inf mean=0 sd=0	Variability (Continuous)	NHANES BOOTSTRAP
WT	Type=Normal min=-Inf max=Inf mean=70 sd=10	Variability (Continuous)	NHANES BOOTSTRAP
Subject Variability			
ETAS		Distribution	
ETA_KA	Type=Normal min=-Inf max=Inf mean=0 variance=OMEGA_KA	Variability (Continuous)	ETAS
ETA_V	Type=Normal min=-Inf max=Inf mean=0 variance=OMEGA_V	Variability (Continuous)	ETAS
ETA_CL	Type=Normal min=-Inf max=Inf mean=0 variance=OMEGA_CL	Variability (Continuous)	ETAS
Model Parameters			
KA	THETA_KA*exp(ETA_KA)	Expression	
CL	THETA_CL*(WT/70)**0.75*exp(ETA_CL)	Expression	
V	THETA_V*(WT/70)*exp(ETA_V)	Expression	
KE	CL/V	Expression	
Initial Values			
ABS	0	ODE (initial value)	
CENTER	0	ODE (initial value)	
ELIM	0	ODE (initial value)	
Event Variability			
Structural Equations			
dABS	-KA*ABS	ODE (derivative)	
dCENTER	KA*ABS - KE*CENTER	ODE (derivative)	
dELIM	KE*CENTER	ODE (derivative)	
CONC	CENTER/V	Expression	
Residual Variability			
ERR (Independent)		Distribution	
ERR	Type=Normal min=-Inf max=Inf mean=0 sd=0.05	Variability (Continuous)	ERR
OBS_CONC	CONC *(1 + ERR)	Expression	
Conditional Events			

Figure 5 – Drug model implementation for pediatrics based on the adult model

3. EXPLORE YOUR MODEL

The typical adult profile can be compared directly to the typical child profile (see Figure 6). Extreme weights can also be drawn. That way, we can already get a good idea of the dose amount and whether a weight-adjusted dose should be considered.

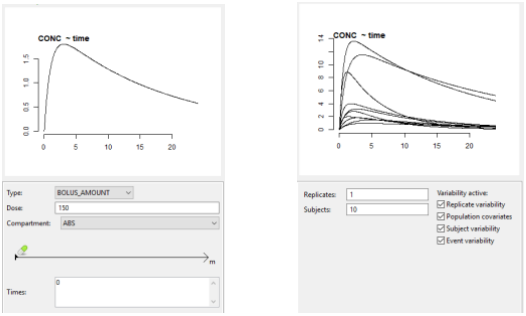

Figure 6 – Reference typical adult profile (left) compared to multiple pediatric profiles (right)

4. DESIGN YOUR CLINICAL TRIAL

As a base study, we design a protocol identically to adults: 150mg orally administered every day and a rich sampling schedule to measure PK concentrations.

To answer the question concerning the dose itself, a population simulation with a very high number of subjects can be derived and different scenarios can be created for each dose investigated. One example of candidate dose is shown on Figure 7. With regards to the question on the study design, it will be answered in one single scenario in which we will really need to limit the number of subjects to 16.

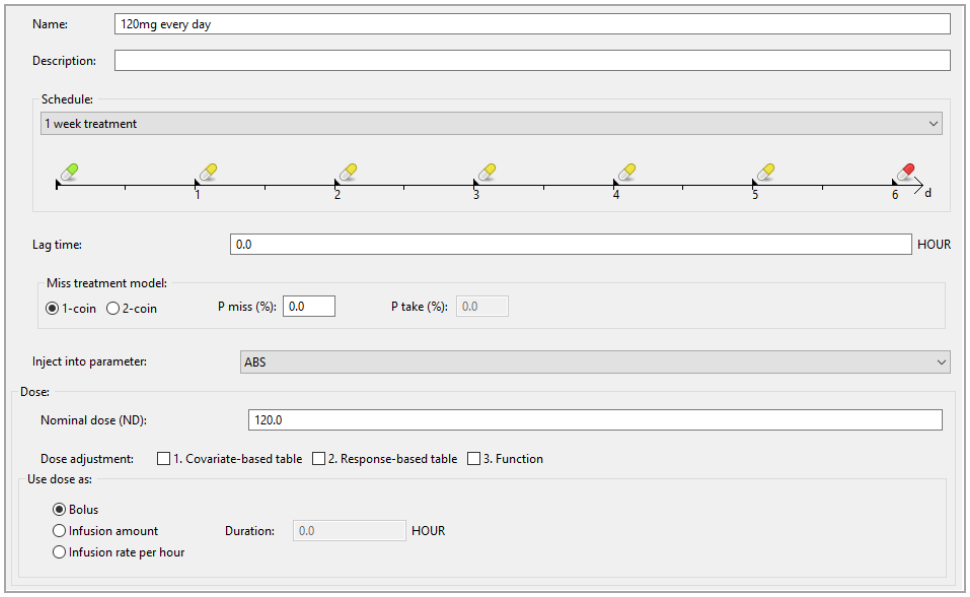

Figure 7 – A candidate dose of 120 mg is implemented in the tab Treatments of Simulo

5. SIMULATE

Population simulation scenarios can be run as some single replicates. The study design scenario must be replicated many times after the first question has been answered. In both cases, we can write a short analysis script that will only output AUC statistics for each scenario and replicate.

6. ANALYSIS FOR DECISION

The population simulation results conclude the dose of 120mg is the most appropriate (see Figure 8).

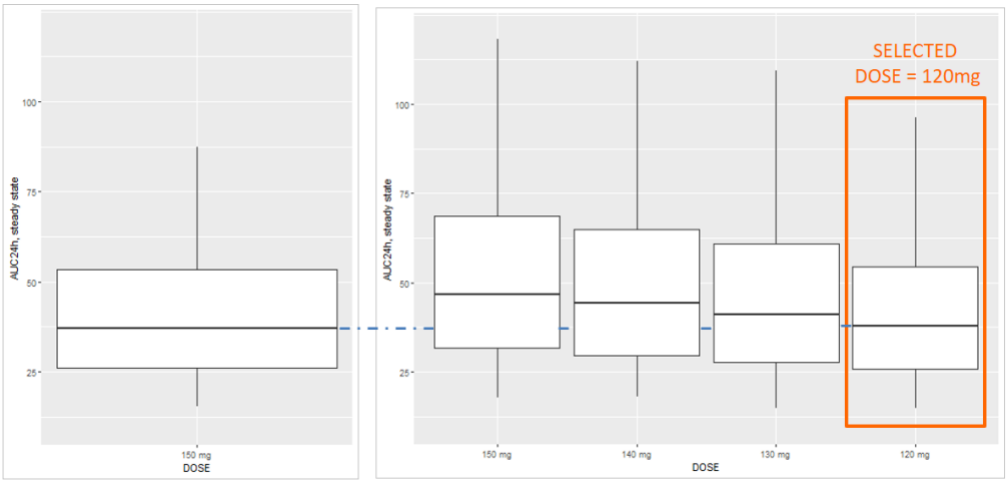

Figure 8 – Results for investigated doses 120, 130, 140 & 150 mg

The simulation replicates for small groups of 16 children concludes that the proposed protocol is convenient (see Figure 9).

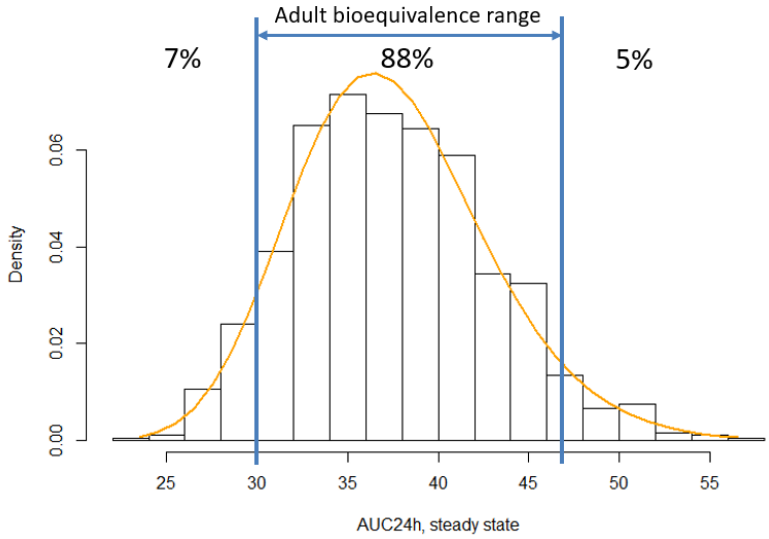

Figure 9 – Result of the probability of success analysis

CONCLUSION

Simulo is a platform for all sorts of model-based simulation activities for every player in drug development and clinical trials. Recent applications have shown how simulations can help in predicting the effect of dose adaptation on clinical endpoints as well as comparing different study designs and data analysis approaches.

REFERENCES

[1] Leirens Q, Faelens R, Gisleskog PO, et al. PAGE 26 2017. Abstr 7331 [www.page-meeting.org/?abstract=7331].

[2] European Medicines Agency. Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. 2008. p. 1e8.

[3] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:
clinicalresearch@sgs.com
EUROPE: +32 15 27 32 45
AMERICAS: + 877 677 2667
WWW.SGS.COM/CRO