R YOU READY FOR SIMULO: A USER-FRIENDLY CLINICAL TRIAL SIMULATOR (SD02)

Quentin Leirens, IT scientist, Belgium

Nicolas Luyckx, IT scientist, Belgium

Phuse EU Connect – Amsterdam | 10-13 November 2019

WHEN YOU NEED TO BE SURE

SGS

WHO ARE WE?

Quentin Leirens

Scientist

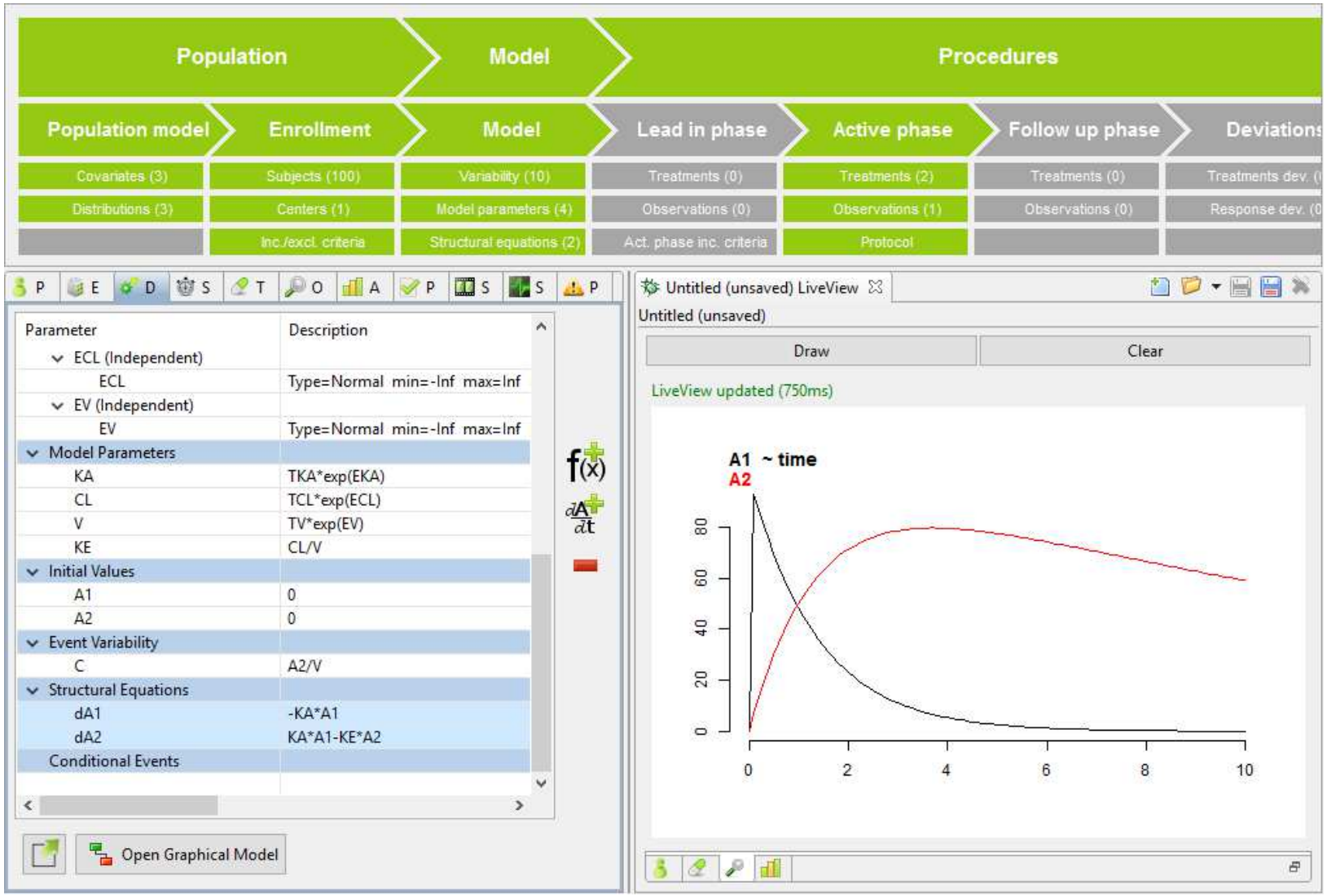
- Scientist at SGS Exprimo since 2011
- Engineer by training
- 9 years of experience in Modelling & Simulation
- Developer of Simulo
- Specialty: complex simulation projects for the pharma industry

Nicolas Luyckx

IT Scientist

- IT scientist at SGS Exprimo since 2017
- Engineer by training
- 8 years of experience in software development
- Developer of Simulo
- Specialty: R & Java development

WHAT IS SIMULO ?

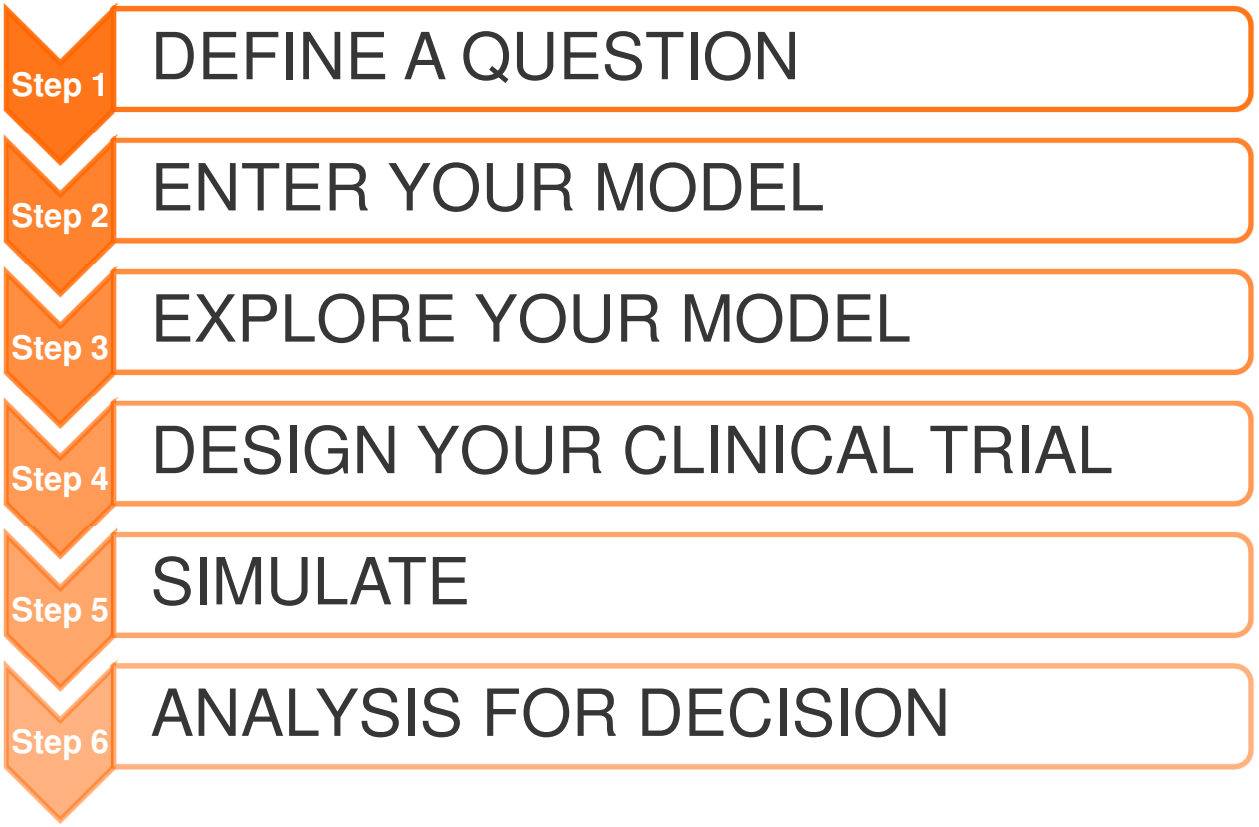


IMPLEMENT A PEDIATRIC CASE INTO SIMULO

- Context:
  - You successfully developed a drug for the adults
  - You would like to scale this drug to pediatrics
  - You plan to execute a pediatric clinical trial
  - Assume we want to target the 12-years-old children

- Drug characteristics:
  - Oral drug
  - 150mg given once daily
  - Steady state is reached after 1 week

BUILD YOUR SIMULATION IN 6 STEPS



DEFINE A QUESTION

Step 1

- Questions:
  - What pediatric dose should be used in the clinical trial?
  - We plan to execute the trial with 18 children, is it enough?
- Issues:
  - What criteria to compare children exposures with adults exposures?
    - C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{ss}
    - Geometric mean of child and adult metrics as close as possible
  - How can I answer the second question with Simulo?
    - “Target a 95% confidence interval within 60% and 140% of the geometric mean estimates in each pediatric subgroup with at least 80% power” *

*General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, FDA

ENTER YOUR MODEL

Step 2

FLEXIBILITY

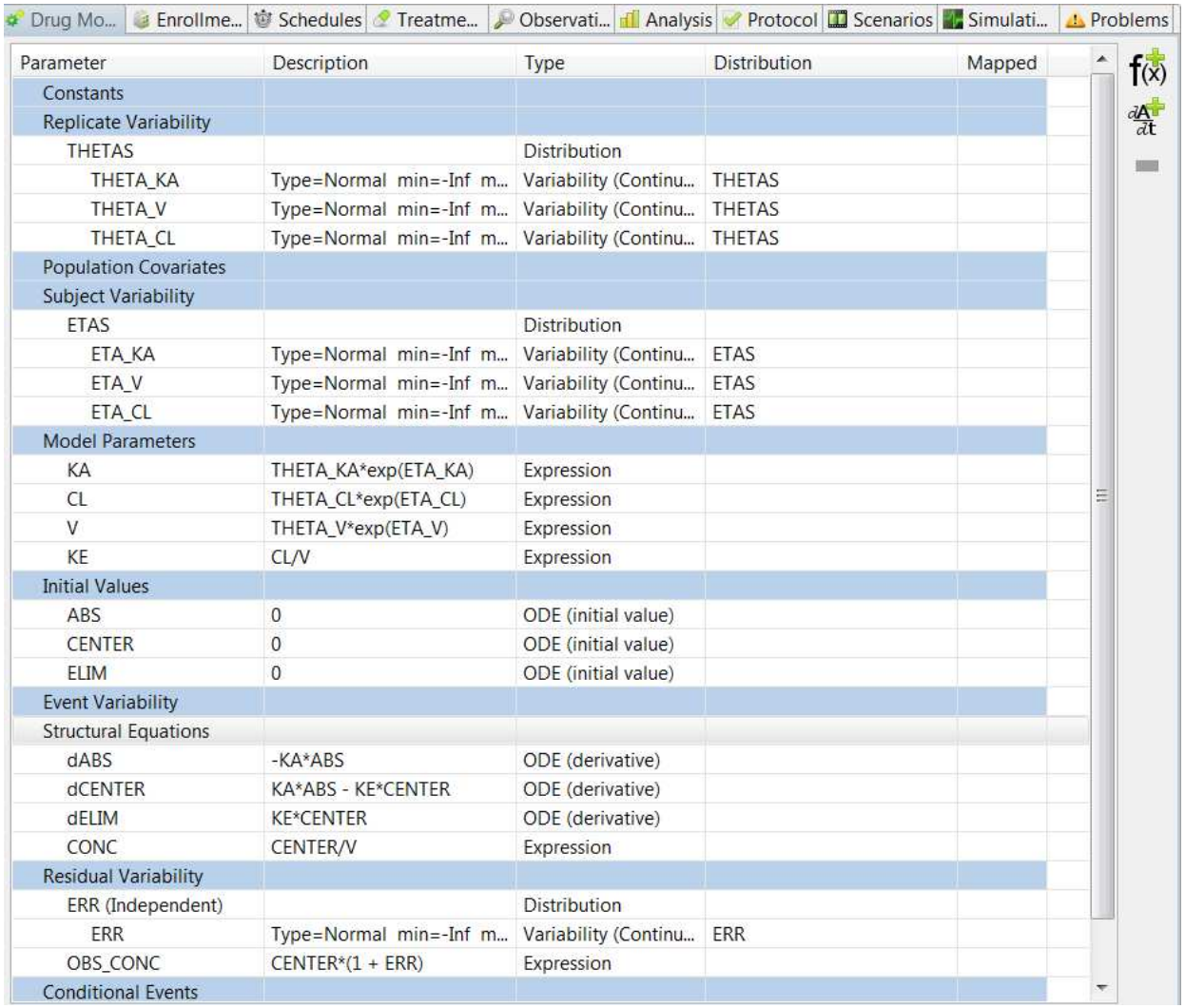
- Any drug-disease model
  - From publication
  - From Simulo library
  - From a model developed internally
- All levels of variability
  - Patient characteristics
  - Random sampling
  - Uncertainty
  - Error

ENTER YOUR MODEL

Step 2

USER-FRIENDLY

- No complex scripting
- Clear framework
- Share and collaborate !



Parameter	Description	Type	Distribution	Mapped
Constants				
Replicate Variability				
THETAS		Distribution		
THETA_KA	Type=Normal min=-Inf m...	Variability (Continu...	THETAS	
THETA_V	Type=Normal min=-Inf m...	Variability (Continu...	THETAS	
THETA_CL	Type=Normal min=-Inf m...	Variability (Continu...	THETAS	
Population Covariates				
Subject Variability				
ETAS		Distribution		
ETA_KA	Type=Normal min=-Inf m...	Variability (Continu...	ETAS	
ETA_V	Type=Normal min=-Inf m...	Variability (Continu...	ETAS	
ETA_CL	Type=Normal min=-Inf m...	Variability (Continu...	ETAS	
Model Parameters				
KA	THETA_KA*exp(ETA_KA)	Expression		
CL	THETA_CL*exp(ETA_CL)	Expression		
V	THETA_V*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 m...	Variability (Continu...	ERR	
OBS_CONC	CENTER*(1 + ERR)	Expression		
Conditional Events				

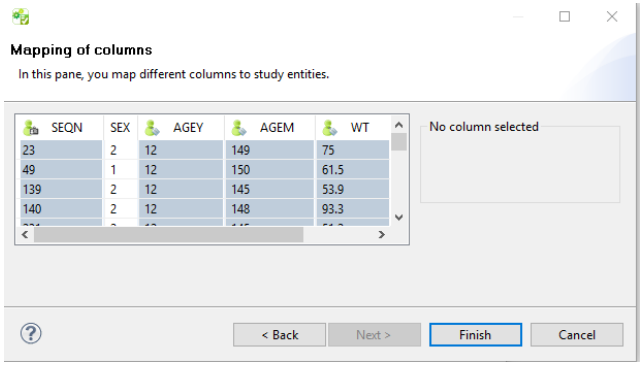
ENTER YOUR MODEL

Step 2

- Scale your model to children using allometric scaling:
  - $CL_{pediatric} = CL_{adult} * \left(\frac{WT}{70}\right)^{0.75}$
  - $V_{pediatric} = V_{adult} * \left(\frac{WT}{70}\right)^{1.0}$
- Recommended by FDA
- Bootstrap demographics and measurement data:

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

NHANES dataset



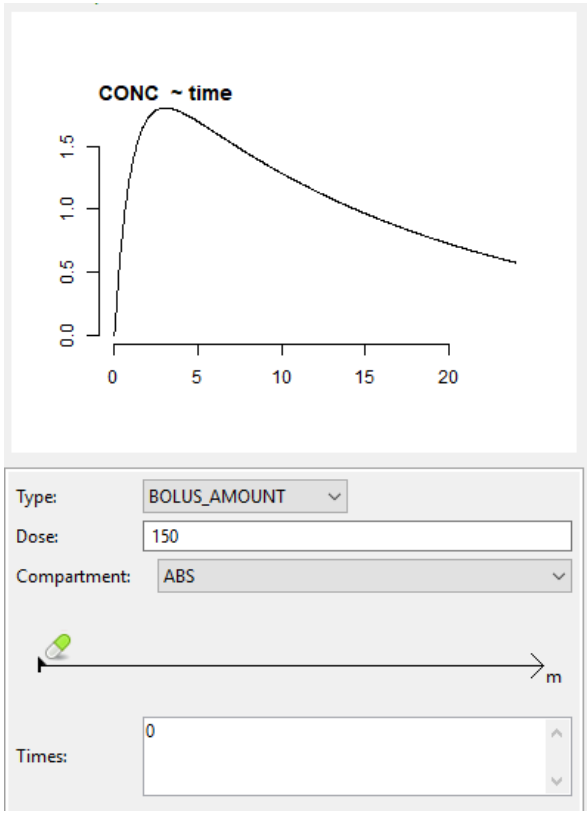
Bootstrap of Weight & Age

simulo by SGS Exprimo

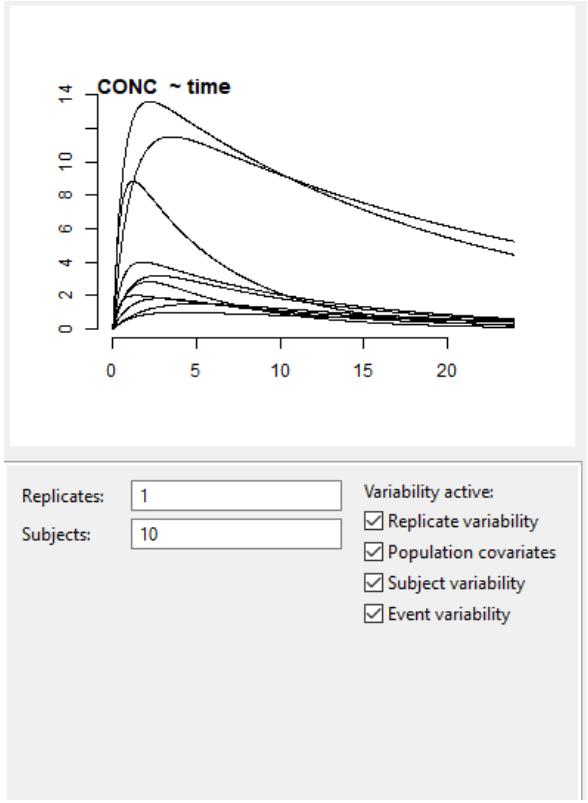
EXPLORE YOUR MODEL

Step 3

- Explore individual profiles in the liveview:



- Typical profiles
- Give a single dose

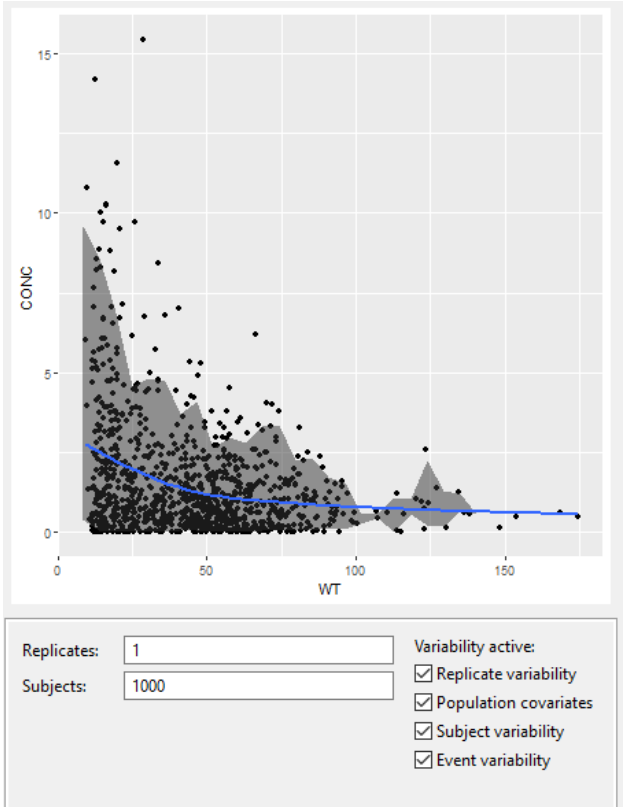


- Different single profiles
- Explore the different levels of variabilities

EXPLORE YOUR MODEL

Step 3

- Plot children population statistics (aged 2-18)

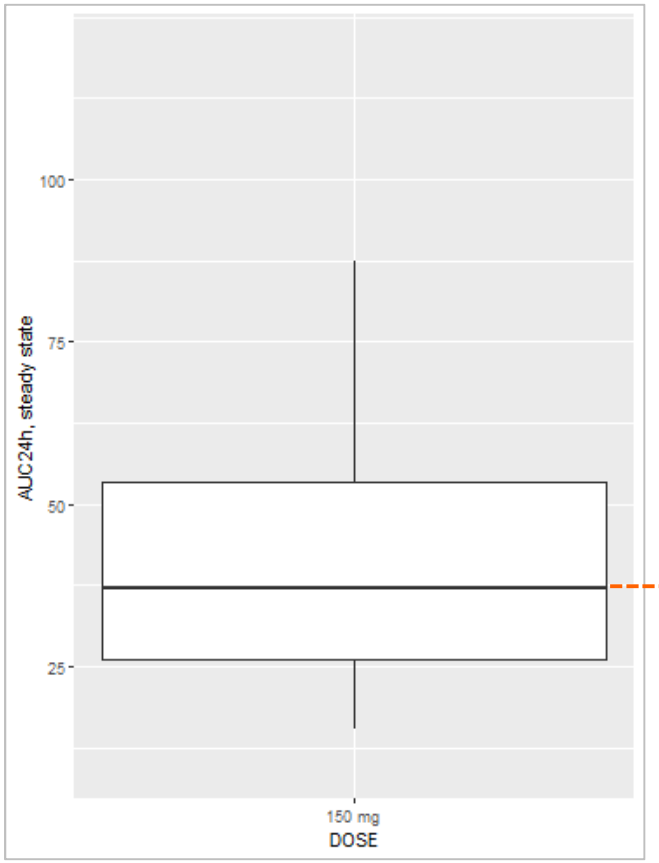


  - Population simulation
  - Weight / Concentration plot

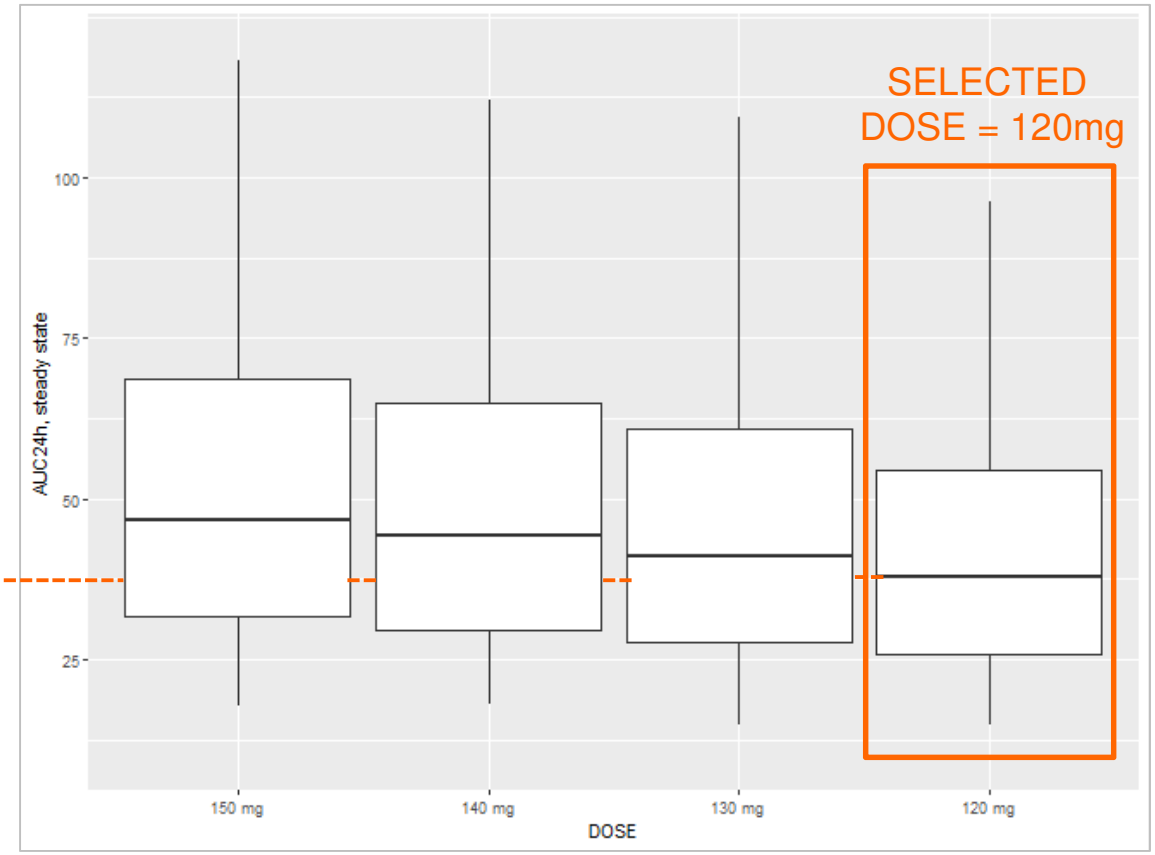
EXPLORE YOUR MODEL

Step 3

- Find dose for 12-years-old children



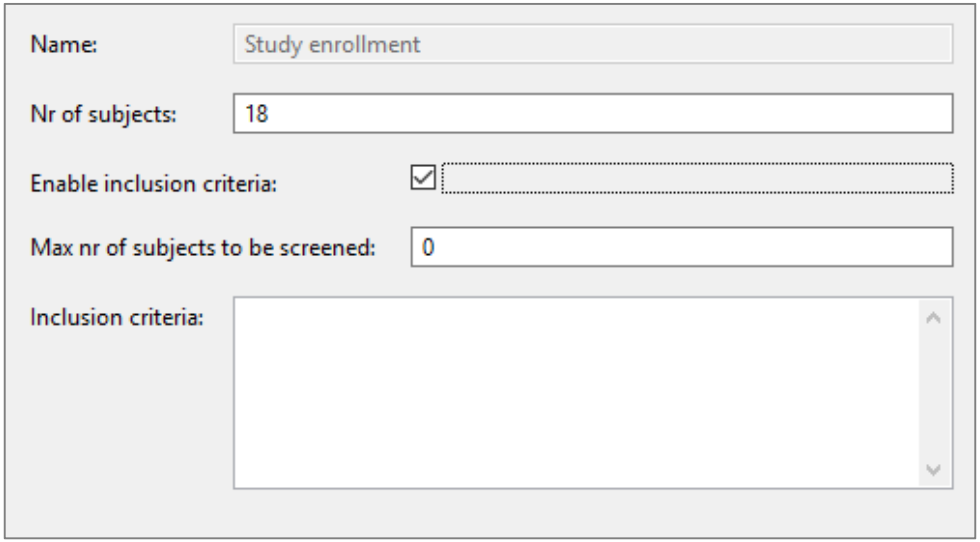
- AUC 24h - Adult PK model



- AUC 24h - Children PK model (4 doses)

DESIGN YOUR CLINICAL TRIAL

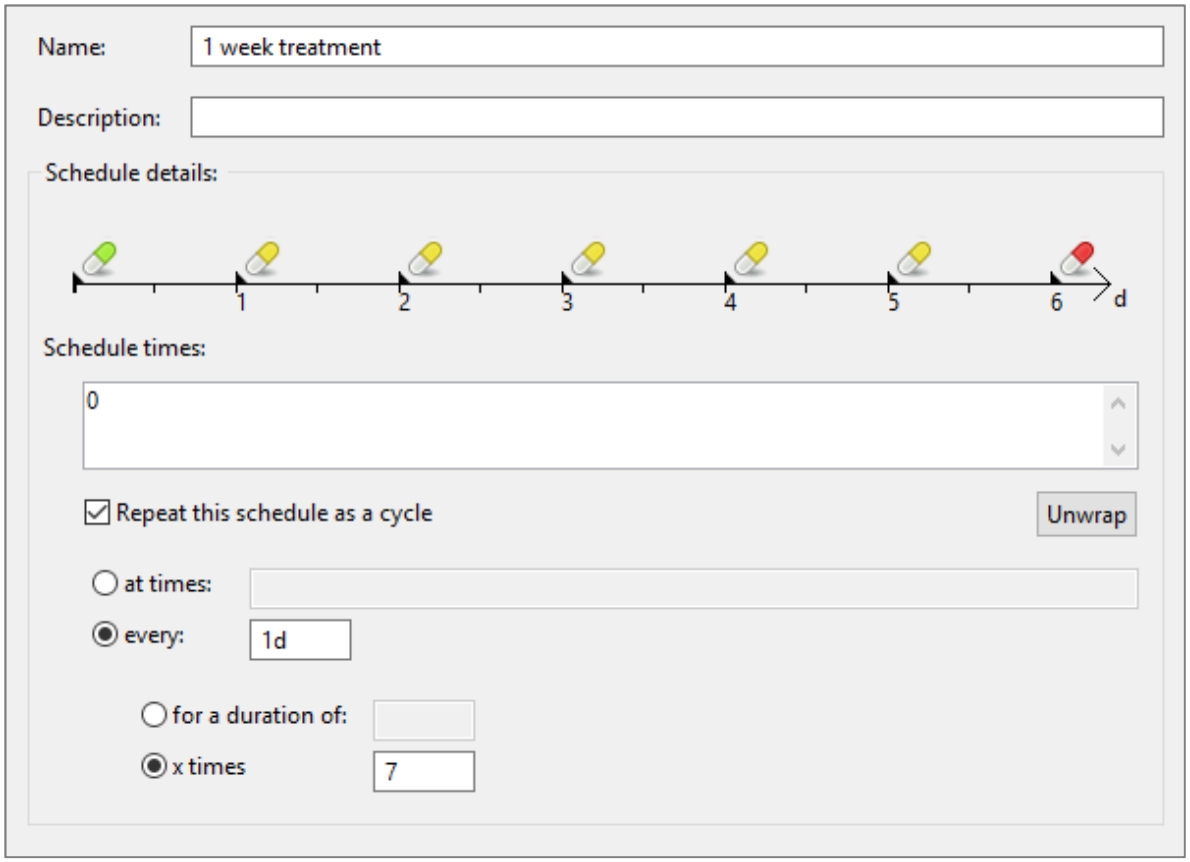
Step 4



- ✓ Enroll 18 children
- ✓ Enable/disable inclusion criteria
- ✓ Criteria: an R condition (e.g. WT > 30 & WT < 100)

DESIGN YOUR CLINICAL TRIAL

Step 4



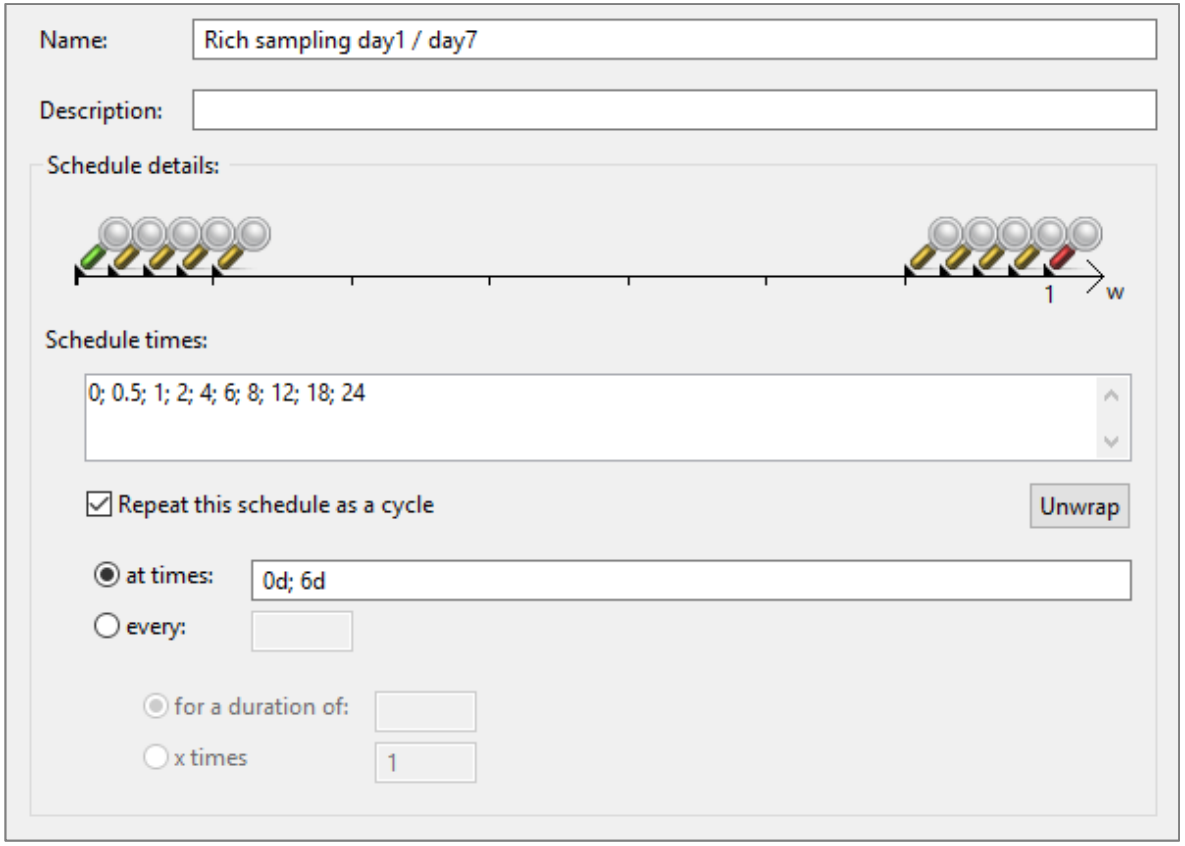
- ✓ Schedule name
- ✓ Schedule description

- ✓ Timeline

- ✓ Starting time(s)
- ✓ Repeat time(s)
- ✓ Useful options to define the cycle

DESIGN YOUR CLINICAL TRIAL

Step 4



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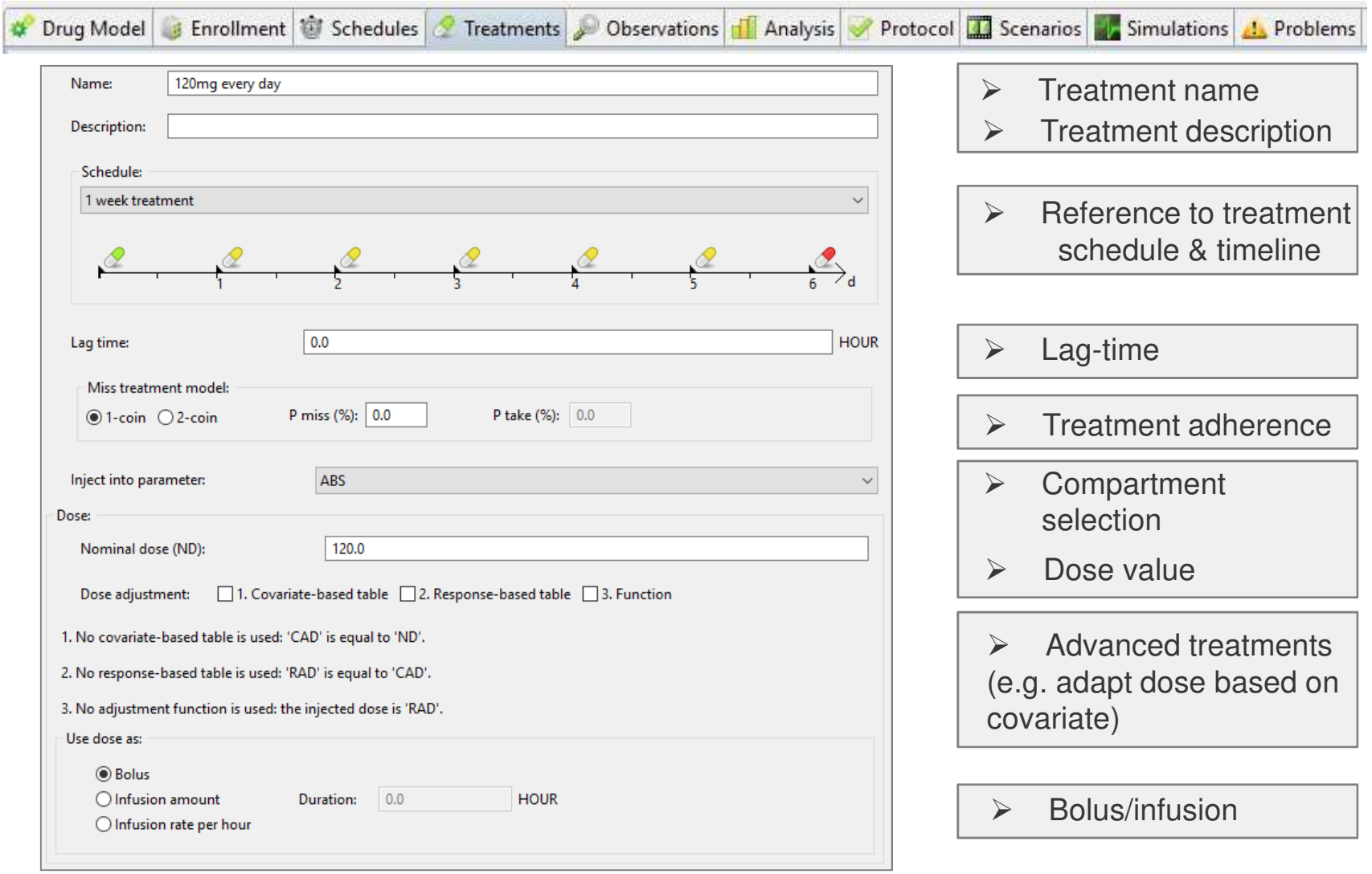
DESIGN YOUR CLINICAL TRIAL

Step 4



- Treatment name
- Treatment description

- Reference to treatment schedule & timeline

- Lag-time

- Treatment adherence

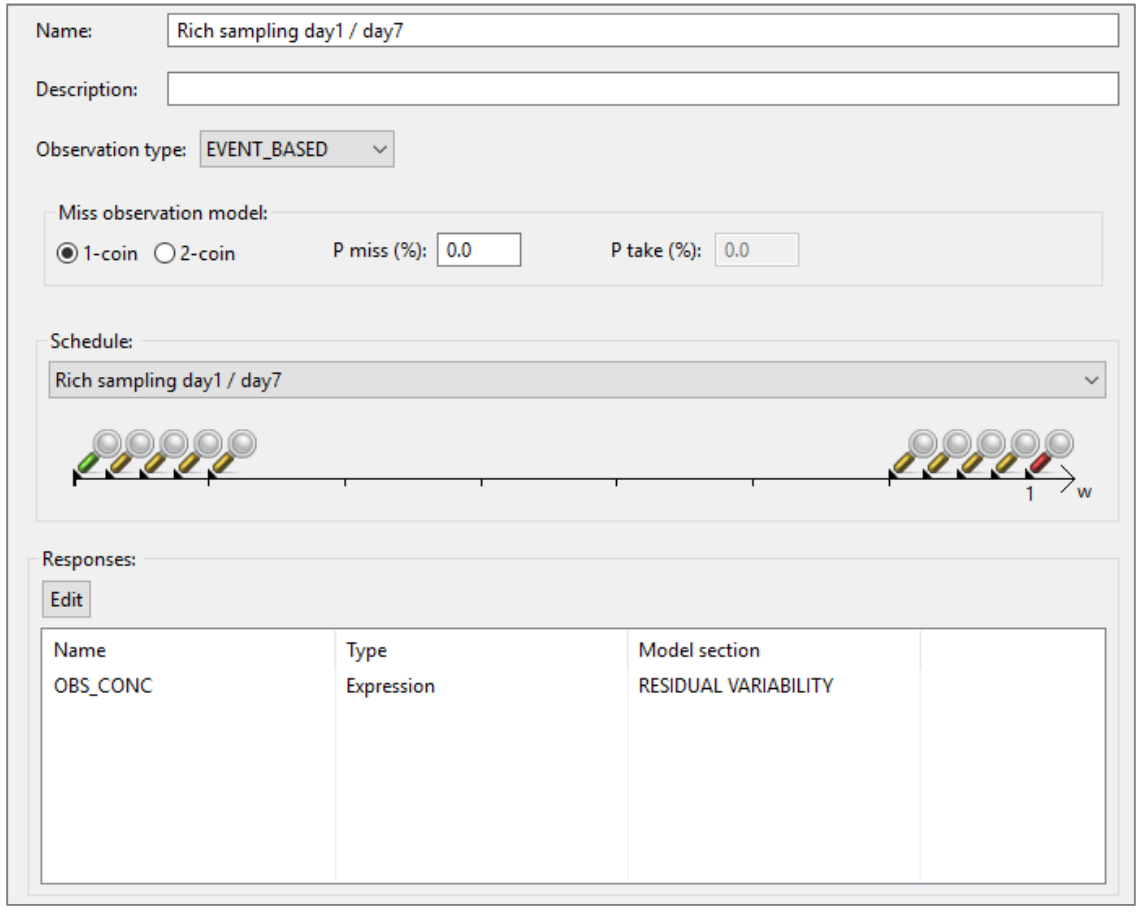
- Compartment selection
- Dose value

- Advanced treatments (e.g. adapt dose based on covariate)

- Bolus/infusion

DESIGN YOUR CLINICAL TRIAL

Step 4



- Observation name
- Observation description

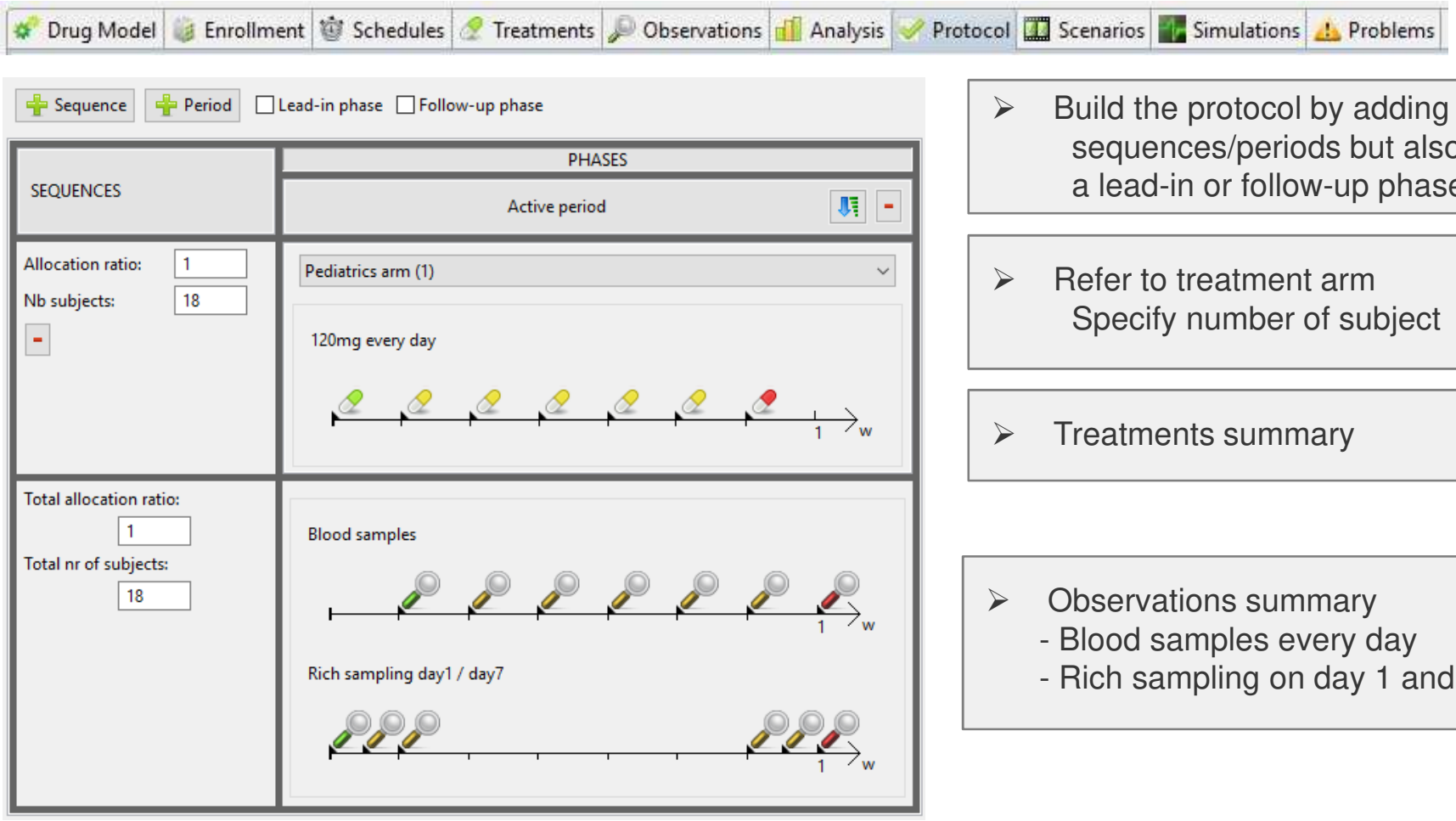
- Miss observation model

- Reference to observation schedule & timeline

- Variables of interest (exported in CSV output files)

DESIGN YOUR CLINICAL TRIAL

Step 4

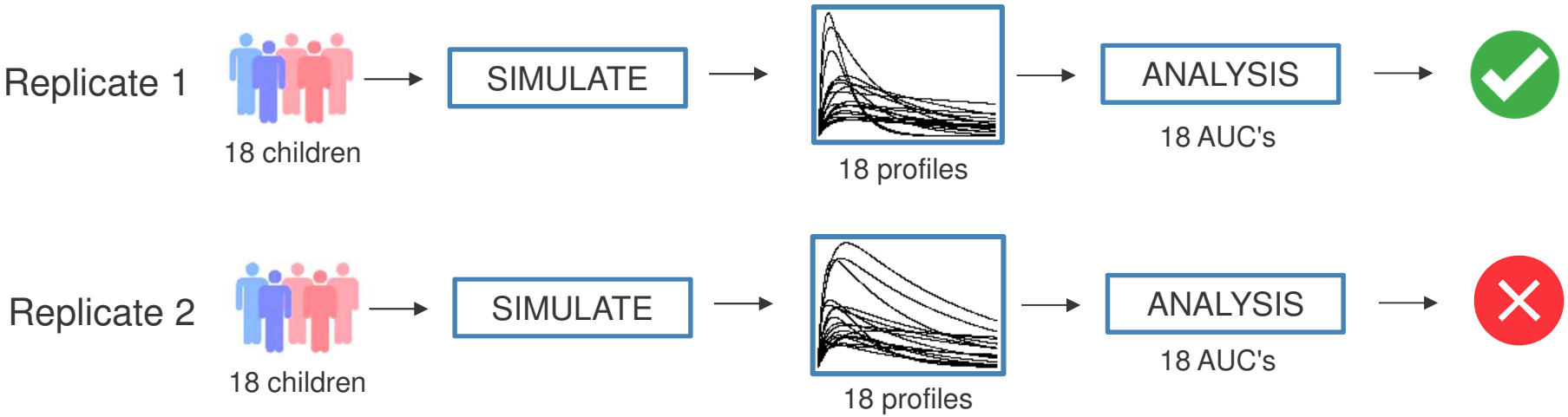


- Build the protocol by adding sequences/periods but also a lead-in or follow-up phase
- Refer to treatment arm Specify number of subject
- Treatments summary
- Observations summary
  - Blood samples every day
  - Rich sampling on day 1 and 7

SIMULATE

Step 5

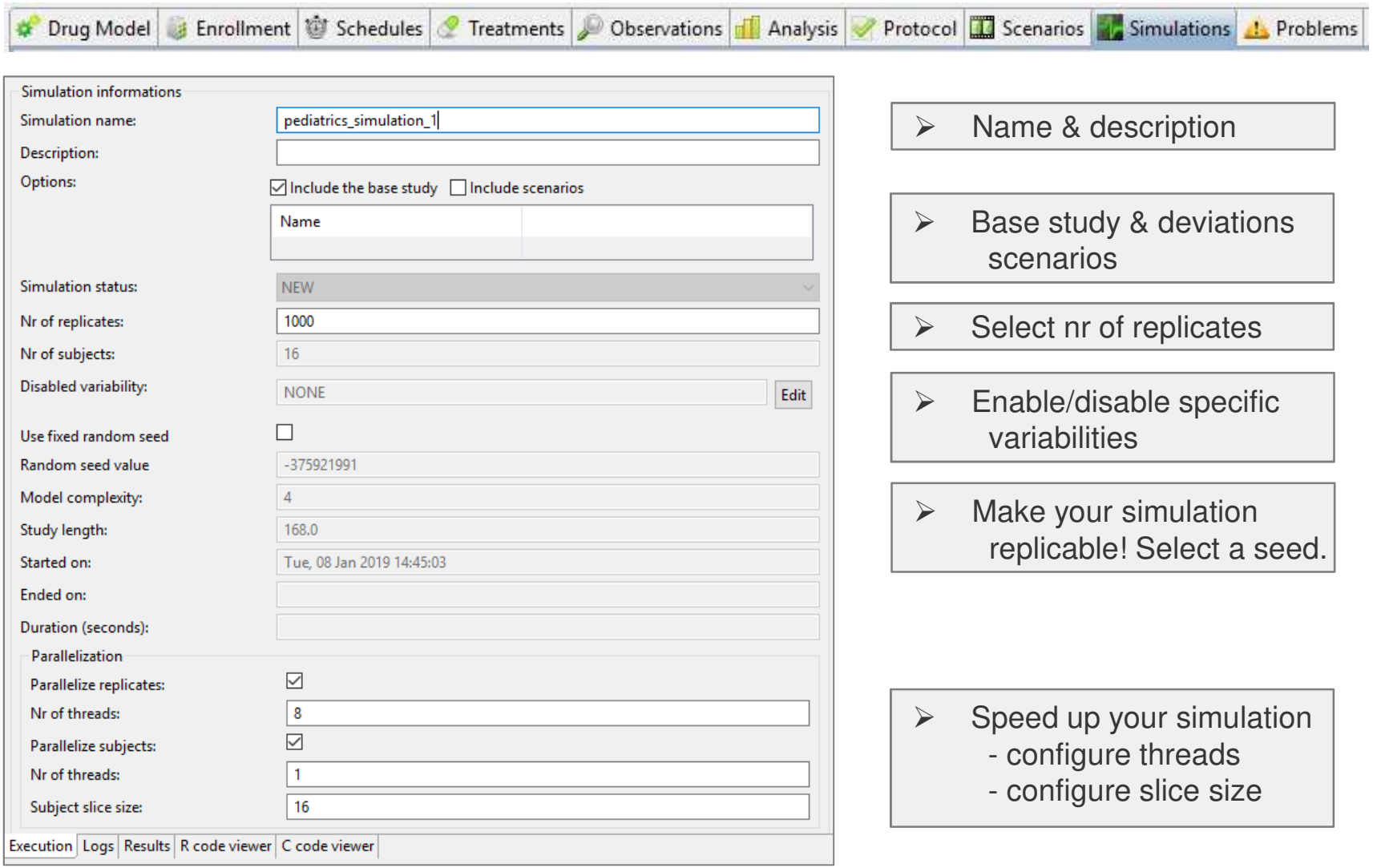
- Power analysis



Probability of success = $\frac{\sum}{N}$

SIMULATE

Step 5



- Name & description
- Base study & deviations scenarios
- Select nr of replicates
- Enable/disable specific variabilities
- Make your simulation replicable! Select a seed.
- Speed up your simulation
  - configure threads
  - configure slice size

ANALYSIS FOR DECISION

Step 6

Name: Probability of Success

Analysis script:

R script:

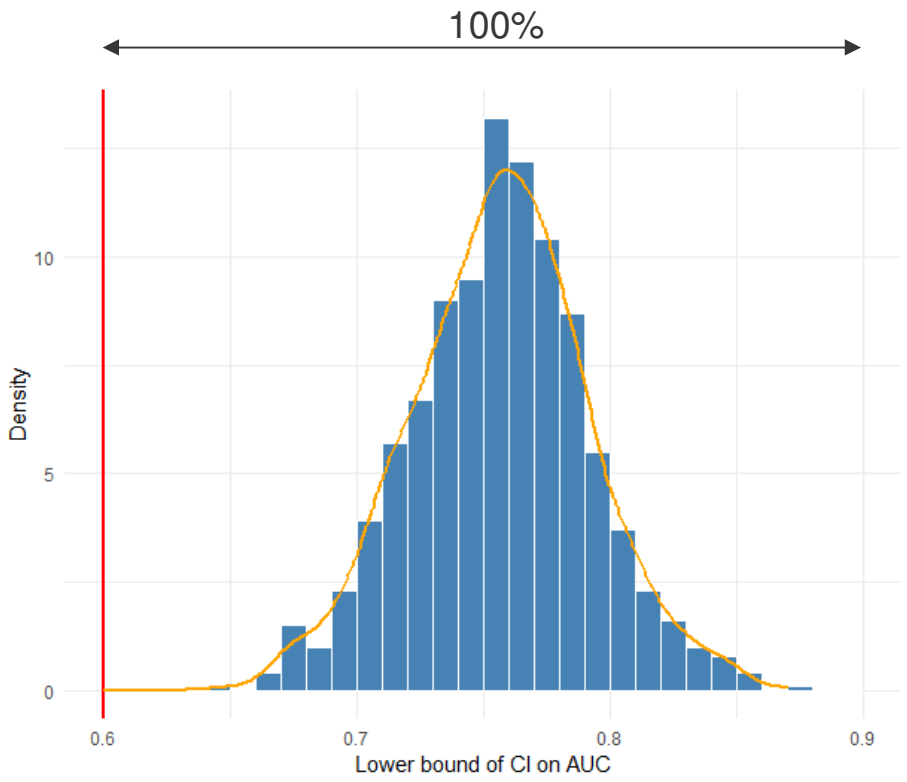
```
library(plyr)
library(tidyverse)

# Retrieve all SIMULO results files
files <- list.files(pattern = "*.csv" , recursive = F, full.names = T)
db <- adply(files, 1, .fun = read.csv, .id = "replicate")

# Select rich sampling profile on day 7
richSamplingTable <- db %>%
  filter(event == "Rich sampling day1 / day7", t >= 144) %>%
  select(replicate, subject, t, OBS_CONC)

# Compute AUC steady state for each subject
aucTable <- richSamplingTable %>%
  group_by(replicate, subject) %>%
  summarise(AUC=computeAUC(t, OBS_CONC))

# Compute the 95% CI of geometric mean of AUC in each replicate
aucSummary <-
  aucTable %>% group_by(replicate) %>% summarise(
    gm = geoMean(AUC),
    gm.lo = geoMean(AUC)*exp(-qt(0.975, df=(n() - 1))*sd(log(AUC))/sqrt(n())),
    gm.up = geoMean(AUC)*exp(qt(0.975, df=(n() - 1))*sd(log(AUC))/sqrt(n()))
  )

# Compute the probability of success
PoS <- aucSummary %>% group_by() %>%
  summarise(PoS=sum(gm.lo/gm > 0.6 & gm.up/gm < 1.4)/n())
```

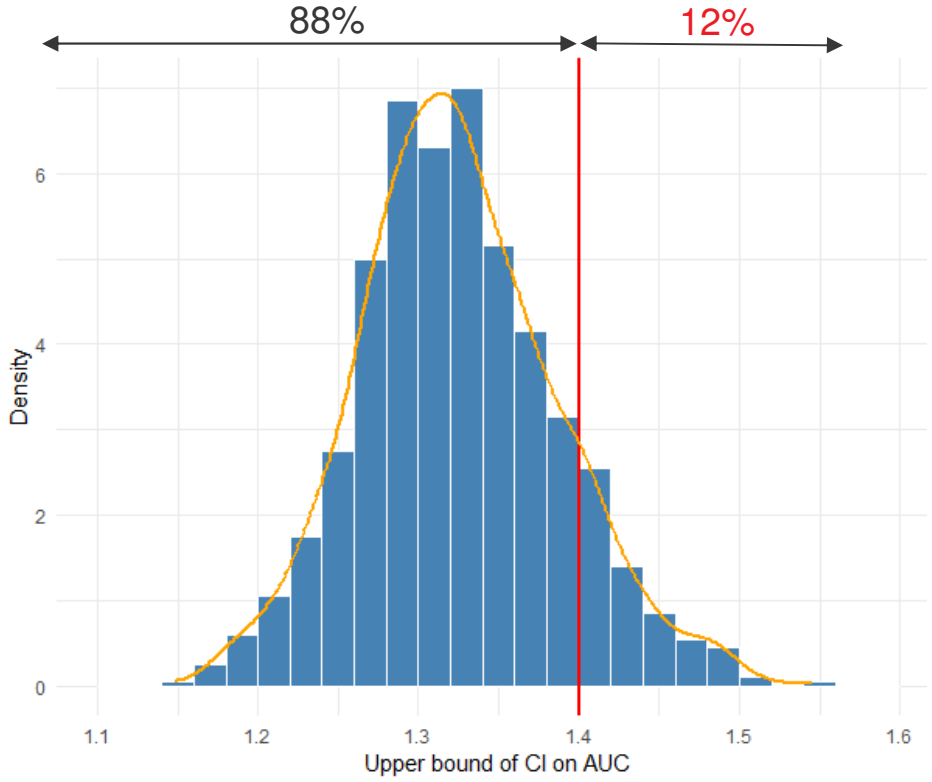
- Retrieve all CSV files in a R dataframe
- Select the rich sampling observations on day 7
- Compute AUC for each subject in a replicate
- Compute CI on geometric mean in each replicate
- Count how many trials are successful

ANALYSIS FOR DECISION

Step 6

Solution: probability of success = 88 %

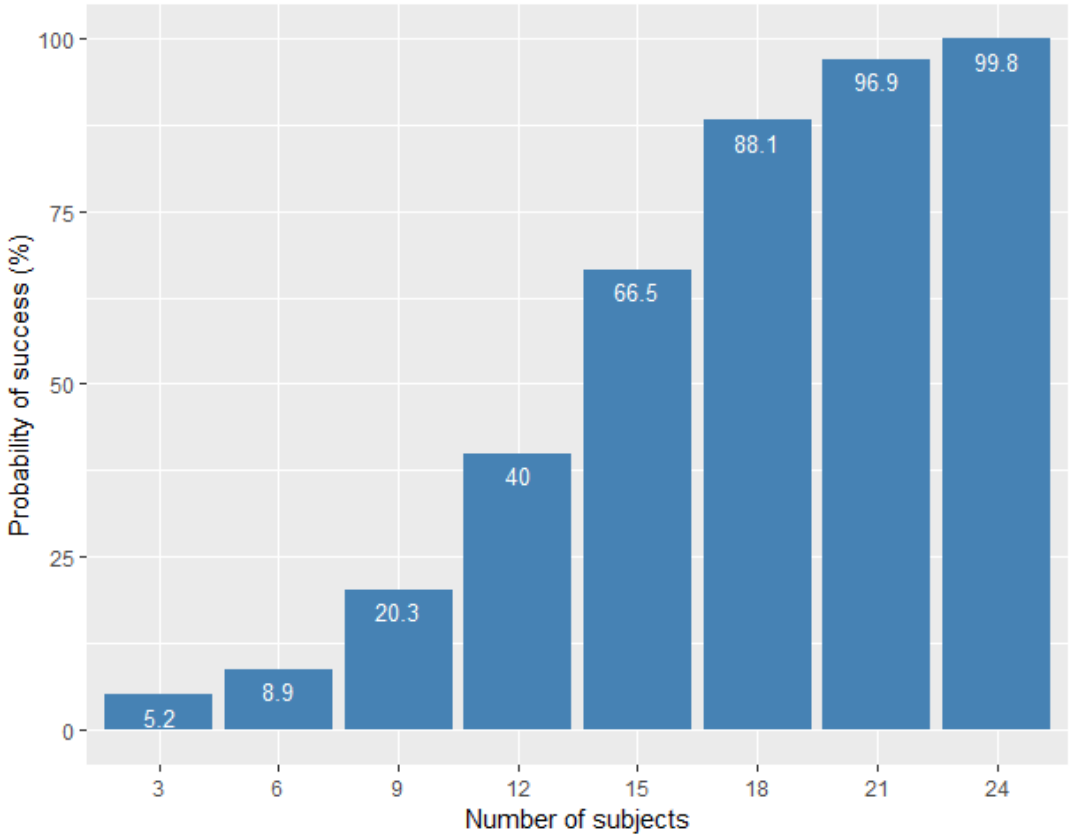




ANALYSIS FOR DECISION

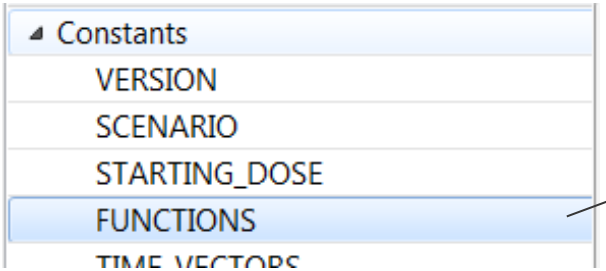
Step 6

- Further investigation



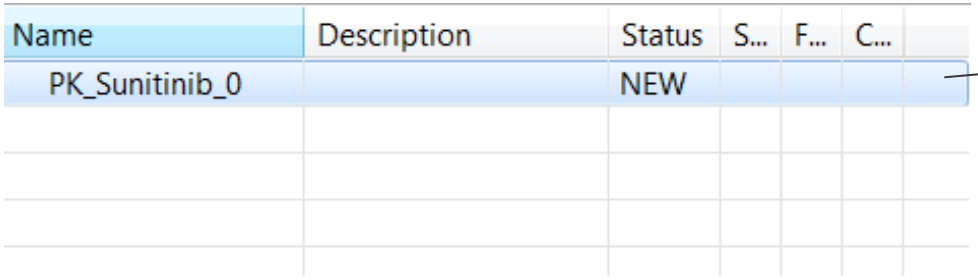
ADVANCED FEATURES: R BACKEND

- Custom R code anywhere




```r
# this defines some utility functions

doses <- c(2.5, 5, 7.5, 10, 12.5, 15)
uptitrate <- function(x) {
i <- match(x, doses)
i <- ifelse(i==length(doses), i, i+1)
doses[i]
}
downtitrate <- function(x) {
i <- match(x, doses)
i <- ifelse(i==1, i, i-1)
doses[i]
}
```

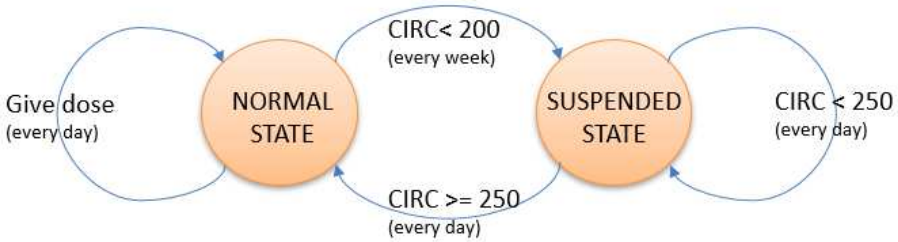
- Full standalone R script



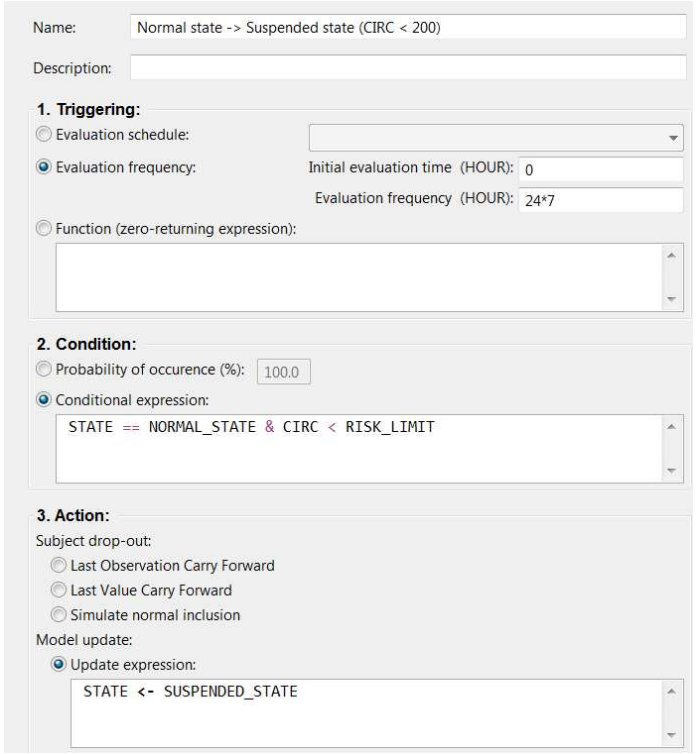

```r
library(MASS)
library(deSolve)
suppressMessages(library(data.table))
Sys.setlocale("LC_NUMERIC", "C");

# set environment parameters
set.seed(0)

SIM_Bootstrap <- new.env()
SIM_Environment <- new.env()
SIM_SliceSize <- 1
SIM_SequentialSampling <- new.env()
SIM_BootstrapReplacement <- new.env()

# evaluate Study Variability
    SIM_Environment$NORMAL_STATE <- local(local( {

    0

     } ), envir=SIM_Environment)

    SIM_Environment$SUSPENDED_STATE <- local(local( {

    1

     } ), envir=SIM_Environment)

    SIM_Environment$RISK_LIMIT <- local(local( {

    200

     } ), envir=SIM_Environment)

    SIM_Environment$SAFE_LIMIT <- local(local( {
```

ADVANCED FEATURES: CONDITIONAL EVENTS

- Complex study protocols

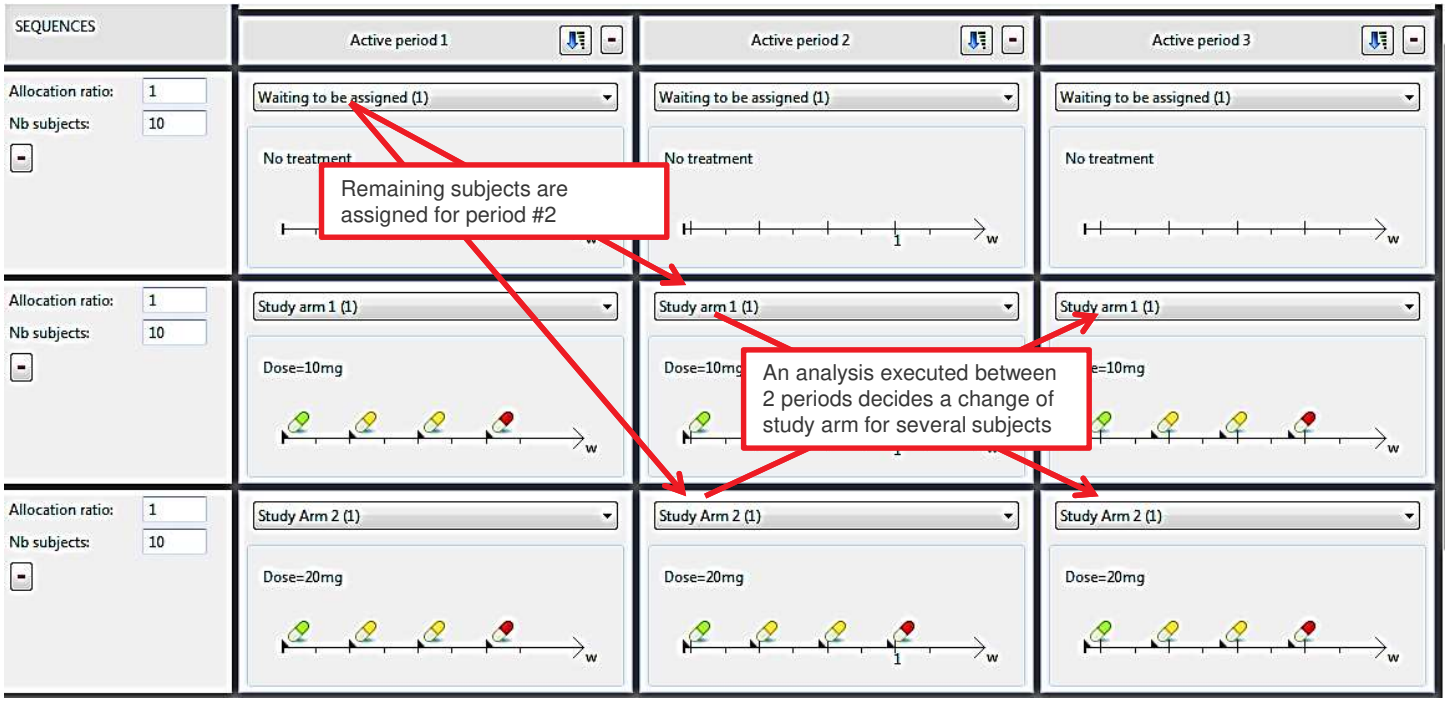


- 3-step interface
  - When?
  - Who?
  - What?



ADVANCED FEATURES: ADAPTIVE DESIGNS

- Interim analyses between each period
- Subject reassignment



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clinicalresearch@sgs.com

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