



SIMULO

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PhUSE US 2019

WHEN YOU NEED TO BE SURE

SGS

Population		Model	Procedures			
Population model	Enrollment	Model	Lead in phase	Active phase	Follow up phase	Deviations
Covariates (3)	Subjects (100)	Variability (10)	Treatments (0)	Treatments (2)	Treatments (0)	Treatments dev. (0)
Distributions (3)	Centers (1)	Model parameters (4)	Observations (0)	Observations (1)	Observations (0)	Response dev. (0)
	Inc./excl. criteria	Structural equations (2)	Act. phase inc. criteria	Protocol		

Parameter

- ▼ ECL (Independent)
 - ECL
- ▼ EV (Independent)
 - EV
- ▼ Model Parameters
 - KA
 - CL
 - V
 - KE
- ▼ Initial Values
 - A1
 - A2
- ▼ Event Variability
 - C
- ▼ Structural Equations
 - dA1
 - dA2
- Conditional Events

Description

- Type=Normal min=-Inf max=Inf
- Type=Normal min=-Inf max=Inf
- $TKA \cdot \exp(EKA)$
- $TCL \cdot \exp(ECL)$
- $TV \cdot \exp(EV)$
- CL/V
- 0
- 0
- $A2/V$
- $-KA \cdot A1$
- $KA \cdot A1 - KE \cdot A2$

Untitled (unsaved) LiveView

Untitled (unsaved)

Draw Clear

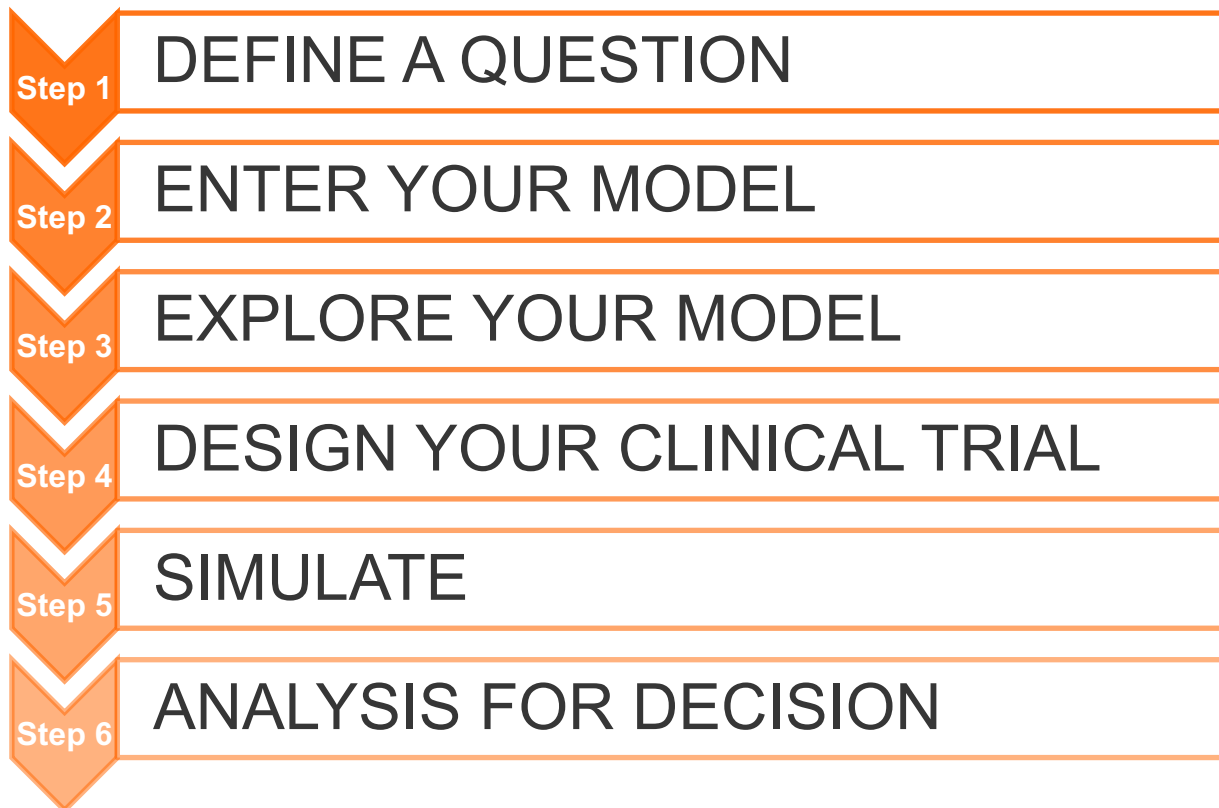
LiveView updated (750ms)

■ 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



■ 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

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

USER-FRIENDLY

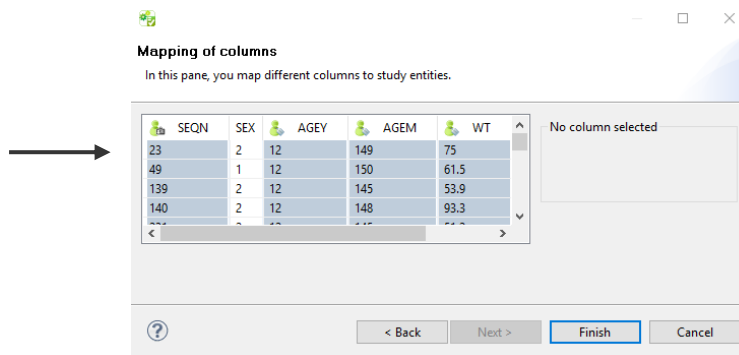
- No complex scripting
- Clear framework
- Share and collaborate !

Drug Mo... Enrollment... Schedules Treatment... Observati... Analysis Protocol Scenarios Simulati... Problems				
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				

- 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:



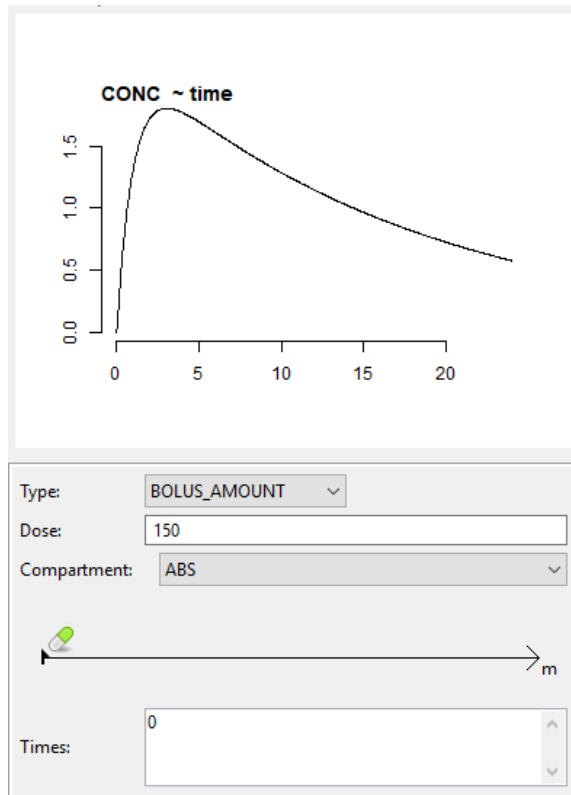
NHANES dataset



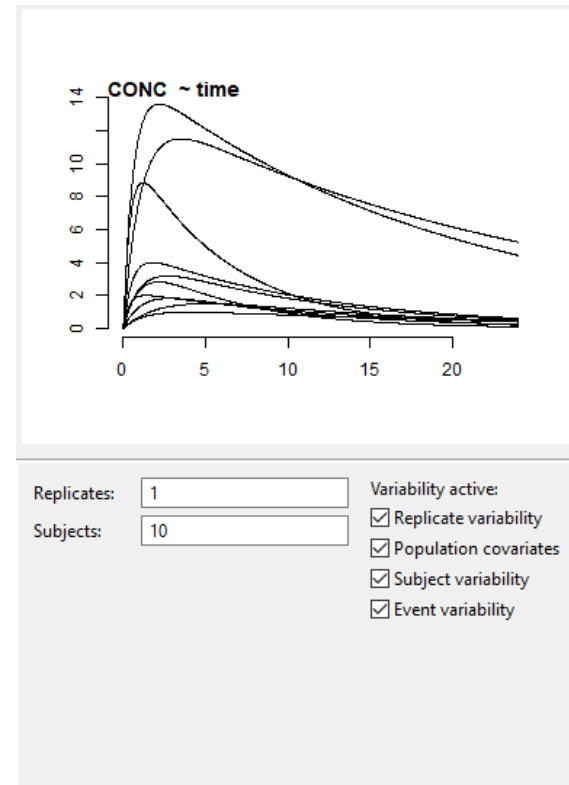
Bootstrap of Weight & Age



■ Explore individual profiles in the liveview:

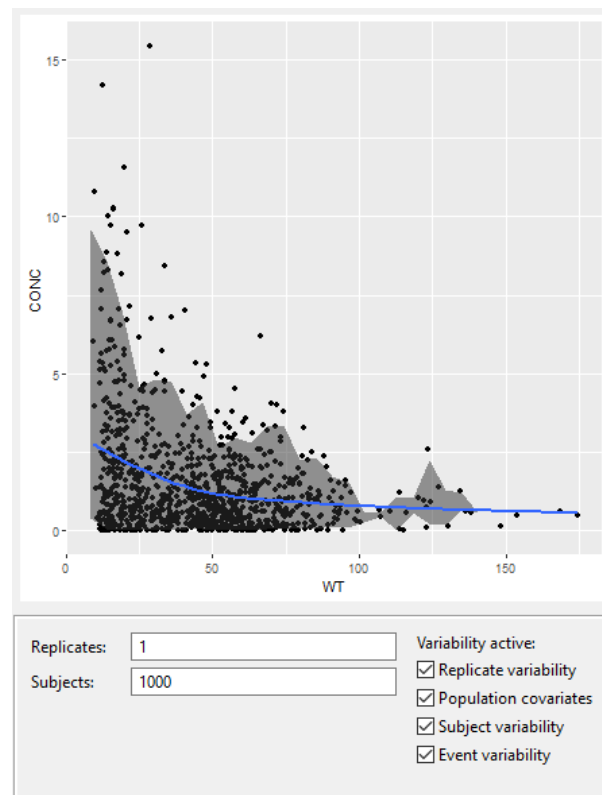


- Typical profiles
- Give a single dose



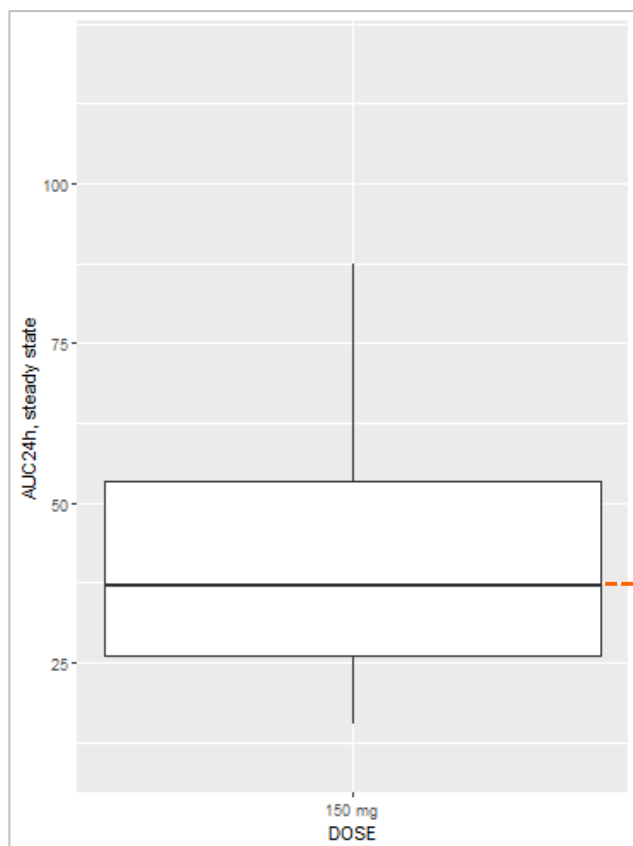
- Different single profiles
- Explore the different levels of variabilities

■ Plot children population statistics (aged 2-18)

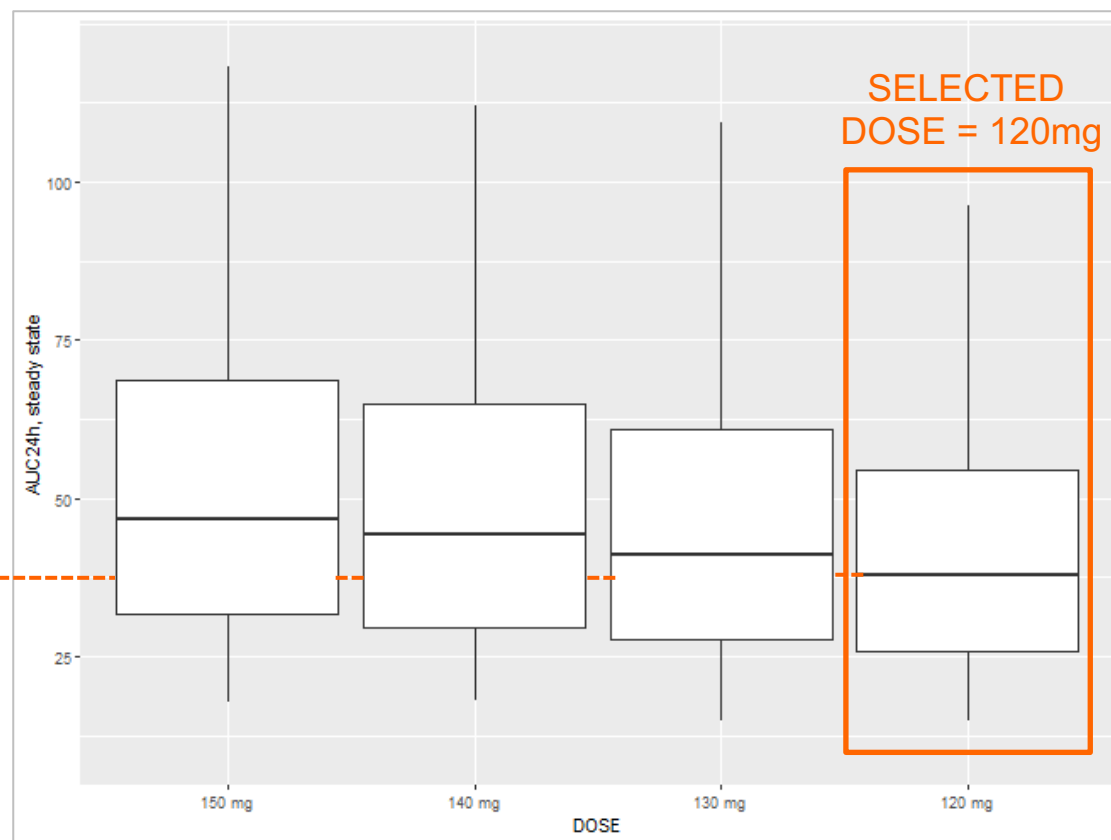


- Population simulation
- Weight / Concentration plot

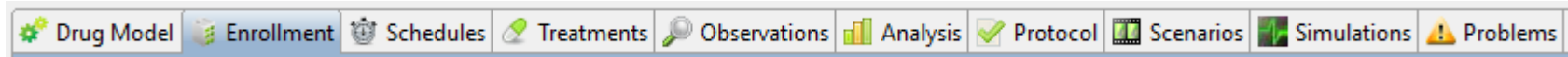
■ Find dose for 12-years-old children



■ AUC 24h - Adult PK model



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



Name:

Nr of subjects:

Enable inclusion criteria: ☒

Max nr of subjects to be screened:

Inclusion criteria:

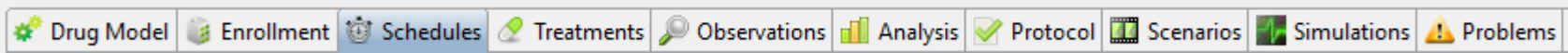
^

v

✓ Enroll 18 children

✓ Enable/disable inclusion criteria

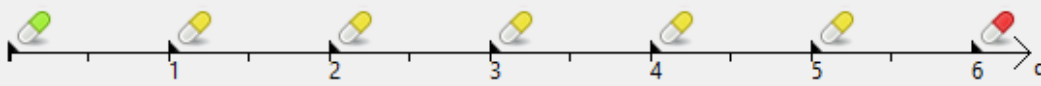
✓ Criteria: an R condition
(e.g. $WT > 30$ & $WT < 100$)



Name:

Description:

Schedule details:



Schedule times:

☒ Repeat this schedule as a cycle Unwrap

☐ at times:

☒ every:

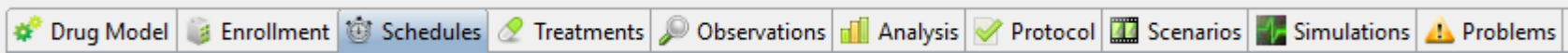
☐ for a duration of:

☒ x times

- ✓ Schedule name
- ✓ Schedule description

- ✓ Timeline

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



Name:

Description:

Schedule details:



Schedule times:

☒ Repeat this schedule as a cycle

☒ at times:

☐ every:

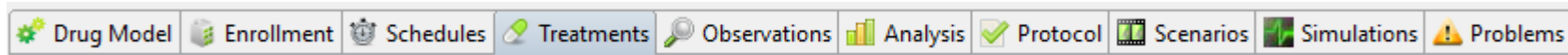
☐ for a duration of:

☐ x times

- ✓ Schedule name
- ✓ Schedule description

- ✓ Timeline

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



Name:

Description:

Schedule:

Lag time: HOUR

Miss treatment model:
☒ 1-coin ☐ 2-coin
P miss (%): P take (%):

Inject into parameter:

Dose:
Nominal dose (ND):

Dose adjustment: ☐ 1. Covariate-based table ☐ 2. Response-based table ☐ 3. Function

1. No covariate-based table is used: 'CAD' is equal to 'ND'.
2. No response-based table is used: 'RAD' is equal to 'CAD'.
3. No adjustment function is used: the injected dose is 'RAD'.

Use dose as:
☒ Bolus
☐ Infusion amount Duration: HOUR
☐ Infusion rate per hour

- Treatment name
- Treatment description

- Reference to treatment schedule & timeline

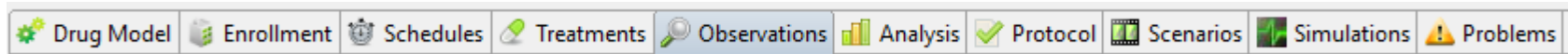
- Lag-time

- Treatment adherence

- Compartment selection
- Dose value

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

- Bolus/infusion



Name:

Description:

Observation type: EVENT_BASED ▼

Miss observation model:

☒ 1-coin ☐ 2-coin P miss (%): P take (%):

Schedule:

Rich sampling day1 / day7 ▼

Responses:

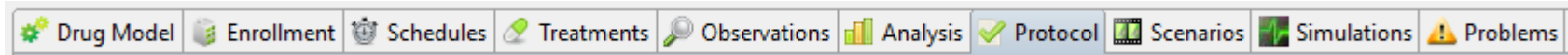
Name	Type	Model section
OBS_CONC	Expression	RESIDUAL VARIABILITY

- Observation name
- Observation description

- Miss observation model

- Reference to observation schedule & timeline

- Variables of interest (exported in CSV output files)



+ Sequence **+ Period** ☐ Lead-in phase ☐ Follow-up phase

SEQUENCES		PHASES	
Allocation ratio:	1	Active period	
Nb subjects:	18	Pediatrics arm (1) 120mg every day	
Total allocation ratio:	1	Blood samples	
Total nr of subjects:	18	Rich sampling day1 / day7	

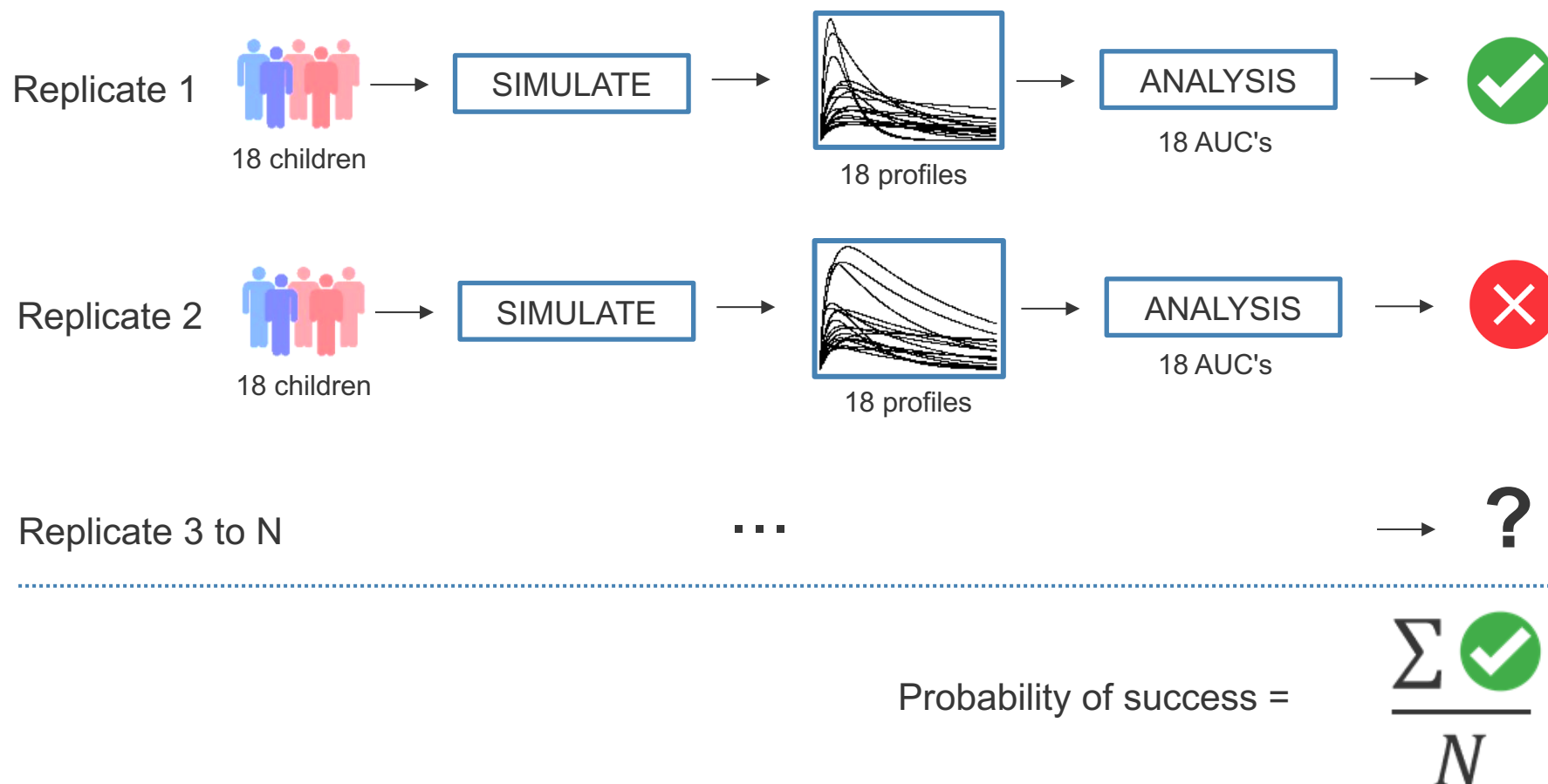
➤ Build the protocol by adding sequences/periods but also a lead-in or follow-up phase

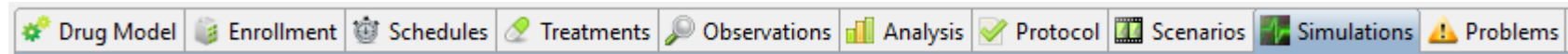
➤ Refer to treatment arm
Specify number of subject

➤ Treatments summary

➤ Observations summary
- Blood samples every day
- Rich sampling on day 1 and 7

Power analysis





Simulation informations

Simulation name:

Description:

Options: ☒ Include the base study ☐ Include scenarios

Name

Simulation status: NEW

Nr of replicates:

Nr of subjects:

Disabled variability: Edit

Use fixed random seed ☐

Random seed value:

Model complexity:

Study length:

Started on:

Ended on:

Duration (seconds):

Parallelization

Parallelize replicates: ☒

Nr of threads:

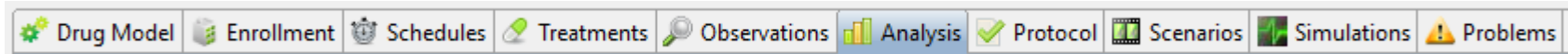
Parallelize subjects: ☒

Nr of threads:

Subject slice size:

Execution | Logs | Results | R code viewer | C code viewer

- 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



Name:

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))

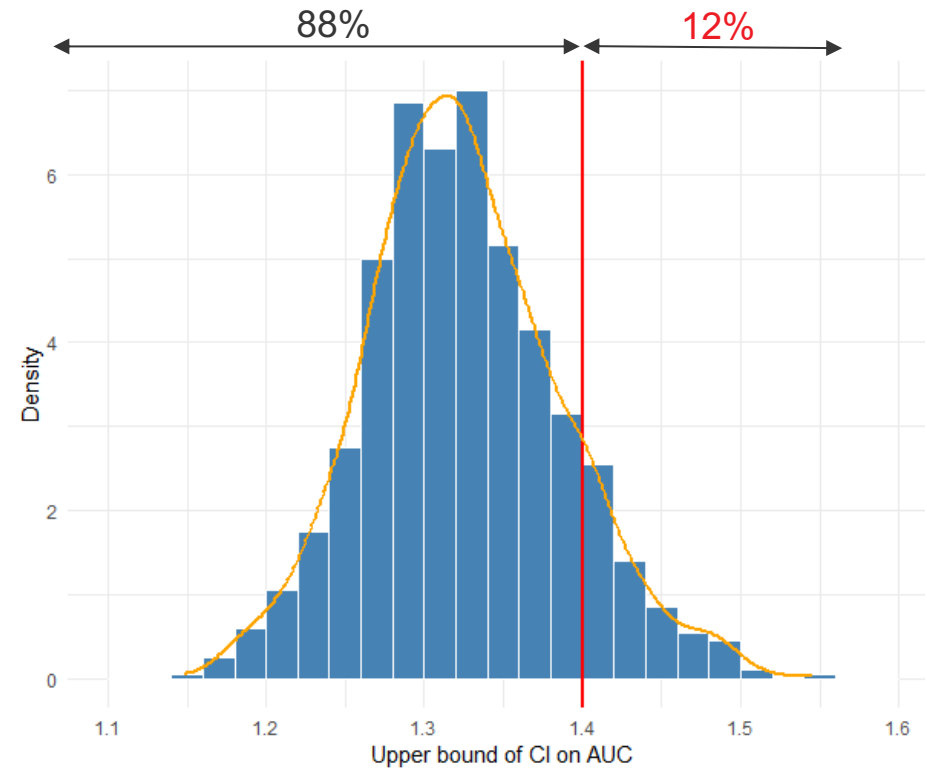
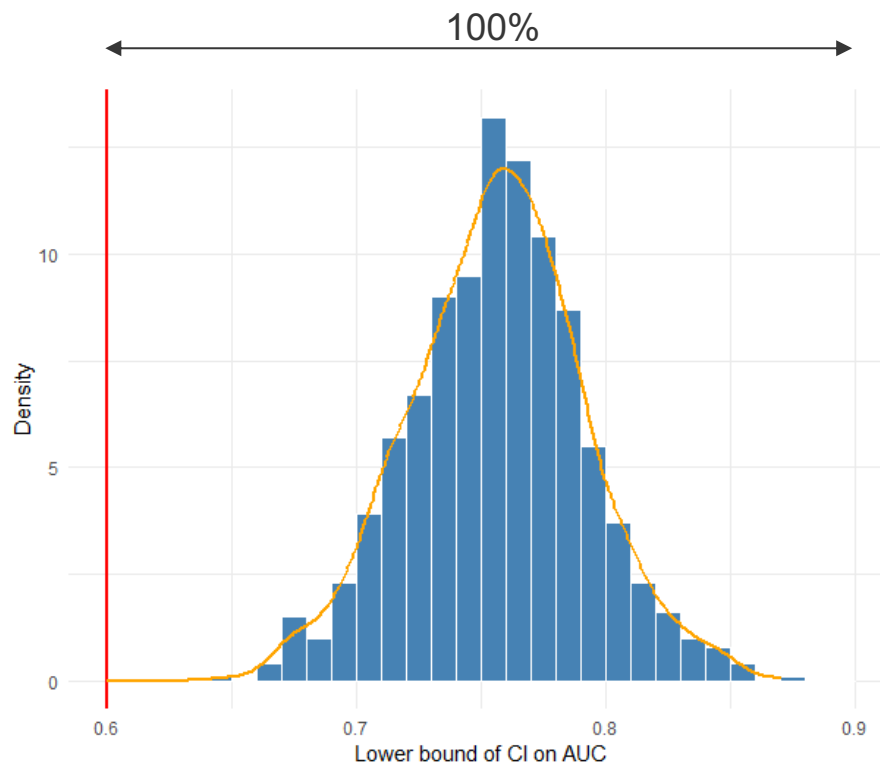
# Compute the 95% CI of geometric mean of AUC in each replicate
aucSummary <-
  aucTable %>% group_by(replicate) %>% summarise(
    gm = geoMean(AUC),
    gm.lo = geoMean(AUC)*exp(-qt(0.975, df=(n() - 1))*sd(log(AUC))/sqrt(n())),
    gm.up = geoMean(AUC)*exp(qt(0.975, df=(n() - 1))*sd(log(AUC))/sqrt(n()))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

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

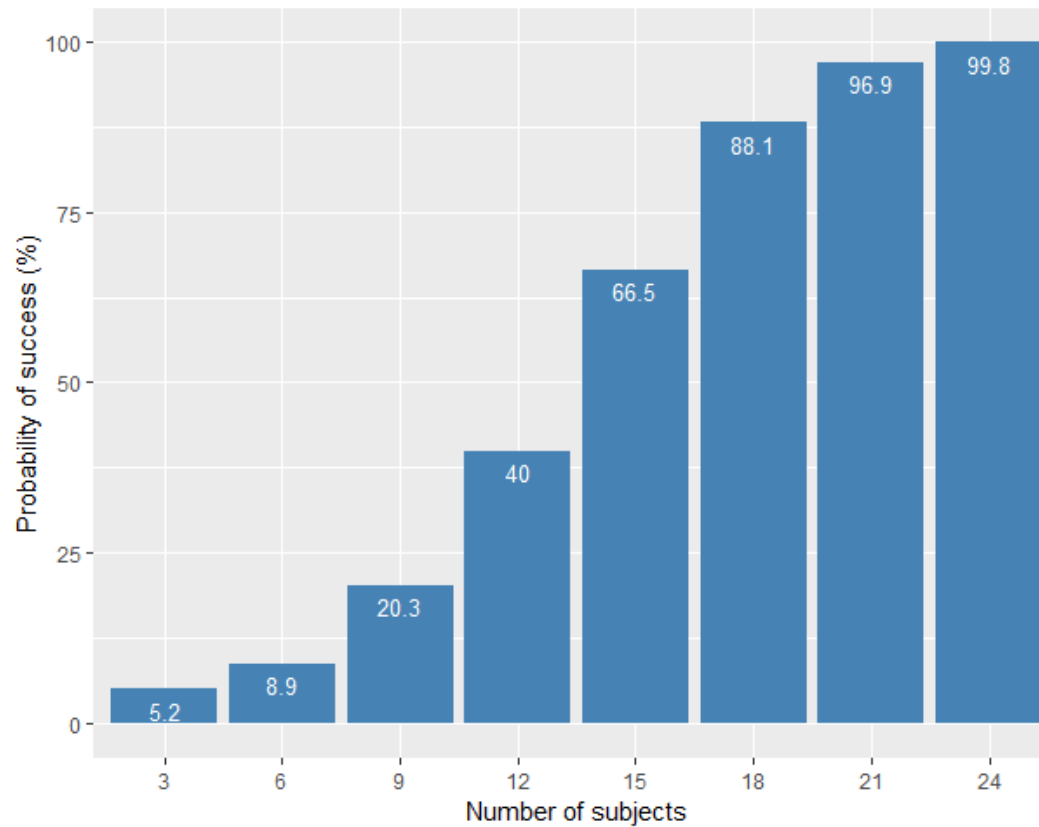
- Retrieve all CSV files in a R dataframe
- Select the rich sampling observations on day 7
- Compute AUC for each subject in a replicate
- Compute CI on geometric mean in each replicate
- Count how many trials are successful



Solution: probability of success = 88 %



■ Further investigation



Custom R code anywhere

Constants
VERSION
SCENARIO
STARTING_DOSE
FUNCTIONS
TIME VECTORS

```
# 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

Name	Description	Status	S...	F...	C...
PK_Sunitinib_0		NEW			

```
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)

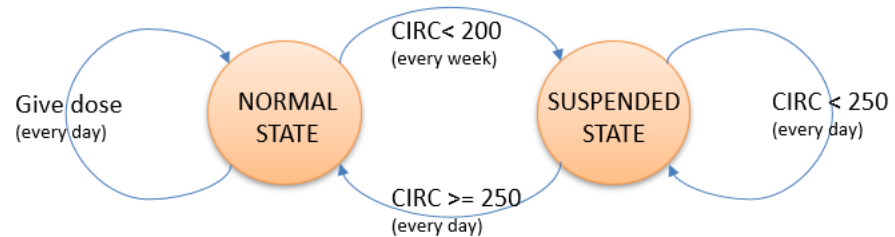
SIM_Environment$SUSPENDED_STATE <- local(local( {
  1
}), envir=SIM_Environment)

SIM_Environment$RISK_LIMIT <- local(local( {
  200
}), envir=SIM_Environment)

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

Execution | Logs | Results | R code viewer | C code viewer

■ Complex study protocols



■ 3-step interface

- When?
- Who?
- What?

Name: Normal state -> Suspended state (CIRC < 200)

Description:

1. Triggering:

☐ Evaluation schedule:

☒ Evaluation frequency: Initial evaluation time (HOUR): 0
Evaluation frequency (HOUR): 24*7

☐ Function (zero-returning expression):

2. Condition:

☐ Probability of occurrence (%): 100.0

☒ Conditional expression:
STATE == NORMAL_STATE & CIRC < RISK_LIMIT

3. Action:

Subject drop-out:

☐ Last Observation Carry Forward

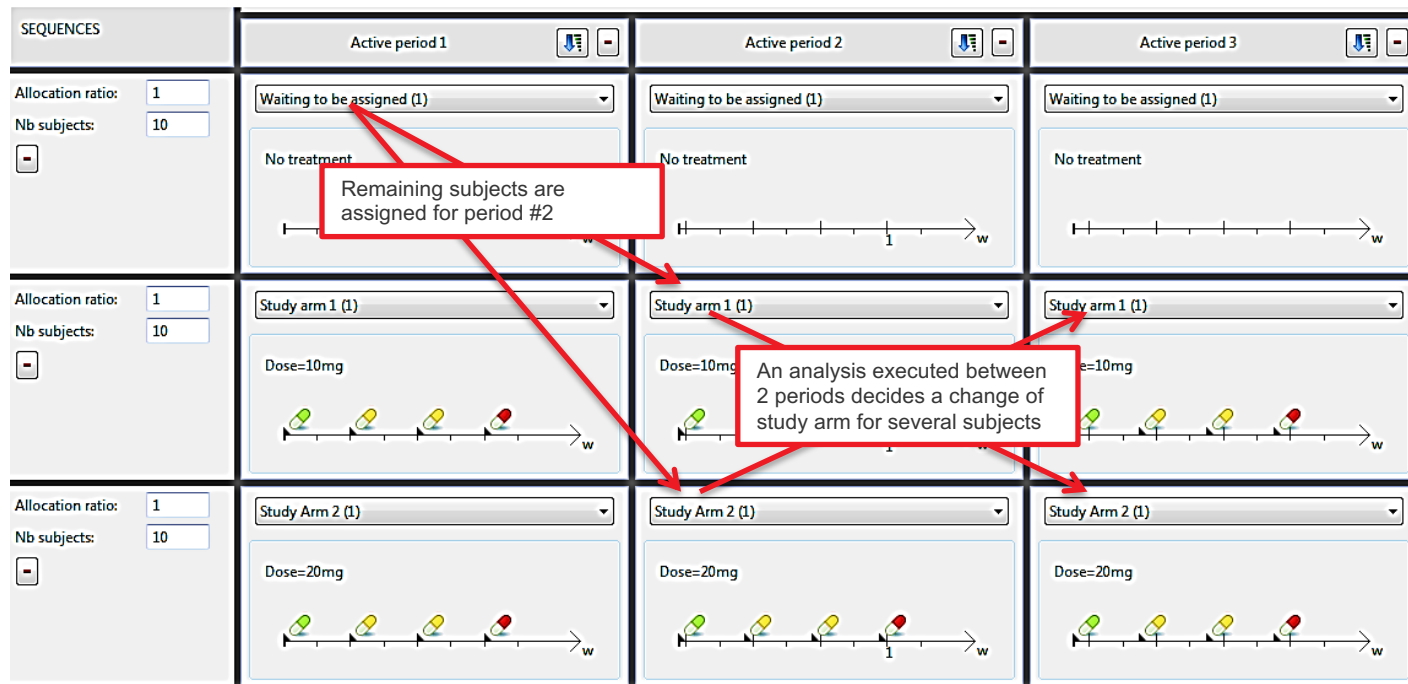
☐ Last Value Carry Forward

☐ Simulate normal inclusion

Model update:

☒ Update expression:
STATE <- SUSPENDED_STATE

- Interim analyses between each period
- Subject reassignment



THANK YOU FOR YOUR ATTENTION



Questions ?

Meet us at the SGS booth 13

Download Simulo for free: <https://exprimo.com/simulo>

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