

EXPERTISE

SAFETY

SOLUTIONS

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

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WHEN YOU NEED TO BE SURE

SGS



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 ?

| 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 | Description |
|---|--|
| <ul style="list-style-type: none"> <ul style="list-style-type: none"> ECL (Independent) ECL <ul style="list-style-type: none"> EV (Independent) EV <ul style="list-style-type: none"> Model Parameters KA CL V KE <ul style="list-style-type: none"> Initial Values A1 A2 <ul style="list-style-type: none"> Event Variability C <ul style="list-style-type: none"> Structural Equations dA1 dA2 <ul style="list-style-type: none"> Conditional Events | <ul style="list-style-type: none"> 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

Draw Clear

LiveView updated (750ms)

IMPLEMENT A PEDIATRIC CASE INTO SIMULO

■ Context:

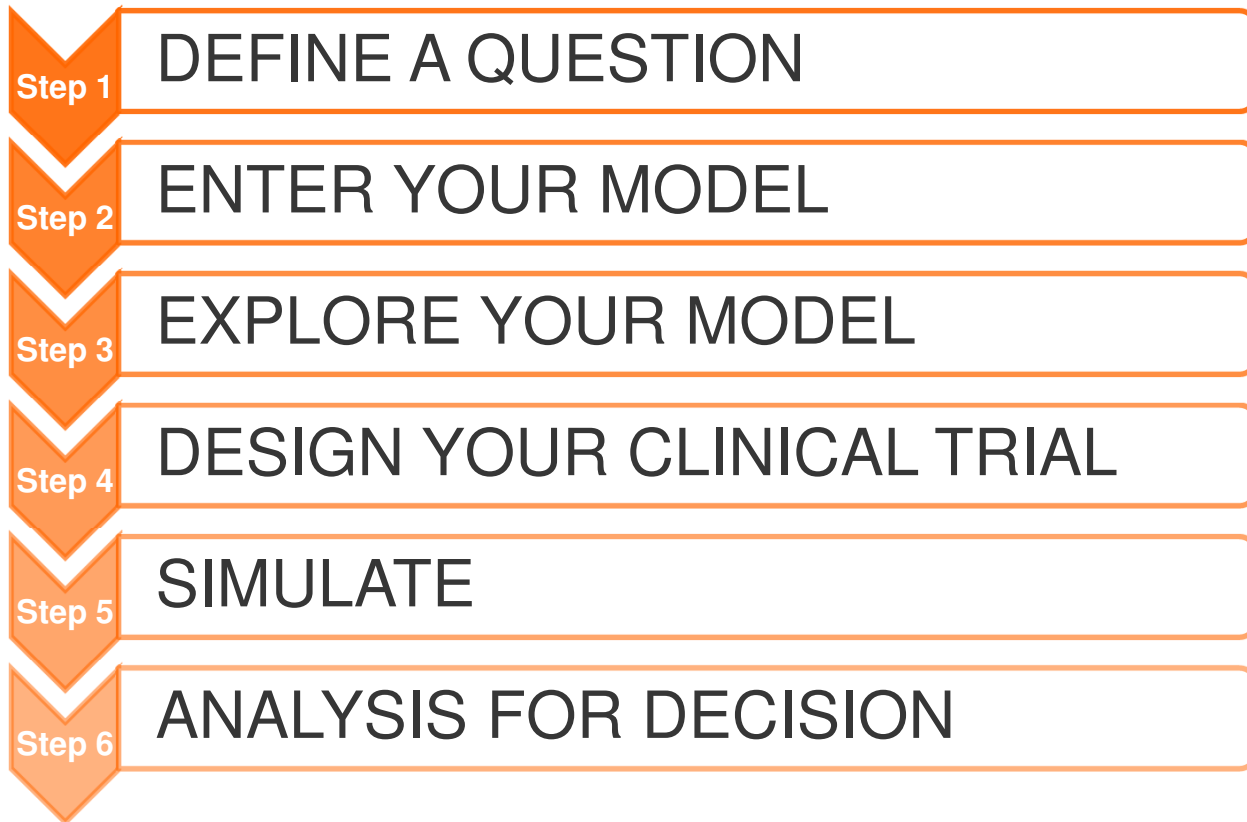
- You successfully developed a drug for the adults
- You would like to scale this drug to pediatrics
- You plan to execute a pediatric clinical trial
- Assume we want to target the 12-years-old children

■ Drug characteristics:

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



BUILD YOUR SIMULATION IN 6 STEPS



- 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

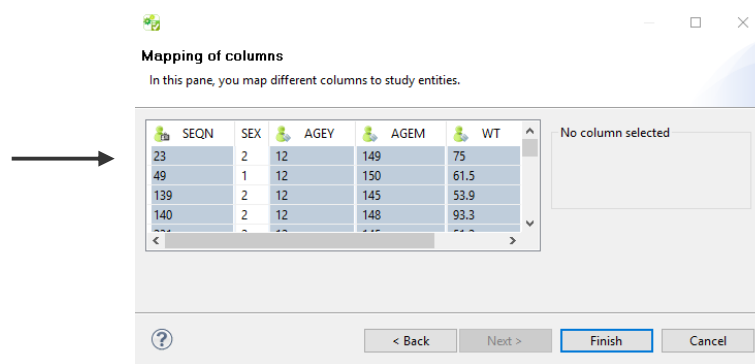
- No complex scripting
- Clear framework
- Share and collaborate !

| 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:



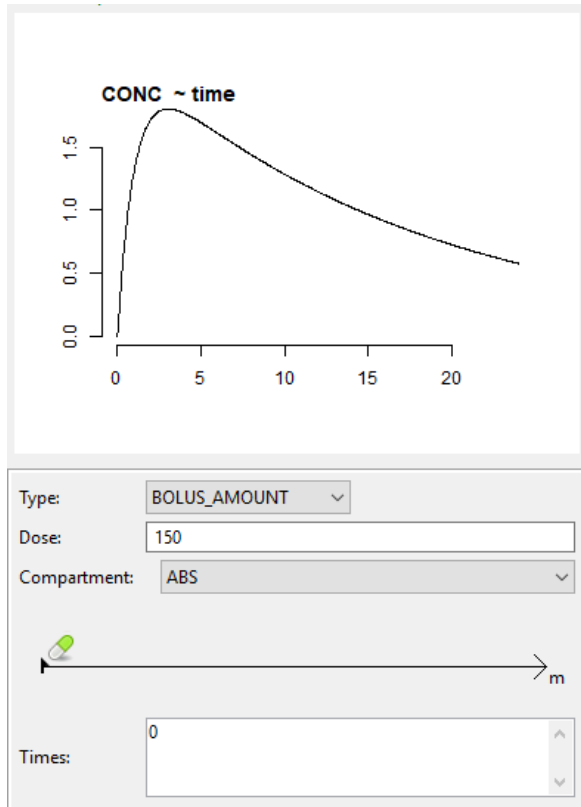
NHANES dataset



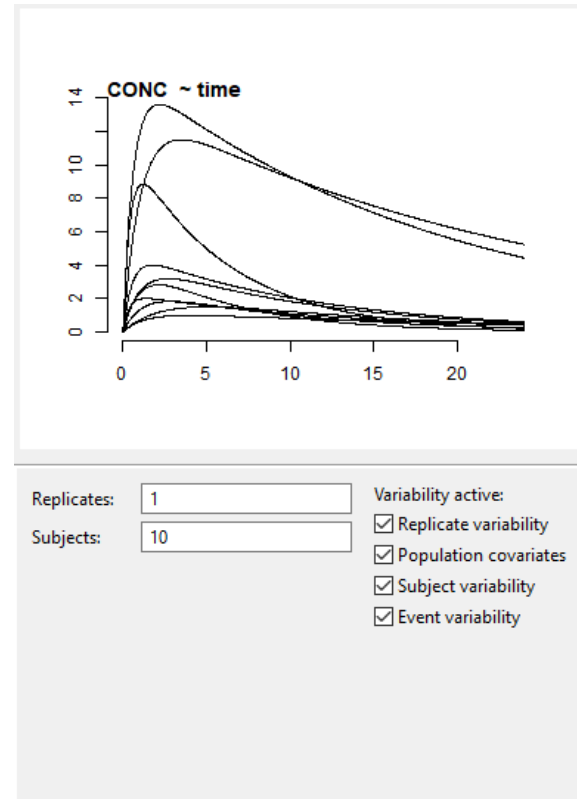
Bootstrap of Weight & Age



- Explore individual profiles in the liveview:

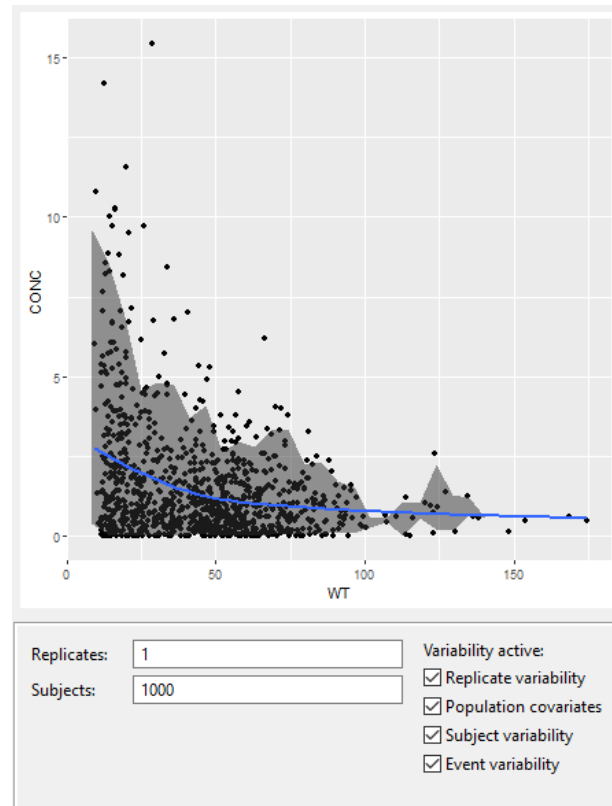


- Typical profiles
- Give a single dose



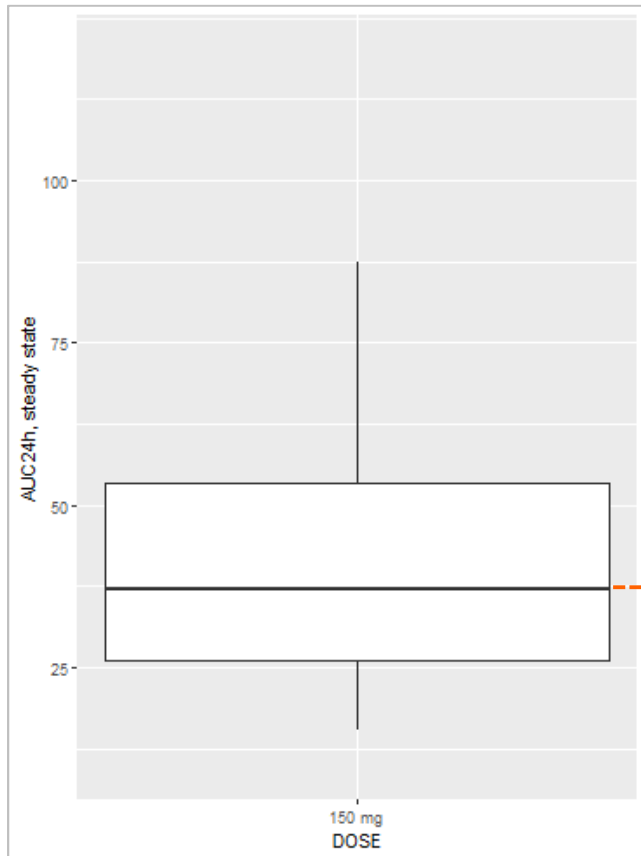
- Different single profiles
- Explore the different levels of variabilities

- Plot children population statistics (aged 2-18)

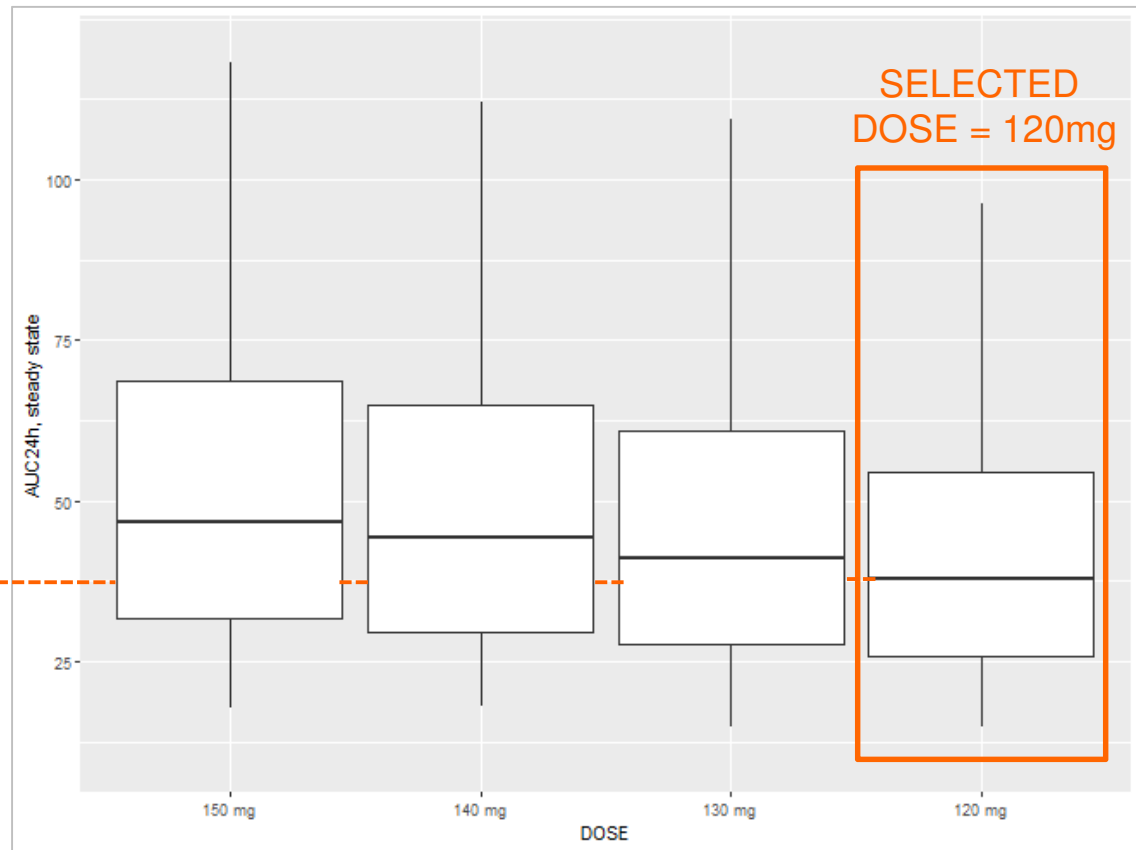


- Population simulation
- Weight / Concentration plot

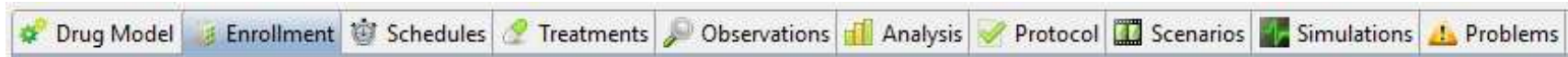
■ Find dose for 12-years-old children



■ 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:

- ✓ 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

at times:

every:

for a duration of:

x times

✓ Schedule name

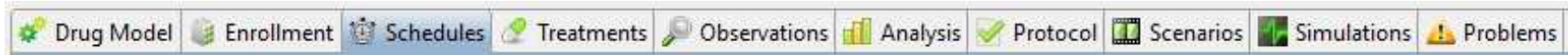
✓ Schedule description

✓ 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:

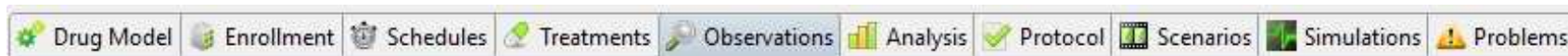
Dose:
 Nominal dose (ND):

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:

Miss observation model:

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

Schedule:

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: | <input type="text" value="1"/> | Active period | |
| Nb subjects: | <input type="text" value="18"/> | Pediatrics arm (1) | |
| | | 120mg every day | |
| | | | |
| Total allocation ratio: | <input type="text" value="1"/> | Blood samples | |
| Total nr of subjects: | <input type="text" value="18"/> | | |
| | | Rich sampling day1 / day7 | |
| | | | |

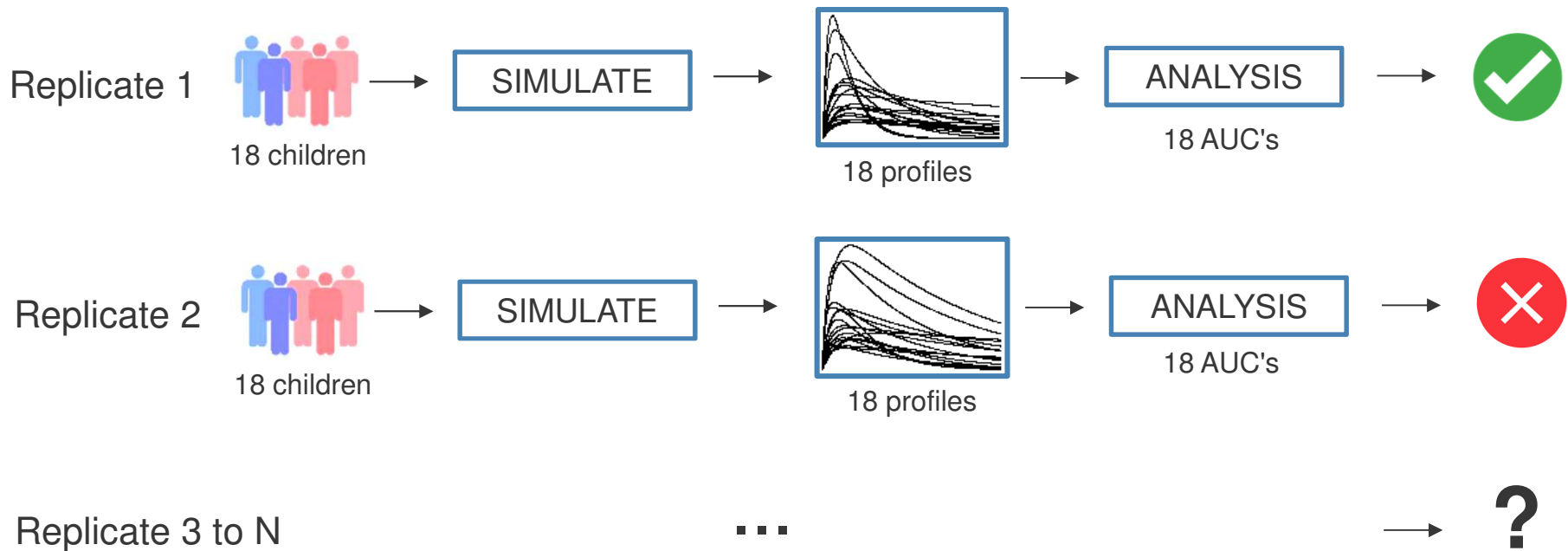
➤ Build the protocol by adding sequences/periods but also a lead-in or follow-up phase

➤ 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



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



Simulation informations

Simulation name:

Description:

Options: Include the base study Include scenarios

| Name | |
|------|--|
| | |

Simulation status:

Nr of replicates:

Nr of subjects:

Disabled variability:

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

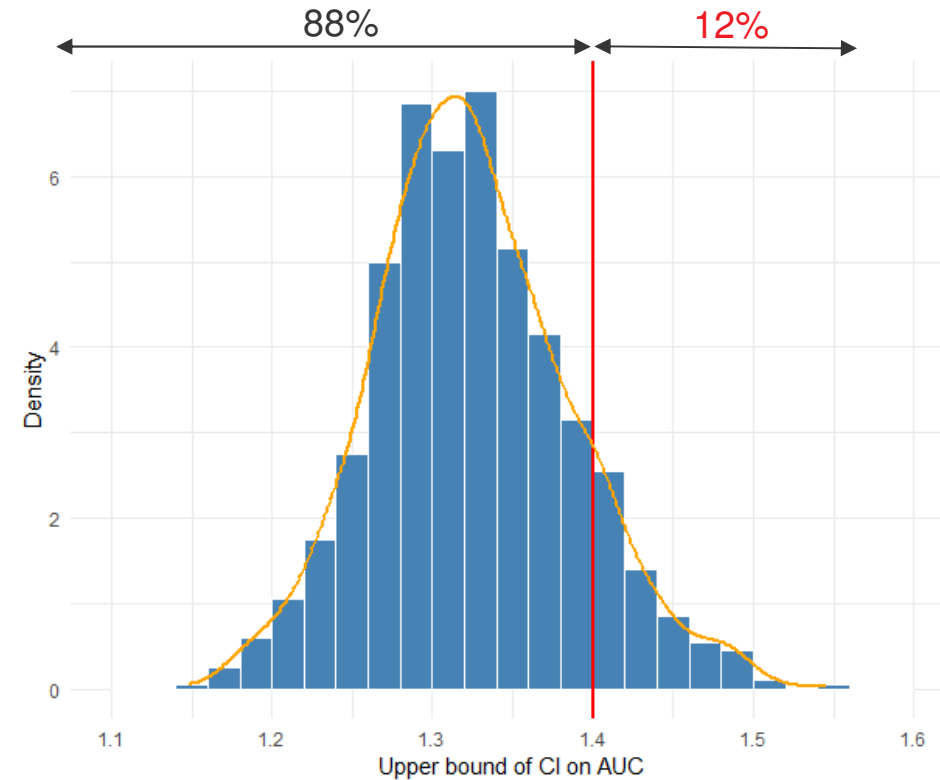
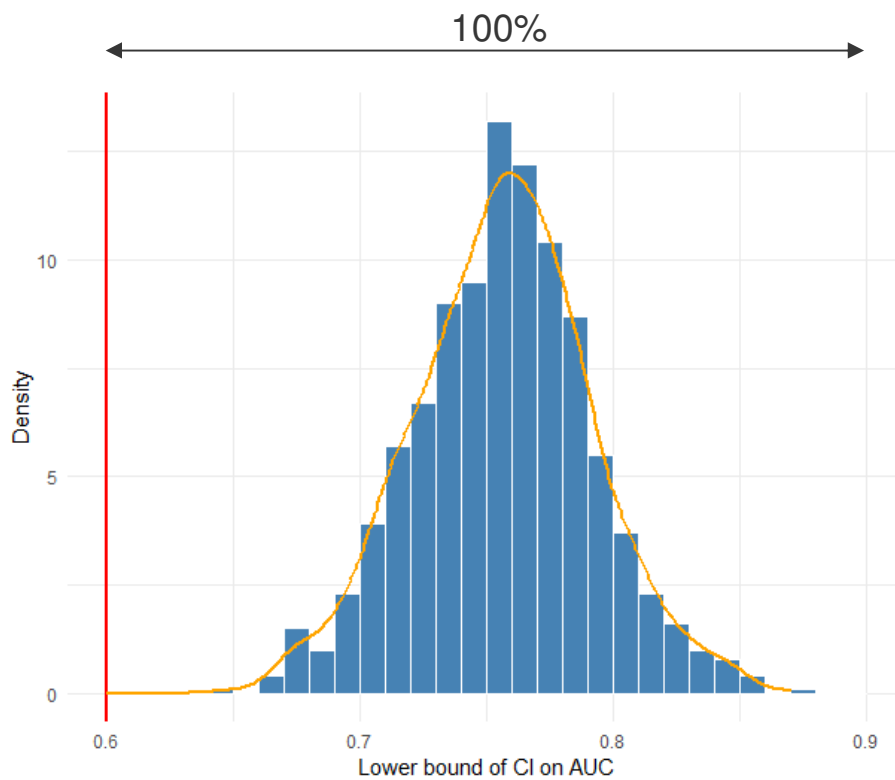
➤ Compute AUC for each subject in a replicate

➤ Compute CI on geometric mean in each replicate

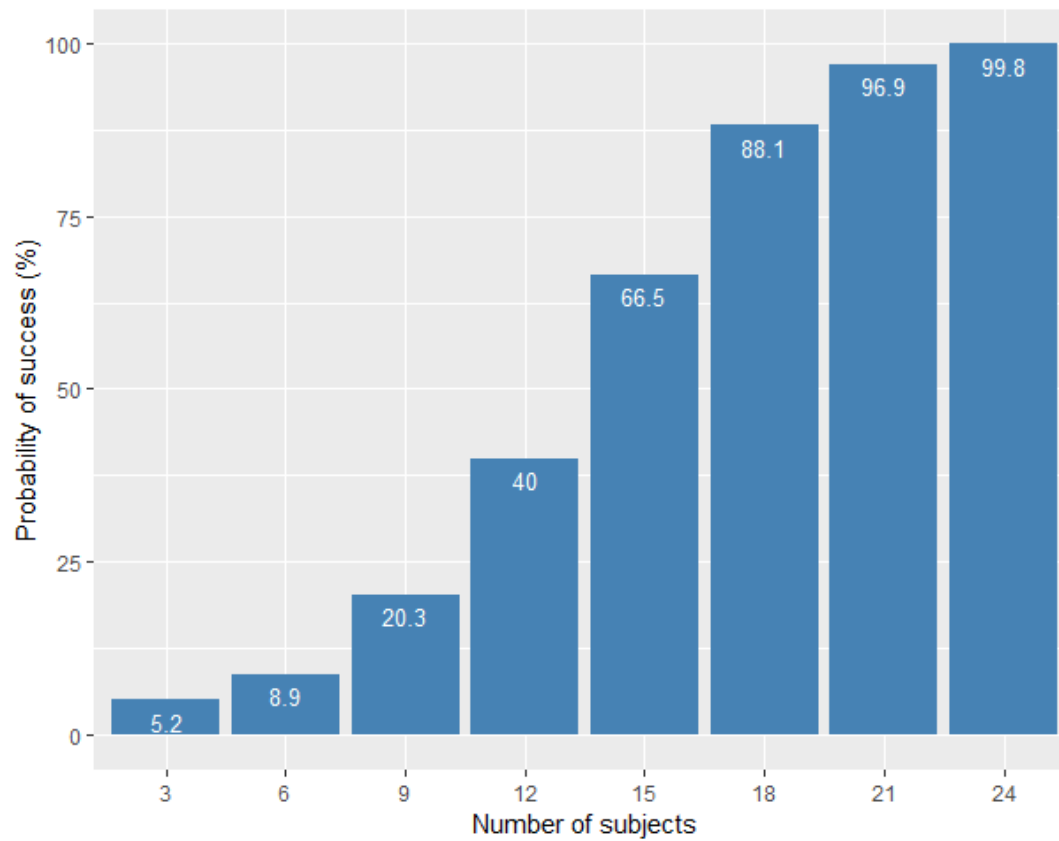
➤ Count how many trials are successful



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()

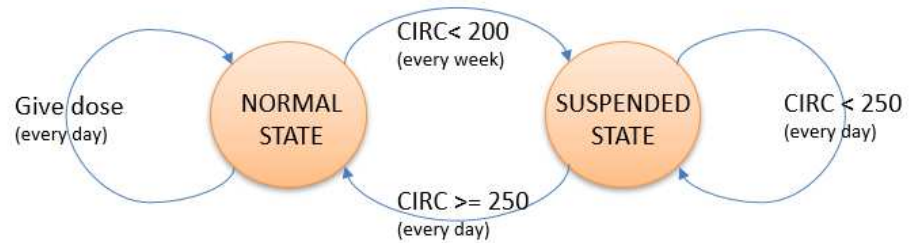
# evaluate Study Variability
SIM_Environment$NORMAL_STATE <- local(local( {
  0
} ), envir=SIM_Environment)

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( {
  ...
} ), envir=SIM_Environment)
```


- 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




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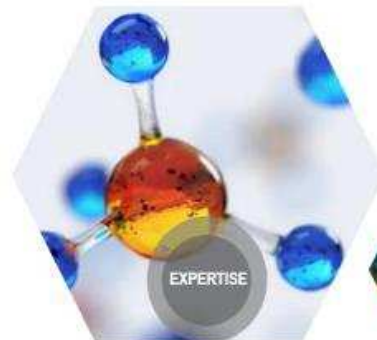
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