Simulx webinar: Optimizing Sample Size of a Phase III trial

We will start soon

Introduction

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Reference asthma treatment

- Current standard-of-care
- Approved globally (also in China)

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Plan a bridging study for approval in China

Introduction

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Reference asthma treatment

- Current standard-of-care
- Approved globally (also in China)

New asthma treatment

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- does not include Chinese patients

Plan a bridging study for approval in China

What is the sample size required for a trial in Chinese patients to show a difference in response between the two treatments?

Workflow

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Data

phase III, NEW treatment,
NO Chinese patients

phase III, REF treatment,
NO Chinese patients

phase II, REF treatment,
ONLY Chinese patients

Workflow

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Data

phase III, NEW treatment,
NO Chinese patients

phase III, REF treatment,
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phase II, REF treatment,
ONLY Chinese patients

Population modeling in Monolix

- single population model covering the 3 datasets
- Investigate the impact of the covariates for Chinese and non-Chinese patients

Workflow

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Data

phase III, NEW treatment, NO Chinese patients

phase III, REF treatment, NO Chinese patients

phase II, REF treatment, ONLY Chinese patients

Population modeling in Monolix

- single population model covering the 3 datasets
- Investigate the impact of the covariates for Chinese and non-Chinese patients

Clinical trial simulations in Simulx

- Predict the response to the new treatment in Chinese asthma patients
- Suggest a minimal sample size for China bridging study

Clinical trial simulation

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Clinical trial simulation (CTS) = abstraction of the clinical trial process based on a longitudinal model

It can be used to:

- investigate assumptions such as:
  - sample size
  - study duration
  - treatment schedules
  - population characteristics
  - …
- quantify their influence on trial designs with:
  - outcomes
  - type I error
  - study power
  - …
- evaluate the adequacy and efficiency of potential trial designs

Population Modeling with Monolix

Dataset

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Measurements:

- FEV1: forced expiratory volume = maximum amount of air one can forcefully exhale in one second

Studies:

- 2 studies from phase III (global) comparing the two treatments + placebo
- 2 studies from phase II (Chinese) for reference treatment only + placebo

Covariates:

- age, sex, weight, height, race, treatment, baseline FEV1, disease severity

Dataset: observations

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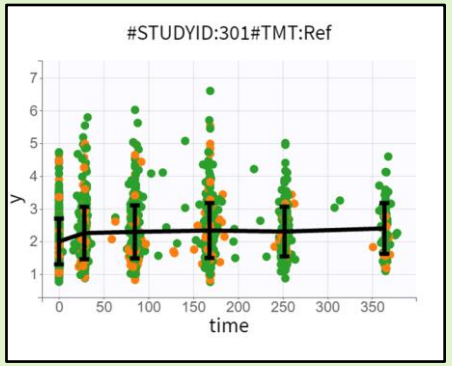
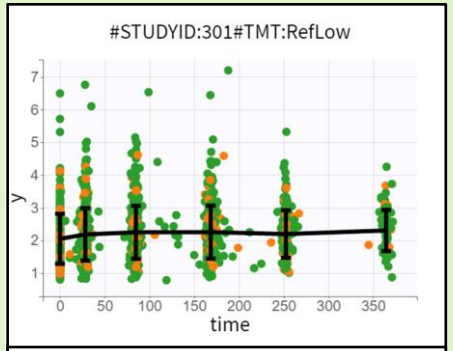
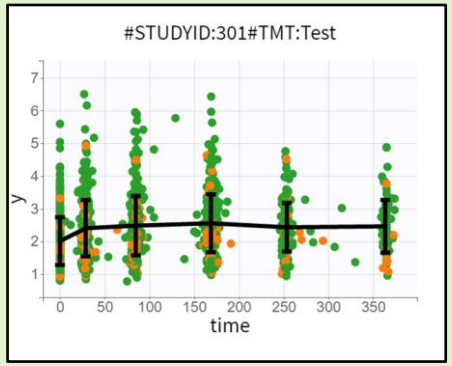
Treatments: **Reference** | **Reference lower dose** | **Test** | **Test lower dose** | **Placebo**

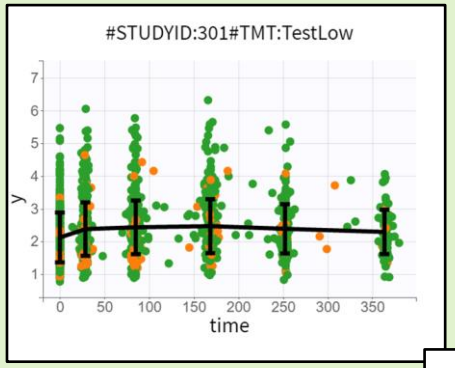
Phase III studies

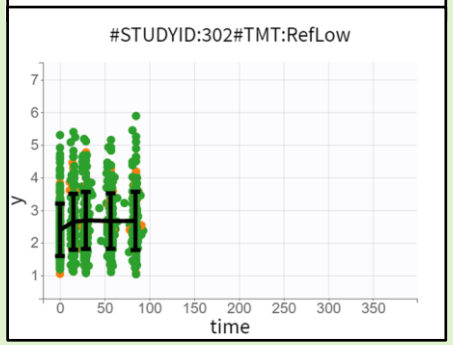
Population:
White
Other

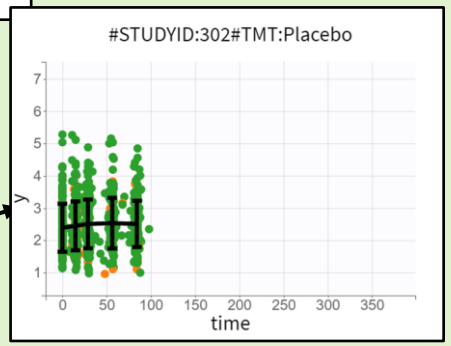








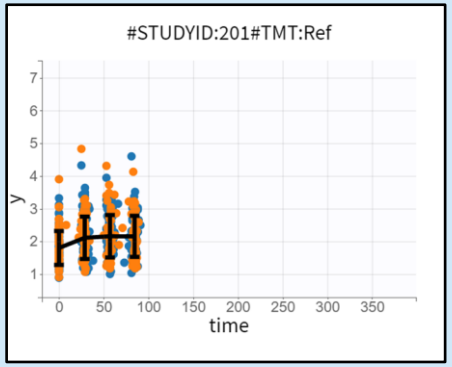


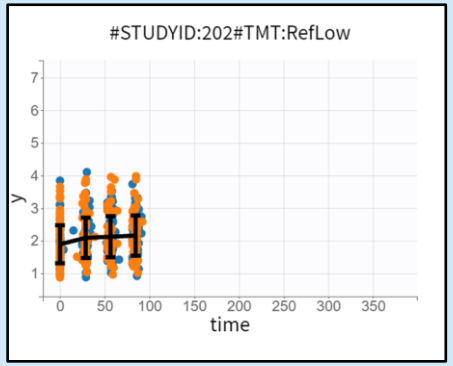


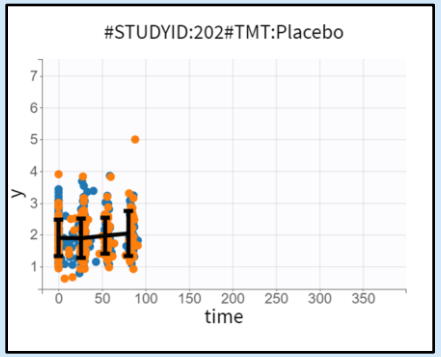
y = forced expiratory volume: maximum amount of air one can forcefully exhale in one second

Phase II studies

Population:
Chinese
Other







Dataset: covariates

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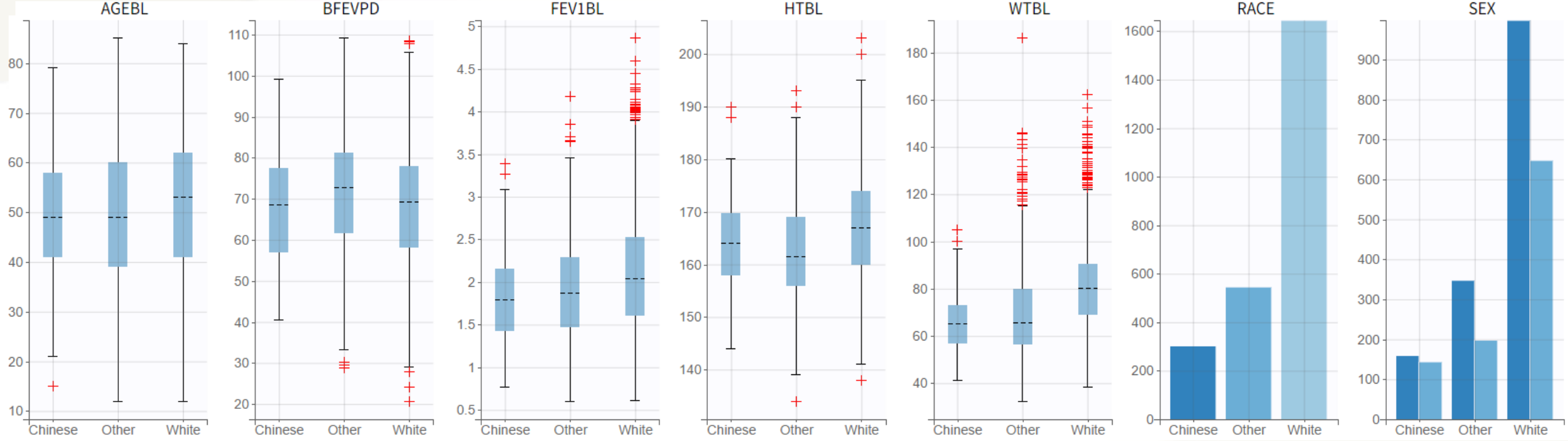
Comparison of covariate distributions in the different populations



PD model

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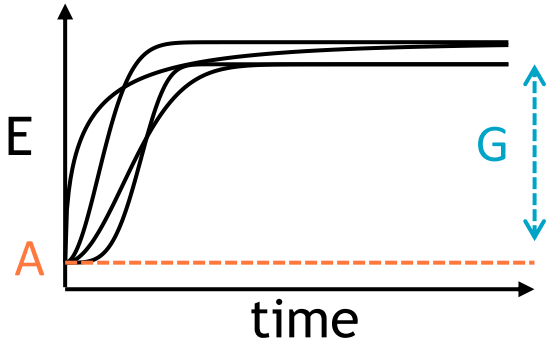
Structural model:

```
[LONGITUDINAL]
input = {A, G, Td, gamma}
EQUATION:
S = G * (1-exp(-(1/Td*t)^gamma))
E = max(1e-3, A + S)
OUTPUT:
output = E
```



We use an exponential model to describe the placebo FEV1 trajectory over time.

PD model

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Structural model: exponential

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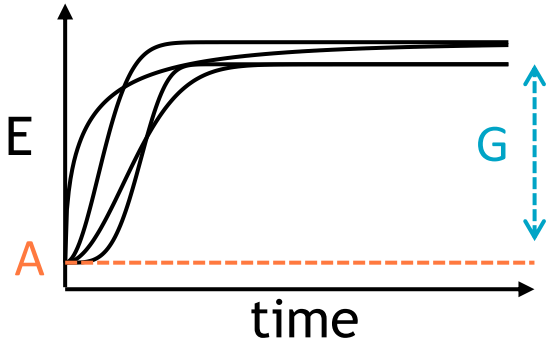

The final statistical model includes many covariate effects.

Statistical model

PARAMETERS	DISTRIBUTIONS	RANDOM EFFECTS	– CORRELATION +	AGEBL	AGEC	BFEVC	BFEVPD	FEV1BL	HTBL	HTC	RACE	SEX	STUDYID	TMT	WTBL	logtAGEBL	logtBFEVPD	logtHTBL	logtWTBL	tRACE
		Select: All | None	#1																
A	LOGNORMAL	☑	☐	☐	☐	☐	☐	☑	☐	☑	☐	☑	☐	☐	☐	☑	☑	☐	☐	☑
G	NORMAL	☑	☐	☐	☑	☐	☑	☐	☐	☐	☐	☐	☐	☑	☐	☐	☐	☐	☑	☐
Td	LOGNORMAL	☑	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☑	☑	☑	☐	☐
gamma	LOGNORMAL	☑	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PD model

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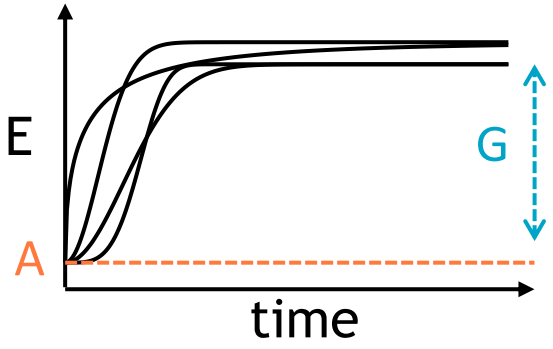

The treatment has an effect on the gain parameter G

Statistical model

PARAMETERS	DISTRIBUTIONS	RANDOM EFFECTS	CORRELATION	AGEBL	AGEC	BFEVC	BFEVPD	FEV1BL	HTBL	HTC	RACE	SEX	STUDYID	TMT	WTBL	logtAGEBL	logtBFEVPD	logtHTBL	logtWTBL	tRACE
		Select: All | None	#1																
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G	NORMAL	☑	☐	☐	☑	☐	☑	☐	☐	☐	☐	☐	☐	☑	☐	☐	☐	☐	☑	☐
Td	LOGNORMAL	☑	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☑	☑	☑	☐	☐
gamma	LOGNORMAL	☑	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PD model

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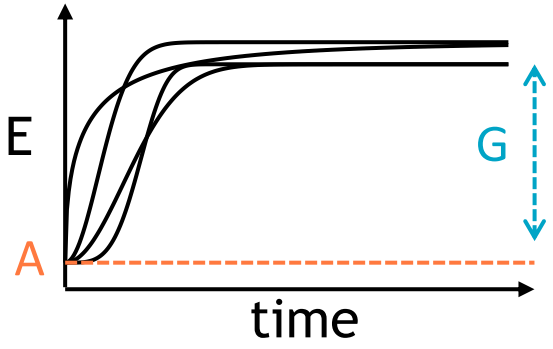

TMT	Typical G
Placebo	0.9
RefLow	1.34
Ref	1.59
TestLow	1.72
Test	2.30

Statistical model

PARAMETERS	DISTRIBUTIONS	RANDOM EFFECTS (Select: All | None)	CORRELATION #1	AGEBL	AGEC	BFEVC	BFEVPD	FEV1BL	HTBL	HTC	RACE	SEX	STUDYID	TMT	WTBL	logtAGEBL	logtBFEVPD	logtHTBL	logtWTBL	tRACE
A	LOGNORMAL	☑	☐	☐	☐	☐	☐	☑	☐	☑	☐	☑	☐	☐	☐	☑	☑	☐	☐	☑
G	NORMAL	☑	☐	☐	☑	☐	☑	☐	☐	☐	☐	☐	☐	☑	☐	☐	☐	☐	☑	☐
Td	LOGNORMAL	☑	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☑	☑	☑	☐	☐
gamma	LOGNORMAL	☑	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PD model

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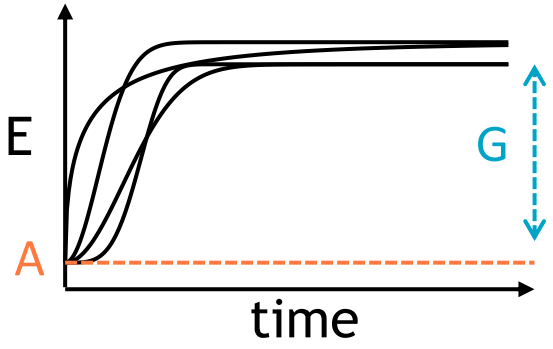

RACE and FEV1BL have an effect on the baseline parameter A

Statistical model

PARAMETERS	DISTRIBUTIONS	RANDOM EFFECTS	CORRELATION	AGEBL	AGEC	BFEVC	BFEVPD	FEV1BL	HTBL	HTC	RACE	SEX	STUDYID	TMT	WTBL	logtAGEBL	logtBFEVPD	logtHTBL	logtWTBL	tRACE
		Select: All | None	#1																
A	LOGNORMAL	☑	☐	☐	☐	☐	☐	☑	☐	☑	☐	☑	☐	☐	☐	☑	☑	☐	☐	☑
G	NORMAL	☑	☐	☐	☑	☐	☑	☐	☐	☐	☐	☐	☐	☑	☐	☐	☐	☐	☑	☐
Td	LOGNORMAL	☑	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☑	☑	☑	☐	☐
gamma	LOGNORMAL	☑	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PD model

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Structural model: exponential

```
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output = E
```

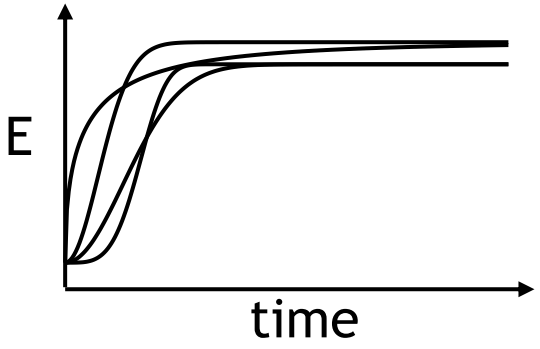

RACE	Typical A
White	1.32
Chinese	1.26
Other	1.27

Statistical model

PARAMETERS	DISTRIBUTIONS	RANDOM EFFECTS	CORRELATION #1	AGEBL	AGEC	BFEVC	BFEVPD	FEV1BL	HTBL	HTC	RACE	SEX	STUDYID	TMT	WTBL	logtAGEBL	logtBFEVPD	logtHTBL	logtWTBL	tRACE
		Select: All | None																		
A	LOGNORMAL	☑	☐	☐	☐	☐	☐	☑	☐	☑	☐	☑	☐	☐	☐	☑	☑	☐	☐	☑
G	NORMAL	☑	☐	☐	☑	☐	☑	☐	☐	☐	☐	☐	☐	☑	☐	☐	☐	☐	☑	☐
Td	LOGNORMAL	☑	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☑	☑	☑	☐	☐
gamma	LOGNORMAL	☑	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PD model estimated in Monolix

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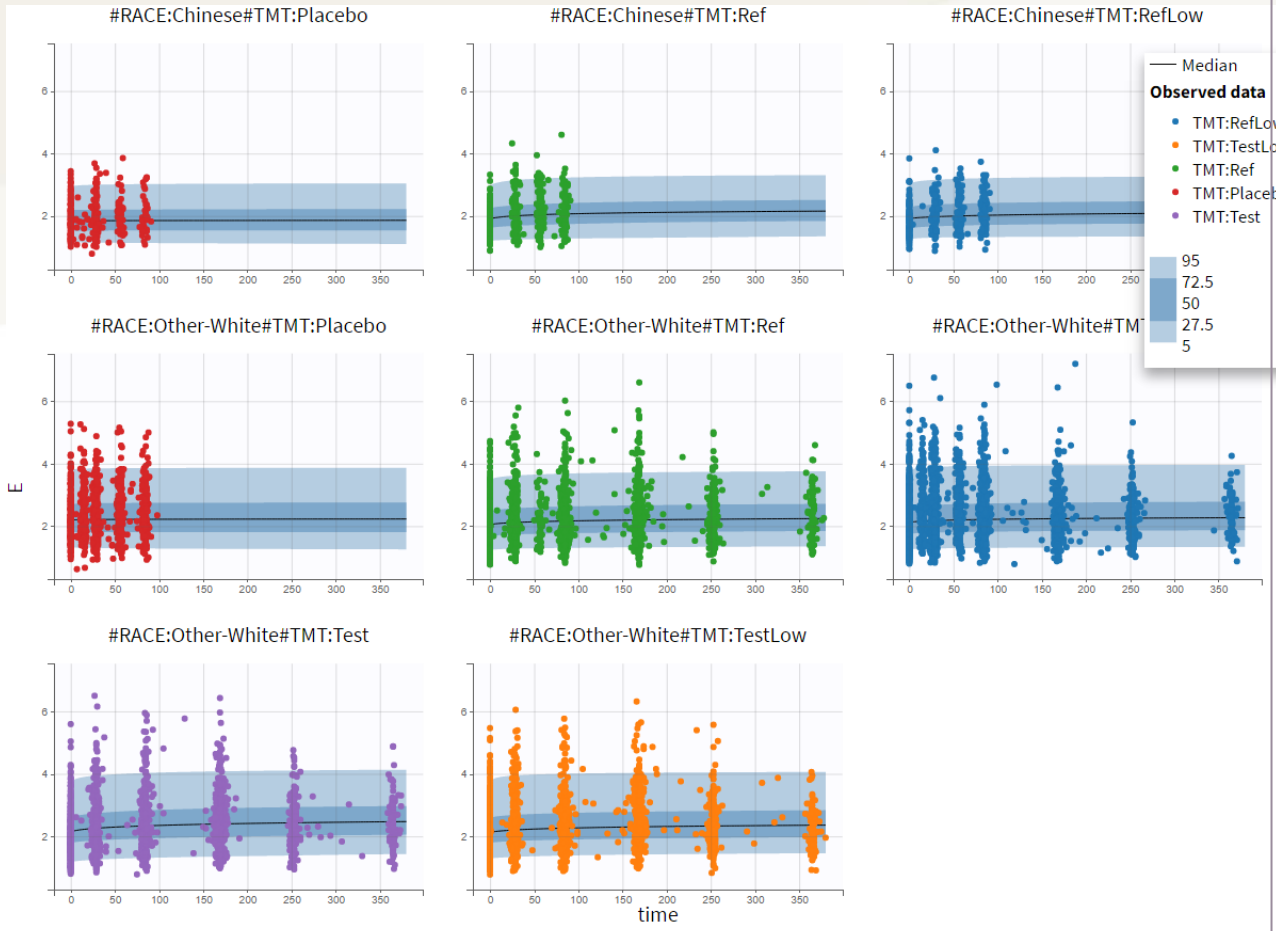

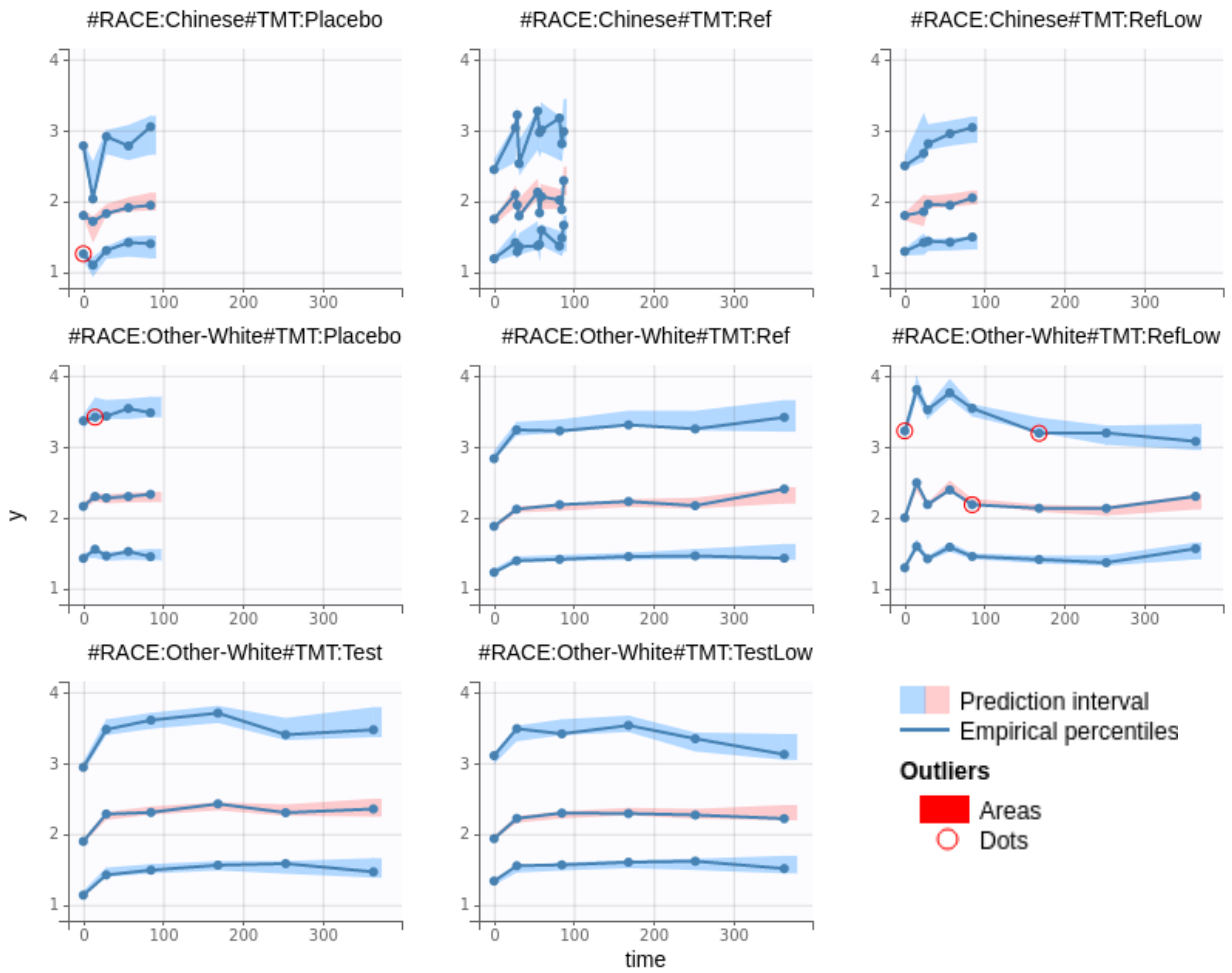

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Clinical Trial Simulation with Simulx

What is Simulx?

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- Advanced simulator of clinical trials and decision-making tool
- Easy-to-use and interactive interface
- Interconnected with MonolixSuite applications
- Intuitive workflow
- Flexible in building simulation scenarios
- Advanced computational capabilities with C++ engine
- Immediate visual feedback
- Export of plots and results

Simulx: how does it work?

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Model defined in Mlxtran
From Monolix project
Or User defined

Treatments
From data set Or User defined

Covariates
From data set
Or User defined

Monolix project

Mlxtran model

Nb of subjects
From data set
Or User defined

Pop. parameters
From Monolix outputs
Or User defined

Simulx user

Outputs
From data set
Or User defined

DEFINITION

EXPLORATION

SIMULATION

Simulating a phase III clinical trial

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Simulation

Comparing reference and new treatment in a population of **75 Chinese patients**, **during 3 months or 6 months**.

Simulating a phase III clinical trial

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Simulation

Comparing reference and new treatment in a population of **75 Chinese patients**, **during 3 months or 6 months**.

Quantitative Outcome and Endpoint

What is the **mean FEV1 change from baseline at the end of the study**?

Simulating a phase III clinical trial

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Simulation

Comparing reference and new treatment in a population of **75 Chinese patients, during 3 months or 6 months**.

Quantitative Outcome and Endpoint

What is the **mean FEV1 change from baseline at the end of the study**?

Trial Success

Is the mean FEV1 change from baseline **significantly higher with the new treatment**?

Simulating a phase III clinical trial

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Simulation

Comparing reference and new treatment in a population of **75 Chinese patients, during 3 months or 6 months**.

Quantitative Outcome and Endpoint

What is the **mean FEV1 change from baseline at the end of the study**?

Trial Success

Is the mean FEV1 change from baseline **significantly higher with the new treatment**?

Power of the study = probability of success

Variability between replicate studies and uncertainty of our model can affect the results

Scripting Simulx in R

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LixoftConnectors

- API for R that allows to create/modify/run a Monolix, Simulx or Pkanalix project from R
- R package provided with the MonolixSuite installation

⇨ To automate a workflow

Additional R packages

- R functions calling the connectors to go beyond what the interface allows
- Packages RsMlx, RsSimulx, and RsPkx

⇨ To run advanced specific tasks

Sample size optimization with LixoftConnectors

```
library(lixoftConnectors)
initializeLixoftConnectors(software="simulx")

loadProject(projectFile = "ChineseTrial.smlx")

sample_sizes <- c(30, 50, 65, 75, 80, 90, 100, 125, 135, 150, 200)

for(N in sample_sizes){

  setGroupSize("test_treatment", N)
  setGroupSize("ref_treatment", N)
  runSimulation()

  sim <- getSimulationResults()$res$y
  …
}
```

Sample size optimization with LixoftConnectors

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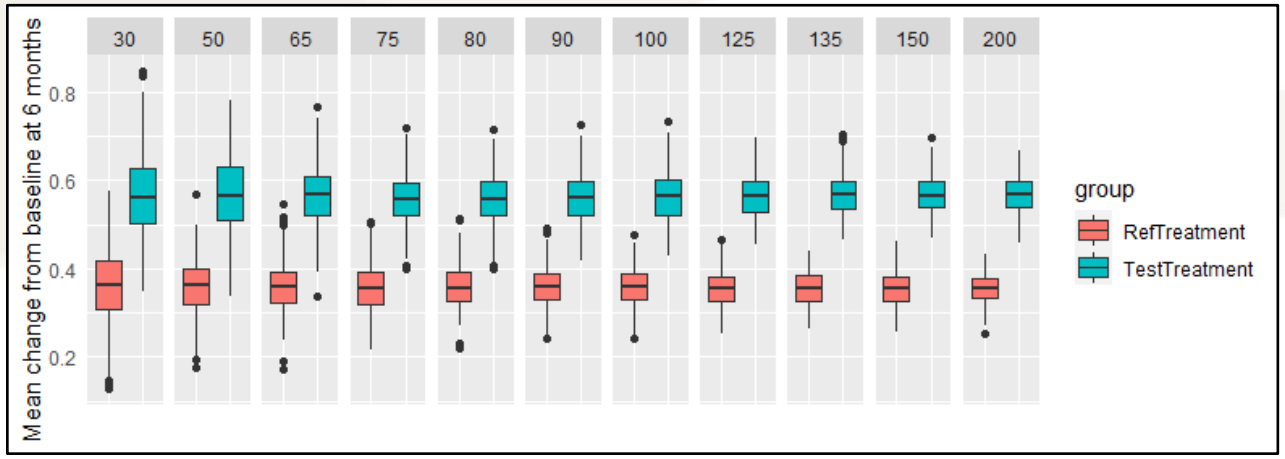
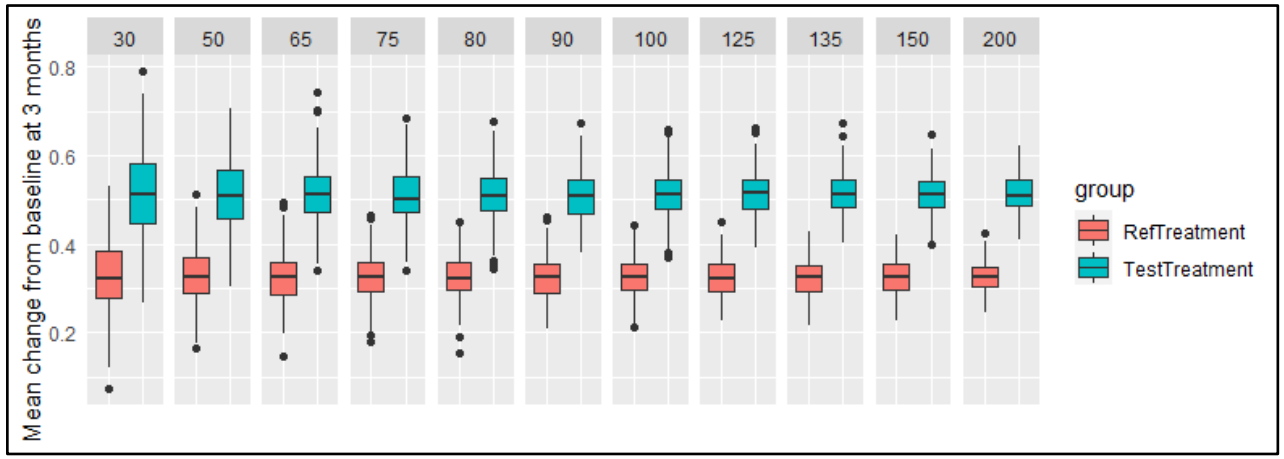
Study Duration

6 months



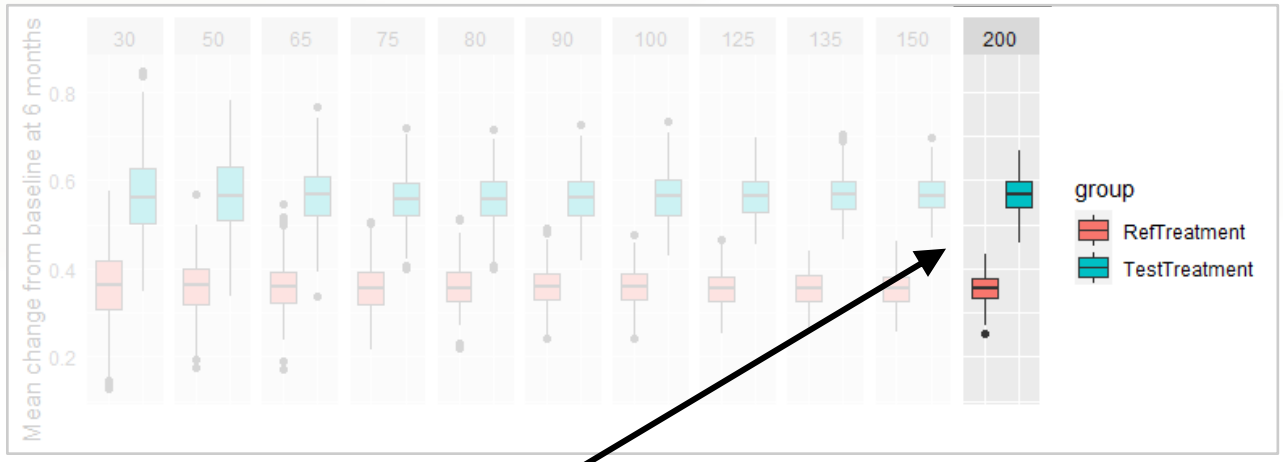
3 months



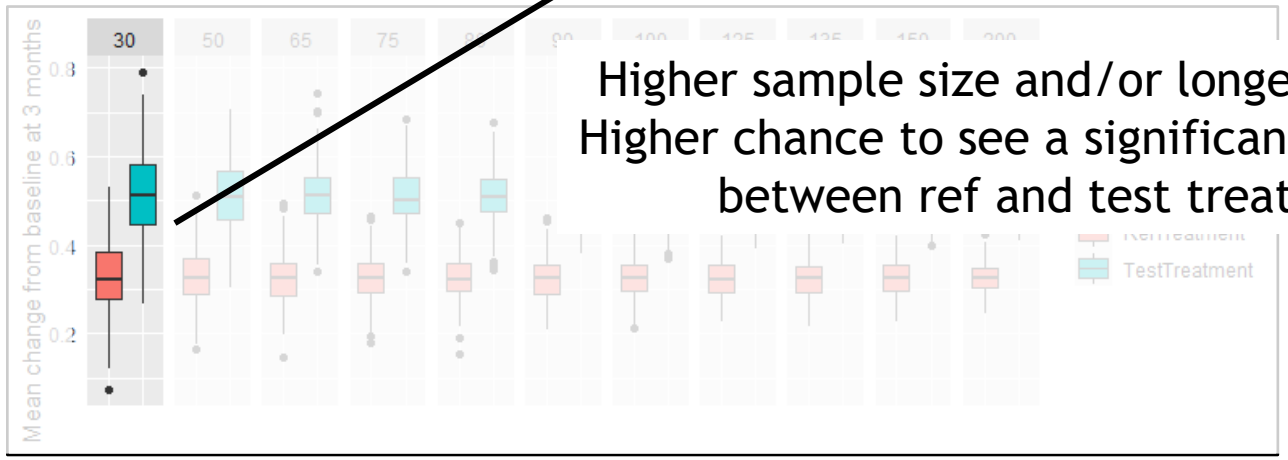
Sample Size

Sample size optimization with LixoftConnectors

6 months



3 months



Higher sample size and/or longer duration:
Higher chance to see a significant difference
between ref and test treatment

Sample size optimization with LixoftConnectors

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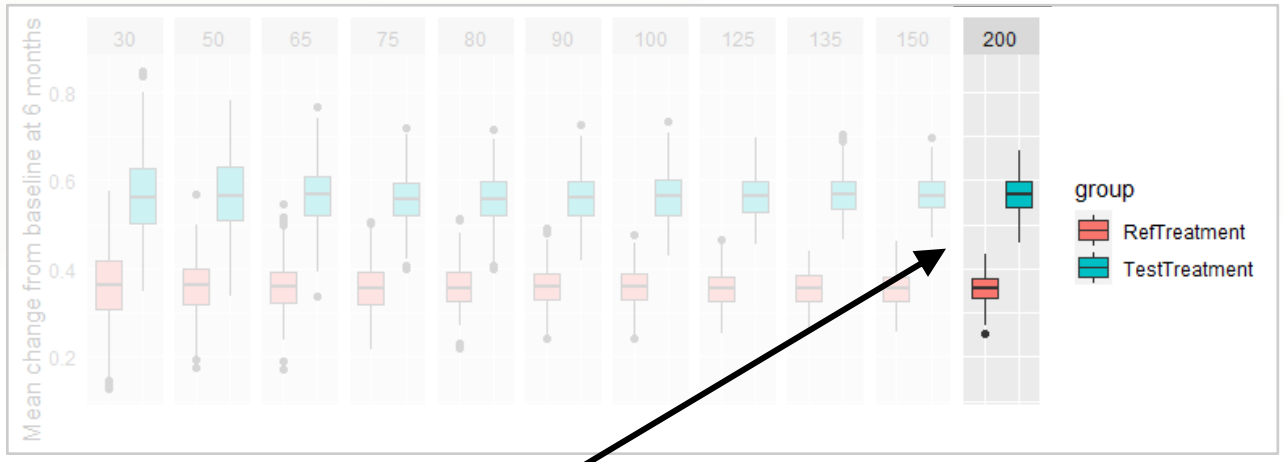
6 months



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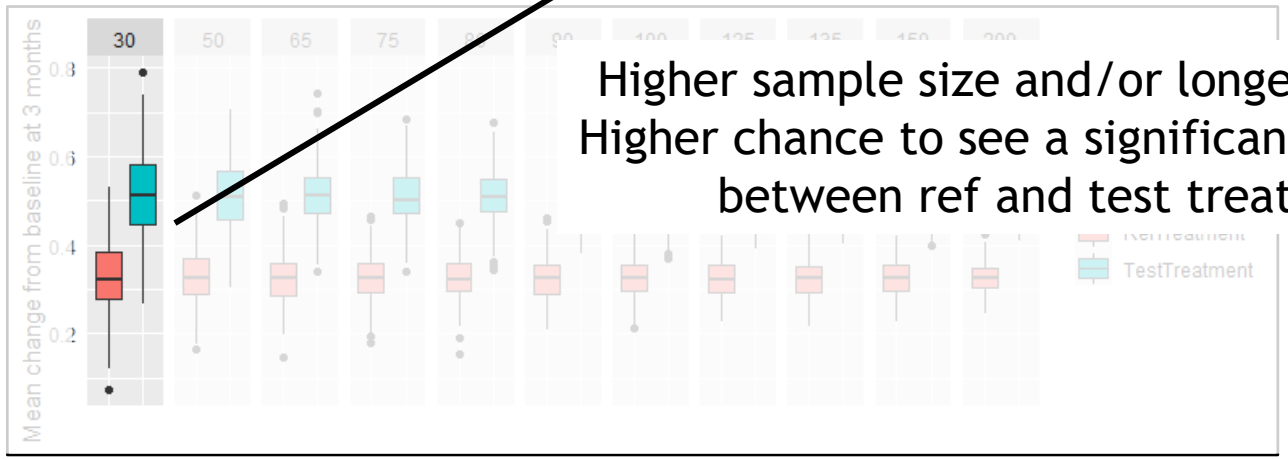

Higher sample size and/or longer duration:
Higher chance to see a significant difference between ref and test treatment

Which minimum sample size is required to reach 85% probability of success?

Sample size optimization with LixoftConnectors

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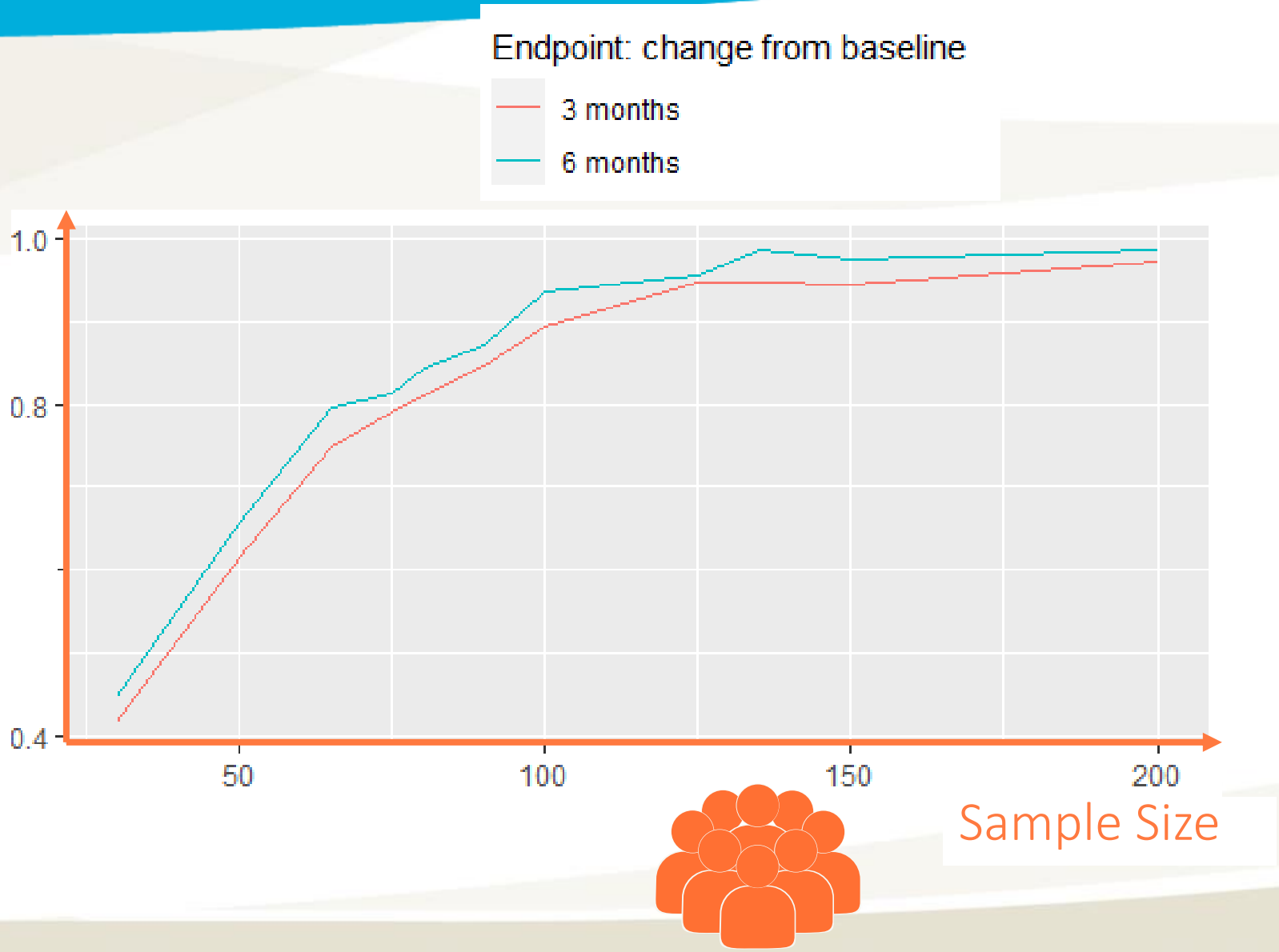
Power of Study: probability of success



Sample size optimization with LixoftConnectors

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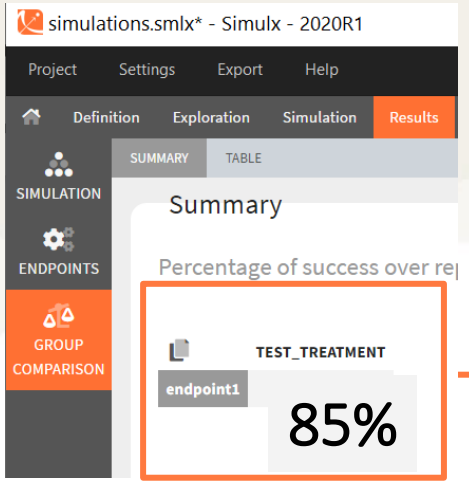
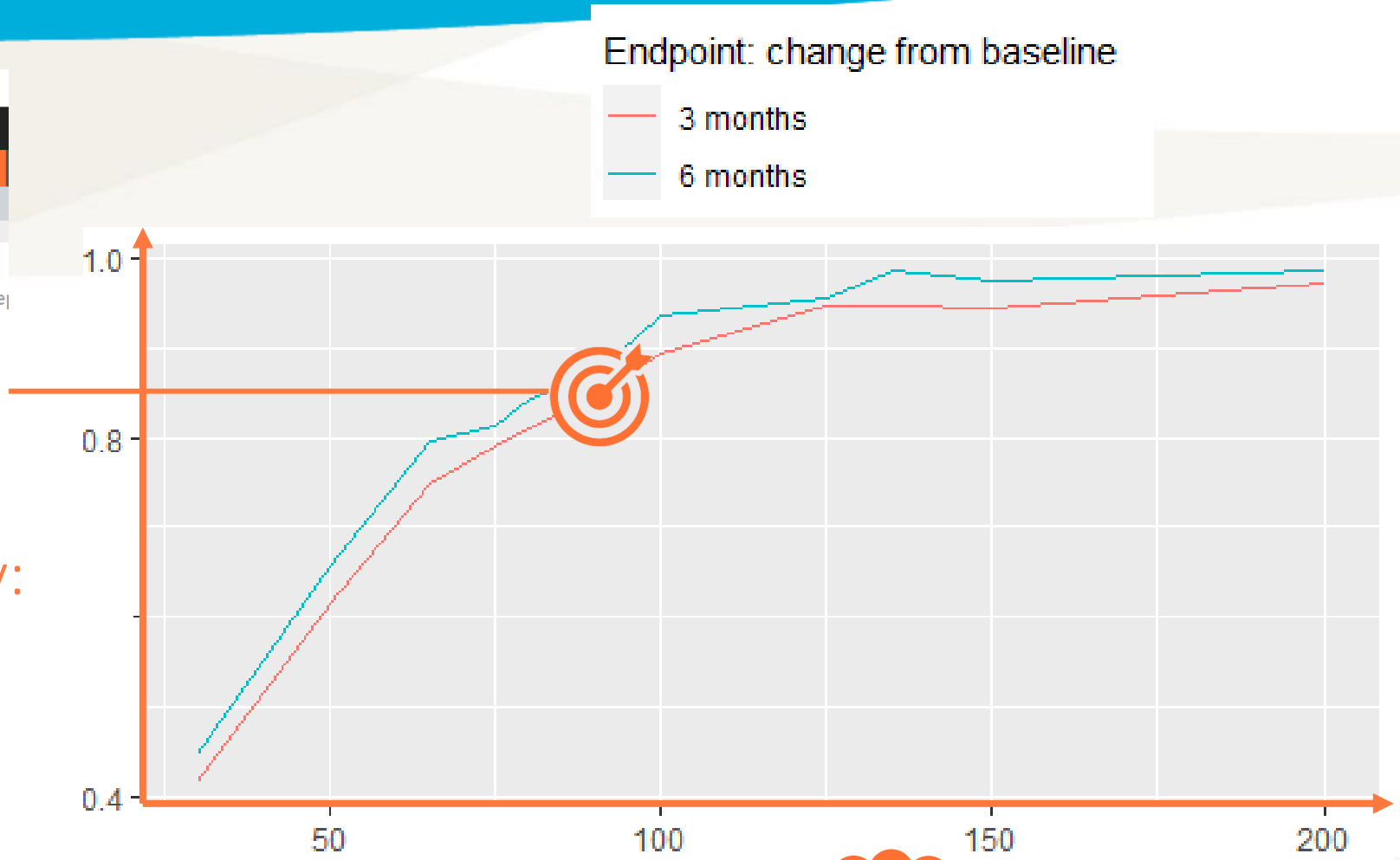
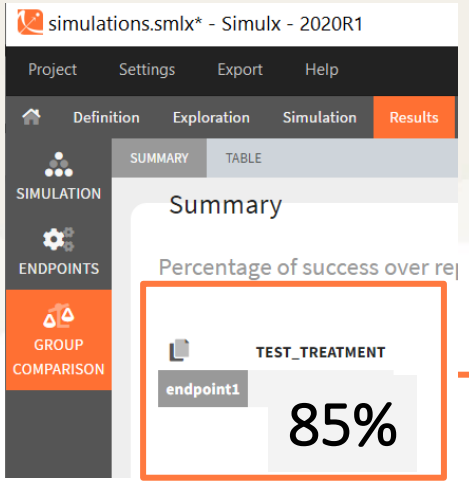


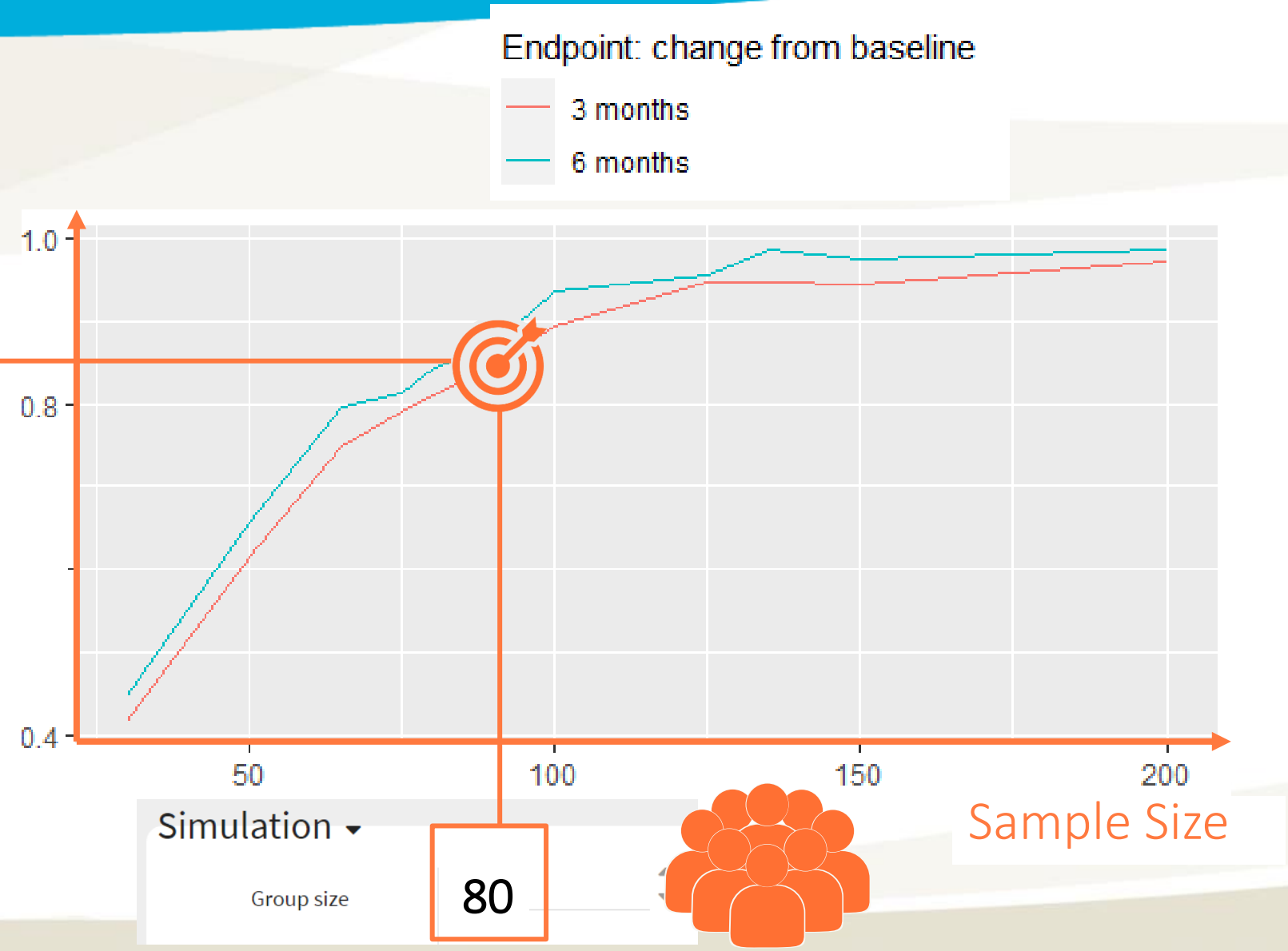


Power of Study: probability of success

Sample Size

Sample size optimization with LixoftConnectors





Power of Study: probability of success

More complex simulations

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Assumptions for this clinical trial simulation:

1. Covariates can be described with simple independent distributions
2. Population parameter estimates are reliable

More complex simulations

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Assumptions for this clinical trial simulation:

1. Covariates can be described with simple independent distributions
2. Population parameter estimates are reliable

Using external tables for more complex simulations:

1. Sampling covariates from an existing table of covariates
2. Sampling population parameters to consider uncertainty

Sampling from a table of covariates

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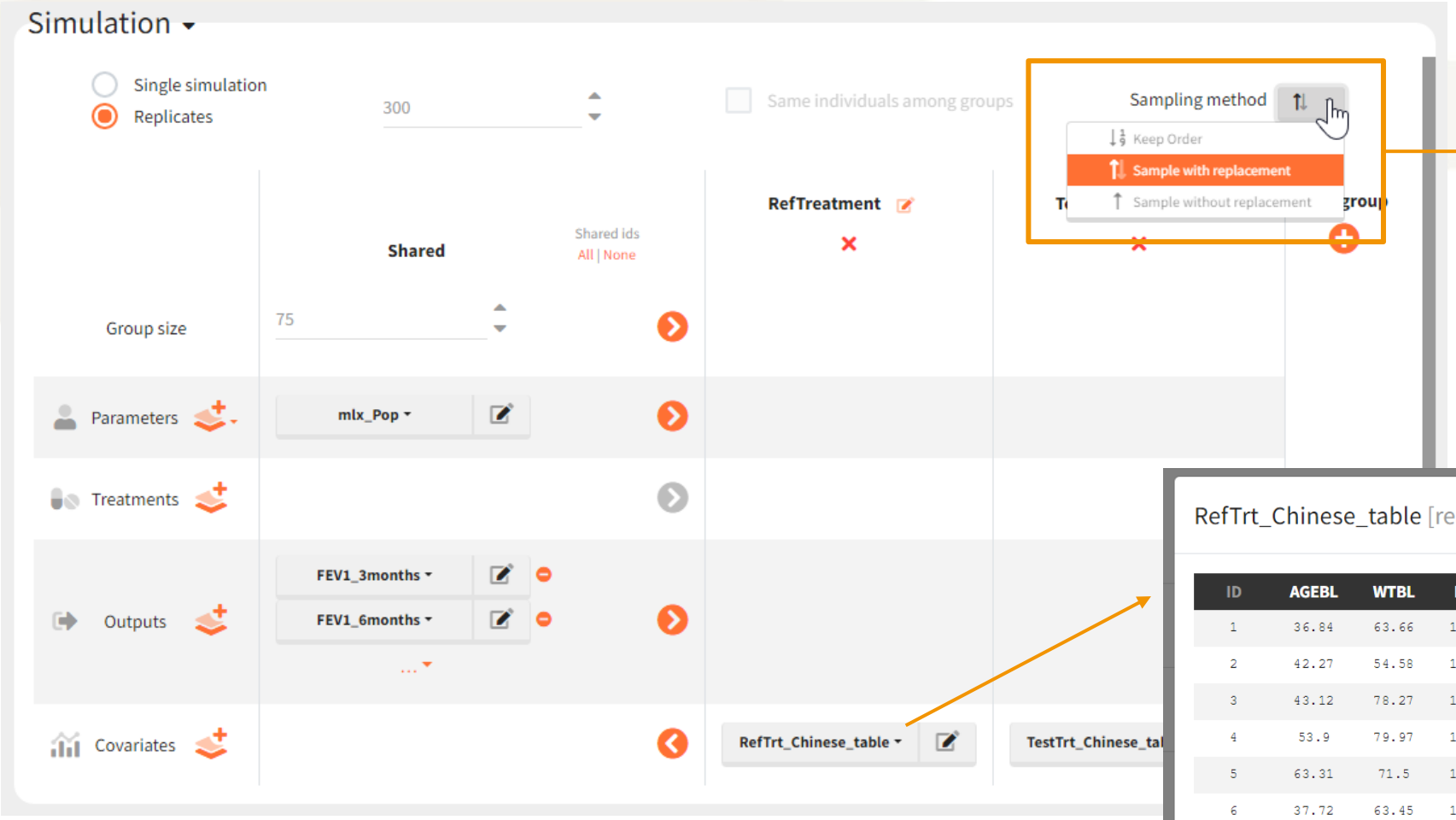

Different sampling methods to choose between:

- Using all covariate values
- Covariate bootstrapping

RefTrt_Chinese_table [read-only]

ID	AGEBL	WTBL	HTBL	BFEVPD	FEV1BL	SEX	RACE	TMT
1	36.84	63.66	172.73	45.52	2.44	Female	Chinese	Ref
2	42.27	54.58	160.06	88.93	1.57	Female	Chinese	Ref
3	43.12	78.27	153.92	51.19	1.19	Female	Chinese	Ref
4	53.9	79.97	159.19	69.82	2.12	Female	Chinese	Ref
5	63.31	71.5	160.88	65.92	0.84	Female	Chinese	Ref
6	37.72	63.45	179.78	64.47	2.27	Female	Chinese	Ref
7	59.7	89.09	160.91	39.59	1.98	Female	Chinese	Ref
8	51.36	60.59	163.13	78.78	2.45	Female	Chinese	Ref
9	37.02	59.38	175.72	90.89	1.81	Male	Chinese	Ref

CSV

Parameter uncertainty with replicates

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Simulation

Single simulation
Replicates 100

mlx_Pop

Parameters

mlx_Pop [read-only]

A_pop	1.3
beta_A_FEV1BL	0.25
beta_A_HTC	0.0065
beta_A_logtAGEBL	-0.12
beta_A_logtBFEVPD	0.54
beta_A_SEX_Female	-0.068

Parameter uncertainty with replicates

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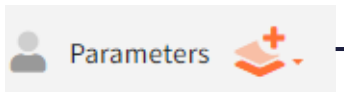

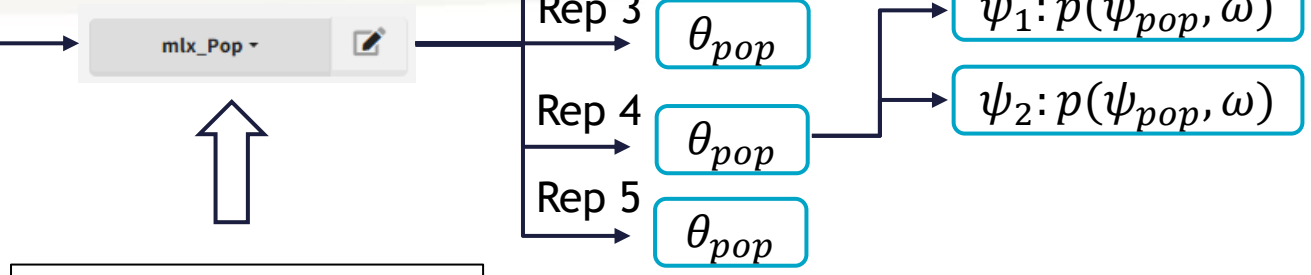

mlx_Pop [read-only]

A_pop	1.3
beta_A_FEV1BL	0.25
beta_A_HTC	0.0065
beta_A_logtAGEBL	-0.12
beta_A_logtBFEVPD	0.54
beta_A_SEX_Female	-0.068

Individual parameters in all replicates are simulated using THE SAME population parameters

Parameter uncertainty with replicates

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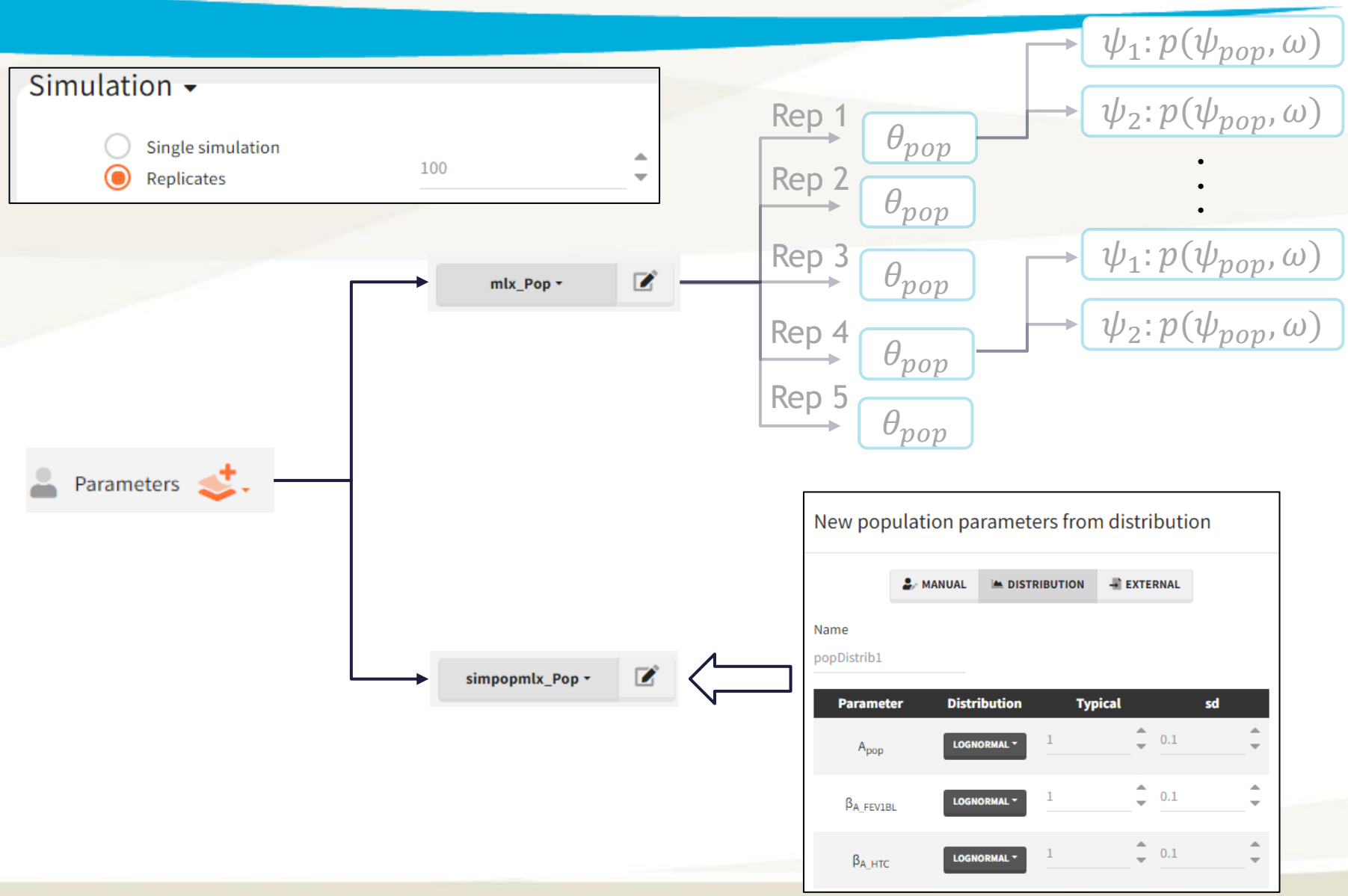

Parameter uncertainty with replicates

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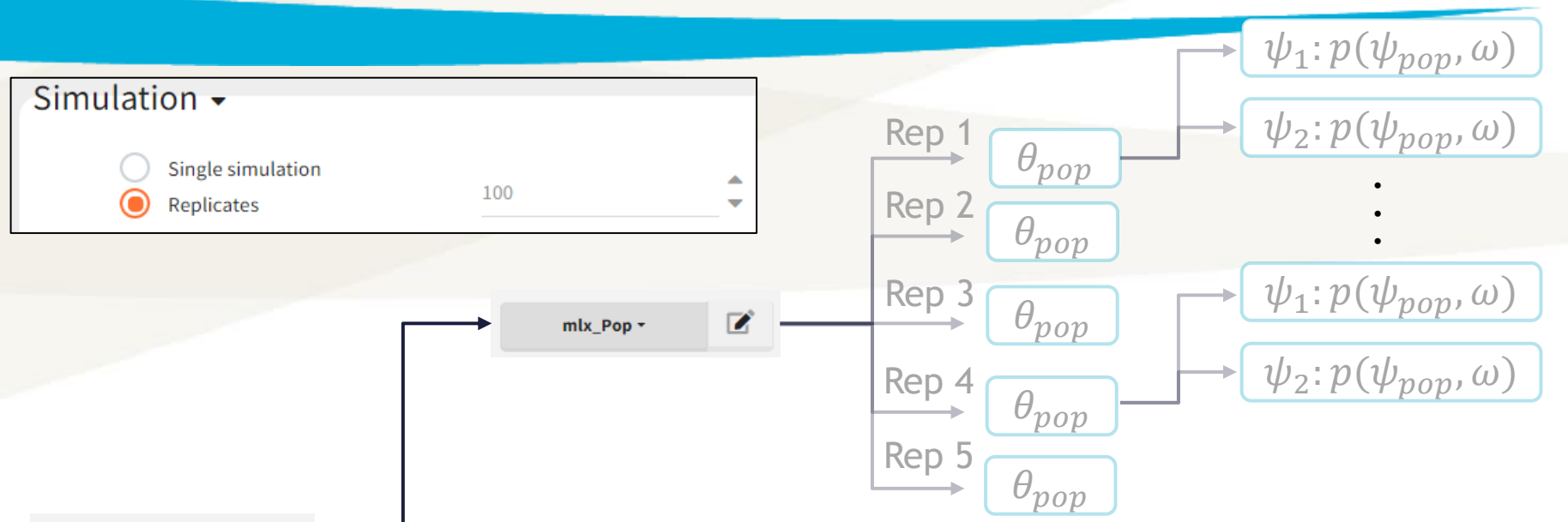

popUncertainty [read-only]

ID	Rep 1	Rep 2	Rep 3	Rep 4
A_pop	1.3	1.28	1.31	1.28
beta_A_FEV1BL	0.25	0.25	0.25	0.26
beta_A_HTC	0.0066	0.0064	0.0066	0.0067
beta_A_logtAGEBL	-0.12	-0.12	-0.14	-0.12
beta_A_logtBFEVPD	0.54	0.52	0.54	0.53

Parameter uncertainty with replicates

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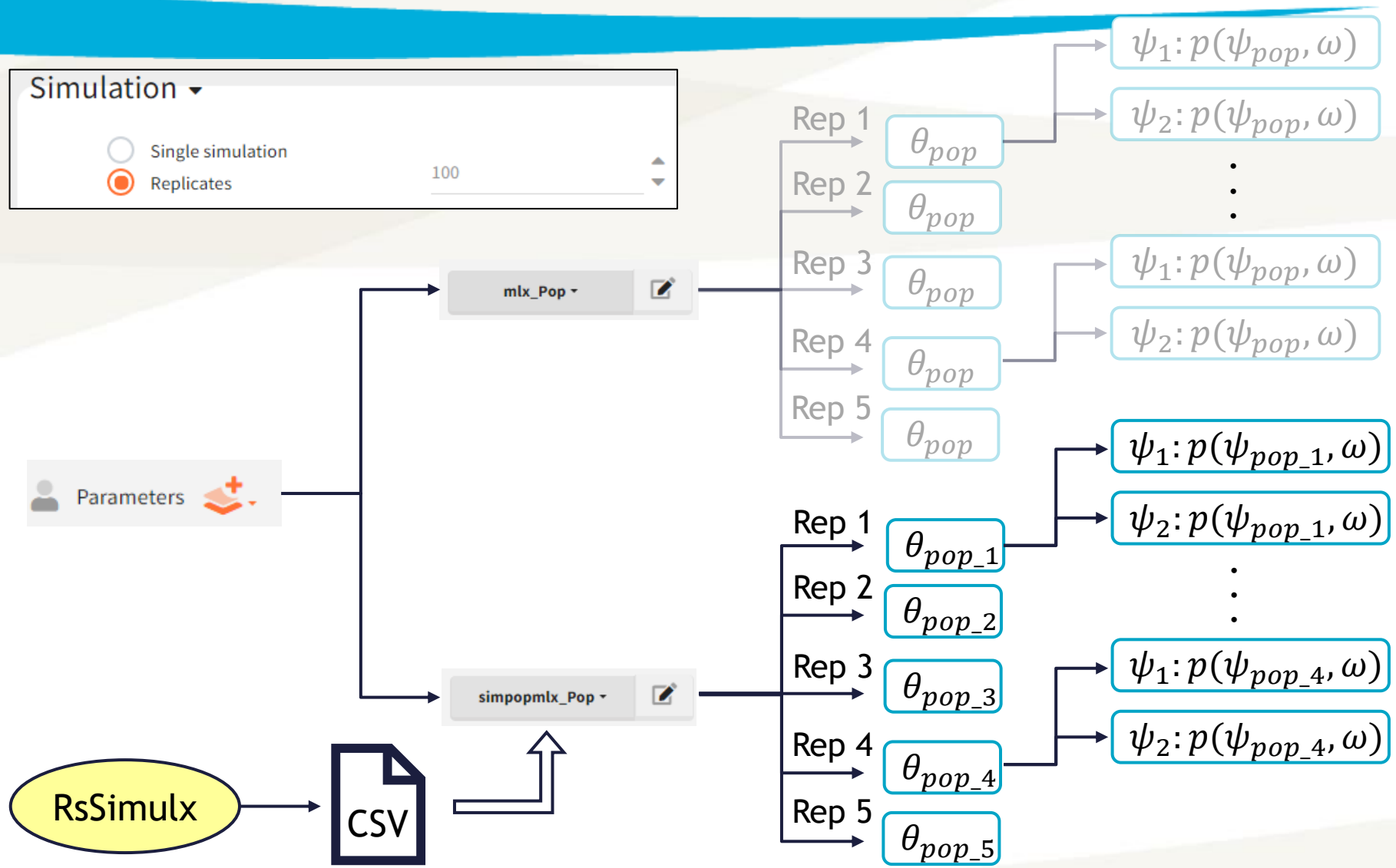

Individual parameters in all replicates are simulated using DIFFERENT population parameters

Summary

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Already available data

Population modeling in Monolix

Clinical trial simulations in Simulx

Optimize trial design with LixoftConnectors

Result:

A sample size of 90 individuals per treatment arm is sufficient to obtain a successful clinical trial showing the greater effect of the new drug in a 3-months study, with an 85% probability.

Summary

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Already available data

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Summary

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Population modeling in Monolix

Clinical trial simulations in Simulx

Simulation
of clinical trial arms (parallel, cross-over) with different treatments

Summary

LIXOFT
A SIMULATIONS PLUS COMPANY

Already available data

Population modeling in Monolix

Clinical trial simulations in Simulx

Simulation

Quantitative outcome

post-processing results

Summary

LIXOFT
A SIMULATIONS PLUS COMPANY

Already available data

Population modeling in Monolix

Clinical trial simulations in Simulx

Simulation

Quantitative outcome

Trial success

comparison of different groups using post-processed target

Summary

LIXOFT
A SIMULATIONS PLUS COMPANY

Already available data

Population modeling in Monolix

Clinical trial simulations in Simulx

Simulation

Quantitative outcome

Trial success

Power of study

Accounting for inter-individual variability and uncertainty of parameter estimates

Summary

LIXOFT
A SIMULATIONS PLUS COMPANY

Already available data

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Quantitative outcome

Trial success

Power of study

Optimize trial design with LixoftConnectors

Questions & Answers

Please type your questions in the Q&A section of the Zoom interface

The recordings and the slides will be available on our webpage by the end of the week

Endpoints & statistical tests in Simulx

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Outcome	Endpoint	Metric	Statistical test	
			Same indiv = True	Same indiv = False
Continuous	Geometric mean	Ratio of means	Paired t-test on log-transformed	Unpaired t-test on log-transformed
	Arithmetic mean	Difference of means	Paired t-test	Unpaired t-test
	Median	Difference of medians	Wilcoxon signed rank test	Wilcoxon rank sum test
Binary true/false	Percent true	Odds ratio	McNemar's exact test	Fisher's exact test
Time-to-event	Median survival	Difference in median survival	Logrank test with variance correction	Logrank test