Model-Informed Drug Development

MIDD+

2021 Virtual Conference

Optimizing sample size of a phase III trial with Simulx using a phase II popPD model

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SimulationsPlus
Cognigen | DILIsym Services | Lixoft

Goal: design of a bridging study

Reference asthma treatment

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

New asthma treatment

- FDA approved
- 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

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

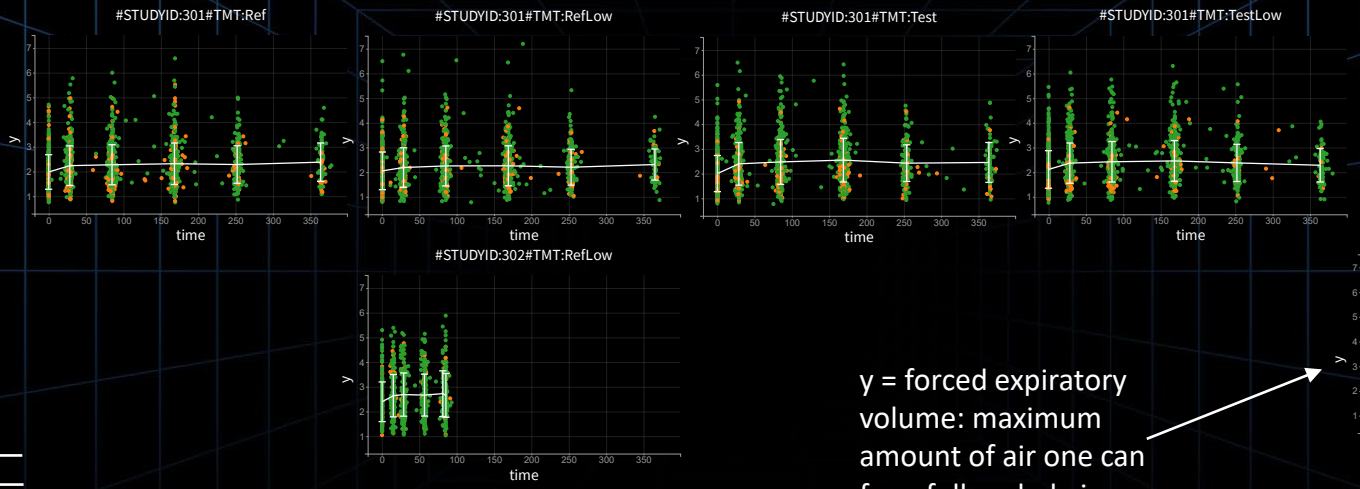
Clinical trial simulations in Simulx

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

Dataset: observations

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

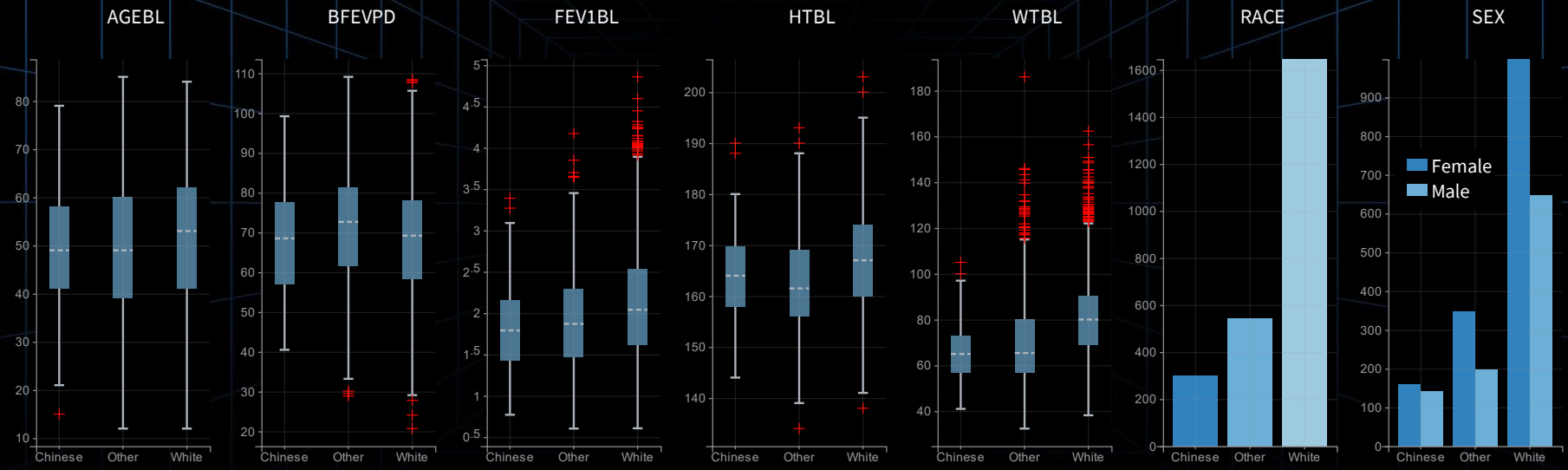
Phase III studies Population:
White
Other



Phase II studies Population:
Chinese
Other

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

Dataset: covariates

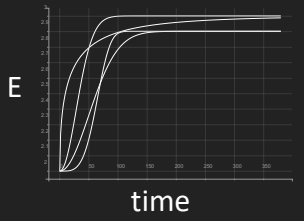


PD Model

Structural model: exponential

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

OUTPUT:
output = E



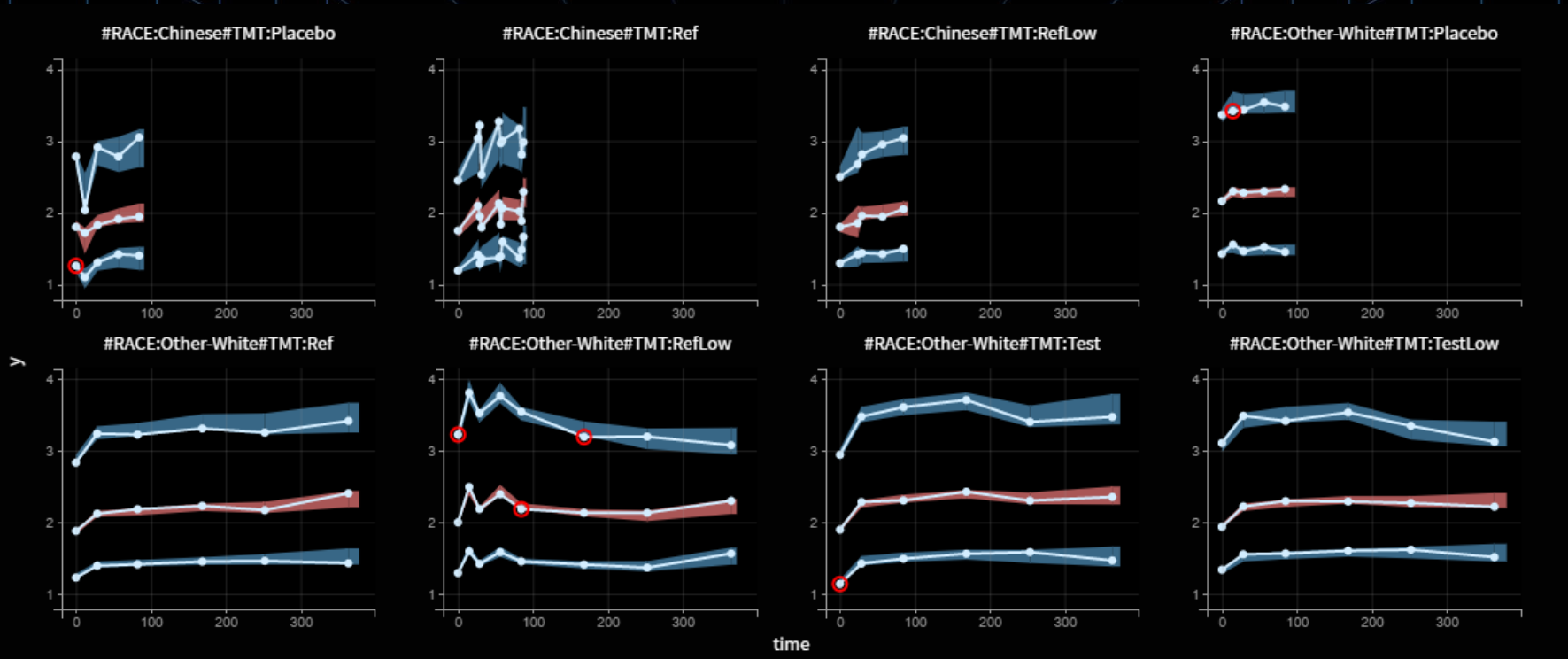
TMT	Typical G
Placebo	0.9
RefLow	1.34
Ref	1.59
TestLow	1.72
Test	2.30

RACE	Typical A
White	1.32
Chinese	1.26
Other	1.27

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 evaluation



Simulating a phase III clinical trial

Simulate a new population of Chinese patients

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

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

What is the probability of such a trial to succeed?

Run scenario for ≠ sizes/durations.

Which minimum design is needed to reach an 85% probability of success?

Simulating a phase III clinical trial

Simulate a new population of Chinese patients

→ Choose **sample size** and **study duration**

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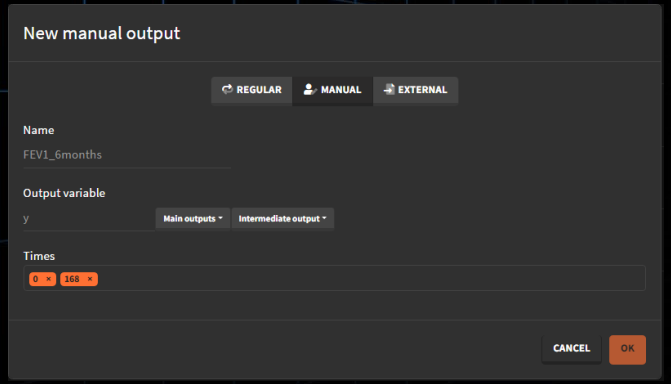
Setting up simulation elements

- Define endpoint times: 0 and 6 months to observe a change from baseline



- Define new covariate distributions

Distributions derived from data, can be adapted to characterize better Chinese population

New distribution: Chinese, receiving the test treatment

DISTRIBUTION

Name

Ref_Treatment_Chinese

Continuous covariates

Covariate	Distribution	Typical	sd	Limits
AGEBL	normal	49.99	14.73	
WTBL	normal	77.06	18.96	
HTBL	normal	165.75	9.46	
BFEVPD	normal	68.53	14.12	
FEV1BL	normal	2.03	0.67	

Categorical covariates

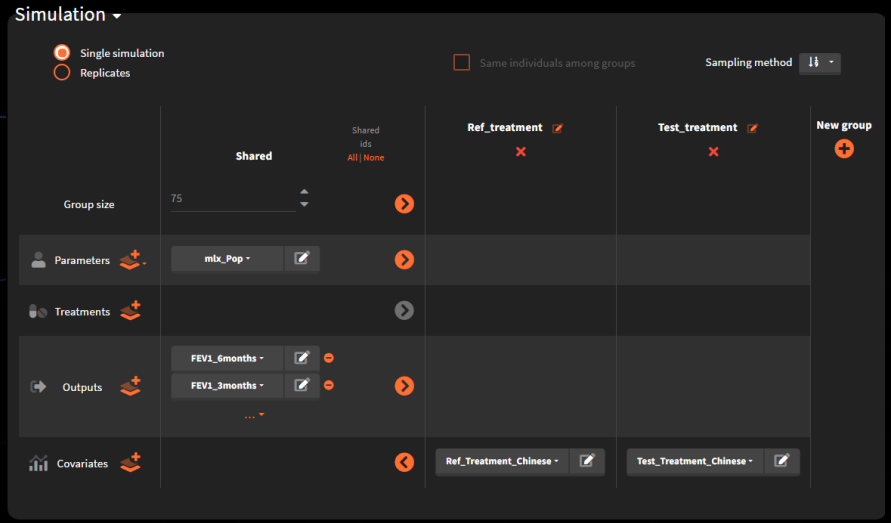
Covariate	Category	Probability
SEX	Female	0.6
	Male	0.4
RACE	Chinese	1
	Other	0
	White	0
TMT	Placebo	0
	Ref	1
	RefLow	0
	Test	0
	TestLow	0

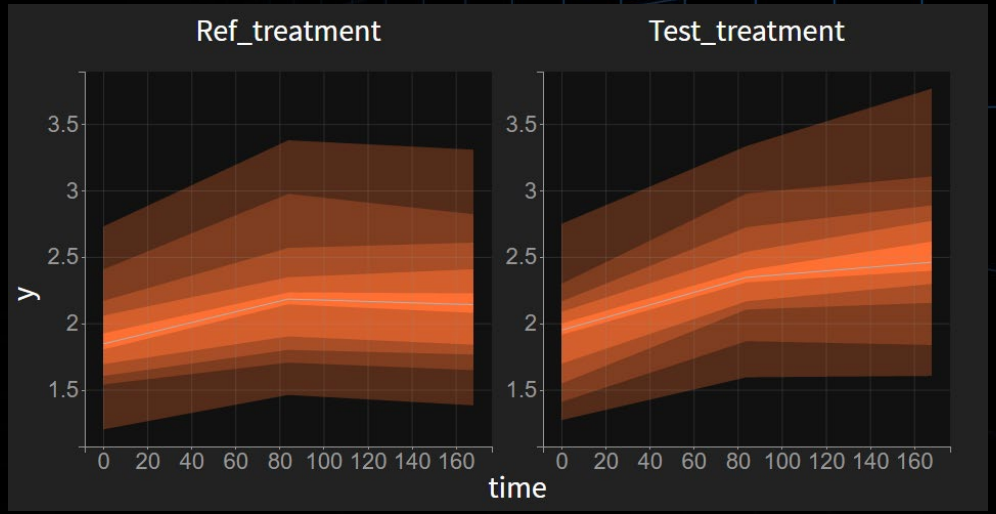
CLOSE

Simulating a Chinese population

- Simulate 2 groups of 75 subjects: ref and test treatments

- Output distribution





Simulating a phase III clinical trial

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

→ Post-process predictions to get a quantitative result

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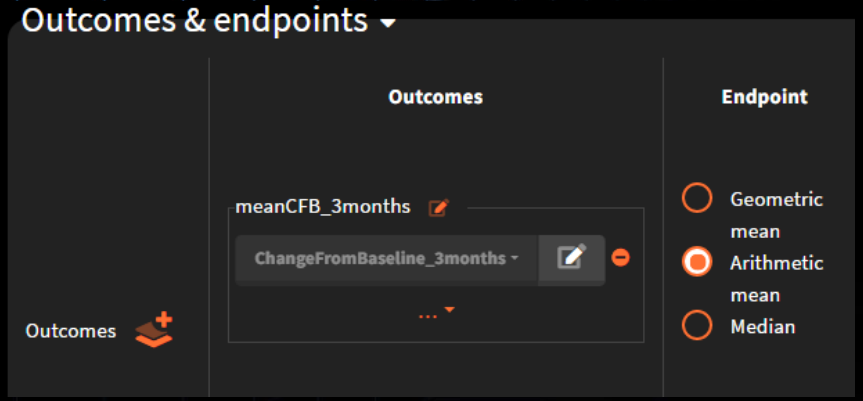
Quantitative results

- Compute change from baseline for each id, get the mean over ids for each condition



The test treatment has a higher outcome than the ref, after 3 and after 6 months.

mean_CFB_3months

Ref_treatment		Test_treatment	
arithmeticMean	standardDeviation	arithmeticMean	standardDeviation
0.33	0.41	0.56	0.48

mean_CFB_6months

Ref_treatment		Test_treatment	
arithmeticMean	standardDeviation	arithmeticMean	standardDeviation
0.31	0.49	0.62	0.46

Simulating a phase III clinical trial

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

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

→ Check success of a simulated clinical trial

What is the probability of such a trial to succeed?

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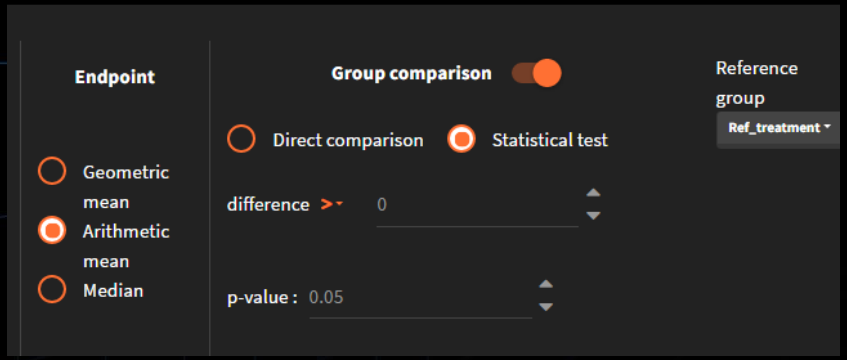
Which minimum design is needed to reach an 85% probability of success?

Is the clinical trial successful?

- Compare groups with an unpaired t-test

➡ Difference statistically significant = trial successful



Group comparison

mean_CFB_3months

REP	TEST_TREATMENT		
	DIFFERENCE	P-VALUE	SUCCESS
1	0.24	7.6e-4	✓

mean_CFB_6months

REP	TEST_TREATMENT		
	DIFFERENCE	P-VALUE	SUCCESS
1	0.31	4.41e-5	✓

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What is the probability of such a trial to succeed?

→ Replicate study with different samples to obtain the power of the study

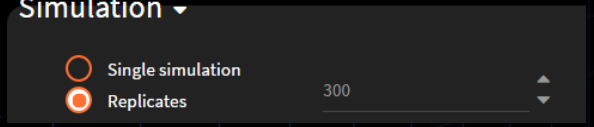
Run scenario for ≠ sizes/durations.

Which minimum design is needed to reach an 85% probability of success?

Power of the study

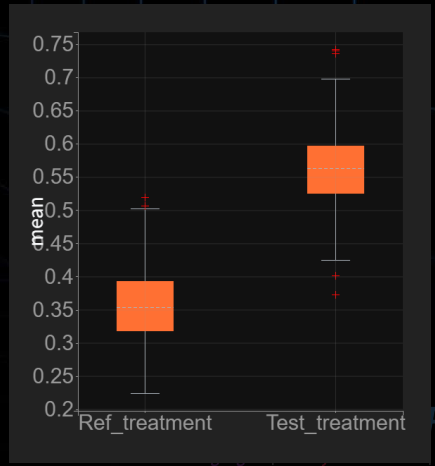
- Run replicates of the study

- Probability of the trial to succeed = power of the study
- Distribution of mean change from baseline over replicates



Percentage of success over replicates

	TEST_TREATMENT
mean_CFB_3months	78
mean_CFB_6months	83



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Run scenario for ≠ sizes/durations.

Which minimum design is needed to reach an 85% probability of success?

Simulx: find minimum required sample size

- Repeat scenario for ≠ sample sizes with LixoftConnectors (R functions calling Simulx)

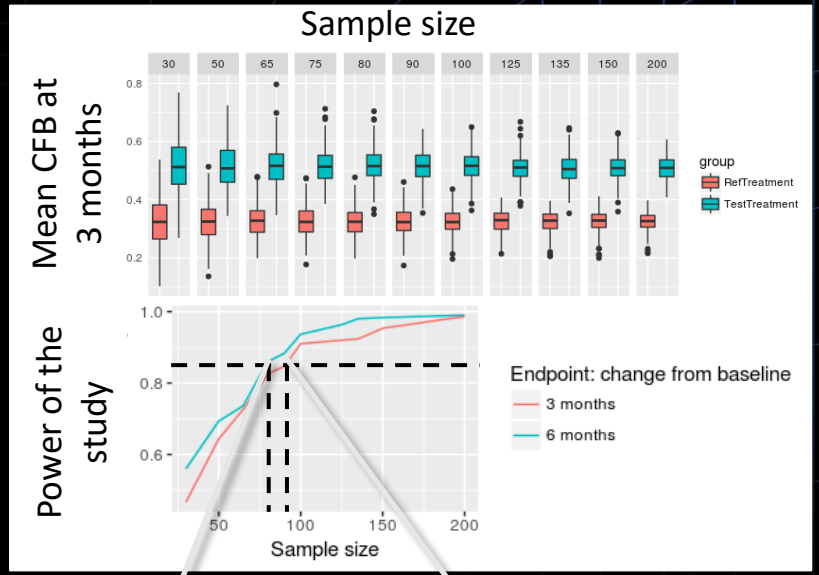
```
library(lixoftConnectors)
initializeLixoftConnectors(software="simulx")

loadProject(projectFile = "ChineseTrial.smlx")

sample_sizes <- c(50, 75, 100, 125, 150)
for(N in sample_sizes){

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

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



Optimal designs for 85% power

6 months, 80 subjects per arm	3 months, 90 subjects per arm

Summary: design of a bridging study

Already available data

Population modeling in Monolix

Clinical trial simulations in Simulx

Simulation

Quantitative outcome

Trial success

Power of study

Optimize trial design with LixoftConnectors

Q&A

Questions & Answers

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Additional: endpoints & statistical tests in Simulx

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