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Rapid sample size calculations for a defined likelihood ratio test-based power in mixed effects models

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Department of Pharmaceutical Biosciences
Uppsala University

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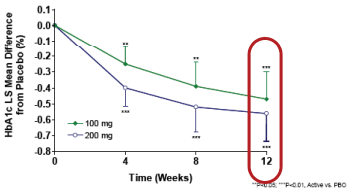
Motivating example

Phase II study in Diabetes

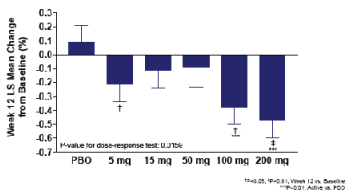
- ☑ Power to detect a significant drug effect on reduction in HbA1c
- ☑ 12 week study
- ☑ FPG and HbA1c
- ☑ Placebo + 5 dose groups

Placebo-Adjusted HbA1c Change from Baseline to Week 12 in the 100 mg and 200 mg Treatment Arms



HbA1c Efficacy

Week 12 Change from Baseline in HbA1c



Rosenstock et al., 69th ADA Scientific Sessions, 2009

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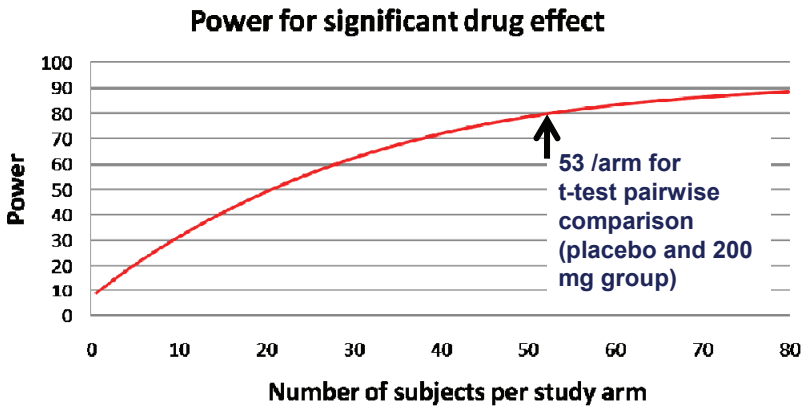
Power with traditional group wise comparison (t-test)



3

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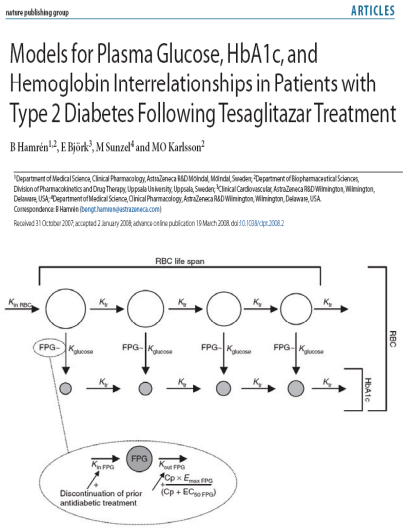
Model-based approach


nature publishing group ARTICLES

Models for Plasma Glucose, HbA1c, and Hemoglobin Interrelationships in Patients with Type 2 Diabetes Following Tesaglitazar Treatment

B Hamrén[1,2], E Björk[3], M Sunzel[4] and MO Karlsson[2]

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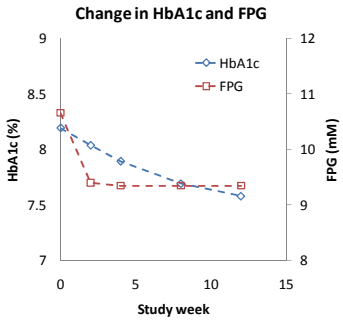
Correspondence: B Hamrén (bengt.hamren@astrazeneca.com)

Received 31 October 2007; accepted 2 January 2008; advance online publication 19 March 2008; doi:10.1038/clpt.2008.2



4

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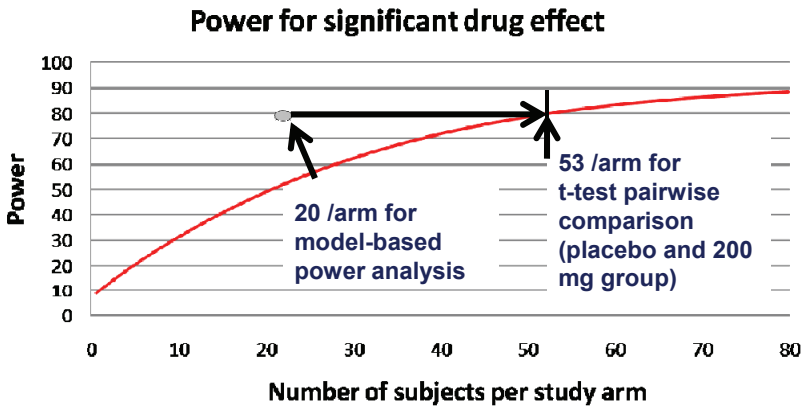
Power with traditional group wise comparison (t-test)



5

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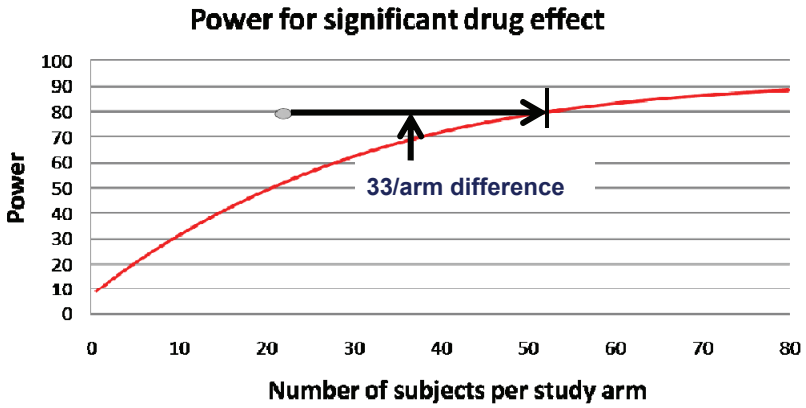
Power with traditional group wise comparison (t-test)



⇨Higher power with NLME models

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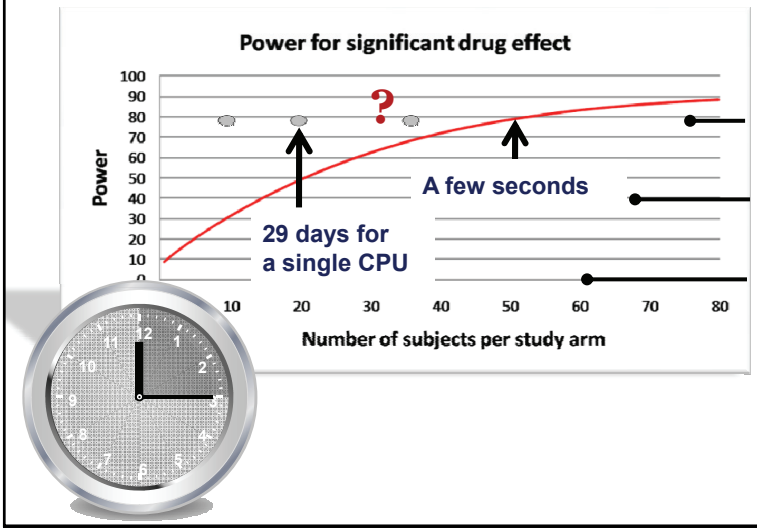
Time computation comparison



7

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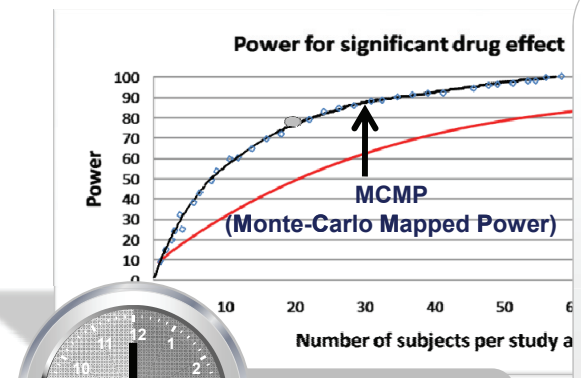
Objectives



9 hours

- ☑Power for Likelihood Ratio Test (LRT)
- ☑Fast and easy method to map **complete** power curve

8

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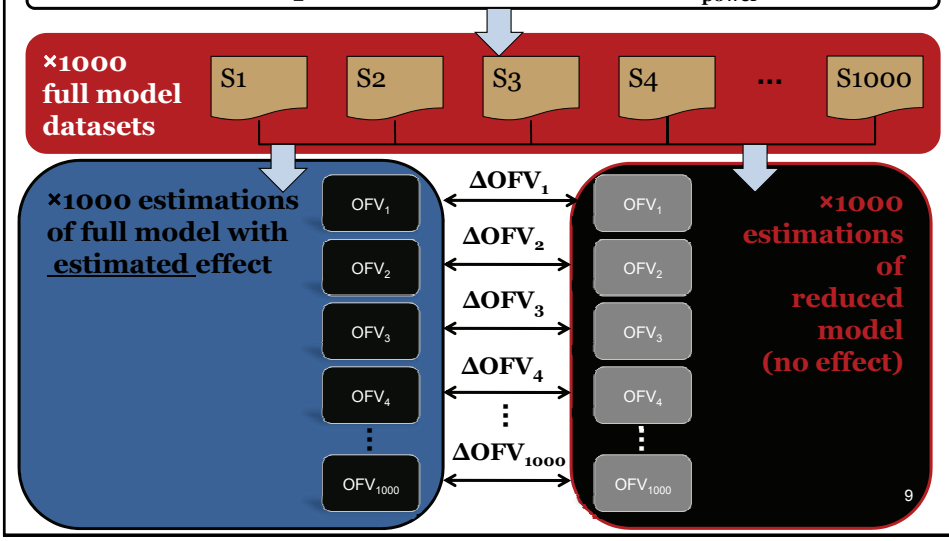
Standard power calculation for NLME models 1

1 full model with specified effect and assumed N_{power} individuals



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Standard power calculation for NLME models 2

ΔOFV_1
ΔOFV_2
ΔOFV_3
ΔOFV_4
⋮
ΔOFV_{1000}

×1000 ΔOFVs

Count if ΔOFV> cut-off value

Fraction = POWER For this N /group

⇨Stochastic Simulation and Estimation (SSE)

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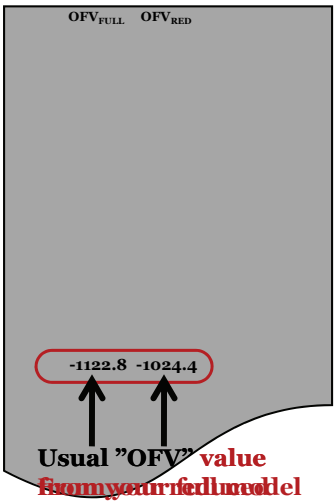
Methodology

- Likelihood minimized during a NONMEM 7® run:

Objective Function Value=



11

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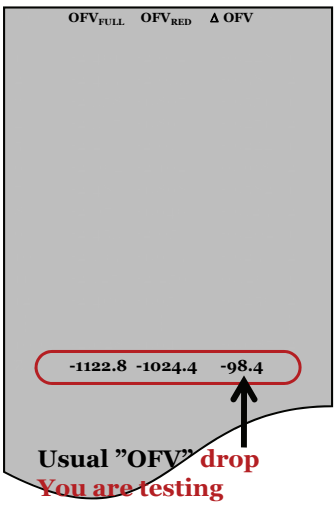
Methodology

- Likelihood minimized during a NONMEM 7® run:

Objective Function Value=



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Methodology

- Likelihood minimized during a NONMEM 7® run:

$$\text{Objective Function Value} = \sum_{i=1}^{n} \text{iOFV}$$

- Can be directly found in NM7 in .phi file
- Can be computed in NM6 with –iofv in PsN

ID	$iOFV_{FULL}$	$iOFV_{RED}$
1	-2.461	-2.012
2	-2.413	-2.033
3	-2.358	-1.807
4	-2.367	-1.896
5	-2.26	-2.016
6	-2.094	-2.102
7	-2.48	-1.898
8	-2.07	-1.946
9	-2.453	-2.05
10	-2.193	-1.963
11	-2.127	-2.256
12	-2.409	-1.95
⋮		⋮
1000	-2.028	-1.941
Σ	-1122.8	-1024.4

13

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Methodology

- Likelihood minimized during a NONMEM 7® run:

$$\text{Objective Function Value} = \sum_{i=1}^{n} \text{iOFV}$$

- Drop between two nested models (i.e. χ^2-distribution):

$$\Delta \text{OFV}_{(\text{FULL}-\text{REDUCED})} = \sum_{i=1}^{n} \left(\text{iOFV}_{\text{FULL}} - \text{iOFV}_{\text{REDUCED}} \right)$$

ID	$iOFV_{FULL}$	$iOFV_{RED}$	ΔiOFV	STRAT
1	-2.461	-2.012	-0.448	1
2	-2.413	-2.033	-0.38	2
3	-2.358	-1.807	-0.551	1
4	-2.367	-1.896	-0.471	2
5	-2.26	-2.016	-0.244	1
6	-2.094	-2.102	0.008	2
7	-2.48	-1.898	-0.582	1
8	-2.07	-1.946	-0.123	2
9	-2.453	-2.05	-0.402	1
10	-2.193	-1.963	-0.23	2
11	-2.127	-2.256	0.129	1
12	-2.409	-1.95	-0.459	2
⋮		⋮		⋮
1000	-2.028	-1.941	-0.087	2
Σ	-1122.8	-1024.4	-97.4	

Principle of MCMP

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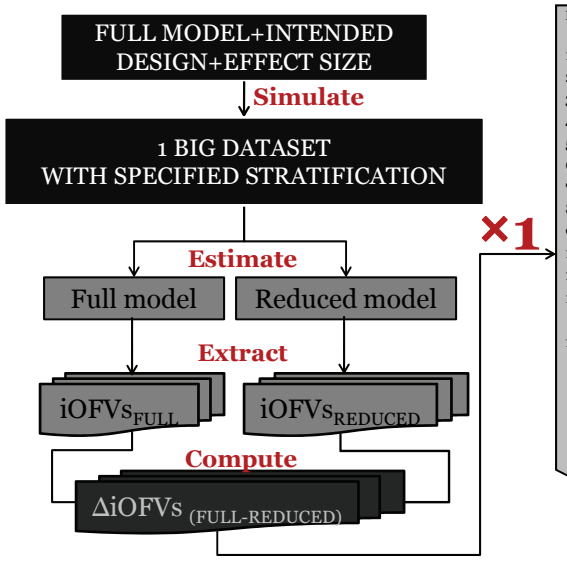
MCMP Methodology – step 1



ID	$iOFV_{FULL}$	$iOFV_{RED}$	ΔiOFV	STRAT
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10	-2.193	-1.963	-0.23	2
11	-2.127	-2.256	0.129	1
12	-2.409	-1.95	-0.459	2
⋮		⋮		⋮
1000	-2.028	-1.941	-0.087	2

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MCMP Methodology – step 2

ID	$iOFV_{FULL}$	$iOFV_{RED}$	ΔiOFV	STRAT
1	-2.461	-2.012	-0.448	1
2	-2.413	-2.033	-0.38	2
3	-2.358	-1.807	-0.551	1
4	-2.367	-1.896	-0.471	2
5	-2.26	-2.016	-0.244	1
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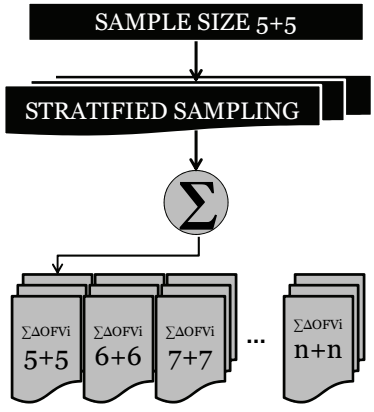
11	-2.127	-2.256	0.129	1
12	-2.409	-1.95	-0.459	2
⋮		⋮		⋮
1000	-2.028	-1.941	-0.087	2



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MCMP Methodology – step 2

ID	$iOFV_{FULL}$	$iOFV_{RED}$	ΔiOFV	STRAT
1	-2.461	-2.012	-0.448	1
2	-2.413	-2.033	-0.38	2
3	-2.358	-1.807	-0.551	1
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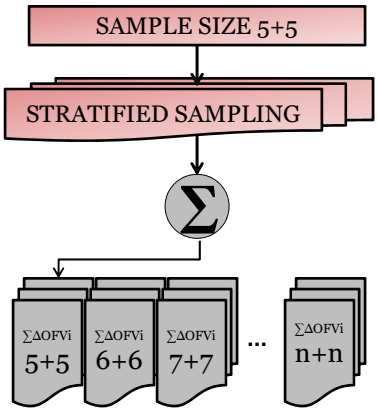
10	-2.193	-1.963	-0.23	2
11	-2.127	-2.256	0.129	1
12	-2.409	-1.95	-0.459	2
⋮		⋮		⋮
1000	-2.028	-1.941	-0.087	2



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MCMP Methodology – step 2

ID	$iOFV_{FULL}$	$iOFV_{RED}$	ΔiOFV	STRAT
1	-2.461	-2.012	-0.448	1
2	-2.413	-2.033	-0.38	2
3	-2.358	-1.807	-0.551	1
4	-2.367	-1.896	-0.471	2
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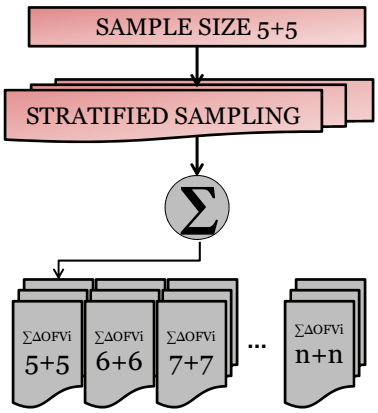
9	-2.453	-2.05	-0.402	1
10	-2.193	-1.963	-0.23	2
11	-2.127	-2.256	0.129	1
12	-2.409	-1.95	-0.459	2
⋮		⋮		⋮
1000	-2.028	-1.941	-0.087	2



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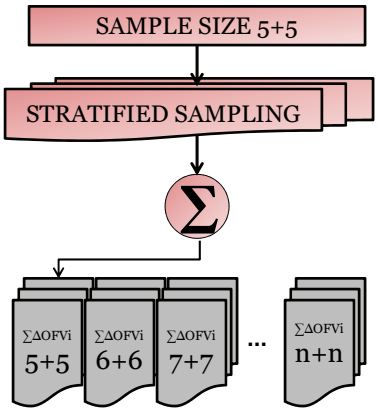
MCMP Methodology – step 2

ID	$iOFV_{FULL}$	$iOFV_{RED}$	ΔiOFV	STRAT
1	-2.461	-2.012	-0.448	1
2	-2.413	-2.033	-0.38	2
3	-2.358	-1.807	-0.551	1
4	-2.367	-1.896	-0.471	2
5	-2.26	-2.016	-0.244	1
6	-2.094	-2.102	0.008	2
7	-2.48	-1.898	-0.582	1
8	-2.07	-1.946	-0.123	2
9	-2.453	-2.05	-0.402	1
10	-2.193	-1.963	-0.23	2
11	-2.127	-2.256	0.129	1
12	-2.409	-1.95	-0.459	2
⋮		⋮		⋮
1000	-2.028	-1.941	-0.087	2

∑ ΔiOFV = -2.278



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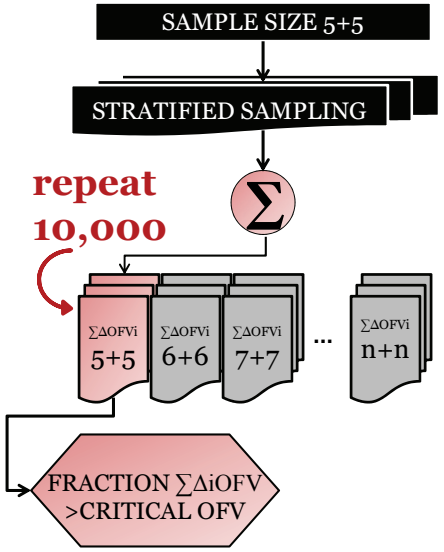
MCMP Methodology – step 2

∑ ΔiOFV = -2.278
∑ ΔiOFV = -5.037
∑ ΔiOFV = -0.641
∑ ΔiOFV = 0.488
...
∑ ΔiOFV = -3.694



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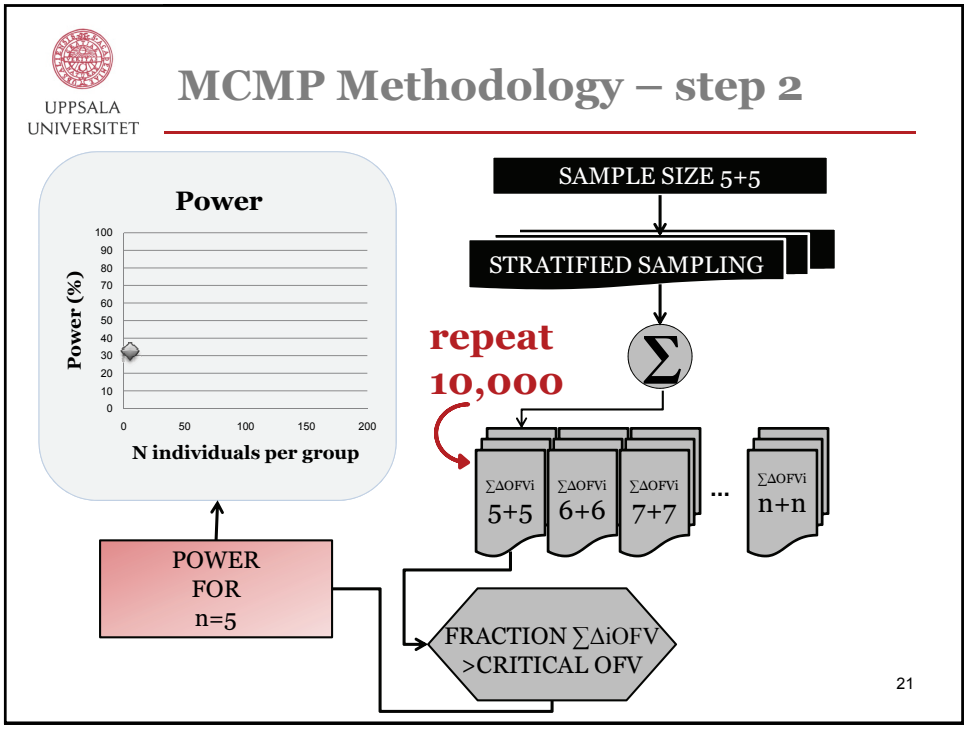
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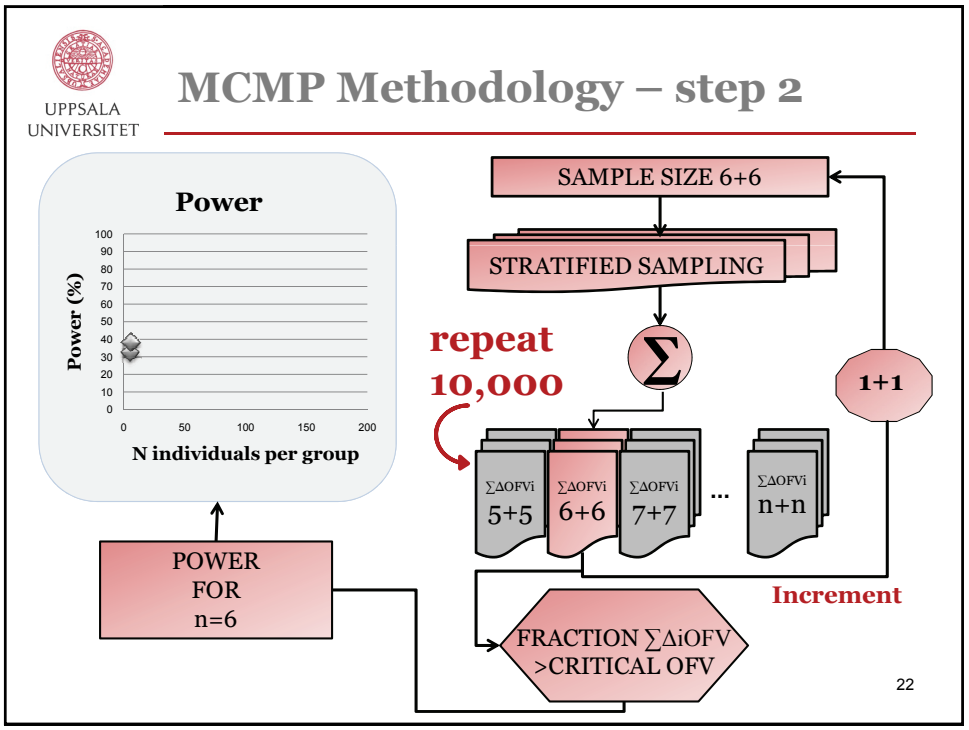
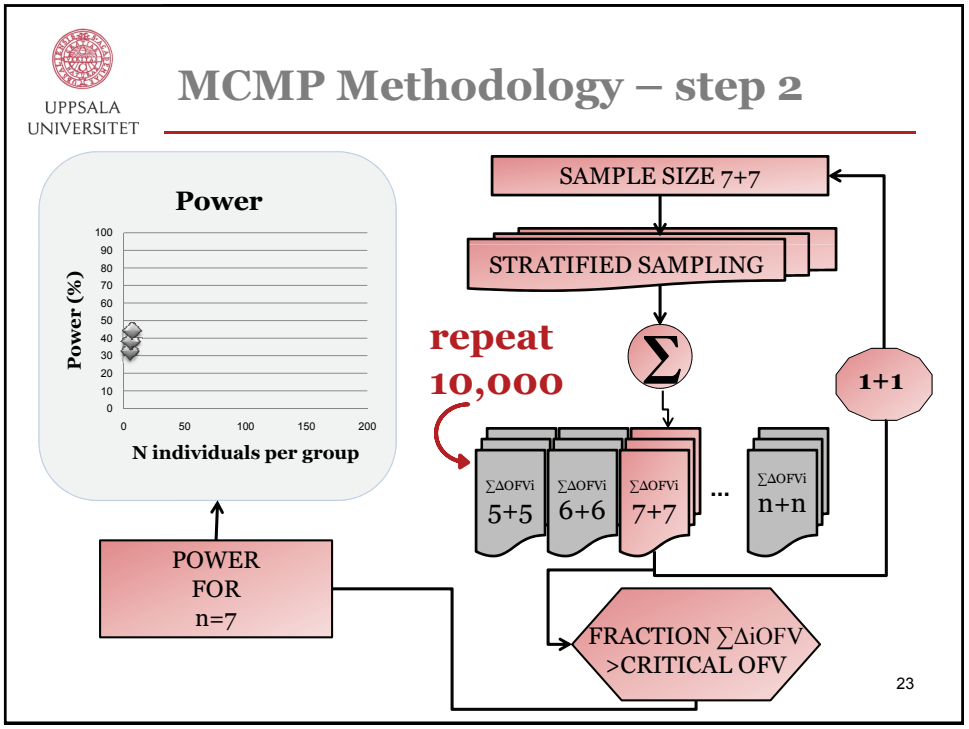
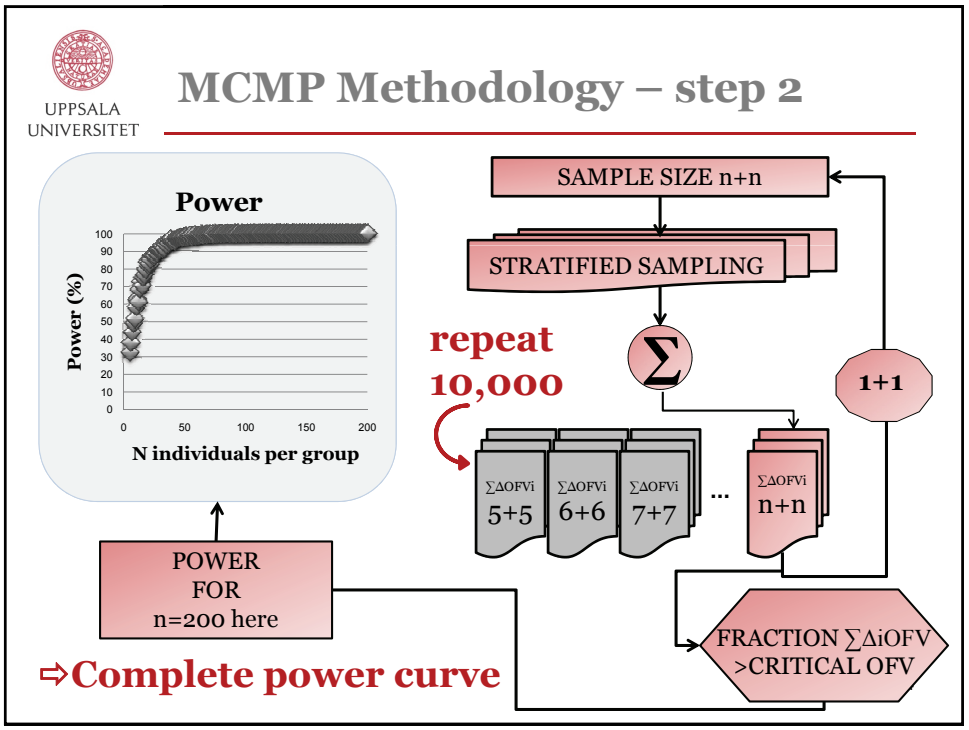
MCMP Methodology – step 2
Power
Power (%)
N individuals per group
SAMPLE SIZE 5+5
STRATIFIED SAMPLING
repeat 10,000
∑
∑ΔOFVi 5+5
∑ΔOFVi 6+6
∑ΔOFVi 7+7
...
∑ΔOFVi n+n
POWER FOR n=5
FRACTION ∑ΔiOFV >CRITICAL OFV
21


UPPSALA UNIVERSITET
MCMP Methodology – step 2
Power
Power (%)
N individuals per group
SAMPLE SIZE 6+6
STRATIFIED SAMPLING
repeat 10,000
∑
1+1
∑ΔOFVi 5+5
∑ΔOFVi 6+6
∑ΔOFVi 7+7
...
∑ΔOFVi n+n
Increment
POWER FOR n=6
FRACTION ∑ΔiOFV >CRITICAL OFV
22


UPPSALA UNIVERSITET
MCMP Methodology – step 2
Power
Power (%)
N individuals per group
SAMPLE SIZE 7+7
STRATIFIED SAMPLING
repeat 10,000
1+1
∑ΔOFVi 5+5
∑ΔOFVi 6+6
∑ΔOFVi 7+7
...
∑ΔOFVi n+n
POWER FOR n=7
FRACTION ∑ΔiOFV >CRITICAL OFV
23


UPPSALA UNIVERSITET
MCMP Methodology – step 2
Power
Power (%)
N individuals per group
SAMPLE SIZE n+n
STRATIFIED SAMPLING
repeat 10,000
1+1
∑ΔOFVi 5+5
∑ΔOFVi 6+6
∑ΔOFVi 7+7
...
∑ΔOFVi n+n
POWER FOR n=200 here
FRACTION ∑ΔiOFV >CRITICAL OFV
⇨Complete power curve

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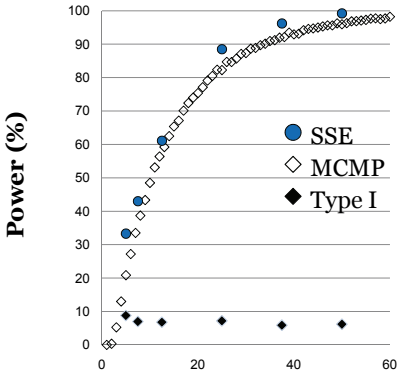
Results

IV bolus 1-compartment with/out covariate



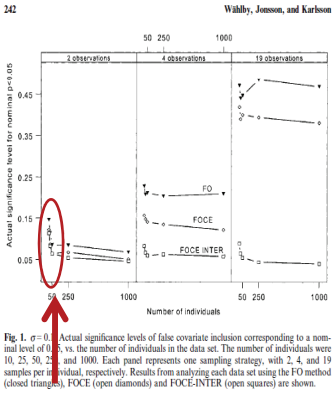


Fig. 1. $\sigma = 0.$ Actual significance levels of false covariate inclusion corresponding to a nominal level of 0. vs. the number of individuals in the data set. The number of individuals were 10, 25, 50, 2 and 1000. Each panel represents one sampling strategy, with 2, 4, and 19 samples per individual, respectively. Results from analyzing each data set using the FO method (closed triangles), FOCE (open diamonds) and FOCE-INTER (open squares) are shown.

Asymptotic normality requires calibration for Type I error inflation[1]

1. U. Wahlby, E. N. Jonsson, and M. O. Karlsson. Assessment of actual significance levels for covariate effects in NONMEM. J. Pharmacokinet. Pharmacodyn. 28:231–252 (2001).

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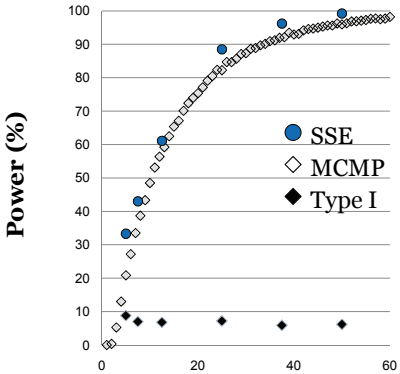
Results

IV bolus 1-compartment with/out covariate



1) Check if nominal cut-off value (i.e. for α=0.05, 5% False Positive)
2) If not, re-assess appropriate cut-off value

⇨ Large number of Simulations and Estimations for each sample size

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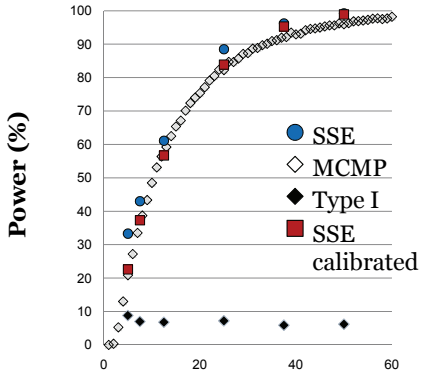
Results

IV bolus 1-compartment with/out covariate



1) Check if nominal cut-off value (i.e. for α=0.05, 5% False Positive)
2) If not, re-assess appropriate cut-off value

⇨ Large number of Simulations and Estimations for each sample size

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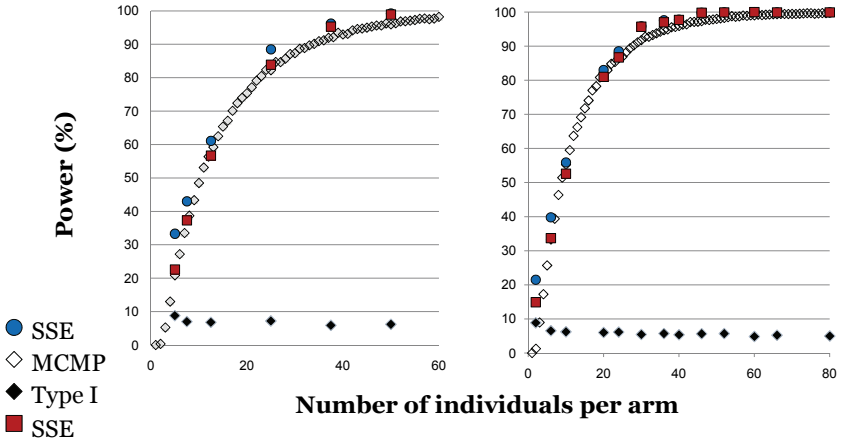
Results

IV bolus 1-compartment with/out covariate

Infusion 1-compartment with/out covariate



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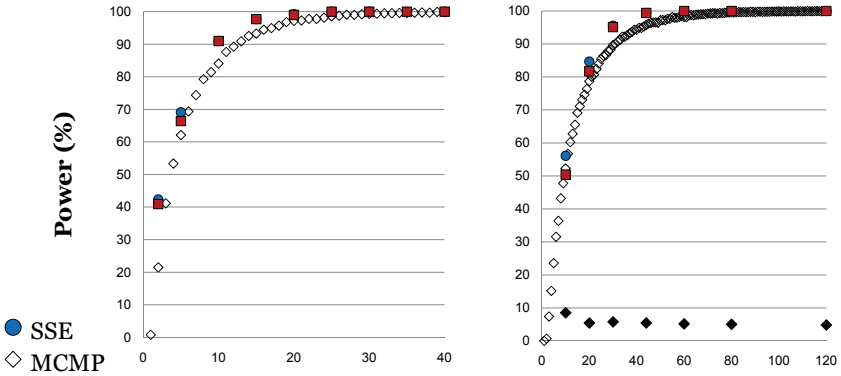
Results

FPG-HbA1c model with/out drug effect on Kout

Linear disease model with/out slope effect



- SSE
- MCMP
- Type I
- SSE calibrated

Number of individuals per arm

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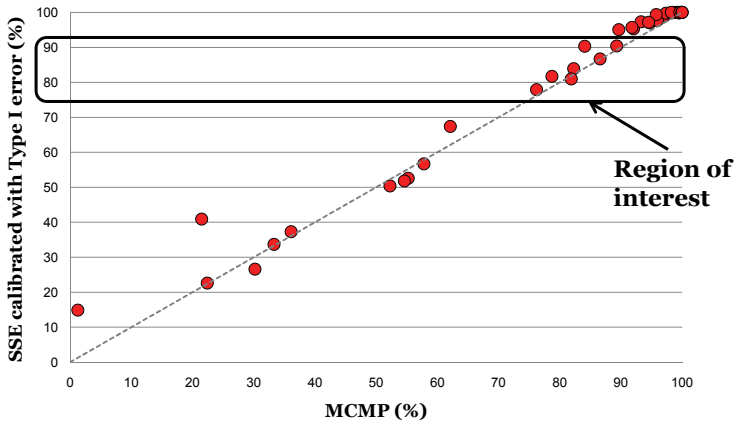
Pool of all tested models results

Calibrated SSE vs. MCM Power



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2nd Application

nature publishing group ARTICLES

A Pharmacodynamic Markov Mixed-Effects Model for Determining the Effect of Exposure to Certolizumab Pegol on the ACR20 Score in Patients With Rheumatoid Arthritis

BD Lacroix[1,2], MR Lovern[1], A Stockis[1], ML Sargentini-Maier[1], MO Karlsson[2] and LE Friberg[2]

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CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 86 NUMBER 4 | OCTOBER 2009 387

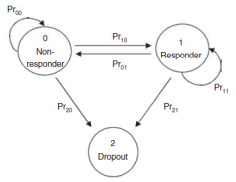

Figure 1 Transitions between the three possible states (ACR20 nonresponder, ACR20 responder, and dropout, defined by the scores 0, 1, and 2, respectively). ACR20, American College of Rheumatology 20% preliminary definition of improvement in rheumatoid arthritis.

Proof of Concept study with categorical data

- ☑ **Power to detect difference with PK samples vs. only dose**
- ☑ **Placebo + 4 dose groups**
- ☑ **GO/NO GO criterion : number of inclusion between the two studies**

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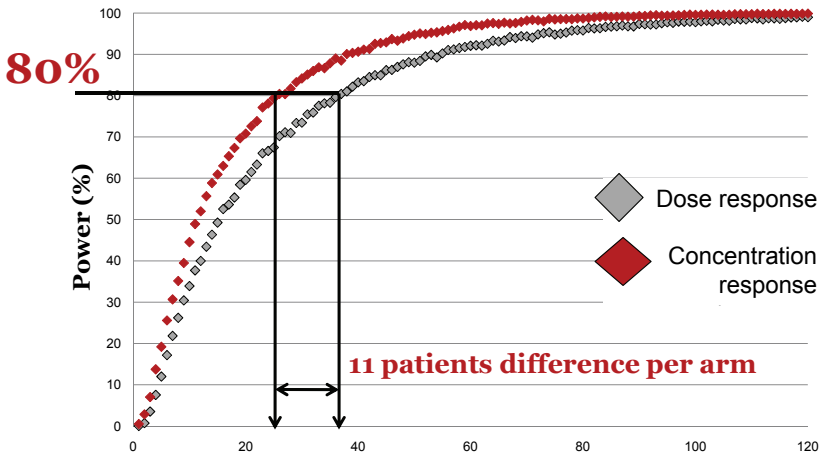
2nd Application



~30minutes

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Summary

☑ **A fast method for powering LRT**
- ✓ Possibility to obtain a complete power curve
- ✓ No calibration of type I error
- ✓ Opportunity for rapid response to design changes proposed by study team
- ✓ Increase feasibility for sensitivity analyses

⇨**Increase possibility to demonstrate added value of mechanism-based models**

☑ **Future work**
- ✓ Soon to be embedded in PsN software

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⌘ The Pharmacometrics Group at Uppsala University

⌘ Institut de Recherches Internationales SERVIER for research funding

And… 34

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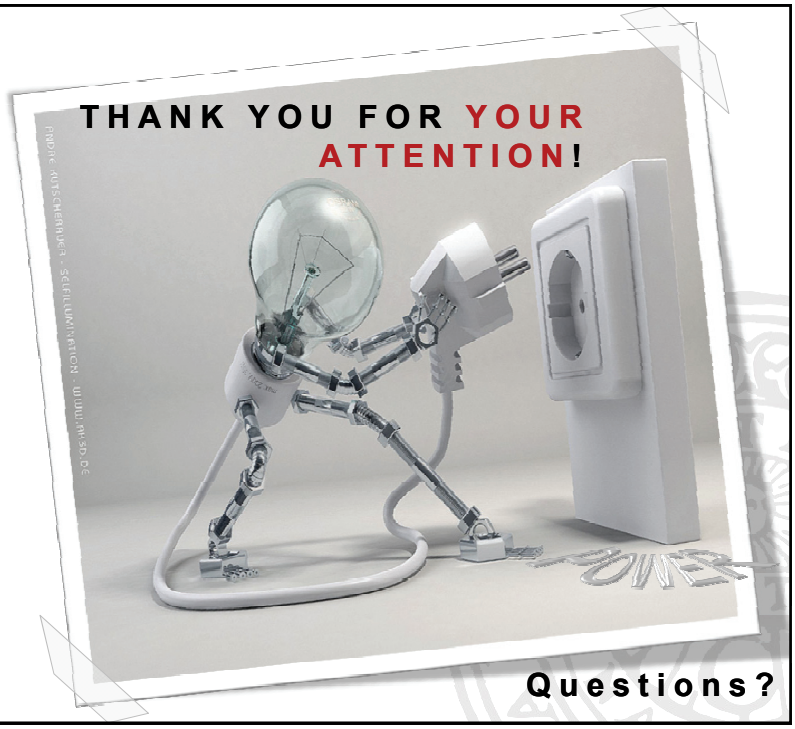

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EXTRA SLIDES

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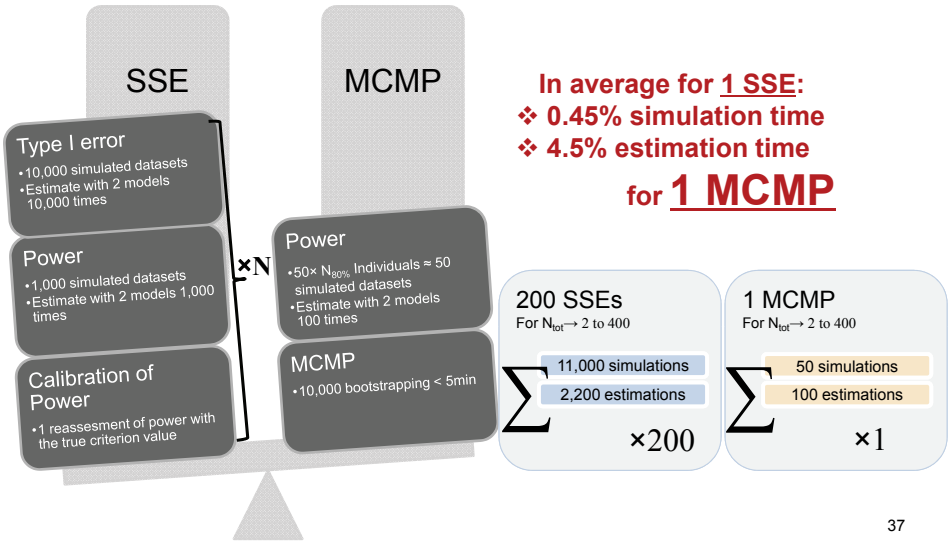
How fast is fast?



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