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Explicit Optimization of Clinical Trials for Statistical Power

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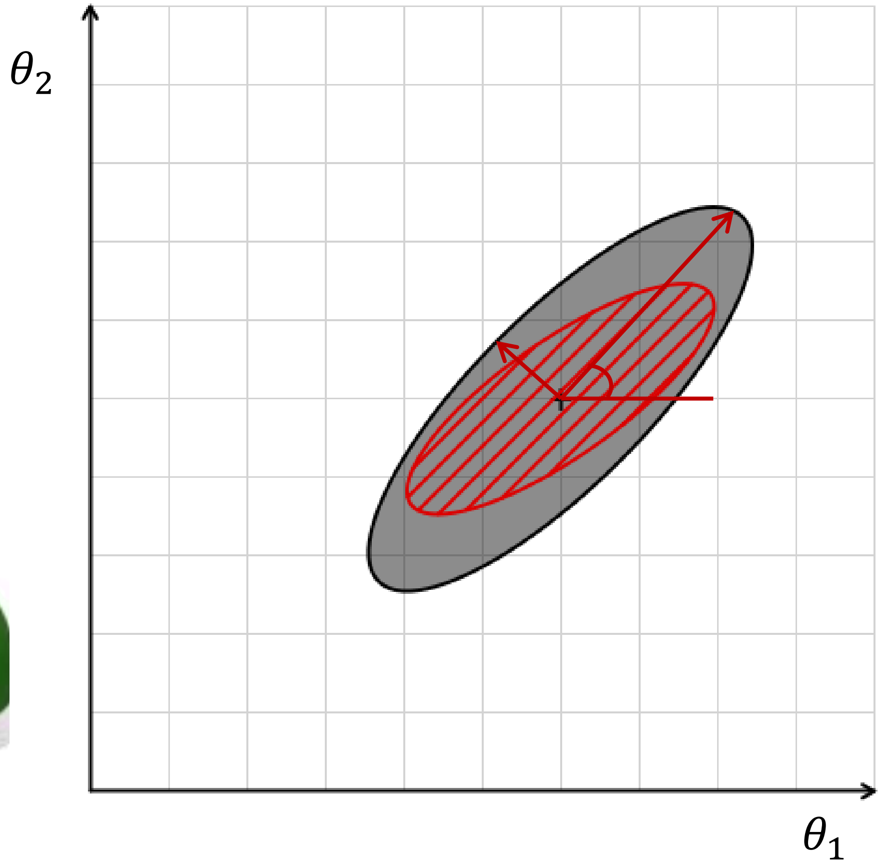
CLINICAL TRIAL

Optimal Design

Cramer-Rao bound:

$$var\ (\hat{\theta}) > I(\hat{\theta})^{-1}$$



$$\left|\begin{pmatrix}\boxed{var\ \theta_1} & cov\ \theta_{12}\\ \boxed{cov\ \theta_{12}} & \boxed{var\ \theta_2}\end{pmatrix}\right|$$

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SUCCESS

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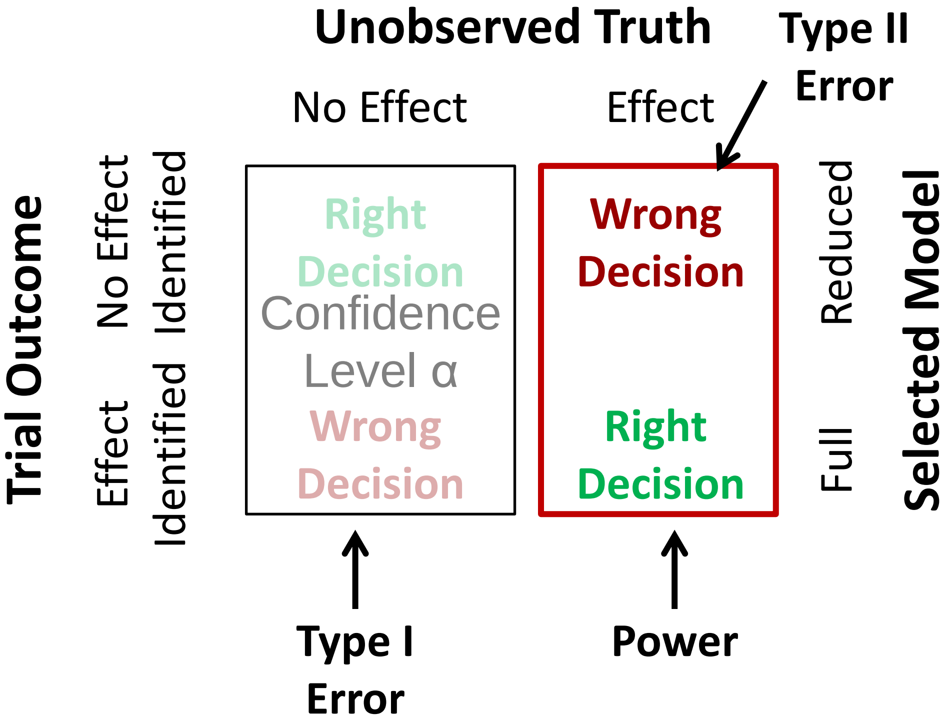
Success ⇔ Power



Unobserved Truth

		No Effect	Effect	
Trial Outcome	No Effect Identified	Right Decision	Wrong Decision	Reduced
	Effect Identified	Wrong Decision	Right Decision	Full

Selected Model

Confidence Level α

Type I Error

Type II Error

Power

$$Eff = \mathrm{f}(\dots) + g(\theta, t, a)$$

$$\theta = \theta_0 \qquad g(\theta_0, t, a) = 0$$

$$\theta \in \mathbb{R}$$

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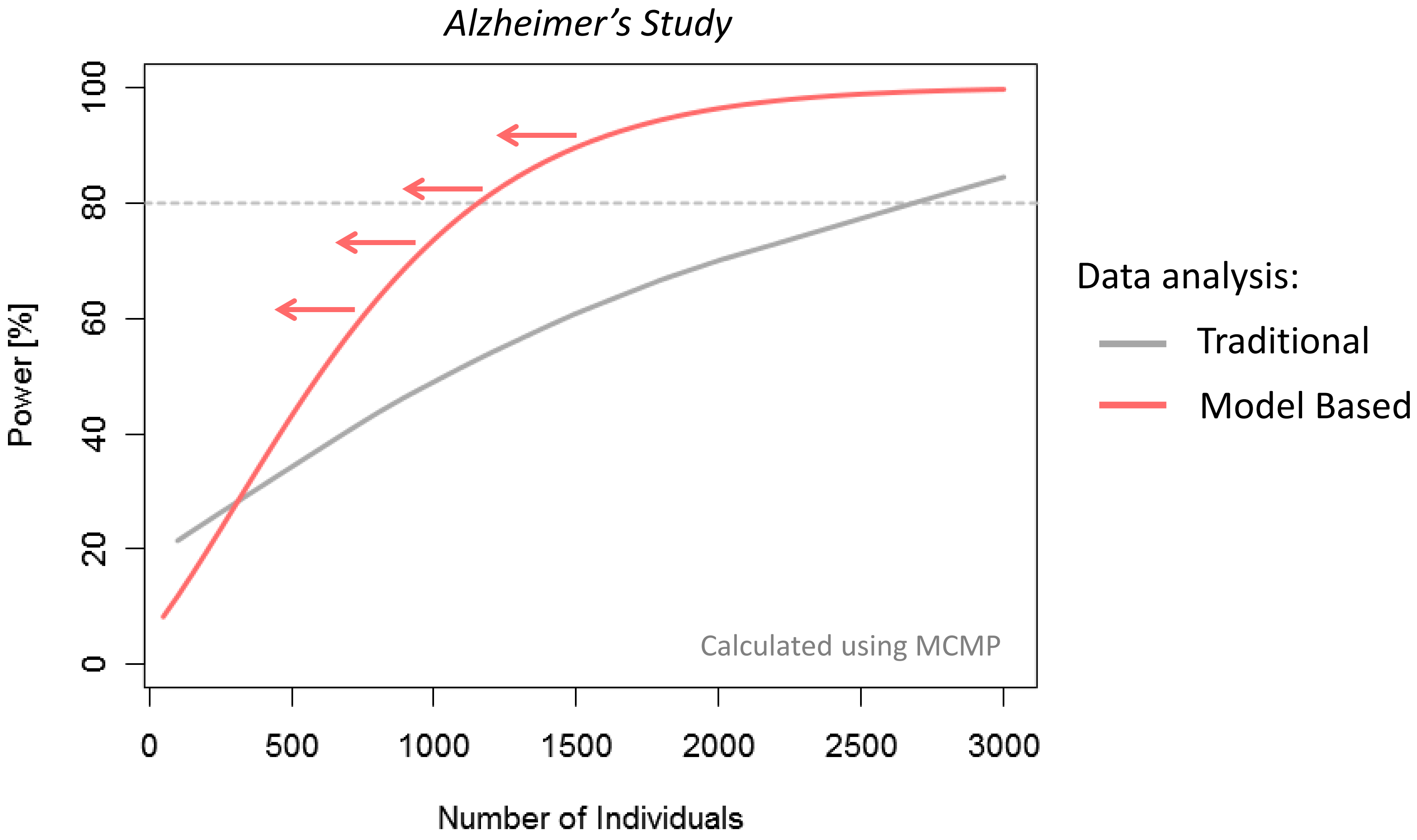
Aim



C. Vong et al., *PAGE 19 2010,* Abstr 1863

K. E. Karlsson, *Doctoral Thesis Uppsala University 2010*

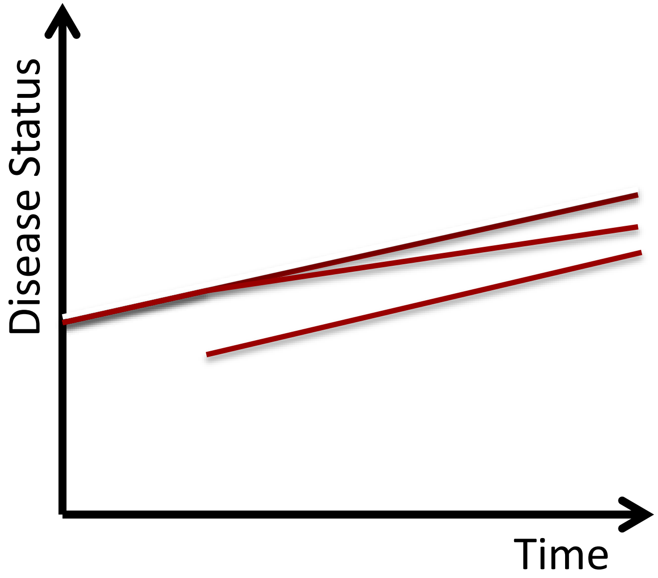
Steps

1. Find a statistic t
   - Predicts power accurately
   - Fast to calculate
2. Optimize on t
   - Find design variables that maximize t

STEP I: THE RIGHT STATISTIC

Illustrating Example

- Disease Progression Trial
    - Duration: 12 month
    - Monthly observations
    - One group
    - Start of treatment after 3 month
- Linear disease progression model
    - Symptomatic
    - Disease modifying

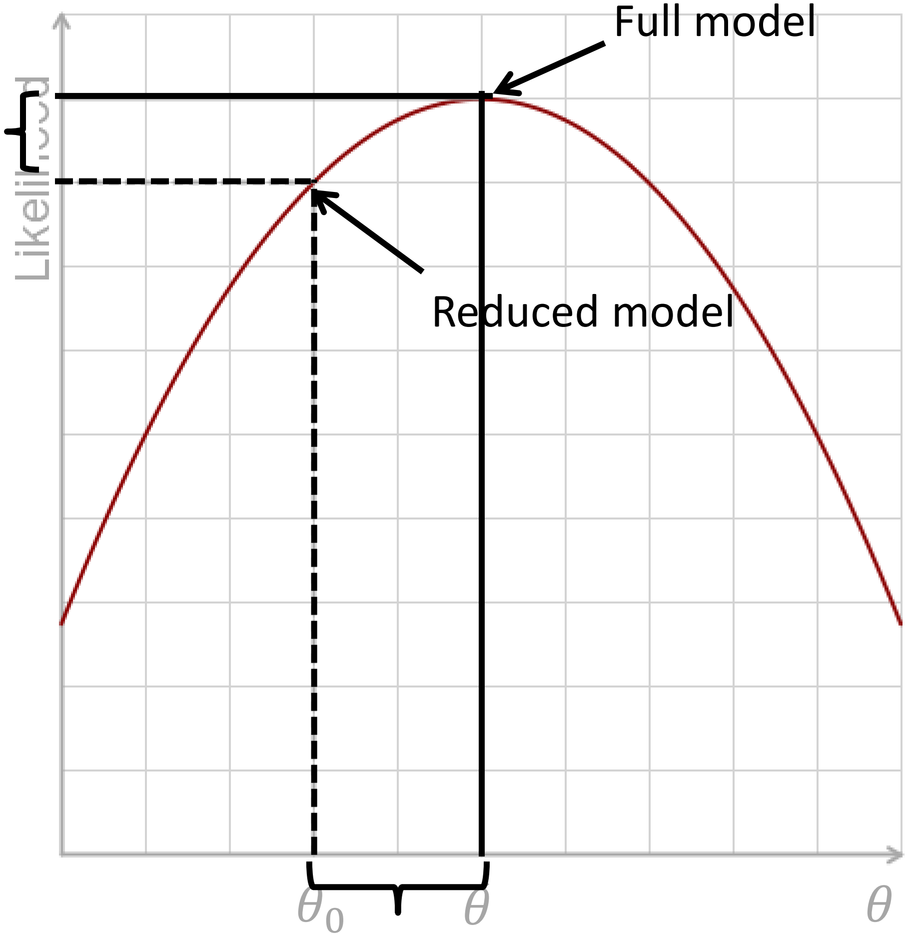


NH intercept	100	IIV	30%
NH slope	2 month^{-1}	Add RUV	10
Sympt. effect	- 10 %	Prop RUV	0.05
DM effect	- 90 %		

S. Hennig et al., *Journal of Clinical Pharmacology 49*, no. 3 (March 2009): 323-335.

Different Perspectives

$$\Delta = \log L(y, \hat{\theta}) - \log L(y, \theta^0)$$



$$\text{W} = \frac{(\hat{\theta} - \theta^0)^2}{Var(\hat{\theta})}$$

LRT vs. Wald-test

$$\Delta = \log L(y, \hat{\theta}) - \log L(y, \theta^0)$$

Observed Data

$$W = \frac{(\hat{\theta} - \theta^0)^2}{Var(\hat{\theta})}$$

Expected Effect

FIM

- Asymptotically equivalent
- χ^2 distributed

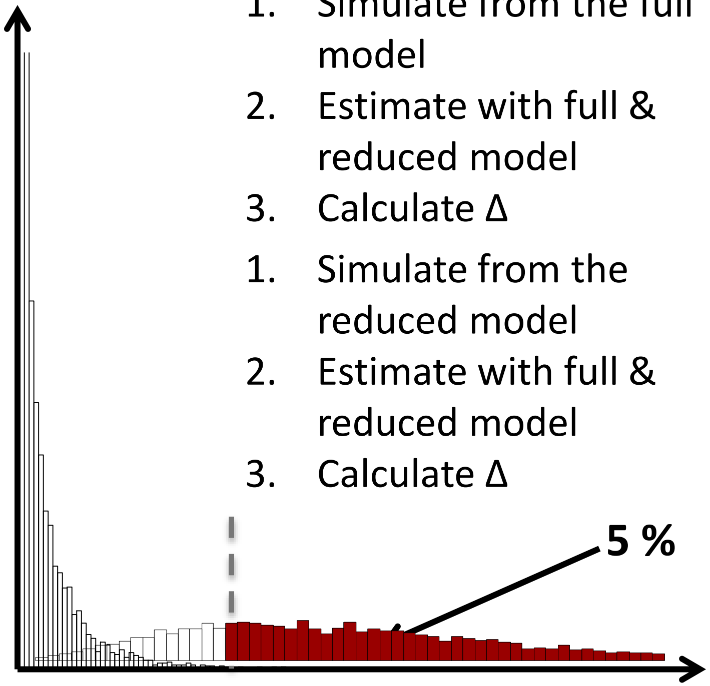
1. Simulate from the full model
2. Estimate with full & reduced model
3. Calculate Δ

10,000

1. Simulate from the reduced model
2. Estimate with full & reduced model
3. Calculate Δ

1,000

$$\pi = 1 - \int_{-\infty}^{\chi^2_{k,1-\alpha}} f(t, k, W)\,dt$$



K. Ogungbenro and L. Aarons, JPKPD 37, no. 1 (February 2010): 67-83.

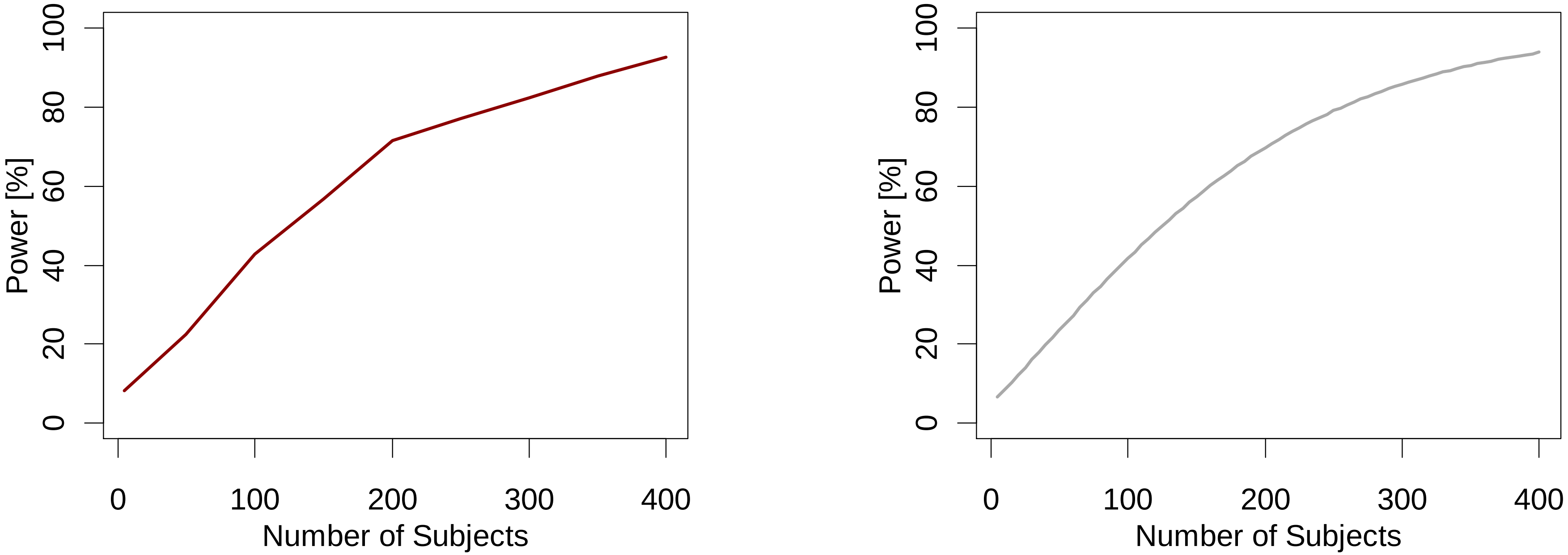
S. Retout et al., *Statistics in Medicine* 26, no. 28 (December 10, 2007): 5162-5179.

LRT vs. Wald-test

$$\Delta = \log L(y, \hat{\theta}) - \log L(y, \theta^0)$$

$$W = \frac{(\hat{\theta} - \theta^0)^2}{Var(\hat{\theta})}$$

Symptomatic Drug Effect



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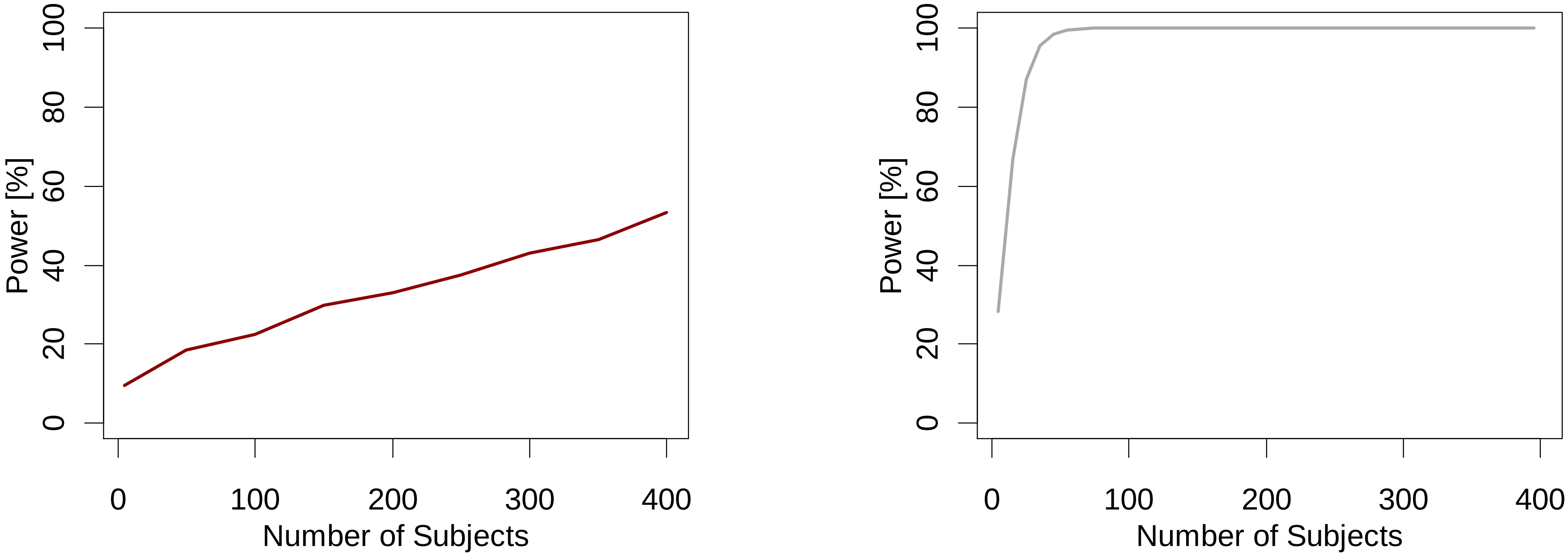
LRT vs. Wald-test

$$\Delta = \log L(y, \hat{\theta}) - \log L(y, \theta^0)$$

$$\mathrm{W} = \frac{(\hat{\theta} - \theta^0)^2}{Var(\hat{\theta})}$$

Disease Modifying Drug Effect



A Modified Wald Statistic

$$\mathrm{W} = \left(H\hat{\theta} - \theta^0\right)^T \left(HI\left(\hat{\theta}\right)^{-1}H\right)^{-1} \left(H\hat{\theta} - \theta^0\right)$$

- Full & reduced model are equivalent if $W = 0$
- $W = 0$ if $H\hat{\theta} = \theta^0$

⇨ Not all parameters are considered

⇨ To high power predicted

$W = 0$ if $E_\theta[y_i] = E_{\theta^0}[y_i]$

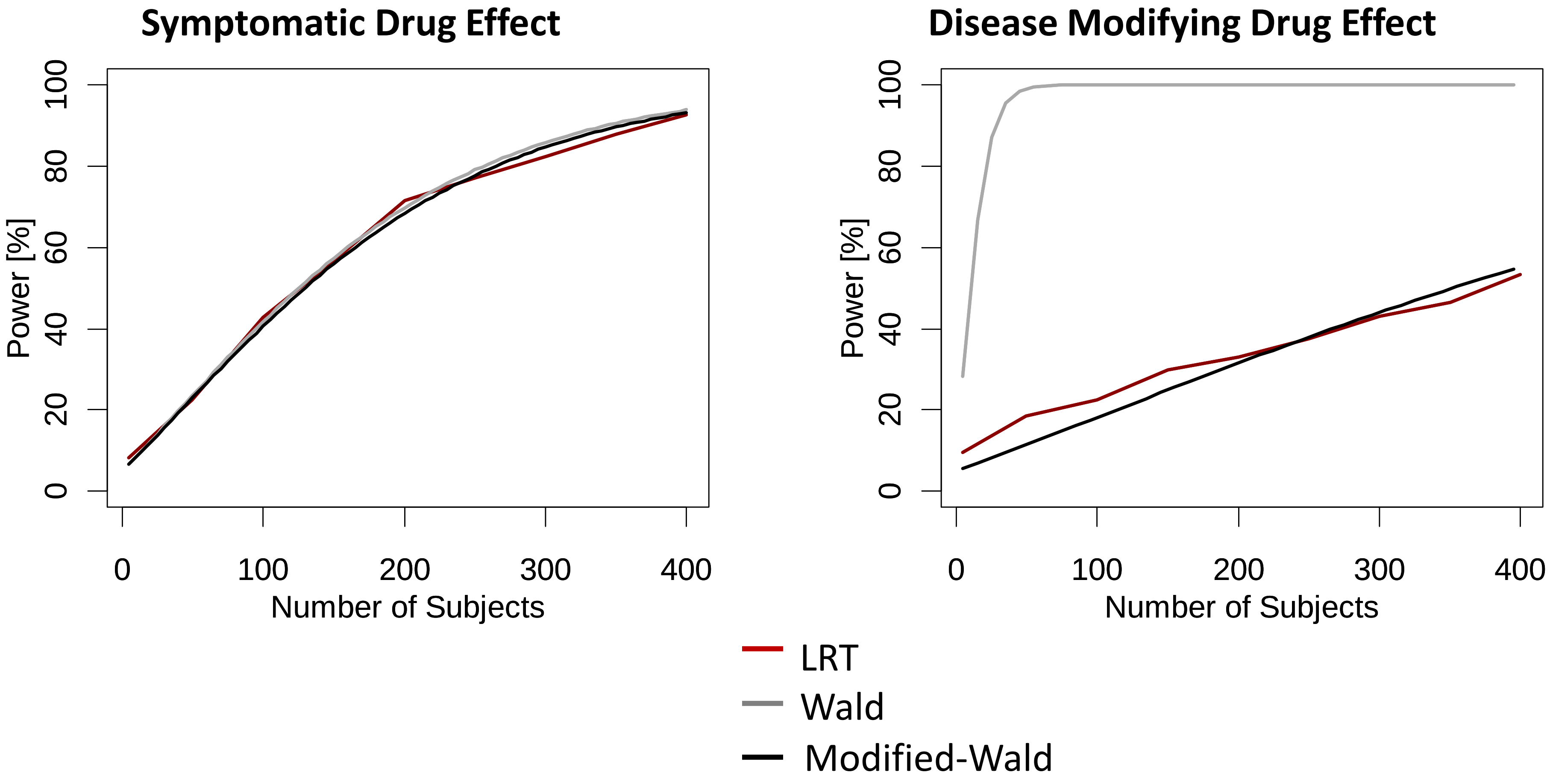
$$\Psi(\theta) = Eff(t, \theta, a) - Eff(t, \theta^0, a)$$

$$\mathrm{W_M} = \Psi(\theta)^T \left(\frac{\partial\Psi}{\partial\theta} I\left(\hat{\theta}\right)^{-1} \frac{\partial\Psi^{\mathrm{T}}}{\partial\theta}\right)^{-1} \Psi(\theta)$$

$$\mathrm{W_M} = \Psi(\theta)^T \left(\frac{\partial\Psi}{\partial\theta} I\left(\hat{\theta}\right)^{-1} \frac{\partial\Psi^{\mathrm{T}}}{\partial\theta}\right)^{+} \Psi(\theta)$$

M. G Dagenais and J. M Dufour, *Econometrica* 59, no. 6 (1991): 1601–1615.

LR vs. Wald vs. Modified-Wald



STEP II: OPTIMIZING ON POWER

Optimization on Power

- Direct optimization of

$$\mathrm{W_M} = \Psi(\theta)^T \left(\frac{\partial\Psi}{\partial\theta} I\left(\hat{\theta}\right)^{-1} \frac{\partial\Psi^{\mathrm{T}}}{\partial\theta}\right)^{+} \Psi(\theta) \qquad \pi = 1 - \int_{-\infty}^{\chi^2_{k,1-\alpha}} f(t, k, \mathrm{W}_M)dt$$

with respect to:

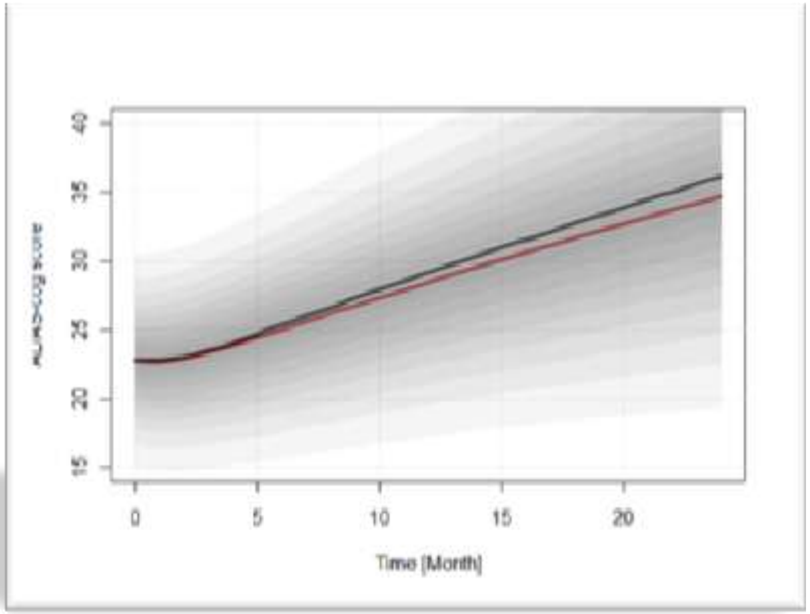
  - Sample size
  - Group assignment
  - Sampling schedule
  - Dosing schedule
  - Covariates
  - …

Application – Alzheimer's Disease

Alzheimer's & Dementia

ELSEVIER

Disease progression meta-analysis model in Alzheimer's disease



Alzheimer's & Dementia

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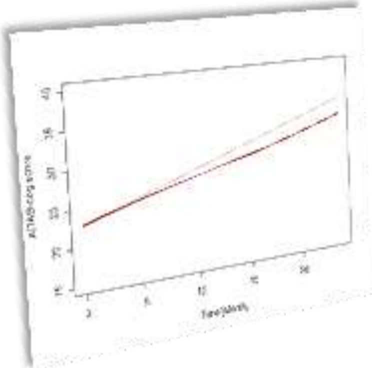
Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database



Hooker et. al, *ACOP 2011* (www.go-acop.org/2011/schedule)

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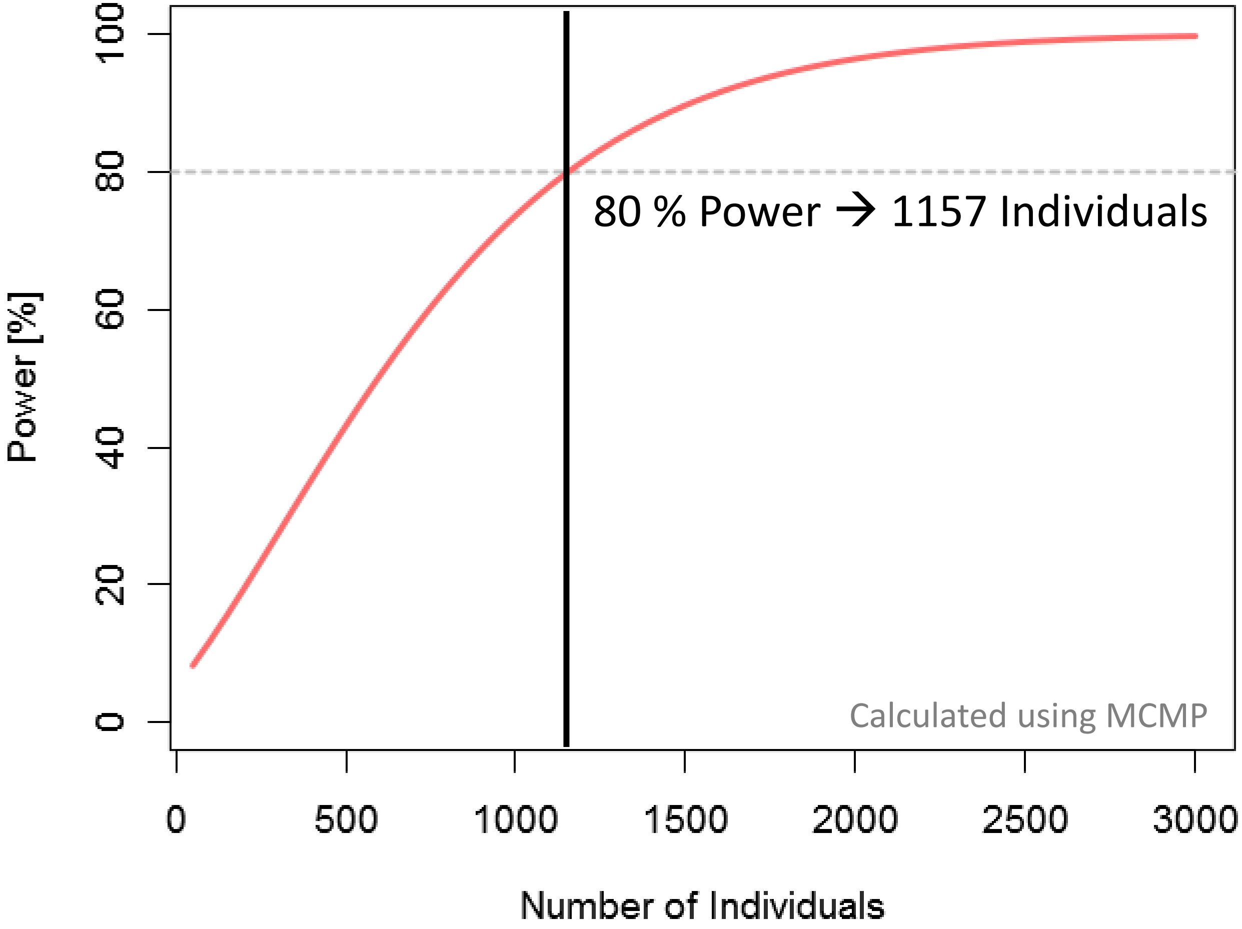
Sample Size Calculation



80 % Power → 1157 Individuals

Calculated using MCMP

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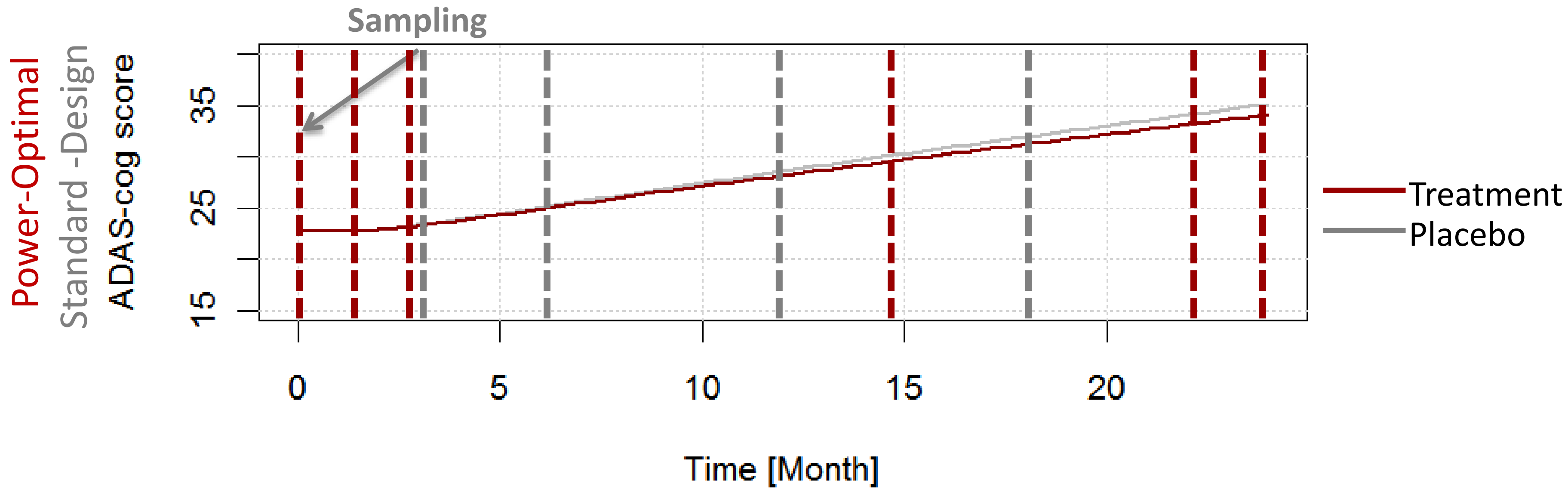
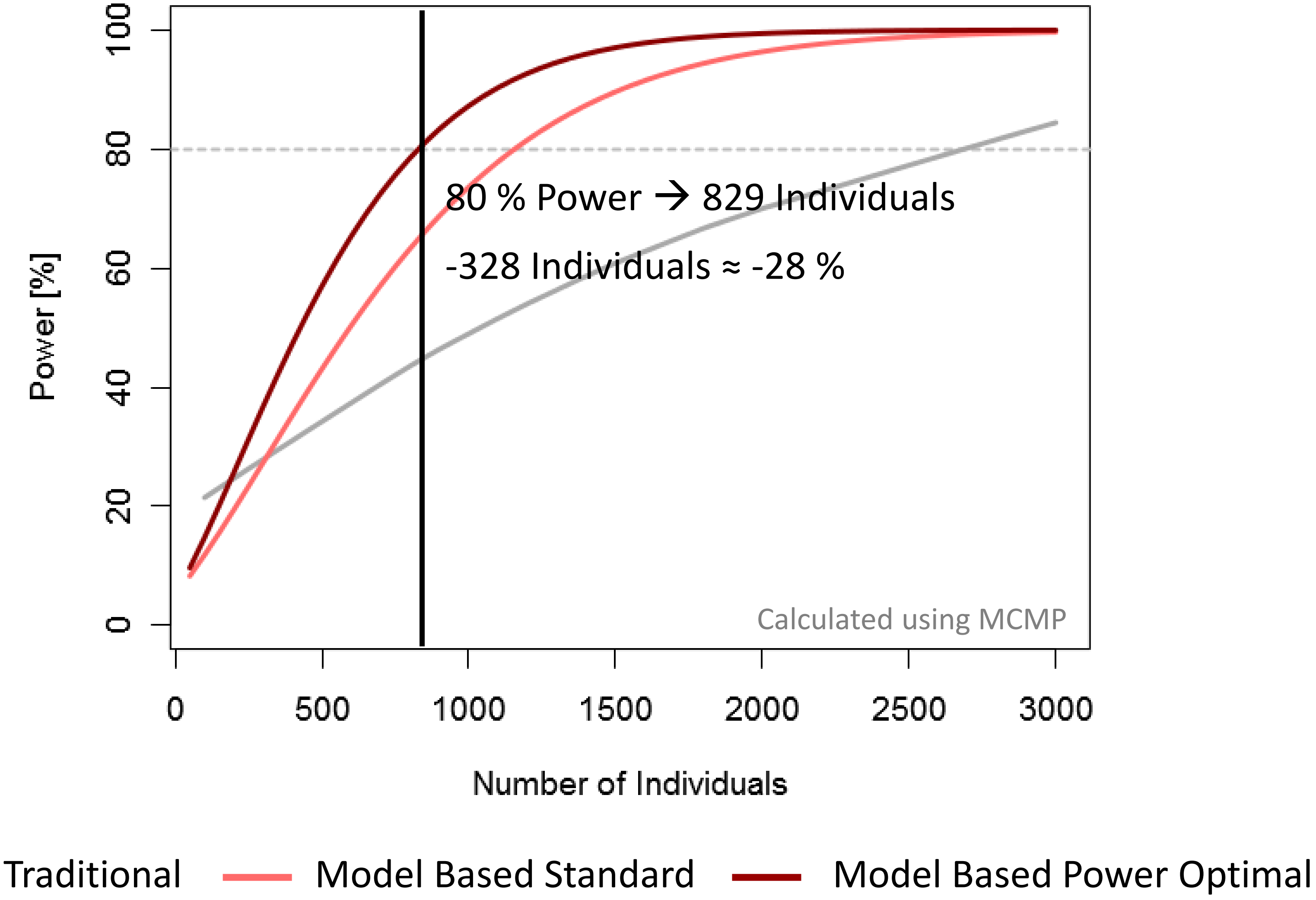
Power Optimization – Sampling



Power Optimization – Sampling



80 % Power → 829 Individuals

-328 Individuals ≈ -28 %

Calculated using MCMP

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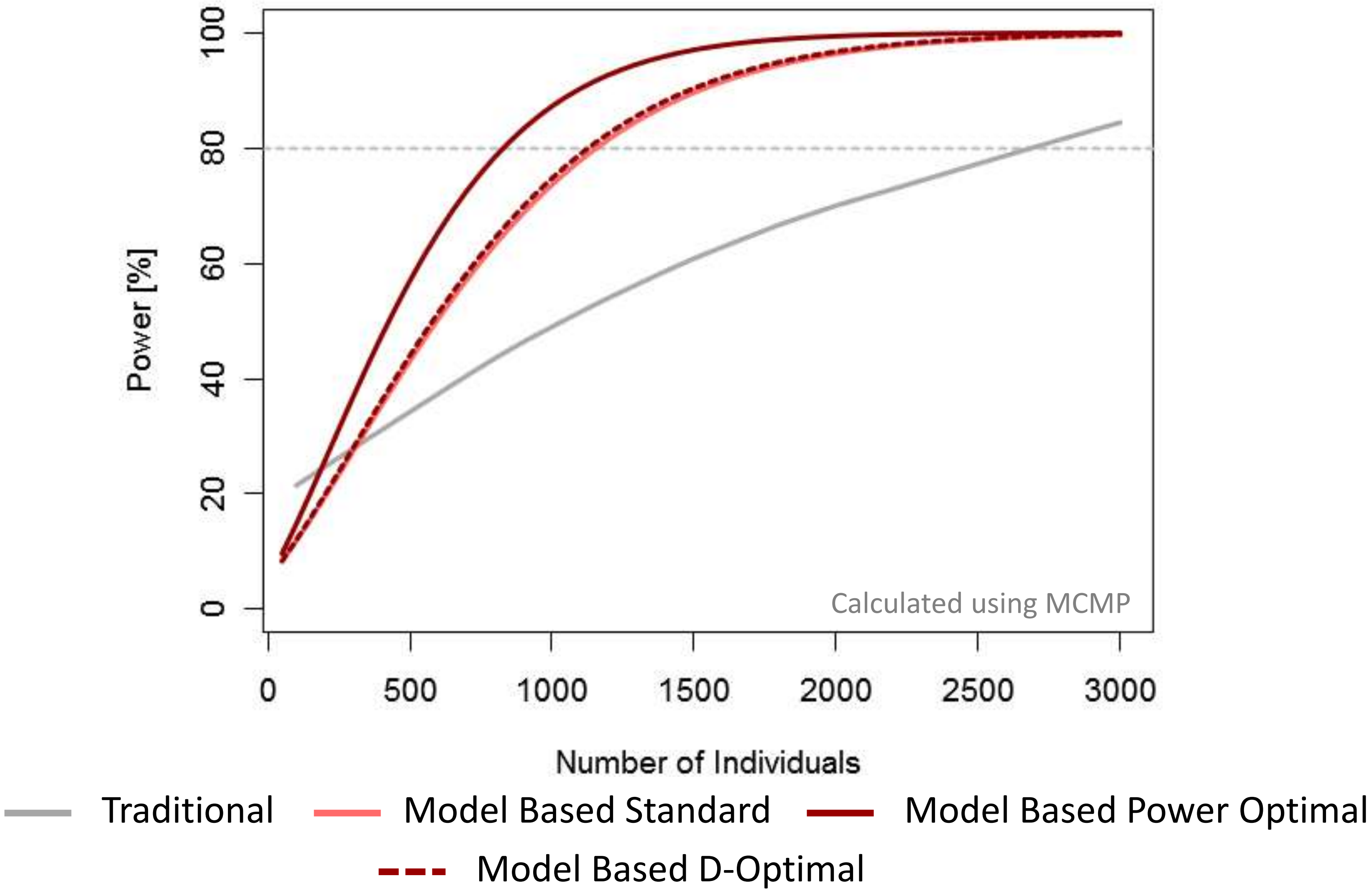
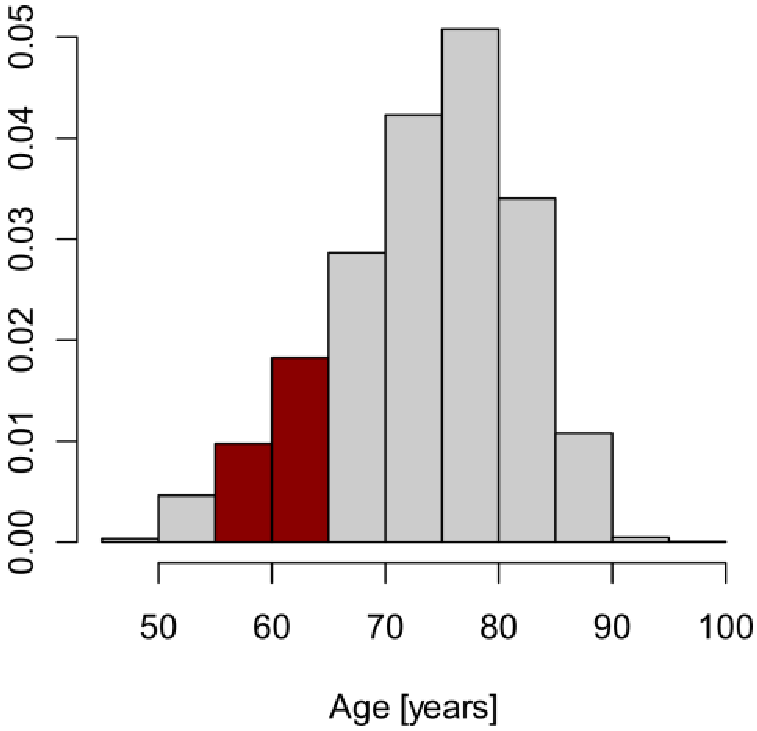
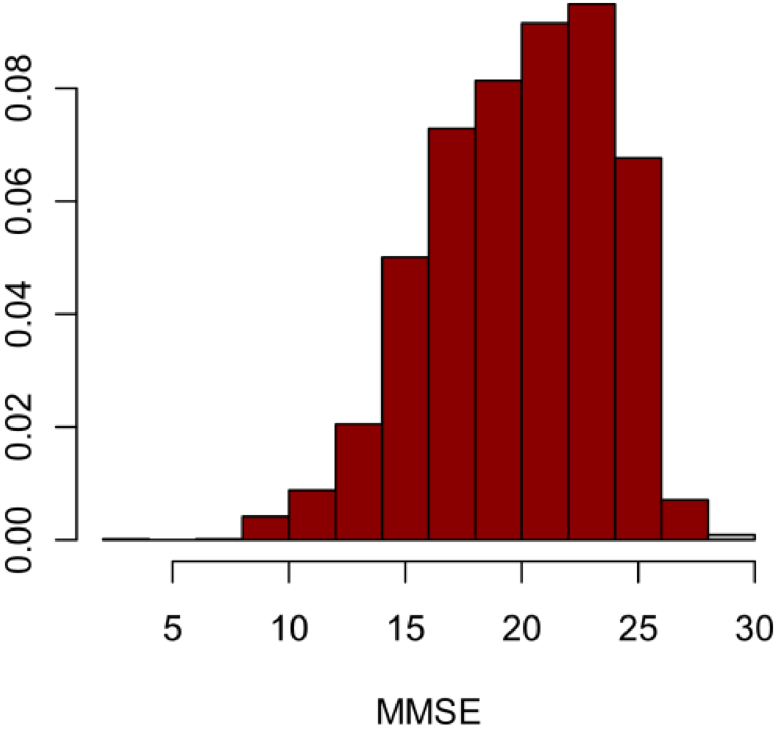
Power Optimization – Sampling



Calculated using MCMP

Power Optimization – Covariates





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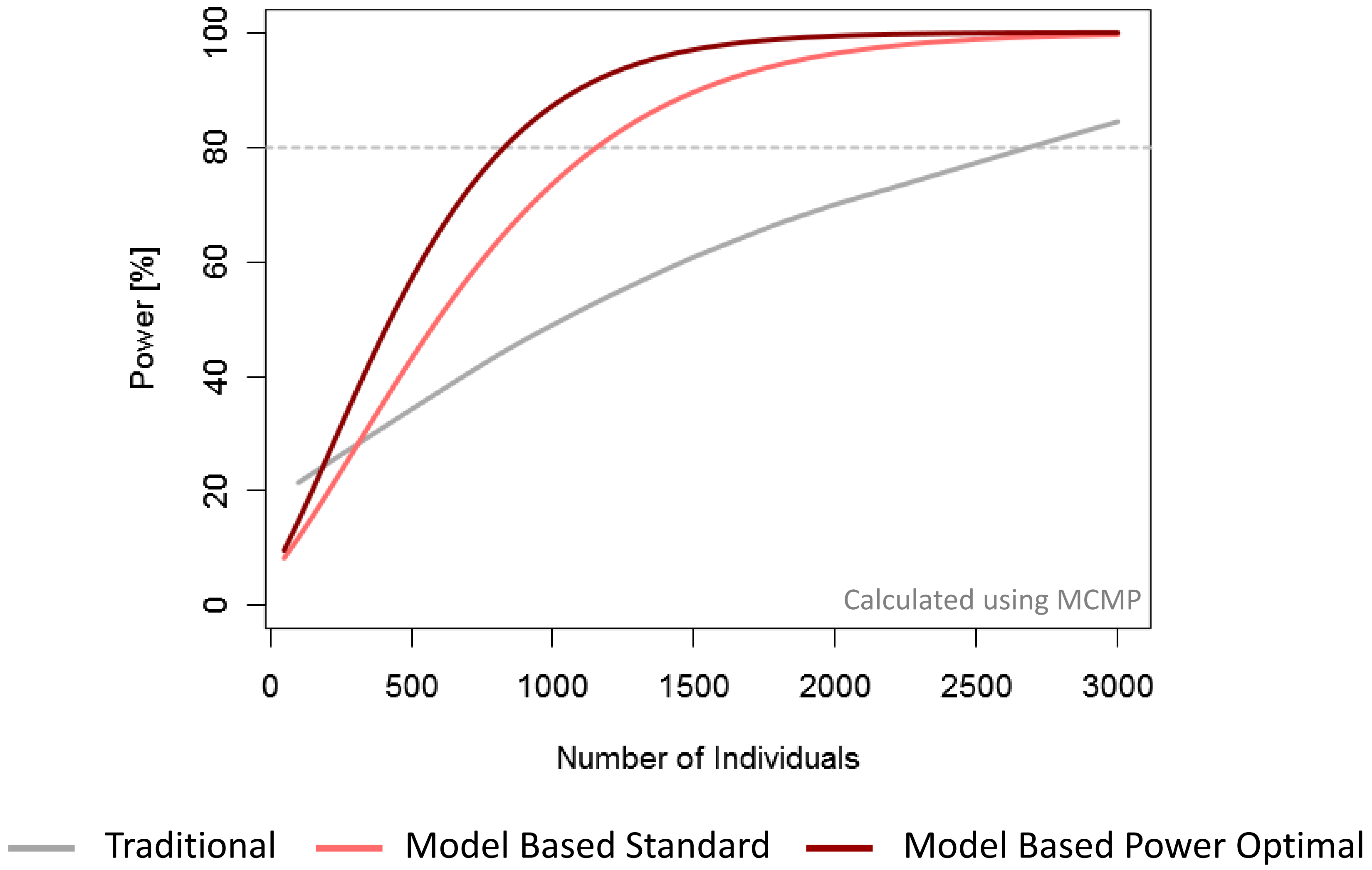
Power Optimization – Covariates



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Conclusions

- Suggested novel approach to optimize study design for statistical power
    - Better agreement with LRT than classical Wald test
    - Potential to significantly improve power

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THANK YOU!