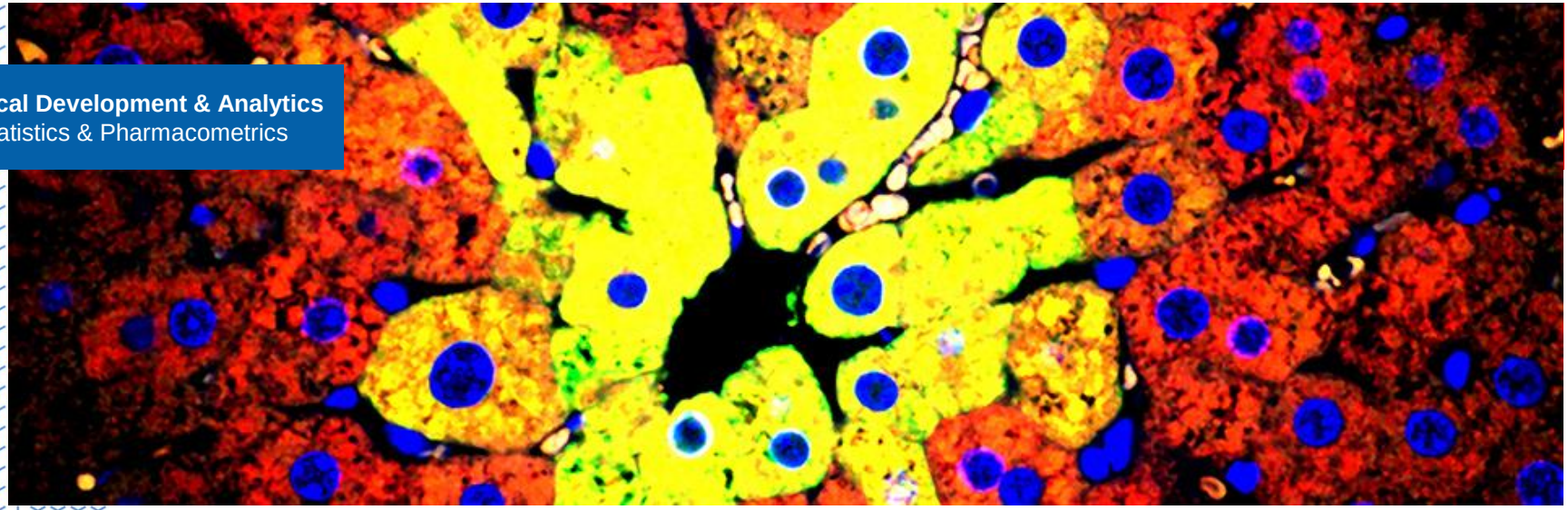
Clinical Development & Analytics
Biostatistics & Pharmacometrics



When is a longitudinal test better than a cross-sectional one?

Björn Bornkamp, joint work with Ines Paule
PSI webinar
November 18, 2019

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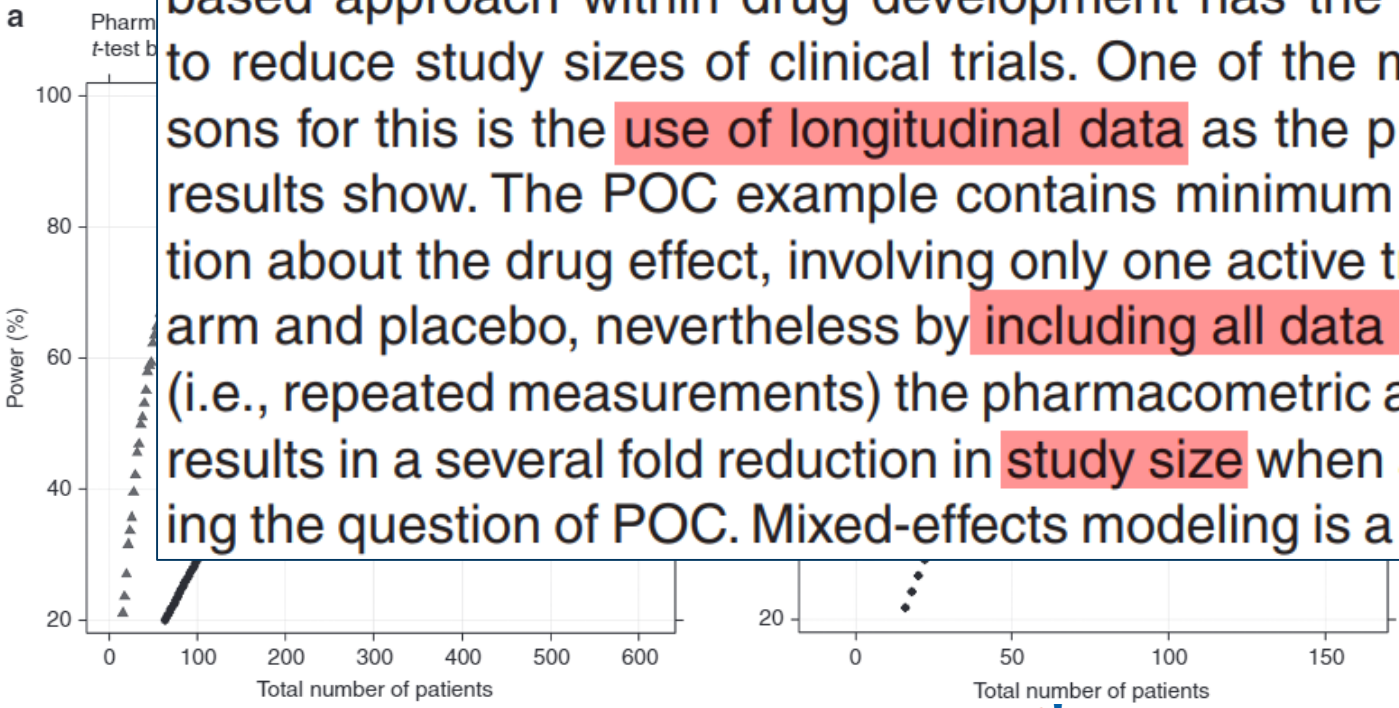
compare a pharmacometric model–based analysis to a *t*-test with respect to study power of proof-of-concept (POC) trials. In all investigated examples and scenarios, the conventional statistical analysis resulted in several fold larger study sizes to achieve 80% p … etween the conve … . Although

As these results show, the use of a pharmacometric model–based approach within drug development has the potential to reduce study sizes of clinical trials. One of the main reasons for this is the use of longitudinal data as the pure POC results show. The POC example contains minimum information about the drug effect, involving only one active treatment arm and placebo, nevertheless by including all data available (i.e., repeated measurements) the pharmacometric approach results in a several fold reduction in study size when addressing the question of POC. Mixed-effects modeling is a powerful



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Results

II. Weak drug effect & N=50

Type I error & Power

Simulation model

Test

		Linear	Log-linear	Emax	Sigmoid	No-DE
		Power (%)				Type-I error [3.2-7%]
LRT	Linear	75.8	72.4	79.6	89.4	4.8
	Log-linear	62.0	83.0	84.8	91.8	4.0
	Emax	65.2	81.6	84.4	91.2	5.6
	Sigmoid	67.8	40.4	47.2	57.2	3.8
	MS	79.0	86.6	89.6	93.6	7.6
cLRT		71.2	81.2	83.8	90.6	5.6
MCP		14.2	11.2	12.4	16.4	3.0

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Our aim today

- Investigate which factors determine potential gains in efficiency with a longitudinal approach (vs cross-sectional) for signal detection/testing
- Approach
  - Scope of a two-arm PoC trial (treatment effect detection)
  - Use simple statistical method of using longitudinal measurements for testing
    - Allows for analytical approximations and fast exploration of factors
  - Assessment on theoretical and real case examples

Agenda

- Statistical methodology
- Case examples
- Exploring factors
- Comparison to parametric mixed effect model
- Conclusions

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Statistical Model

Data

Y_{ijt}: $i = 0{,}1$ (control vs treatment); $j = 1, \ldots, n_i$ (patient); $t = 1, \ldots, T$ (visit)

Distributional assumption (per patient)

$$(Y_{ij1}, \ldots, Y_{ijT}) \sim MVN(\mu_i, \Sigma_i)$$

Notation

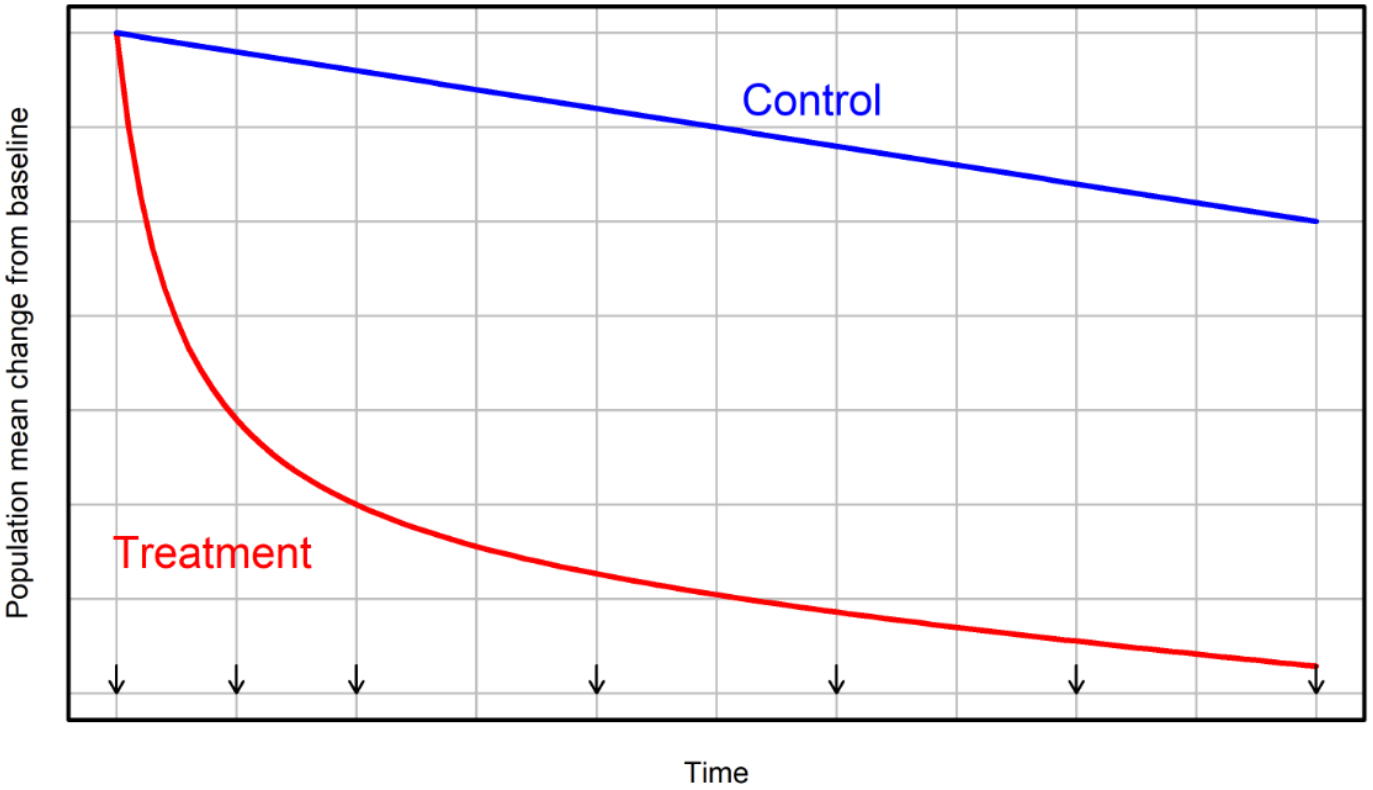
μ_i - population mean vector per treatment group

Σ_i - Covariance matrix for treatment i (individual random effects and residual error)

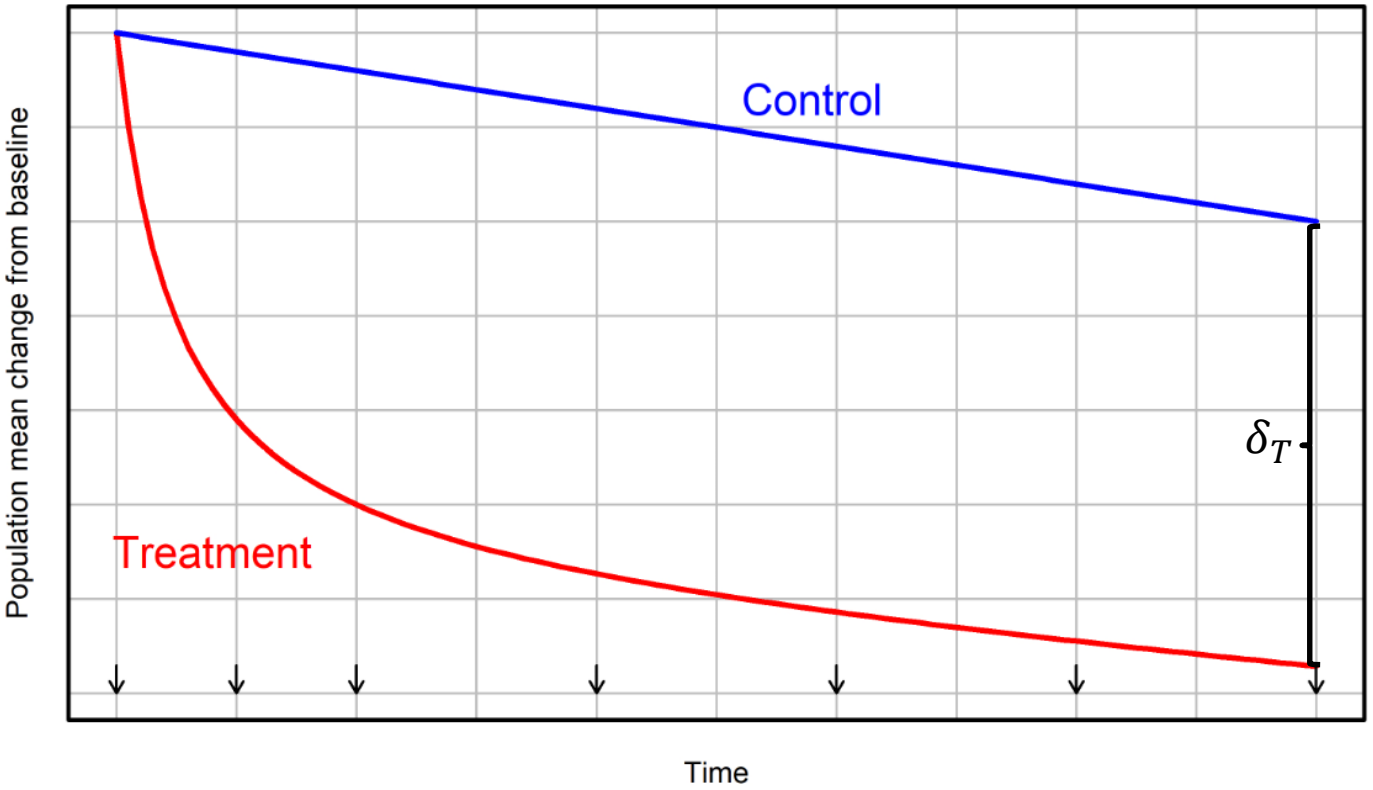
Note:

- Standard „MMRM“ model (can also include covariates)

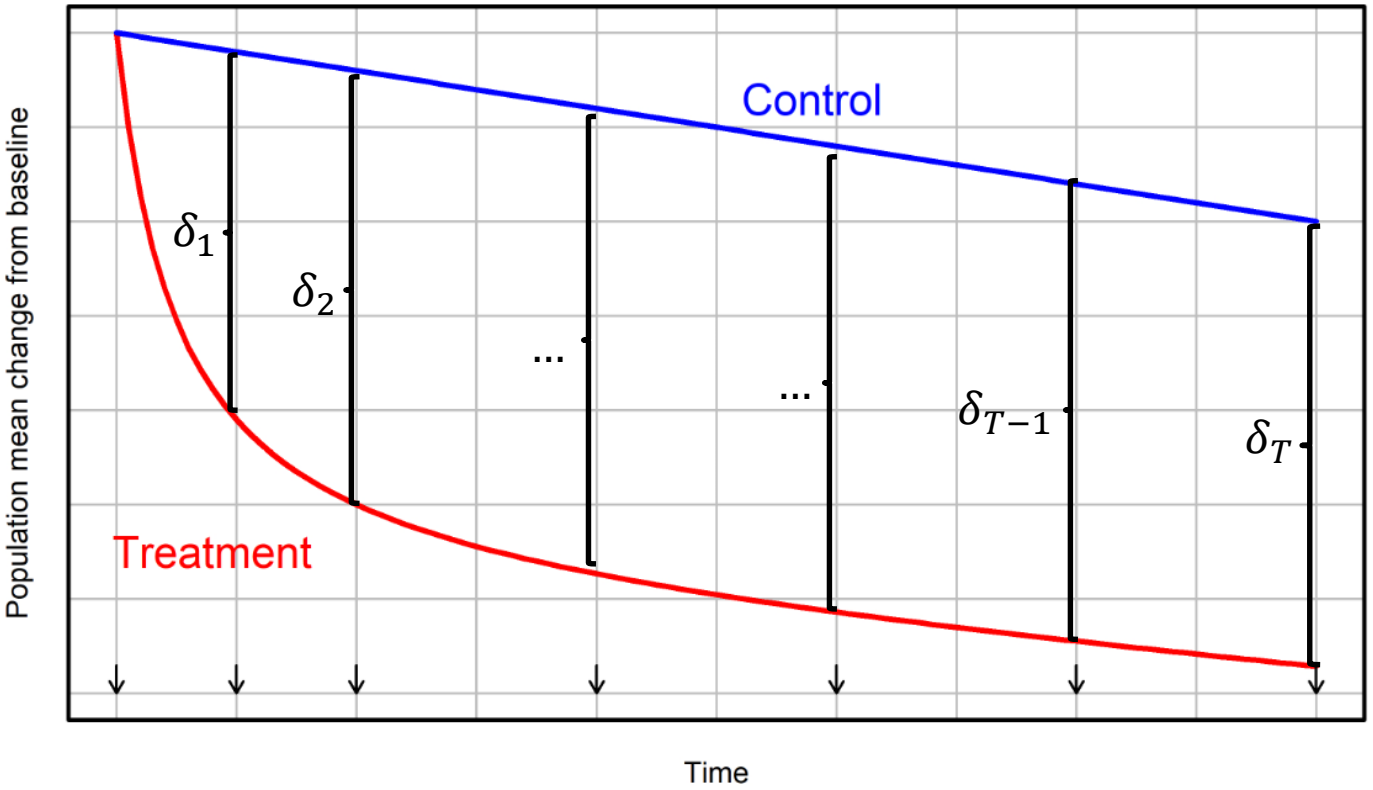
Average control & treatment response



Instead of testing only at time T…



...use weighted average of time-points



Test statistic (weighted treatment differences over time)

$$Z = \frac{\boldsymbol{w}'\widehat{\boldsymbol{\delta}}}{\sqrt{\boldsymbol{w}'\left(\frac{\widehat{\boldsymbol{\Sigma}_1}}{n_1} + \frac{\widehat{\boldsymbol{\Sigma}_0}}{n_0}\right)\boldsymbol{w}}}$$

Notation

$\overline{Y_{i.t}}$ - mean per time-point and study arm

$\hat{\delta}_t = \overline{Y_{1.t}} - \overline{Y_{0.t}}$ treatment effect over time, $\widehat{\boldsymbol{\delta}} = (\hat{\delta}_1, \ldots, \hat{\delta}_T)'$

$\boldsymbol{w}$: weight vector for time-points.

Notes: Z is asymptotically normally distributed

- $\boldsymbol{w} = (0, 0, \ldots, 0, 1)'$ corresponds to cross-sectional test at the last time-point
- Scaling of $\boldsymbol{w}$ is irrelevant (scalars cancel out in Z)

Optimal weights

- Frison & Pocock (1997) showed how to determine optimal weights
- Assume we know $\boldsymbol{\delta}, \boldsymbol{\Sigma}_1, \boldsymbol{\Sigma}_0$. Non-centrality parameter of Z is $\frac{\boldsymbol{w}'\boldsymbol{\delta}}{\sqrt{\boldsymbol{w}'\left(\frac{\boldsymbol{\Sigma}_1}{n_1}+\frac{\boldsymbol{\Sigma}_0}{n_0}\right)\boldsymbol{w}}}$
- Optimal weights (maximizing the non-centrality parameter) are proportional to

$$\boldsymbol{w}_{opt} \propto \boldsymbol{\delta}'\boldsymbol{S}^{-1} \text{ where } \boldsymbol{S} = \frac{\boldsymbol{\Sigma}_1}{n_1} + \frac{\boldsymbol{\Sigma}_0}{n_0}$$

- Weights might get negative (hard to interpret).
  - We will use constrained numerical optimization subject to $w_i \geq 0 \ \forall \ i$ & normalize weights to sum to 1 (just for convenience)

Factors influencing optimal weights: $\delta(t)$, SD(t), correlation over time

- Optimal weights will depend on
  (1) $\boldsymbol{\delta}(t)$ (treatment effect over time),
  (2) standard deviation of Y_{ijt} over time (*SD(t)*) and
  (3) within patient correlation over time (→ (2) and (3) determine $\boldsymbol{S}$)
- In practice $\boldsymbol{\delta}$ and $\boldsymbol{S}$ not known
  - Could use a set of candidates and corresponding optimal weight vectors
    → Like MCP-Mod
- We propose here to simply use maximum test over
  $\boldsymbol{w}_1 = (0, 0, \ldots, 0, 1)'$, $\boldsymbol{w}_2 = (0, 0, \ldots, 0, 1/2, 1/2)'$, … , $\boldsymbol{w}_T = (1/T, \ldots, 1/T)'$

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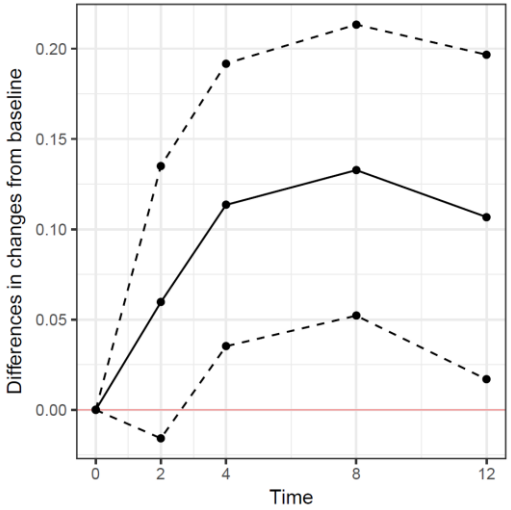
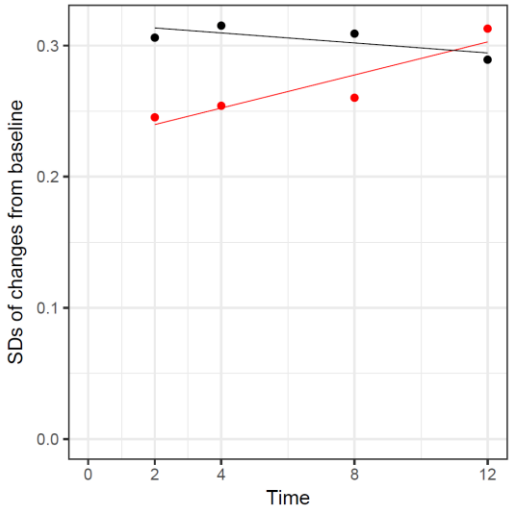
Example 1

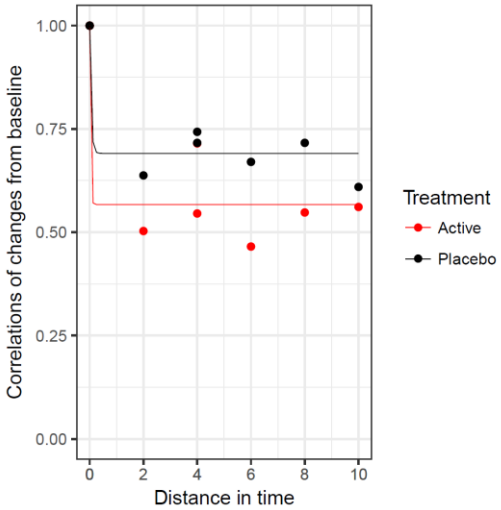
(i) $\delta(t)$



(ii) $SD(t)$

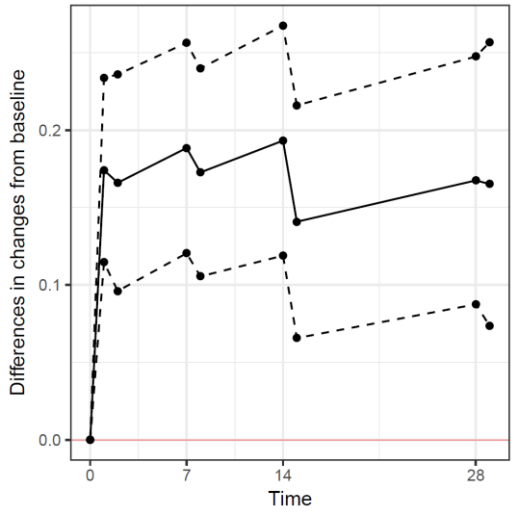


(iii) Correlation

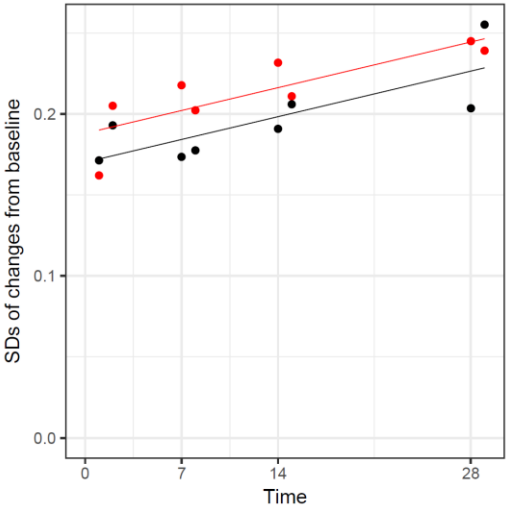


Example 2

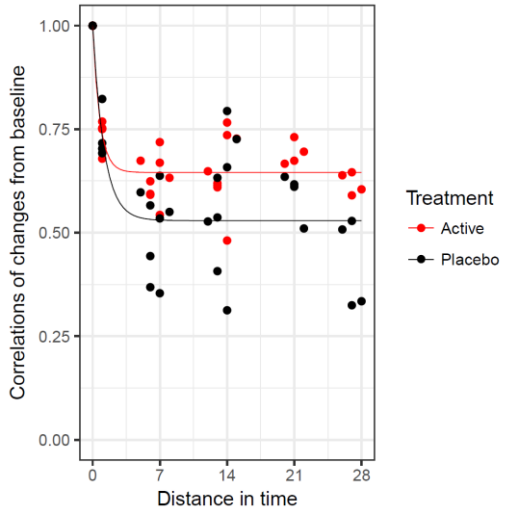
(i) $\delta(t)$



(ii) $SD(t)$

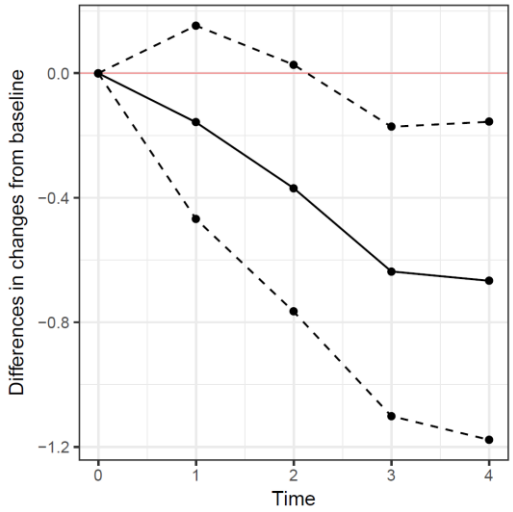


(iii) Correlation

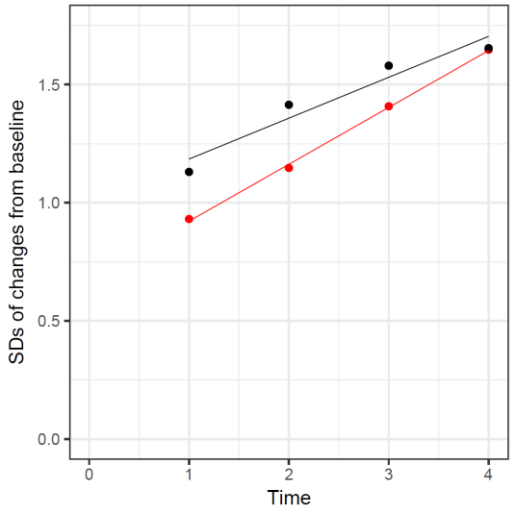


Example 3

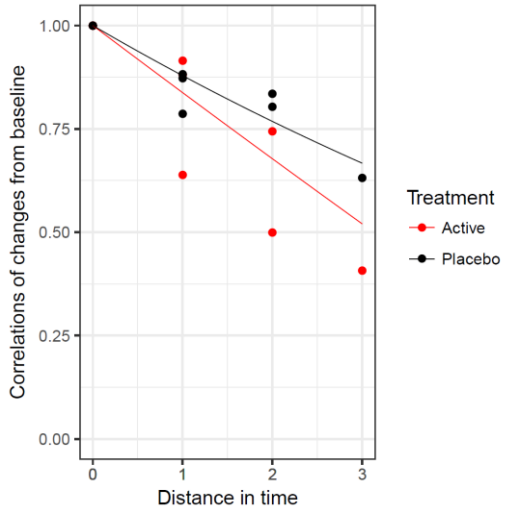
(i) $\delta(t)$



(ii) $SD(t)$

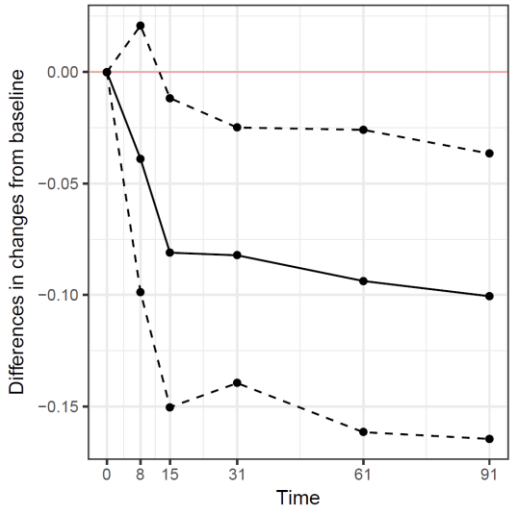


(iii) Correlation

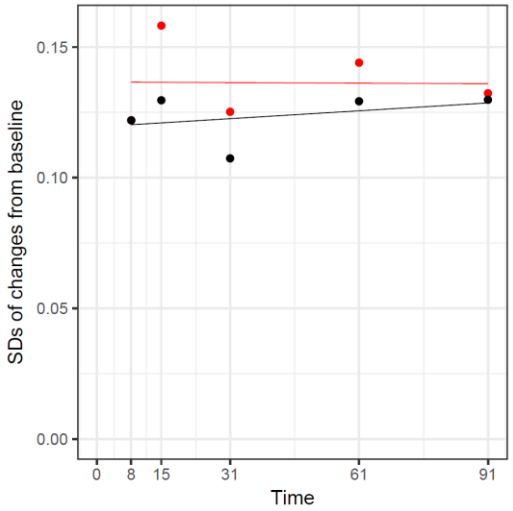


Example 4

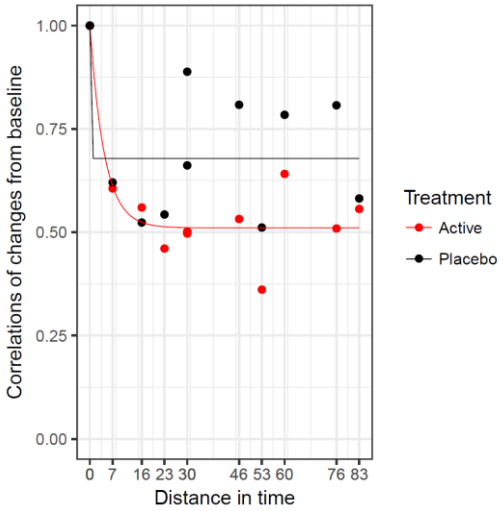
(i) $\delta(t)$



(ii) $SD(t)$

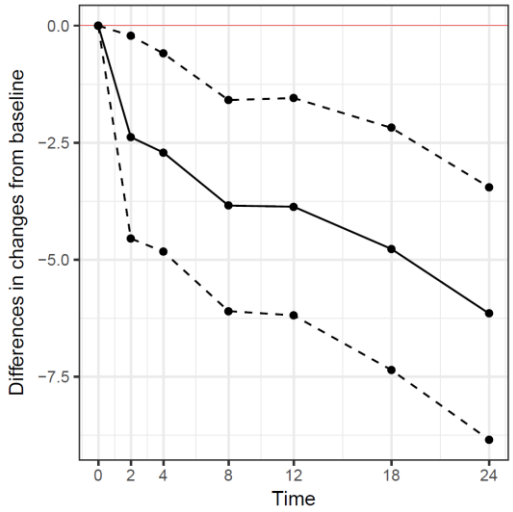


(iii) Correlation

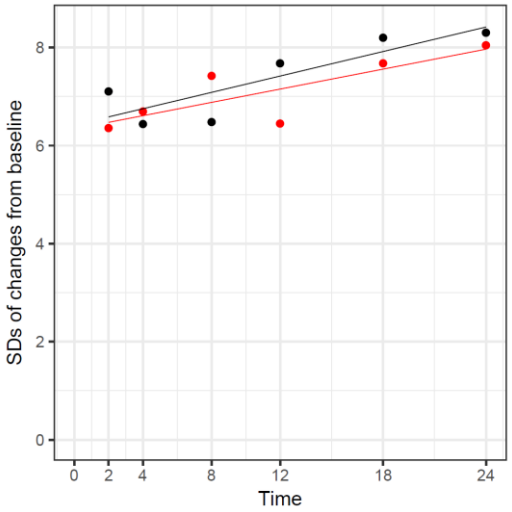


Example 5

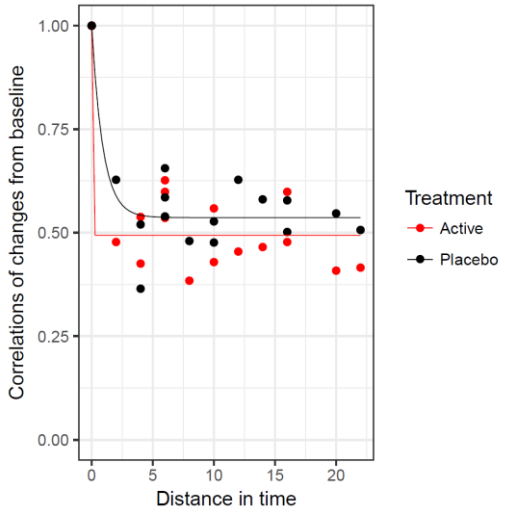
(i) $\delta(t)$



(ii) $SD(t)$

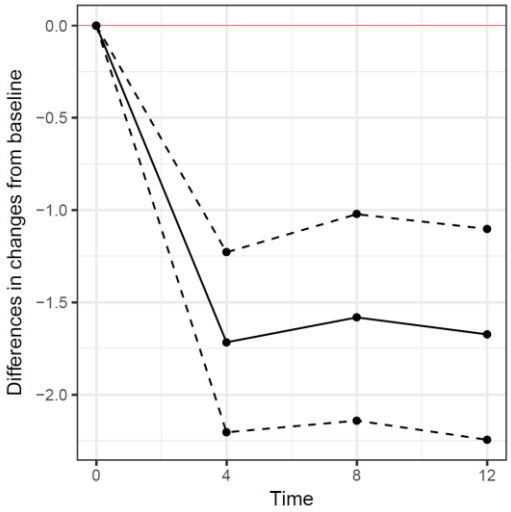


(iii) Correlation

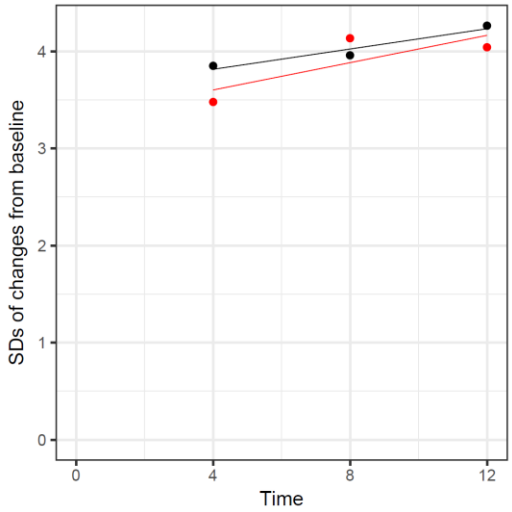


Example 6

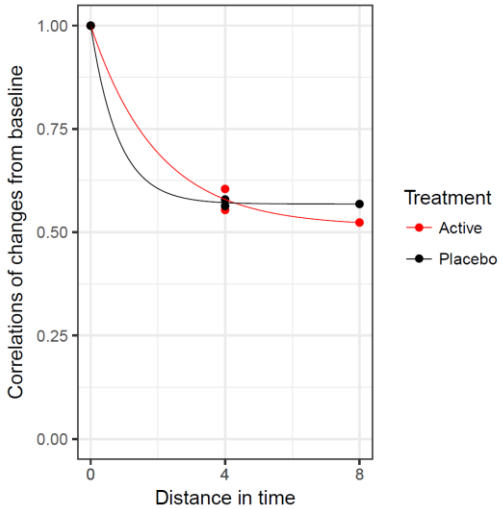
(i) $\delta(t)$



(ii) $SD(t)$



(iii) Correlation



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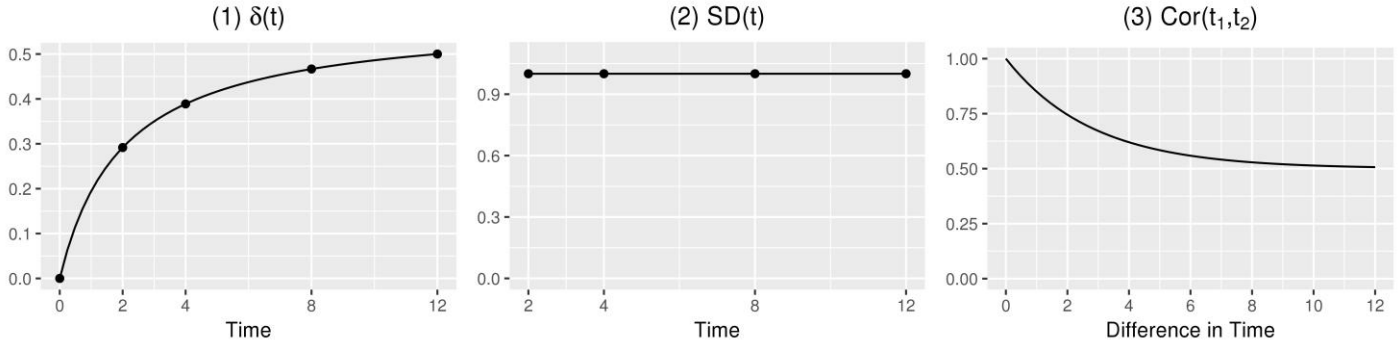
Systematic exploration of factors: Defining scenarios

- For scenarios: parametric specification of $\delta(t)$, $SD(t)$ and correlation
  - Emax model for $\delta(t)$
  - Linear function for $SD(t)$, parametric form for correlation
  - Assume same covariance function for both arms (details in slide notes)
- Analysis model: Multivariate normal (MMRM) model & Z test described earlier
  - Time & treatment categorical variables (with interaction)
  - Analytical formulas available for sample size
- We compare sample size needed for a test
  - 5% one-sided type 1 error, 90% power

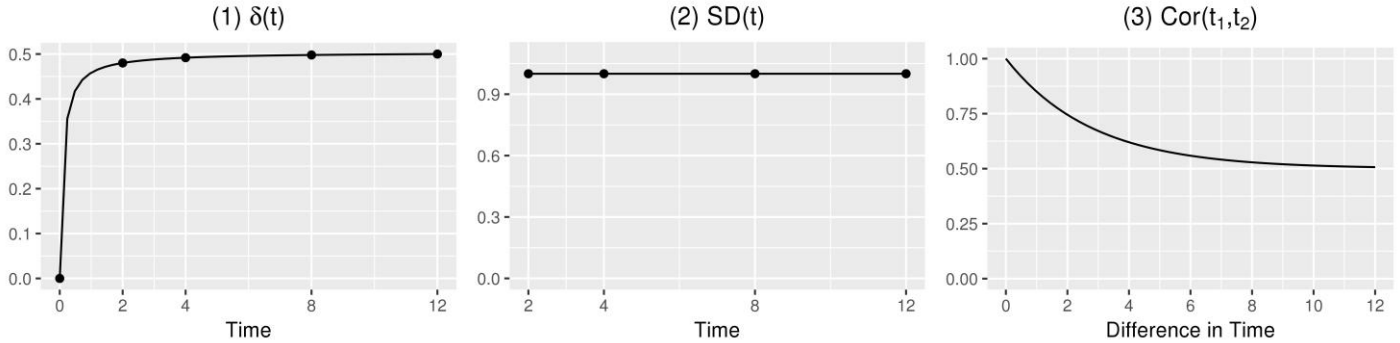
Rather typical scenario (base case)



Test	Weights	(Samp. Size Long.)/ (Samp. Size Cross-Sect.)
last 2 visits	0.00,0.00,0.50,0.50	0.87
last 3 visits	0.00,0.33,0.33,0.33	0.89
all visits	0.25,0.25,0.25,0.25	1.03
max T		0.90
optimal w	0.00,0.14,0.34,0.52	0.85

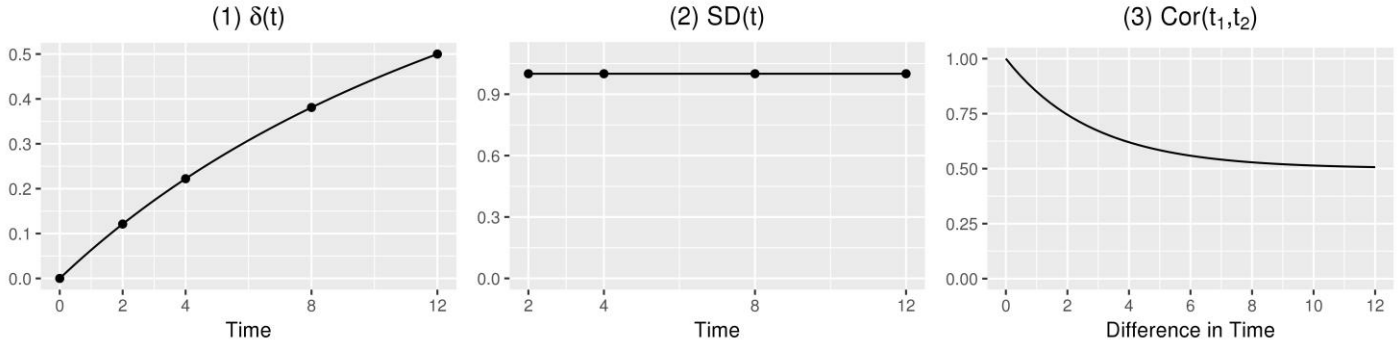
0.87 means longitudinal needs 13% less patients than cross-sectional for the same power

$\delta(t)$: Early onset
→ More benefit for longitudinal



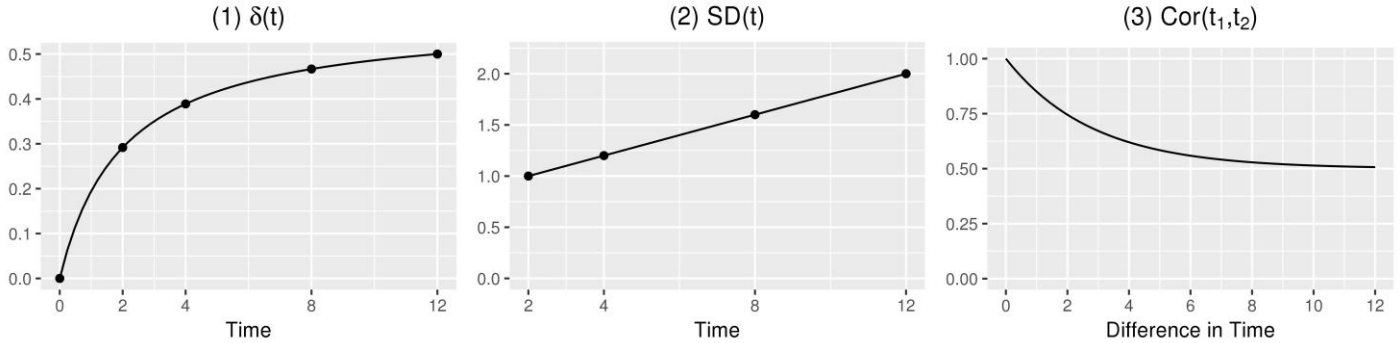
Test	Weights	(Samp. Size Long.)/ (Samp. Size Cross-Sect.)
last 2 visits	0.00,0.00,0.50,0.50	0.81
last 3 visits	0.00,0.33,0.33,0.33	0.74
all visits	0.25,0.25,0.25,0.25	0.72
max T		0.77
optimal w	0.22,0.20,0.25,0.33	0.71

$\delta(t)$: Late onset
→ Less benefit for longitudinal



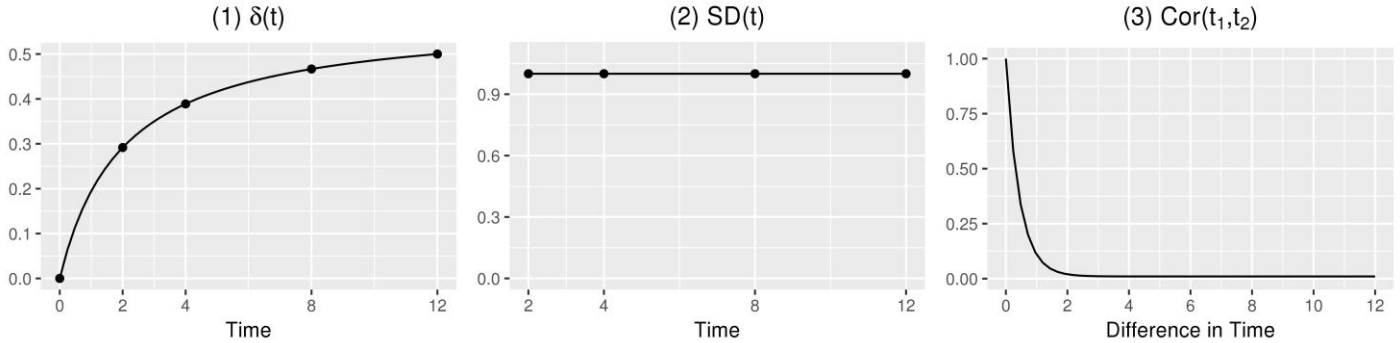
Test	Weights	(Samp. Size Long.)/ (Samp. Size Cross-Sect.)
last 2 visits	0.00,0.00,0.50,0.50	1.04
last 3 visits	0.00,0.33,0.33,0.33	1.34
all visits	0.25,0.25,0.25,0.25	1.86
max T		1.07
optimal w	0.00,0.00,0.21,0.79	0.97

$SD(t)$: Increasing with time
→ Higher gains (than with constant SD). Beneficial to give more weight to earlier points



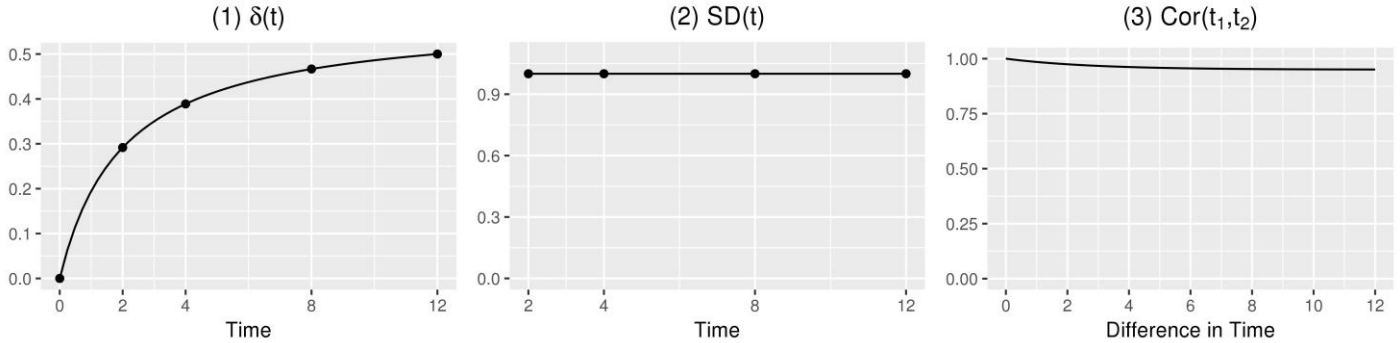
Test	Weights	(Samp. Size Long.)/ (Samp. Size Cross-Sect.)
last 2 visits	0.00,0.00,0.50,0.50	0.70
last 3 visits	0.00,0.33,0.33,0.33	0.57
all visits	0.25,0.25,0.25,0.25	0.54
max T		0.61
optimal w	0.24,0.46,0.22,0.08	0.51

$\mathrm{Cor}(t_1, t_2)$: Low within patient correlation → Better for longitudinal



Test	Weights	(Samp. Size Long.)/ (Samp. Size Cross-Sect.)
last 2 visits	0.00,0.00,0.50,0.50	0.54
last 3 visits	0.00,0.33,0.33,0.33	0.42
all visits	0.25,0.25,0.25,0.25	0.38
max T		0.42
optimal w	0.17,0.23,0.29,0.31	0.37

$\mathrm{Cor}(t_1, t_2)$: High within-patient correlation → Less benefit for longitudinal



Test	Weights	(Samp. Size Long.)/ (Samp. Size Cross-Sect.)
last 2 visits	0.00,0.00,0.50,0.50	1.05
last 3 visits	0.00,0.33,0.33,0.33	1.19
all visits	0.25,0.25,0.25,0.25	1.43
max T		1.05
optimal w	-0.00,0.00,0.00,1.00	1.00

Summary

- If onset of treatment effect early
  → Benefit of longitudinal approach expected to be larger
- If the standard deviation increases over time
  → Longitudinal approach expected to be more beneficial (than with a time-constant SD)

  → More benefit with more weight on earlier time-points
- If within-patient correlation is high (i.e. within-patient variance is low)
  → less benefit from a longitudinal approach

Sample size savings for longitudinal across six case examples

- Ratio of sample sizes compared to cross-sectional analysis
  - Assuming observed $\delta(t)$, SD(t) and correlations are „true“

Approach	Mean (Min, Max)
Optimal Test	0.68 (0.29, 0.99)
Maximum Test	0.83 (0.59,1.03)

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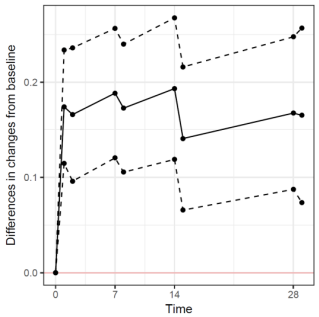
Comparison to parametric mixed effect model

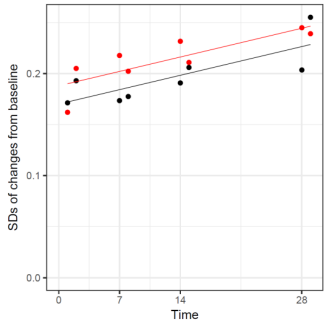
- For two of examples presented
  - Fit adequate parametric mixed effect model to data, using parametric model over time (details in appendix)
  - Simulate new trials (same design) from fitted mixed effect model
  - Compare
    1) Test based on treatment effect parameter in mixed effect model
    2) Cross-sectional analysis on last time-point
    3) max T test based on different weighted averages
       $\boldsymbol{w}_1 = (0, 0, \ldots, 0, 1)'$, $\boldsymbol{w}_2 = (0, 0, \ldots, 1/2, 1/2)'$, …, $\boldsymbol{w}_T = (1/T,\ \ldots, 1/T)'$
    4) Test based on optimal weights (optimized on true scenario)

Comparison example 1

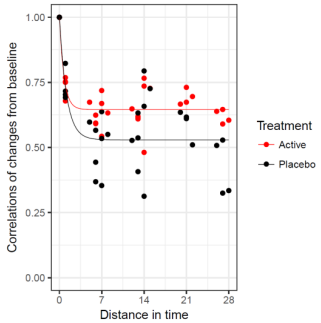
(i) $\delta(t)$



(ii) $SD(t)$



(iii) Correlation

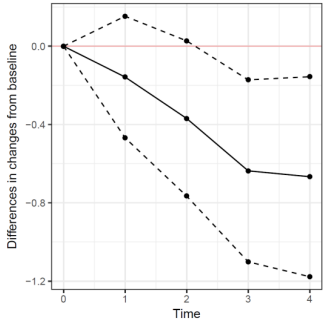


Approach	Power
Parametric mixed model	84.9
Cross-sectional test	58.0
Maximum Test	70.2
Optimal Test	73.3

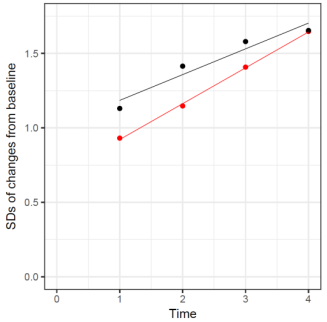
- Parametric time mixed effect model improves over „MMRM“ → Fewer parameters
- Longitudinal models both improve over cross-sectional

Comparison example 2

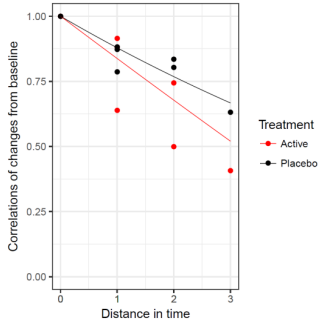
(i) $\delta(t)$



(ii) $SD(t)$



(iii) Correlation



Approach	Power
Parametric mixed model	90.1
Cross-sectional test	88.8
Maximum Test	87.5
Optimal Test	89.2

- No big differences across methods, primarily due to linearity of treatment effect over time and high within-patient correlation

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Conclusions

- Including longitudinal measurements can bring substantial gains in specific situations
- The most gain from the longitudinal approach is expected for situations with:
  - early onset of treatment effect,
  - SD increasing over time,
  - most variability is within-patient (= low within-patient correlation).
- The presented simple “time-point-weighting” approach provides benefits almost „for free“: no additional implementation effort, can use standard analyses (MMRM), only need to specify the contrasts of interest over time
- Parametric mixed-effects model-based approach (including covariate effects, using more pharmacological prior knowledge, etc) can potentially bring even higher gains
- Limitation of this work: focused only on the treatment effect detection. In practice, understanding the time-course is equally of interest

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Thank you

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Appendix

Mixed effect model used in example 1

$$y_i = \alpha + \alpha_k + (\delta + \delta_k) I_{t_i>0 \,\&\, trt_i>0} + \epsilon_i$$

- $\epsilon_i \sim N(0, \sigma^2)$ iid
- $\alpha_k, \delta_k \sim MVN(0, \Omega)$ patient specific correlated random effects

Mixed effect model used in example 2

$$y_i = \alpha + \alpha_k + (\beta + \beta_k + \delta * trt_i)t_i + \epsilon_i$$

- $\epsilon_i \sim N(0, \sigma^2)$ iid
- $\alpha_k, \beta_k \sim MVN(0, \Omega)$ patient specific correlated random effects