Decision-making using longitudinal modelling presence of model uncertainty

Longitudinal modelling: Time to take the next step?

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Objective

„Making the best possible decision at the earliest time-point in the most efficient manner“

Increasing efficiency in drug development:

– Adaptive study designs, Biomarker, Portfolio optimization

What else to increase efficiency?

- Ensure that the collected data is actually utilized (e.g. longitudinal)
- Ensure that we leverage internal/external knowledge in our designs (e.g. MBMA, (Bayesian) modelling)

Implications:

- Do the right decision with higher certainty: Better informed decisions
- Do the same decision earlier: Quicker transition to next phase

Leveraging Longitudinal Data

Longitudinal data are **routinely** collected in our experiments

- e.g. body weight, viral load, blood pressure, heart rate, tumor growth, …

Often, primary analyses focus on AUC analyses, cross-sectional endpoint analyses or changes from baseline. Good practice to reflect on:

- The question of interest:
  - What is the study objective? Any difference between groups or specific difference?
  - What is the pattern of change? Is the pattern different over treatment groups?
    - ↳ Earlier onset iso size of effect as differentiator?
- Possible suboptimal use of information:
  - Do we use all measurements? Which assessments provide valuable information?
  - Do we use optimal analysis techniques? Dichotomization = loss of information!

What is longitudinal modelling?

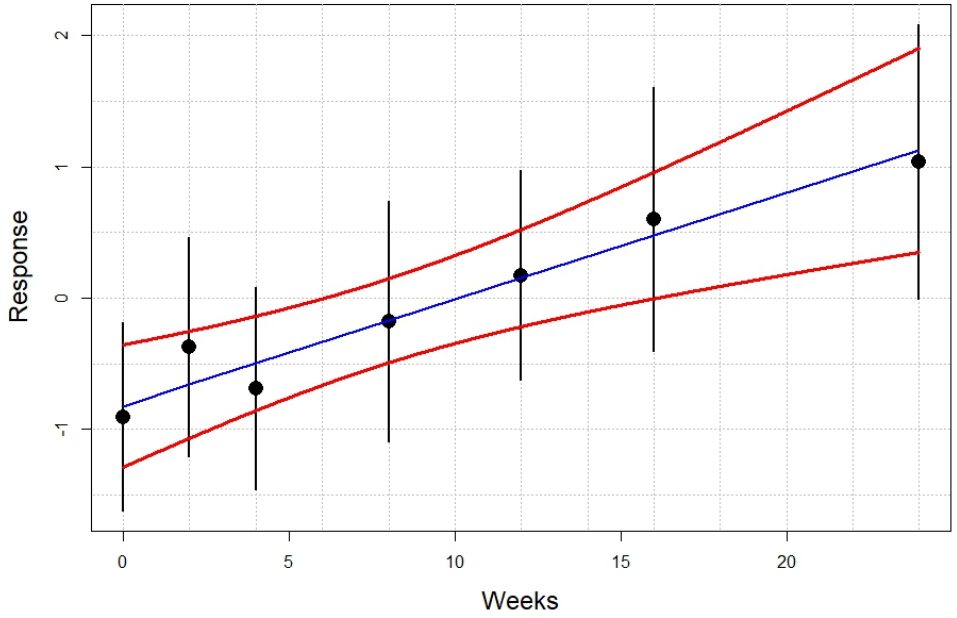
Variety of methods combining multiple assessments into the analysis via model

E.g. looking at binary endpoints:

- Direct modelling of transition probabilities:
  - What is probability that non-responder at week 12 becomes responder at week 24?
- Fitting generalized linear (mixed) models
  - Are dependencies appropriately taken into account?
- Modelling as time-to-event variable if only one “0”-> “1” transition possible
  - Timing of event to provide additional information
- Modelling of an underlying continuous model, driving “response”
  - Fit continuous endpoint and estimate response probabilities from continuous model => more info

Here focus on: Continuous endpoint and mixed effects models.

Why (longitudinal) modelling…



Too nice to be true…

Fitting linear model through 2 points:

- No benefit on these points
- … but for points in between: yes

Fitting linear model through 3 points:

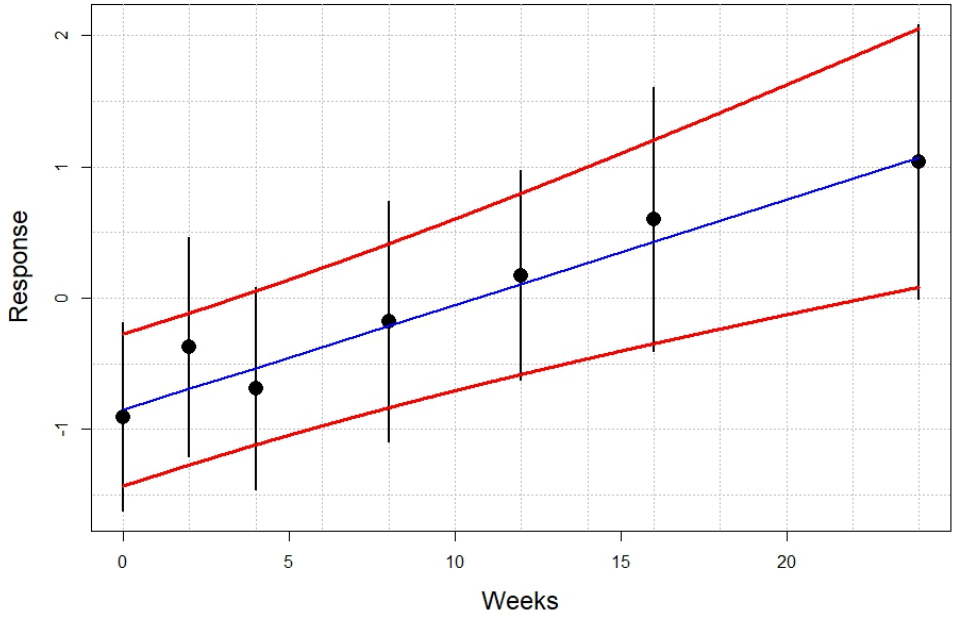
- Also CI on boundaries shrinks

… but best is to use all visits

Visits used in analysis	Efficiency	Required size	Equivalent size
2	100%	50	50
3	89.75%	45	55
4	73.57%	37	68
7	55.08%	27	90

… and what to consider: Correlation of observations

7 measurements on one subject ≠ 7 subjects with one measurement

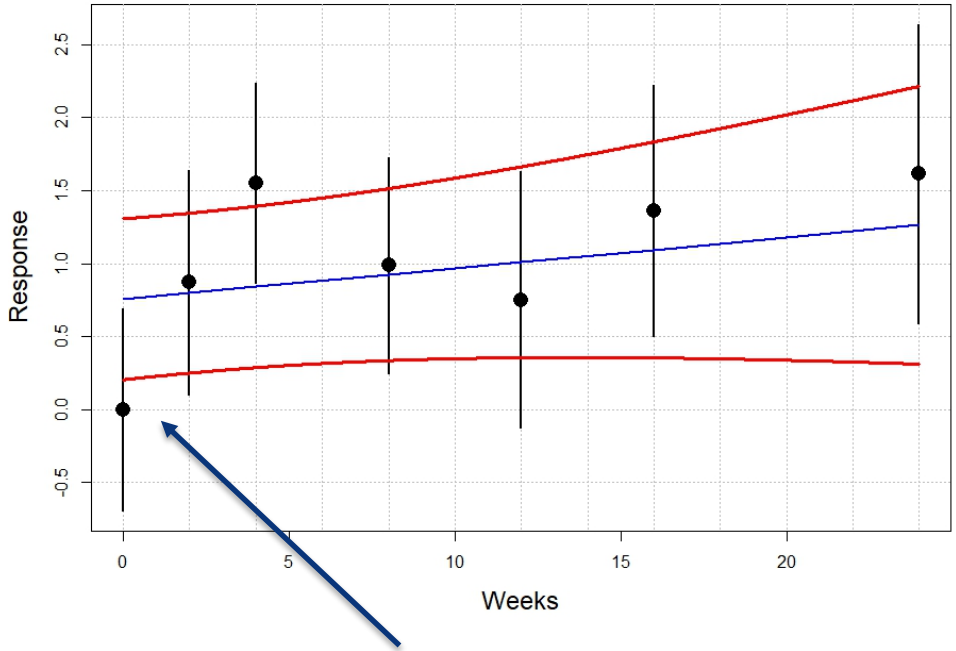


… 6 patients can make 1 month

- Observations from one experimental unit (e.g. patient) are correlated
- Benefit depends on correlation within subject:
  - High correlation => less learnings

Visits used in analysis	Efficiency	Required size	Equivalent size
2	100%	50	50
3	96.37%	48	52
4	92.45%	46	54
7	88.48%	44	56

… and what else to consider: Uncertainty on the model



Problems with wrong shape:

- Biased estimator
- False coverage probability

↳ Misleading results

Does this mean: Don't use modelling?

- No.
- Be cautious and aware of uncertainty.
- Include uncertainty in design evaluation.

Model-based CI doesn't include observed mean => "Too bad to be correct?"

The question of interest: What is the objective?

Apply statistical methodology to support efficient ***decision making***

What is the considered rule for decision making?

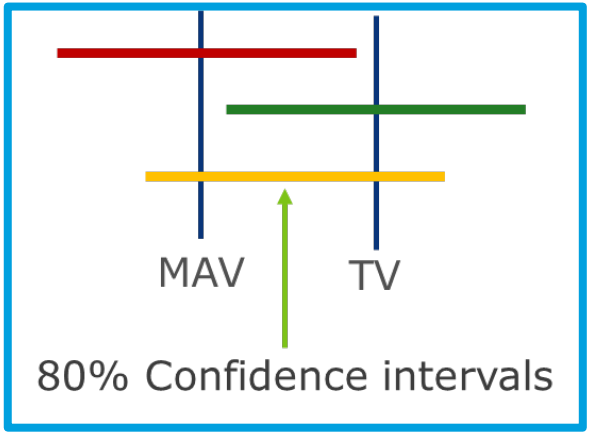
Situation 1

Is there any difference between control and test at any time?

H_0: $\cap_{i=1}^{T} \mu_i^1 \leq \mu_i^0$ at α_0

Situation 2

Do we reach a targeted effect size



Situation 3

What is the conditional or predictive power?

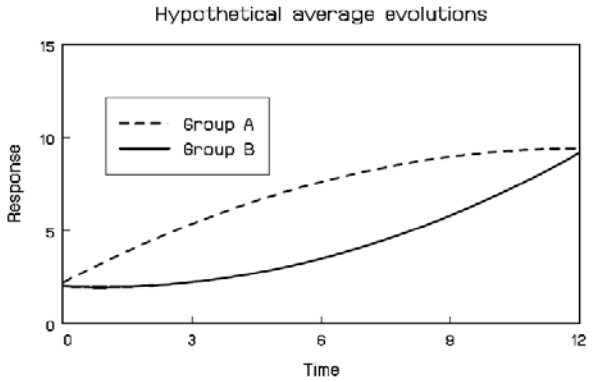
Probability of study/program success given data <x?

Situation 1: Test for any difference => Look at Björn's part

Is there any difference between control and test at any time?

- Summarize multiple assessments into one
- Optimal weighting of assessments:

$$P_\delta\left(\frac{c^T(\bar{Y}^1-\bar{Y}^0)}{\sqrt{2c^T\Sigma c}} > z_{1-\alpha}\right) = 1-\Phi\left(z_{1-\alpha}-\frac{c^T\delta}{\sqrt{2c^T\Sigma c}}\right)$$



Benefit: Higher power as compared to standard cross-sectional

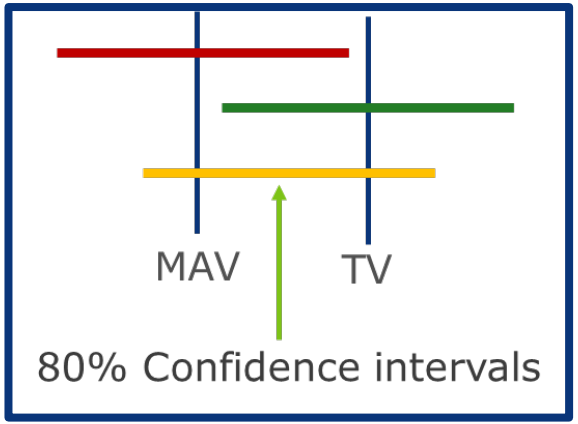
- ***Does not severely depend on distribution of data***

Limitation: No insight on size of effect.

Situation 2: Test for relevant difference $\Delta = \mu_T^1 - \mu_T^0$

Dual "Go – No go" approach (Lalonde 2007)

- Is the effect worth continued investment?
  - **"Stop"** if Δ significantly below some target effect at some α_{TV}
- Was a minimum relevant effect observed?
  - **„Go"** if Δ above max. non-acceptable effect at some level α_{MAV}



Properties/Problems:

1. Model-based approach: info is drawn from model ➔ **Error-control not guaranteed**
2. Non-model based approach: significant amount of data not utilized
3. Definition of Δ: Parameter in a longitudinal model or difference at certain time?

Situation 3: Conditional Power

Final analysis:

Test $H_0: \mu_T^1 \leq \mu_T^0$ *at level* α*=5% (two-sided), using standard methods*

Interim analysis: *What is the probability of a positive study at final analysis?*

$$Conditional\ Power = P_{\delta,\sigma}\left(\sqrt{w_1}z_1 + \sqrt{w_2}Z_2 + \sqrt{w_3}Z_3 > z_{1-\alpha} \middle| Z_1, Z_2^*\right)$$

δ, σ: Assumption on effects: Estimated from all data using parametric model

z_1: Completers at interim analysis: We know their data

Z_2: Some data available at interim analysis: We can predict how they develop

Z_3: No data available at interim analysis: We can estimate their effect

Situations 2 & 3: How does it work?

1. **Assume a parametric model, e.g. (N)LME:**

$$Y_{ij} = \eta(\beta_i, t_j, trt) + \epsilon_{ij}, \beta_i \sim N(\beta, D), \epsilon_{ij} \sim N(0, \sigma^2), i = 1, \ldots, N, j = 1, \ldots, m$$

   - Linear / non-linear?
   - Interpretation? $1 + trt \times time$ vs. $1 + trt + trt \times time$?

2. **Given data, fit model:**
   - Estimates for: $\beta, D, \sigma^2, \beta_i$ together with measures of uncertainty (FIM)

3. **Calculate decision metrics of interest:**
   - Model based confidence interval (simple, using estimates of β, D, σ^2)
   - Conditional power (a bit trickier, using estimates of $\beta, D, \sigma^2, \beta_i$ and actual data)

Impact of model uncertainty: Impacts of wrong model

Test for any difference: No loss of validity

- Loss in power: Likely still better than cross-sectional approach

Test for relevant difference: Loss of validity

- Biased estimator results in wrong coverage probability
- Short confidence intervals are possible, suggesting wrong stop/go decisions

Conditional power: Potentially misleading results

- Biased estimator and model lead to biased estimates of conditional power

Some strategies for mitigating model uncertainty

1. **Use flexible model**
   - MMRM: While validity not harmed, no gain in efficiency
2. **Fit several models to the data and pick the best***
   - Not best model in terms of “maximum effect”: Standard multiplicity problem
   - Best model in terms of best fit: Underestimation of variability => false coverage probability
3. **Fit several models to the data and conduct model averaging*:**
   - Similar to “2”, but characteristics potentially better
4. **Use of longitudinal modelling as back-up only**

Given all these complexities: What is the opportunity space?

What is the potential benefit?

Example: Phase 3 study designs in IPF

Based on publication:

*"Efficacy & Safety of Nintedanib in Idiopathic Pulmonary Fibrosis"**

Primary endpoint:

- Annual rate of decline in FVC (measured in milliliters per year)
- Assessments at weeks: 0, 2, 4, 6, 12, 24, 36, 52 and 56

Secondary endpoint: Absolute change from baseline at week 52

Analysis: RCR model with random intercept and slopes

Sample size: 90% power to detect…

- between group difference of 100ml in annual rate of decline
- … assuming standard deviation of 300ml on change from baseline
- … and 3:2 randomization

Richeldi et al., NEJM 2014, 370:2071-2082

Example: Phase 3 study designs in IPF

*"Efficacy & Safety of Nintedanib in Idiopathic Pulmonary Fibrosis"**

Sample size planned looking only at change from baseline week 52

… no need to make assumptions on within-subject correlation

… more assessments: information will increase => conservative sample size

What we'll look at instead:

1. What would be the power using all assessments?

   … and what is the impact of variance composition on operating characteristics?

2. How would deviations from assumed linear model impact power?

   … and how would model selection/averaging compare

Richeldi et al., NEJM 2014, 370:2071-2082

Example: Phase 3 study designs in IPF

*What would be the power using all assessments? (*0, 2, 4, 6, 12, 24, 36, 52)

Looking at standard LME:

$$Y_{ij} = \beta_{i1} + (\beta_{i2} + trt \times \beta_{i3})t_{ij} + \epsilon_{ij} \text{ with } \beta_i \sim N(\beta, D) \text{ and } \epsilon_i \sim N(0, \Sigma)$$

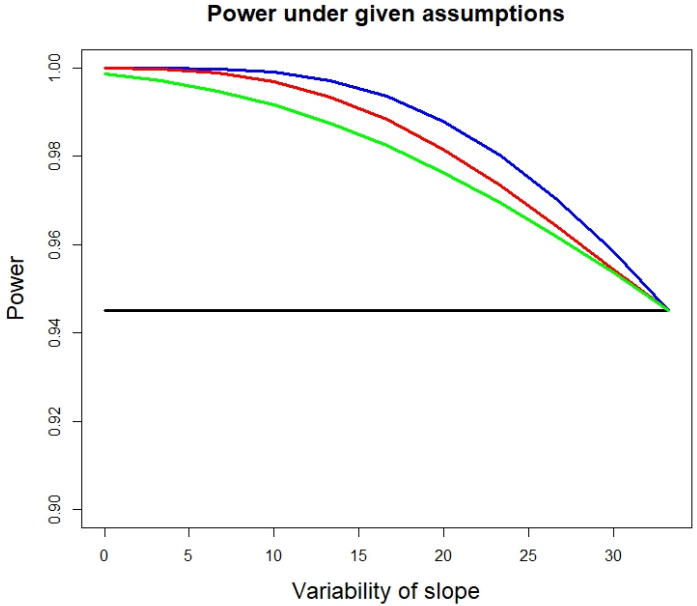
Assumption on change from baseline: $c^T Y_i \sim N(\mu, \sigma^2_{CFB})$ $(c = (-1, 0, \ldots, 0, 1)^T)$

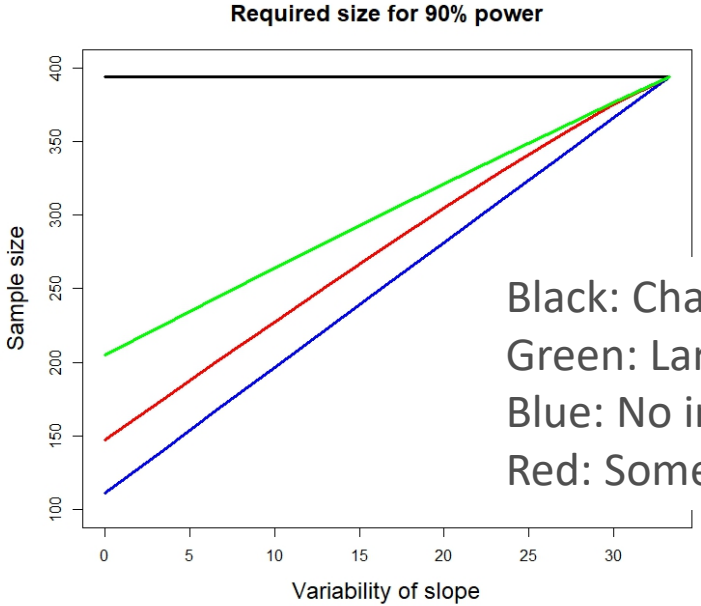
- Assuming no intra-subject correlation: $\Sigma = \sigma^2_\epsilon I_m$
- Assuming no random treatment effects $(Var(\beta_{i3}) = 0)$
- … resulting assumption on variability: $\sigma^2_\epsilon = (\sigma^2_{CFB} - t^2_m Var(\beta_{i2}))/2$

Given Unknown

Example: Phase 3 study designs in IPF

- *What would be the power using all assessments?*





Black: Change from baseline
Green: Large intercept variability
Blue: No intercept variability
Red: Something in between

Result: potentially overly conservative study design

Example: Phase 3 study designs in IPF

2. How would deviations from assumed linear model impact power?

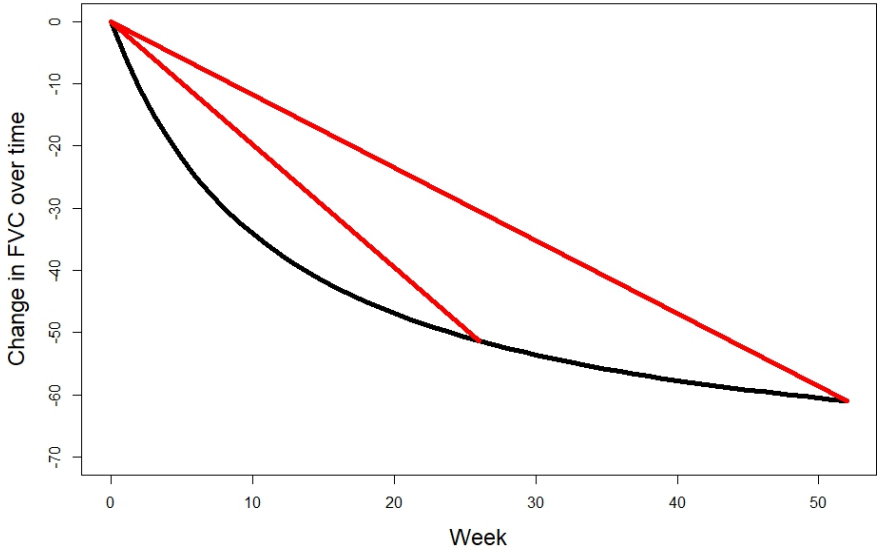
What is the annual rate of decline?

- **Linear progression: simple**
- **Non-linear progression: depends on study duration**

Looking at landmark (e.g. estimate on wk52 change from baseline informed from longitudinal model) may resolve this problem:

$$\mathbf{H_0}: \boldsymbol{\Delta = \mu_{52}^1 - \mu_{52}^0 \leq 0}$$

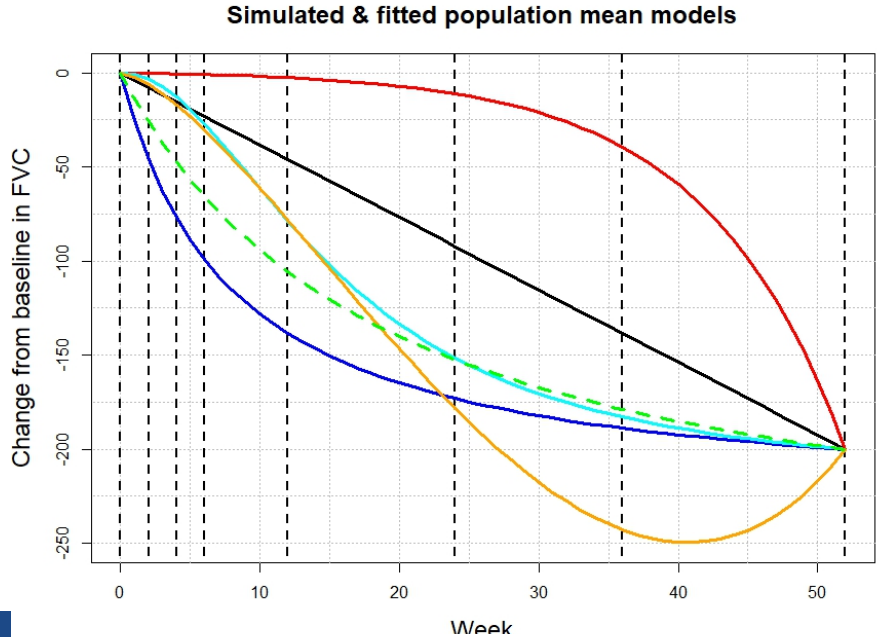
… but will be different endpoint.

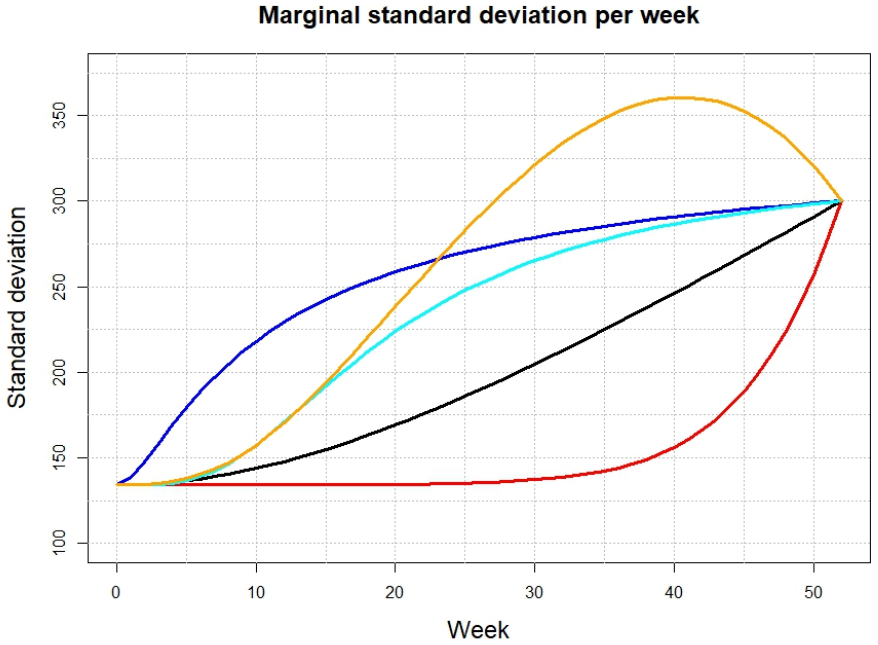


Example: Phase 3 study designs in IPF

2. How would deviations from assumed linear model impact power?

Simulated & fitted scenarios:





Note: linear models were fitted (but non-linear in time)!

Example: Phase 3 study designs in IPF

2. How would deviations from assumed linear model impact power?

Coverage probabilities of 95%-confidence interval:

		Fitted shape						
		Linear	Emax	Exponential	Sigmoidal	Beta model	Selection (1)	Selection (2)
Simulated shape	Linear	95,10%	83,13%	88,57%	91,77%	79,70%	95,10%	91,77%
	Emax	78,03%	94,47%	45,30%	76,10%	58,93%	94,47%	76,10%
	Exponential	88,03%	48,23%	95,13%	59,33%	41,97%	95,13%	88,03%
	Sigmoidal	94,10%	90,80%	73,47%	94,67%	92,17%	94,67%	92,17%
	Beta model	92,40%	93,20%	70,63%	93,60%	94,87%	94,87%	93,60%
	Emax (2)	94,00%	94,47%	53,97%	92,00%	78,30%	93,23%	93,23%

- Selection (1/2): Simulated shape available / not available for selection
- Model averaging: performs like model selection as difference in profiles detected
- Model selection can mitigate some concerns, but not all (need adequate model)

Example: Phase 3 study designs in IPF

2. How would deviations from assumed linear model impact power?

Type 1 error:

		Fitted shape						
		Linear	Emax	Exponential	Sigmoidal	Beta model	Selection (1)	Selection (2)
Simulated shape	Linear	2,40%	2,60%	2,70%	2,60%	2,60%	2,40%	2,60%
	Emax	2,40%	2,30%	1,10%	2,30%	2,60%	2,30%	2,30%
	Exponential	2,20%	2,50%	2,00%	2,60%	3,20%	2,00%	2,20%
	Sigmoidal	2,70%	2,70%	3,20%	2,60%	2,90%	2,60%	2,90%
	Beta model	2,40%	2,00%	1,80%	2,50%	2,50%	2,50%	2,50%
	Emax (2)	2,20%	2,30%	2,70%	2,00%	1,80%	2,50%	2,50%

Type-1 error less of an issue here:

- Model selection not conducted to establish some effect, but to get best fit.
- Within each analysis model, the type-1 error is controlled

Example: Phase 3 study designs in IPF

2. How would deviations from assumed linear model impact power?

Power (assuming effect of 100):

		Fitted shape						
		Linear	Emax	Exponential	Sigmoidal	Beta model	Selection (1)	Selection (2)
Simulated shape	Linear	96,10%	91,70%	89,50%	95,90%	95,80%	96,10%	95,90%
	Emax	83,60%	96,90%	41,60%	87,70%	86,30%	96,90%	87,70%
	Exponential	94,60%	88,60%	96,80%	94,80%	94,00%	96,80%	94,60%
	Sigmoidal	96,60%	91,70%	80,30%	96,80%	96,70%	96,80%	96,70%
	Beta model	96,70%	90,20%	71,30%	97,30%	97,30%	97,30%	97,30%
	Emax (2)	97,70%	98,90%	82,60%	98,10%	97,80%	98,30%	98,30%

Power affected by model:

- Wrong model selected for fitting => impact on power
- True EMax but different model fitted => effect underestimated => lower power

Summary

Longitudinal modelling:

- … may add substantial efficiency, allowing earlier decision making
- … but requires more specifications/assumptions in design stage (e.g. variability)

Wrong model may lead to incorrect conclusions:

- … but approaches like model averaging may yield robust and efficient results
- … worthwhile at least for internal decision making

And a last thought:

- Do we really need the right model?
- Estimator from wrong model may still be informative due to numerics:
  - E.g. estimator of effect at final visit vs. maximum information from final visit in linear model

Summary: Uncertainty on the model ≠ don't try to utilize modelling

References

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