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Leveraging Longitudinal Modeling to Improve Drug Development Efficiency

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Outline

- Motivation: improving efficiency of drug development
- Case study: sample size strategies
- Modeling longitudinal data
- Benefits and challenges of parametric longitudinal modeling
- Concluding remarks

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Motivation

- Escalating costs of drug development creates sustainability challenge for pharmaceutical industry
- Increasing efficiency is essential
- A number of approaches have been pursued and/or are under consideration, e.g., adaptive designs, use of biomarkers, platform trials, risk-based monitoring, etc.
- Most involve significant changes to drug development practice and processes
- Will focus here on simple approaches to improve data analysis efficiency resulting in sample size reduction and/or increase in power

Motivation (Cont.)

- Longitudinal data are routinely collected in most clinical trials: endpoints measured at multiple visits, e.g., HbA1c, weight, lab results, etc.
- Often analyses are focused on change from baseline, discarding observations between baseline and final visit
  - inefficient use of information
  - require imputation for last visit, if missing
- Efficiency gains can result from utilizing all data collected in trial, but additional assumptions are required

Case Study: Background

- Chronic indication, pediatric phase III study
- Study design:
  - Randomized, double-blind, placebo-controlled, multi-center
- Primary outcome:
  - Continuous outcome (change in exercise capacity)
  - Measured at baseline and 2 post-baseline time points (during therapy, end of therapy)
- Primary analysis model:
  - Linear mixed effects model for repeated measurements (MMRM):
    - Models two post-baseline time points
    - Baseline measurement as covariate

Sample size planning

Initial planning & agency‘s request

- Fixed sample size design
  - Based on t-test, known to be conservative, but traditionally used for sample size calculation
  - High uncertainty about assumptions (variability, within-subject correlations), based on only one observational study
- Agency requested to have a sample size re-estimation at 90% of the initially planned enrollment
- Design with sample size re-estimation

1) Calculate initial sample size
2) Estimate unknown variability at a pre-specified time point during the study
3) Increase sample size if the variability is higher than assumed. Final sample size
   - should not be lower than initial sample size (restricted design)
   - should not be higher than upper bound

Initial sample size and re-estimation approach

- Initial sample size based on t-test was already large
- Increasing sample size would be challenging
  - hard to recruit population
  - the study should be completed within a specific timeframe

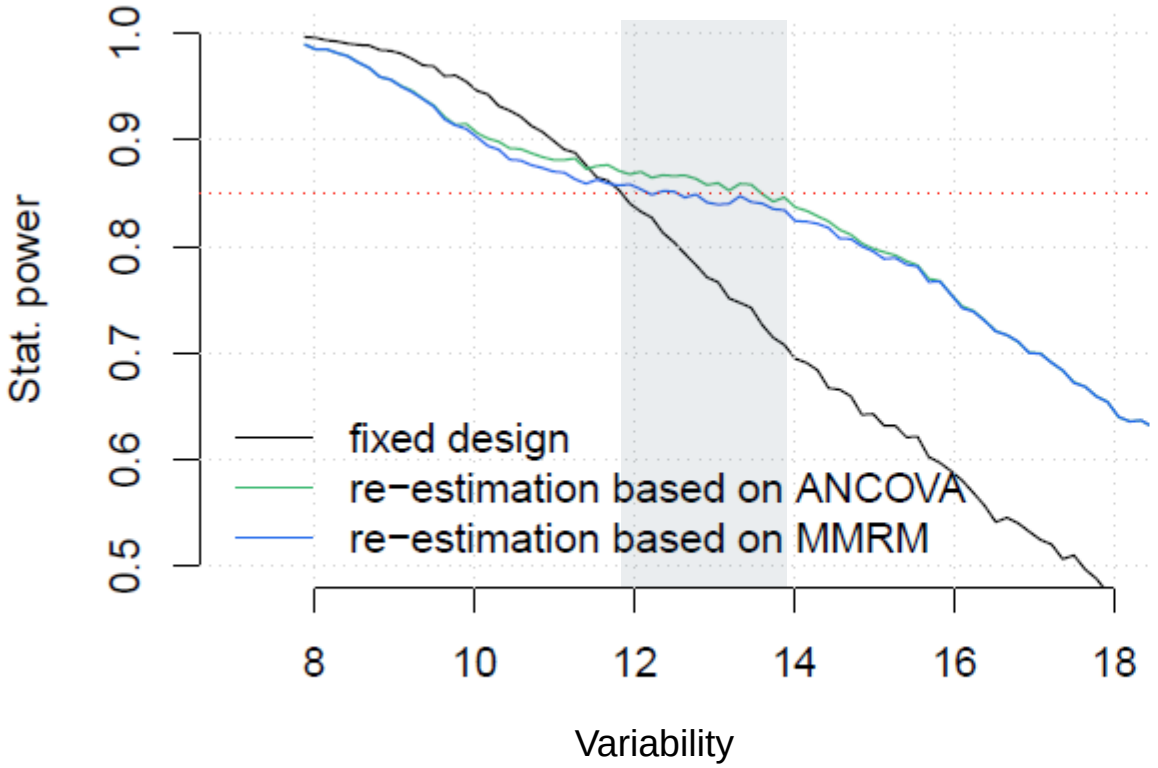
Initial sample size and re-estimation method:

- No need for conservative initial sample size planning (i.e., t-test)
- Non-conservative initial sample size planning, i.e. $n_{initial} = 180 \neq n_{fixed} = 220$
- Use powerful method for sample size re-calculation (ANCOVA, MMRM)
  - using observed (i) correlations, (ii) variance, (iii) missing value rate
- Implement maximum sample size based on feasibility

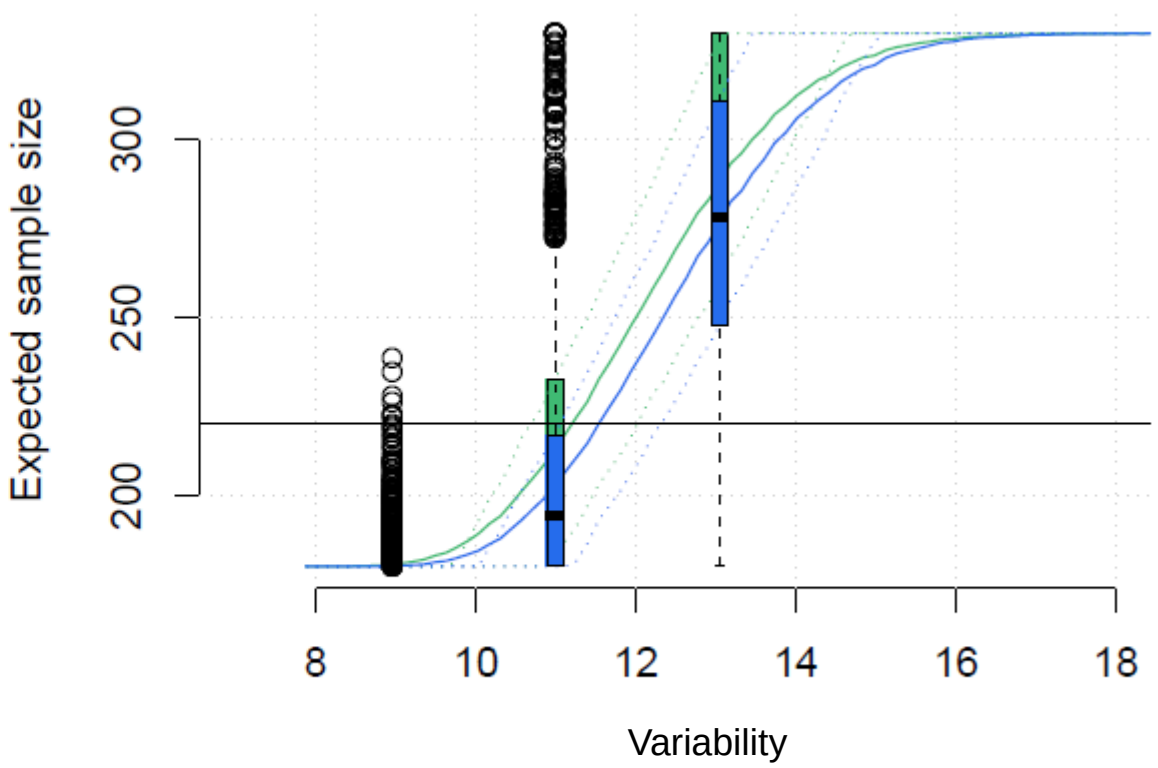
Fixed sample size vs. sample size re-estimation: Simulation Results

Setting with missing values ($p_{w10} = 10\%, p_{w26} = 20\%$)

a) Power



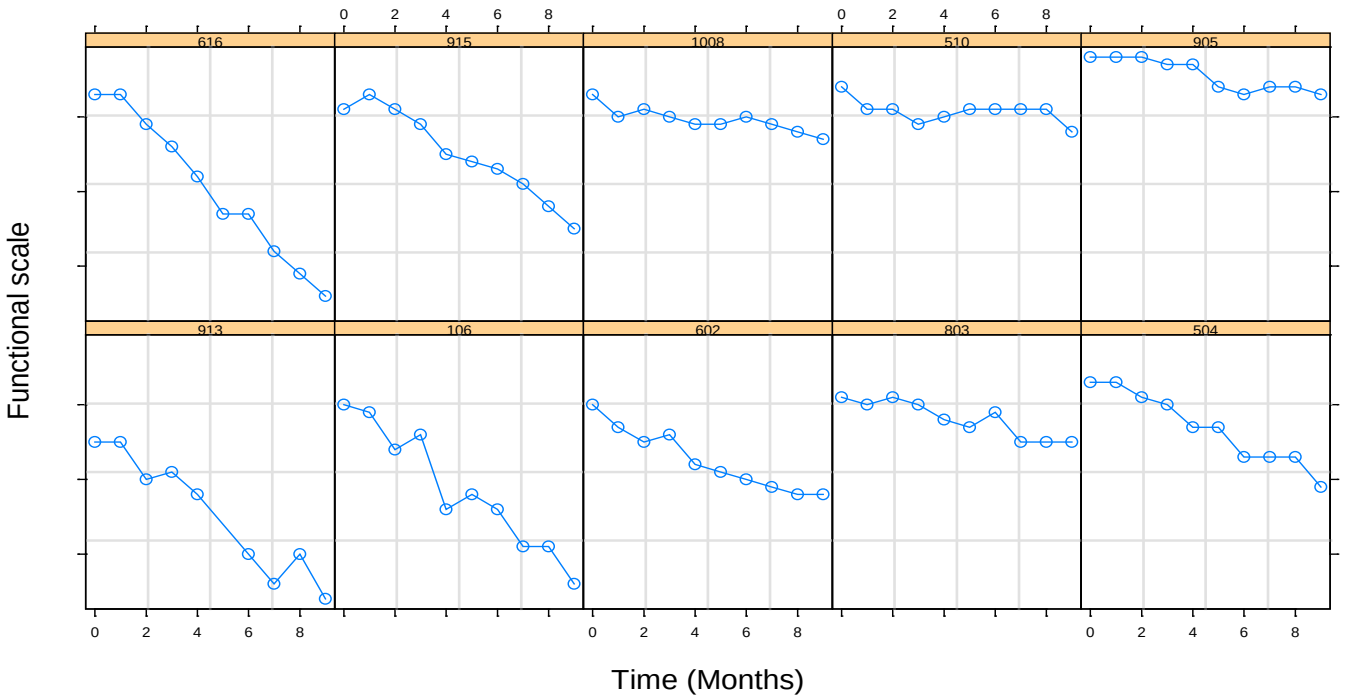
b) Expected sample size & variability



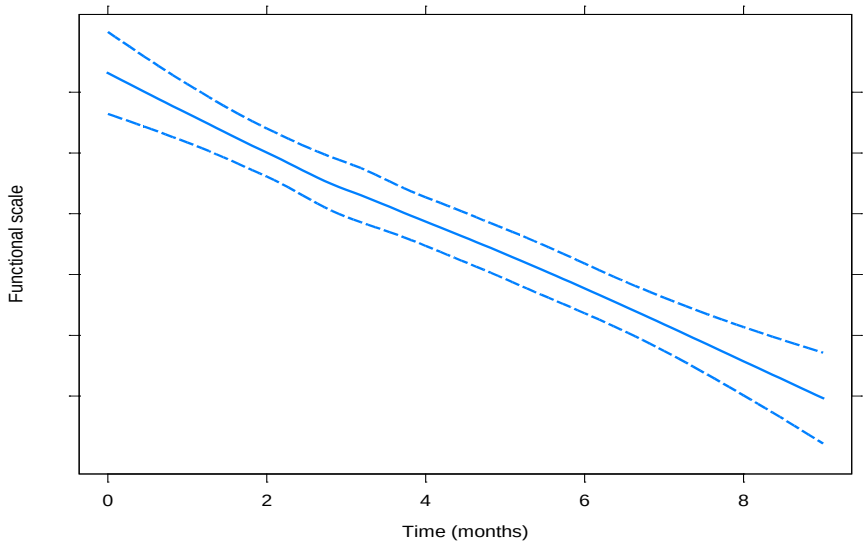
Initial sample size and re-estimation: discussion

- Evaluation of analysis methods and corresponding sample sizes is an important step
- Making assumptions based on available information is a part of design planning
- Taking time to evaluate and simulate designs might save substantial amount of time during negotiation with regulators and study conduct
- Trying to change a design or strategy during a discussion with regulators might be problematic

Another example of longitudinal data: ALS disease



Individual time profiles: similar linear shapes, different intercepts and slopes; correlated within-patient observations



Nonparametric fit of registry data

Parametric longitudinal models

- Longitudinal data collected on same subject often correlated and with non-constant variance: require specialized analysis methods
- Assume specific profiles for observed response over time, with functional specification: e.g. linear change over time, monotonic increase converging to an asymptote (such as Emax model)
- Number of parameters to estimate is fixed, independent of number of time points observed: e.g., intercept and slope for linear model
- Assumed profile typically derived from historical data, based on biological or physiological knowledge, earlier studies, literature

MMRM longitudinal models

What‘s the difference

Mixed-Effects Model for Repeated Measures (MMRM) is commonly used to analyze longitudinal data with missing observations (no need for imputations)

- Fixed effects representing visits and treatment are as in ANCOVA models: no assumptions required on time profile shape
- Flexible, but no substantial improvement in “analysis efficiency” (as measured by precision of estimates and power of hypothesis tests) vs. change from baseline analyses (in fact can have identical properties, in no-missing data case)
- Main motivation is providing valid analysis of data with missing visits (under MAR)

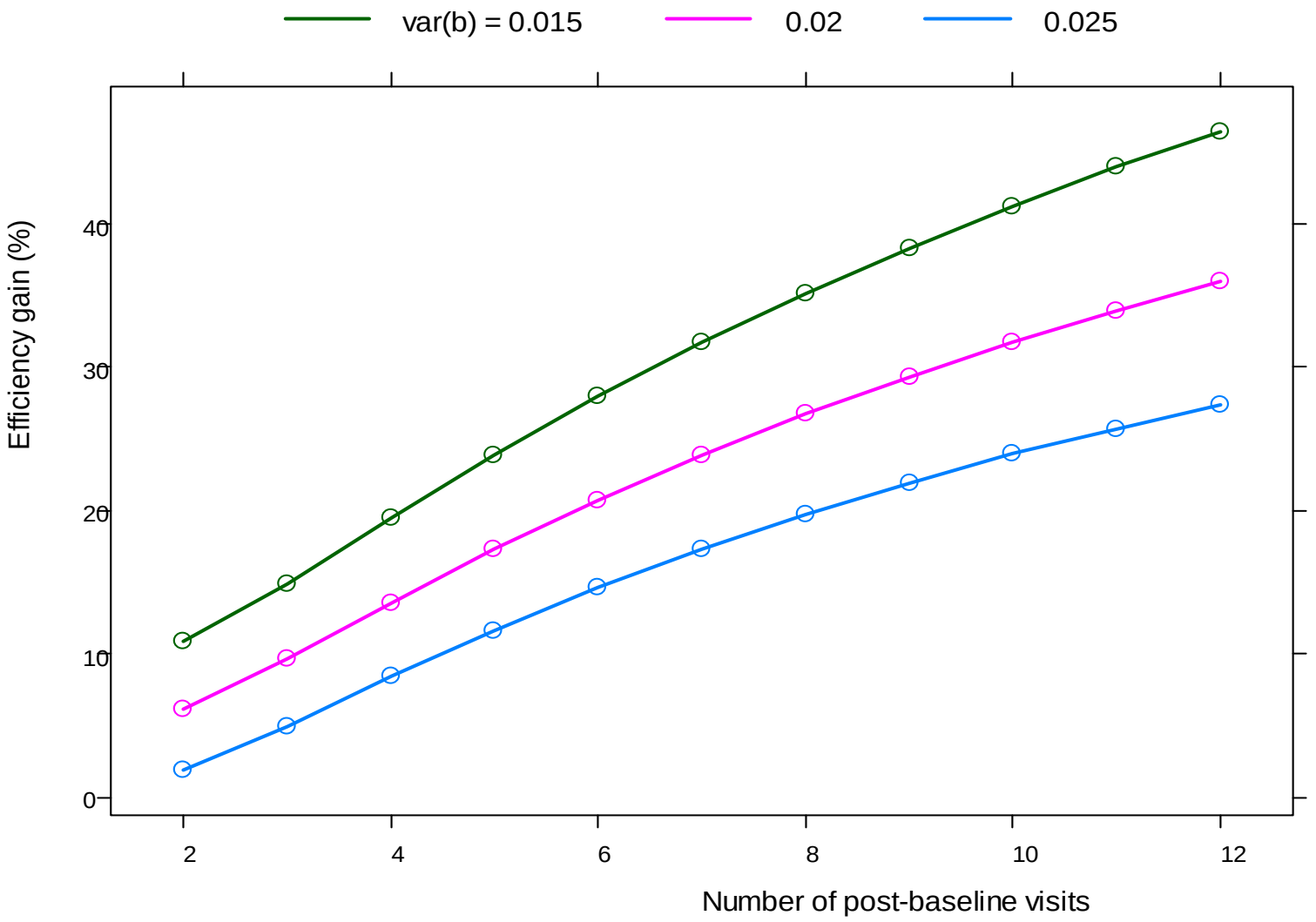
Parametric longitudinal models
ALS example

- Parametric model assumed for time profile: e.g., linear decrease in time for ALSFRS endpoint

$$y_{ij} = \alpha_i + \beta_i t_j + \epsilon_{ij}$$

- Subject-specific parameters are decomposed into fixed and random effects: $\alpha_i = \alpha + a_i, \beta_i = \beta + b_i$
- Treatment effects tested using fixed effects – e.g., β
- Only two fixed effects per arm needed in linear parametric model, irrespective of number of visits
- MMRM model: #visits x #arms fixed effects – same precision/power as change from baseline in ALS example (when no missing data)
- Parametric longitudinal models can produce substantial gains, at the price of more assumptions

Longitudinal model efficiency gains



Efficiency gains

Parametric longitudinal modeling

- Efficiency gain: increase in sample size needed under change from baseline/MMRM approach for same power as linear mixed model approach
- Increases with number of visits and decreases with variance of slope random effect
- Parametric longitudinal modeling would lead to increased power for same N, or reduced N for same power – does not require change in design
- Even for moderate number of visits, say 4, could get reductions in sample size around 10%
- Additional assumptions needed in trial design and analysis of results

Concluding remarks

- Parametric modeling of longitudinal data can produce substantial analysis efficiency gains, at the price of additional assumptions
  - Requires more assumptions and complex methodology than more traditional approaches (e.g., MMRM), but potential benefits justify its routine consideration
  - Not always leading to significant improvements: careful evaluation, often involving simulations and considering various scenarios, is essential
- Parametric longitudinal modeling is underused in clinical drug development, especially in confirmatory studies
- Worthwhile in learning trials, needs consultation and buy-in from regulators in studies intended to serve for registration
- Useful for interim decision making (e.g., futility rule, adaptation) in learning and confirmatory trials

Concluding remarks (Cont.)

- Increasing interest in modeling and simulation (e.g., MIDD and CID goals in PDUFA VI) creates opportunities for discussions with regulators on qualification and acceptance of parametric longitudinal modeling approaches.
- Ongoing discussions on potential MIDD ICH topic may open door for opportunities at global stage.

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Thank you!