Impact of correlation structure assumptions on Model-Based Meta-Analyses (MBMA)

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Value of Model Based Meta-Analyses

- Benchmarking of efficacy against existing treatment options
- Understanding of disease progression and time courses of placebo and treatment responses

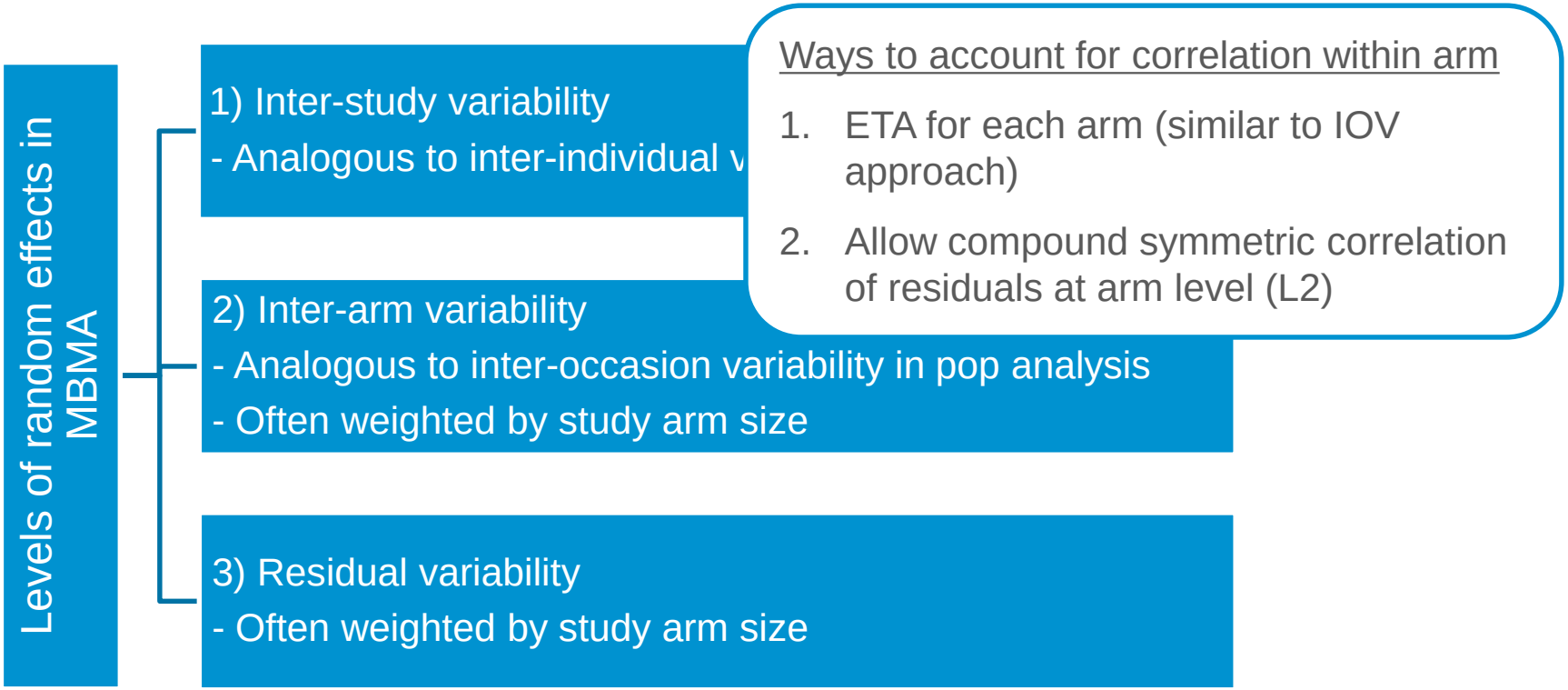
- Guide study design
- Product positioning
- Key decision making (includes go/no go decision)

- Meta-analysis of individual patient data is preferred over aggregate data, but realistically often unavailable

Multi-level correlations in MBMA

- Observations within study are correlated
  - Patients from common population, study-specific factors
- Mean observations over time within an arm are correlated
  - Same set of patients contributing to the aggregate values

Ignore → Inflation of variability



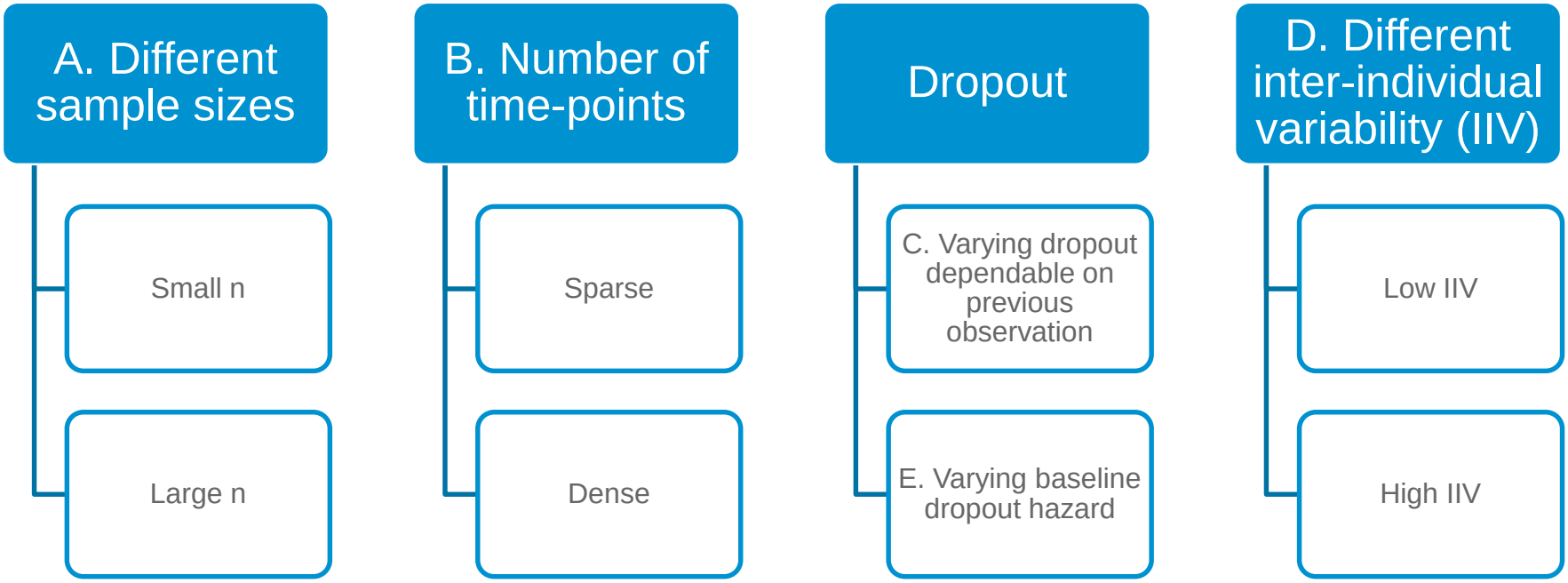
Ahn and French. J Pharmacokinet Pharmacodyn (2010) 37:179–201

Objective

Examine impact of different correlation structure assumptions at arm level on aggregate level data analyses, under a MBMA framework

- M1: Compound symmetry of residual errors at arm level
- M2: Autoregressive residual errors at arm level
- M3: Independent residual errors (no arm level correlation)

Scenarios:



Overview

Simulation

Simulate 100 datasets (each with 10 studies) from assumed individual model:

$$Response\ (t) = BL \times \left(1 - Pmax \times \left(1 - e^{-KPBO \times time}\right)\right) \left(1 - \frac{Emax \times Dose}{ED50 + Dose}\right)$$

Generate aggregate level data

For each simulated dataset, compute the average at each time-point for each study-arm

Estimation

- Model M1: Compound symmetry
- Model M2: Autoregressive
- Model M3: Independence

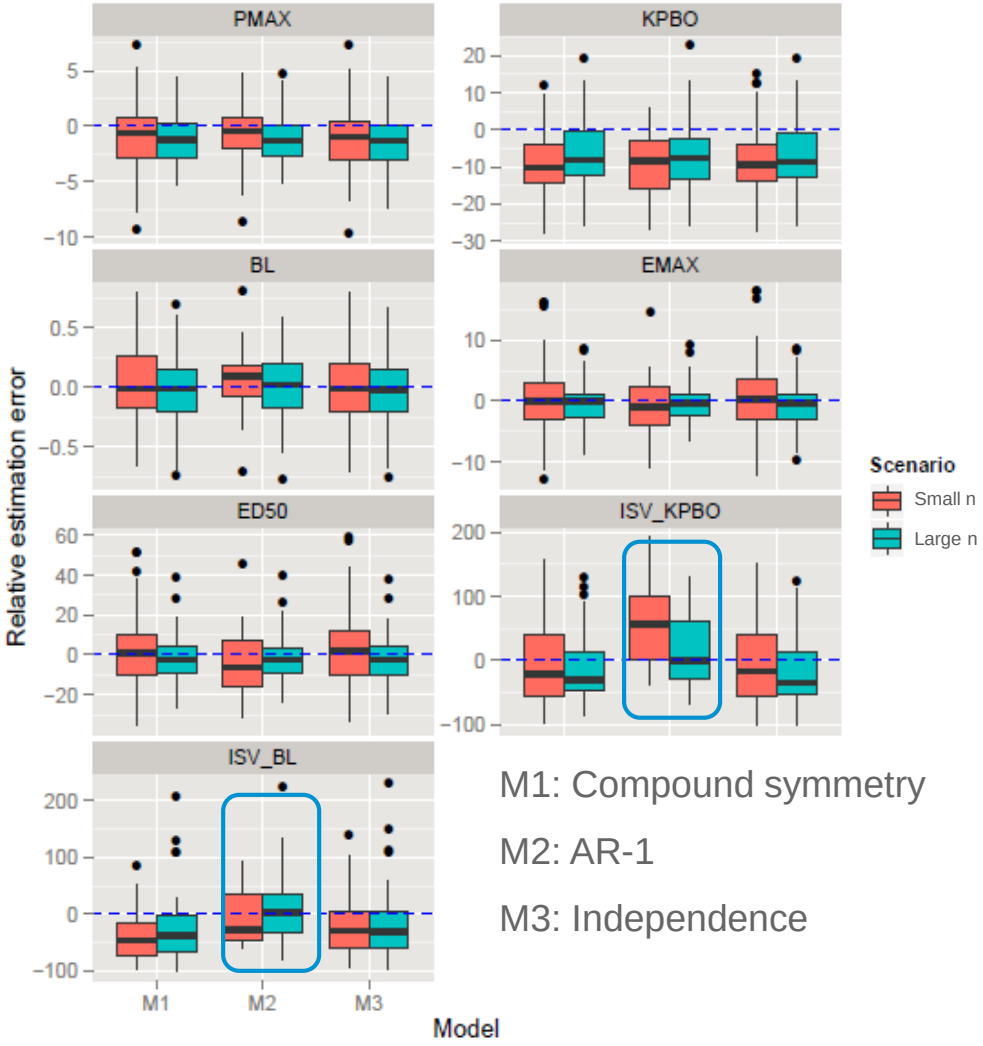
Evaluation

- Visual predictive checks
- Estimation errors in the parameters
- Estimation errors in model-based prediction of mean and variance of week 12 mean change from baseline (CFBL)

$$Estimation\ error = \frac{Model\ estimated - True}{True} * 100\%$$

Scenario A: Different study size (n)

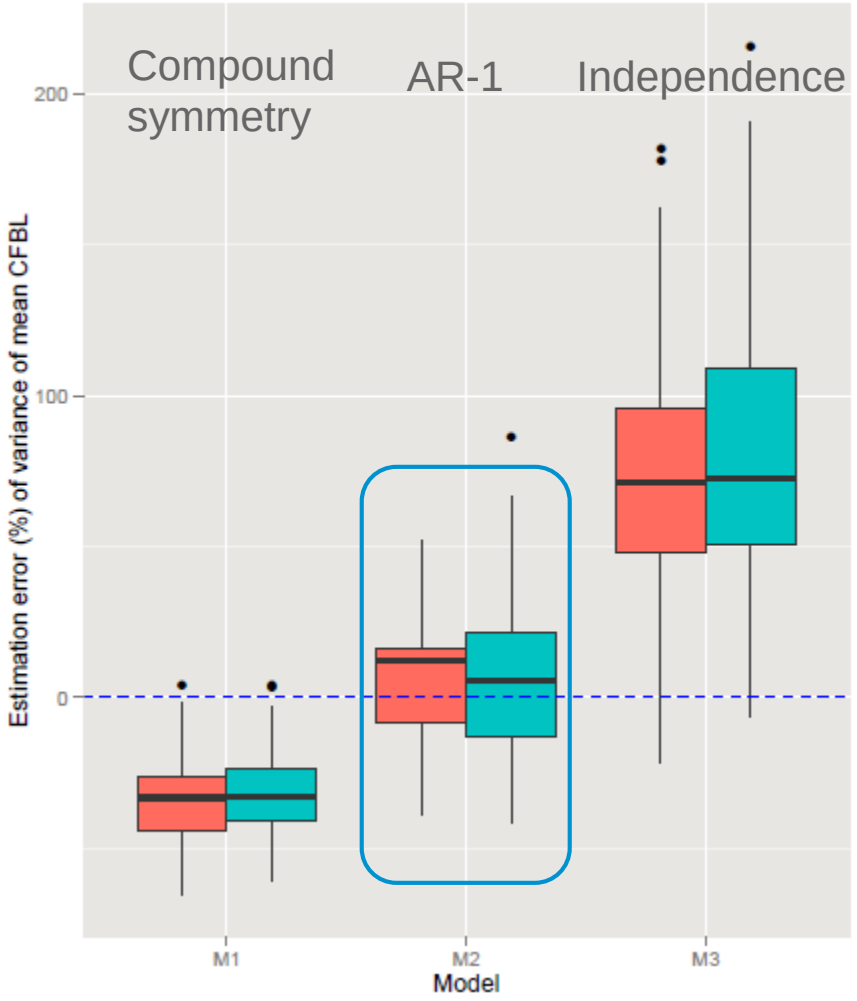
- No appreciable differences; slight improvement in precision of some parameters with larger n



M1: Compound symmetry

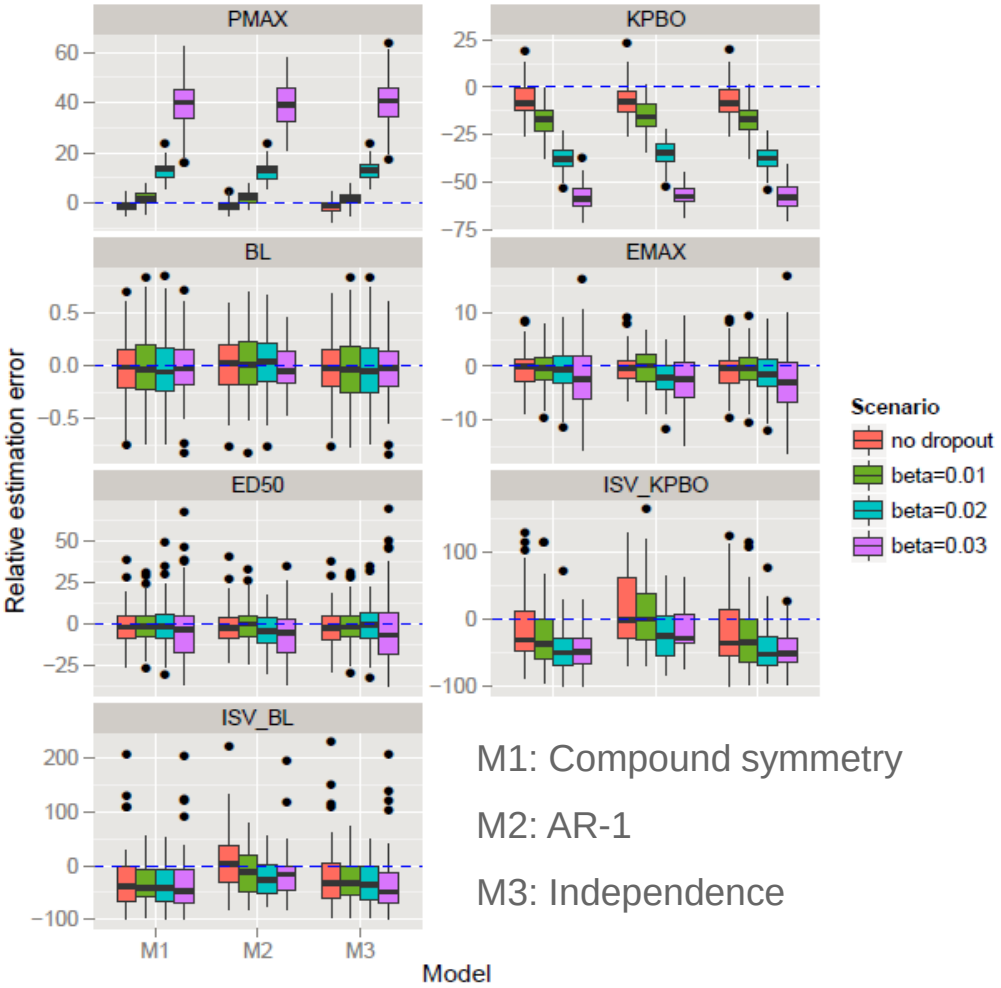
M2: AR-1

M3: Independence



Scenario C: Varied dropout

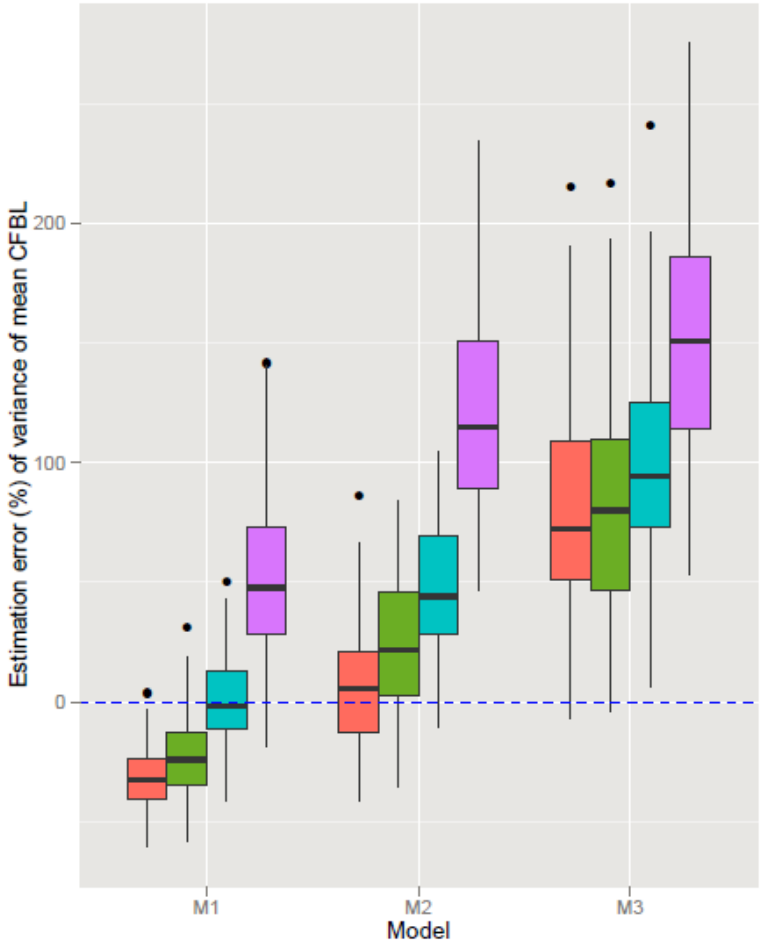
- Bias in PMAX and KPBO estimates in the presence of dropout; increase with higher dropout (0, ~15, 30, 50%)
- Overestimation of mean week 12 CFBL; inflation of the variance



M1: Compound symmetry

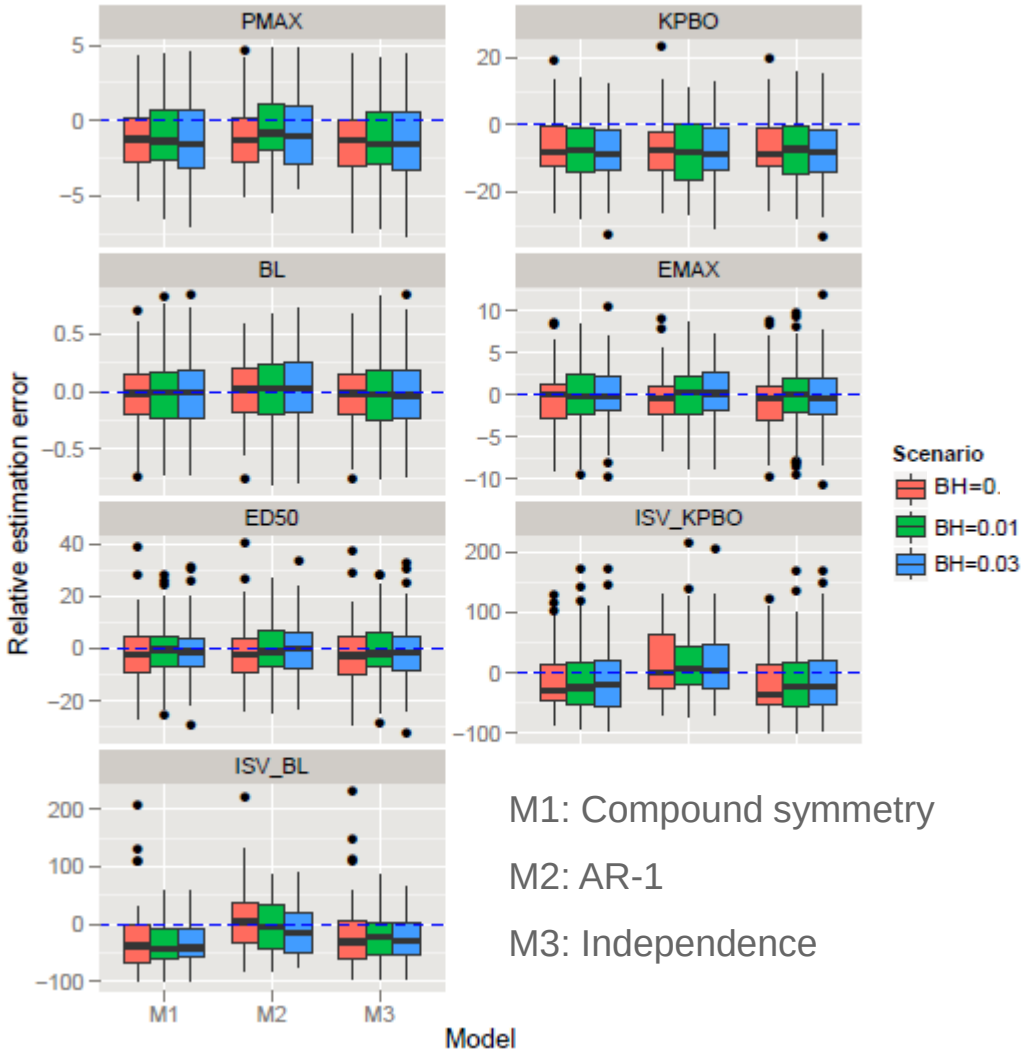
M2: AR-1

M3: Independence



Scenario E: Varied baseline dropout hazard

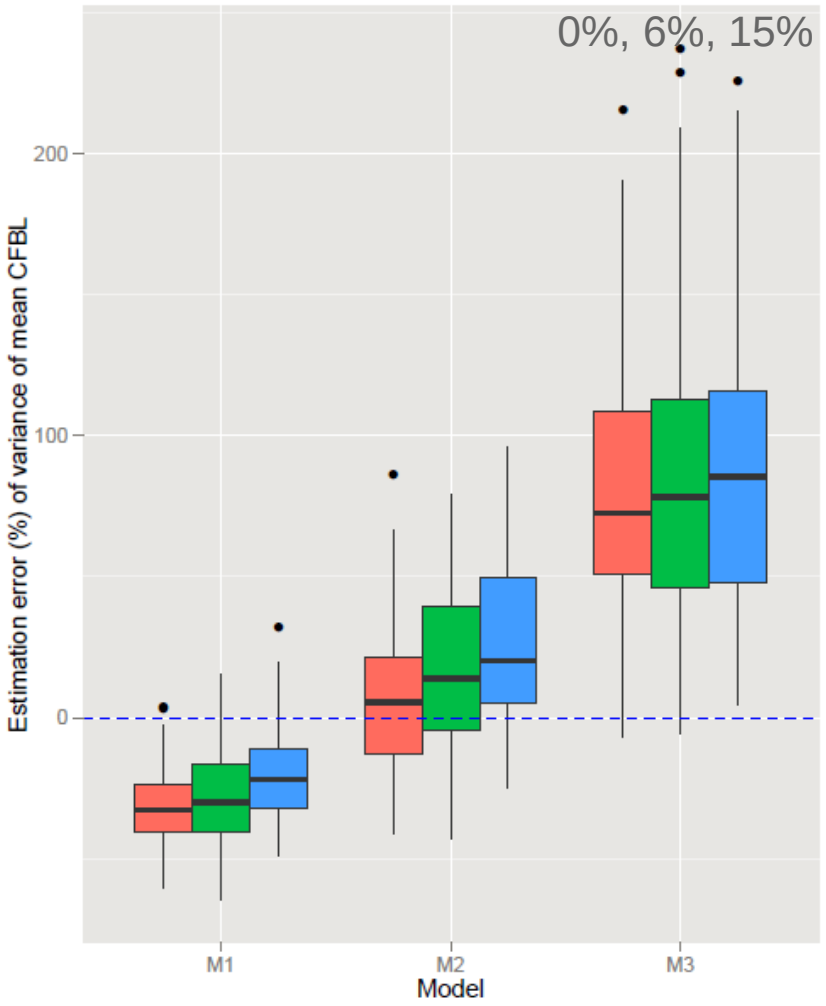
- No differences in parameters and mean CFBL
- Tendency towards increase in variance of mean CFBL with larger dropout



M1: Compound symmetry

M2: AR-1

M3: Independence



Conclusions

1. Dropout at the individual level affects the ability to estimate some model parameters at the aggregate level (both accuracy and precision)
2. Incorporation of correlated error structures at the arm level:
   - Similar estimates of fixed effect parameters and prediction of the mean week 12 change from baseline for all models
   - Autoregressive correlation structure seems to perform better for estimation of variance of the mean week 12 change from baseline, but minimal differences so independent residual error model may be sufficient
   - Recommendation: Explore models (e.g. autoregressive model) that incorporate correlation and include it where possible

Acknowledgements

Timothy Nicholas, PhD

Tom Tensfeldt, PhD

Jae Eun Ahn, PhD

Sridhar Duvvuri, PhD

Pfizer Clinical Pharmacology and Pharmacometrics group

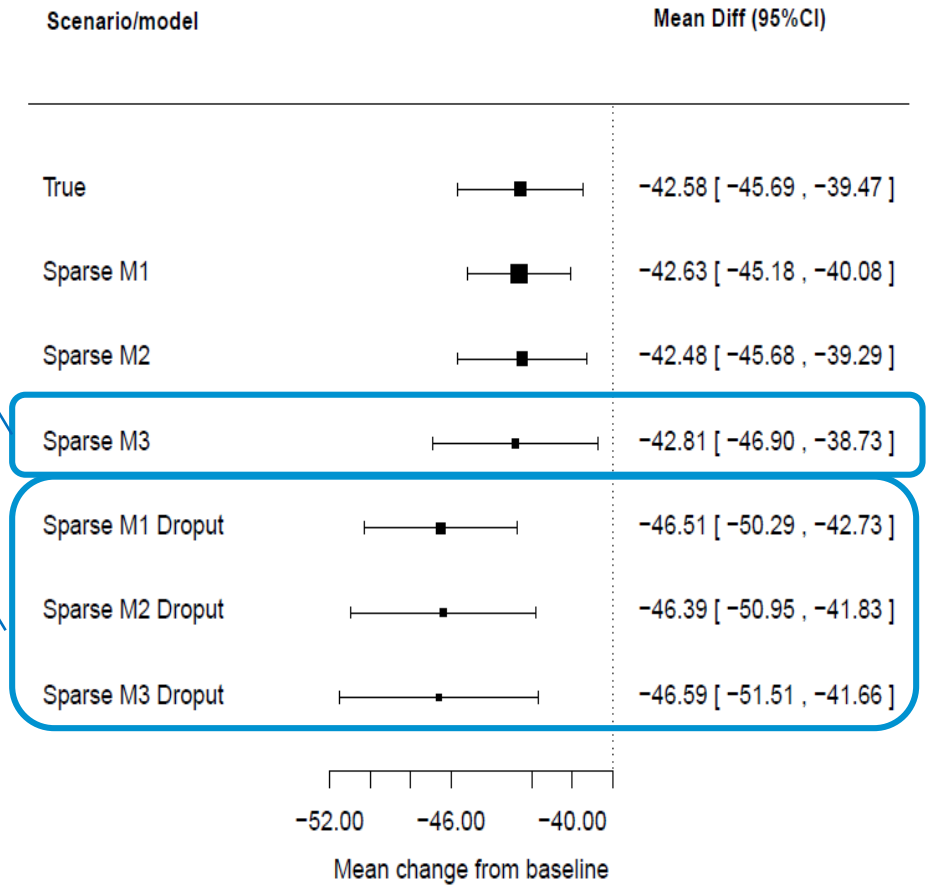
Angela Birnbaum, PhD

BACKUP SLIDES

Implications in application to clinical trial design/success criteria

1. If the purpose of the MBMA is to use the comparator information to design a study for a similar drug of interest

- Slight overestimation of variance by M3 can lead to slight inflation of sample size
- Failure to account for dropout can lead to overoptimistic effect benchmark
  - May not have effect on sample size



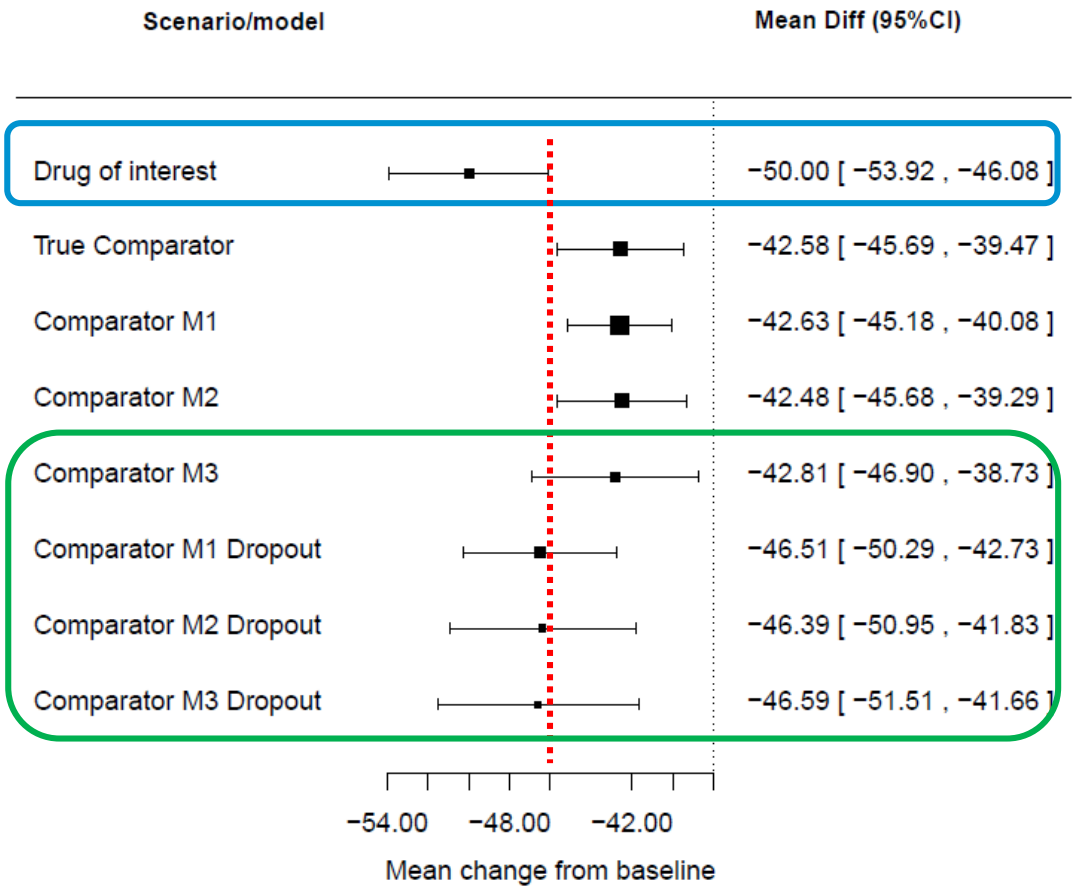
Implications in application to clinical trial design/success criteria

2. If the purpose is to make a decision about whether a drug of interest sufficiently differentiate from a comparator

Assuming success criteria:

-95% CI of week 12 mean CFBL excludes 38

-95%CI does not overlap with the comparator



Study designs

Study ID	Sample size (per dose)		Doses	Time-points	
	Small	Large		Sparse	Dense
1	50	100	0, 50, 100, 200, 400	0, 3, 6	0, 1, 3, 6
2	50	100	0, 100, 300, 500,1000	0, 3, 6	0, 1, 3, 6
3	50	100	0, 100, 200, 300, 400	0, 3, 6, 12	0, 1, 3, 6, 9, 12
4	50	100	0, 300, 400, 500, 600	0, 3, 6, 12	0, 1, 3, 6, 9, 12
5	100	200	0, 200, 400	0, 6	0, 3, 6
6	100	200	0, 400, 600	0, 6	0, 3, 6
7	100	200	0, 200, 600	0, 6	0, 3, 6
8	250	500	0, 200, 400	0, 6, 12	0, 3, 6, 9, 12
9	250	500	0, 400, 600	0, 6, 12	0, 3, 6, 9, 12
10	250	500	0, 200, 600	0, 6, 12	0, 3, 6, 9, 12

Simulation model

Assume individual model:

$$Yij(t) = BL_{ij}(1 - PBO_{ij})(1 - DRUG_{ij})$$

$$BL_{ij} = BL + \eta_{ij}^{BL,ind} + \eta_{i}^{BL,study}$$

$$PBO_{ij} = (PMAX + \eta_{ij}^{PMAX,ind}) *$$

$$(1 - exp^{-KPBO(\exp(\eta_{ij}^{KPBO,ind} + \eta_{i}^{KPBO,study}))time})$$

$$DRUG_{ij} = \frac{EMAX * Dose}{ED50 + Dose}$$, where i=study, j=subject

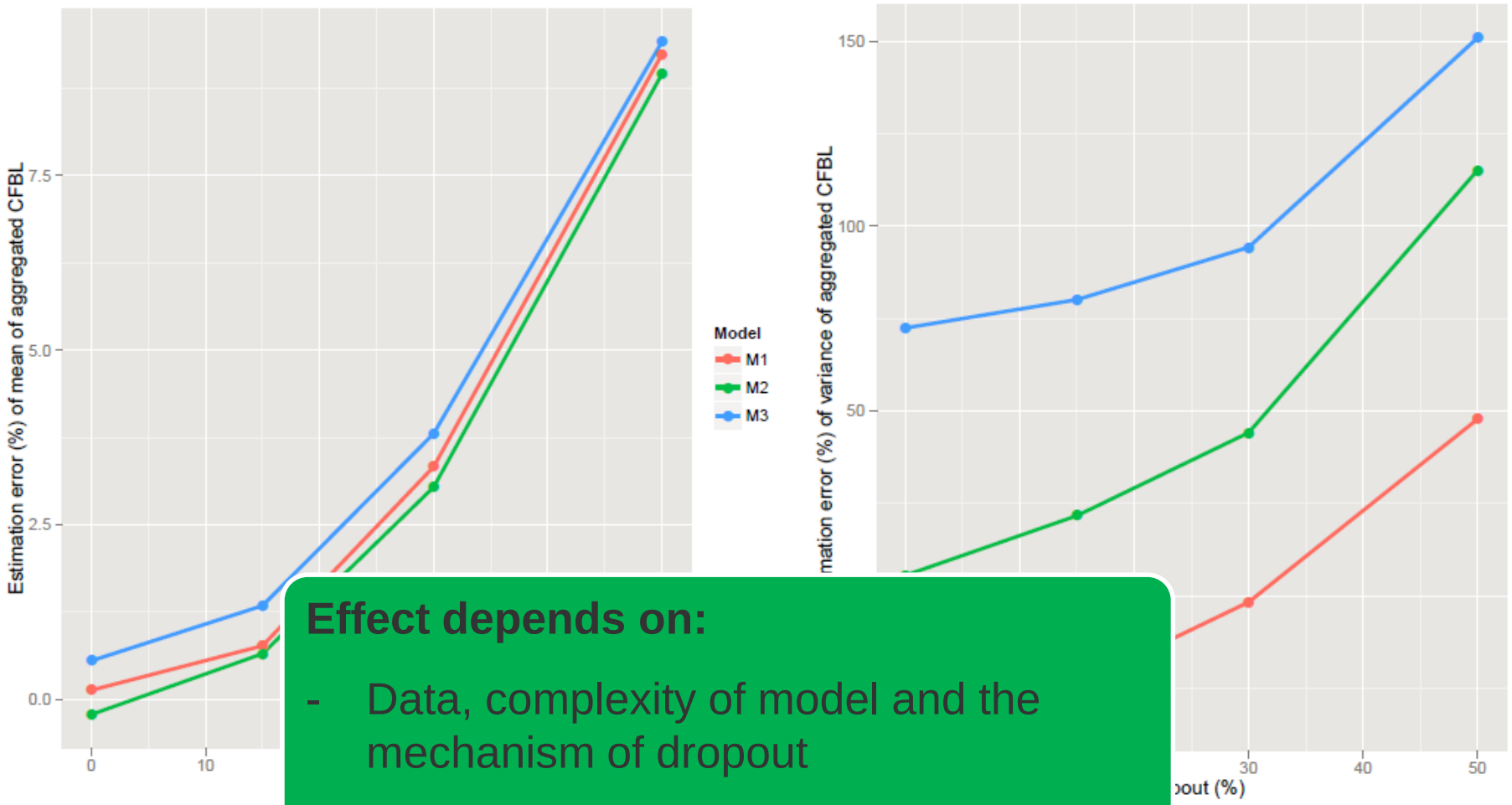
Dropout model:

Censor simulated data based on hazard function:

$$h(t) = \text{baseline hazard} * \exp(beta * previous\ observation)$$

Parameters	Values
PMAX	0.2
KPBO	0.5
BL	100
EMAX	0.4
ED50	200
Baseline hazard	0, 0.01, 0.03
Beta	0, 0.01, 0.02, 0.03
IIV PMAX	0.05
IIV KPBO	D1: 0.2 D2: 0.4
IIV BL	D1: 4 D2: 8
ISV BL	1
ISV KPBO	0.1
SIGMA	1

Sizable estimation error beyond 30%



Effect depends on:

- Data, complexity of model and the mechanism of dropout

Example of estimating IAV

```
IAV=0
IF(ARM.EQ.1) IAV=ETA(1)
IF(ARM.EQ.2) IAV=ETA(2)
IF(ARM.EQ.3) IAV=ETA(3)
IF(ARM.EQ.4) IAV=ETA(4)
IF(ARM.EQ.5) IAV=ETA(5)
IF(ARM.EQ.6) IAV=ETA(6)

BASE=TVBASE*EXP(IAV)

$OMEGA BLOCK (1) 0.05
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) SAME
```