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

Levels of random effects in MBMA

1) Inter-study variability
   - Analogous to inter-individual variability in pop analysis
2) Inter-arm variability
   - Analogous to inter-occasion variability in pop analysis
   - Often weighted by study arm size
3) Residual variability
   - Often weighted by study arm size

Ways to account for correlation within arm

1. ETA for each arm (similar to IOV approach)
2. Allow compound symmetric correlation of residuals at arm level (L2)
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:

A. Different sample sizes
   - Small n
   - Large n

B. Number of time-points
   - Sparse
   - Dense

Dropout

C. Varying dropout dependable on previous observation
D. Different inter-individual variability (IIV)
   - Low IIV
   - High IIV

E. Varying baseline dropout hazard
Simulation
Simulate 100 datasets (each with 10 studies) from assumed individual model:

\[
Response(t) = BL \times \left( 1 - P_{max} \times \left( 1 - e^{-K_{BO} \times \text{time}} \right) \right)
\]

\[
\left( 1 - \frac{E_{max} \times \text{Dose}}{ED_{50} + \text{Dose}} \right)
\]

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
<th>Small n</th>
<th>Large n</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMAX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPBO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<tr>
<td>ISV_BL</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

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

0%, 6%, 15%
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

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Angela Birnbaum, PhD
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.

### Table: Mean Diff (95%CI)

<table>
<thead>
<tr>
<th>Scenario/model</th>
<th>Mean Diff (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True</td>
<td>-42.58 [-45.69, -39.47]</td>
</tr>
<tr>
<td>Sparse M1</td>
<td>-42.63 [-45.18, -40.08]</td>
</tr>
<tr>
<td>Sparse M2</td>
<td>-42.48 [-45.68, -39.29]</td>
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<tr>
<td>Sparse M3</td>
<td><strong>-42.81 [-46.90, -38.73]</strong></td>
</tr>
<tr>
<td>Sparse M1 Dropout</td>
<td>-46.51 [-50.29, -42.73]</td>
</tr>
<tr>
<td>Sparse M2 Dropout</td>
<td>-46.39 [-50.95, -41.83]</td>
</tr>
<tr>
<td>Sparse M3 Dropout</td>
<td>-46.59 [-51.51, -41.66]</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Sample size (per dose)</th>
<th>Doses</th>
<th>Time-points</th>
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<tbody>
<tr>
<td></td>
<td>Small</td>
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</tr>
<tr>
<td>10</td>
<td>250</td>
<td>500</td>
<td>0, 200, 600</td>
</tr>
</tbody>
</table>
Simulation model

Assume individual model:

\[ Y_{ij}(t) = B_{Lij} (1 - PBO_{ij})(1 - DRUG_{ij}) \]

\[ B_{Lij} = BL + \eta_{ij}^{BL,ind} + \eta_{i}^{BL,study} \]

\[ PBO_{ij} = (P_{MAX} + \eta_{ij}^{P_{MAX},ind}) * (1 - e^{-KPBO(\exp(\eta_{ij}^{KPBO,ind} + \eta_{i}^{KPBO,study})))time}) \]

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

Dropout model:

Censor simulated data based on hazard function:

\[ h(t) = \text{baseline hazard} * \exp(betata * \text{previous observation}) \]
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