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Missing Data Sensitivity Analysis of a Continuous Endpoint – An Example from a Recent Submission
Missing Data

Missing data can make results ambiguous!

In recent years there has been an increased focus on missing data issues by

- Regulatory authorities (FDA, EMA, PMDA, HealthCanada)
- Reviewers from high-ranked journals, eg NEJM (Ware et al., 2012)
- FDA advisory committees (AdComs)
Missing data guidance

• Issues are not new, renewed interest mainly driven by “new” regulatory guidance:
  ▪ CHMP Guideline on Missing Data in Confirmatory Clinical Trials (2010)
  ▪ The Prevention and Treatment of Missing Data in Clinical Trials (2010)
    Panel on Handling Missing Data in Clinical Trials by the National Research Council (initiated by the FDA)
Terminology-1

- Missing completely at random (MCAR): Probability of an observation being missing does not depend on observed or unobserved measurements
  - Example: Lab sample accidentally broken, Patient moves to another city for non-health reasons

- Missing at random (MAR): Probability of an observation being missing depends only on observed measurements
  - Example: Probability of patient withdrawal may depend on baseline. After accounting for baseline, it is independent of follow-up outcome
Terminology-2

- Missing not at random (MNAR): Missingness mechanism depends on the unobserved variable, even after taking into account information of the observed variables.
  - Example: After a series of visits with favourable outcome, a subject drops out - due to unobserved lack of efficacy.
  - MNAR requires explicit modeling of the missingness mechanism.
Example: Riociguat in PAH

- Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by high pressure in the pulmonary arteries, which can ultimately lead to right heart failure and death.

- Riociguat is the first member of a new drug class, the sGC stimulators.

- It has been investigated in patients with pulmonary arterial hypertension in the randomized, placebo-controlled, phase III study PATENT-1

- PATENT-1 and its sister study CHEST-1 (in CTEPH patients, another PH subtype) finalized middle of 2012
  - Submission EMA and FDA February 2013
  - FDA AdCom August 2013
PATENT-1 study

- Primary outcome: Change from baseline in 6 minute walking distance (6MWD) after 12 weeks, a measure of exercise capacity.
- 6MWD has been measured at baseline and week 2, 4, 6, 8 and 12.
- 6MWD values can be assumed to be approximately normally distributed, although there is a tendency for outlying observations.
- Primary analysis: ANCOVA of week 12 values, with baseline 6MWD, stratification factors and treatment group as fixed effects.
- Primary p-value based on stratified Wilcoxon test, in case of rejection of normality of ANCOVA residual through Shapiro-Wilk test.
PATENT-1 study

- Missing data for primary analysis imputed using last observation carried forward (LOCF) and worst case imputation (0m) in case of death or clinical worsening without termination visit
- Single imputation method, generally not recommended as primary by guidelines
- Analysis strategy planned in 2008
- No criticism at that time
Preplanned sensitivity analysis - 1

- Got advice from Mike Kenward from London University

- Descriptive analysis, Plots for mean change from baseline by time of drop-out (spaghetti plot), Kaplan-Meier plot for time to drop-out

- Analysis under missing at random assumption (MAR):
  - Mixed model repeated measures (MMRM) analysis of whole longitudinal profile with unconstrained time profiles and covariance matrices
MMRM model

- Can be implemented in SAS using PROC MIXED
- No explicit imputation of missing data
- Implicitly, the future statistical behaviour of those who dropout given their past measurements is assumed to be the same as those who remain with the same history.

- Estimand is the effect that would have been seen, if all patients had completed the study.
Preplanned sensitivity analysis - 2

- Analysis under missing not at random assumption (MNAR):
  - Assumed that on average patient’s 6MWD deteriorates by a certain amount for each visit after drop-out
  - Used several scenarios, eg riociguat 20m decrease per visit after drop-out and no decrease for placebo
  - Falls into the class of pattern mixture models, also called delta method of sensitivity analysis (Carpenter & Kenward, 2008)
  - Implemented using multiple imputation to get correct variability estimate
Application of multiple imputation requires three steps:

i) imputation
ii) analysis
iii) pooling
Multiple imputation – 2

i) Imputation

- Imputations done via Markov Chain Monte Carlo (MCMC) method
- Creates multiple imputations by drawing simulations from a Bayesian predictive distribution, using all available 6MWD measurements and covariates from ANCOVA
- PROC MI in SAS for normal data
- Generated 50 completed data sets
- Penalties for delta method subtracted from completed data
Multiple imputation – 3

ii) Analysis
   • Primary ANCOVA applied to week 12 data for each completed data set

iii) Pooling
   • Combining individual point estimates and variance estimates according to Rubin’s rule using PROC MIANALYSE
Additional analysis for AdCom/EMA

• Additional single imputation methods:
  • Pure LOCF
  • Completer’s analysis

• Tipping point analysis for delta method
  • Increase penalty for riociguat while having no penalty for placebo, until result no longer statistically significant
Observed data

- 6MWD at week 12 measured for 233/254 (92%) of riociguat and 112/126 (89%) placebo patients (2:1 randomization)

<table>
<thead>
<tr>
<th>Method</th>
<th>Treatment effect</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis: LOCF with worst case imputation</td>
<td>35.8m</td>
<td>[20.1m; 51.5m]</td>
</tr>
</tbody>
</table>
Observed data (cont.)

Spaghetti plot 6MWD for riociguat

![Spaghetti plot image]

N=3  N=4  N=233

-240  -220  -200  -180  -160  -140  -120  -100  -80  -60  -40  -20  0

**Change from BL (m)**

- **fully observed**
- **dropout week 2**
- **dropout week 4**
- **dropout week 6**
- **dropout week 8**

**Weeks from BL**

0  2  4  6  8  12
Patients dropping out tend to have lower values than completers.

Far more pronounced for placebo patients.

Assumption of further deterioration after drop-out seems reasonable.
## Results of planned sensitivity analyses

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Decreasing slope penalty/visit</th>
<th>Treatment effect</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRM</td>
<td>-</td>
<td>30.0m</td>
<td>[16.1m; 43.9m]</td>
</tr>
<tr>
<td>Delta method, „Conservative“</td>
<td>Rio -20m / Plac -0m</td>
<td>27.2m</td>
<td>[13.4m; 41.0m]</td>
</tr>
<tr>
<td>Delta method, „Fair“</td>
<td>Rio -20m / Plac -20m</td>
<td>35.0m</td>
<td>[20.5m; 49.6m]</td>
</tr>
</tbody>
</table>

- Lower confidence interval limit always above 0m  
  => clear evidence of statistically significant treatment effect

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Results of further sensitivity analyses

- Also for extra single imputation analyses

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<th>Method</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Completer’s analysis</td>
<td>25.4m</td>
<td>[13.0m; 37.8m]</td>
</tr>
<tr>
<td>LOCF</td>
<td>30.7m</td>
<td>[17.9m; 43.4m]</td>
</tr>
</tbody>
</table>

- Lowest treatment effect estimate for completer’s analysis, due to more drop-outs in the placebo group, which also had lower values prior to drop-out.
- Explains also that MMRM gives lower treatment effect, drop-outs are brought closer to completers
### Results of further sensitivity analyses-1

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<tr>
<td>Delta, „Tipping point“</td>
<td>Rio -71m / Plac -0m</td>
<td>16.8m</td>
<td>[-0.2m; 33.8m]</td>
</tr>
</tbody>
</table>

- Need to increase penalty for riociguat to -71m per visit after drop-out until statistical significance is lost
- Would imply a very steep decline after drop-out, even giving negative 6MWD values for many patients (Mean 6MWD at baseline 364m, some patients in the 200’s)
- So positive treatment effect seems unquestionable
FDA comments

- FDA Statisticians in the AdCom Briefing Book:

  “PAH trials are in general, prone to have substantial missing data. Handling those missing observations is difficult and the best way to deal with it is to try to avoid it. These two trials had relatively few subjects with missing data.”

  “… the sponsor conducted many sensitivity analyses to examine the effect of different assumptions on the missing data. These sensitivity analyses consistently showed a moderately large effect on the primary endpoint.”

=> Missing data were not an issue at the AdCom, most discussion about which maximum dose to licence

• Vote 11:0 for approval

• Approved in the US for both PAH and CTEPH in October 2013
Other authority comments

- **EMA**
  - Some clarifying questions on the delta method and implementation of multiple imputation
  - Asked for pure LOCF and completer’s analysis, also a different imputation for some secondary end points
  - No further questions with respect to missing data after first round
  - Approved for PAH/CTEPH March 2014

- **Other authorities**
  - No missing data questions
If a similar trial was planned today…

- Would try to have more follow-up after treatment discontinuation (although maybe difficult for 6MWD)
- Would not use single imputation as primary analysis anymore
  - Would propose the mixed model, relatively simple and no simulation required
  - Although delta method useful and sensible, difficult to specify one scenario as the primary in advance
- The range of preplanned sensitivity analyses was generally adequate, but add pure LOCF and completer’s analysis upfront
Conclusions

• In our case the chosen range of sensitivity analysis demonstrated the robustness of the study results.

• Preplanning a missing data sensitivity analysis adds to its credibility and is in line with regulatory recommendations.

• Important to consider how to avoid missing data in planning stage.
References


Thank you!
Back-up slides
Multiple imputation – Pooling

iii) Pooling:

• With $m$ imputations, $m$ sets of the point and variance estimates for a parameter $\theta$ can be computed. The combined point estimate for $\theta$ is the average of the $m$ complete-data estimates:

$$\hat{\theta}_{MI} = \frac{1}{m} \sum_{i=1}^{m} \hat{\theta}_i$$

• The within-imputation variance is the average of the $m$ complete-data $\hat{U}_i$ estimates

$$\overline{U} = \frac{1}{m} \sum_{i=1}^{m} \hat{U}_i$$

• and the between-imputation variance is

$$B = \frac{1}{m-1} \sum_{i=1}^{m} (\hat{\theta}_i - \overline{\theta}_{MI})^2$$

• Then the variance estimate associated with $\overline{\theta}_{MI}$ is the total variance

$$T = \overline{U} + (1 + \frac{1}{m})B$$
KM plot for time to withdrawal

Figure: Kaplan-Meier plot for time to withdrawal (safety analysis set)