Missing values in clinical trials:
Regulatory requirements and two examples

Workshop “Missing Data”
Köln, 2004-12-03

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Overview

ICH: Guideline E9, Section 5.3
CPMP: Points to consider on Missing Data
Common approach, problems
Example 1 (patients without data)
Example 2 (extrapolation)
References
Missing values

- potential source of bias
- every effort should be undertaken ... concerning collection of data
- there will almost always be some missing data
- trial may be valid if methods of dealing with missing data are sensible and pre-defined
- no universally applicable method of handling missing data available
- assess sensitivity of the results to the method of handling missing data
CPMP: Points to Consider on Missing Data

- Complete case analysis cannot be recommended as primary analysis in confirmatory trials
- LOCF / best or worst case imputation likely to be acceptable
- Simple imputation methods may be considered if applied conservatively, although variability may be underestimated
- Options
  - Maximum Likelihood using EM algorithm
  - Multiple imputation
Common Approach, problems

• In summary, guidelines provide neither any guidance on more complex, model-based methods, nor any comparison of different analysis strategies
  - correct, guidelines describe “what” but not “how”

• Definition of the Full Analysis Set typically excludes patients with
  - failure to take at least one dose of trial medication
  - lack of any data post randomisation
  - lack of baseline data
Common Approach, problems

• Handling of missing data is mainly restricted to simple imputation methods like LOCF

• Censoring now not considered

• Little experience with more complex, model-based methods for quantitative data

• Current practice - as above - is accepted by regulators *(as long as the number of excluded patients is small and balanced between treatments)*
Example 1 (patients without data)

- Placebo controlled double-blind study
- 2 groups of 150 patients each
- Primary endpoint: Number of events / week, by patient diary
- Treatment duration: 3 months, recording in weeks 4, 8, 12 + baseline

- 30 patients without data on treatment, 25 on active, 5 on placebo
  - *mostly early drop-outs due to expected AEs*
Example 1 (patients without data)

Initial analysis:
• based on set of patients with at least one value on treatment

Authority response:
• Primary analysis should include all randomised subjects, irrespective of receiving post-baseline measurements.
• The protocol should address a data imputation plan to manage such cases.
• A “modified ITT” group, defined as all subjects who are randomised and have at least one post-baseline measurement, may be acceptable as sensitivity analysis.
Example 1 (patients without data)

Decision made to use imputation.

Imputation strategy (for subjects without post-baseline value):
• Subjects who discontinue due to one of the 5 most common AEs leading to discontinuation
• Subjects who discontinue due to any other AE
• Subjects who discontinue due to lack of efficacy
Example 1 (patients without data)

• Subjects who discontinue due to one of the 5 most common AEs leading to discontinuation, get their post-baseline value imputed using the median percent change
  - for subjects in their treatment group
  - who report one of these AEs
  - but have a value on treatment.

• Subjects who discontinue due to any other AE, get their post-baseline value imputed using the median percent change
  - for subjects in their treatment group
  - who do not have any of the 5 most common AEs leading to discontinuation
  - who do not discontinue due to lack of efficacy
  - but have a value on treatment.
Example 1 (patients without data)

Imputation for subjects without post-baseline value (cont.):
• Subjects who discontinue due to lack of efficacy get their baseline value carried forward.

Remarks:
(1) The **median % change** has no predictive distribution; however, variability comes in via the baseline values.
(2) The MAR assumption can be medically justified by the dropout mechanism (expected AE, unrelated to efficacy).

Subjects with post-baseline values and no 12-week values: LOCF.
Example 1 (patients without data)

Results of additional analysis not yet ready

Feed-back of authority not yet received
Example 2 (extrapolation)

- Active-controlled double-blind study (noninferiority trial)
- 2 groups of patients (diabetics with albuminuria):
  - 120 Angiotensin Receptor Blocker
  - 130 Angiotensin-Converting Enzyme inhibitor
- Primary endpoint: GFR [mL/min/1.73m**2] (typically declining over time)
- Treatment duration: 5 years, recording yearly + baseline
Example 2 (extrapolation)

- 17 patients dropped out in each group before 1st post-baseline measurement
- Further 21 patients dropped out on ARB, 27 on ACEi
- Drop-out unrelated to efficacy (with 3 exceptions), therefore MAR assumption reasonable
- LOCF applied to drop-outs may
  - overestimate mean value at study termination
  - underestimate variation
Example 2 (extrapolation)

Possible options:
• LOCF
• Regression methods to calculate individual slopes
• Multiple imputation
Example 2 (extrapolation)

Multiple imputation procedure:

1. Impute missing values using an appropriate model that incorporates random variation (e.g. MCMC, regression). Do this M times (usually 3 – 10), producing M “complete” datasets.

2. Perform analysis on each dataset using standard complete-data methods.

3. Average values of parameter estimates across the M samples to produce a single point estimate; calculate standard errors by
   a) averaging the squared SEs of the M estimates
   b) calculating the variance of the M estimates across samples
   c) combining the two quantities
Example 2 (extrapolation)

Model for data:

\[ Y_{im[t]} = \mu + [t*] \alpha * y_{bas} + \tau_m + \epsilon_{im}, \]

whereby

- \( y_{im} \) is the GFR measurement for patient \( i \) in treatment group \( m \),
- \( \mu \) is the overall mean,
- \( y_{bas} \) is the baseline GFR value,
- \( t \) is the time (in years) (not relevant for LOCF analysis)
- \( \alpha \) is the linear regression coefficient for the baseline dependence,
- \( \tau_m \) is the effect of treatment \( m \), fixed (with boundary condition \( \tau_1 = 0 \))
- \( \epsilon_{im} \) is the residual error, i.i.d. according to \( N(0, \sigma) \).

This is extended to a mixed model by the multiple imputation.
### Example 2 (extrapolation)

#### Results:

<table>
<thead>
<tr>
<th></th>
<th>$\alpha$</th>
<th>SE($\alpha$)</th>
<th>$\tau_2$</th>
<th>SE($\tau_2$)</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCF</td>
<td>-0.080</td>
<td>0.053</td>
<td>2.52</td>
<td>2.30</td>
<td>16.8</td>
</tr>
<tr>
<td>Extrapol. from 1 year decline</td>
<td>-0.020</td>
<td>0.079</td>
<td>3.76</td>
<td>3.39</td>
<td>24.8</td>
</tr>
<tr>
<td>Mult. imp., M=5 (*)</td>
<td>-0.018</td>
<td>0.064</td>
<td>3.25</td>
<td>2.95</td>
<td></td>
</tr>
<tr>
<td>From - to</td>
<td>-0.053 – +0.007</td>
<td>0.056 – 0.061</td>
<td>1.88 – 5.36</td>
<td>2.46 – 2.65</td>
<td>18.0 – 19.4</td>
</tr>
</tbody>
</table>

(*) Predictive distribution from MCMC, multivariate normal distribution, Jeffreys’ prior, ML startpoint
Example 2 (extrapolation)

Results:

For the investigation of changes per year, at least 1 post-baseline value is still necessary.

Work in Progress!
References


2. Committee for Proprietary Medicinal Products: “Points to Consider on Missing Data”. November 2001
   http://www.emea.eu.int/pdfs/human/ewp/177699EN.pdf


5. Mallinckrodt CH et al.: The effect of correlation structure on treatment contrasts estimated from incomplete clinical trial data with likelihood-based repeated measures compared with last observation carried forward ANOVA. Clinical Trials 2004; 1: 477-489