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Missing values in clinical trials: Regulatory requirements and two examples

Workshop “Missing Data”

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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

ICH: Guideline E9, Section 5.3

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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

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- 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

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- 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)

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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)

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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)

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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)

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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)

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- 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)

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Possible options:

- LOCF
- Regression methods to calculate individual slopes
- Multiple imputation

Example 2 (extrapolation)

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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)

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Model for data:

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

whereby

y_{im} is the GFR measurement for patient i in treatment group m,

μ is the overall mean,

y_{bas} is the baseline GFR value,

t is the time (in years) (not relevant for LOCF analysis)

α is the linear regression coefficient for the baseline dependence,

τ_m is the effect of treatment m, fixed (with boundary condition $\tau_1=0$)

ε_{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)

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Results:

	α	SE(α)	τ_2	SE(τ_2)	σ
LOCF	-0.080	0.053	2.52	2.30	16.8
Extrapol. from 1year decline	-0.020	0.079	3.76	3.39	24.8
Mult. imp., M=5 (*)	-0.018	0.064	3.25	2.95	
From - to	-0.053 - +0.007	0.056 – 0.061	1.88 – 5.36	2.46 – 2.65	18.0 – 19.4

(*) Predictive distribution from MCMC, multivariate normal distribution, Jeffreys' prior, ML startpoint

Example 2 (extrapolation)

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Results:

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

Work in Progress!

References

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