Handling Missing Data in Clinical Trials

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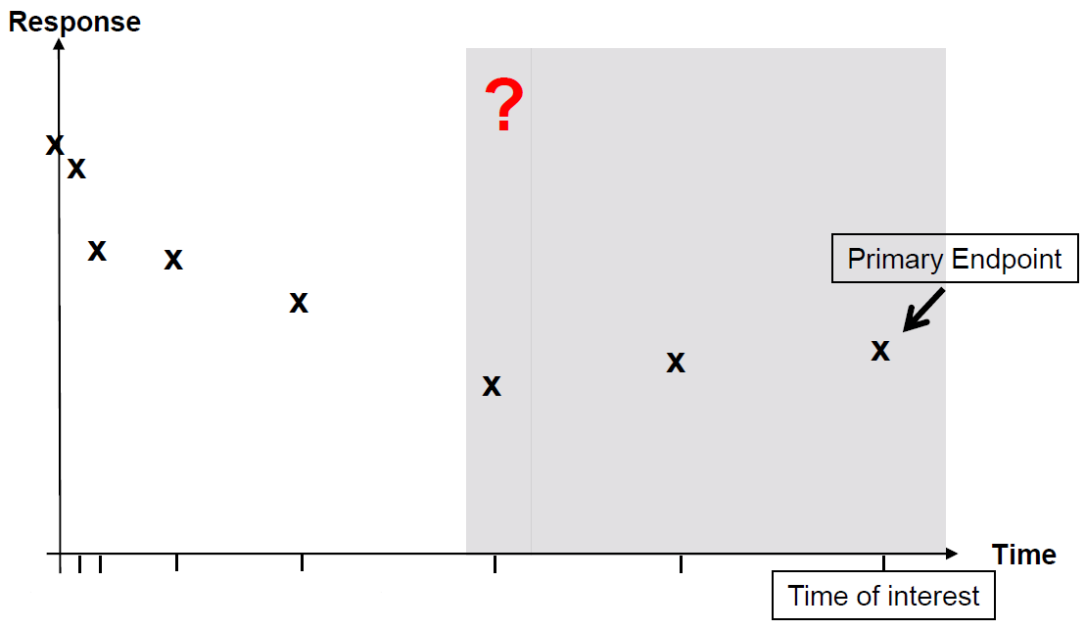
Missing data in clinical trials

- In a clinical trial context, missing data are data we intended to collect, but for one reason or another did not
- Patients may skip a single visit or drop out/discontinue from the study such that the primary endpoint of interest is missing



Reasons for missing data

Primary endpoint may be missing because of

- lack of efficacy
- patients consider themselves to have fully recovered
- unacceptable adverse event
- practical or administrative reason (e.g. patient moves away)

Problematic as related to efficacy or safety

Missing data and ICH-E9

- Missing data are a potential source of bias.
- Avoid if possible (!)
- With missing data, a trial may still be regarded as valid if the methods are sensible, and preferably predefined.
- There can be no universally applicable method of handling missing data
- The sensitivity of conclusions to methods should thus be investigated, particularly if there are a large number of missing observations

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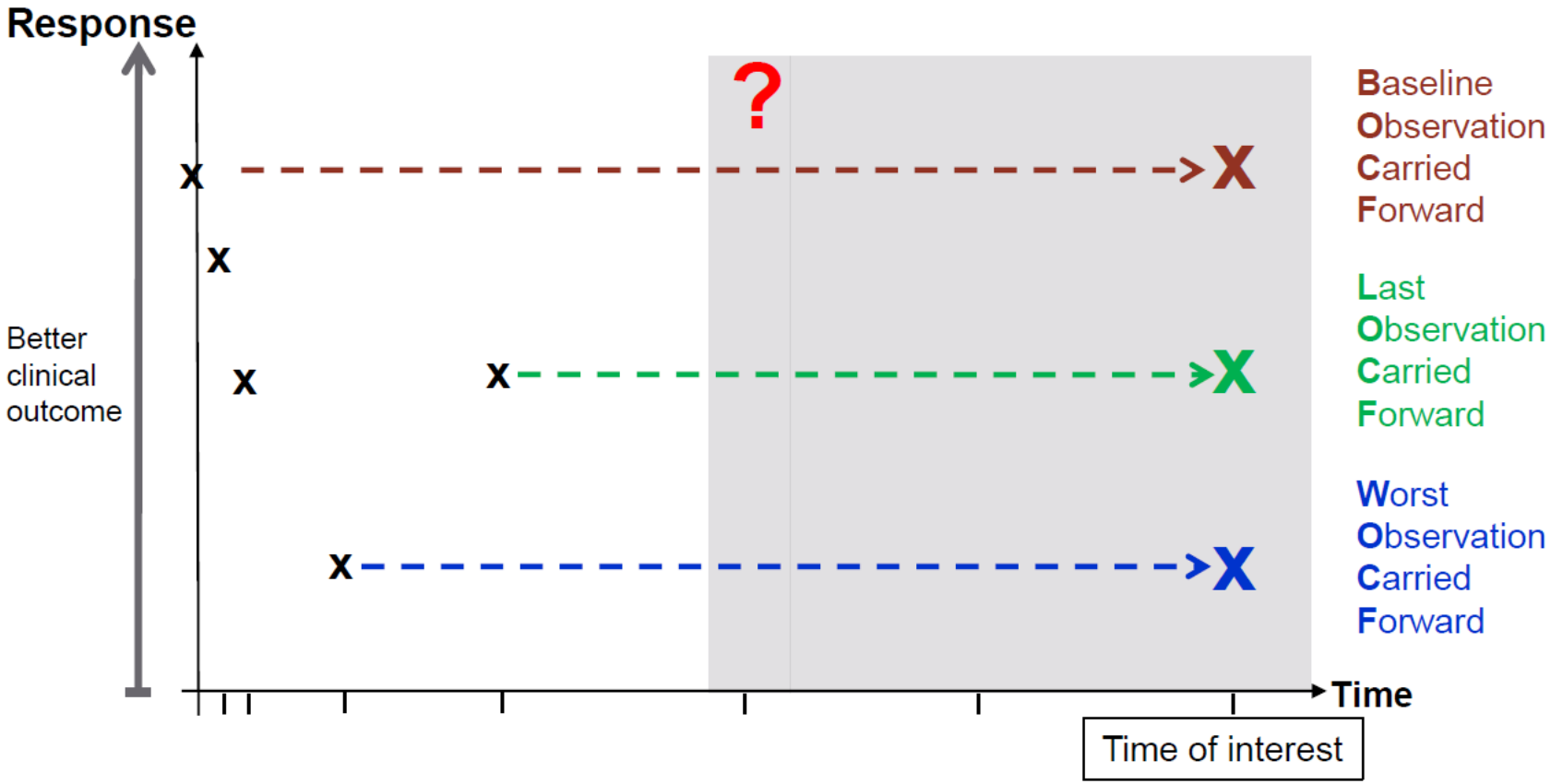
Guideline on Missing Data in Confirmatory Clinical Trials

Missing data may compromise randomisation

- Randomization is needed to achieve comparable groups such that differences between groups must be due to treatment
- If subjects that drop out are excluded from the final analysis, it may create important systematic differences among groups $\rightarrow$ complete case analyses are potentially biased
- For example, consider 2-arm comparison where:
  - many active arm patients with poor outcomes drop out
  - no placebo arm patients drop out
  - treatment effect estimate based on completers is larger than in reality
- Maintain comparable groups by including every subject who is randomized regardless of drop out
- Question: How to include a subject for whom the primary endpoint is missing?

Carry forward analysis



Last Observation Carried Forward as a Conservative Approach?

- Alzheimer's disease and LOCF:
  - Patient's condition is expected to deteriorate over time
  - LOCF is likely to give overly optimistic estimates for both treatment (Active/Placebo)
  - Earlier withdrawals in the Active treatment group (e.g. due to adverse events)
  - Biased estimate of treatment difference in favour of Active

Last Observation Carried Forward as a Conservative Approach?

- Depression and LOCF:
  - Patient's condition improve over time
  - LOCF is likely to give conservative estimates for both treatment (Active/Placebo)
  - Earlier withdrawals in the Active treatment group (e.g. due to adverse events)
  - Biased estimate of treatment difference in favour of placebo
  - LOCF is considered as appropriate

Regulatory authorities and LOCF

- FDA 2012: "... you proposed to apply LOCF approach to impute missing data. In general, this approach is not acceptable because it assumes that patient outcome does not change after dropout."
- FDA 2013: "... using the LOCF method for dealing with missing data is no longer recommended by the Division ..., please specify a primary statistical analysis that does not rely on LOCF and that is in line with NAS recommendations."
- CHMP 2013: "... the adequacy of the LOCF approach is particularly questionable, since ... cannot be assumed as being stable over time, hence contradicting the LOCF assumption. Furthermore it is known that deterministic imputations may bias the variance estimates downward."

Mixed-effects Model Repeated Measurements (MMRM) and missing data

- The MMRM uses all the observed data from repeated measurements to adjust the data which was missing on an individual subject
- The MMRM takes the correlation of the repeated observations within subjects into account

Sensitivity analyses

- Sensitivity analyses can be defined as a set of analyses where the missing data are handled in a different way as compared to the primary analysis
- It should be noted that obtaining similar results from a range of methods that make similar or the same assumptions does not constitute an adequate set of sensitivity analyses
- The sensitivity analyses should show how different assumptions influence the results obtained

Binary outcomes and missing data

- Response ($\geq$ 50% reduction in MADRS) and remission (MADRS$\leq$ 10) in depression study
- Complete case, LOCF, non-reponse/remission imputation