EU regulatory concerns about missing data: Issues of interpretation and considerations for addressing the problem

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• No conflicts of interest

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Agenda

• Current regulatory basis
• Sources of missing data
• Missing data and trial validity
• Example: Simulation of a depression trial
• Interpretational issues
  • Estimands
• Addressing the problem
• Sensitivity analyses
• Conclusions
Regulatory discussion on missing data in confirmatory Phase III studies (1)

- Relevant regulatory documents
  - EMA Guideline on Missing Data in Confirmatory Clinical Trials (2010)
  - ICH Concept Paper E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials (2014)
Regulatory discussion on missing data in confirmatory Phase III studies (2)

• Issues to discuss:
  • How to avoid missing data?
  • How to consider/address (non-)adherence?
  • measuring efficacy assuming
    • perfect adherence or
    • real adherence or
    • in those patients who tolerate treatment
  • How to treat missing data?
    • how to treat missing data w.r.t. adherence?
    • and how to interpret analysis/missing data imputation
Sources of missing data in confirmatory Phase III studies

- **Treatment discontinuation**
  - due to
    - adverse events
    - lack of efficacy
    - others
  - often leads to missing data
    - follow-up of discontinuing patients avoids missingness

- **Study drop-out**
  - treatment discontinuation and no follow-up

- **Intermediate missing data**
  - usually less relevant
Missing data in CNS trials

• Substantial amount of drop-outs in
  • depression
  • drop-out may be up to 50%
  • average drop-out rate 20 to 30%
  • others: schizophrenia, Alzheimer

• Follow-up
  • usually poor follow-up of patients that discontinue treatment
  • lack of information on non-adherent patients
  • but: estimation of “de-facto” efficacy would require
    • follow-up of patients that discontinue treatment
    • targeting a “treatment-policy estimand”
      • treatment benefit in all subjects irrespective of treatment adherence
Regulatory concerns about missing data in confirmatory clinical trials (1)

- **Analysis in completers only**
  - not compliant with ITT principle
  - treatment dependent patient selection
  - biased effect estimates and lack of type-1 error control
  - invalid conclusions (e.g. false positive decisions ↑)

- **Missing data imputation**
  - based on specific assumptions regarding (unknown) missing data
  - requires definition of a relevant estimation target (*estimand*), e.g.
    - treatment benefit if all patients adhered
    - treatment benefit in all patients regardless of adherence
    - treatment benefit attributable to the randomized treatment
    - treatment benefit in those who adhere to treatment
Regulatory concerns about missing data in confirmatory clinical trials (2)

- **Missing data imputation**
  - potential concerns about underlying assumptions and resulting validity
    - e.g. LOCF usually invalid in progressive diseases (e.g. dementia)
  - potential concerns about target of estimation
    - e.g. longitudinal models may target treatment benefit if all patients adhered to treatment
      - hypothetical target that appears less relevant
  - usually several sensitivity analyses required
    - to show robustness of the results w.r.t. to underlying assumptions
    - to evaluate different estimands
“De-facto” and “de-jure” estimands

- treatment dropout
- "retrieved" data
- placebo active treatment
- de-facto (difference in all randomized patients)
- de-jure (difference if all patients adhered)

end of trial
Example: Simulation of depression trials
BfArM research project on missing data and non-adherence

• Longitudinal data (Hamilton Score)
• Non-adherence: Treatment discontinuation
• Some data were collected after treatment discontinuation
• Different drop-out mechanisms
  • treatment dropout (TD)
  • study dropout (SD)
    • SD time ≥ TD time
    • “retrieved data” from TD to SD
• Data generation
  • according to a two-piece linear mixed model

Example: Simulation of depression trials
BfArM research project on missing data and non-adherence

Bias of different analysis strategies for de-jure and de-facto estimands

- **true de-jure effect = 2** (difference if all subjects adhered)
- **true de-facto (treatment policy) effect = 0** (difference in all subjects)
- **Analysis strategies**
  - 1: Multiple Imputation (Pattern-Mixture Model)
  - 2: Joint Model of drop-out and outcome
  - 3: Mixed Model, all data
  - 4: Mixed Model, only data under treatment

Example: Simulation of depression trials

Conclusions

• Longitudinal Mixed Model analysis of on-treatment data
  • targets de-jure estimand
• Longitudinal Mixed Model analysis of all data (off- and on-treatment)
  • still shows relevant bias w.r.t. de-facto (treatment policy) estimand if follow-up is poor
• “Joint model” of outcome and time to drop-out
  • behaves best
  • but would require further investigation on robustness
Proposed procedure

Be clear about the trial’s objective (i.e. primary estimand) before deciding trial design and analysis

- Primary estimand
  - Clinical trial design
    - Customize the design considering the primary estimand
  - Analysis method
    - Choose a primary analysis applicable for the chosen design and addressing the primary estimand
  - Sensitivity analyses
    - Select a number of different sensitivity analyses

Regulatory conclusions on missing data and estimands (1)

Which estimand addresses best clinical relevance?

- “Treatment policy” estimand
  - most likely targets clinical relevance for a given population
- Treatment effect in tolerators
  - may be relevant for patients
  - but require complex causal inference and assumptions for a valid conclusion (without active run-in)
- “De-jure” like estimands (if all patients adhered)
  - are hypothetical parameters difficult to justify
  - but: may be most sensitive for non-inferiority conclusions
- Many other options to be discussed
  - e.g. composite of different estimands related to reasons for drop-out
Regulatory conclusions on missing data and estimands (2)

“Treatment policy” estimand

- fails if no or only few “de-facto” (retrieved) data are available
  - requiring unverifiable assumptions
  - difference between de-facto and de-jure can hardly be substantiated without data
- strong de-facto conclusions require de-facto data
  - patient follow-up after drop-out needed
Sensitivity analyses

... to assess the robustness of trial results!

Robustness of the estimation method

Robustness of the estimand

→ Robustness with regard to
generalizability of trial results

Internal validity

external validity
Conclusions

• Missing data highly relevant issue in depression trials
  • interpretational issues related to missing data
• Primary estimand to be agreed upon first
  • design and analyse accordingly
• Sensitivity analyses relevant to address
  • internal validity (concerning underlying assumptions)
  • external validity (concerning clinical relevance addressed by different estimands)
• Treatment policy or attributable estimand relevant for population based conclusions
  • treatment policy estimand require follow-up of (most) patients
  • lack of follow-up result in the need for unverifiable assumptions
References

- ICH concept paper (2014) E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials