Missing Data in Clinical Trials: the NRC report

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Panel's Charge

- To prepare "a report with recommendations that would be useful for USFDA's development of guidance for clinical trials on appropriate study designs and follow-up methods to reduce missing data and appropriate statistical methods to address missing data for analysis of results."
- Focus is on confirmatory randomized controlled trials of drugs, devices, and biologics
  - With some differences in emphasis, also pertinent for academic and NIH-funded trials, and more generally for various biostatistical investigations

Defining Missing Data

- Missing data are unrecorded values that, if recorded, would be meaningful for analysis. Outcomes that are not defined for some participants are not considered by the panel as missing data
  - Missed clinic visit: yes
  - QOL for individuals who die: no
  - Outcomes if individuals who discontinue drug if they had not discontinued: maybe

Key Take-Home Messages

- Missing data undermines randomization, the lynchpin of inferences in confirmatory trials
- Limiting missing data should be a major consideration when weighing alternative study designs
  - Analysis methods come with unverifiable assumptions, and limiting these assumptions is crucial
- Careful attention to avoiding missing data in trial conduct can greatly limit the scope of the problem
- Analysis methods need to be driven by plausible scientific assumptions
- Sensitivity analyses to assess robustness to alternative analysis models are needed
  - Lack of robust treatment effect from these analyses reinforces the need to limit missing data in trial design and conduct

Design issues

- The estimand: summary outcome measure of interest defined for the population under study
  - a key starting point for the design of a clinical trial
- Alternative choices of estimand may have important implications for trial design and implementation and on the rate of missingness
- Limiting missing data should be a consideration in choice of estimand
- One estimand that limits missing data is an on-treatment summary (Little and Kang, 2015)

On-treatment summary

- A measure of the effectiveness of a treatment that only uses information while individuals are on the assigned treatment. Examples:
  - Dropout as failure. Define a binary measure for success or failure, and treat discontinuers are failures
  - Area under curve (measured relative to baseline value) while on treatment. Dropout is penalized in that area is restricted to time while on assigned treatment.
  - Change from baseline to min(dropout, end of study). This estimate is the same change from baseline to end with LOCF for dropouts, but it avoids (unreasonable) assumption of no change after dropout
  - Impute zero change for dropouts. Estimate same as BOCF.

Design to reduce the occurrence of missingness

1. Run-in periods before randomization to identify who can tolerate or respond to the study treatment
2. Flexible-dose (titration) studies
3. Restrict trial to target population for whom treatment is indicated
4. Reduce length of follow-up period
5. Allow rescue medication in the event of poor response
6. Define outcomes that can be ascertained in a high proportion of participants

Benefits of these options need to weighed against costs

Some Trial Conduct Strategies to Reduce Missing Data

- Limit participant burden
  - Reduce the number of visits and assessments
  - Allow a relatively large time window for each follow-up assessment
- Set maximal acceptable rates of missing data, and monitor during the trial
- Provide incentives for investigators and participants to stay in the try, subject to ethical guidelines
- Continuous update of contact information
- Educate study staff on importance of limiting missing data

Analysis Methods: Principles

1. Missing data: missingness hides a true underlying value that is meaningful for analysis
2. Formulate the analysis for inference about an appropriate and well-defined causal estimand
3. Document, to the degree possible, the reasons for missing data, and incorporate in the analysis
   Some may be MAR, others not
4. Decide on a defensible primary set of assumptions about the missing data mechanism
5. Conduct a statistically valid analysis under the primary missing data assumptions
6. Assess the robustness of the treatment effect inferences by prespecified sensitivity analyses.

Some missing-data analysis methods

- Complete-case analysis
- Single imputation methods, including LOCF, BOCF
- Inverse probability-weighted methods, simple and augmented
- Likelihood – based methods
  - Maximum likelihood, Bayes, Multiple imputation

Preferred methods

Sensitivity Analysis

- Parameters of MNAR models cannot be reliably estimated – identifiability requires structural assumptions that are often questionable
- Varying certain parameters in a sensitivity analysis is the preferred approach
- In many (not all) situations, it would be reasonable to choose an MAR primary model, and look at MNAR models via a sensitivity analysis to assess plausible deviations from MAR

MNAR: Models for Y and R

Let (y_i, r_i) denote the complete-data vector and response indicator for the ith unit, z_i fixed covariates, and assume independent units. Two generic modeling approaches are:

Selection models, which factor:

$$f(y_i, r_i \mid z_i, \theta, \psi) = f(y_i \mid z_i, \theta) \times f(r_i \mid z_i, y_i, \psi)$$

complete-data model $\times$ model for md mechanism

Pattern-mixture models, which factor:

$$f(y_i, r_i \mid z_i, \phi, \gamma) = f(y_i \mid z_i, r_i, \phi) \times f(r_i \mid z_i, \gamma)$$

model for y's within pattern r_i $\times$ probability of pattern r_i

For deviations from MAR, I like pattern-mixture models – simple, easy to interpret

Application: ATLAS ACS 2 TIMI 51 Trial

- Large clinical trial that assessed Rivaroxaban for its ability to reduce the risk of cardiovascular death, myocardial infarction or stroke in patients with acute coronary syndrome (ACS) (Mega et al. 2012)
- 15,526 patients randomized into three treatment groups: rivaroxaban 2.5 mg b.i.d., rivaroxaban 5 mg b.i.d and placebo.
- Primary analysis: Cox proportional hazards model
- Study showed a statistically significant reduction in the primary efficacy outcome: the composite of cardiovascular (CV) death, myocardial infarction (MI) and stroke for the combined rivaroxaban doses compared to placebo (Hazard Ratio (HR) and 95% CI 0.84 (0.74-0.96))

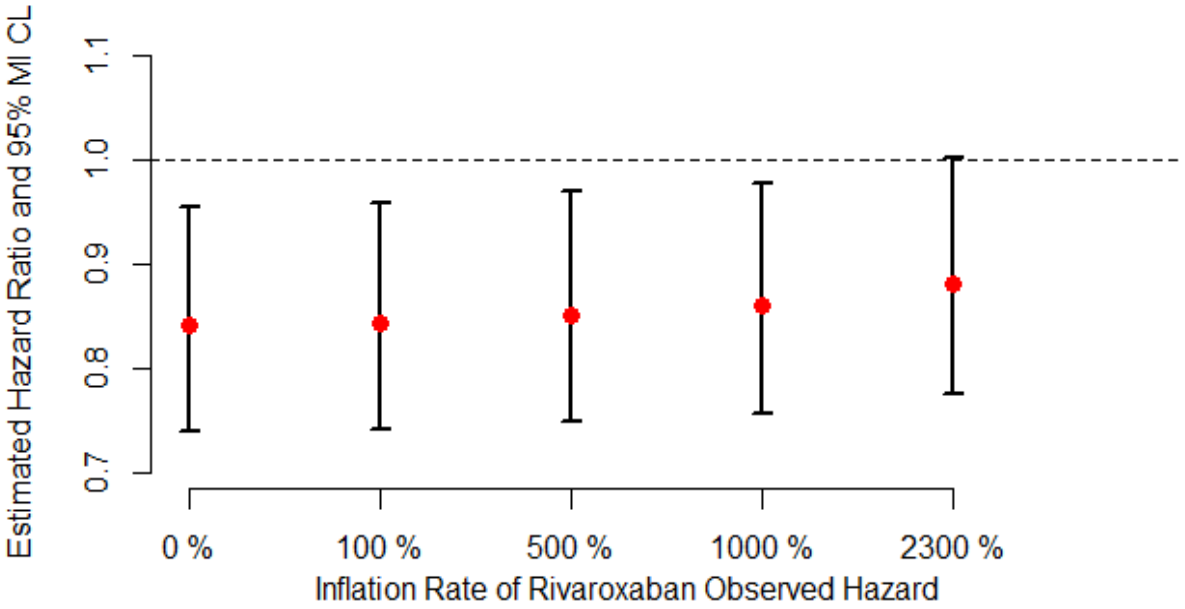
Sensitivity analysis

- There were concerns about 5-10% who dropped out prior to final endpoint – what if dropouts had worse than expected outcomes (informative censoring) that biased the treatment comparison (differential informative censoring)?
- Sensitivity analysis was applied to assess the impact of deviations from non-informative censoring on two key analyses:
- intent-to treat (ITT)
  - included all events occurring up until the end of study.
- modified intent-to-treat (mITT, primary)
  - events of all randomized participants up to the earlier of: (a) the end of study, (b) 30 days after the last study treatment, or (c) 30 days after randomization for those who had not received any study medication.

Overview of method

- Estimate hazard for each dropout at time of dropout, under non-informative censoring
- Differentially increase the hazard of the primary outcome in the rivaroxaban treatment groups,
- Multiply-impute events between drop-out and the end of the study, assuming Weibull distribution
- Combine results using MI combining rules
- Tipping point F: increase in hazard at which significance is lost
  - (Little, Wang, Sun et al. 2016 *Clinical Trials*)

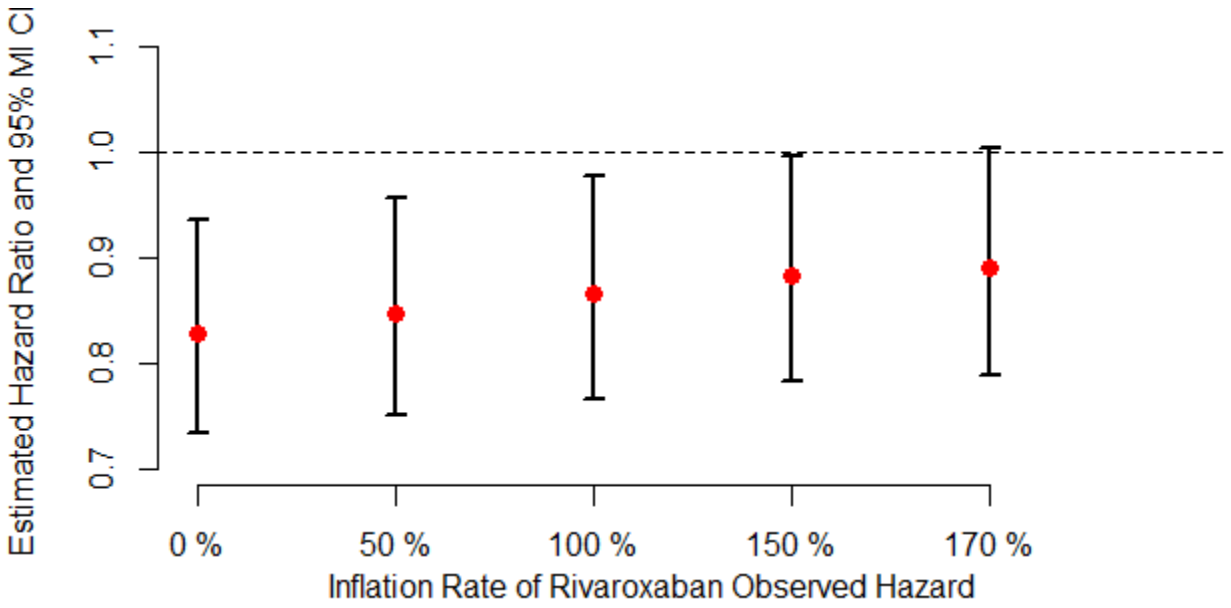
Hazard Ratio and 95% confidence interval for combined rivaroxaban vs. placebo, mITT analysis of primary outcome. Sensitivity analysis, inflating the individually estimated hazard in the rivaroxaban groups by known factors. Tipping Point = 2300%



Mean Number of Imputed Events:

Rivar	3	4	10	17	34
Placebo	2	2	2	2	2

Hazard Ratio and 95% confidence interval for combined rivaroxaban vs. Placebo, ITT analysis of primary outcome. Sensitivity analysis, inflating the individually estimated hazard in the rivaroxaban groups by known factors. Tipping point = 160%.



Mean Number of Imputed Events:

Rivar	41	58	73	88	94
Placebo	21	21	21	21	21

Summary

- Sensitivity analysis is a scientific way of attempting to reflect uncertainty arising from potentially MNAR missing data
- Deciding on how to implement and interpret a sensitivity analysis in the regulatory setting is challenging
- The need and importance of sensitivity analysis increases with the amount of potentially MNAR missing data
- This reinforces the need to limit missing data in the design and implementation stage
  - Avoiding substantial amounts of missing data is key!

References

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Thanks to Janssen for data application.