Sensitivity Analyses for Partially Observed Recurrent Event Data

Mouna Akacha[1] Emmanuel Ogundimu[2]

[1]Statistical Methodology Group,
Novartis Pharma AG, Switzerland

[2]Centre for Statistics in Medicine,
University of Oxford, United Kingdom

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Recurrent Event Data

Recurrent Event

An event that occurs repeatedly over time

Examples include

- seizures in epileptic studies;
- flares in gout studies;
- tumors in cancer studies;
- heart-failure hospitalizations in cardiovascular studies;
- exacerbations in COPD studies.

Objective and Challenge

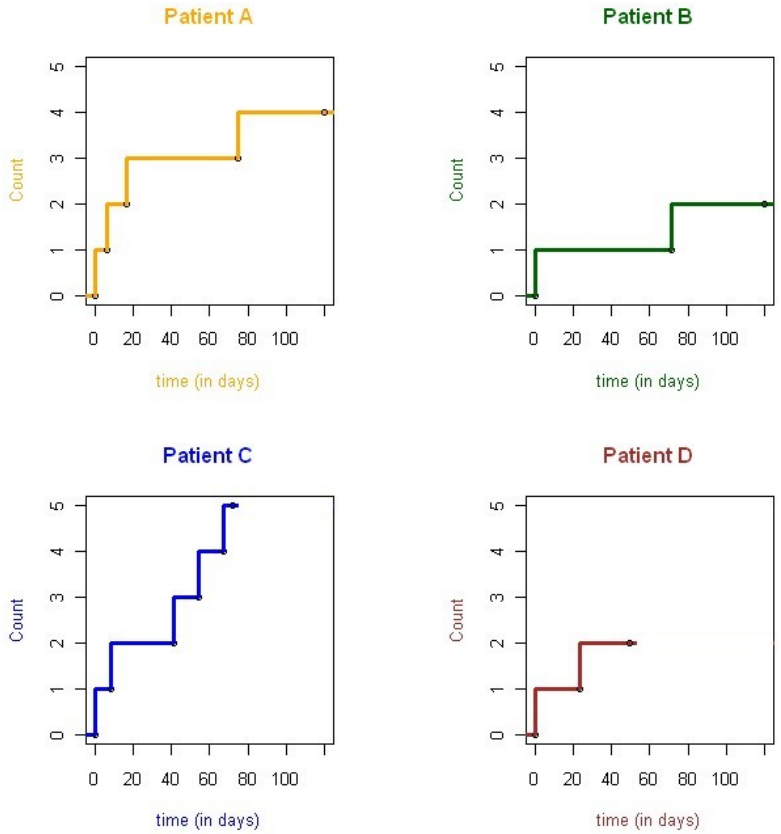
Objective

Assess covariate effects, e.g. treatment effect, on the number of events that occur over a fixed period of time.

One Challenge

Incomplete data because of early discontinuation.

Individual Recurrent Event Data Processes



For a given patient, the counting process by end of study can be partitioned: $N_i = (N_{i,obs}, N_{i,mis})$

Potential Problems caused by Early Discontinuation

- Introduces ambiguity which may undermine the trial integrity.
- Especially, if 'completers' are not representative for patients that discontinue early.

Extent of problems depends on:

- the proportion of early discontinuation; and
- the strength of the relationship between the unobserved data and the probability of dropout.

Missingness Processes

- **Missing Completely at Random** (MCAR)
  - dropout may be related to covariates but is conditionally independent of the recurrent event data $N_i = (N_{i,obs}, N_{i,mis})$;
  - unrealistic!
- **Missing at Random** (MAR)
  - dropout may be related to covariates and observed outcomes $N_{i,obs}$ but is conditionally independent of $N_{i,mis}$;
  - ignorable / non-informative dropout;
- **Missing not at Random** (MNAR)
  - dropout may be related to covariates, observed outcomes $N_{i,obs}$ and missing outcomes $N_{i,mis}$;
  - informative dropout.

Implication on Post-Discontinuation Behaviour - MAR

- Given $N_{i,obs}$ and covariates, the future behaviour of dropouts can be modelled using future behaviour of those who remain $\rightarrow$ treatment behaviour is borrowed

- EMA Guideline on Missing Data:

  "For count data (e.g. the number of exacerbations) a weighted approach with time-in-study as an offset variable (e.g. Poisson regression) is sometimes used. Although this approach is intuitively appealing it should be noted that it assumes there is no relationship between the response and the missing outcome i.e., the method assumes that event rate after withdrawal from trial is the same as event rate on study treatment. For this reason it will often not be an appropriate primary analysis of count data in the presence of missing data."

Implication on Post-Discontinuation Behaviour - MNAR

- The future behaviour of dropouts can be quite different from the future behaviour of those who remain (even after conditioning on $N_{i,obs}$ and covariates).

Sensitivity Analysis

- Missing data methods require assumptions regarding the (unobserved) post-discontinuation outcomes.
- Statistical models make these assumptions explicit but do not remove the problem.
- Unwise to rely on the conclusions of a single analysis based on a particular MAR or MNAR model

$\rightarrow$ Need to assess the impact of missing data based on (multiple) sensitivity / supportive assessments.

Outline for the Remaining Talk

In the following we will:

- Discuss a MAR analysis model;
- Discuss how this approach can be extended to allow for MNAR processes;
- Illustrate the approaches based on a case study.

Notation and Assumptions

- $N_i(t)$ denotes the number of events of patient i by time t which occur according to a counting process;
- x_i summarizes the explanatory variables of subject i;
- T_i corresponds to the time of discontinuation (if $T_i = T$ then end of study);
- U_i is a Gamma-distributed subject-specific random effect with mean 1 and $\text{Var}(U_i) = \phi$;
- $N_i(t)|U_i$ is a Poisson process.

Recurrent Event Data Analysis Model

Event intensity of conditional process $N_i(t)|U_i$

$$\lambda_{x_i}(t,\theta|U_i) = \lambda_{x_i}(t,\theta)\ U_i = \lambda_0(t,\theta)\ \exp(x_i^\top \theta)\ U_i,$$

e.g. $\lambda_0(t,\theta)$ is a constant or Weibull baseline intensity function.

Event intensity of marginal process $N_i(t)$

$$\tilde{\lambda}_{x_i}(t,\theta,\phi) = \frac{1+\phi\, N_i(t-)}{1+\phi\,\Lambda_{x_i}(t,\theta)}\,\lambda_{x_i}(t,\theta)$$

where $\Lambda_{x_i}(t,\theta) = \int_0^t \lambda_{x_i}(u,\theta)\mathrm{d}u$.

Recurrent Event Data Analysis under MAR

- Under MAR (or more precisely: ignorability), likelihood-based inference for θ can be based on all observed information $N_{i,obs} = \{N_i(t)|t \leq T_i\}$ ('Direct Likelihood Approach').

- For example, the Negative Binomial model with offset $\log(T_i)$ is valid under MAR, as long as model assumptions hold.

MAR: Given $N_{i,obs}$ and x_i, the statistical behaviour of the post-discontinuation event rate of a patient who discontinues is assumed to be the same as for a subject who remains in the study.

How can we relax the MAR assumption?

Main Idea - Modify Post-Discontinuation Event Intensity

Modify $\tilde{\lambda}_{x_i}(t, \theta, \phi)$ for $t \in (T_i, T]$ to assess departures from MAR, e.g.

- after discontinuation the event intensity is higher or lower than under MAR;
- after discontinuation the event intensity for treated patients is assumed to correspond to the event intensity of placebo patients;
- other assumptions on post-discontinuation intensity which may differ by reason of discontinuation

and impute event occurrences according to the modified intensity for the time interval $(T_i, T]$.

Approximate Bayesian MI under MNAR – 1

1. Draw a series of bootstrap samples with replacement from the original data, one for each imputed data set.

2. Fit recurrent event data model under MAR to the bootstrap samples; the resulting ML estimates $\hat{\theta}^{(k)}, \hat{\phi}^{(k)}$ approximate draws from the posterior distribution.

3. Use $\hat{\theta}^{(k)}, \hat{\phi}^{(k)}$ to determine the 'MNAR intensity function' which is used to impute event times after discontinuation, e.g. use
   - MNAR -1: $\tilde{\lambda}_{placebo}(t, \hat{\theta}^{(k)}, \hat{\phi}^{(k)})$ for active arm patients; or
   - MNAR -2: $\tilde{\lambda}_{x_i}(t, \hat{\theta}^{(k)}, \hat{\phi}^{(k)}) \times \tau$ with $\tau > 1$.

Approximate Bayesian MI under MNAR – 2

4. Based on these event times calculate for each subject the total number of events that occur before the end of the study.

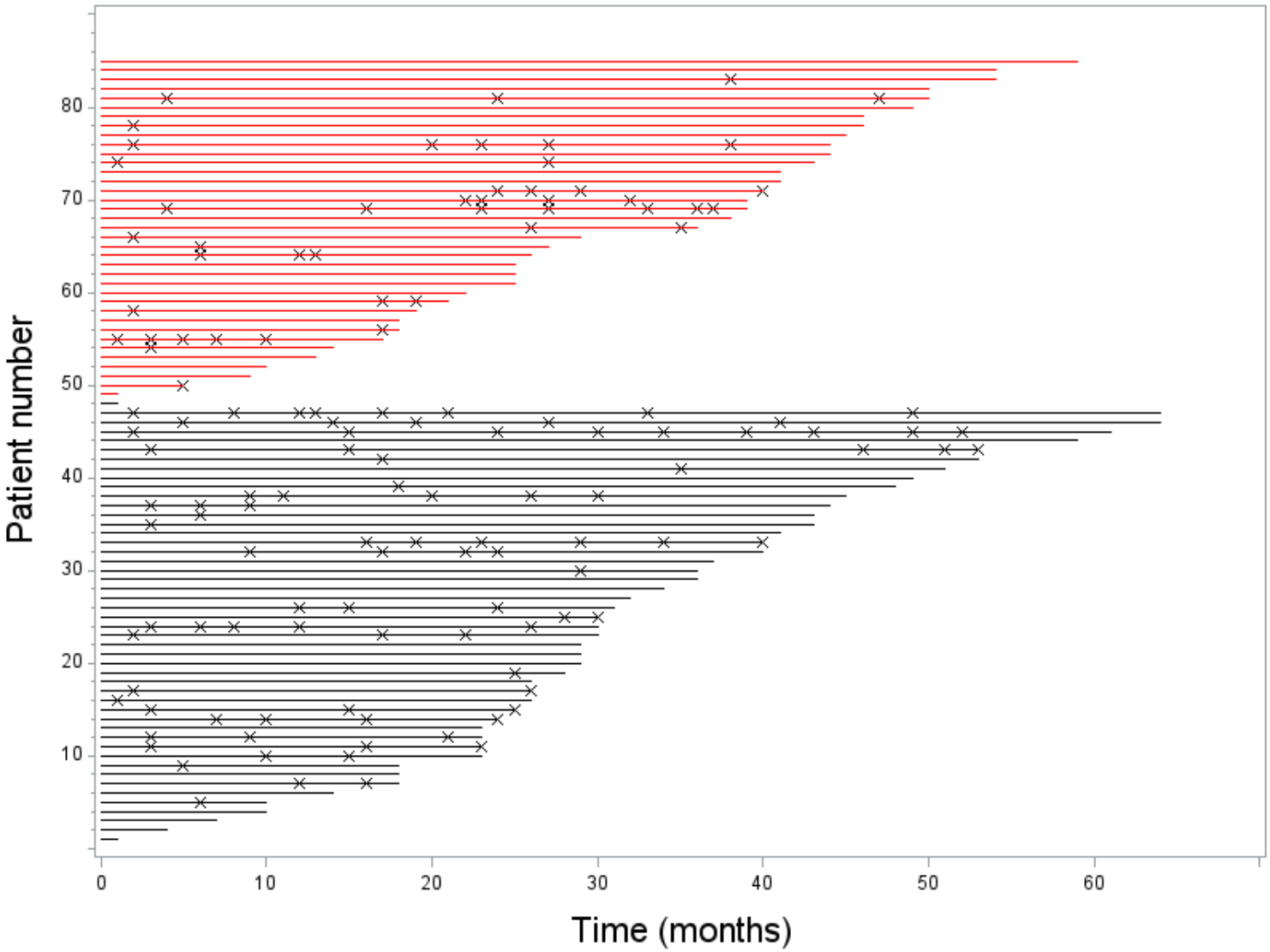
5. Analyze each imputed dataset, e.g. using the Negative Binomial model.

6. Combine results using Rubin's rules.

Example

- Bladder tumor study by the Veteran Administration Co-operative Urological Research Group (Byar, 1980).
- 116 patients suffering from superficial bladder cancer are randomized to receive, placebo, pyridoxine or thiotepa.
- Only consider placebo and thiotepa arms here.
- The recurrent event of interest is the occurrence of new bladder tumors.
- Maximum follow-up time observed was 64 months.
- Design did not foresee a fixed follow-up time.
- Assume: Primary endpoint is the number of newly developed bladder tumors over 45 months.

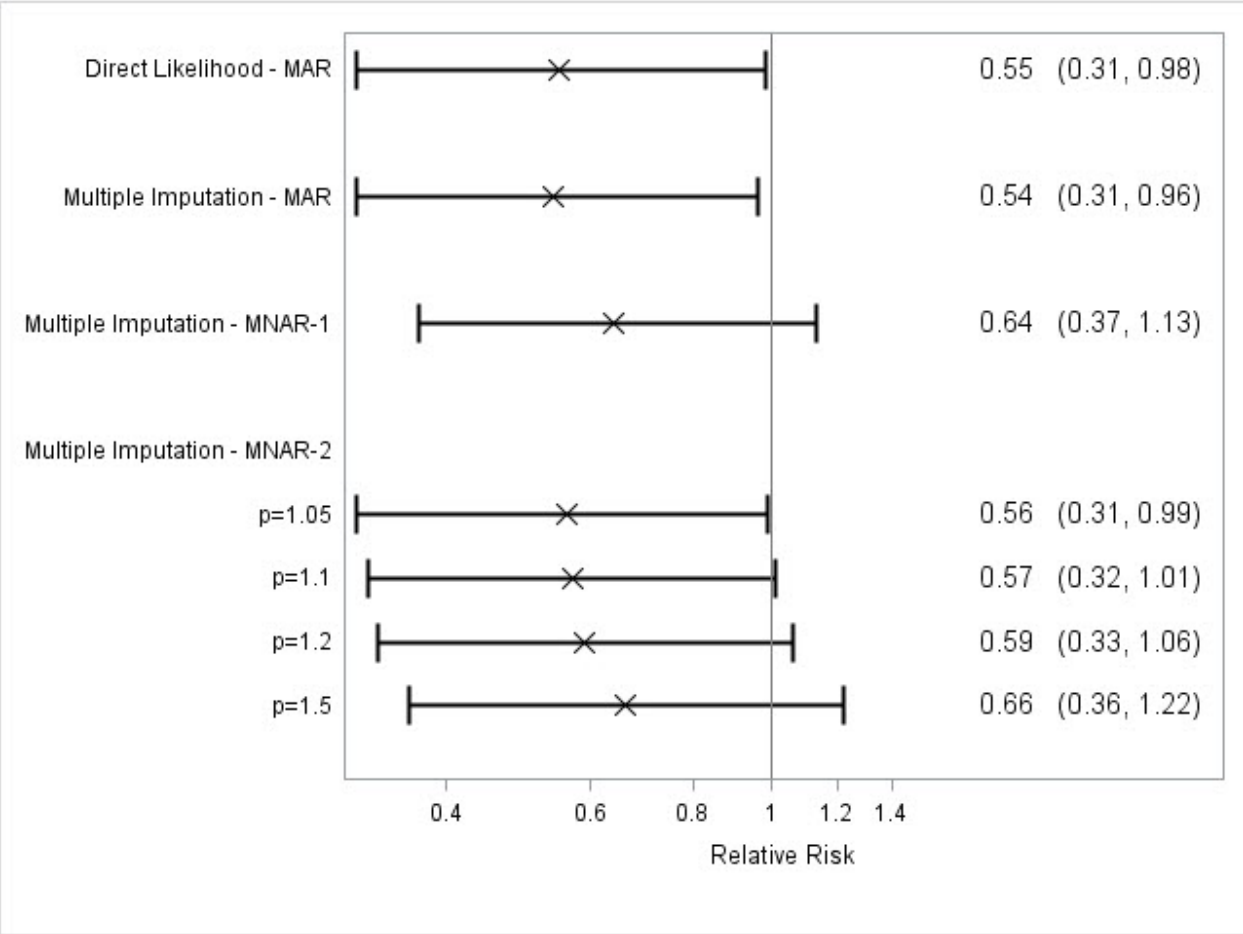
Thiotepa (red) and Placebo (black)



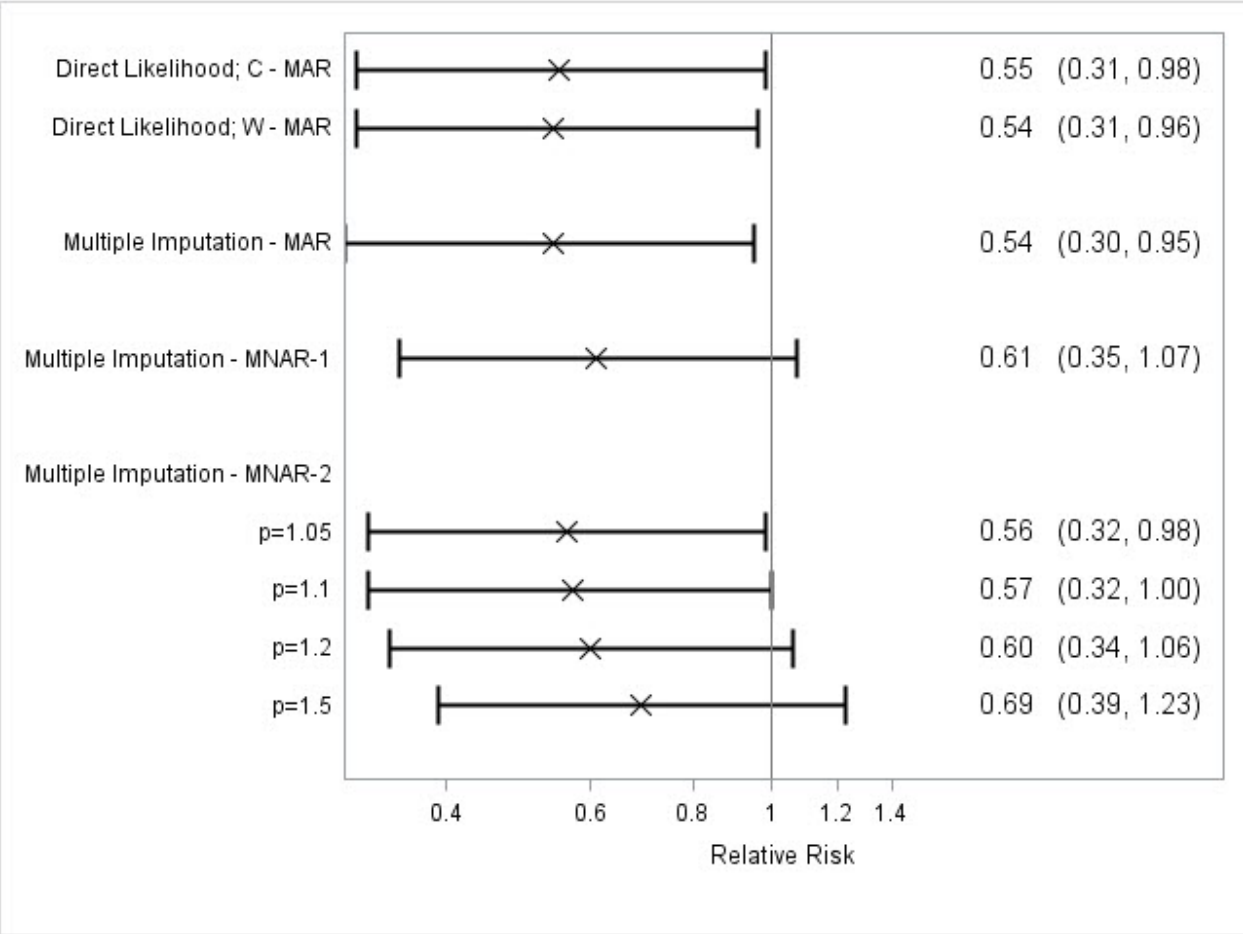
Bladder Tumor Study: Sensitivity Analysis

- Missing Data Handling
  - Direct Likelihood Approach (MAR)
  - MAR Multiple Imputation
  - MNAR Multiple Imputation
    - MNAR -1: after discontinuation the event intensity for Thiotepa patients is assumed to correspond to the event intensity of placebo patients;
    - MNAR -2: after discontinuation the event intensity for Thiotepa patients is assumed to be a certain percentage $(5\%, 10\%, 20\%, 50\%)$ higher than the MAR intensity;
    - assume MAR for placebo arm patients.
- Imputation Model
  - Poisson-Gamma mixture model with constant (C) or Weibull (W) baseline intensity.
- Analysis Model: Negative Binomial model
  $(=$ Poisson-Gamma mixture model with constant baseline intensity)

Results - Constant Baseline Intensity for Imputations



Results - Weibull Baseline Intensity for Imputations



Conclusions

- Important to assess the robustness of conclusions through sensitivity / supportive analyses;
- Traditional methods, e.g. the NB regression, make at best the assumption that data are MAR;
- MAR may not always be sensible;
- Clinically interpretable assumptions about the future behavior of dropouts dependent on reasons for dropout and received treatment can be incorporated.
- Approach fits in the framework of controlled imputations which is being increasingly used for continuous data.