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Controlled multiple imputation in time-to-event data using tipping point analysis

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Overview

I. Missing data in survival analysis

II. Tipping Point Analysis (TPA)

III. Simulation and results

IV. Conclusion

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Missing data in survival analysis

Context

In survival analysis context, when the event can't be observed we talk about **censoring**.

The **censoring reason** can be:

Administrative (end of study, cut-off)	**Non-administrative** (lost to follow-up, treatment discontinuation).

Informative censoring can lead to **biased estimates**.

Administrative censoring can be considered as **ignorable** and **non-informative**

- **Informative censoring assumption** (**CAR**).

Non-administrative censoring is more likely to be **related to study treatment** and to be considered as **non-ignorable** (**informative censoring**, **CNAR**).

CAR: censored at random
CNAR: censored not at random

Missing data in survival analysis

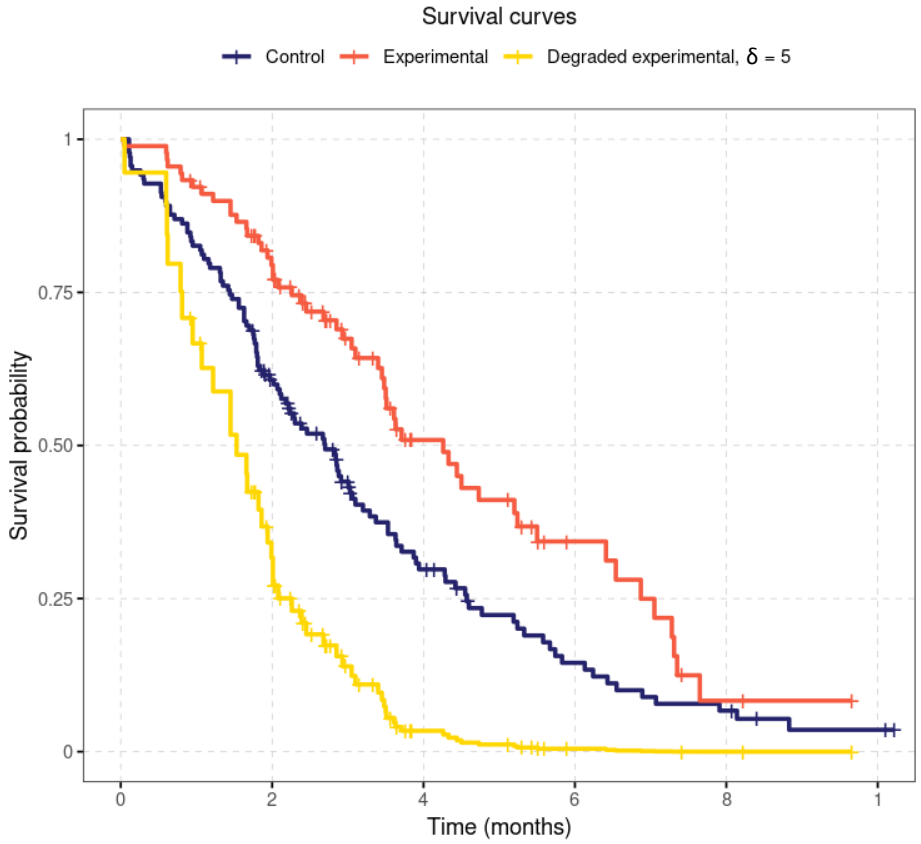
Methods for missing data: Tipping point analysis

Sensitivity analyses can be performed to evaluate the **robustness** of the endpoint **results** to **deviations** from the **ignorable censoring assumption** (CAR).

Tipping point analysis (TPA) is a sensitivity analysis that is increasingly requested by **health authorities**.

- TPA is based on:
  - Survival model (e.g. Cox, Kaplan Meier) imputation,
  - Controlled multiple imputation.
- TPA consists of:

  Incrementally penalizing (by δ) the imputed event times in the experimental arm until the result between the 2 groups is **no longer statistically significant** (tipping point)



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The Tipping Point - interpretation

Tipping Point is defined as the lowest δ value for which the result between the 2 arms is no longer statistically significant

- Example: A **Tipping Point** equal to **3** would mean that:

  in order to **switch our results** to non-significant,

  the **hazard** following discontinuation of informatively censored participants from the experimental arm would need to be **3 times larger** than the hazard of similar participants remaining in the study.

The **greater** the Tipping Point, the more **robust** the results are to **deviation** from the **ignorable censoring assumption** (CAR).

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Objectives

- **Stress-test the results under the non-ignorable censoring assumption** (CNAR)
- **Study the accuracy of the Tipping Point Analysis methods**
- **Identify the parameters of a clinical trial that drive the value of δ**

Method: Tipping point analysis in survival analysis

For a participant i discontinued at time c_i ,

- let $h_1(t)$ be his hazard at any given time point t following discontinuation,
- let $h_2(t)$ be his hazard at the same time t if he/she had continued the study.

$$h_1(t) = \delta * h_2(t)$$

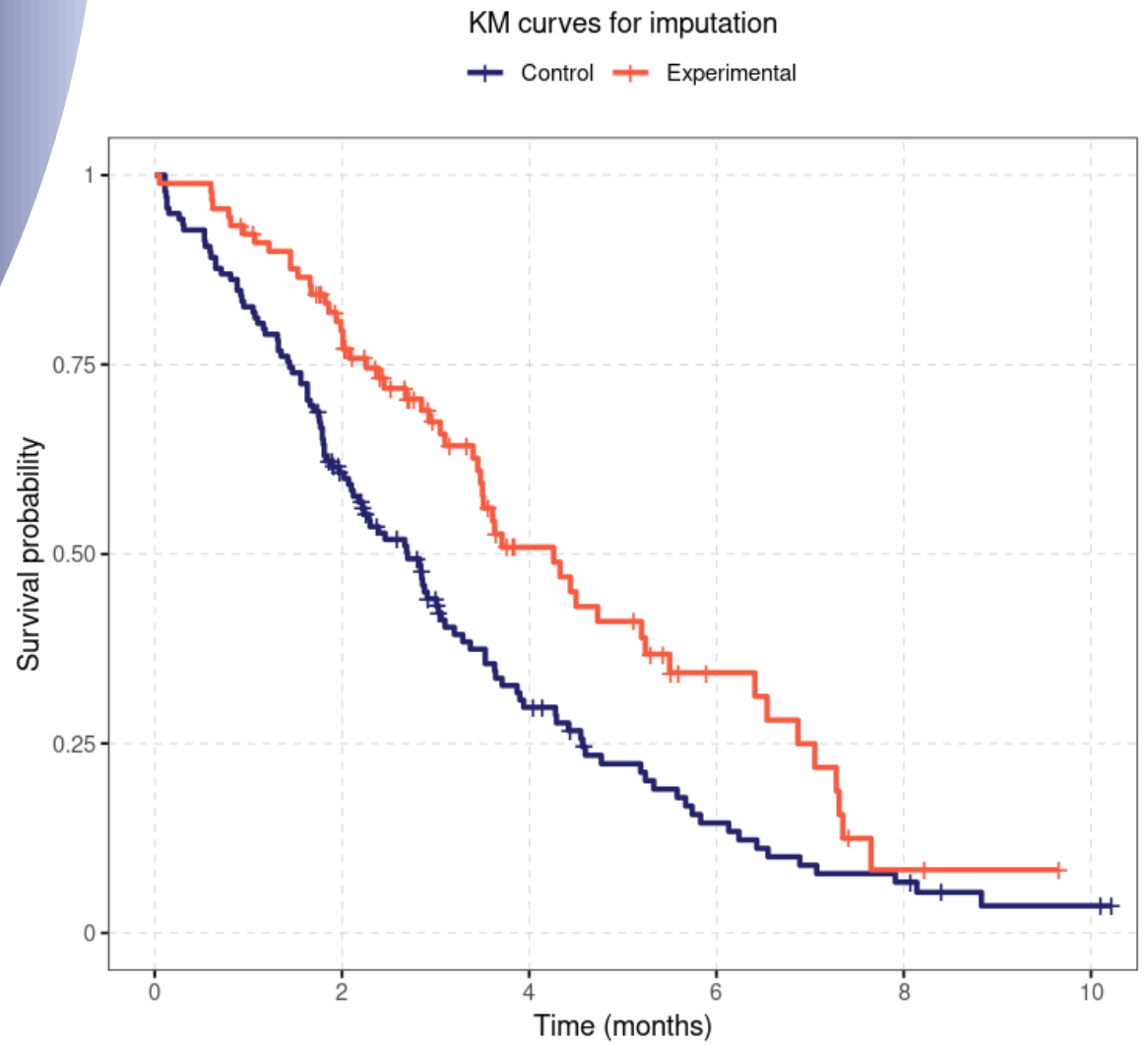
- **δ = 1**, **same hazard** following discontinuation as **if he had remained in the study**,
- **δ > 1**, **greater hazard** following discontinuation than the one he would've had

δ penalty is only applied to:

- **Informatively** censored participants
- Participants from the **experimental** arm

Algorithm

1. Evaluate the survival function $S(t)^{\delta}$
2. For a participant i censored at time c_i, let $p_i = \hat{S}(c_i|x_i, \hat{\beta})^{\delta}$
3. Draw $u_i \sim U(0, p_i)$
4. Impute the event time t_i^* as the solution of $u_i = \hat{S}(t|x_i, \hat{\beta})^{\delta}$
5. Analyze the new dataset with imputed event times



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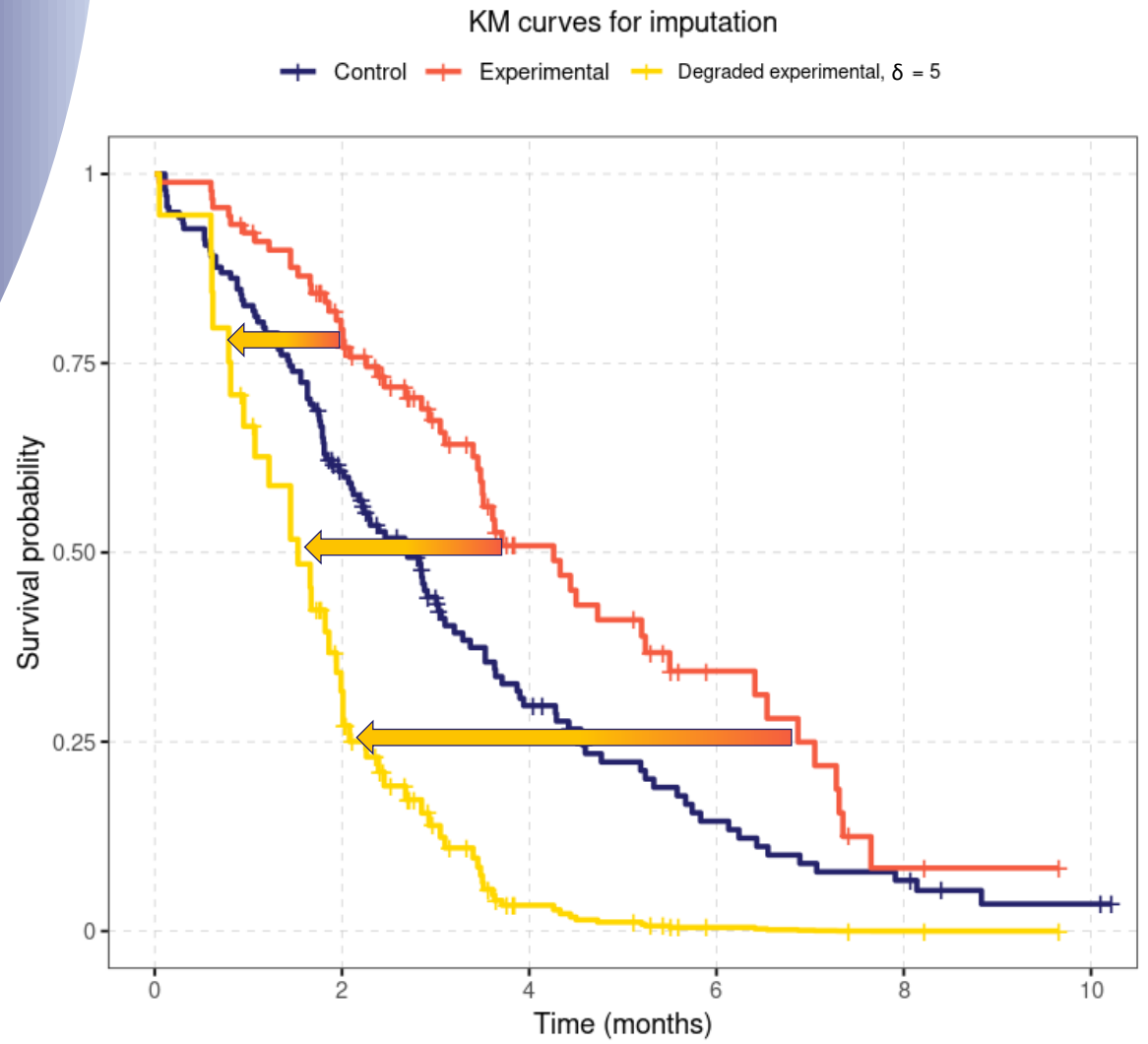

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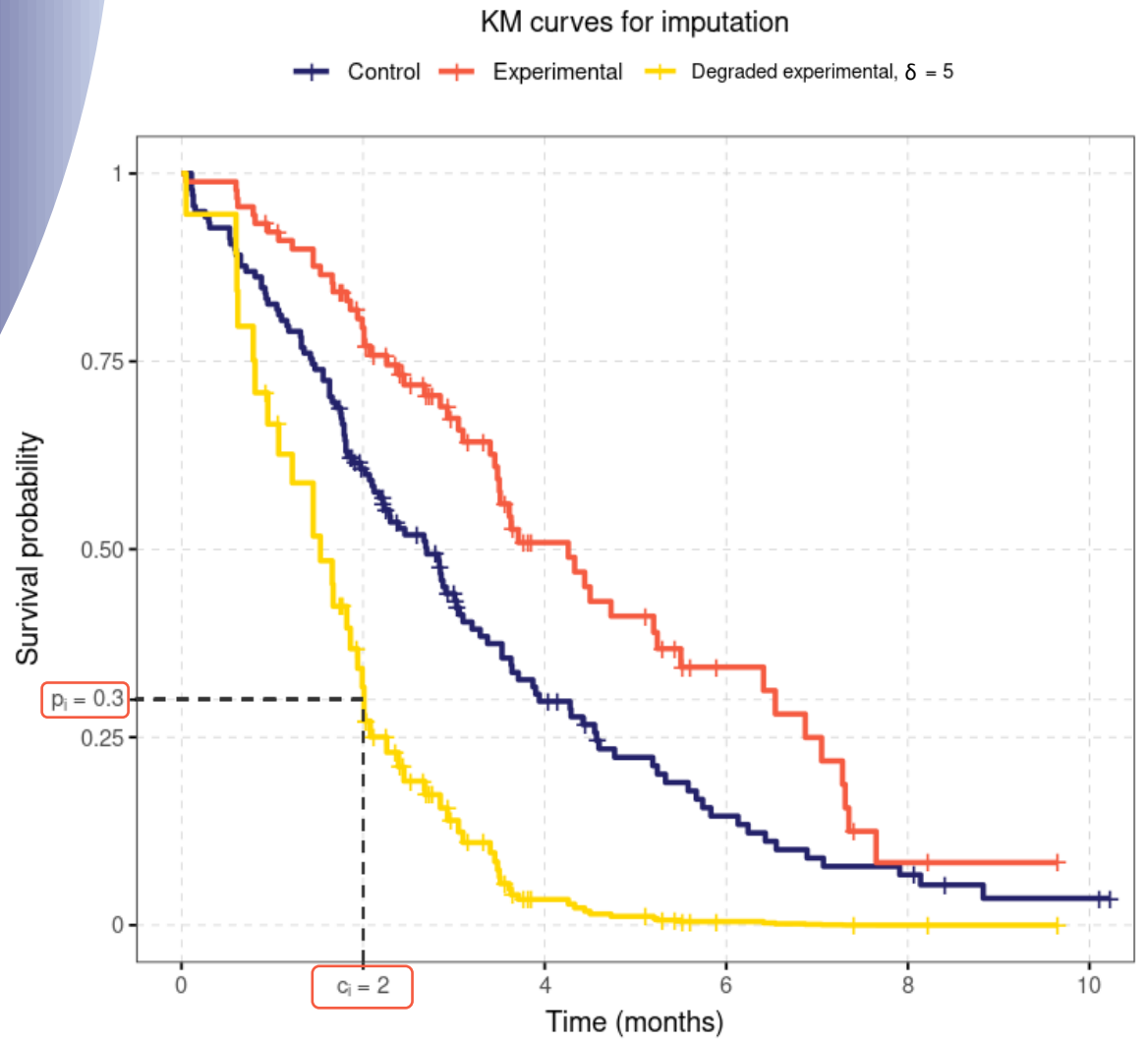

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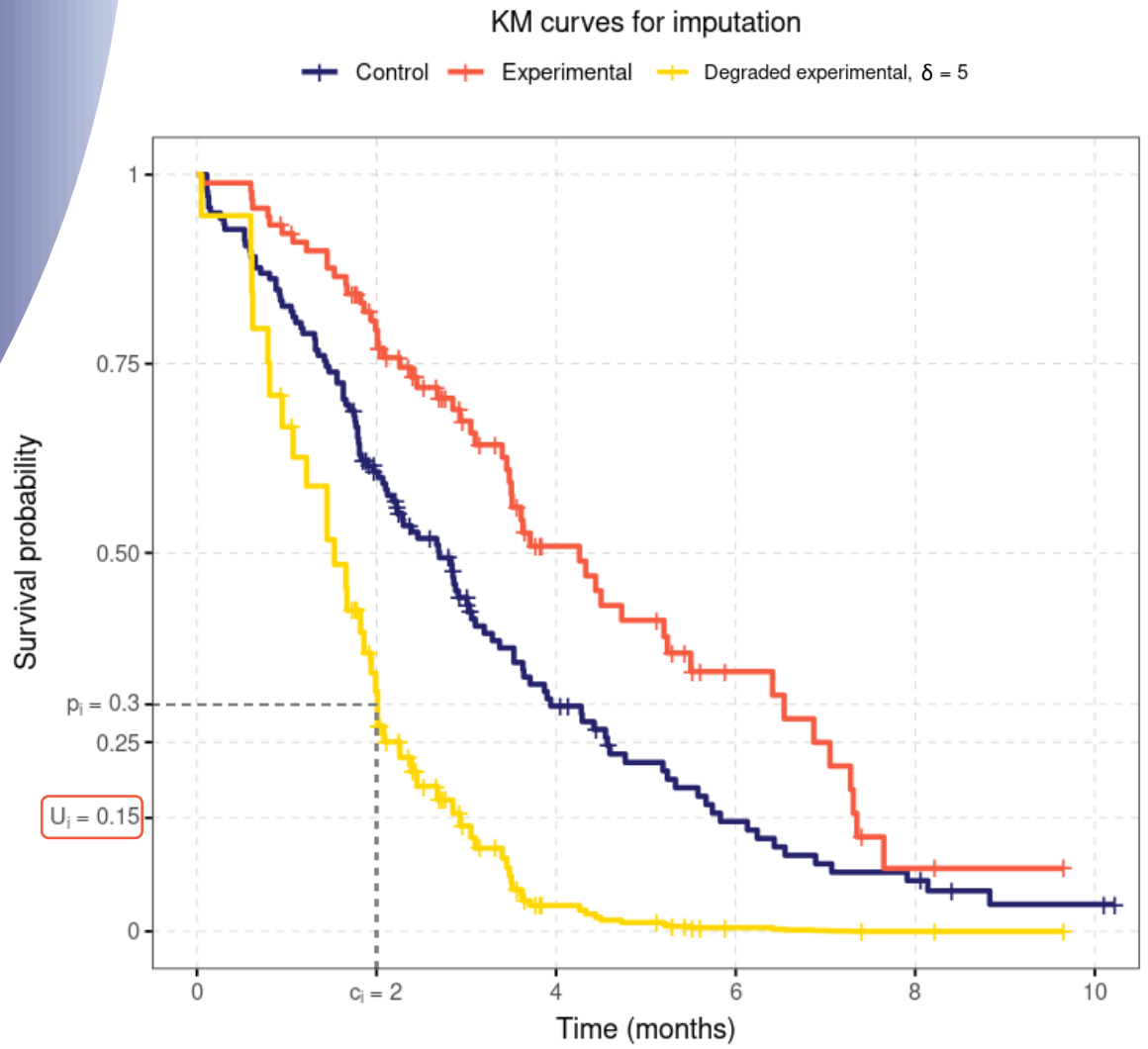

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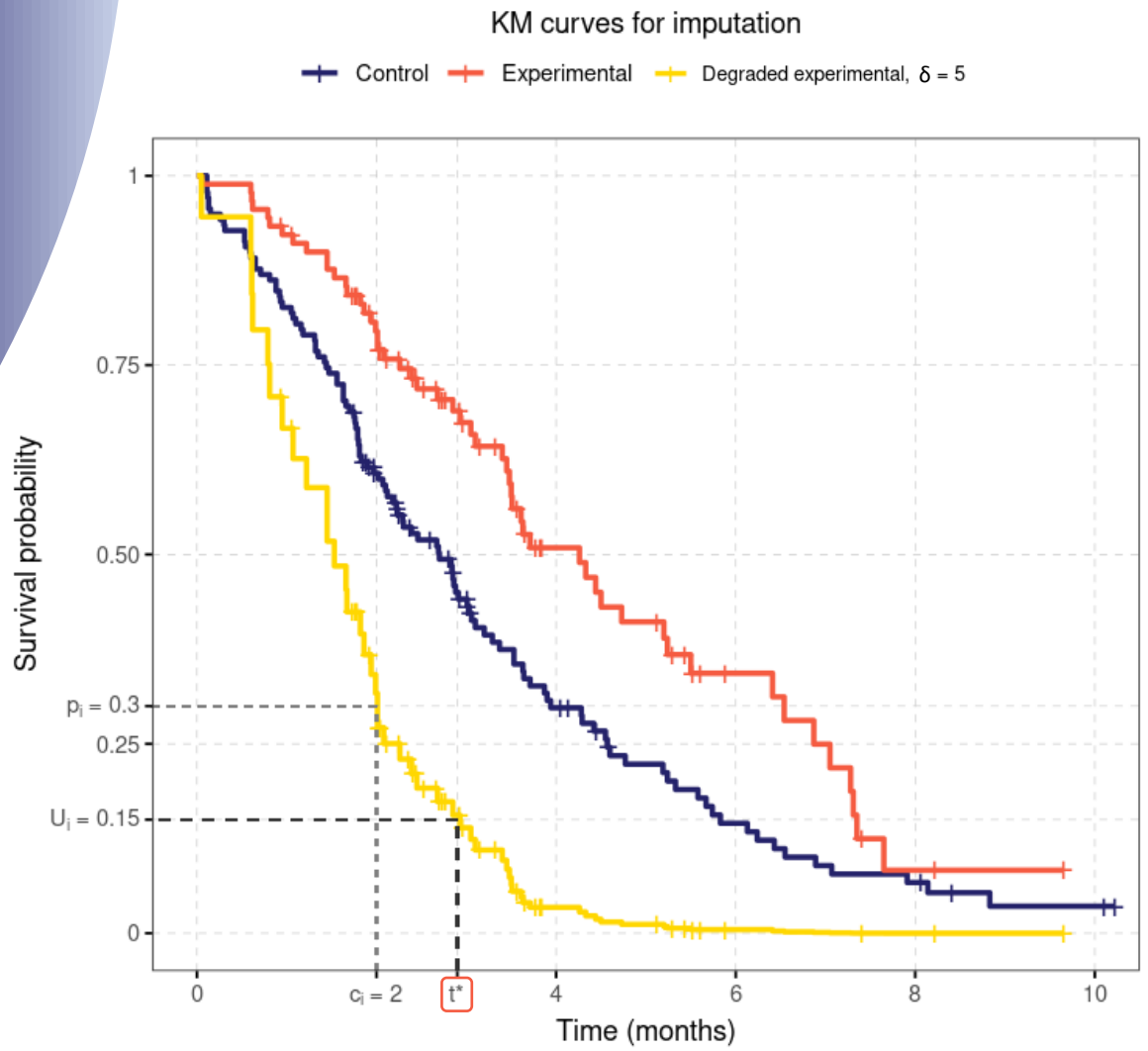

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- Repeat m times
- Pool results by using Rubin's rules (multiple imputation)

Donald B. Rubin [1987]

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Studied methods

To perform TPA, different methods can be used to estimate $S(t)$.
The other steps of the algorithm remain the same.

We investigated 2 methods to estimate $S(t)$:

- Non-parametric **Kaplan-Meier** multiple imputation (KMMI)
  - Allows to stratify on any factor assumed to be related to survival or censoring

- **Cox** proportional hazards multiple imputation (COXMI)
  - Allows to stratify the imputation method to be aligned with the usual model used for survival analysis (Cox model)

Result process

Scenario / Simulation

Simulate 2-arm trial dataset

For non-administratively censored patients, simulate their **event times:**

- by **penalizing** their hazard by **δ** and study for which value of δ ($\delta_{theoretical}$) the result switches to non-significant (Tipping Point).

Evaluation method

Apply TPA on the original (non-penalized) censored dataset and observe for **which** value of **δ** it **switches** to **non-significant** ($\delta_{imputation}$).

Compare the **theorical** δ ($\delta_{theoretical}$) and the δ **retrieved** by **imputation** ($\delta_{imputation}$) using TPA.

Simulation setup

Common parameters

- 2 arms
- Sample size = 800 (1:1)

Varying parameters

- HR = {0.70; 0.80; 0.85}
- C_{na} = {5%; 10%}
- Accrual time & study duration

For each scenario,

- **1000** datasets are simulated
- **Both** TPA methods (**COX**MI and **KM**MI) are applied

C_{na}: informative censoring rate

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Results

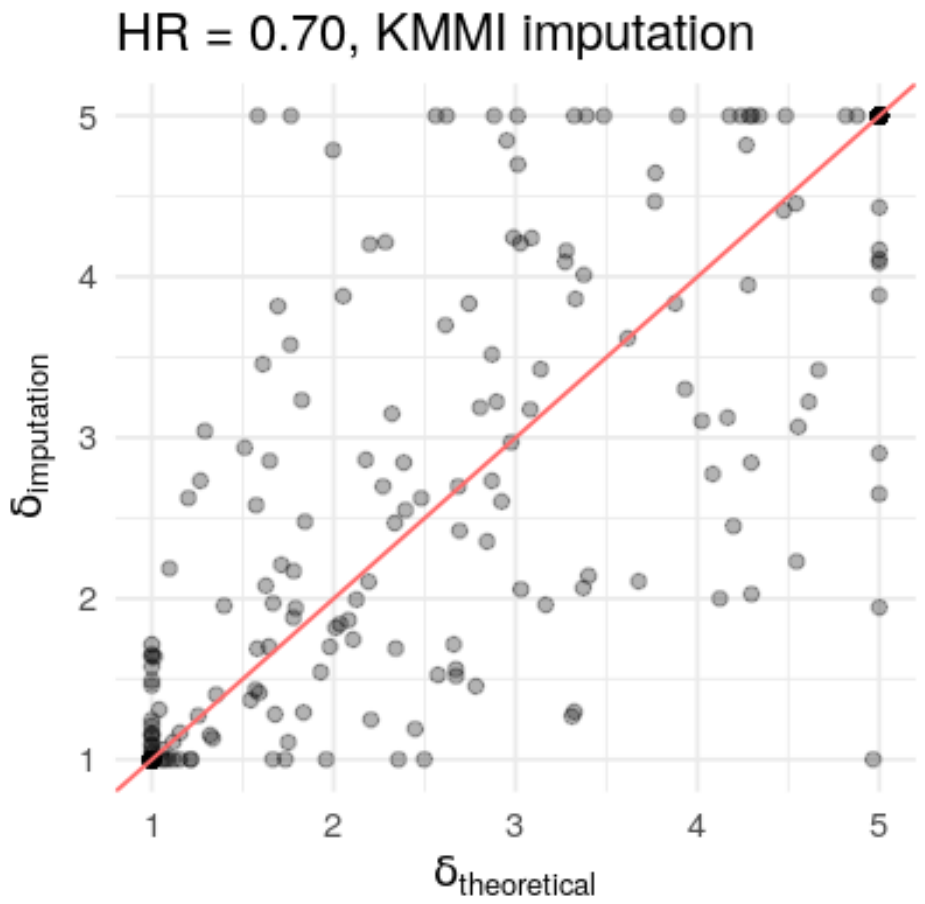
Observation

	Scenario					
	Sample size = 800 (1:1)					
HR	0.70	0.70	0.80	0.80	0.85	0.85
C_{na}	5%	10%	5%	10%	5%	10%
Estimated $\delta_{theoretical}$	5	4.06	5	1.65	1.20	1.10
Estimated $\delta_{imputation}$ **COX**MI	5	4.38	5	2.18	1.37	1.12
Estimated $\delta_{imputation}$ **KM**MI	5	4.52	5	2.28	1.39	1.12
MSE (COXMI)	0.145	0.271	0.442	0.453	0.425	0.606
MSE (KMMI)	0.381	0.366	0.549	0.550	0.487	0.731

MSE: mean squared error

Results

Observation



Results

Interpretation

Based on our simulations:

- In average, TPA based on COXMI/KMMI is efficient for recovering the theoretical δ value of a clinical trial

- Choice of the method (COXMI / KMMI) should be motivated by their pros and cons

- The δ value might be driven by:
  - sample size
  - informative censoring rate
  - informative censoring times distribution

Conclusion

- TPA can be used to test the **robustness** of results to deviations from the ignorable censoring assumption (CAR).
- It provides **clinically interpretable** results
- Range of methods allows to **match** a method with the analysis planned for a particular clinical trial
- Tipping Point value is driven by different parameters of a clinical trial

To go further

Explore other methods

to test the ignorable censoring assumption

- Copy-reference,
- Jump-to-reference
- …

Explore and compare TPA variants

- improving control arm ($\delta < 1$),
- imputing only the experimental arm
- …

Produce a user guide

with recommendations on the most appropriate method to use, depending on the studied case.

References

Ilya Lipkovich, Bohdana Ratitch & Michael O'Kelly. Sensitivity to censored-at-random assumption in the analysis of time-to-event endpoints. *Pharmaceutical Statistics; 2016*

Donald B. Rubin. *Multiple Imputation for Nonresponse in Surveys.* John Wiley and Sons Inc. New York, 1987

Thank you for your attention

Questions ?

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Rubin's rules

Estimate pooling

$$\bar{\theta} = \frac{1}{m}\left(\sum_{i=1}^{m} \theta_i\right)$$

$\bar{\theta}$ Pooled parameter estimate

θ_i Parameter estimated at the i^{th} imputation

m Number of imputations

Total variance pooling

$$V_{Total} = V_W + V_B + \frac{V_B}{m}$$

$$V_W = \frac{1}{m}\sum_{i=1}^{m} SE_i^2$$

$$V_B = \frac{\sum_{i=1}^{m}(\theta_i - \bar{\theta})^2}{m-1}$$

V_B Between imputation variance

V_W Within imputation variance

Wald testing

$$Wald_{Pooled} = \frac{(\bar{\theta} - \theta_0)^2}{V_{Total}}$$

Pooled wald value follows a t-distribution, used to derive a p-value

θ_0 Parameter value under the null hypothesis

Simulation scenarios

Scenario	n	HR	C_{na}	$median_{exp}$	$median_{control}$	Accrual period	Study duration
1	800 (1:1)	0.7	5%	14.3	10	12	12
2	800 (1:1)	0.7	10%	14.3	10	12	12
3	800 (1:1)	0.80	5%	12.5	10	36	36
4	800 (1:1)	0.80	10%	12.5	10	36	36
5	800 (1:1)	0.85	5%	11.8	10	48	48
6	800 (1:1)	0.85	10%	11.8	10	48	48

n: sample size
C_{na}: non-administrative censoring rate

Tipping point algorithm