CO119

Methodological Considerations for Time-to-Event Analyses of Non-Interventional Studies (NIS) Collecting Real-World Data (RWD) Prospectively: A Simulation Study

J. Feifel,[1] A. Johne,[1] S. H. Mahmoudpour[1]

[1]Merck Healthcare KGaA, Darmstadt, Germany

Correspondence: Seyed Hamidreza Mahmoudpour
hamid.mahmoudpour@merckgroup.com

CONCLUSION

Using all patient data and applying multi-state modelling (MSM) to estimate the overall survival (OS) is superior to the Kaplan-Meier (KM) methods approach in prospective RWD analysis, particularly if signing the informed consent forms (ICF) is associated with the treatment outcome. This simulation highlights the value of MSM in analyses of the clinical data.

INTRODUCTION

- There are several non-interventional registries, that aim to collect high-quality primary data from routine clinical practice for rare diseases particularly in oncology.[1,2]
- NIS using prospective RWD collected from the registries have gained prominence as a primary data source, aiming to overcome limitations of secondary data sources.
- According to several regulatory guidelines on registries and registry-based studies, the patients are typically eligible with a diagnosis of cancer, start of treatment etc. but prospective data collection only starts once informed consent is given.[3,4,5]
- The sequence of eligibility for data collection and the requirement for patients to be alive at the time of ICF signature may introduce bias in OS analysis.

OBJECTIVES

This study aims to quantify potential bias introduced by the time gap from eligibility to ICF signature in different scenarios and propose a robust analysis to address this bias.

METHODS

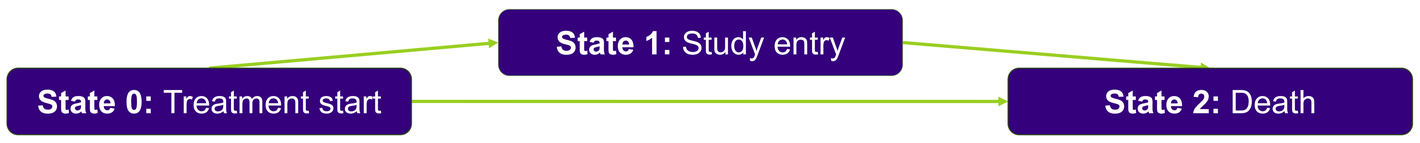
Simulation

- Two situations were considered for cancer patient data collection:
  a) ICF signed and the treatment started (early consent).
  b) The treatment was started and then ICF was signed (late consent).
- The overall goal was assessing the mortality risk associated with the treatment.
- Simulations are based on a parametric framework modelling the transitions displayed in **Figure 1**.[6] Two scenarios were simulated:
  1. ICF signature date independent of treatment outcome.
  2. ICF signature date associated with treatment outcome (e.g. patients who are sicker than average, or on the other hand, patients who are healthier than average, may not want to participate in the registry before treatment start. This effect is often referred to as selection bias).

Analysis

- The data was generated following a parametric illness-death model with exponential hazard functions as implemented in R package simIDM.[6]
- For each scenario, the median OS (mOS) was estimated using the conventional KM methods and the Aalen-Johansen (AJ) estimator of progressive illness death models.[7] The KM and the mOS were then compared to the true known survival probability and time of the simulation defining parametric model.
- The sensitivity analysis was conducted on group (a) patients that started the treatment after enrolment.
- **Figure 1** elaborate the MSM model. To assess the probability of death or survival under the treatment, patients for both possible paths 0–>2 and 0–>1–>2 can contribute. The AJ estimator respects both paths, allowing for a holistic estimation of the treatment effect. Ignoring the subpath 0–>1 is often leading to immortal time.

Figure 1. The different states a patient can occupy



RESULTS

- For scenarios (1) and (2), 1000 samples with data for 1000 patients were simulated. Sample have median follow-up times of 41.6 and 35.2 months from treatment initiation, and 25.5% and 33.3% of patients died during follow-up.
- The median time from treatment initiation to ICF signature in group (b) patients was 11.2 and 17.6 months, in scenarios (1) and (2), respectively for a sample.

Table 1. Sample description

Scenario (1)	Early consent[a] (N=495)	Late consent[b] (N=505)	Overall (N=1000)
Censored patients n (%)	134 (27.1)	121 (24.0)	255 (25.5)
Median time to ICF (range)	0 (0–0)	11.2 (0–24.1)	0 (0–24.1)
Mean time to ICF (SD)	0 (0)	28.7 (39.5)	14.5 (31.5)
Median follow-up time (range)	44.7 (0.06–614.0)	41.8 (0.1–367.0)	41.6 (0.06–614.0)
Scenario (2)	**Early consent[a] (N=522)**	**Late consent[b] (N=956)**	**Overall (N=1478)**
Censored patients n (%)	222 (42.5)	270 (28.2)	492 (33.3)
Median time to ICF (range)	0 (0–0)	17.6 (0–162.0)	6.6 (0–162.0)
Mean time to ICF (SD)	0 (0)	25.6 (25.6)	16.6 (23.9)
Median follow-up time (range)	19.0 (0.1–174.0)	50.8 (2.4–224.0)	35.2 (0.1–224.0)

[a]ICF signed then the treatment started; [b]The treatment was started and then ICF was signed.

- In scenario (1), both KM and AJ methods showed non-significant difference of mOS with true mOS (black curve) in main and sensitivity analysis **(Figure 2).**
- In scenario (2), KM considerably underestimated the mOS in sensitivity analysis, analysing only patients who started treatment at the time of the ICF **(Figure 3).**

Figure 2. Estimations from KM and AJ methods in scenario (1) in example sample

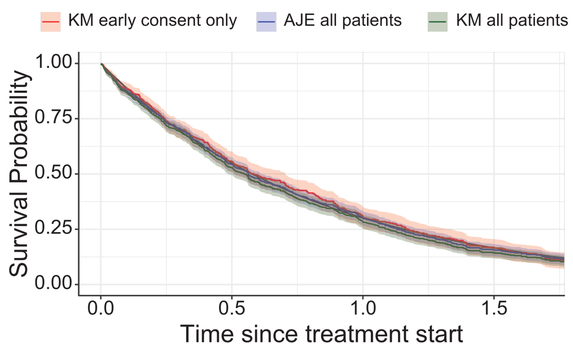


Figure 3. Estimations from KM and AJ methods in scenario (2) in example sample

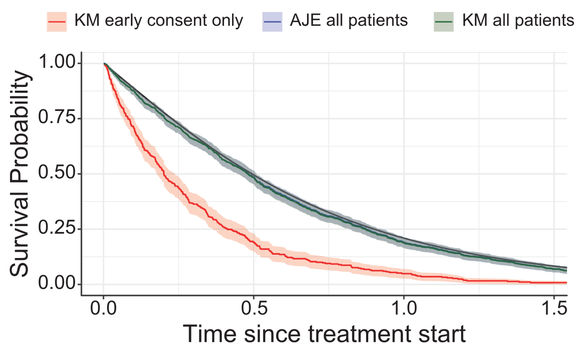


Figure 4. Bias evaluation of estimators across all samples in scenario (1)

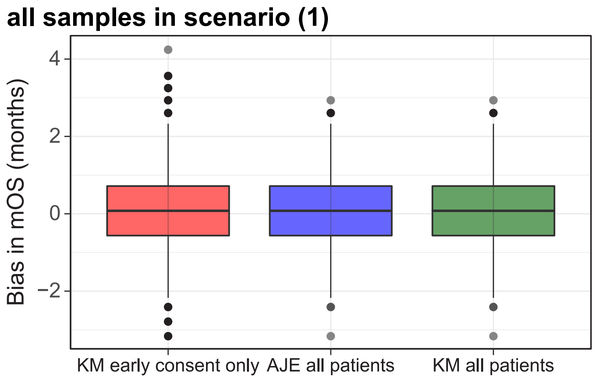
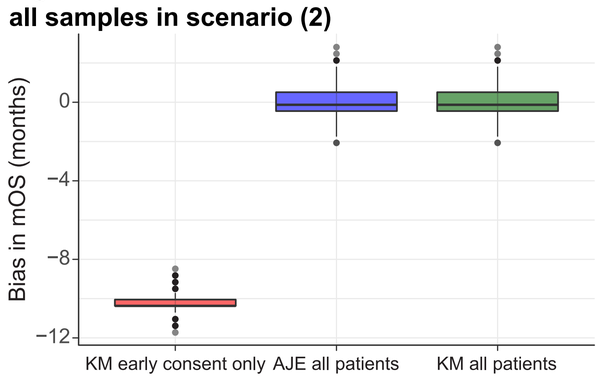


Figure 5. Bias evaluation of estimators across all samples in scenario (2)



- These observations hold for the mOS the entire probability estimation.
- The results are independent of the rate of censored observations and allow even for event-driven censoring patterns.
- Although not modelled here, the results also transfer to Cox estimators in scenarios with influential covariates.

References: 1. Christopoulos P, et al. *Journal of Thoracic Oncology.* 2022;17(9):S463. 2. Becker JC, et al. *Annals of Oncology.* 2023;34:S685–S686. 3. European Medicines Agency. Guideline on registry-based studies. 2021. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf. 4. United States Food and Drug Administration. Guidance for Industry. Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products. 2021. Available at: https://www.fda.gov/media/154449/download. 5. Miksad RA, et al. *Clinical Pharmacology & Therapeutics.* 2018;103(2):202–205. 6. Meller M, et al. *Statistics in Medicine.* 2019;30(38):4270–4289; 7. Meira-Machado L, et al. *Biometrical Journal.* 2019;61(2):245–263.

Abbreviations: AJ, Aalen-Johansen; KM, Kaplan-Meier; ICF, informed consent form; (m)OS, median overall survival; MSM, multi-state modelling; NIS, non-interventional studies; RWD, real-world data; SD, standard deviation.

Disclosures: J. Feifel reports employment by Merck KGaA, Darmstadt, Germany; A. Johne reports employment by Merck KGaA, Darmstadt, Germany; S. H. Mahmoudpour reports employment by Merck KGaA, Darmstadt, Germany.

Acknowledgements: This study was sponsored by Merck KGaA, Darmstadt, Germany.

Presented at ISPOR Europe | 17-20 November 2024 | Barcelona, Spain