Estimands, interval censoring, and COVID-19-related disruptions to oncology clinical trials

Emily C. Zabor
Department of Quantitative Health Sciences

Biostatistics Seminar Series
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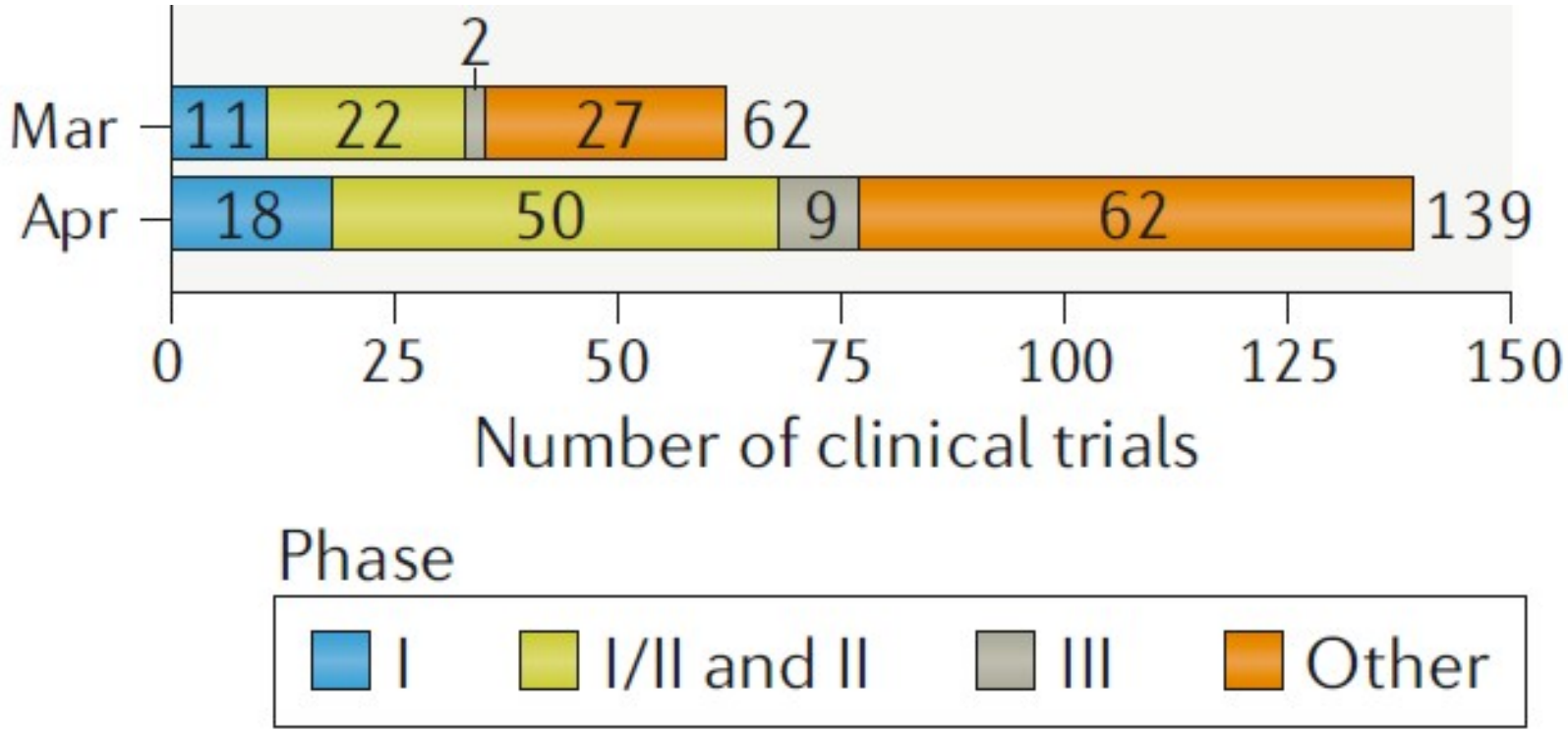
Cleveland Clinic

This work was a joint effort

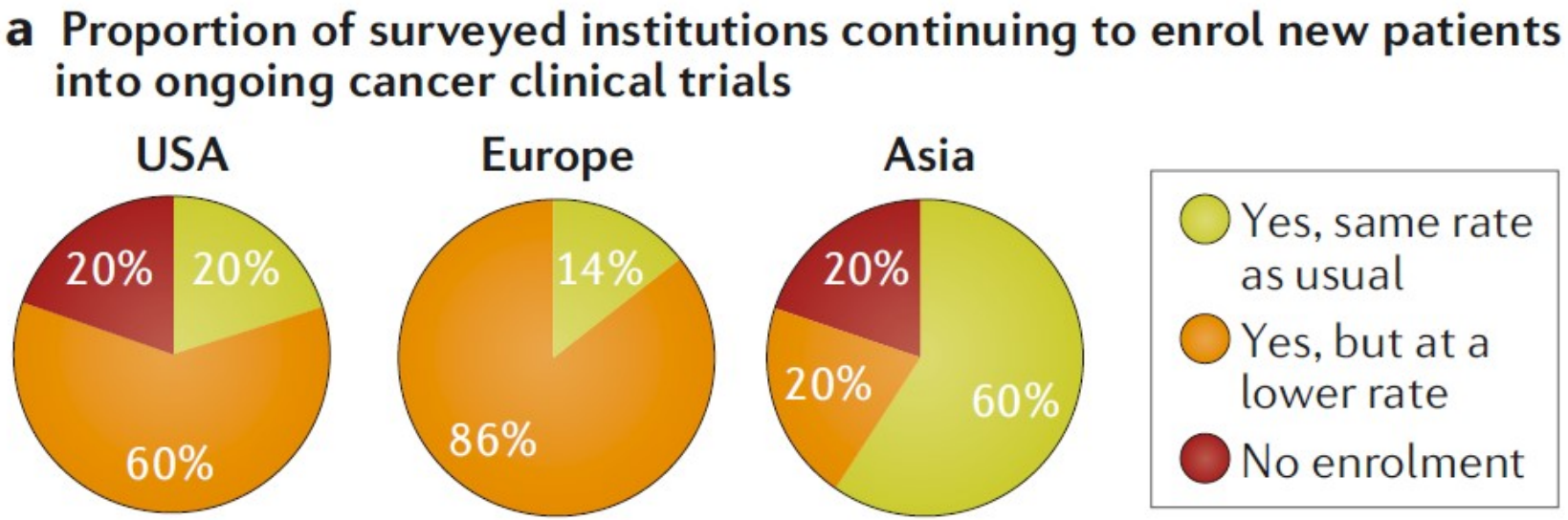
Anne A. Eaton
Division of Biotatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA

Many ongoing oncology studies were suspended when the COVID-19 pandemic began



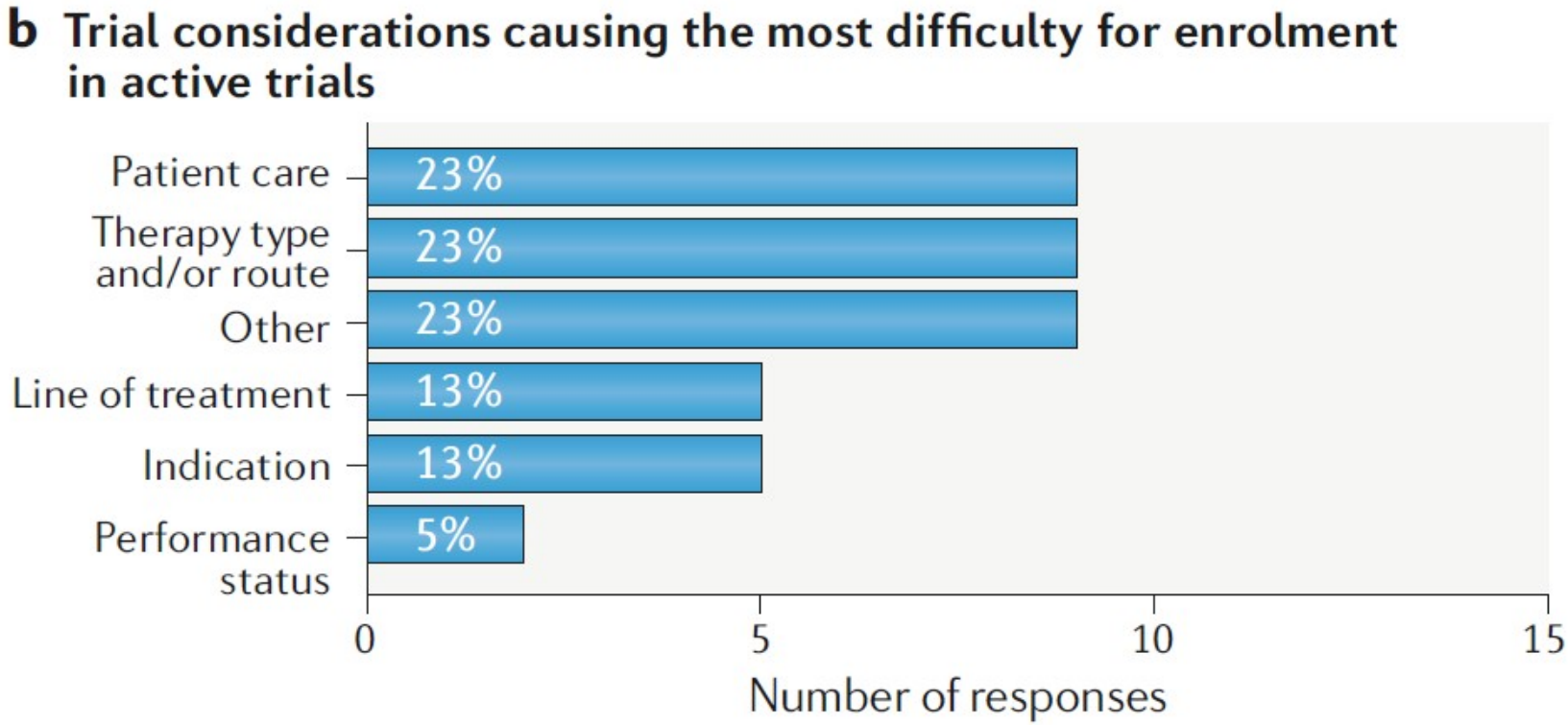
Upadhaya S, Yu JX, Oliva C, Hooton M, Hodge J, Hubbard-Lucey VM. Impact of COVID-19 on oncology clinical trials. Nat Rev Drug Discov. 2020 Jun;19(6):376-377.

Ongoing trials had issues such as slow or stopped enrolment



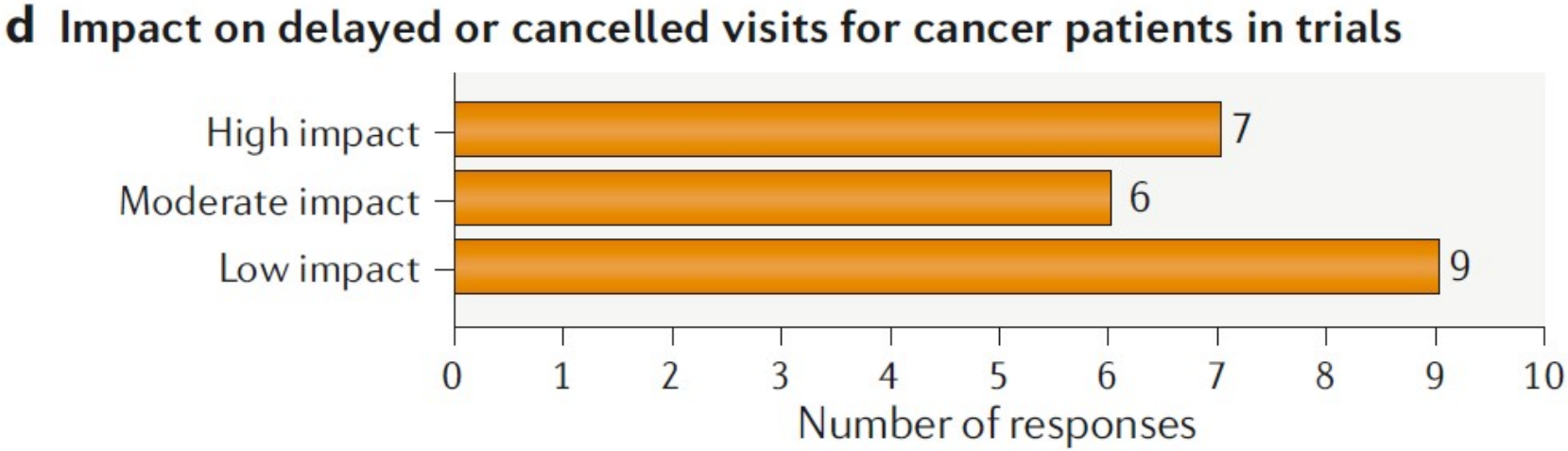
Upadhaya S, Yu JX, Oliva C, Hooton M, Hodge J, Hubbard-Lucey VM. Impact of COVID-19 on oncology clinical trials. Nat Rev Drug Discov. 2020 Jun;19(6):376-377.

Enrolment was often delayed due to concerns about patient care



Upadhaya S, Yu JX, Oliva C, Hooton M, Hodge J, Hubbard-Lucey VM. Impact of COVID-19 on oncology clinical trials. Nat Rev Drug Discov. 2020 Jun;19(6):376-377.

Delayed or cancelled visits had an impact on many oncology trials



Upadhaya S, Yu JX, Oliva C, Hooton M, Hodge J, Hubbard-Lucey VM. Impact of COVID-19 on oncology clinical trials. Nat Rev Drug Discov. 2020 Jun;19(6):376-377.

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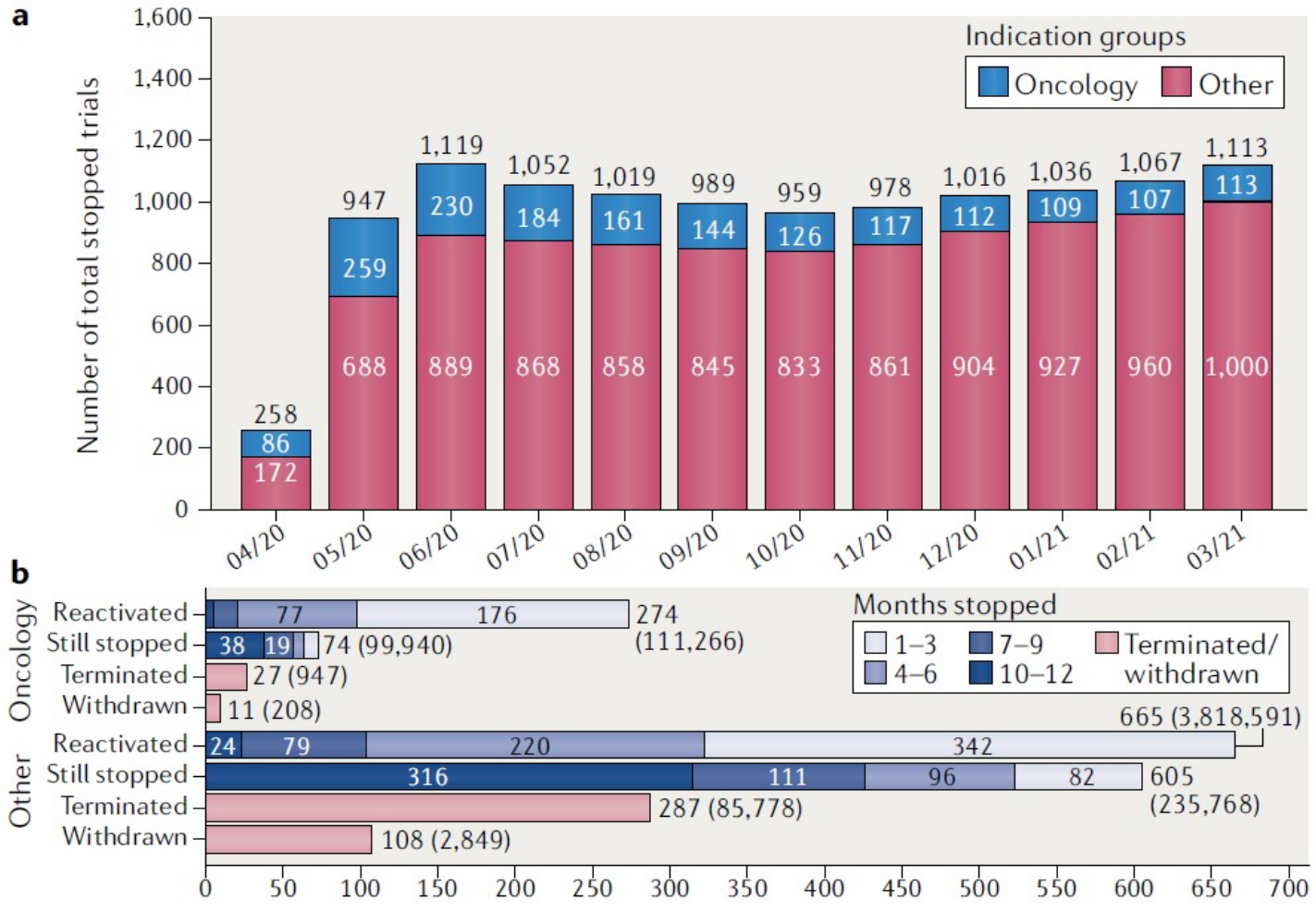
The impacts continued well beyond the first several months of the COVID-19 pandemic



Upadhaya S, Yu JX, Hodge J, Campbell J. COVID-19 impact on oncology clinical trials: a 1-year analysis. Nat Rev Drug Discov. 2021 Jun;20(6):415.

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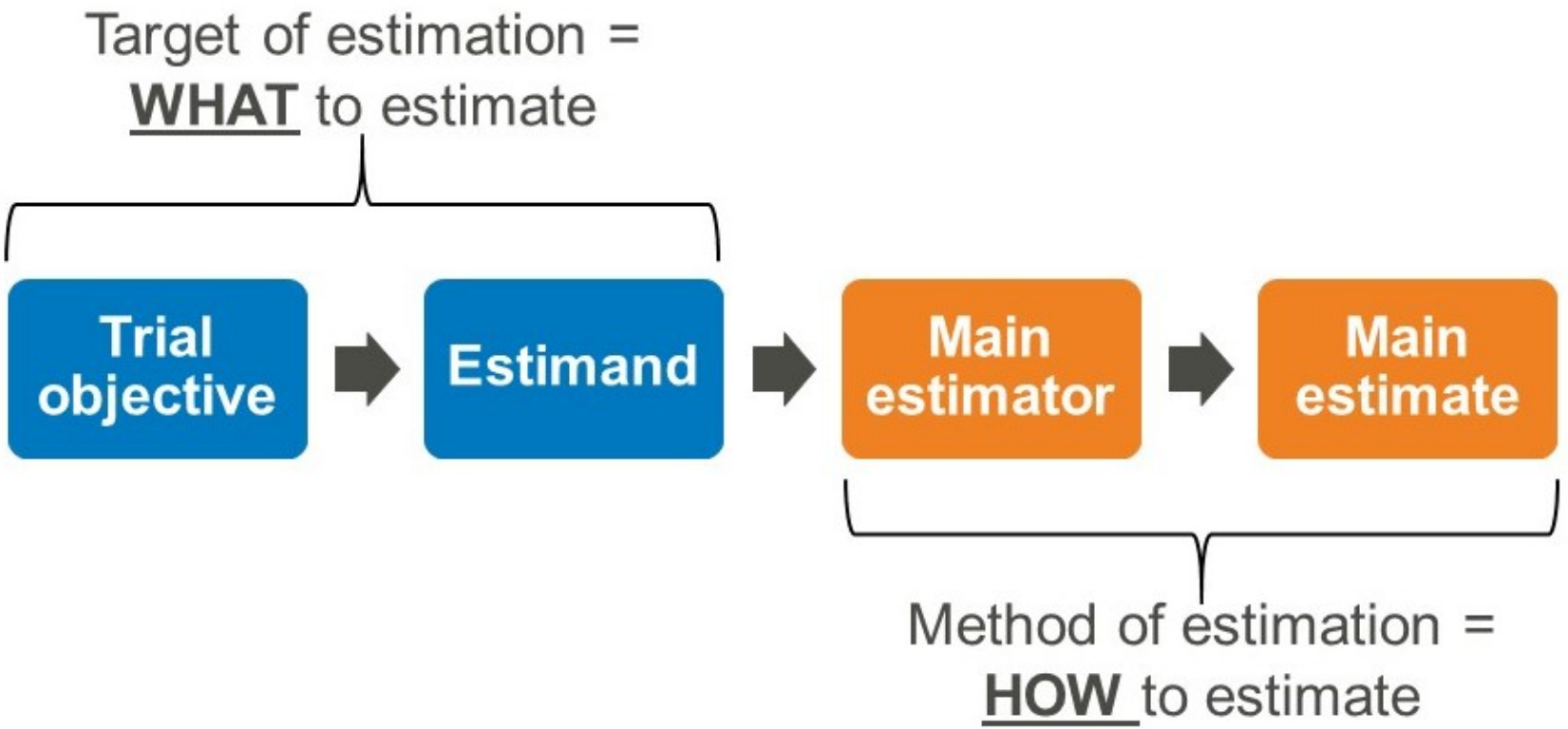
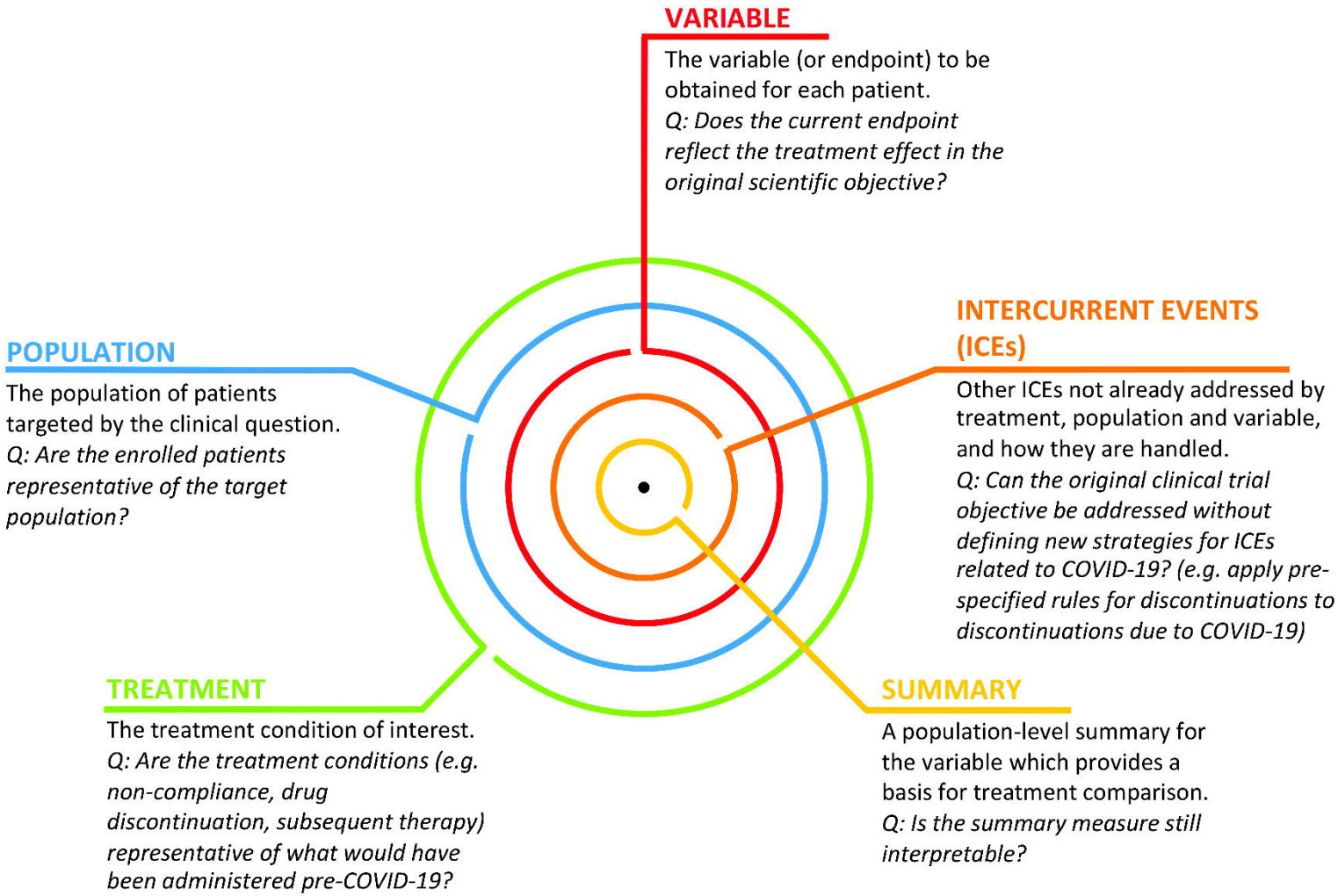
The estimand framework was introduced in 2019 to aid in planning clinical trials



International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Addendum on estimands and sensitivity analyses in clinical trials to the guideline on statistical principles for clinical trials, ICH E9 (R1). https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf

An estimand consists of five key aspects



Degtyarev E et al. Assessing the Impact of COVID-19 on the Clinical Trial Objective and Analysis of Oncology Clinical Trials-Application of the Estimand Framework. Stat Biopharm Res. 2020 Jul 14;12(4):427-437.

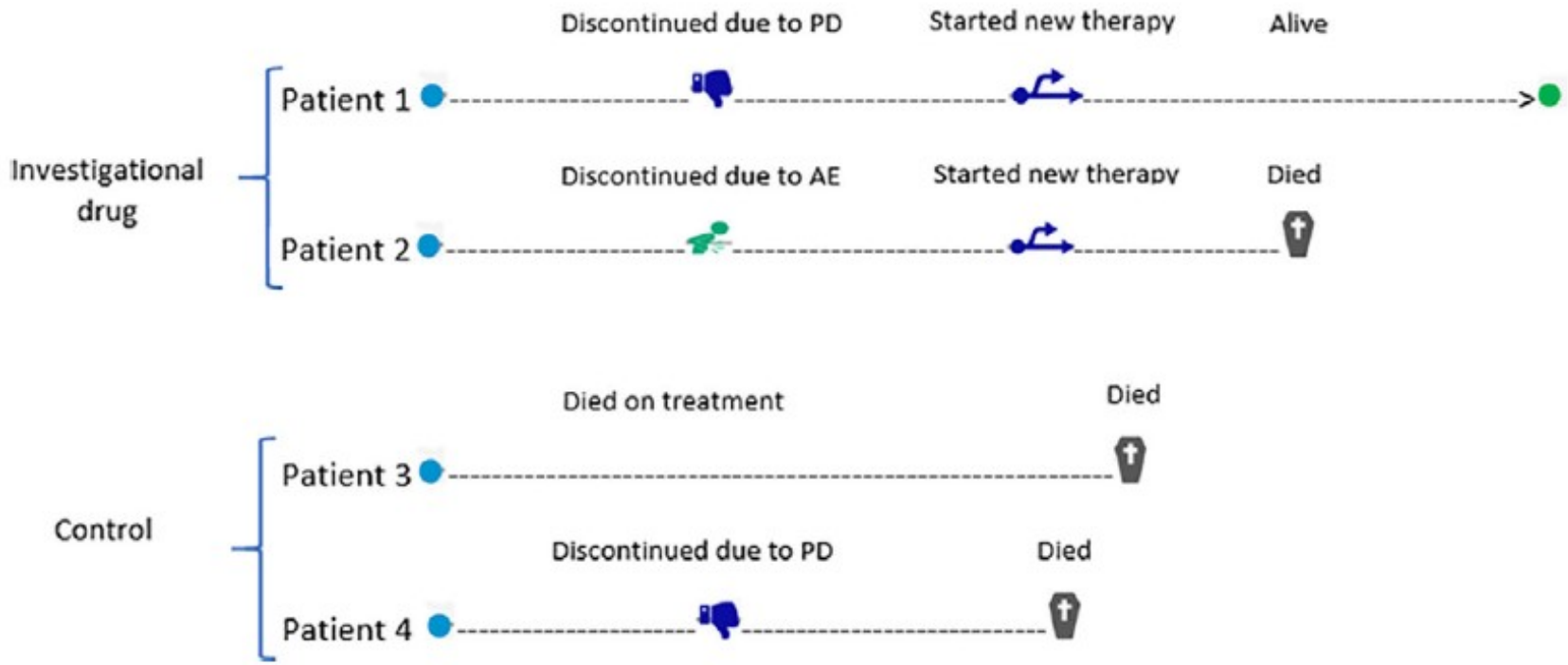
An estimator is a numerical estimate of the estimand

Estimand: The hazard ratio (summary) of overall survival (variable) for an investigational drug compared to a standard of care drug (intervention) regardless of any subsequent treatments received (intercurrent event) in adult patients with a certain type of cancer (population).

Estimator: $\lambda(t|X_i) = \lambda_0(t)exp(\beta X_i)$

Estimate: $\hat{\beta}$

Intercurrent events impact the interpretation or collection of outcome data



Manitz J et al. Estimands for overall survival in clinical trials with treatment switching in oncology. Pharm Stat. 2022 Jan;21(1):150-162.

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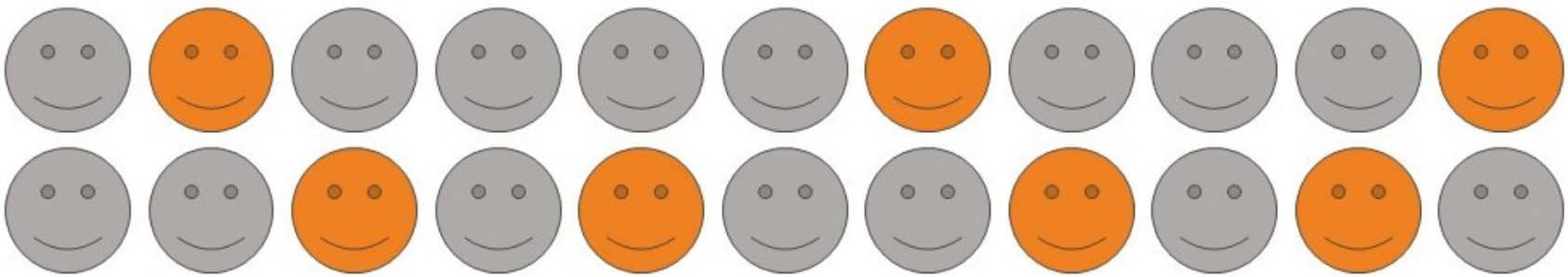
Consider the intercurrent event of treatment discontinuation due to AE

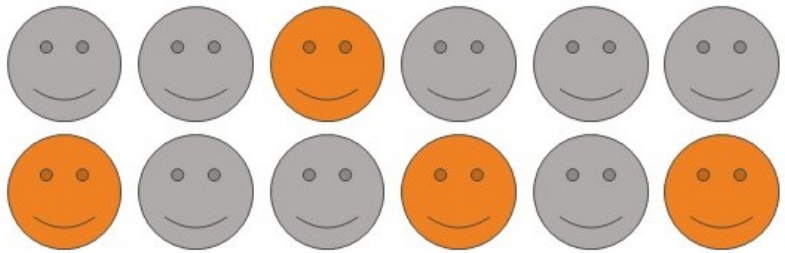


Some patients will discontinue treatment due to adverse events, others will not.

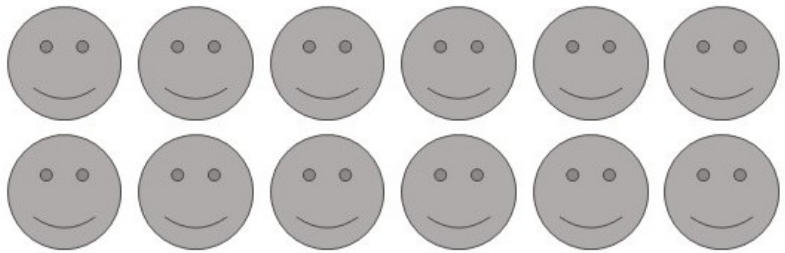
What treatment effect do we really want to estimate? Not all possible, or important.

Some patients will discontinue treatment due to adverse events, others will not.
So we can estimate the effect of treatment…

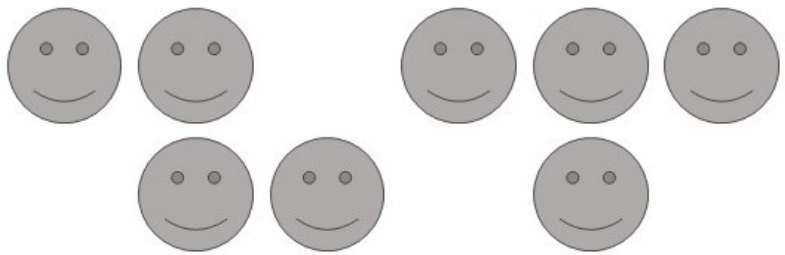
…**regardless of whether** treatment was discontinued due to adverse events.



…in the **hypothetical setting** where treatment was not discontinued due to adverse events.



…in the **population subset** in which treatment was not discontinued due to adverse events.



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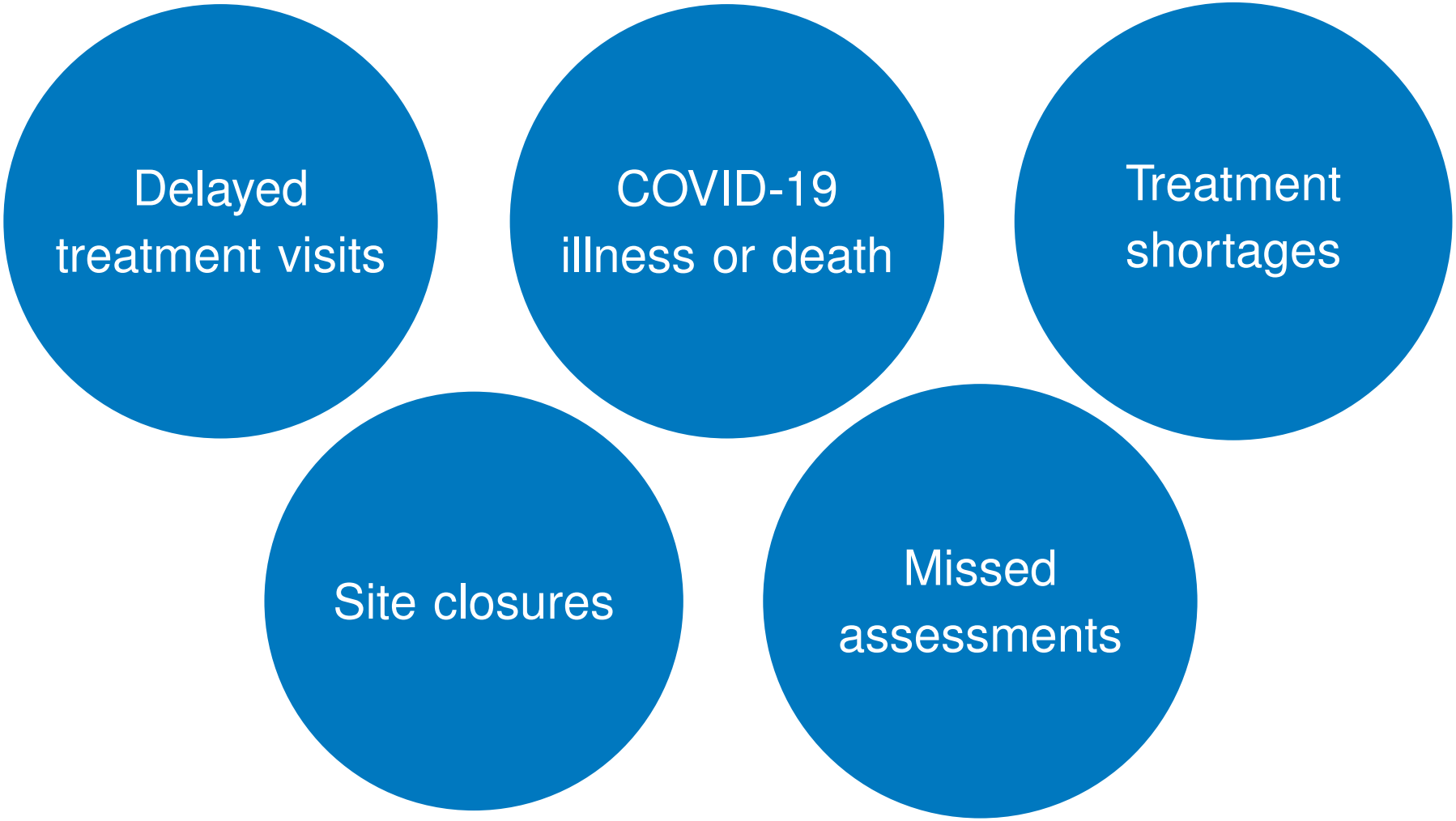
The COVID-19 pandemic introduced many possible intercurrent events to oncology studies



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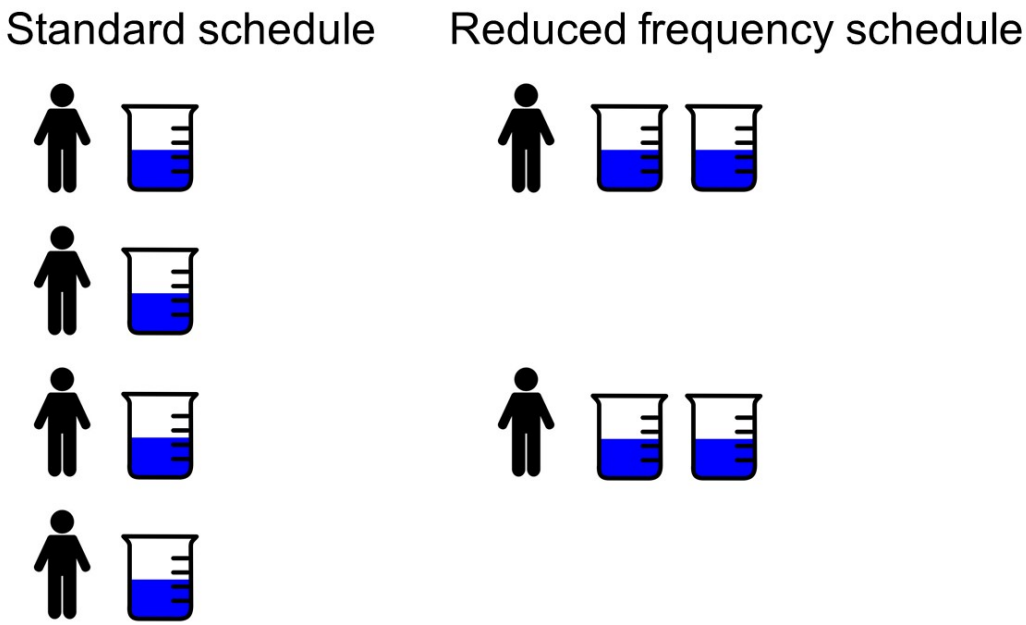
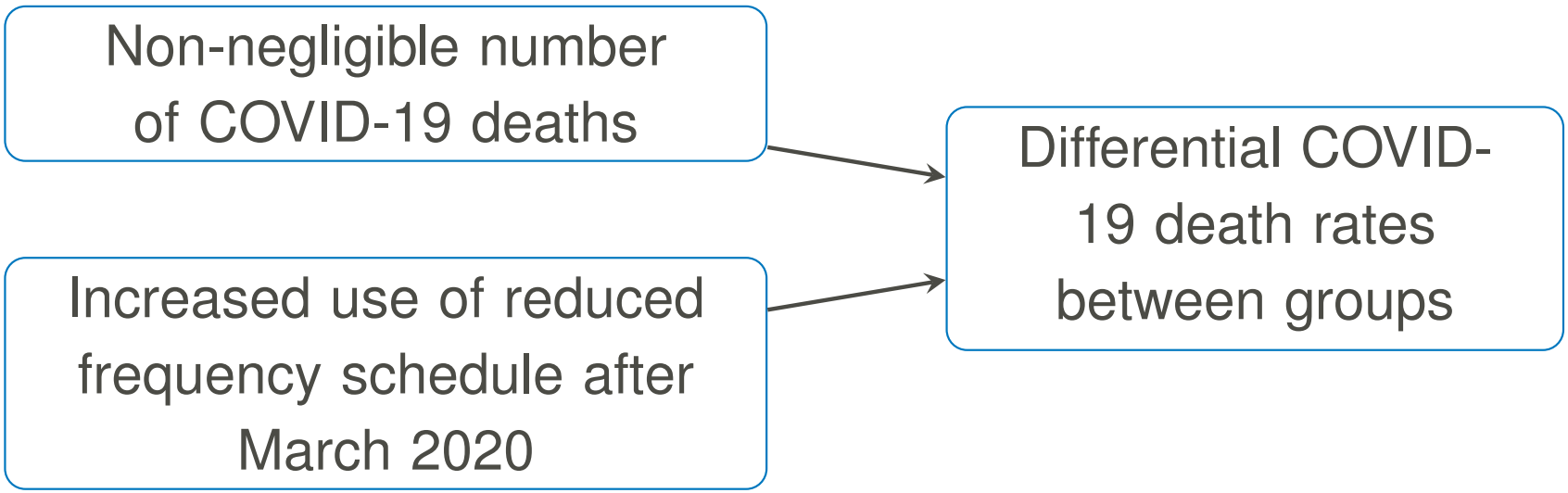
Hypothetical example 1: Differential deaths due to COVID-19

Estimand of interest: The difference in 1-year overall survival rate between the two treatment groups in consecutive metastatic breast cancer patients from 2018-2021.



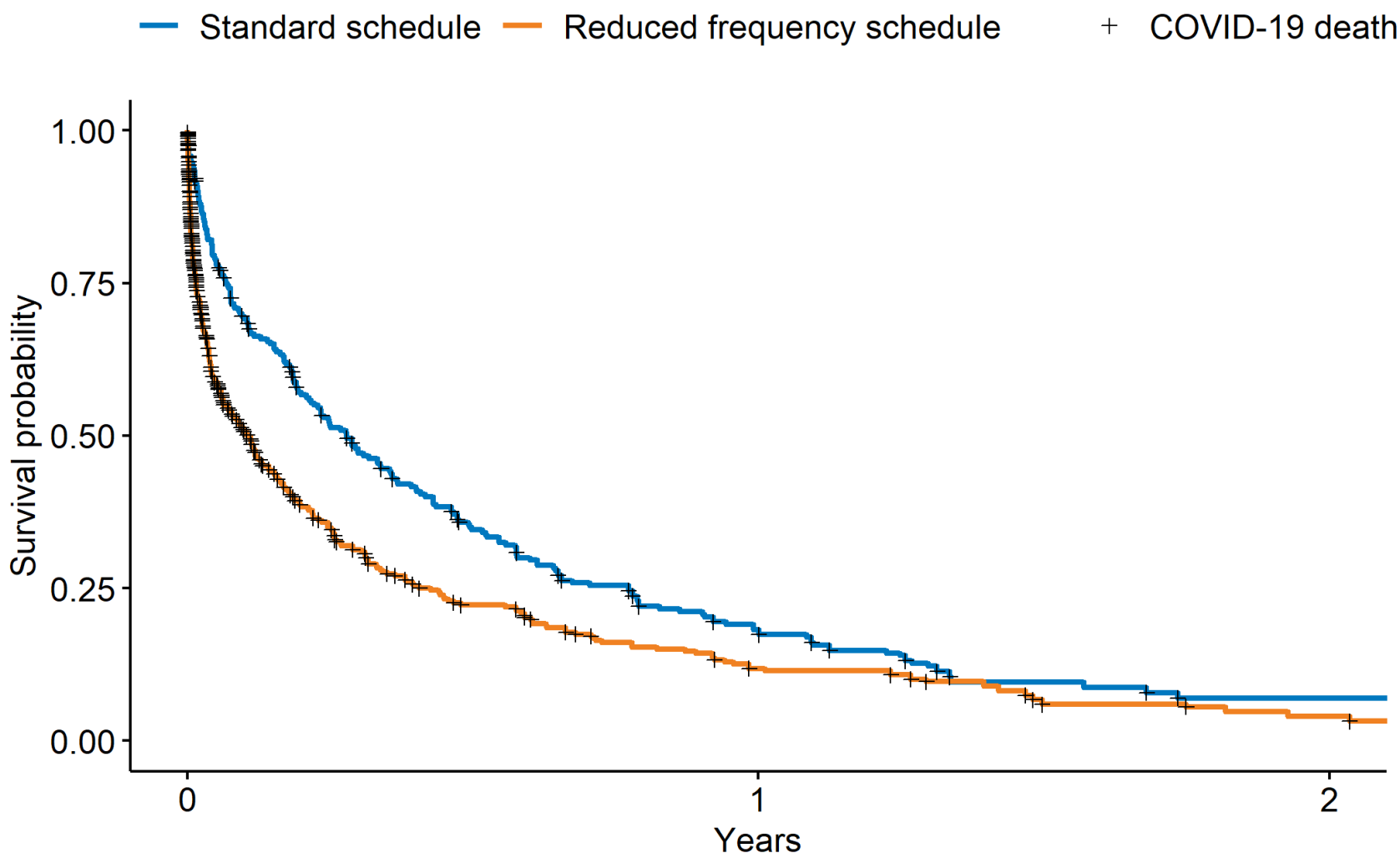
The study was impacted by the COVID-19 pandemic in multiple ways



In simulated data there is no association between treatment schedule and death

- 500 patients
- Increased age associated with increased risk of cancer death and increased risk of COVID-19 death
- Patients in the standard schedule die from COVID-19 less frequently simply because they were diagnosed and followed prior to the onset of the COVID-19 pandemic in the area

Originally planned estimator was the Kaplan-Meier estimator for overall survival



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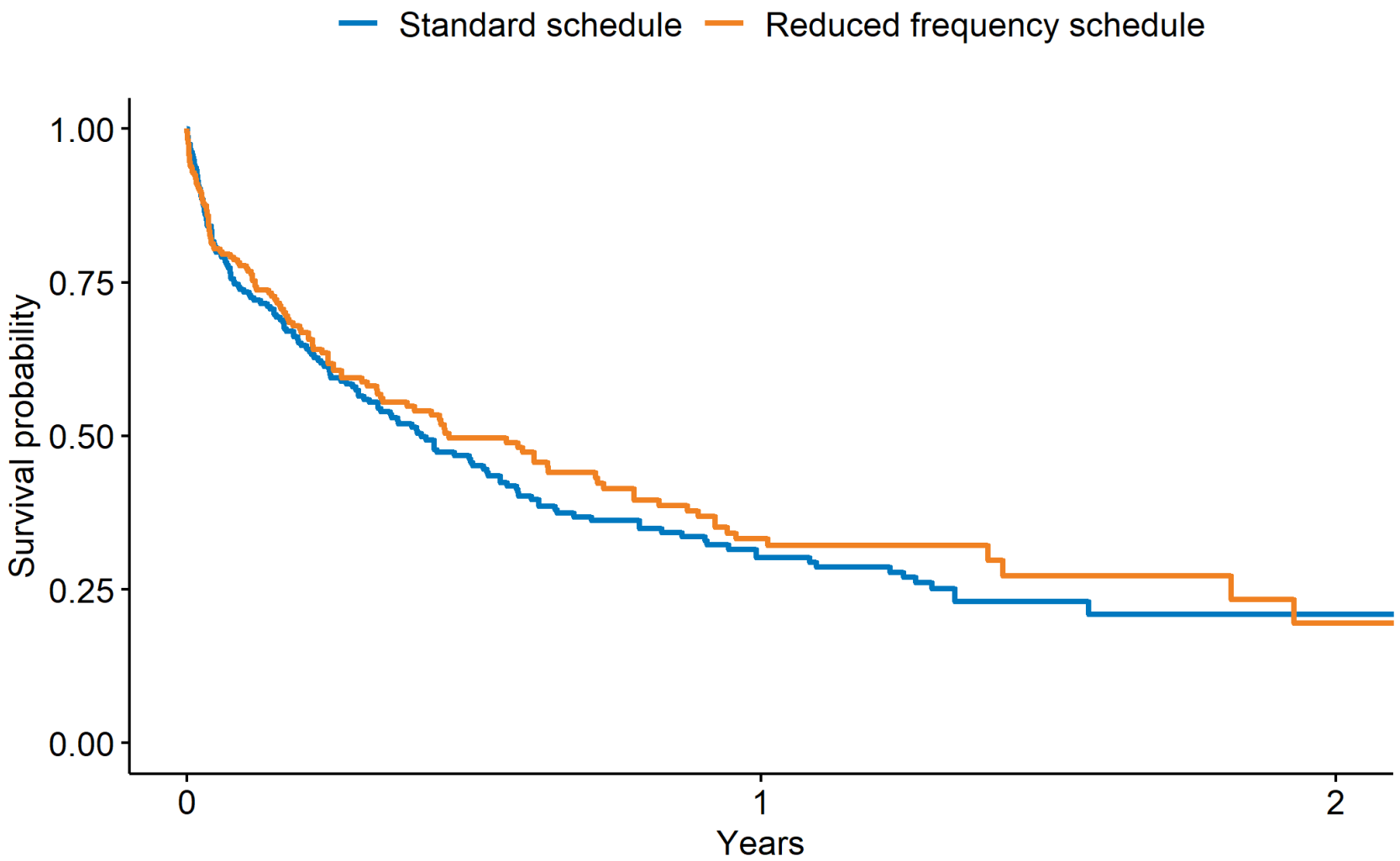
Revise estimand and estimator for “hypothetical world without COVID-19”



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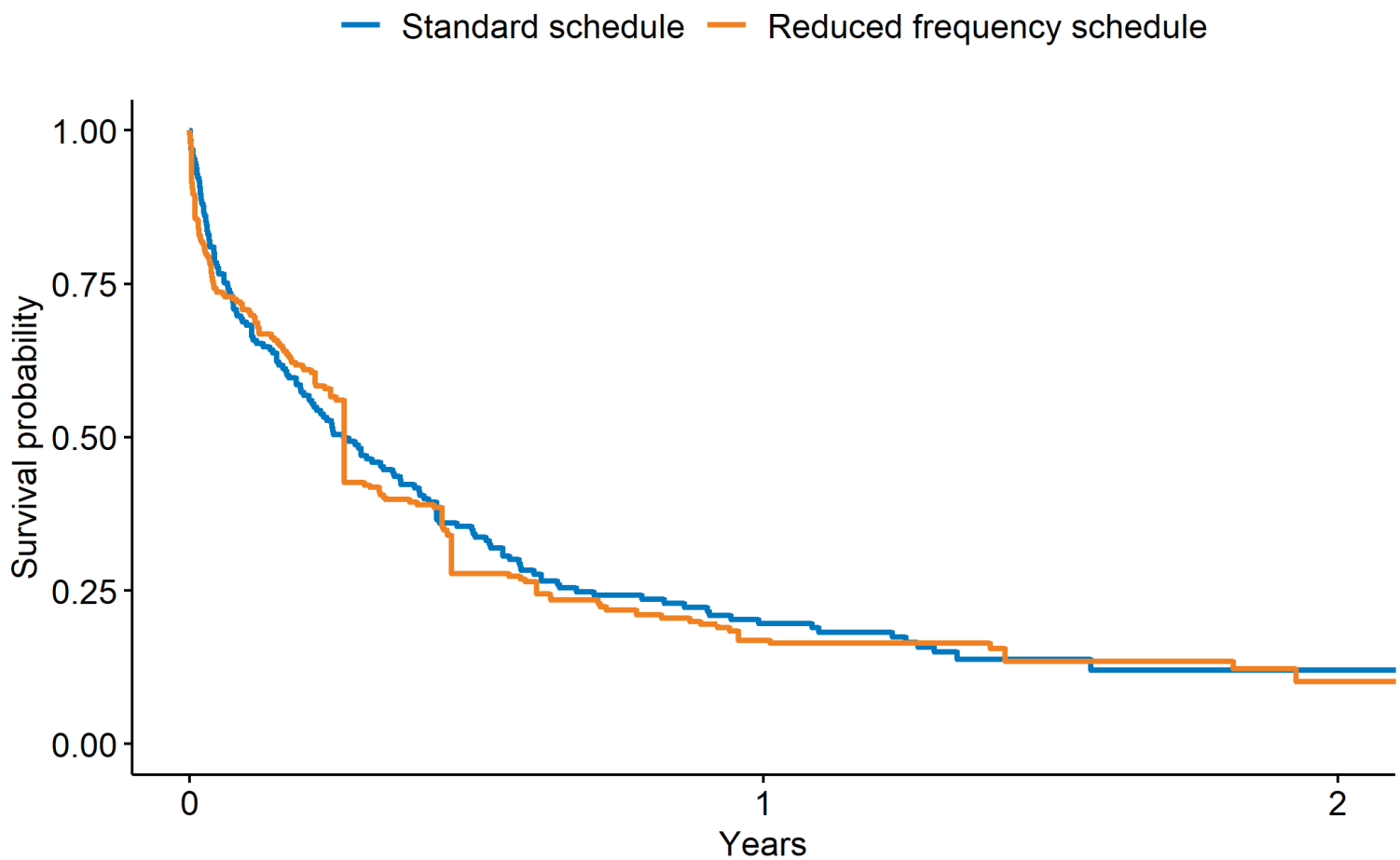
Kaplan-Meier estimator with IPCW accounts for non-informative censoring



Willems S, Schat A, van Noorden MS, Fiocco M. Correcting for dependent censoring in routine outcome monitoring data by applying the inverse probability censoring weighted estimator. Stat Methods Med Res. 2018 Feb;27(2):323-335.

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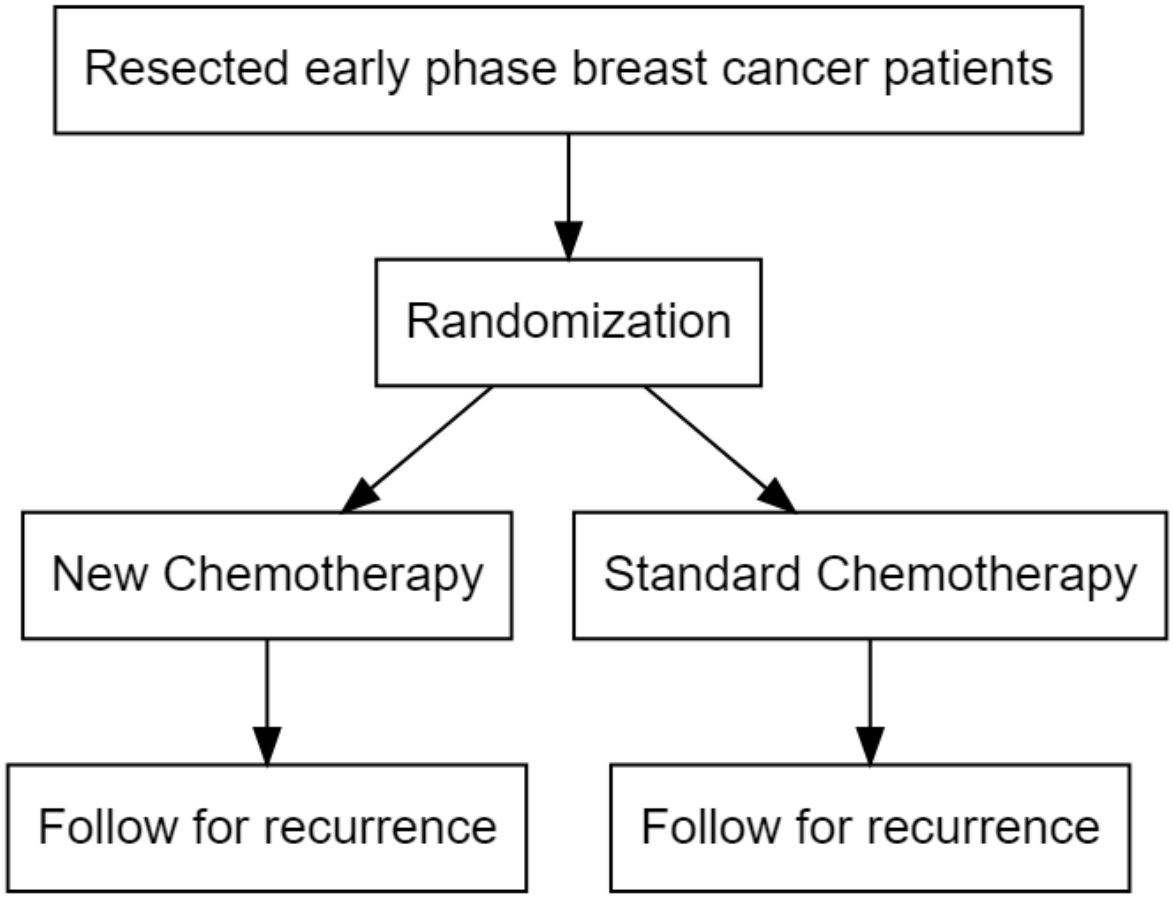
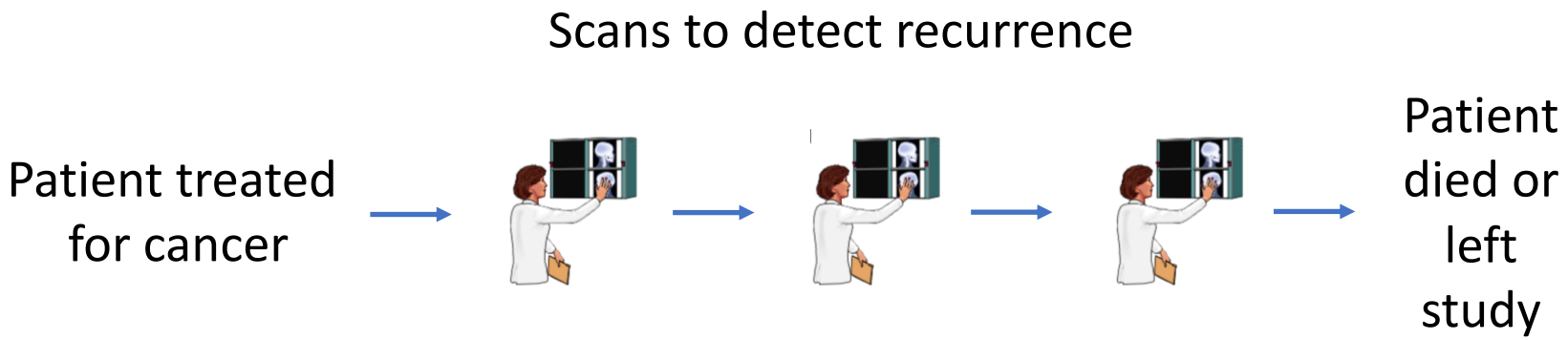
Hypothetical example 2: Delays in imaging assessments



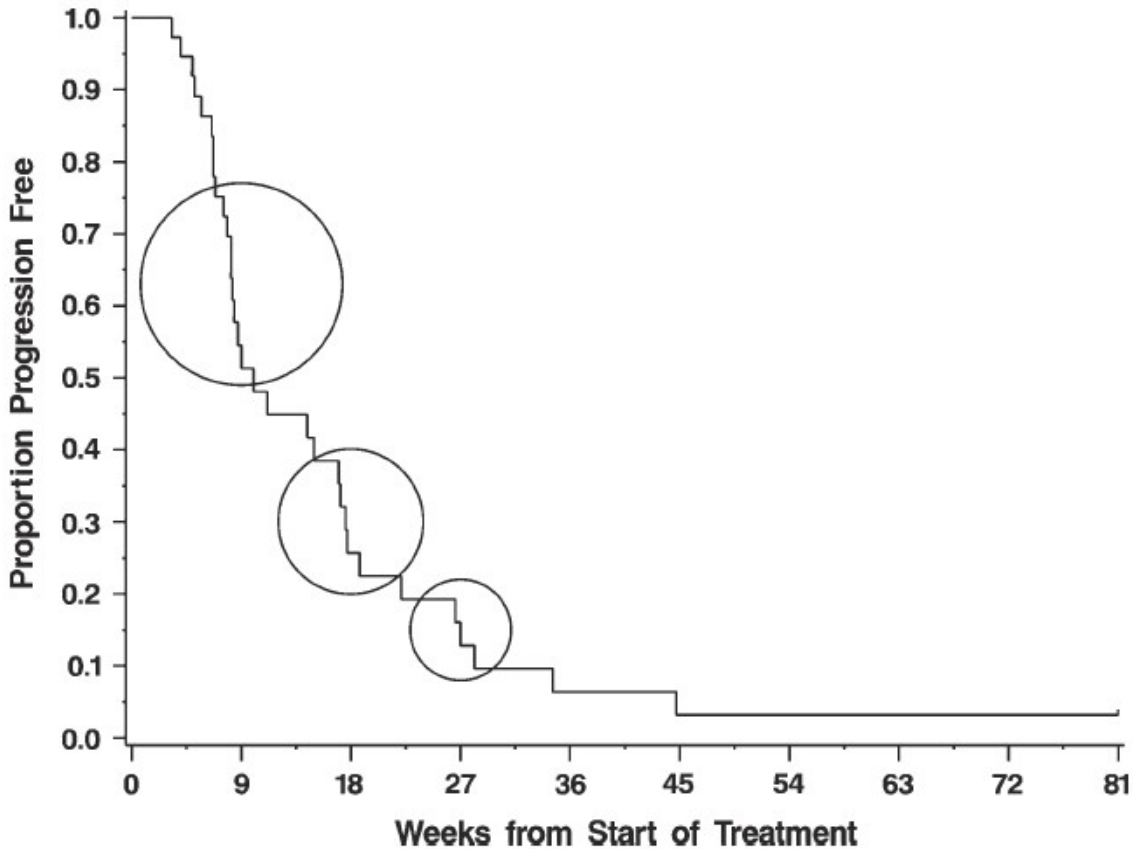
At the start of the COVID-19 pandemic, the interval between scans was extended from 6 to 12 weeks

Primary outcome: **Recurrence-free survival**

Recurrence is an interval-censored event, only detected at visits for a scan



This has a known impact in clinical trials, which exhibit clusters of events around assessment times



Panageas KS, Ben-Porat L, Dickler MN, Chapman PB, Schrag D. When you look matters: the effect of assessment schedule on progression-free survival. J Natl Cancer Inst. 2007 Mar 21;99(6):428-32.

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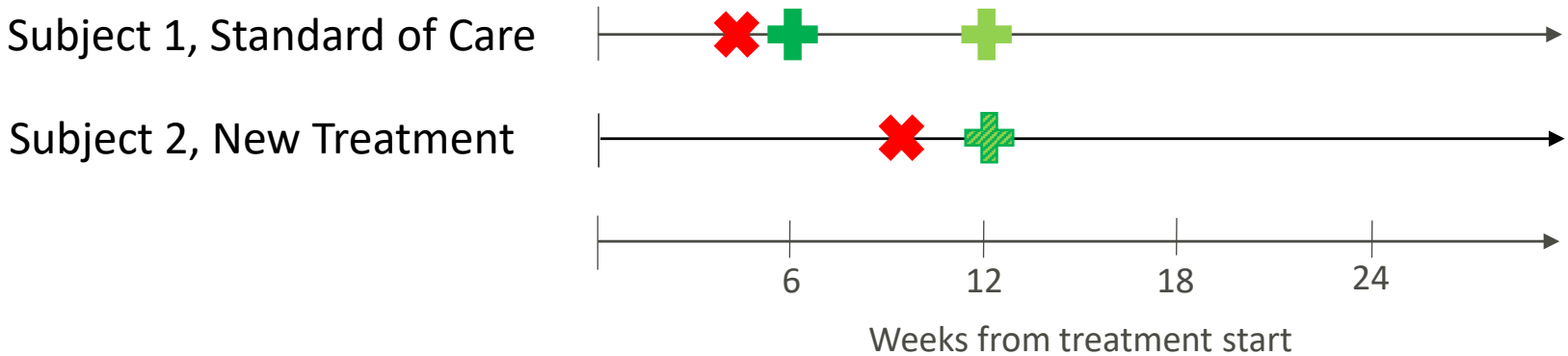
The impact is exacerbated by a delay in the scan schedule due to the COVID-19 pandemic



Legend

= true recurrence

= observed recurrence, original visit schedule

= observed recurrence, new visit schedule

= observed recurrence, both visit schedules

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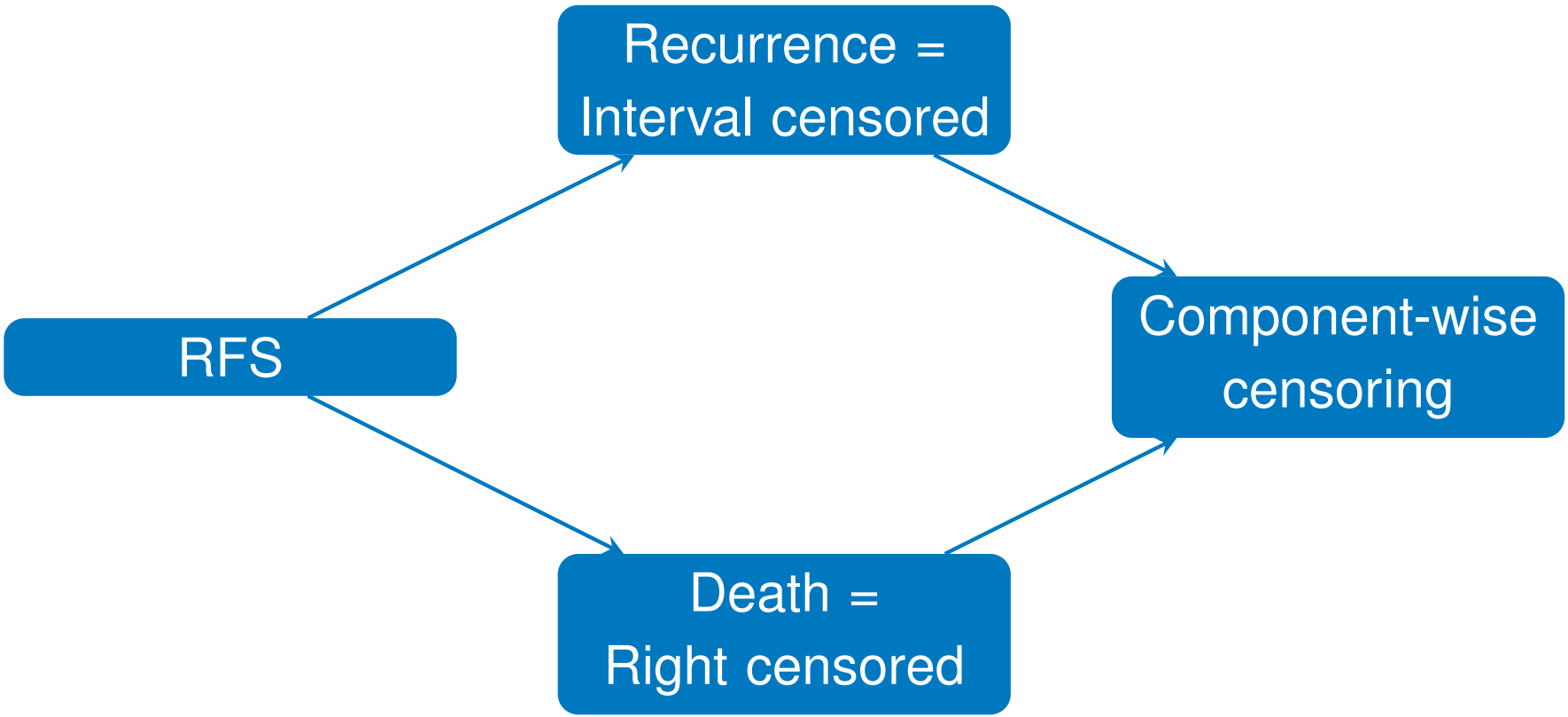
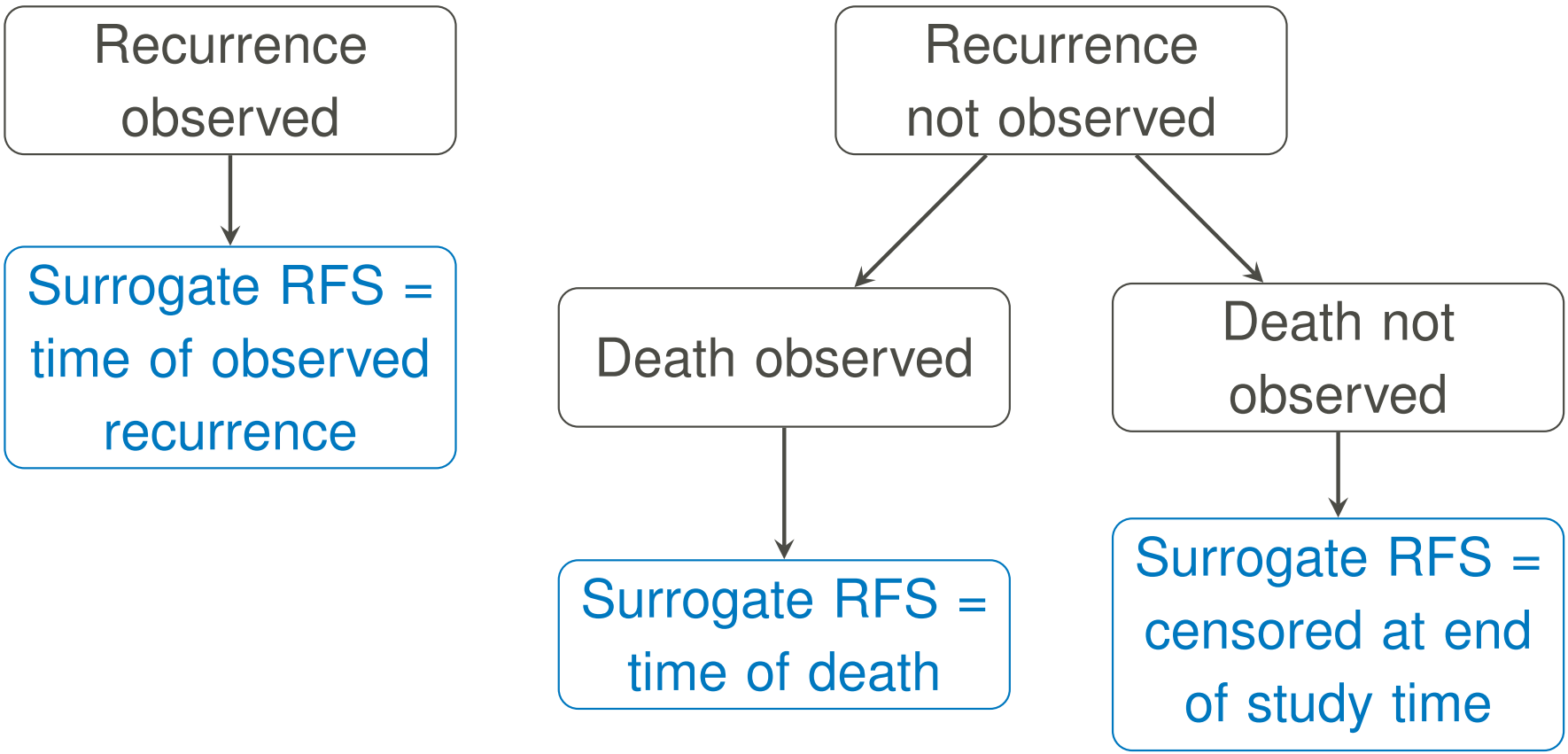
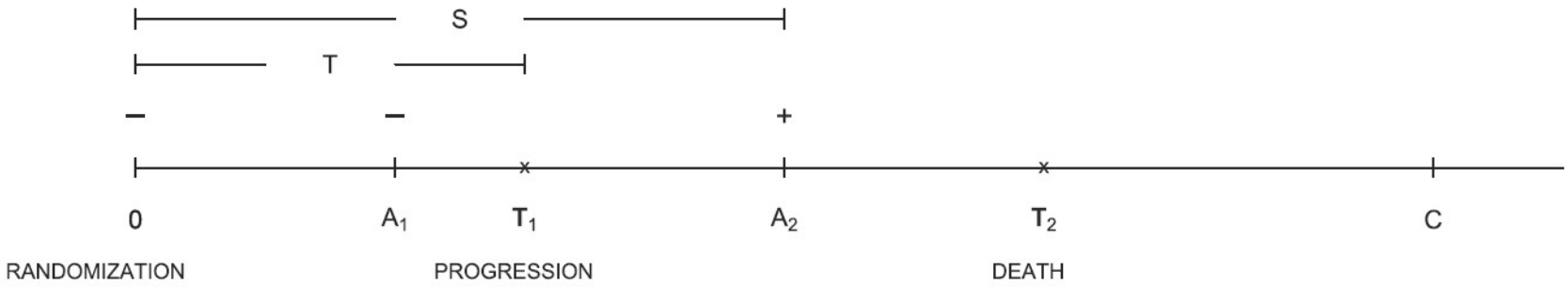
Recurrence-free survival is a composite endpoint with component-wise censoring



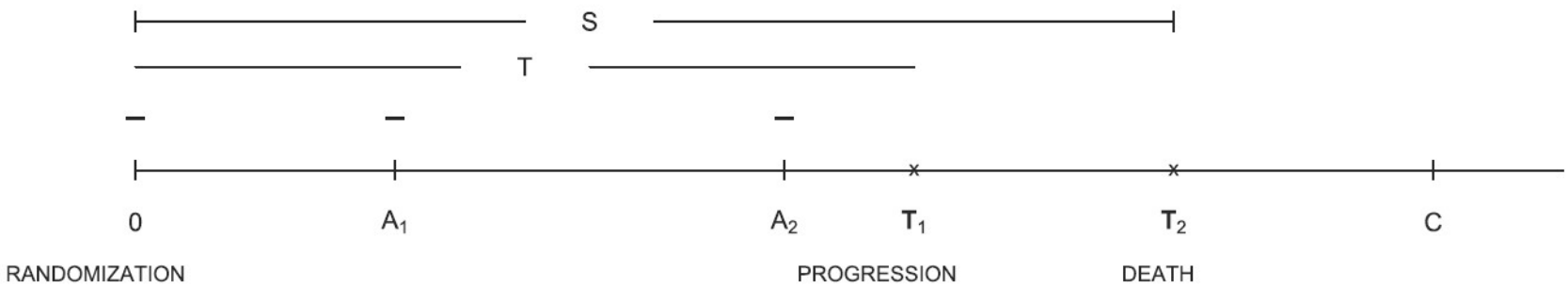
Typically a “surrogate” RFS time is defined, and analyzed using methods for right-censored data



Surrogate RFS is known to overestimate survival time



(a) A timeline diagram for events in which progression is detected



(b) A timeline diagram for events in which progression is not detected due to death

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Zeng L, Cook RJ, Wen L, Boruvka A. Bias in progression-free survival analysis due to intermittent assessment of progression. Stat Med. 2015 Oct 30;34(24):3181-93.

Standard right-censored Cox model was already misaligned with the desired estimand

Desired estimand: HR for RFS for new chemotherapy vs standard chemotherapy

Originally targeted estimand: HR for *surrogate* RFS for new chemotherapy vs standard chemotherapy *when patients visit every 6 weeks*

Newly targeted estimand: HR for *surrogate* RFS for new chemotherapy vs standard chemotherapy *when patients visit every 12 weeks*

Can treating the recurrence component of RFS as interval-censored overcome this issue?

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RESEARCH ARTICLE

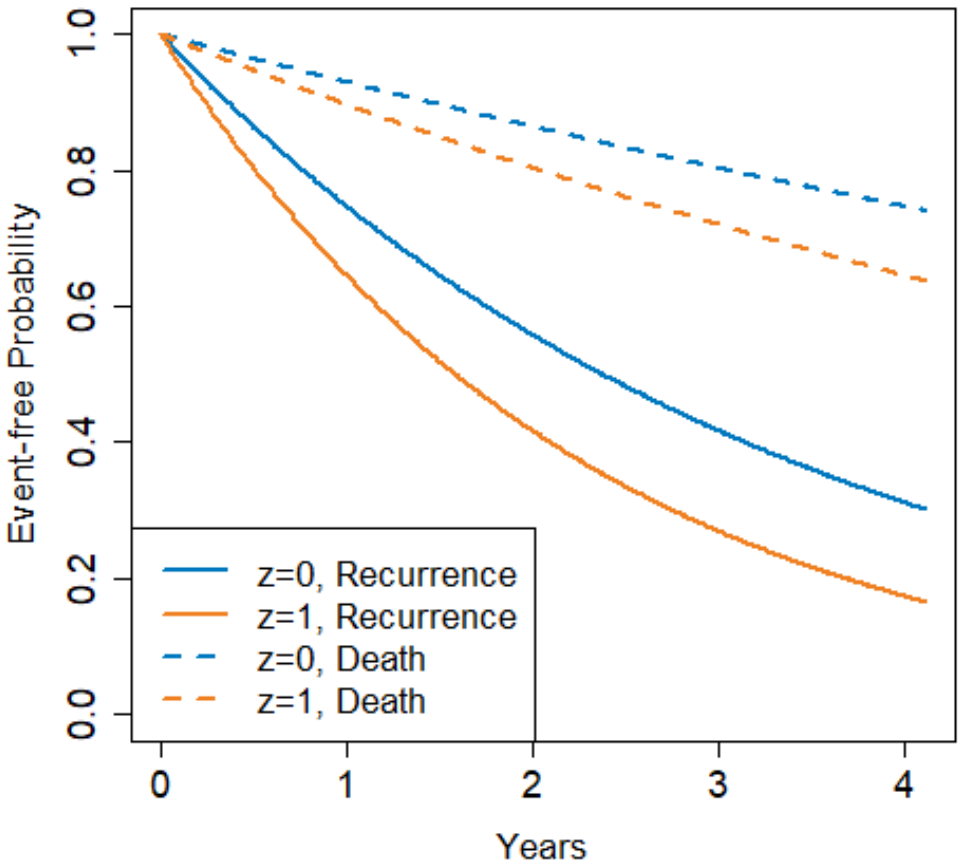
Statistics in Medicine WILEY

Analysis of composite endpoints with component-wise censoring in the presence of differential visit schedules

Anne A. Eaton[1] | Emily C. Zabor[2]

Eaton AA, Zabor EC. Analysis of composite endpoints with component-wise censoring in the presence of differential visit schedules. Stat Med. 2022 Apr 30;41(9):1599-1612.

Survival data simulated for recurrence-free survival with a single binary covariate z



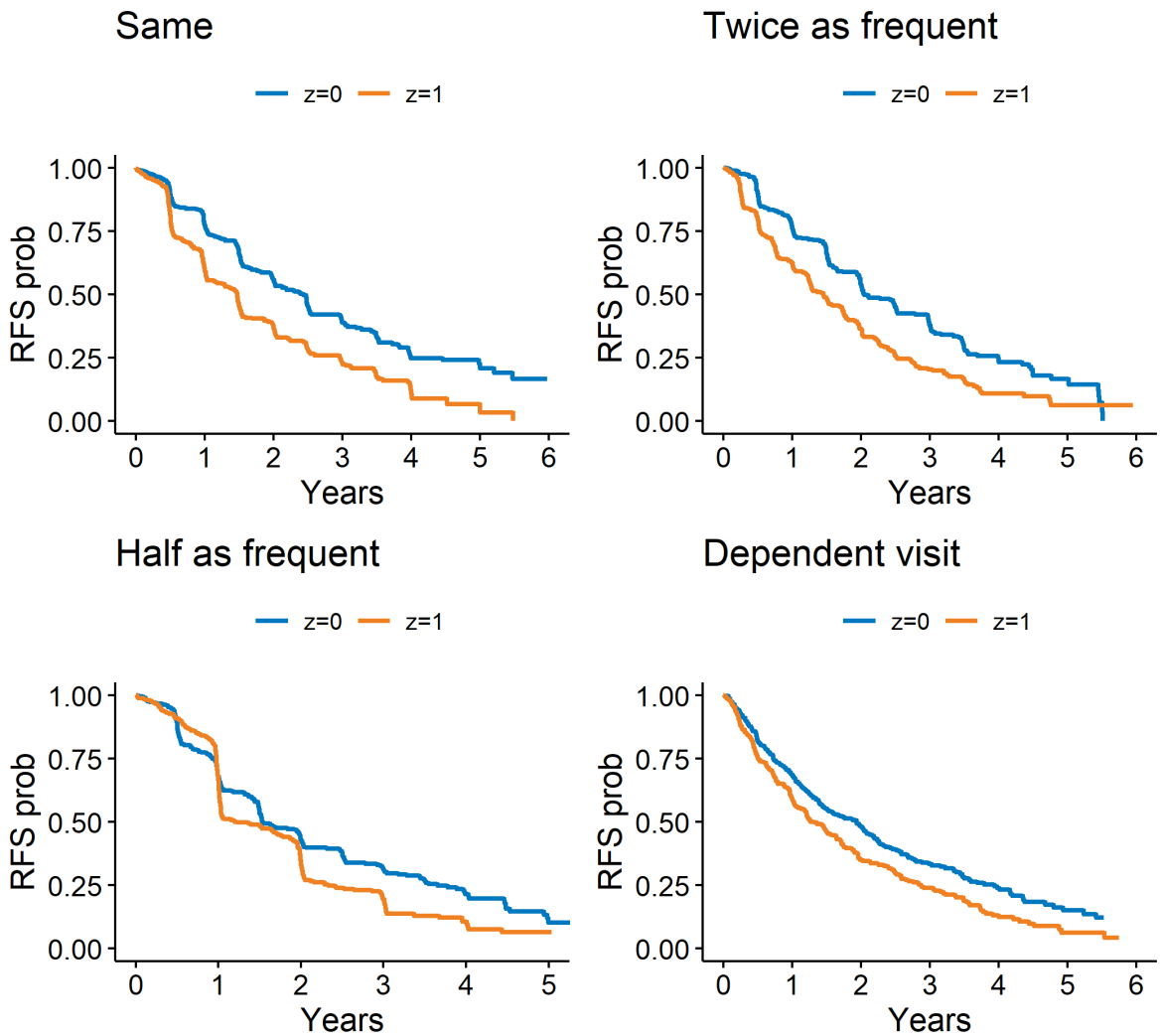
$$h_r(t|z) = h_{0r}(t)\exp(z\gamma) = 0.0008$$

$$h_d(t|z) = h_{0d}(t)\exp(z\eta) = 0.0002$$

$$h(t|z) = h_0(t)\exp(z\beta)$$

$$\beta = \gamma = \eta = \log(1.5)$$

Settings explored differential visit processes and recurrence-dependent visits



Visits normally distributed around scheduled days with 10 day variance.

Recurrence-dependent visits at true recurrence days $+ \sim N(30, 10)$.

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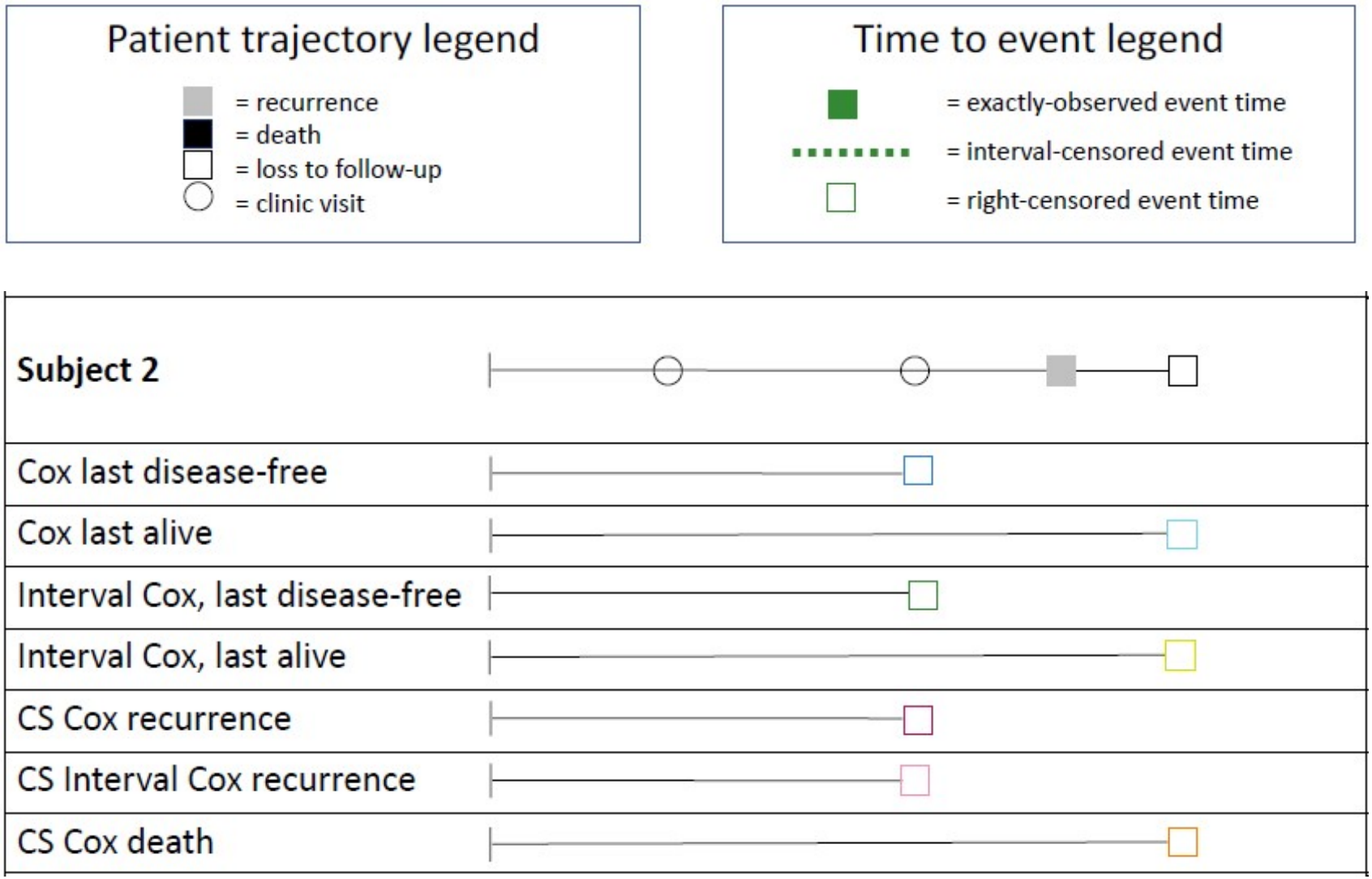
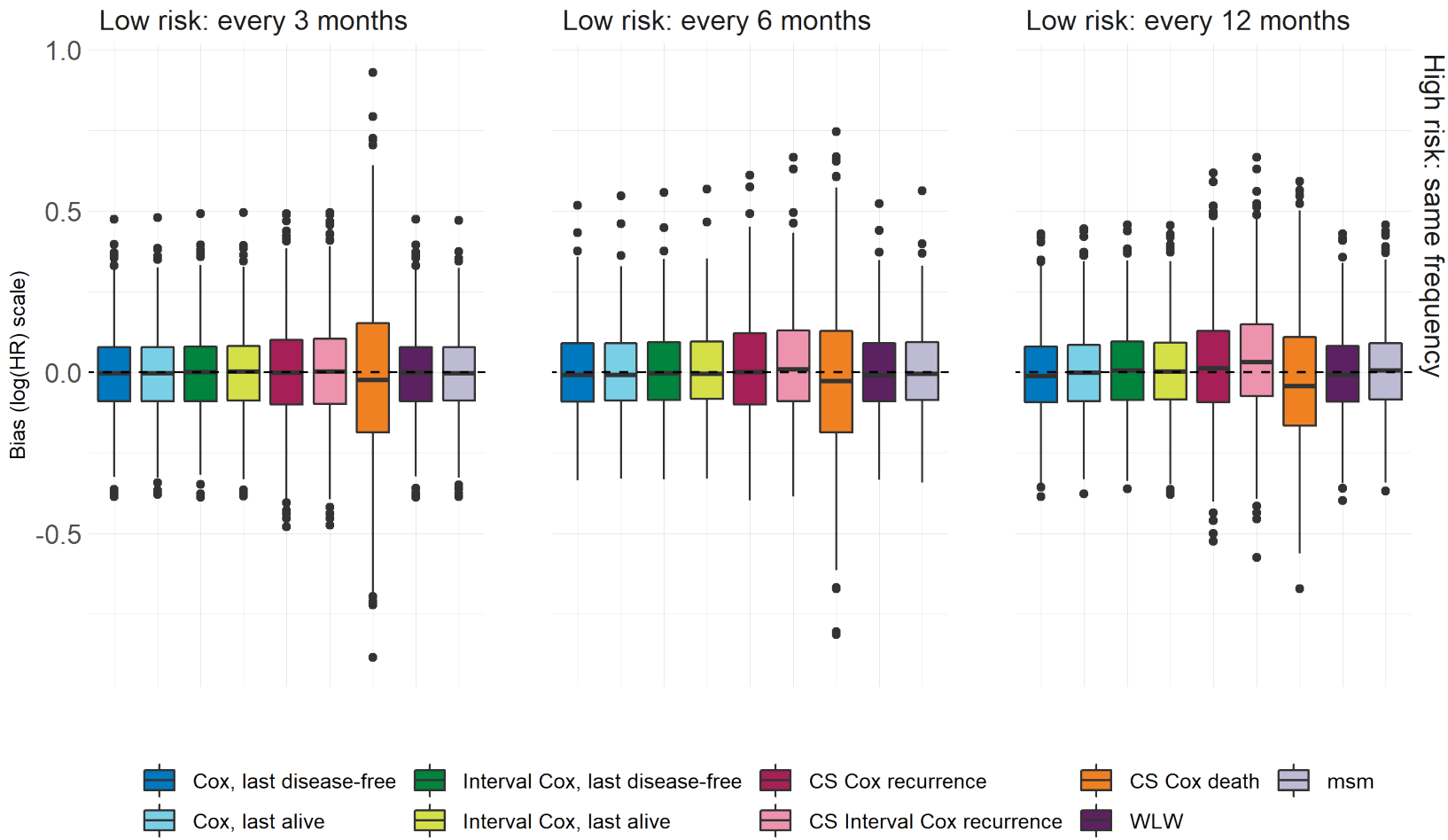
Hypothetical subject 1 had a recurrence between two clinic visits, then was lost to follow-up

Hypothetical subject 2 had a recurrence after the last clinic visit, then was lost to follow-up



Hypothetical subject 3 had a recurrence after the last clinic visit, then died

Biases are less than 0.039 absolute when the visit schedules are the same



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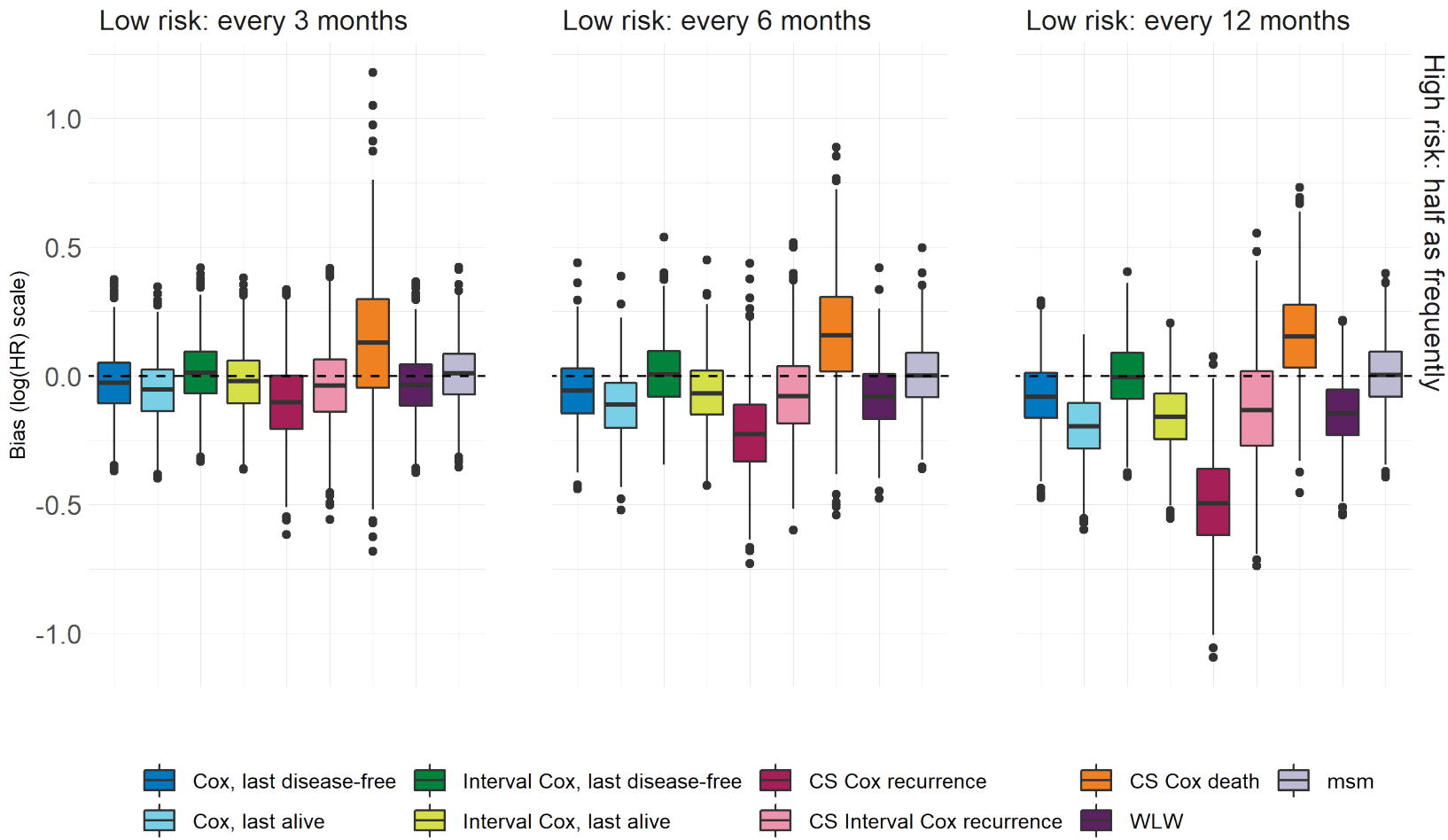
Interval Cox censored at last disease-free had minimal bias when high risk group visits half as frequently



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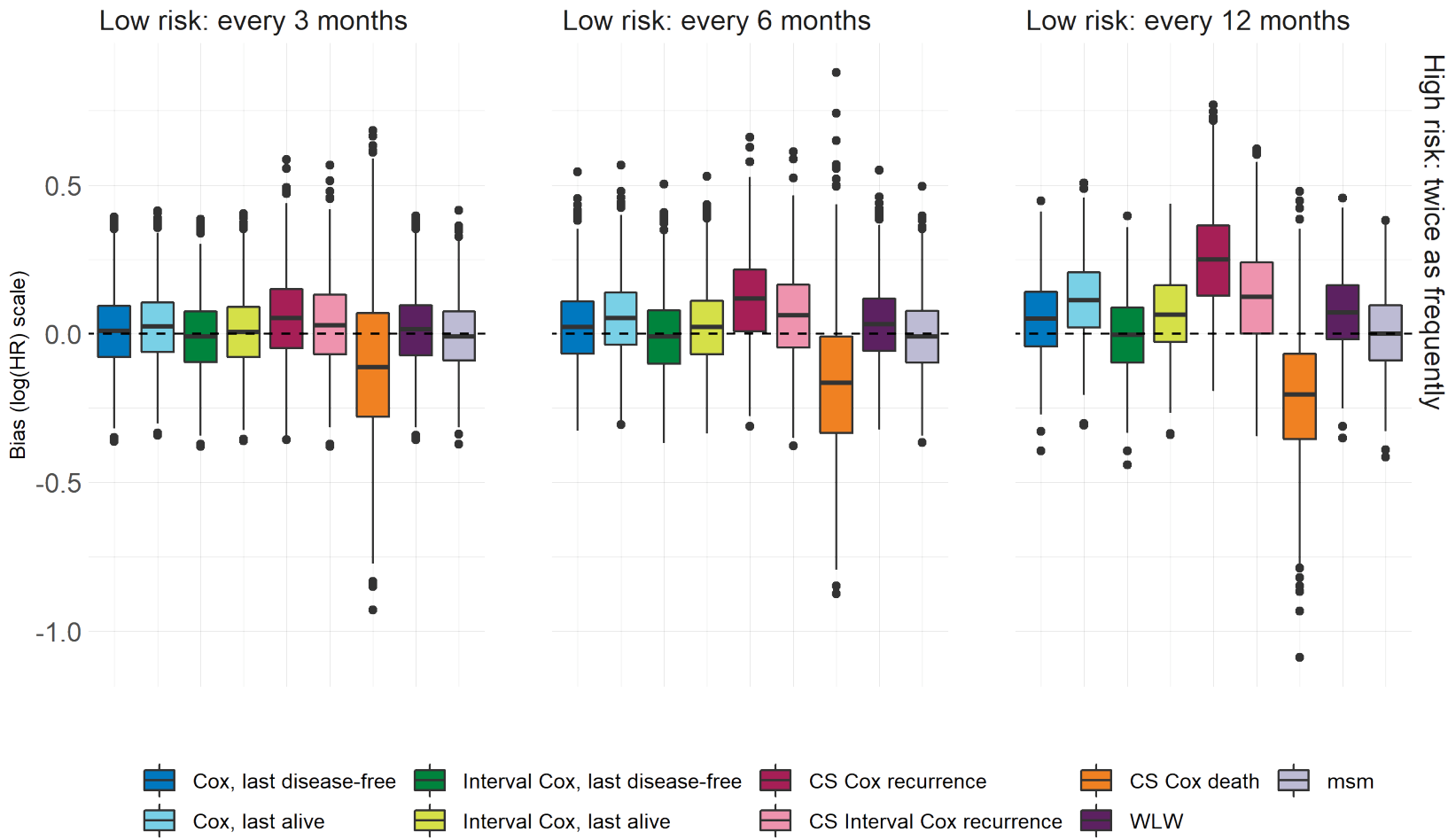
Pattern of results is simply reversed when high risk group visits twice as frequently



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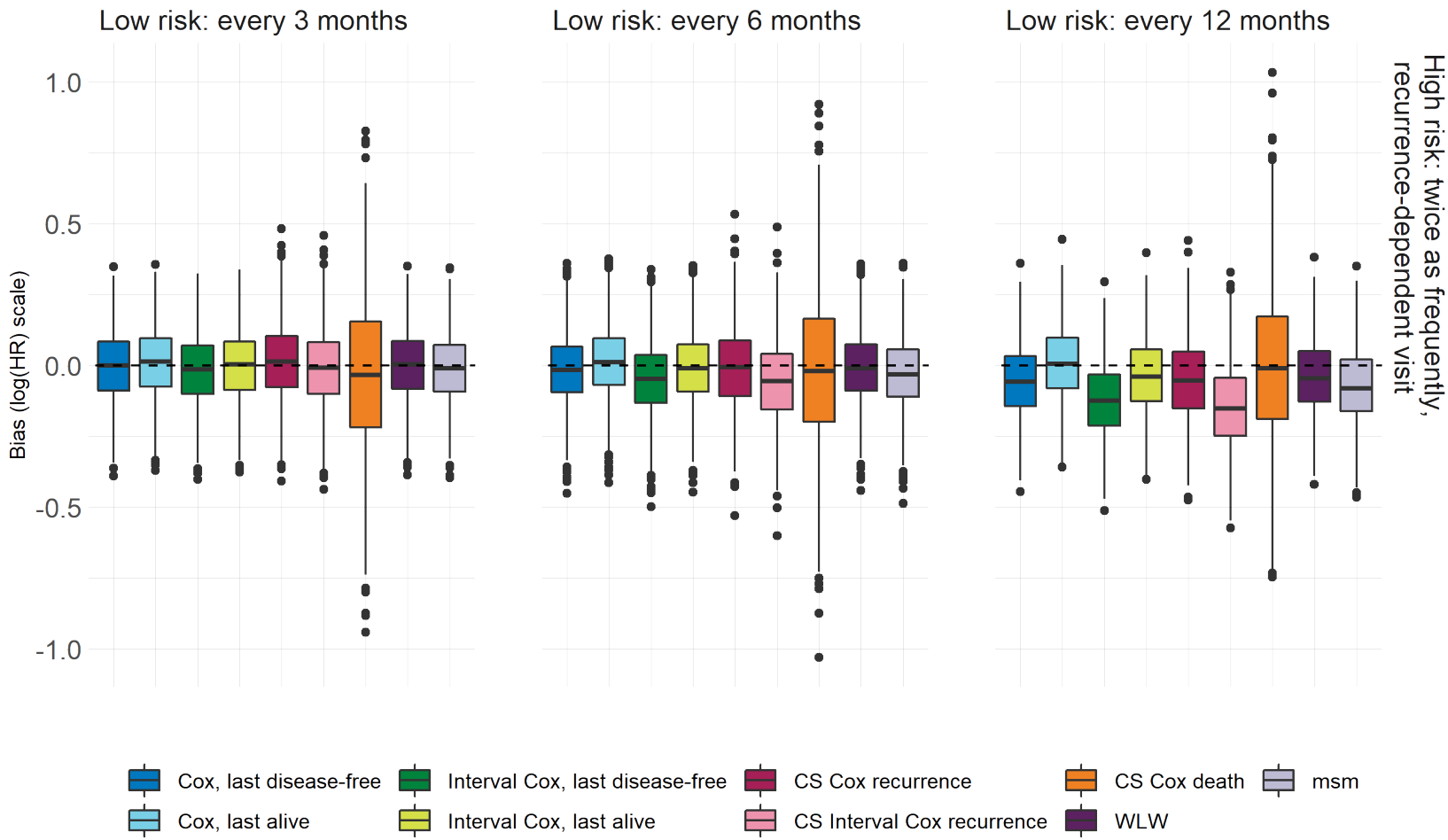
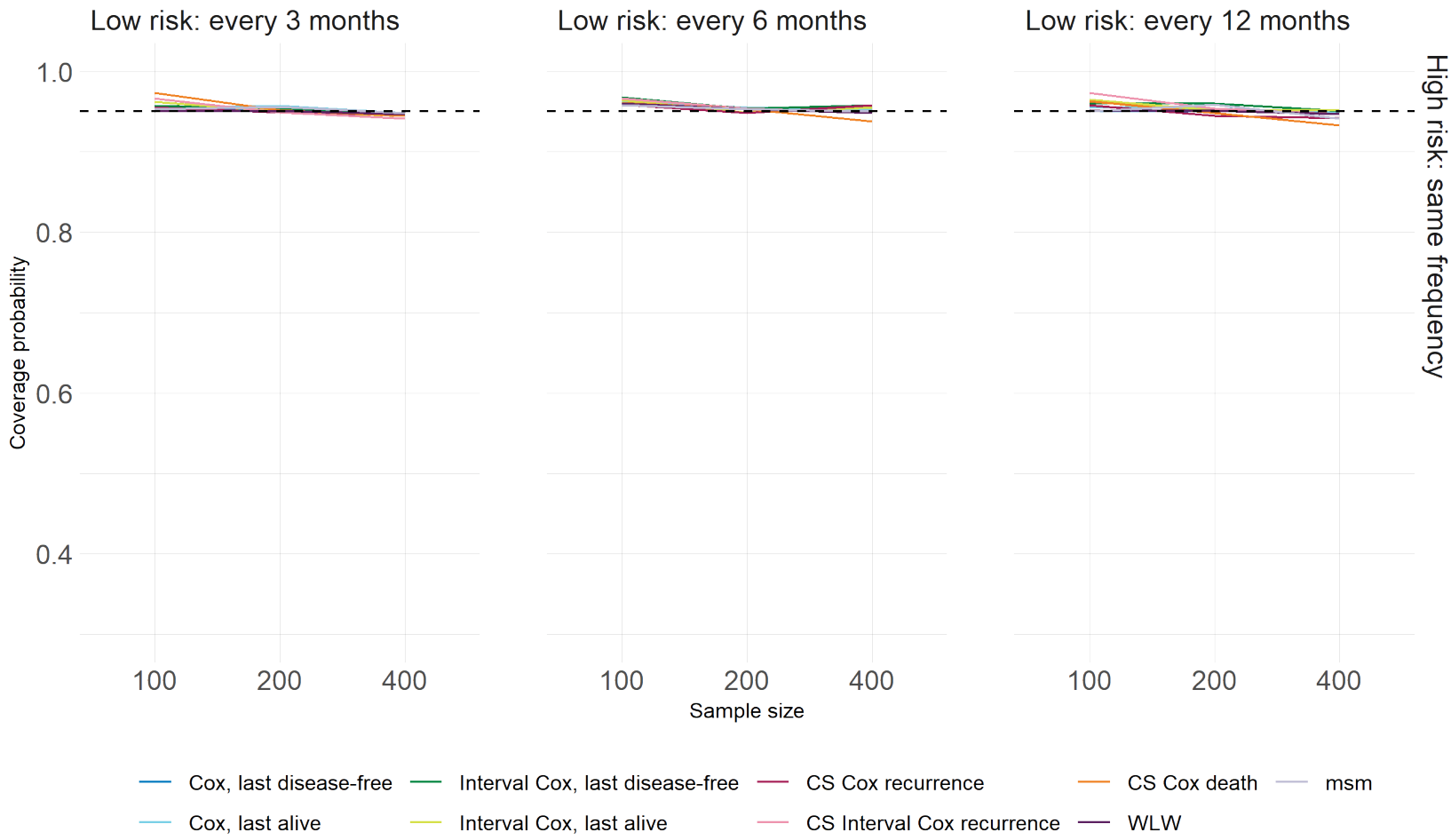
Recurrences detected closer to true occurrence time in both groups when there is a dependent visit



Coverage probabilities around the nominal 0.95 level in all settings where bias was small



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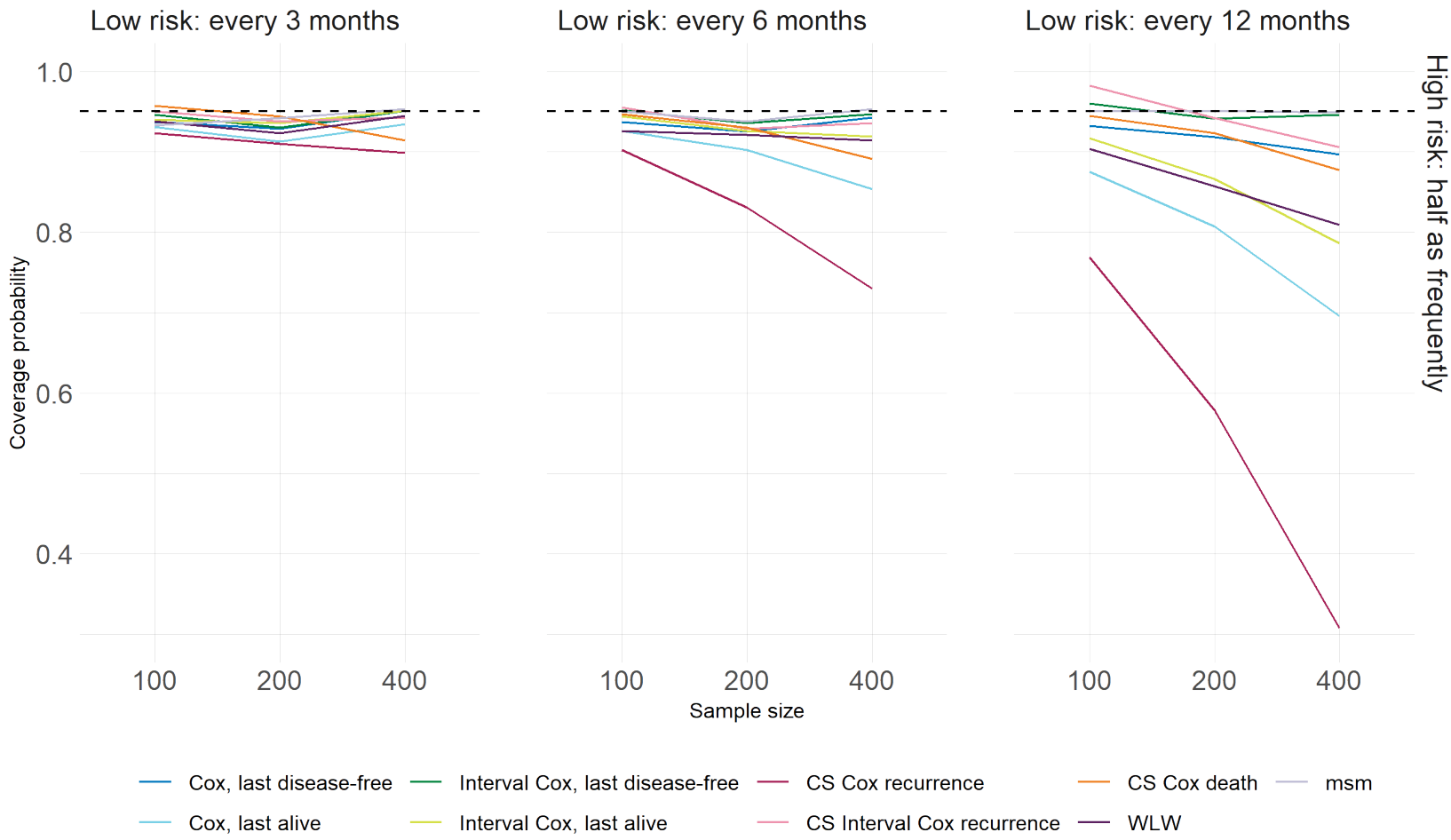
When bias larger, the CP is lower; worse with larger sample size due to reduced variance



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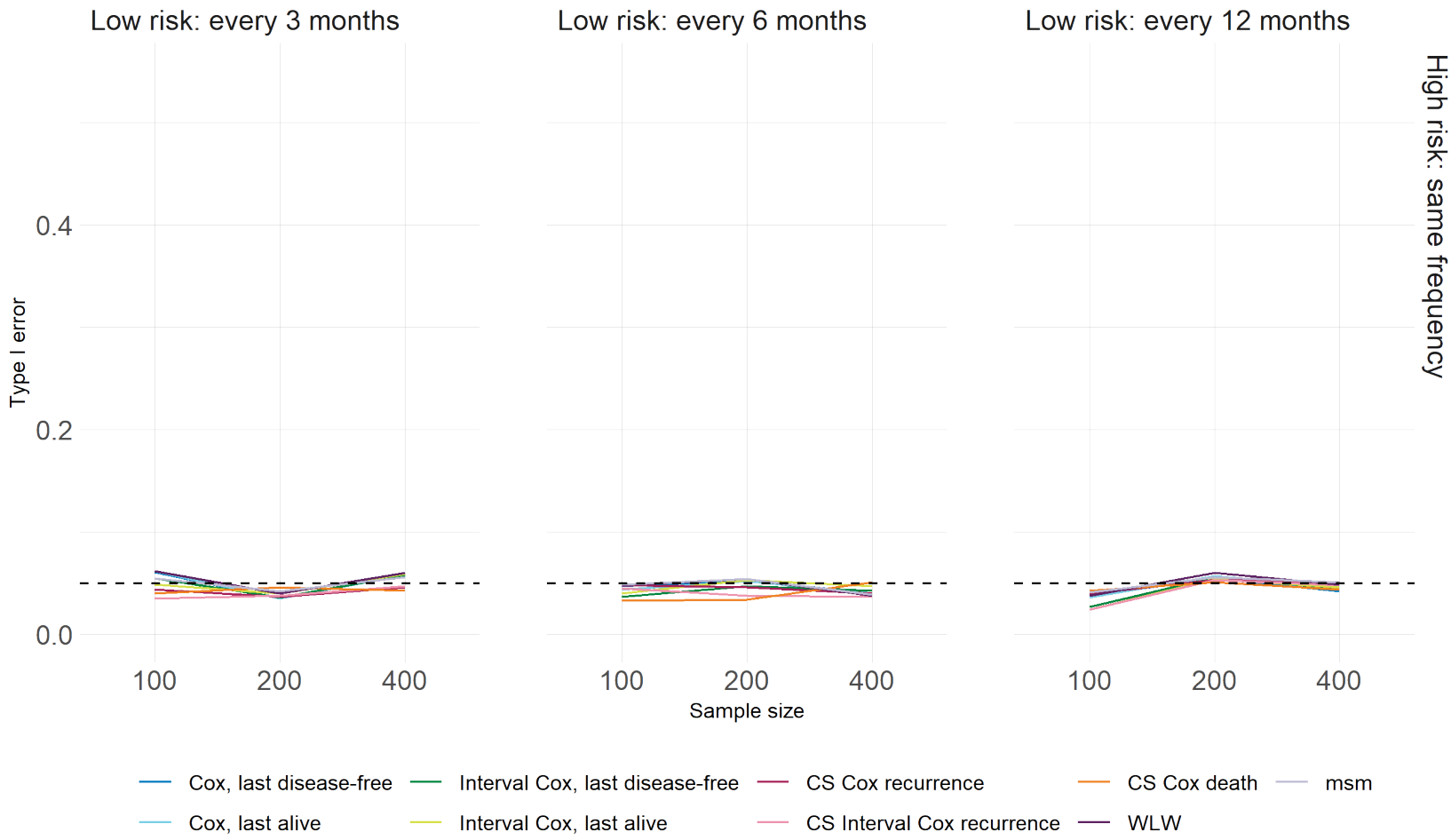
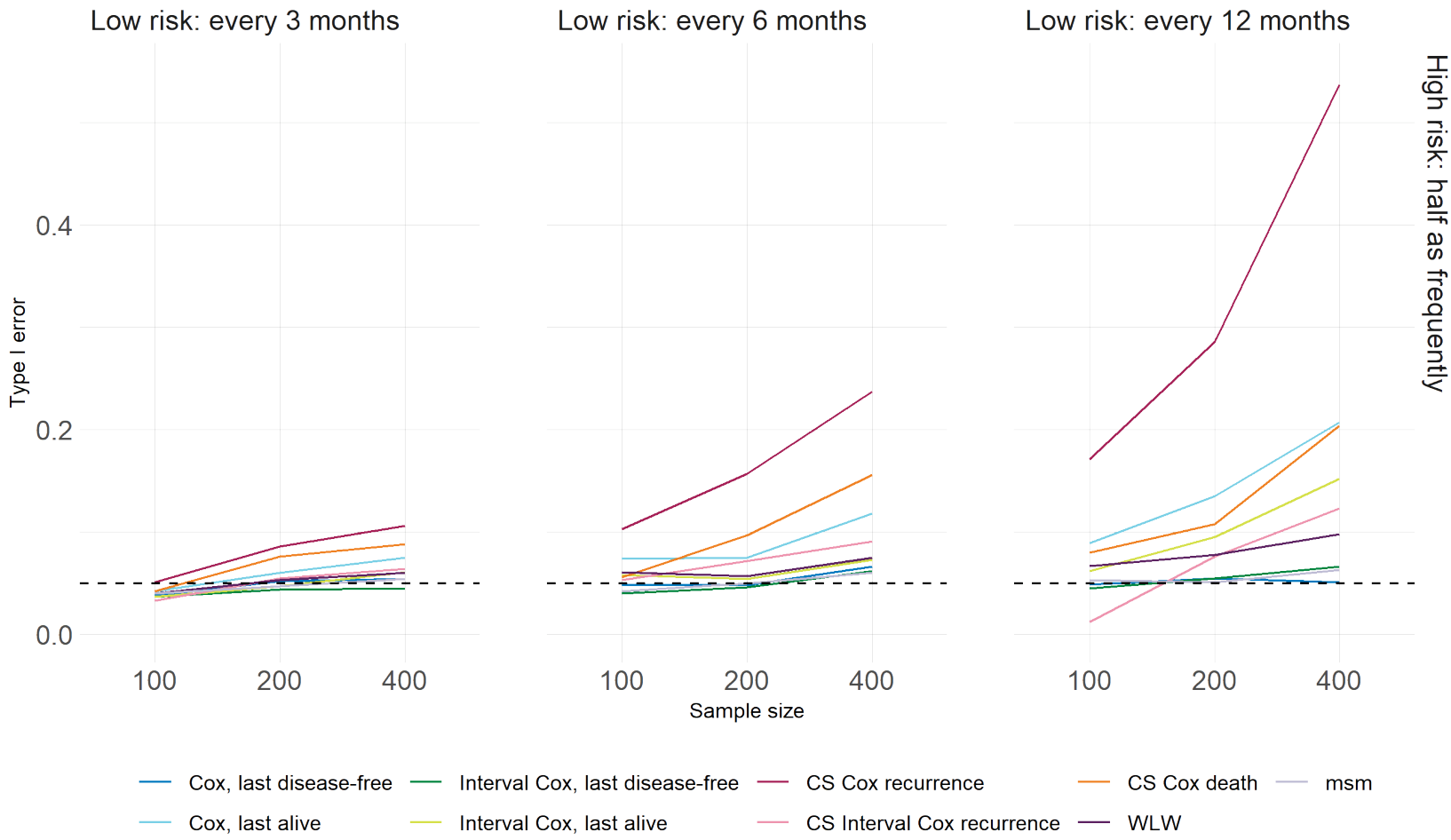
Type I error was low when bias was low and variance was small



When bias was high or variance was high, type I error was inflated



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The results guide selection of an alternative estimator to avoid underestimating the treatment effect

Desired estimand: HR for RFS for new chemotherapy vs standard chemotherapy

Original estimator: Right-censored Cox model for surrogate RFS

Alternative estimators:

- Maximum likelihood estimator implemented by the {msm} package in R
- Cox model estimator for interval-censored data, censoring patients without recurrence at their last disease-free date

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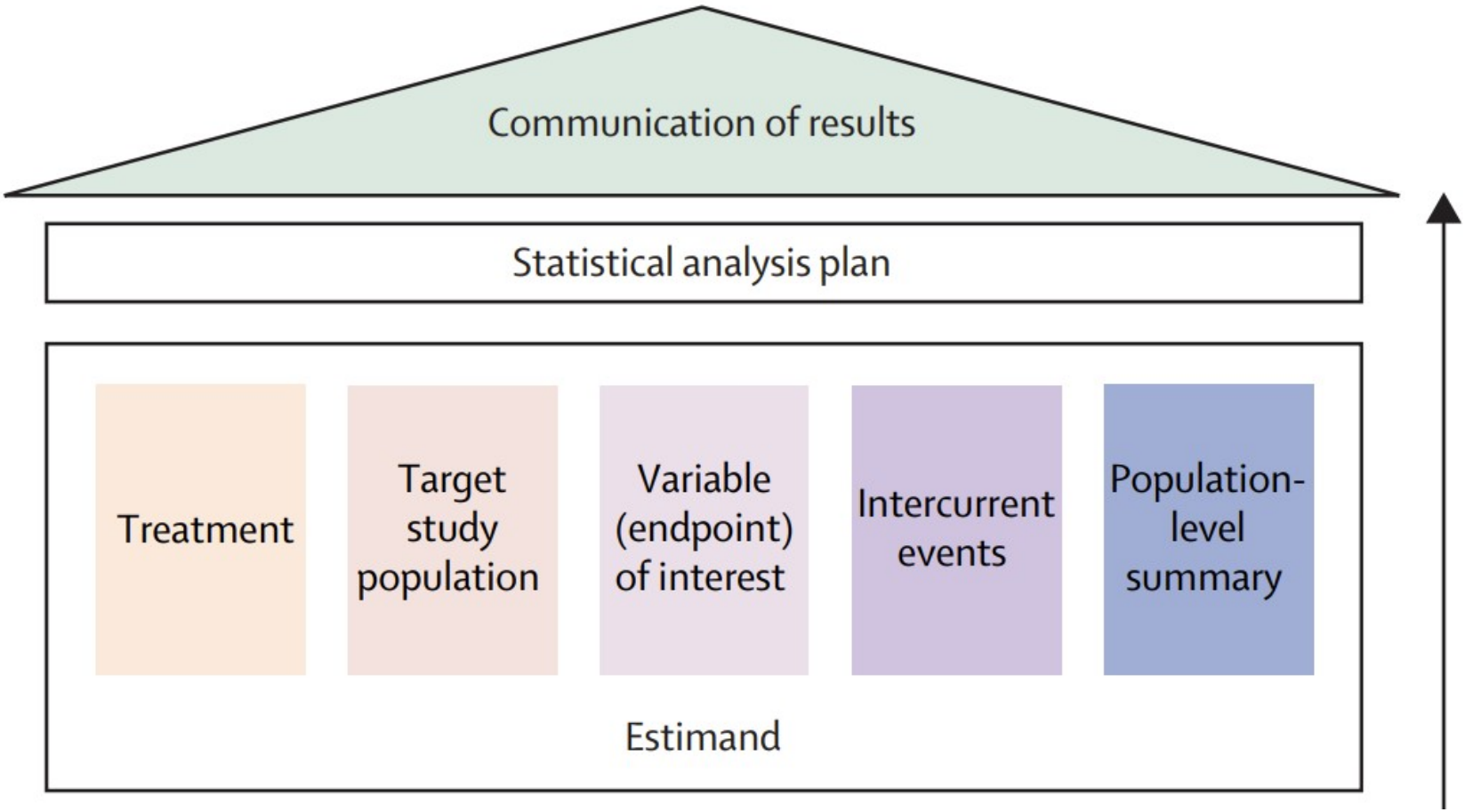
Jackson CH. Multi-State Models for Panel Data: The msm Package for R. J Stat Softw. 2011;38(8):1-28.

The estimand framework is broadly useful beyond studies impacted by the COVID-19 pandemic



Fiero MH, Pe M, Weinstock C, King-Kallimanis BL, Komo S, Klepin HD, Gray SW, Bottomley A, Kluetz PG, Sridhara R. Demystifying the estimand framework: a case study using patient-reported outcomes in oncology. Lancet Oncol. 2020 Oct;21(10):e488-e494.

Thank you! Questions?

Contact me:
zabore2@ccf.org
@zabormetrics
@zabore