Stop the abuse: A plea for a more principled approach to the analysis of time-to-event endpoints with competing risks, with a focus on analysis of AEs

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Acknowledgments

- Thomas Künzel.
- SAVVY consortium, specifically Regina Stegherr, Jan Beyersmann, Claudia Schmoor, Tim Friede.
- X-industry working group on estimands for time-to-event endpoints.
- Competing risks + estimands: Jan Beyersmann, Marcel Wolbers.
- Comments on linkedin post.

Take home messages

Need accurate estimates of P(AE) + comparison between arms.

IP and (1 - KM) biased irrespective of what we use them for.

Bias "does not cancel out" when comparing P(AE) between arms in RCT.

No need to force competing risks into ICH E9(R1) addendum framework.

Let me explain.

Agenda

1. Take home messages
2. Estimation of P(AE)
   - The SAVVY project
   - Bias of common estimators of AE risk
   - Bias of common estimators of relative AE risk
3. Competing risks and the estimand addendum
4. Take home messages
5. Resources and future plans
6. Backup

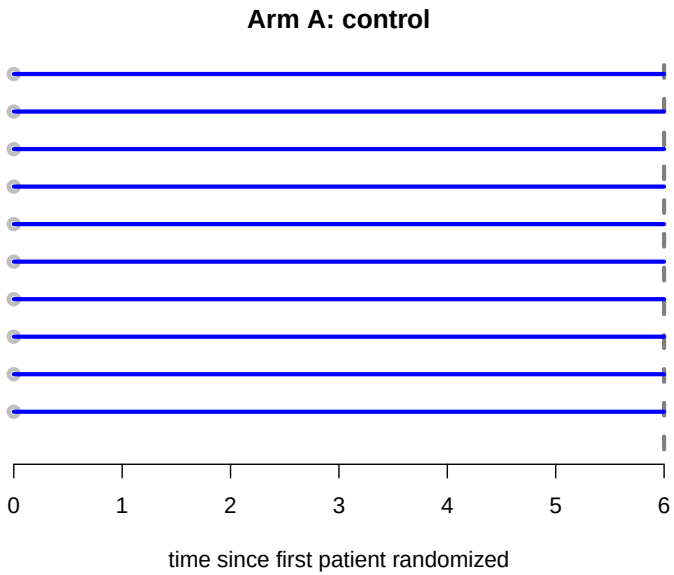
Assume you want to assess whether a new drug prolongs OS in an RCT with staggered recruitment.

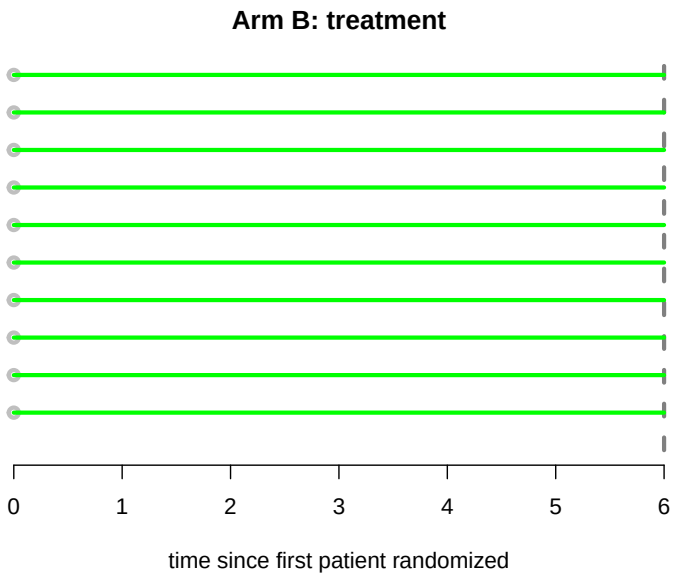
Clinicians proposal: cut data at four years and compare proportions of those who died.

What would you say?

Estimation of P(AE)

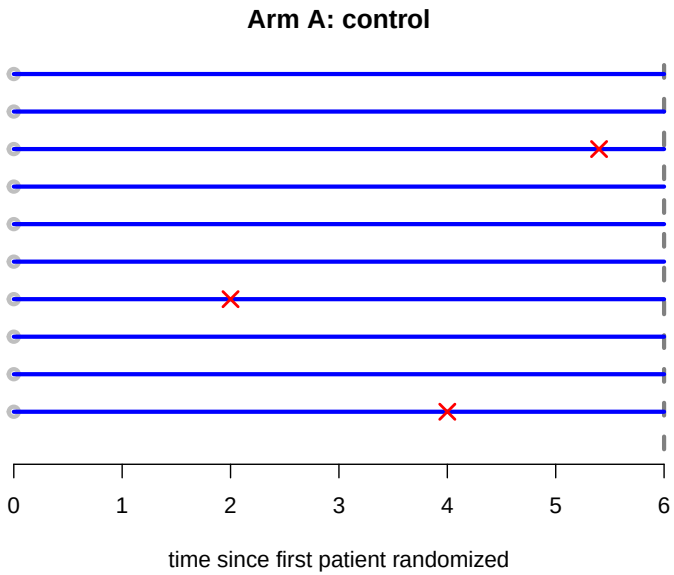
Estimation of P(AE)





- 2-arm RCT.
- 10 patients per arm.
- All patients randomized on same day.
- All patients observed for 6 months.

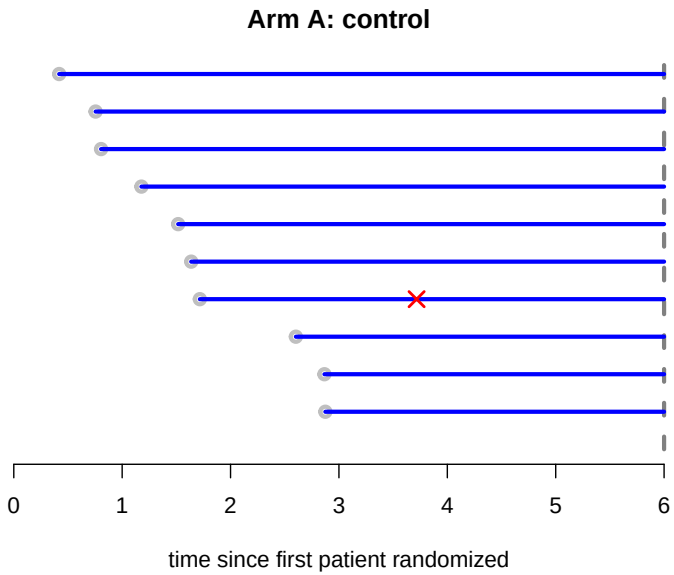
Estimation of P(AE)

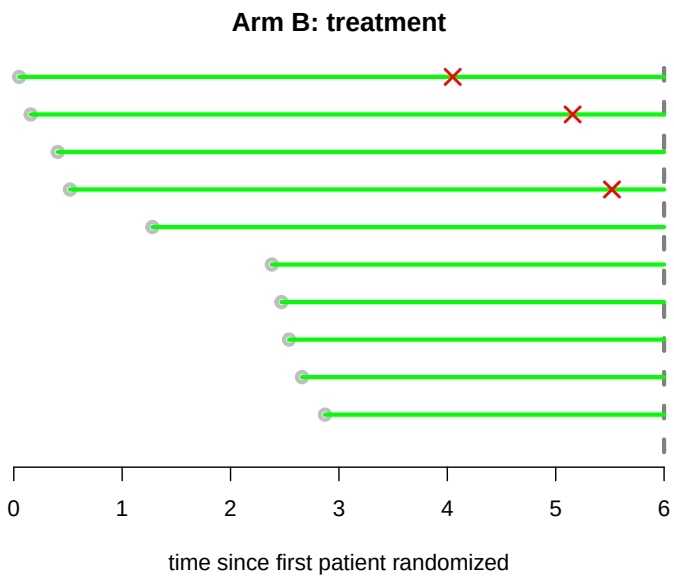


- 2-arm RCT.
- 10 patients per arm.
- All patients randomized on same day.
- All patients observed for 6 months.

$$\text{P(AE in A)} = 3 \,/\, 10 = 0.30,$$
$$\text{P(AE in B)} = 4 \,/\, 10 = 0.40.$$

Estimation of P(AE): staggered entry





- 2-arm RCT.
- 10 patients per arm.
- Patients enter the trial over time.
- All patients observed until cutoff.

P(AE in A) = 1 / 10 = 0.10,
P(AE in B) = 3 / 10 = 0.30.

Is this what we want?

Staggered entry / censoring only
removes AE events $\Rightarrow$ **underestimation**.

What do these proportions estimate?

Incidence proportion in experimental arm in interval from 0 to t:

$$\widehat{IP}_E(t) \quad = \quad \frac{\text{Number of patients with AE in } [0,t] \text{ and that this AE is observed}}{n_E}.$$

$\widehat{IP}_E(t)$ estimates:

P(AE happens in $[0,t]$ and that this AE is observed **before censoring**).

$\widehat{IP}_E(t) \leq \widehat{P}(\text{AE happens in } [0,t]) \Rightarrow \widehat{IP}_E(t)$ **underestimates** absolute AE risk.

With censoring it is unclear which quantity $\widehat{IP}_E$ is estimating.

Simple incidence proportion is biased
if we have unequal follow-up or censoring.

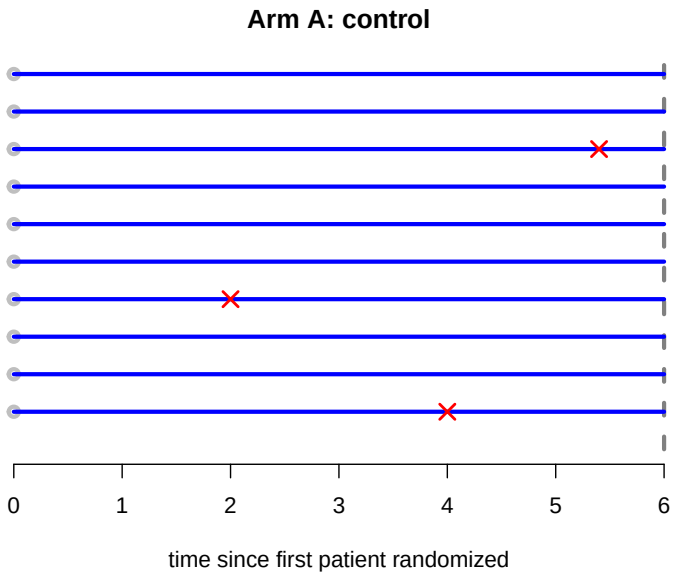
Estimate P(AE) using time-to-AE

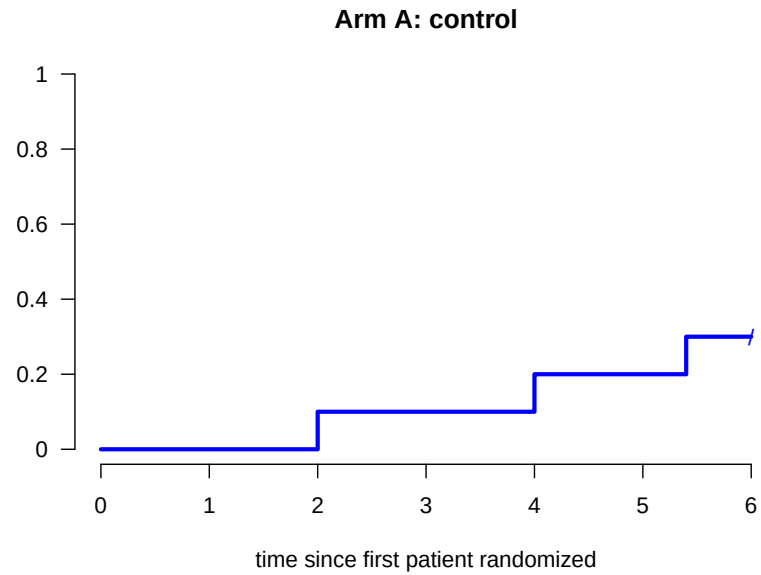
Consider time-to-first-AE

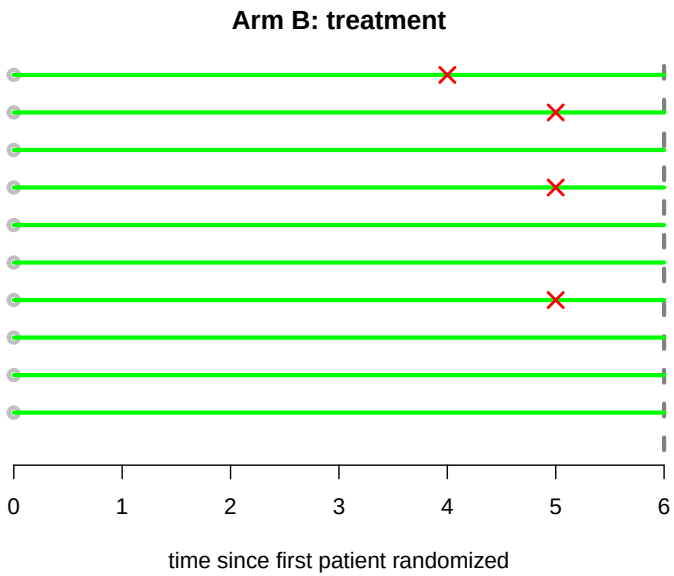
Redefine question: Consider **time-to-first-AE**.

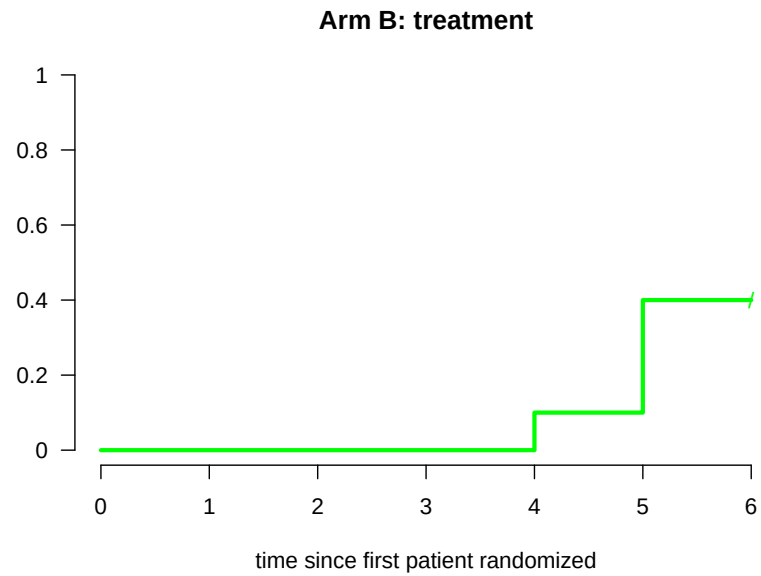
- Estimate P(AE happens in $[0, t]$) using 1 - Kaplan-Meier.
- Correctly accounts for **censoring**.
- Consistently estimates AE risk at t, accounting for varying follow-up.

Estimation of P(AE)

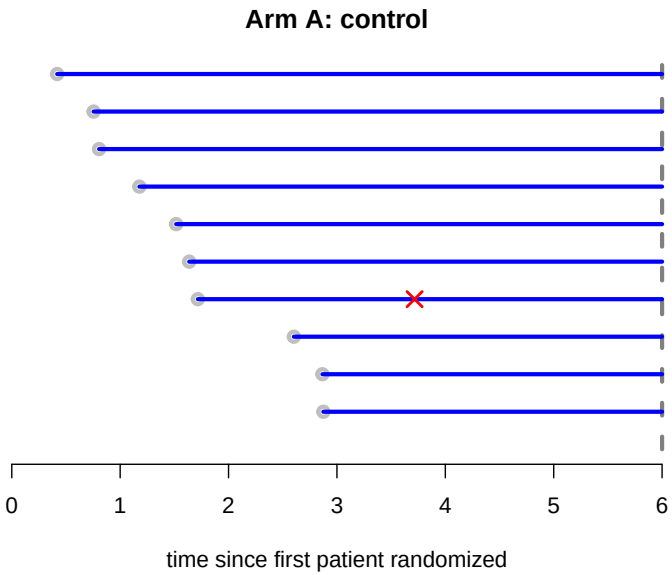


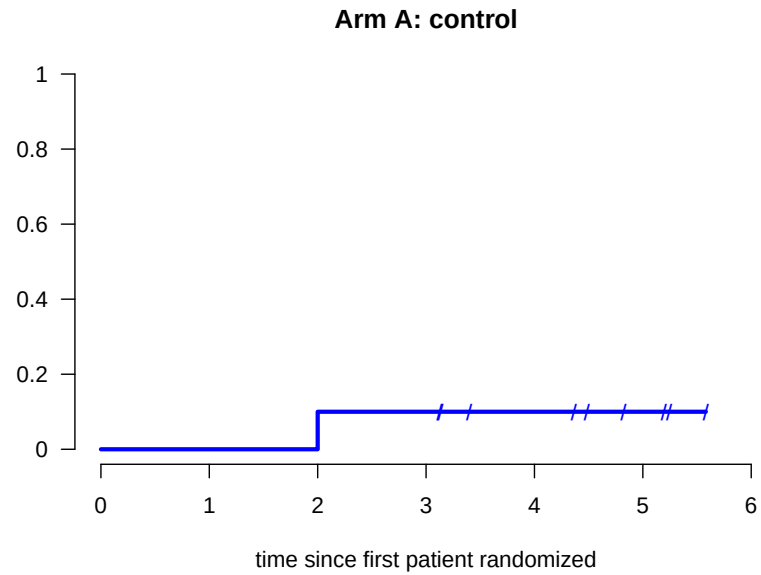


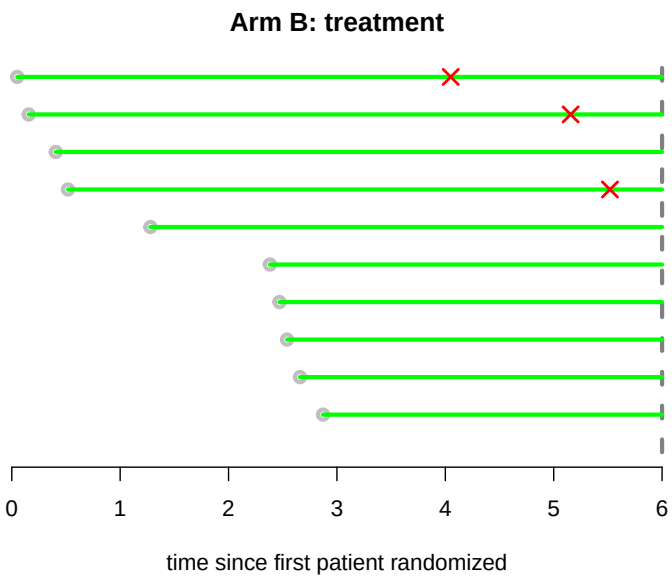


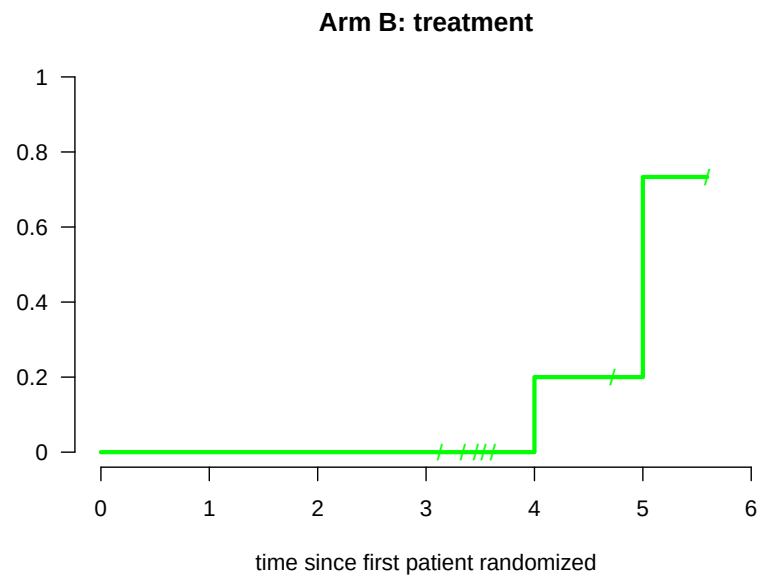


Estimation of P(AE): staggered entry





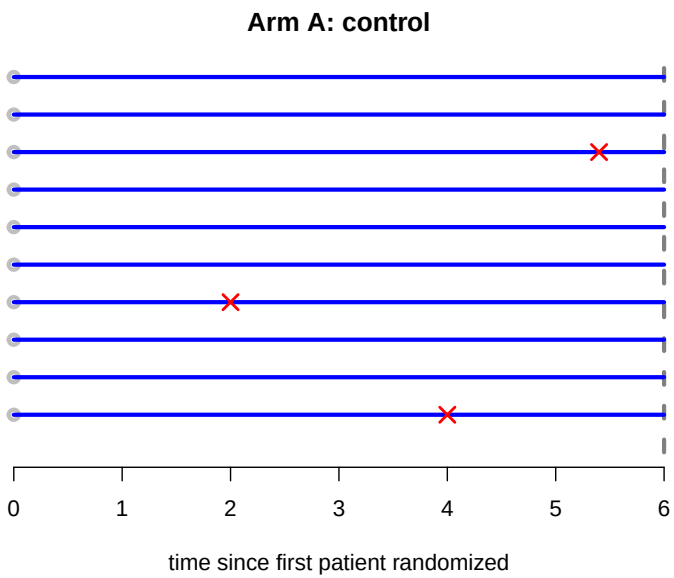


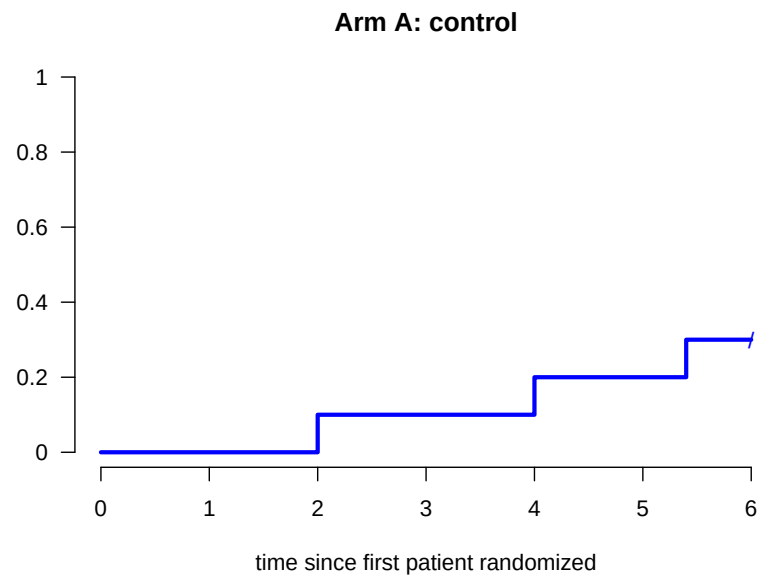


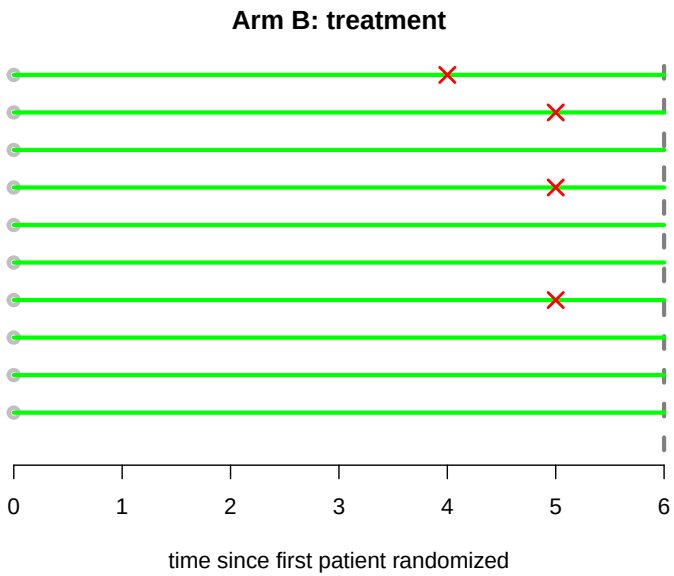
Competing events

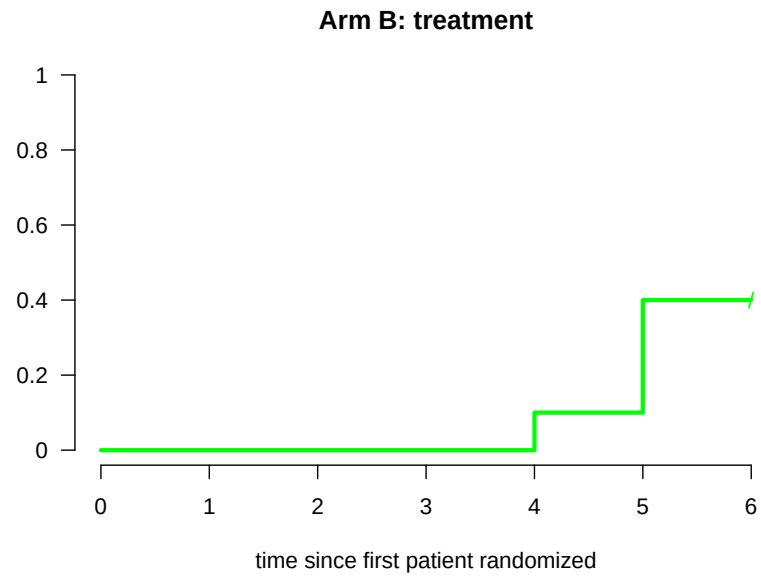
(= competing risk)

Estimation of P(AE)

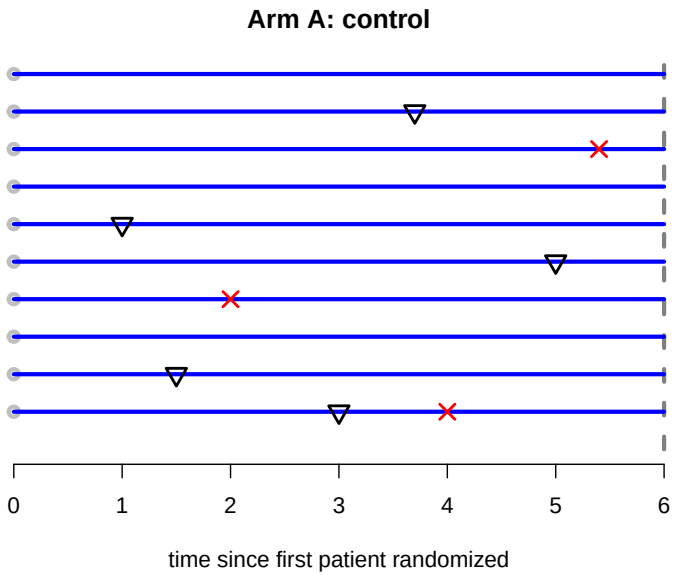


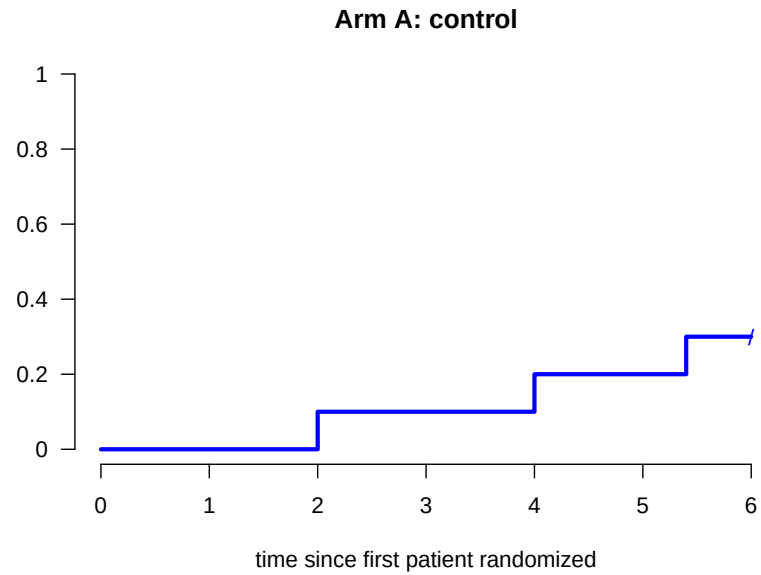


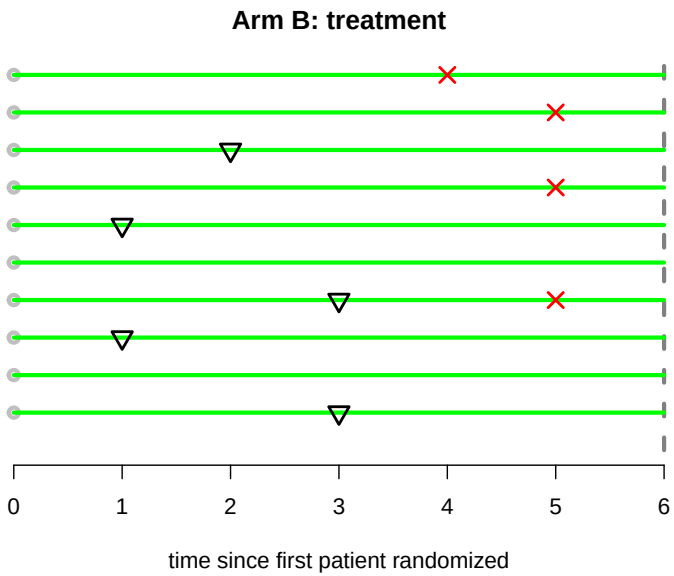


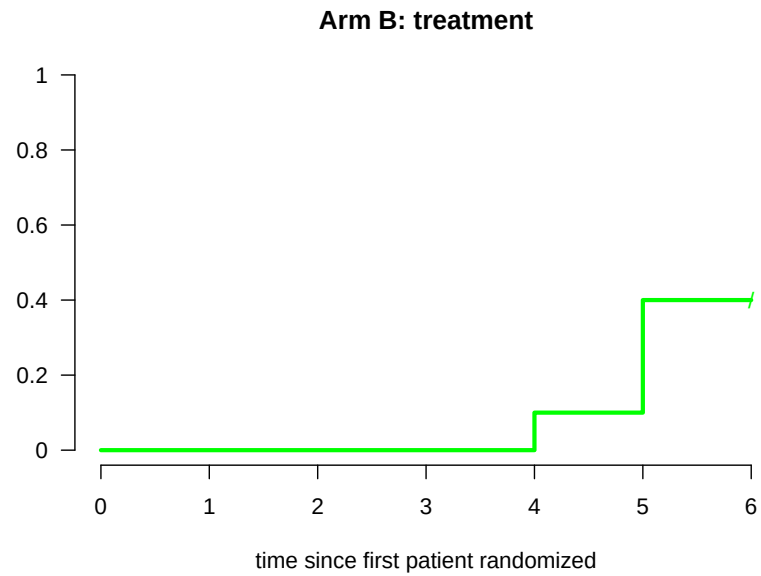


Estimation of P(AE): competing event of death

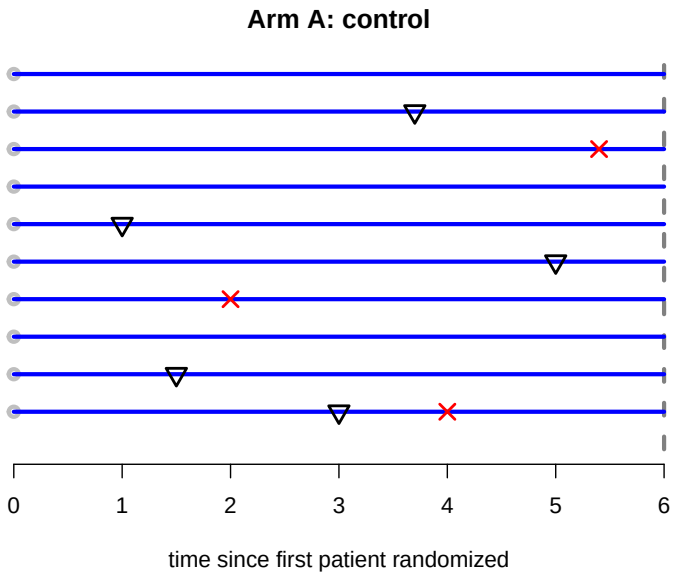


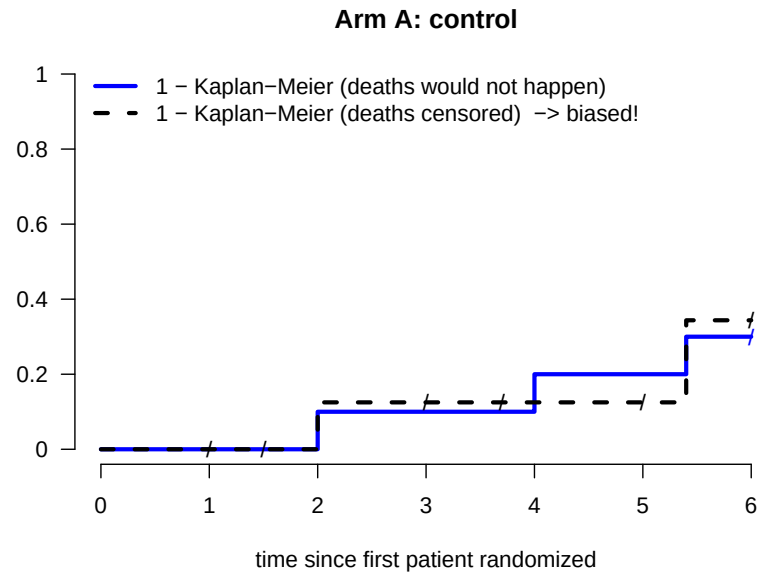


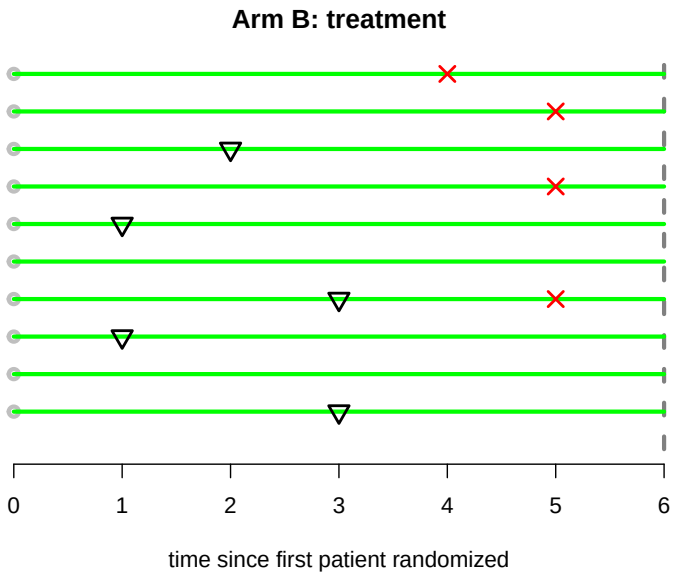


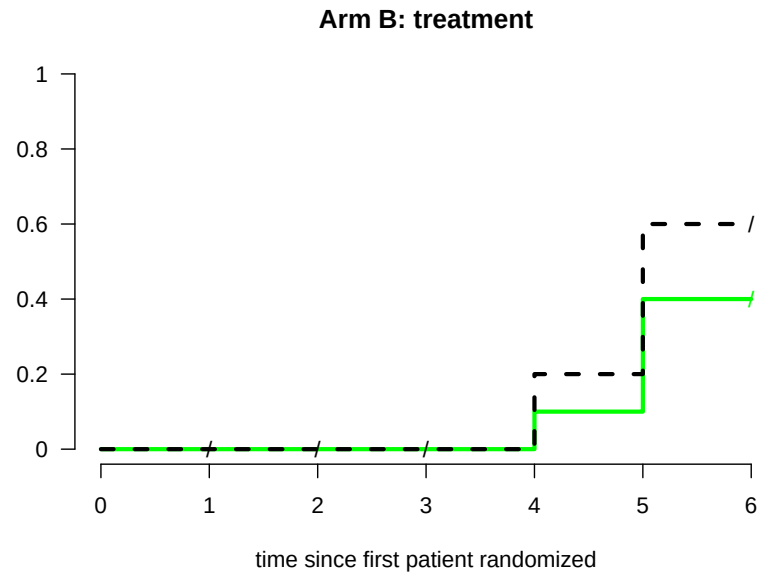


Estimation of P(AE): competing event of death









What does (1 - $\widehat{\text{KM}}$) with censoring of CEs estimate?

Administrative censoring: patients may still experience event at later time point.

Not for CEs!

What does (1 - $\widehat{\text{KM}}$) with censoring of CEs estimate?

- **Violates independent censoring assumption**:
  - Patient censored at death will NEVER experience AE.
  - Patients who will never experience AE treated as if they could still have one.
- Less than 100% of patients experience AE **before** death:
  - Some die before AE $\Rightarrow$ P(AE) < 1.
  - But (1 - $\widehat{\text{KM}}$) approaches 1 $\Rightarrow$ naive (1 - $\widehat{\text{KM}}$) **overestimates** P(AE).

Abandon!

Although tutorial articles are available, too many studies are susceptible to competing risk bias which **can be avoided by using adequate statistical methodology**. *There is* **no excuse not to use it**, *and Kaplan-Meier methodology should be completely abandoned in the analysis of end points with competing risks in all journals.*

Schumacher et al. (2016)

1 - Kaplan-Meier is biased if we have competing events.

Is this relevant at all?

How large can the bias be?

The SAVVY project

The SAVVY project

Survival analysis for **A**d**V**erse events with **V**ar**Y**ing follow-up times:

Goal: improve analyses of AE data in clinical trials through use of **survival techniques** appropriately dealing with

- varying follow-up times,
- censoring,
- competing events.

SAVVY webpage

9 pharma


MERCK
Boehringer Ingelheim
Bristol Myers Squibb
Roche
Lilly
janssen
Pfizer
NOVARTIS
BAYER

9 pharma + 3 universities

The SAVVY project

Federated learning: central analysis team:

- Developed macros (R + SAS). Validated R package under development.
- Every sponsor ran them on their data.
- Only share aggregated data.
- Central team performed meta-analysis.

Data from **17 RCTs** in various indications.

200 - 7171 patients.

186 AEs: selected by sponsor.

The SAVVY project

Estimate P(AE) at latest available follow-up with various estimators:

- Estimate **P(AE) in one arm** (the experimental).
- Estimate **relative risk** in RCTs using risk and hazard ratio.

CEs in SAVVY:

- **Hard**: Death - AE after death impossible.
- **Soft**: lost to follow-up, withdrawal of consent, treatment discontinuation $\Rightarrow$ AE of interest can in principle still occur but is not observed due to end of follow-up.

Interest in estimation of P(AE), not in P(specific CE) $\Rightarrow$ lump all CEs together, not interested in cumulative incidence of CE.

Goal: compare bias of estimators.

What is "gold standard"?

Gold standard: Aalen-Johansen estimator

SAVVY: **Empirical** bias evaluation within RCTs.

What is "best" estimator to benchmark against?

Estimator	Accounts for censoring	Accounts for CEs
Incidence proportion	No	Yes
1 - Kaplan-Meier	Yes	No
Aalen-Johansen estimator	Yes	Yes

All **nonparametric**: no constant hazard assumption.

Aalen-Johansen:

- Generalizes Kaplan-Meier to competing risk and general multistate models.
- **No censoring**: Aalen-Johansen = incidence proportion.
- **No competing events**: Aalen-Johansen = (1 - Kaplan-Meier).

Bias of common estimators of AE risk

Estimation of AE risk: incidence proportion

Experimental arm.

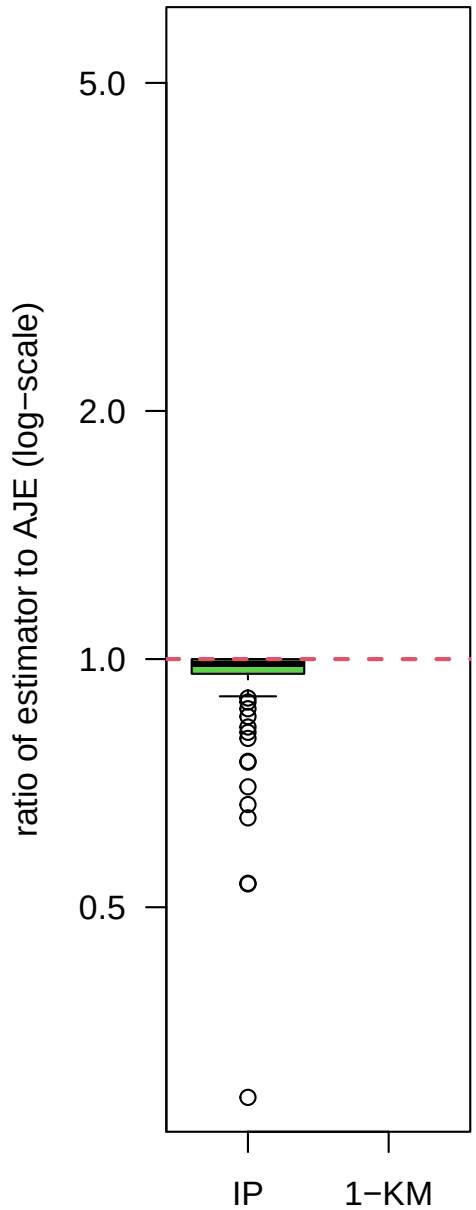
Evaluated at maximal observed follow-up time τ.

Incidence proportion:

- Accounts for CEs but not censoring.
- Point in boxplot: corresponds to ratio of $\widehat{IP}_E(\tau)$ to gold standard for given AE.
- Ratio $= 1$: $\widehat{IP}_E(\tau)$ gives same AE risk estimate as gold standard.
- **Underestimation of P(AE) up to factor THREE!**

Overall performance not too bad. Why?

Datasets have many **soft** CEs $\Rightarrow$ little censoring.



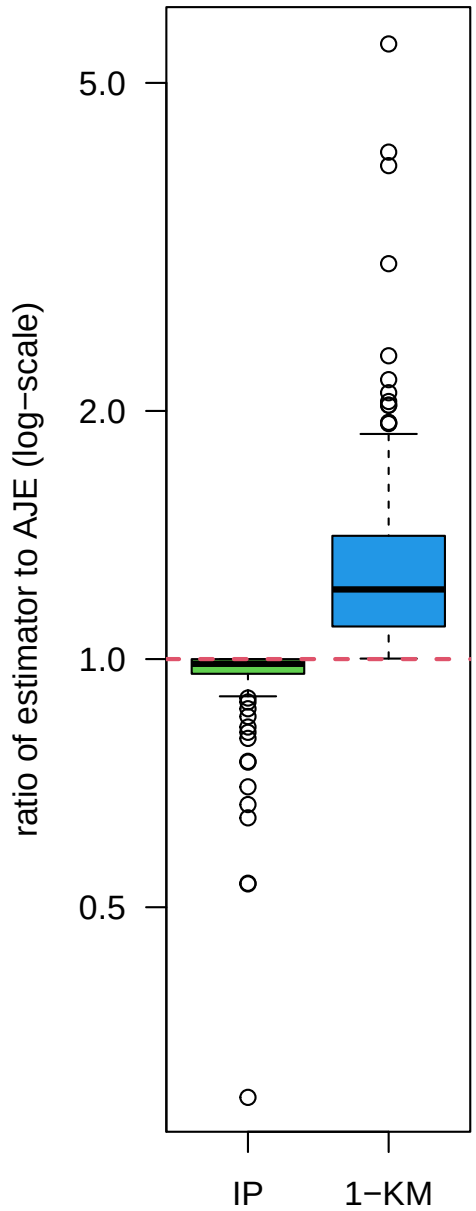
Estimation of AE risk: 1 - Kaplan-Meier

Experimental arm.

Evaluated at maximal observed follow-up time τ.

1 - Kaplan-Meier:

- Accounts for censoring but not CEs.
- Point in boxplot: corresponds to ratio of (1 - $\widehat{KM})_E(\tau)$ to gold standard for given AE.
- Ratio = 1: (1 - $\widehat{KM})_E(\tau)$ gives same AE risk estimate as gold standard.
- **Overestimation of P(AE) up to factor FIVE!**



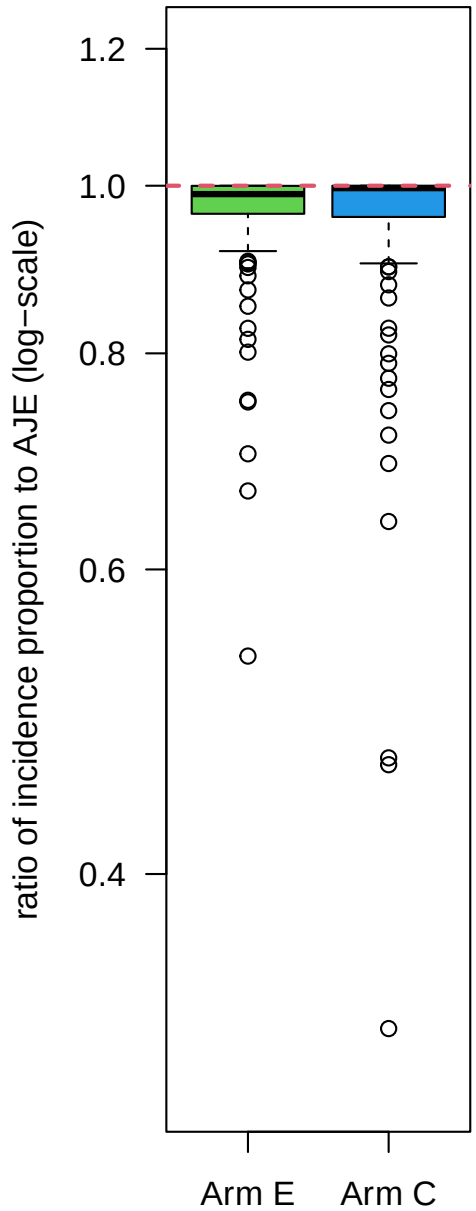
Bias of common estimators of relative AE risk

Estimation of relative AE risk: incidence proportion

Evaluated at minimum of maximal observed follow-up τ.

Incidence proportion:

- Point in boxplot: corresponds to ratio of $\widehat{IP}(\tau)$ to gold standard for given AE and treatment arm.
- Ratio $= 1$: $\widehat{IP}(\tau)$ gives same AE risk estimate as gold standard.
- **Underestimation** of P(AE) compared to gold standard.

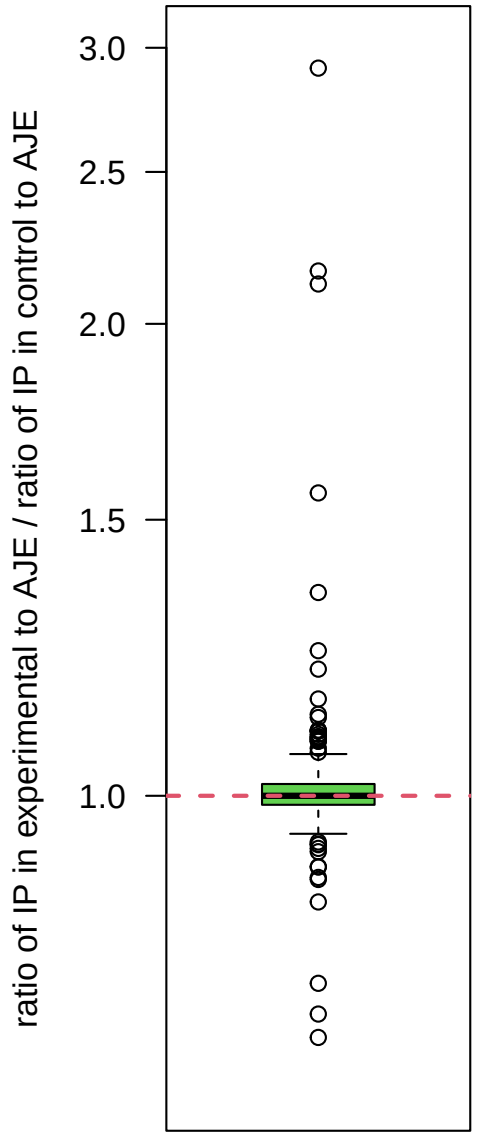


Estimation of relative AE risk: incidence proportion

Evaluated at minimum of maximal observed follow-up τ.

Incidence proportion:

- Point in boxplot: corresponds to ratio of $\widehat{IP}_E(\tau)/\widehat{IP}_C(\tau)$ to gold standard for given relative AE risk.
- Ratio $= 1$: $\widehat{IP}_E(\tau)/\widehat{IP}_C(\tau)$ gives same relative AE risk estimate as gold standard.
- Over- and underestimation observed.
- **Overestimation of RR up to factor of almost 3.**

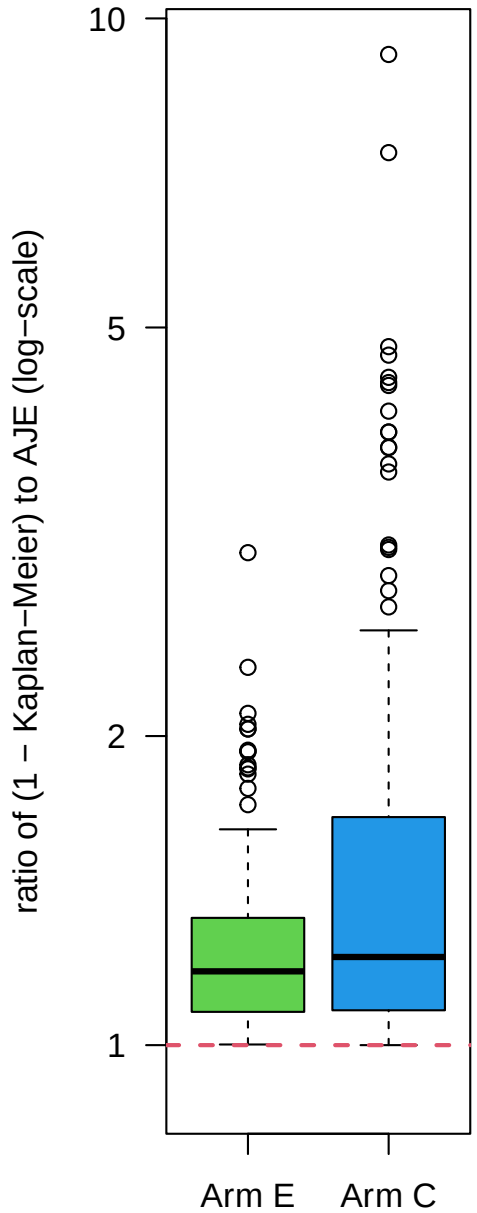


Estimation of relative AE risk: (1 - KM)

Evaluated at minimum of maximal observed follow-up τ.

1 - Kaplan-Meier:

- Point in boxplot: corresponds to ratio of (1 - $\widehat{KM}$)(τ) to gold standard for given AE and treatment arm.
- Ratio = 1: (1 - $\widehat{KM}$)(τ) gives same AE risk estimate as gold standard.
- **Overestimation** of P(AE) compared to gold standard.

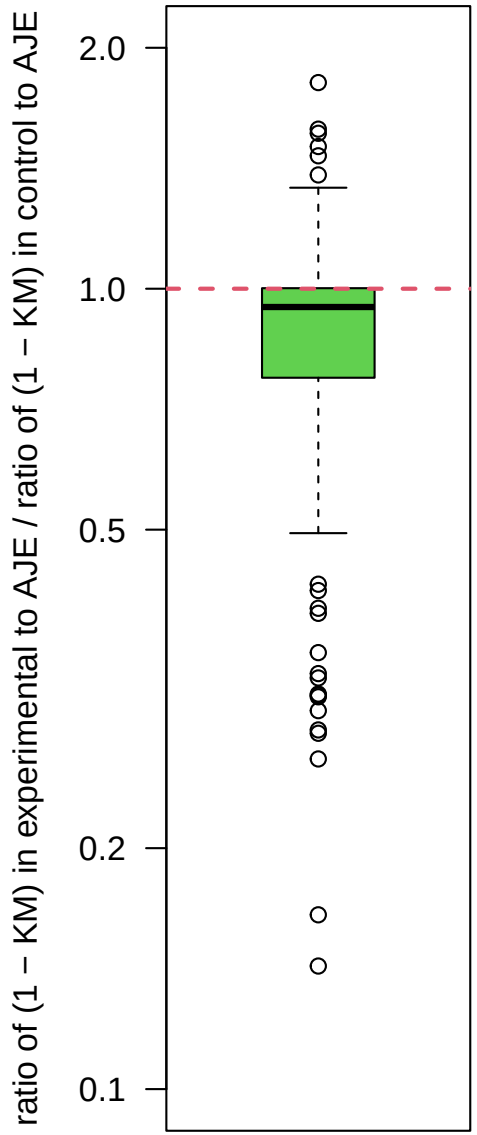


Estimation of relative AE risk: (1 - KM)

Evaluated at minimum of maximal observed follow-up τ.

1 - Kaplan-Meier:

- Point in boxplot: corresponds to ratio of (1 - $\widehat{KM})_E(\tau)$ / (1 - $\widehat{KM})_C(\tau)$ to gold standard for given AE.
- Ratio = 1: (1 - $\widehat{KM})_E(\tau)$ / (1 - $\widehat{KM})_C(\tau)$ gives same relative AE risk estimate as gold standard.
- Over- and underestimation observed.
- **Underestimation of RR up to factor of >4.**



Arm-wise bias does not cancel out in relative comparisons.

Now we have seen what does not work.

But what does work?

Aalen-Johansen: properly accounts for varying follow-up times and competing risks.

Before you ask...

Before you ask...

Focus on bias - what about variability?

- Focus today with IP rarely on variability either!
- Simulation study for 2-arm comparisons: Stegherr et al. (2021c).

We do not collect data necessary to estimate P(AE) with AJE?

- ICH E9(R1) estimands addendum: **clinical trial objective** dictates data collection and analytical method!
- Clarify **clinical trial objective** also for analysis of safety!
- **Proper definition of CE** requires understanding and discussion of therapeutic area.

Before you ask...

Does normalization by exposure time not solve the problem?

- **Incidence density**. See backup for details.
- A priori estimates **AE hazard**, not P(AE). Can be turned into estimator of P(AE).
- Assumes **exponentiality** of AE hazard.
- Incidence density for each CE.

Can we use IP for "signal detection" or other purposes?

Biases = statistical properties of IP, (1 - KM).

Independent of what we use estimates of P(AE) for!

But wait...

What about causality?

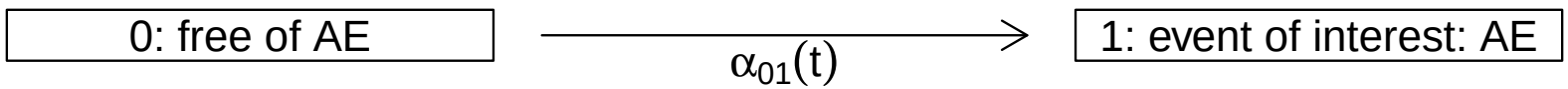
Rima's question

Aalen-Johansen:

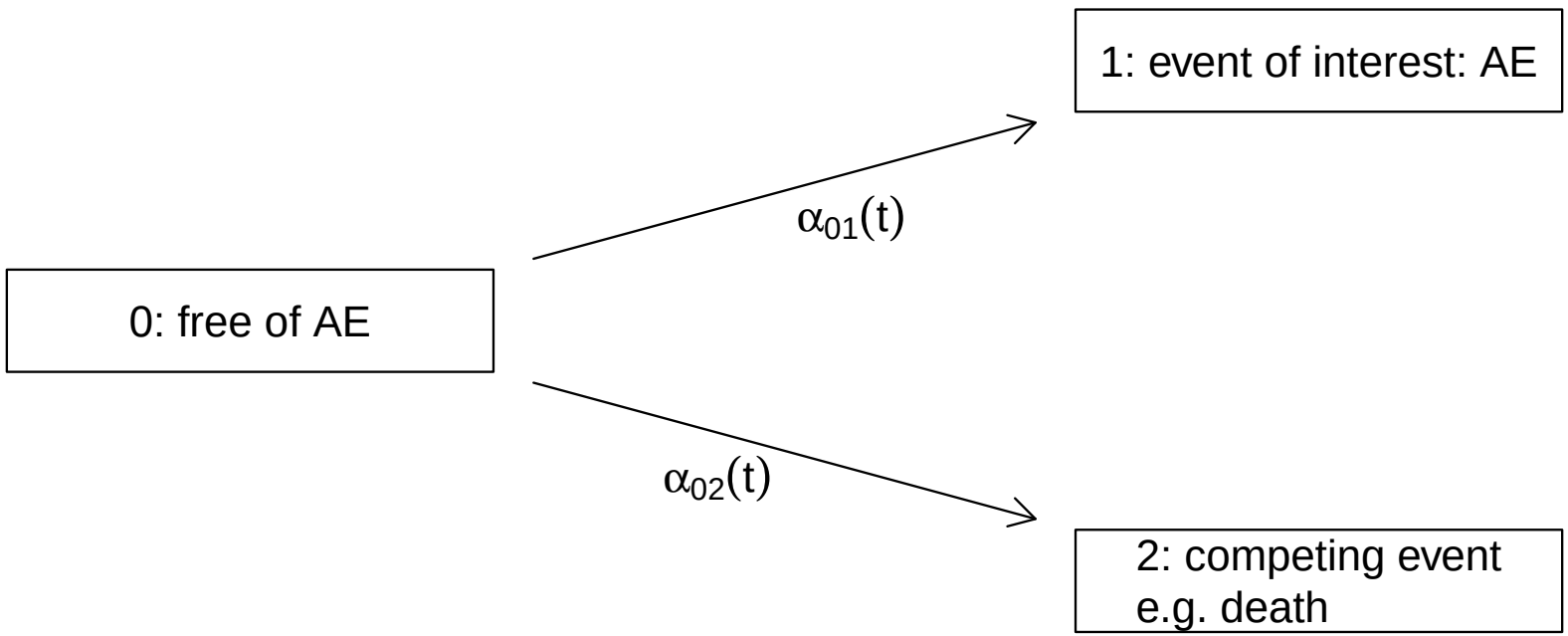
- Estimates cumulative incidence function.
- **Censoring**: if random, e.g. administrative censoring $\Rightarrow$ does not destroy causal interpretation.
- Competing events: intervention on observation process differs from intervention affecting the patient. Young et al. (2020), Rufibach et al. (2022).

Competing risks and the estimand addendum

One event – time to AE



Add competing event



Competing event vs. intercurrent event

Definition **competing event**, Gooley et al. (1999):

> *We shall define a* **competing risk** *as an event whose occurrence either precludes the occurrence of another event under examination or fundamentally alters the probability of occurrence of this other event.*

Definition **intercurrent event**, ICH (2019):

> *Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.*

Intercurrent event definition $\approx$ competing event definition.

ICH (2019) does not say anything about competing risks though.

Death: competing risk + intercurrent event (?).

Clinical questions of interest and their estimators

Extending Table 1 in Varadhan et al. (2010).

Clinical question	**Target of inference**	**Estimator**	**Comment**
What is hazard / probability of AE or death, whatever happens earlier?	Event-free survival ("composite")	Kaplan-Meier	1to1 correspondence between hazard and probability.
What is hazard / probability of AE, accounting for the possibility that patients may die before experiencing an AE?	Cause-specific hazards	Nelson-Aalen	- Key measure to compare groups in RCT. - Evaluate impact of risk factors.
	Cumulative incidence	Aalen-Johansen	- Interest in absolute risk ("probability"). - Benefit-risk of an intervention.
What is hazard / probability of AE in world where patients would not die?	Survival function ("hypothetical")	1 - KM with censoring deaths	**- Rarely (to say the least) of clinical interest.** **- Maybe for other CEs.** **- Estimation: assumption about "independence" of competing events - neither sensible nor needed!**

Did we get our clinical questions answered?

Yes!

Did we need ICH E9(R1) language or strategies?

No!

Conclusions:

Clearly formulate clinical question.

None of the five strategies in the addendum needed to model competing risk.

Random variable vs. stochastic process formulation

Endpoints like OS: model using **random variable** X with CDF F, hazard h, etc.

Competing risk, multistate models:

- Avoid random variables: temptation of latent failure time models (backup).
- Use **stochastic process** formulation, see e.g. Beyersmann et al. (2012):
  - $X(t) \in \{0, 1, 2\}$, $t \geq 0$: state occupied by individual at time $t \geq 0$.
  - $X(t) = j$ if event j has occurred in $[0, t]$.
  - $T := \inf\{t \ : \ X_t \neq 0\}$, $X_T =$ state occupied at T.
  - Competing risk data: (T, X_T).

Andersen et al. (1985):

> *In life history analysis, time and random phenomena occurring in time play an essential role, and it seems therefore more natural to study life history analysis in terms of the theory of* **stochastic processes**. *Thus, the formulation in terms of random variables may have contributed to hampering the researchers working in the field of survival analysis, or failure time analysis, from extending their otherwise fine methodology to more general life history models.*

Marry competing risk with ICH E9(R1) if you must

Definition of **variable** in ICH E9(R1) addendum:

> *The variable (or endpoint) to be obtained for each patient that is required to address the clinical question.*

No one says this must be **univariate**!

Marry competing risk with ICH E9(R1) **if you must**:

Attribute	**Definition**
Treatment	generic
Population	generic
Variable	(T, X_T)
Intercurrent event(s)	None left from competing risk, maybe others.
Summary measure	Depends on clinical question: hazard ratio, cumulative incidence.

Alternative proposal for general estimands for MSMs: Bühler et al. (2022).

Take home messages

Need accurate estimates of P(AE) + comparison between arms.

IP and (1 - KM) biased irrespective of what we use them for.

Bias "does not cancel out" when comparing P(AE) between arms in RCT.

No need to force competing risks into ICH E9(R1) addendum framework.

Resources and future plans

Resources

SAVVY webpage:

- Exemplary code for all methods.
- All papers and talks.
- Papers:
  - SAP: Stegherr et al. (2021a).
  - Methods: Stegherr et al. (2021c).
  - 1-sample: Stegherr et al. (2021b).
  - 2-sample: Rufibach et al. (2022).
- Effective statistician podcasts:
  - About SAVVY: https://theeffectivestatistician.com/the-analysis-of-adverse-events-done-right-savvy/.
  - 200th episode with 10% most downloaded podcasts: https://theeffectivestatistician.com/200th-episode/.

Slides will be posted on BBS webpage.

Future plans

Estimate **disease-specific P(AE)'s**, properly discussing therapeutic area specific CEs.

Influence **updating of guidelines**.

Thank you for your attention.

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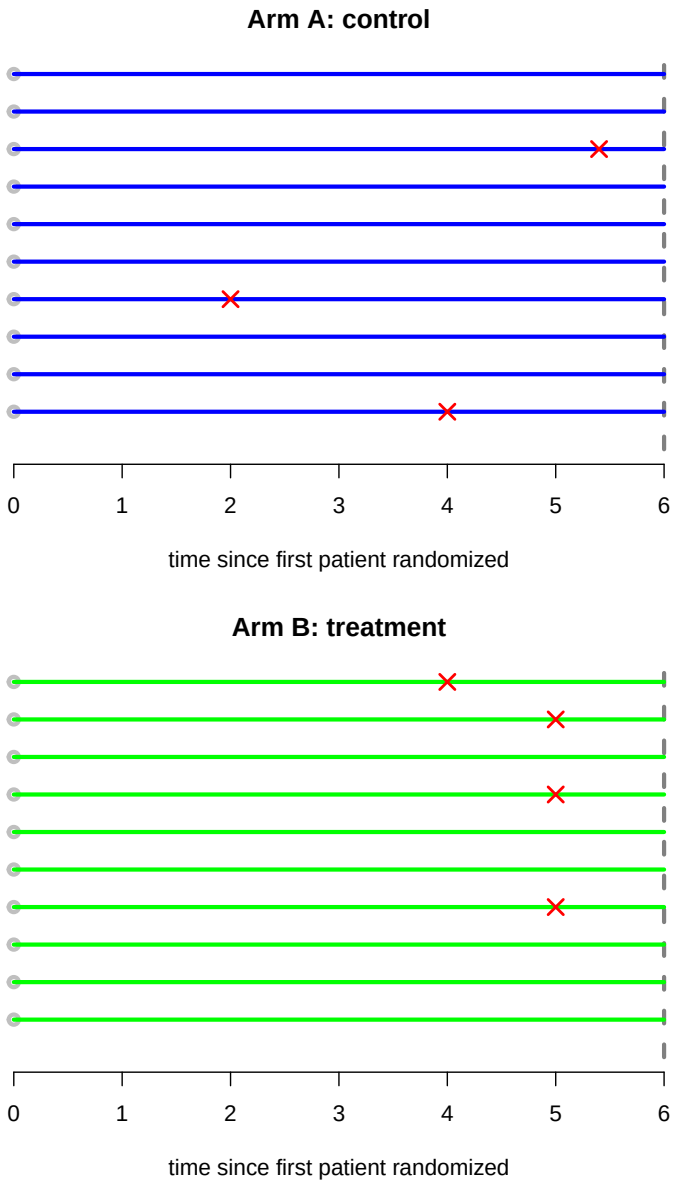
Backup

Treatment works

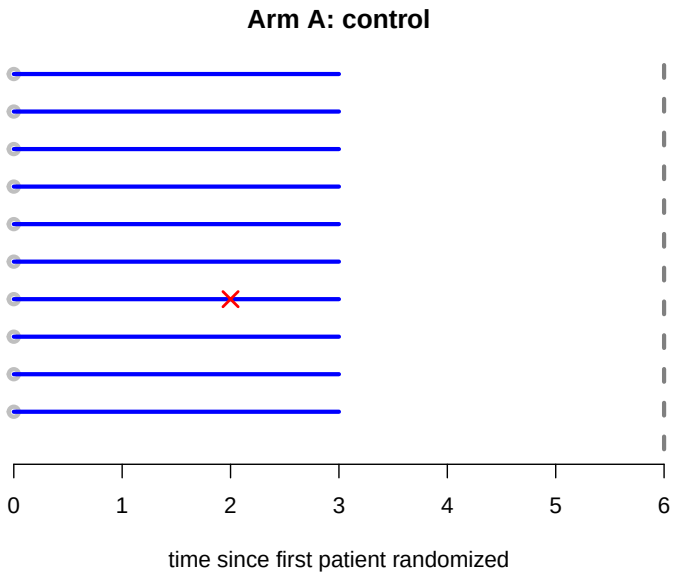
Estimation of P(AE)



- 2-arm RCT.
- 10 patients per arm.
- All patients randomized on same day.
- All patients observed for 6 months.

P(AE in A) = 3 / 10 = 0.30,
P(AE in B) = 4 / 10 = 0.40.

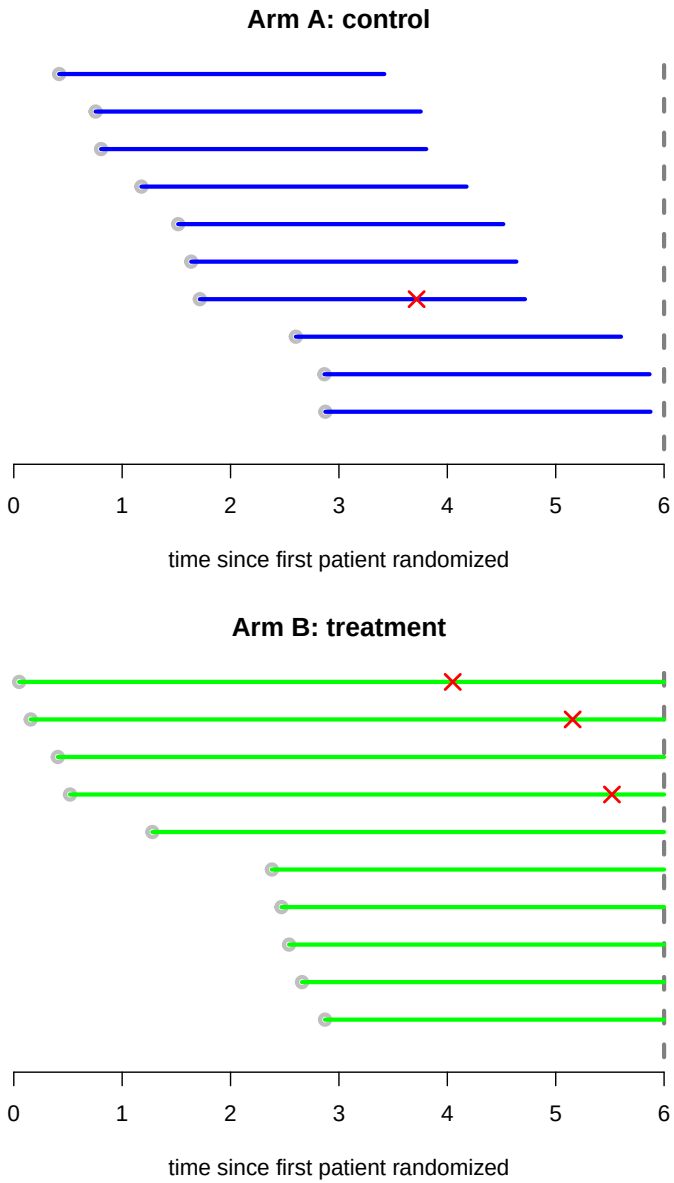
Estimation of P(AE): treatment works



- 2-arm RCT.
- 10 patients per arm.
- All patients randomized on same day.
- Hazard ratio for PFS = 0.5, stop AE recording after PFS event.

P(AE in A) = 1 / 10 = 0.10,
P(AE in B) = 4 / 10 = 0.40.

Estimation of P(AE): treatment works + staggered entry



- 2-arm RCT.
- 10 patients per arm.
- Patients enter trial over time.
- All patients observed until cutoff.
- Hazard ratio for PFS $= 0.5$, stop AE recording after PFS event.

P(AE in A) $= 1 \,/\, 10 = 0.10$,
P(AE in B) $= 4 \,/\, 10 = 0.40$.

Competing risk models: population quantities

"Cause-specific survival function":

$$S_k(t) \quad = \quad \exp[A_{0j}(t)].$$

- S_k is **NOT** marginal survival function!
- Only has this interpretation if competing event time distributions and censoring distribution are **independent**.
- Then marginal distribution describes event time distribution in world where competing events do not occur.

Competing risk models: hazard vs. probability

Transition probabilities in general multistate models:

$$P_{lj}(s,t) \quad := \quad P(X(t) = j | X(s) = l, \text{Past}).$$

Competing risk:

- $P_{0j}(0,t)$ referred to as **cumulative incidence**.
- Expected proportion of patients experiencing event of type j over course of time.

Cumulative incidence for $j = 1, 2$:

$$\begin{aligned} P(T \leq t, X_T = j) &= P_{0j}(0,t) \\ &= P(X(t) = j | X(0) = 0) \\ &= \int_0^t P(T > v-) \alpha_{0j}(v) dv \\ &= \int_0^t \exp\Big(-A_{01}(v-) - A_{02}(v-)\Big) \alpha_{0j}(v) dv. \end{aligned}$$

Competing risk models: population quantities

How is competing risk data generated? Two-step simulation process:

1. Determine time T at which event occurs via all-cause hazard $\alpha(t)$.
2. Event type X_T for given time T: determined via multinomial experiment that decides with probability $\alpha_{0j}(T)/\alpha(T)$ on $X_T = j$.

Beyersmann et al. (2012), Allignol et al. (2011).

Hazards completely determine stochastic behaviour of competing risks process.

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.2.3 (2023-03-15 ucrt)

Base packages: stats / graphics / grDevices / utils / datasets / methods / base

Other packages: ggplot2 / etm / cmprsk / mvna / prodlim / survival / reporttools / xtable

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