Comparison of Adverse Event Risks in Randomized Controlled Trials with Varying Follow-Up Times and Competing Events: Results from an Empirical Study

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ABSTRACT
Analyses of adverse events (AEs) are an important aspect of the evaluation of experimental therapies. The SAVVY (Survival analysis for Adverse events with Varying follow-up times) project aims to improve the analyses of AE data in clinical trials through the use of survival techniques appropriately dealing with varying follow-up times, censoring, and competing events (CE). An empirical study including 17 randomized clinical trials investigates the impact on comparisons of two treatment arms with respect to AE risks. The comparisons of relative risks (RR) of standard probability-based estimators to the gold-standard Aalen-Johansen estimator or hazard-based estimators to an estimated hazard ratio (HR) from Cox regression are done descriptively, with graphical displays, and using a random effects meta-analysis on AE level. The influence of different factors on the size of the bias is investigated in a meta-regression. We find that for both, avoiding bias and categorization of evidence with respect to treatment effect on AE risk into categories, the choice of the estimator is key and more important than features of the underlying data such as percentage of censoring, CEs, amount of follow-up, or value of the gold-standard RR. There is an urgent need to improve the guidelines of reporting AEs.

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1. Introduction
Methods commonly employed in randomized clinical trials (RCT) to quantify absolute adverse event (AE) risk either do not account for varying follow-up times, censoring, or for competing events (CE), although appreciation of these is important in risk quantification; see, for example, Proctor and Schumacher (2016). As noted in Koller et al. (2012) recognition of competing events in the clinical trial community remains marginal.

The SAVVY project group is a collaborative effort from academia and pharmaceutical industry with the aim to improve analyses of AE data in clinical trials through use of survival techniques that account for varying follow-up times, censoring and CEs. To this end, Stegherr et al. (2021b), considering only one trial arm in an opportunistic set of 186 types of AEs from seventeen RCTs from different disease indications, have verified the relevance of using the Aalen-Johansen estimator (Allignol, Beyersmann, and Schmoor 2016) as the nonparametric gold-standard method when quantifying absolute AE risk. The reason is that the Aalen-Johansen estimator is the only (nonparametric) estimator that accounts for CEs, censoring, and varying follow-up times simultaneously, and, being nonparametric, does not rely on restrictive parametric assumptions such as incidence densities do.

Stegherr et al. confirmed that the one minus Kaplan-Meier estimator with simple censoring of CEs overestimates the cumulative AE probability. This is well-known and has been shown either empirically in one single study (Schuster et al. 2020) or analytically (Stegherr et al. 2021c). Here we extend these considerations to comparing AE risk between treatment arms, the challenge being that, say, the fact of overestimation in both arms of the same trial allows for both under- and overestimation of RR when comparing arms. We consider the same six estimators of AE probabilities as in Stegherr et al. (2021b) and extend the results to an assessment of how these same estimators perform when estimating relative risks between two randomized treatment arms. With this, we answer a question raised in Unkel et al. (2019), namely which direction the bias goes for an estimator of a RR when based on biased one-sample estimators. Since in applications very often the RR for AEs is not (only) quantified...
via estimates of AE probabilities but also using an estimate of the hazard ratio (HR) of AE hazards, we extend the analysis to two hazard-based estimators of RR. Here, on the one hand, we investigate to which extent incidence densities may be used to approximate HR estimates from a semi-parametric Cox model. On the other hand, we investigate the relevance of CEs and their CE-specific hazards by investigating conclusions either based on a Cox model for time to AEs or based on a ratio of probabilities using the Aalen-Johansen estimator. Properties and estimands of various estimators to quantify RRs between two randomized arms, and when to prefer which, are discussed elsewhere (Unkel et al. 2019; Stegherr et al. 2021a).

The primary objective of the present article is to provide an empirical quantification of how large the bias for the estimation of relative AE risk compared to the gold-standard Aalen-Johansen estimator can become when using other estimators, in the presence of one or more of varying follow-up times, censoring, or CEs. To this end, we accept common choices of safety patient datasets which may differ from the intention-to-treat datasets. Motivated by the common use of incidence proportions, we assume that primary interest is in probabilities, but that estimation of AE probabilities must account for varying follow-up times and censoring as illustrated in discussions on contrasting incidence proportions and incidence densities.

2. Methods

In the entire article, Arm E is referring to the experimental treatment and Arm C to the control.

2.1. Target of Estimation

As a consequence of our focus on probabilities, the target of estimation or estimand is \( P(\text{AE in } [0, t]) \) to be compared between arms. All the five estimation methods that we compare in what follows target this same estimand. In situations not additionally complicated by varying follow-up times or censoring, that is, when all patients are observed for the same amount of time, \( P(\text{AE in } [0, t]) \) can easily be estimated using the incidence proportion. However, as soon as we have varying follow-up and/or censoring, the incidence proportion will typically be a biased estimate of \( P(\text{AE in } [0, t]) \).

While we are not at all attempting to define what a fit-for-purpose estimand to quantify safety risk could be, but rather focus on statistical properties of commonly used estimators in the presence of varying follow-up and CEs, we have been encouraged to formulate the five attributes of our target of estimation within the ICH E9(R1) estimand framework. Treatment and population are generic, the summary measure is the relative risk based on arm-wise probabilities \( P(\text{AE in } [0, t]) \). The variable should be interpreted in a stochastic process formulation (the backbone of survival analysis), where it is time to composite, that is, time-to-first-of \( \{\text{AE, competing event}\} \), with indication of type of event (a “mark” in stochastic process language). This implies for intercurrent events (ICE) that competing events do not affect the existence of the measurements, because the different competing events are simply different values of precisely one random variable. One could argue that competing events are thus simply made part of the variable attribute of the estimand.

2.2. Organization of Data Analysis

In a big collaborative effort data from seventeen RCTs from different disease indications has been gathered within 10 sponsor organizations (nine pharmaceutical companies and one academic trial center). In order to avoid challenges with data sharing SAVVY used an approach familiar from Health Informatics, see, for example, Budin-Ljøsne et al. (2015). A standardized data structure was defined (Steherr et al. 2021a) based on which SAS and R macros were developed by the academic project group members. These macros where then shared with all participating sponsor organizations and run by them locally on their individual trial data. Only aggregated data necessary for meta-analyses were forwarded to the academic group members to centrally run meta-analyses.

2.3. Focus on AEs

In SAVVY we focus on analysis of AEs, as opposed to efficacy endpoints as in Austin and Fine (2017). This has several reasons: First, acknowledging that estimates of AE risks based on the incidence proportion are very prevalent in RCT reporting and may have major impact on labeling and use of drugs, we consider it paramount to provide good estimates of such risks. Illustrating the biases empirically we aim to change the default methods for AE analysis in the future. Second, for AEs we can use generic CEs such as death or discontinuation of treatment, the former preventing an AE from happening, the latter changing its probability of occurrence (Gooley et al. 1999). Again, looking at primary endpoint data most likely would have required a case-by-case consideration of what constitutes a CE. And third, given that our primary objective is an empirical quantification of the bias of often-used estimators, it is useful to have a substantial amount of data. We are analyzing 186 types of AEs, collecting the same number of time-to-event primary endpoints (including definition of the relevant CEs) would most likely have been impossible.

2.4. Follow-Up Time

Since for a time-to-event endpoint, both AE probabilities and the amount of censoring (Pocock, Clayton, and Altman 2002) are time-dependent, we will consider different evaluation times called \( \tau \). These evaluation times either imposed no restriction, that is, evaluated the estimators until the maximum follow-up time (\( \tau_E \) and \( \tau_C \) in each arm, respectively), or considered the minimum of quantiles of observed times in the two treatment arms; the quantiles were 100% (whose minimum over both arms we denote by \( \tau_{\text{max}} = \min(\tau_E, \tau_C) \)), 90%, 60%, and 30%. For computation of RRs by the ratio of AE probabilities, in this article we always use the same follow-up time in both arms, that is, \( \tau_{\text{max}} \). The rationale to evaluate estimators at the latest meaningful time is that this reflects common practice for the estimation of AE risk using the incidence proportion, where simply the number of patients with a certain AE in a given time
interval is divided through the total number of patients. Analyses for maximum follow-up (which may be arm-specific) were not performed. For hazard-based estimators we use all available data and exclusively look at the arm-specific maximum follow-up time, that is, $t_E$ and $t_C$, also when comparing arms. The partial likelihood estimator of the HR based on Cox regression “self-adjusts” for $t_{\text{max}}$ in that it only requires data up to this time point. To limit the variability of the Cox HR we limit the considered dataset to those AEs with an absolute frequency of $\geq 10$ in each arm for hazard-based analyses; we refer to the book by Therneau and Grambsch (2000) for guidance on Cox regression with rare events.

### 2.5. Estimators of AE Probabilities

As one-sample estimators of the AE probability we use the incidence proportion, the probability transform incidence density ignoring and accounting for CE, one minus Kaplan–Meier, and the Aalen–Johansen estimator. A brief summary of one-sample estimators is given in Stegherr et al. (2021b). An even more detailed Statistical Analysis Plan for the entire SAVVY project has been published elsewhere (Stegherr et al. 2021a). The probability transforms of the incidence density are parametric counterparts based on the exponential distribution of one minus Kaplan–Meier (ignoring CEs) and of Aalen–Johansen (accounting for CEs), respectively. Transforms are required because incidence densities estimate hazards.

### 2.6. Hazard-Based Analyses

For a time-to-event endpoint, the incidence density estimates the hazard function assuming that it is constant (Stegherr et al. 2021a, 2021b). Their ratio therefore estimates a HR under the restrictive assumption that the hazard functions of both treatment arms are constant. The common Cox model is a semiparametric extension which only requires the HR to be constant, but not the hazards in the arms.

If we consider a time-to-event endpoint with just one possible event, for example, death for overall survival, then one minus the survival function, that is, the expected proportion of patients with the event of interest over time, bears a direct relationship to the (cumulative) hazard. However, once we have to consider CEs, the direct relation between the hazard for a given event and the cumulative incidence function, which takes the role of one minus the survival (or “event-probability”) function, breaks down (Latouche et al. 2013). As a consequence, if we want to use a hazard-based analysis to quantify the effect of treatment on the event of interest and all CEs, in theory it is necessary to report all event-specific hazards, or rather the corresponding HRs. For this reason, we will not only report the performance of hazard-based RR estimators for the endpoint of interest, time to (first) AE, but also for the competing endpoints time to a CE of death and time to all CEs (see “Definition of CEs” in Stegherr et al. 2021b and section below). This is in perfect analogy to not only consider a (one minus Kaplan–Meier-like) simple probability transformation of the AE incidence density, but to also consider an (Aalen–Johansen-like) transformation accounting for CEs.

### 2.7. Effect Measures

For given estimators $\hat{q}_E$ and $\hat{q}_C$ of AE probabilities calculated at a specific evaluation time within each treatment arm, one can consider either the risk difference, $\hat{RD} = \hat{q}_E - \hat{q}_C$, the RR, $\hat{RR} = \hat{q}_E/\hat{q}_C$, or the odds ratio, $\hat{OR} = \hat{q}_E/(1 - \hat{q}_E)/(\hat{q}_C/(1 - \hat{q}_C))$. In this article, we will focus on the RR to quantity the treatment effect. The IQWiG summarizes reasons to prefer the RR over the risk difference in Appendix A IQWiG (2017) of their general methods. The key feature therein that leads us to prefer the RR is that the risk difference is an absolute effect measure and as such strongly depends on the baseline risk in the control arm. Finally, we prefer the RR over the OR because it is easier to interpret in the sense that it is an immediate comparison of the cumulative AE probabilities estimated in the one-sample case (Stegherr et al. 2021b). Variance estimators are easily obtained via the delta rule. In the one-sample case, estimates of AE probabilities were benchmarked on the gold-standard Aalen–Johansen estimator with the primary definition of CEs, that is, considering all clinical events described below as CEs. This, because the latter is a fully nonparametric estimator that accounts for censoring, does not rely on a constant hazard assumption, and accounts for CEs, see Table 1 in Stegherr et al. (2021b). Furthermore, as is well-known, simply taking one minus Kaplan–Meier for time-to-first-AE is a biased estimator of the AE probability in presence of CEs. Here, as a straightforward extension for the comparison of AE probabilities between two arms using the RR, we benchmark the latter on the RR estimated using the Aalen–Johansen estimator in each arm.

The gold-standard for estimates of the HR will be the HR from Cox regression. This, because the latter is typically used to quantify a treatment effect not only for efficacy, but also for time-to-first-AE type endpoints. Variances of comparisons of different estimators of the HR will be received via bootstrapping (Stegherr et al. 2021c). The reason to bootstrap is that we compare different estimators of the same quantity based on one dataset, leading to the different estimators being dependent. Note that Cox regression for HRs of an AE technically censors other CEs. This is justified because it does not alter the signal of the AE-specific counting process, ensuring identifiability of AE hazards and their ratios. The link to our earlier probability considerations is that probability transforms must account for the presence of multiple hazards (and HRs). A Kaplan–Meier estimator that only counts AEs and censors other CEs therefore has no proper probability information. It represents some transformation from the hazard scale, and comparing such Kaplan–Meier estimators between treatment groups may be used to illustrate treatment contrasts on the AE hazard, but such Kaplan–Meier estimators do not have a proper probability interpretation as consequence of multiple hazards being present.

As we base our analyses on real datasets we do not know the underlying true effects, either RRs or HRs. This is why we chose the above gold-standard estimators to benchmark the candidate estimators against. In what follows, we will still call the deviation of an estimator under consideration to its respective gold-standard bias, although, of course, the comparison is between estimators. We note however that, say, a comparison...
of one minus Kaplan-Meier and Aalen-Johansen will converge in probability toward the true or asymptotic bias when sample size tends to infinity. As discussed above, the reason not to benchmark against the true value in a simulation setup is that in SAVVY we are explicitly interested in quantifying empirically how much a given estimator can differ compared to the gold-standard Aalen-Johansen estimator.

2.8. Definition of CEs

The definition of events as CE (or “competing risk”) is discussed in detail in Stegherr et al. (2021b). Briefly, both death before AE and any event that would both be viewed from a patient perspective as an event of his/her course of disease or treatment and would stop the recording of the AE of interest will be viewed as a CE, including possibly disease- or safety-related loss to follow-up, withdrawal of consent, and discontinuation. Note that stop of AE recording is included here as a CE in situations where the probability of AE occurrence will have changed. One example is progression of disease that leads to treatment discontinuation and subsequent end of AE recording.

While this is our primary definition of a CE, we will also look at a CE of “death only.” Even though interpretation depends on the severity of the event, a categorization into these two types of CEs is considered here for illustrative purposes. One motivation is that, in a time-to-first-event analysis, the incidence proportion, that is, the number of AEs divided by arm size, should be unbiased in the absence of censoring. To investigate the impact of our primary CE definition, we also included an investigation of an estimator Aalen-Johansen (death only), which only treated death before AE as competing, but not the other CEs that belong to our primary definition.

Consideration of “death only” reduces the list of ICEs and thus changes the estimand. One can argue that we implicitly define a “while on observation” estimand. This, because even if we do not consider the other CEs as ICEs anymore, data collection has still stopped once they have occurred. However, as discussed above, changing the estimand by considering a different set of CEs still begs the question how the different estimation methods perform comparatively.

An overview how the different estimators account for the three sources of bias, that is, censoring, no constant hazards, and CEs is given in Table 1 in Stegherr et al. (2021b).

To explicitly investigate the role of censoring without the methodological complication of CEs, a composite endpoint where AEs and CEs are combined into one single event is considered. As a consequence, the gold-standard in this setting is the one minus Kaplan-Meier estimator which is compared to the incidence proportion.

2.9. Random Effects Meta-Analysis and Meta-Regression

In the meta-analysis and meta-regression, the ratios of the RR estimates, either based on probability or hazard estimates, obtained with one of the other estimators divided by the RR estimate obtained with the gold-standard Aalen-Johansen estimator (for probabilities) or the Cox regression HR (for hazard based) are considered on the log-scale. The standard errors of these log-ratios are calculated with a bootstrap. Then, a normal-normal hierarchical model is fitted and the exponential of the resulting estimate can be interpreted as the average ratio of the two RR estimators.

In a meta-regression it is further investigated which variables impact this average ratio. Therefore, the proportion of censoring, the proportion of CEs, the evaluation time point \( \tau \) in years, and the size of the RR under consideration estimated by the gold-standard are included as covariates in an univariable and a multivariable meta-regression. For the latter, since the sum of the proportion of censoring, the proportion of CEs, and the value of the gold-standard Aalen-Johansen estimator converge to 1, including all of them in the model would lead to collinearity. For that reason, we omit the proportion of CEs in the model. All covariates are centered in the meta-regressions.

2.10. RR Categories

The impact of the use of the different estimators on the conclusions derived from the comparison of treatment arms is investigated by the use of categories. These are typically derived from comparing the confidence interval (CI) of the RR to thresholds. There is no universally accepted standard on how one should combine a point estimate and its associated variability, in our case RR, into evidence categories. As an example, we use a categorization motivated by the methods put forward by the IQWiG (IQWiG 2017) for severe AEs (Table 14) to be used for the German benefit-risk assessment. In contrast to the usual IQWiG procedure, however, we do not only categorize the benefit of a therapy, but also the harm. Thereby, in this first analysis we do not distinguish between a positive and a negative treatment effect. Four categories are possible: (0) “no effect” if 1 is included in the CI, (a) “minor” (“gering”) if the upper bound of the CI is in the interval [0.9, 1) for a RR < 1 or the lower bound in the interval (1, 1.11) for a RR > 1, (b) “considerable” (“beträchtlich”) if the upper bound of the CI is in the interval [0.75, 0.9) for a RR < 1 or the lower bound in the interval (1.11, 1.33] for a RR > 1, and (c) “major” (“erheblich”) if the upper bound is smaller than 0.75 for a RR < 1 or the lower bound greater than 1.33 for a RR > 1. The same categorization is used for the HR instead of RR.

3. Results

3.1. Description of Data

Ten organizations provided 17 trials including 186 types of AEs (median 8; interquartile range [3; 9]). Twelve (71.6% out of 17) trials were from oncology, nine (52.9%) were actively controlled and eight (47.1%) were placebo controlled. Median follow-up was 927 days in Arm E (interquartile range [449; 1380]), 896 days in Arm C (interquartile range [308; 1263]), and 856 days (interquartile range [308; 1234]) in both arms combined. The trials included between 200 and 7171 patients (median: 443; interquartile range [411; 1134]). In Arm E, estimated values from the Aalen-Johansen estimator ranged from 0 to 0.95 with a median of 0.09; in Arm C the range was from 0 to 0.77 with a median of 0.05. RRs based on these estimates ranged from 0.28
Figure 1. Relative frequency of observed events, per treatment arm.

Table 1. The impact of the choice of relative effect estimator for AE probabilities on qualitative conclusions.

|                      | Gold-Standard Aalen-Johansen
|----------------------|-----------------------------|
|                      | (0) No effect   | (a) Minor    | (b) Considerable | (c) Major |
| Incidence proportion | (0) no effect   | 84           | 5                |
|                      | (a) minor       | 3            | 10               |
|                      | (b) considerable| 1            | 2                |
|                      | (c) major       | 1            | 1                | 33               |
| Probability transform incidence density ignoring CE | (0) no effect   | 73           | 13               |
|                      | (a) minor       | 11           | 2                |
|                      | (b) considerable| 2            | 2                |
|                      | (c) major       | 1            | 1                | 21               |
| One minus Kaplan-Meier | (0) no effect | 84           | 9                |
|                      | (a) minor       | 3            | 6                |
|                      | (b) considerable| 2            | 1                |
|                      | (c) major       | 1            | 1                | 18               |
| Probability transform incidence density accounting for CE | (0) no effect   | 77           | 3                |
|                      | (a) minor       | 10           | 12               |
|                      | (b) considerable| 1            | 2                |
|                      | (c) major       | 1            |                  | 34               |
| Aalen-Johansen (death only) | (0) no effect | 86           | 9                |
|                      | (a) minor       | 3            | 6                |
|                      | (b) considerable| 2            | 8                |
|                      | (c) major       | 1            | 1                | 22               |

NOTE: Diagonal entries are set in bold face. Deviations from the gold-standard Aalen-Johansen estimator are the off-diagonal entries. Off-diagonal zeros are omitted from the display.

to 16.81 with a median of 1.71. HRs for AE hazards (restricted to AEs with $\geq 10$ events in each arm) ranged from 0.14 to 10.83, with a median of 1.30.

Figure 1 displays for the 186 types of AEs boxplots of the treatment-arm specific observed relative frequencies, that is, the number of patients with a specific type of event divided by the total number of patients. Events considered are “observed AE,” “observed death before AE,” “observed other CEs” (i.e., excluding death), and “observed censoring.” Within each arm, the figure illustrates a smaller amount of observed censoring compared to observed CEs. That is, AE recording often ended due to death or other CEs such as treatment discontinuation, preventing censoring of the time to AE. Comparing the arms we observe more AEs in the treatment Arm E, a comparable number of deaths, and more CEs in the control Arm C. All combined, this leads to less censoring in the control Arm C.

3.2. Impact on RR Categories and Decisions Based on Probability-Based Relative AE Risk Estimates

In this paragraph we summarize a key finding of this article: namely, that categorization of evidence based on RR crucially depends on the estimator one uses to estimate the RR. Table 1 shows the evidence categories for our considered estimators of the RR of those AEs where neither the estimated AE probability in Arm E nor the estimated AE probability in Arm C is 0 ($n = 155$ types of AEs for one minus Kaplan-Meier and $n = 156$ types of AEs for all other estimators). Overall, we find quite a number of switches to neighboring categories. Reasons for switches are wider CIs of the Aalen-Johansen estimator as well as RR estimates / CI bounds that are close to the cutoffs between categories. As the incidence proportion on average estimates the RR well (third column in Table 2), we see a similar number of switches to a higher ($n = 8$, below the diagonal in Table 1) and
Table 2. Results of the meta-analyses of the log ratio of the estimator of interest divided by the gold-standard Aalen-Johansen estimator.

| Incidence proportion | Control | Ratio of RR with 95% CI |
|----------------------|---------|------------------------|
| 0.974 [0.966;0.982]  | 0.978 [0.970;0.985] | 0.997 [0.991;1.002] |
| Probability transform of the incidence density ignoring CE | 1.187 [1.161;1.214] | 2.424 [2.249;2.613] | 0.732 [0.703;0.763] |
| One minus Kaplan-Meier | 1.321 [1.257;1.389] | 0.838 [0.786;0.894] |
| Probability transform incidence density Accounting for CE | 1.099 [1.080;1.118] | 1.124 [1.093;1.156] | 0.977 [0.957;0.997] |
| Aalen-Johansen (death only) | 1.146 [1.125;1.168] | 1.254 [1.201;1.308] | 0.860 [0.811;0.911] |

NOTE: The first two columns show the estimated average ratio and 95% CI per treatment arm and meta-analyze the data shown in Figure 2. The third column gives results of the meta-analyses of the response variable log ratio of the RRs estimated with the estimator of interest and the gold-standard Aalen-Johansen estimator, the estimated average ratio and 95% CI. The denominator is the RR obtained using the gold-standard Aalen-Johansen estimator. This third column relates to the Panel A in Figure 3.

Figure 2. Ratios of one-sample estimators per treatment arm. The denominator is always the gold-standard Aalen-Johansen estimator.

lower \((n = 9)\) evidence category. Interestingly, while on average the probability transform of the incidence density accounting for CEs is approximately unbiased as well, we see double as many effect upgradings \((n = 14)\) as downgradings \((n = 7)\). Quite logically, for those estimators that underestimate the RR with respect to the gold-standard Aalen-Johansen estimator, namely probability transform incidence density ignoring CEs, one minus Kaplan-Meier, and Aalen-Johansen (death only) we see comparatively more switches to a lower than higher evidence category, namely \(n = 41/n = 16, 32/8, \) and \(28/6, \) respectively.

Switches between categories are more rare for a given estimator for earlier follow-up times, mainly because of increased variability (results not shown).

In summary, the choice of the estimator of the RR does have an impact on the conclusions.

In what follows, we will describe the different properties of the considered estimators that ultimately lead to this relevant number of diverging conclusions.

### 3.3. Estimators of AE Probabilities Compared to Gold-Standard

Figure 2 shows boxplots of the ratio of the one-sample estimators defined earlier divided by the gold-standard Aalen-Johansen estimator, separately per treatment arm. Boxplots for Arm E are slightly different compared to Stegherr et al. (2021b), because we use here \(\tau_{\text{max}}\) as evaluation time. Briefly, incidence proportion and gold-standard often perform comparably. Probability transforms of the incidence density perform worst when ignoring CE, but when accounting for CE perform much better than the other three procedures which are clearly biased with many examples of extreme overestimation. Also, the incidence proportion displays examples of biases (downwards), with underestimation of up to 67%. Comparing the two arms, overestimation of the AE probability is more pronounced in Arm C. These biases become less pronounced when looking at earlier evaluation times which prevent CEs and censoring after the respective horizon to enter calculations (results not shown).

### 3.4. Meta-Analysis for Estimators of AE Probabilities, per Arm

Meta-analyses of all estimators divided by the gold-standard Aalen-Johansen estimator are displayed in the first two columns of Table 2. These results confirm the visual impression gathered from the boxplots in Figure 2, but we note that Figure 2 also displays biases much more pronounced than the meta-analytical averages. In general, the amount of overestimation increased with later evaluation times (results for earlier evaluation times not shown). Further investigations included uni- and multi-variable meta-regressions, see Stegherr et al. (2021b) for Arm E results. Results for Arm C reflect the different event pattern described above and are consistent (data not shown).

### 3.5. Estimators of Relative AE Risk Based on Probabilities Compared to Gold-Standard

Panel A in Figure 3 displays boxplots of ratios of RRs estimated with the estimator of interest and the gold-standard Aalen-Johansen estimator. Interestingly, dividing the two biased estimates of the AE probability based on the incidence
Figure 3. Panel A: Ratio of RRs estimated with estimator of interest and the gold-standard Aalen-Johansen estimator. Panel B: Kernel density estimates of the RR based on AE probabilities of the estimators divided by the gold-standard Aalen-Johansen estimator.

Factors that influence the respective behavior of a given estimator are discussed below.

3.6. Meta-Analyses for Estimators of Relative AE Risk Based on Probabilities

The third column in Table 2 displays the results of the random-effects meta-analyses for the log ratio of the two RRs. These are in line with the results discussed above. The average ratio between the RR calculated with the incidence proportion and RR calculated with the Aalen-Johansen estimator is close to 1. The biggest underestimation is observed for the probability transform incidence density ignoring CE, with an average difference of the risks of about 27%. The Aalen-Johansen (death only) estimator has a more pronounced underestimation compared to its counterpart accounting for all CE, but this reduction is not as pronounced as the one using the one minus Kaplan-Meier or the probability transform of the incidence density ignoring CEs. Finally, the probability transform of the incidence density accounting for CEs only slightly more underestimates on average compared to the incidence proportion. In general, these differences decrease when considering earlier evaluation times (data not shown).

3.7. Uni- and Multivariable Meta-Regressions for Estimators of Relative AE Risk Based on Probabilities

For the meta-regressions, we use as covariates the percentage of censoring (for both arms combined), the percentage of CEs (for both arms combined), the maximum follow-up time, and the size of the RR as estimated by the gold-standard Aalen-Johansen estimator. Covariates were centered, that is, the row "average RR" contains the average RR of the estimator of interest and the Aalen-Johansen estimator if the covariate takes its mean. These means were 28.6% censoring (= percentage of censored observations until \( t_{\text{max}} \)), 53.8% CEs, 2.38 years (781 days) evaluation time, and a RR of 2.55. Table 3 provides results from the uni- and Table 4 from the multivariable analysis.

We illustrate the interpretation of the parameters of the meta regression models by the following example calculation: The average ratio of the RR calculated with the probability transform of the incidence density ignoring CEs and the RR calculated...
with the Aalen-Johansen estimator at \( r_{\text{max}} \) under 28.6% censoring is 0.729. If a trial has 38.6% censoring, that is, an increased censoring proportion of 10 percentage points, the average ratio is estimated as 0.729 \( \cdot 1.066 = 0.777 \).

The biggest average underestimation of the RR compared to the gold-standard is seen for the probability transform of the incidence density ignoring CEs (27 percentage points) and about the same for one minus Kaplan-Meier and Aalen-Johansen (death only), both about 16 percentage points. Increasing the censoring proportion compared to their respective mean leads to less underestimation with respect to the gold-standard while the opposite is true for increasing the proportion of CEs. Increasing the evaluation time or the size of the gold-standard RR compared to their respective mean has no relevant additional effect. For the probability transform incidence density accounting for CEs results are on average comparable to the gold-standard.

These results are confirmed in the multivariable analysis in Table 4.

In summary, these meta-regressions show that (a) the key difference between estimators lies in the value of the average RR and (b) the impact of covariates is overall limited, compared to the average RR the estimated coefficients are close to 1. This emphasizes that the choice of the estimator is key, and that this holds true over a wide range of possible data configurations quantified through the considered covariates.

### 3.8. Variability for Estimators of Relative AE Risk Based on Probabilities

So far, we have primarily discussed how the different estimators perform compared to the gold-standard Aalen-Johansen estimator on average. In a first step, variability of the RRs of every estimator with respect to the gold-standard Aalen-Johansen estimator can be assessed from the switches between RR categories in Table 1 and the boxplots in Panel A in Figure 3. Here, we provide a more detailed account of the variability of the RRs using kernel density estimates of their distribution. As in the one-sample scenario, on average the incidence proportion appears to provide a good estimator of relative AE risk based on probabilities. Considering the plot of the kernel density estimates of the RRs of the AE probability in Panel B of Figure 3, the RR based on the incidence proportion and the gold-standard is most often close to one. However, there is also a peak of the estimated kernel density at larger ratios, indicating that the estimators are not always comparable. For the RR based on the ratio of the probability transform of the incidence density accounting for CEs and the gold-standard we still have clustering around one, but not as pronounced as for the incidence proportion. The ratios of the one minus Kaplan-Meier or Aalen-Johansen (death only) estimator have less values close to one. For these two estimators more values are smaller than one than larger. The estimated kernel density of the probability transform of the incidence density ignoring CE has no peak at one but is bimodal with both modes below one.

Patterns of relative frequencies of the AE itself, censoring, and CEs, that may lead to extreme discrepancies between a given estimator and the gold-standard Aalen-Johansen estimator for estimation of AE probabilities are discussed in detail in Steghear et al. (2021b). Of course, such extreme configurations in one or both arms may lead to extreme RR estimates also for the two arm comparison.

### 3.9. Estimators of Relative AE Risk Based on Hazards Compared to Gold-Standard

Figure 4 displays boxplots of the HRs calculated from Cox regression. The three boxplots display HRs for hazards of AE,
Figure 4. Cox regression HRs (on log-scale) for the three event types AE, all CEs, and CE of death.

all CEs, and a CE of death. Assessing the effect for the endpoint of interest, here time to AE, as well as of any CE, here time to all CEs or time to a CE of death, is generally recommended for any (hazard-based) analysis of competing events (Latouche et al. 2013). We find that the hazard of AE is generally larger for Arm E compared to Arm C, meaning that the instantaneous risk of AE is typically higher, not unexpectedly. For the hazards of CEs, for both types, what we find is that the hazard in Arm E is generally lower than in Arm C, that is, there is an effect of the experimental treatment on the CE. If we simply censored at CEs we would thus introduce arm-dependent censoring, a feature that may lead to biased effect estimates (Schemper and Smith 1996; Clark, Altman, and De Stavola 2002). We will use this to explain observations we make in Table 9.

Boxplots of the ratios of incidence density estimates in each arm, evaluated at $\tau_E$ and $\tau_C$, respectively, and the gold-standard HR calculated from Cox regression, are provided in Panel A in Figure 5, for again the same endpoints as in Figure 4. The ratio of the incidence densities of the AE in the two arms underestimates with respect to the Cox regression HR while for the other two endpoints on the median they turn out to be approximately unbiased compared to the Cox HR, with a tendency to overestimation when accounting for all CEs and underestimation when only accounting for a CE of death.

To appreciate the differences between the two estimators of the RR based on hazards, that is, the incidence density ratio and the gold-standard Cox regression HR, recall the properties of the two methods: Both properly account for censoring and they properly estimate event-specific hazards, or rather the relative effect based on these. The only difference between the two methods is what they assume about the shape of the underlying hazard: the incidence density assumes them to be constant up to the considered follow-up time, which also implies that they are proportional. The gold-standard Cox regression HR only assumes them to be proportional, but not constant. But in addition, we also have different data patterns for the three event causes for which we show boxplots of relative hazard-based risks in Panel A in Figure 5: looking at Figure 1 we find a low proportion of events for AE and an even lower proportion of CEs of death, but a higher proportion of events for all CEs. Furthermore, within a given patient, death happens later than AE. So the results we observe in Panel A in Figure 5 are a result of different tradeoffs between all these aspects.

If we restrict follow-up to earlier timepoints, then variability increases and on average, results persist for the events of AE

Figure 5. Panel A: Ratio of RR estimates with estimator of interest and the gold-standard HR based on Cox regression estimator, all evaluated at $\tau_E$ and $\tau_C$. Panel B: Plots of the kernel density estimates of the HR of the estimators divided by the gold-standard Cox-regression estimator.
Table 5. Results of the meta-analyses of the response variable log ratio of the ratio of the estimator of interest and the HR estimated by the Cox model.

| Estimator | Ratio with 95% CI |
|-----------|------------------|
| Ratio incidence density AE | 0.803 [0.741; 0.871] |
| Ratio incidence density all events CE | 0.908 [0.851; 0.969] |
| Ratio incidence density (death only) CE | 0.958 [0.934; 0.982] |

NOTE: Estimated average ratio and 95% CI. The denominator is the HR obtained using the Cox model.

Table 6. Univariable meta-regression for the response variable log ratio of the HRs, estimated with the estimator of interest and the gold-standard Cox regression.

| Incidence density of AE | Incidence density of all events CE | Incidence density of death only CE |
|-------------------------|-----------------------------------|----------------------------------|
| % Censoring             |                                   |                                  |
| Average HR              | 0.825 [0.784; 0.868]              | 1.063 [1.045; 1.081]              | 0.962 [0.938; 0.986] |
| 10% increase            | 1.052 [1.031; 1.073]              | 0.990 [0.983; 0.996]              | 1.026 [1.015; 1.036] |
| % CEs                   |                                   |                                  |                      |
| Average HR              | 0.786 [0.741; 0.834]              | 1.061 [1.044; 1.079]              | 0.942 [0.913; 0.971] |
| 10% increase            | 0.948 [0.925; 0.971]              | 1.011 [1.004; 1.017]              | 1.041 [1.013; 1.071] |
| Size of HR              |                                   |                                  |                      |
| Average HR              | 0.836 [0.790; 0.884]              | 1.063 [1.048; 1.078]              | 0.959 [0.932; 0.987] |
| increase of 0.1         | 1.004 [1.000; 1.008]              | 0.972 [0.966; 0.977]              | 0.996 [0.987; 1.005] |
| Evaluation time         |                                   |                                  |                      |
| Average HR              | 0.854 [0.809; 0.902]              | 1.053 [1.040; 1.067]              | 0.976 [0.944; 1.010] |
| one additional year     | 0.937 [0.905; 0.970]              | 0.945 [0.936; 0.955]              | 0.977 [0.954; 1.000] |

NOTE: The size of the HR is estimated by the Cox model. Note that for the incidence density of death only CE the percentage of CE's correspond to the percentage of deaths and for the other two estimators its the percentage of all events CEs.

Table 7. Multivariable meta-regression.

| Incidence density of AE | Incidence density of all events CE | Incidence density of death only CE |
|-------------------------|-----------------------------------|----------------------------------|
| Average HR              | 0.846 [0.809; 0.884]              | 1.054 [1.042; 1.066]              | 1.003 [0.979; 1.029] |
| % Censoring 10% increase| 1.058 [1.040; 1.076]              | 1.004 [0.999; 1.009]              | 1.038 [1.029; 1.048] |
| Size of HR increase of 0.1 | 1.005 [1.002; 1.008] | 0.980 [0.974; 0.986] | 0.993 [0.986; 0.999] |
| Evaluation time one additional year | 0.933 [0.907; 0.960] | 0.957 [0.948; 0.966] | 0.949 [0.931; 0.968] |

NOTE: The size of the HR is estimated by the Cox model.

3.10. Meta-Analyses for Estimators of Relative AE Risk Based on Hazards

Table 5 confirms these findings in univariable meta-analyses and provides an average quantification of the amount of underestimation of all three estimators relative to the Cox regression HR.

3.11. Uni- and Multivariable Meta-Regressions for Estimators of Relative AE Risk Based on Hazards

For the meta-regressions reported in Tables 6 and 7, in line with what has been done for RR in Tables 3 and 4, we again use as covariates the percentage of censoring, the percentage of CEs, the maximum follow-up time, and the size of the HR as estimated by the gold-standard Cox regression as covariates. Means at which covariates were centered were 29.6% censoring (= mean percentage of censored observations until τ_E and τ_C), 56.7% CEs, 2.72 years (994 days) maximum follow-up time, and a HR of 1.74. Note that these are slightly different from the ones reported above because we are using a different follow-up time here. In the univariable analyses in Table 6, we find an estimated average RR below one for time to AE and time to a CE of death, that is, a lower average RR compared to the gold-standard Cox regression estimator, for all covariates. For time to all CEs the ratio of incidence densities overestimates on average. Most pronounced covariate effects are found for time to AE, for example the average ratio of the HR based on the incidence density and the gold-standard Cox regression HR under 29.6% censoring is 0.825. If a trial has 39.6% censoring, that is, an increased censoring proportion of 10 percentage points, the estimated average ratio is estimated as 0.825 \cdot 1.052 = 0.868.

These results are confirmed in the multivariable analysis in Table 7.

Similar to the estimation of RRs for AE probabilities we find that the effect of covariates compared to the estimated average HR is rather limited for all three endpoints. This means again that the choice of estimator, which either allows for an unspecified, freely varying baseline hazard (Cox regression) or assumes it to be constant (incidence densities), appears to be more relevant than the configuration of the data as captured by the covariates.

3.12. Variability in Estimation

As for the estimation of RRs based on probabilities, we provide a more detailed account of the variability of the HRs using kernel density estimates of their distribution. Considering the plot of the kernel density estimates of the ratios of the HRs in Panel B in Figure 5, the ratio of the HRs for time to AE has its highest peak just below one, but also further peaks that are even smaller than one, indicating that the estimators are not always comparable. The estimated density for the ratio of HRs for time to a CE of death is multimodal, with the highest peak further below one than for time to AE. A higher proportion of ratios of HRs for

and CE of death, but for all CEs the ratio of incidence densities underestimates with earlier timepoints (data not shown). At earlier timepoints the number of events for all CEs also decreases, so that the tradeoff with the constant hazard assumption starts to resemble that of an event of AE.
time to all CEs is close to one, but also this estimated density is multimodal. All densities are left-skewed, indicating that there is a relevant portion of AEs for which the ratio of incidence densities underestimates compared to the gold-standard Cox regression HR for time to all CEs.

### 3.13. Impact on RR Categories and Decisions Based on Hazard-based Relative AE Risk Estimates

Table 8 provides a comparison of the conclusions drawn from the estimators of a RR for time to AE. The majority of AEs either lead to “no effect” or an effect of “major,” and these are quite consistently detected by the two methods. However, we also observe for 19/94 = 20.2% of AEs a diverging conclusion, following from the combination of bias and variability in estimation described above.

### 3.14. Comparison of Qualitative Decisions on Relative Effect Based on the Two Gold-Standards

We have considered two effect measures to quantify the RR of an AE in two arms: the RR based on AE probabilities evaluated at \( \tau_{\text{max}} \) and the HR with maximum available follow-up in both arms, where Cox’s method of estimating the HR implicitly leads to an evaluation at \( \tau_{\text{max}} \). Our analyses reveal that all the considered estimators are overall inferior to the two gold-standards we considered, either the RR based on the arm-wise Aalen-Johansen estimator or the HR based on Cox regression. One question that remains is whether the qualitative conclusions drawn based on the two gold-standards are relevantly different when relying on the criteria put forward by the IQWiG (Table 14 in their general methods document IQWiG 2017). Table 9 has the results. We observed quite different classifications based on the two estimates of the RR. However, this is not a surprise, as the estimand the two methods look at is not the same (see Varadhan et al. [2010] for an exposition of this issue): Cox HR quantifies a relative effect based on an endpoint of AE hazard, whereas RR based on gold-standard Aalen-Johansen is based on a comparison of probabilities at a evaluation time. The latter integrates the hazard for the endpoint of interest and the hazard for CE into one cumulative effect measure, whereas a Cox regression only considers one hazard at a time, and this is likely the primary reason for the divergent decisions in Table 9. Empirically, if the boxplot for the HR for the CE in Figure 4 would center around one, then (ignoring the fact that the categorization also takes into account uncertainty) in theory the decision based on RR and HR would approximately coincide, that is, we would have no non-diagonal entries in Table 9. But whenever there is an effect on the CE, then it is expected that decisions diverge.

Summarizing all these analyses concerning effect quantification for AEs using Cox regression based HRs, we conclude that the ratio of incidence densities cannot be considered a uniformly good approximation of the HR based on Cox regression. We also find that categorization of the relevance of differences between treatment arms may differ depending on whether it is based on one event-specific hazard alone (Cox for AE) or on a proper probability estimator (Aalen-Johansen, integrating the two event-specific hazards).

### 3.15. Role of Censoring

In this section, we aim to explore how the incidence proportion and one minus Kaplan-Meier compare in the absence of CEs. To this end, we consider a composite endpoint where AEs and CEs are combined into one single event. The gold-standard in this setting is the one minus Kaplan-Meier estimator which is compared to the incidence proportion in Figure 6. Since for this endpoint we do not have CEs, the conclusions on relative effects from the probability- and hazard-based analyses are aligned in the sense of the direction of the effect.

As visible in the left and middle boxplot in Figure 6, in the composite endpoint analysis underestimation by the incidence proportion is more pronounced than in the analysis of

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**Table 8.** Conclusions of the RR calculated with the ratio of incidence densities and the HR calculated with the Cox model, both at \( \tau_E, \tau_C \).

| RR incidence density | (0) No effect | (a) Minor | (b) Considerable | (c) Major |
|----------------------|--------------|-----------|-----------------|----------|
| (a) Minor            | 49           | 1         | 5               | 1        |
| (b) Considerable     | 3            | 5         | 3               | 1        |
| (c) Major            | 2            | 3         | 3               | 18       |

NOTE: The table shows the analysis of those \( n = 94 \) AEs that were observed with an absolute frequency of \( \geq 10 \) in each arm. Diagonal entries are set in bold face. Divergent decisions between the two methods are the off-diagonal entries. Off-diagonal zeros are omitted from the display.

**Table 9.** Conclusions of the RR calculated with the gold-standard Aalen-Johansen estimator at \( \tau_{\text{max}} \) compared to the conclusions of the HR calculated with the Cox model at \( \tau_E, \tau_C \).

| RR gold-standard Aalen-Johansen | (0) No effect | (a) Minor | (b) Considerable | (c) Major |
|---------------------------------|--------------|-----------|-----------------|----------|
| (a) Minor                       | 42           | 3         | 3               | 1        |
| (b) Considerable                | 9            | 2         | 1               | 1        |
| (c) Major                       | 4            | 1         | 3               | 2        |

NOTE: The table shows the analysis of those \( n = 94 \) AEs that were observed with an absolute frequency of \( \geq 10 \) in each arm. Diagonal entries are set in bold face. Divergent decisions between the two methods are the off-diagonal entries. Off-diagonal zeros are omitted from the display.
the AE probability presented above. As discussed by Stegherr et al. (2021b) one reason for this observation is that even in the presence of censoring, for the one minus Kaplan-Meier estimator the type of the last event is most important. If the last event is an AE or CE the one minus Kaplan-Meier estimator is equal to one, even though censoring has been observed at earlier follow-up times. The incidence proportion is only equal to one if no censoring is observed. For the RR this leads to an overestimation compared to the gold-standard one minus Kaplan-Meier estimator.

### 3.16. Role of Follow-Up Time

We focused on the results when evaluating estimators using the maximum follow-up time as evaluation time. When looking at earlier evaluation times where the estimators were evaluated at earlier time points defined by quantiles of the observed times (results not shown in detail), the resulting bias was, in general, less pronounced, due to a reduced relative frequency of CEs and of censoring (see Figure 1). We regarded the situation of including all data up to the maximum follow-up time as the most relevant as this is the usual practice.

### 4. Discussion

Survival analyses accounting for CEs is methodologically well established, but practical use lags behind (Schumacher, Ohneberg, and Beyersmann 2016; Austin and Fine 2017; Phillips and Cornelius 2020). Failure to account for censoring (e.g., incidence proportion) or CEs (e.g., one minus Kaplan-Meier) will generally lead to biased quantification of absolute AE risk, and the possible amount of bias has been investigated in Stegherr et al. (2021b). There, we confirmed that one minus Kaplan-Meier should not be used to estimate the cumulative AE probability, as it is bound to overestimate as a consequence of ignoring competing events. Here, we found that this arm-wise overestimation often leads to an underestimation of the RR when comparing two arms. The same pattern is observed for the probability transform incidence density ignoring CE and Aalen-Johansen (death only), that is, the other two estimators that do not correctly account for CEs.

For estimation of AE probabilities, the incidence proportion performed surprisingly well when compared to the gold-standard Aalen-Johansen estimator. As discussed in Stegherr et al. (2021b), the reason was a high amount of CEs before possible censoring, potentially related to the majority of the 17 trials analyzed coming from oncology. These good arm-wise estimates translate in on average unbiased estimation of RR as well. However, as discussed by Stegherr et al. use of the incidence proportion implicitly assumes events to be competing as defined in the methods section. Furthermore, although on average the incidence proportion performs well, we have still $17/156 = 10.9\%$ AE types that were categorized differently in Table 1, with one being turned from a “major” (incidence proportion) to a “no effect” with the Aalen-Johansen estimator. Finally, we found that incidence densities, typically criticized because of the restrictive constant hazard assumption, led to the worst performance when their probability transform ignored CEs. However, accounting for CEs in an analysis that parametrically mimicked the nonparametric Aalen-Johansen performed better than both one minus Kaplan-Meier and Aalen-Johansen (death only). This confirms the conclusion from the one-sample case that ignoring CEs appeared to be worse than assuming constant hazards in our empirical study. In general, we caution against making conclusions about the amount and direction of bias for estimation of the RR based on the behavior of the one-sample estimators. Overall, in terms of relevance of effects, the choice of the estimator is key and more important than the features of the underlying data such as percentage of censoring, CEs, amount of follow-up, or the value of the gold-standard RR.

Kernel estimates of densities of ratios of estimated RRs by the different estimators divided by the RR estimated by the gold-standard Aalen-Johansen estimator revealed that all estimators except probability incidence density ignoring CEs have a peak just below one. However, all estimators either had further peaks away from one or the estimated density was unimodal but with high variance. This indicates that the considered estimators are not always comparable to the gold-standard Aalen-Johansen estimator. In general, it is not obvious what feature of the data generating mechanism actually leads to observed data for which, for example, the incidence proportion performs much worse than the Aalen-Johansen estimator—we found deviations up to a factor of 3.

Combining bias and variability for estimation of RR for AE probabilities, we analyzed the impact of using different estimators on making decisions about effect size based on the criteria put forward by IQWiG. We found that the number of AE types for which a given estimator deviates from the decision on effect size based on the gold-standard Aalen-Johansen estimator is non-negligible, and that discrepancies by more than one category also occur quite often. This is likely a consequence of both, the bias we see for estimation of RR for some of the estimators and the variability.

The analysis based on hazards reveals that the incidence density underestimates the RR for time to AE and time to a CE of death compared to the gold-standard Cox regression, while no obvious bias was observed for time to all CEs. The discrepancy in conclusions with regard to effect sizes drawn based on the ratio of incidence densities and the Cox regression HR appeared to be a bit less than for the estimators of RR based
on AE probabilities. Still, the ratio of incidence densities cannot be considered a uniformly good approximation of the HR based on Cox regression.

Comparing the evidence categories derived from the two gold-standard estimators, the Aalen-Johansen estimator of the RR and the Cox regression HR for an AE we find quite some discrepancies. However, this is not surprising, as the former is based on probability estimators and as such on cumulative measures integrating the two hazards relating to the primary event of interest (AE) and the potential CE, whereas the latter is an instantaneous measure only considering the AE hazard. In other words, this comparison reiterates the importance of accounting for CEs. There are now as many hazards as there are CEs, and outcome probabilities depend on all event-specific hazards. We are aware that in applications it might not be feasible to look at a hazard-based analysis for the AE and all CEs for every preferred term of AE, say. However, we recommend to consider such an analysis at least for AE of special interest.

Finally, in an analysis of a composite endpoint with a single event of AE or CE, we find an overestimation of RR compared to the gold-standard one minus Kaplan-Meier estimator.

The organizational setup of SAVVY with developing program code centrally and running it within every sponsor organization may be a template for collaborations with similar challenges. The setup avoided issues with data sharing and turned out to be highly efficient in bringing a large amount of data together.

Our empirical study does have shortcomings, some of which were to be anticipated in an opportunistic sample of randomized clinical trials. Inter alia, a large number of trials from oncology came with a high amount of CEs, which, in turn, led to comparable performances of arm comparisons based on incidence proportion and Aalen-Johansen. These shortcomings have been discussed in detail in Stegherr et al. (2021b), but this opportunistic "real world" sample allowed us to investigate and demonstrate which biases can occur in practice when estimating a RR. The observed results motivate future empirical investigations on how to quantify RR with the aim of better generalizability. As a further point, it was not the aim of this investigation to accurately estimate RRs, but to compare different estimators. Our present study does not allow for a meaningful comparison of results in different diseases. Follow-up investigations concentrating on trials in specific disease areas are planned.

Methodological restrictions include a focus on AE occurrence in a time-to-first-event setting, which does not consider recurrent AEs and often excludes AEs after treatment discontinuation. A more detailed discussion in Stegherr et al. (2021b) stresses both the need to consider more complex event histories and the need to still account for CEs in such considerations. In other words, both AEs after treatment discontinuation and recurrent AEs will still be subject to CEs, and this must be accounted for when comparing arms.

We focused here on two effect measures, a comparison of probability estimates and the HR at different evaluation times. This, because we consider these two as the overwhelmingly used effect measures to quantify safety effects and we are interested in assessing potential biases of those often used methods, acknowledging that often in applications AE hazards might actually not be proportional. If nonproportional hazards for estimation of RRs for AE risk are a concern then we recommend to rely on comparison of AE probabilities at a fixed timepoint or of cumulative incidence functions.

Replacing the often used incidence proportion by the gold-standard Aalen-Johansen estimator, while conceptually and empirically indicated, requires careful discussion in trial teams to define CEs, and a more granular data collection. In addition to the date of AEs one also needs to collect dates of CEs, which may lead to more missing data, for example, unknown date of loss to follow-up.

In line with Stegherr et al. (2021b), our recommendation is to "play it safe" when estimating RRs in a time-to-first-event analysis and neither hope for a small amount nor a large amount of CEs nor a favorable interplay of the distributions of the times of AEs, CEs, and censorings. In the former case, one minus Kaplan-Meier might work well, while in the latter two cases the incidence proportion might do so. However, in general the proportion of CEs cannot exclusively explain how an estimator performs compared to the gold-standard Aalen-Johansen estimator. Therefore, playing it safe, we recommend using RR based on the Aalen-Johansen estimator for AE probabilities and the HR from Cox regression for all types of events that are typically considered in a time-to-first-event analysis. Guidelines for reporting AEs should therefore advocate the Aalen-Johansen estimator instead of incidence proportion, incidence density and one minus Kaplan-Meier, see Stegherr et al. (2021b) for an extended discussion on how to update guidelines. We recommend that Aalen-Johansen estimators be used in product labels to quantify AE incidence. A request for results from Cox regression in guidelines should be complemented by also requesting results for CE-specific hazards.

The choice of Aalen-Johansen over Kaplan-Meier has links to causal inference and debates on "cause removal" (Kalbfleisch and Prentice 2002). In the common random censorship model, assuming independence of time-to-event and time-to-censoring, Kaplan-Meier can be given a causal interpretation under the intervention "do(no censoring)," that is, Kaplan-Meier approximates the distribution of the data we would have seen in a world without censoring. It is therefore tempting to interpret Kaplan-Meier censoring a CE in a world where the CE is not active (i.e., cause removal). An important distinction is that the former intervention acts on our observational process, while the latter "CE removal" would affect the patient. Ignoring the question whether such an intervention of "CE removal" exists theoretically, the statistical question is whether Kaplan-Meier censoring a CE can be justified from a causal perspective. The recent work by Young et al. (2020) gives technical counterarguments in an estimand framework. The subject matter intuition is that an intervention on the observation process differs from an intervention affecting the patient.

In this context, we also note as a limitation that our paper has only marginally addressed the current debate on estimands and, in that sense, is a more traditional statistical paper. A major reason behind this is the state of affairs in the statistical analyses of AEs. The ongoing debate on whether to use incidence proportions or incidence densities is far from a serious consideration of estimands. Our approach here has been that the incidence proportion implicitly defines the estimand, because it estimates \( P(AE \in [0, t]) \) in situations not additionally
complicated by varying follow-up times or censoring. Starting from this, the statistical aim of this article has been to establish estimation and comparison of $P(\text{AE} \in [0, t])$ in more complex data situations which are, in particular, characterized by the presence of competing events.

To return to the possible interpretation of Kaplan-Meier under the intervention “do(no censoring)”, we stress that, for example, Kaplan-Meier estimation censoring CEs can not simply be aligned with a “hypothetical estimand” for the inter-current CE. The statistical issue is that more complex causal methodology would be required. The conceptual issue is that hypothetical CE removal may be a mere hypothesis in one case and bear a real life interpretation in another case.

**Supplementary Materials**

A markdown file providing exemplary code to compute all the estimators discussed in this article for a given dataset is available on github: https://github.com/numbersman77/AEprobs. The corresponding output is available as html file: https://numbersman77.github.io/AEprobs/SAVVY_AEprobs.html.

**Disclosure Statement**

KR and TK are employees of F. Hoffmann-La Roche (Basel, Switzerland). VJ and CDB are employees of Novartis Pharma AG (Basel, Switzerland). AA, AB, LE, KK, FL, MT, YZ are employees of Merck KGaA (Darmstadt, Germany), Bayer AG (Wuppertal, Germany), Janssen-Cilag GmbH (Neuss, Germany), Bristol-Myers-Squibb GmbH & Co. KGaA (München, Germany), Pfizer Deutschland (Berlin, Germany), Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim, Germany), Eli Lilly and Company (Indianapolis, USA), respectively. TF has received personal fees for consultancies (including data monitoring committees) from Novartis and Roche, all outside the submitted work. JB has received personal fees for consultancy from Pfizer and Roche, all outside the submitted work. CS has received personal fees for consultancies (including data monitoring committees) from Novartis and Roche, all outside the submitted work. The companies mentioned contributed data to the empirical study. RS has declared no conflict of interest.

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