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Abstract

Objective: To provide Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidance for the consideration of study limitations (risk of bias) due to missing participant outcome data for time-to-event outcomes in intervention studies. Study Design and Setting: We developed this guidance through an iterative process that included membership consultation, feedback, presentation and iterative discussion at meetings of the GRADE Working Group. Results: The GRADE working group has published guidance on how to account for missing participant outcome data in binary and continuous outcomes. When analysing time-to-event outcomes (e.g. overall survival, time-to-treatment failure) data of participants for whom the outcome of interest (e.g. death, relapse) has not been observed are dealt with through censoring. To do so, standard methods require that censored individuals are representative for those remaining in the study. Two types of censoring can be distinguished, end of study censoring and censoring because of missing data, commonly named loss to follow-up censoring. However, both types are not distinguishable with the usual information on censoring available to review authors. Dealing with individuals for whom data is missing during follow-up in the same way as individuals for whom full follow-up is available at the end of the study increases the risk of bias. Considerable differences in the treatment arms in the distribution of censoring over time (early versus late censoring), the overall degree of missing follow-up data and the reasons why individuals were lost to follow-up may reduce the certainty in study results. With often only very limited data available, review and guideline authors are required to make transparent and well-considered judgements when judging risk of bias of individual studies and then come to an overall grading decision for the entire body of evidence. Conclusion: Concern for risk of bias resulting from censoring of participants for whom follow-up data is missing in the underlying studies of a body of evidence can be expressed in the study limitations (risk of bias) domain of the GRADE approach.

Keywords	GRADE; certainty of the evidence; time-to-event outcomes; risk of bias; loss to follow-up; censoring missing data
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Submission Files Included in this PDF

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GRADE_Guidelines - time-to-event_censoring_cover letter.docx [Cover Letter]

GRADE_TTE_guidance_censoring_of_participants_w_missing_data_RESPONSE.docx [Response to Reviewers]

GRADE_TTE_guidance_censoring_of_participants_w_missing_data_TRACK CHANGES.docx [Revised Manuscript with Changes Marked]

GRADE_TTE_guidance_censoring_of_participants_w_missing_data_HIGHLIGHTS.docx [Highlights]

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Figure_1_types_of_censoring.tif [Figure]

Figure_2_KM_curve_1.tif [Figure]

Figure_3_KM_curve_2.tif [Figure]

Appendix-figure_1_original_data_reconstructed.tiff [Figure]

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Figure_3_Martin_RightsLink_Printable_License.pdf [Figure]

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Cologne, January 30th 2020

Dear Prof. Knottnerus,
Dear Prof. Tugwell,

Accompanying this letter, please find our manuscript with the title “GRADE Guideline: Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with missing data in intervention studies” for publication as part of the GRADE Guidelines series in the Journal of Clinical Epidemiology.

The article presents a guidance that aims to assist systematic review and guideline authors with the identification and assement of potiential bias introduced by informative censoring in the analyses of time-to-event outcomes. Furthermore, it discusses the incorporation of the results of such assessments into the GRADE approach. It was developed by the GRADE time-to-event project group and approved by the GRADE working group and the GRADE guidance group.

The guidance builds on previous articles that were developed within the GRADE time-to-event project group and published in the Journal of Clinical Epidemiology. This includes a methodological systematic review where we identified serious diffiuclties of systematic review authors in the calculation and presentation of time-to-event outcomes. Unpublished results have shown that only a minor proportion of authors are aware of potential bias introduced by informative censoring. These findings were confirmed in a survey that authors of this manuscript performed among the editorial straff of multiple Cochrane review groups.
As part of our own daily engagement in systematic reviews as editors, authors, and contributors to Cochrane and the GRADE working group, we have seen the urgent need for a guidance to raise awareness to potential study limitations that are distinct for time-to-event outcomes and their analyes.

We believe that our guidance will be well placed in the Journal of Clinical Epidemiology given its established evidence-based and methodological profile and ensure that our manuscript and the submitted materials have not been published and are not under consideration for publication elsewhere.

Thank you very much for your consideration.
Yours sincerely,

Nicole Skoetz and Marius Goldkuhle

GRADE Guideline 29:

Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with missing data in intervention studies

Response to reviewers

Comments from the editors and reviewers:

-Reviewer 1

The authors provide GRADE guidance for the consideration of study limitations (risk of bias) due to missing participant outcome data for time-to-event outcomes in intervention studies. The article is well written and very clear. I have only one major comment to improve the current manuscript.

> We thank the reviewer for his thoughtful and elaborate comment that substantially improved the manuscript. In order to comply with the comments, we have reconstructed individual participant level data from our example 1 and performed the analyses as suggested by the reviewer.
>
> Furthermore, we have adapted the manuscript on several segments to increase its clarity. All additional changes are marked in the "Revised Manuscript with Changes Marked" file. These changes did neither alter the content nor the structure of the article. We sincerely hope that our additional changes are in line with the peer reviewer's ideas.

The authors often claim that the risk of bias due to missing participant outcome data for time-to-event outcomes in intervention studies can be severe. They discuss two examples. I would recommend to apply the technique by Guyot P et al. (Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012; 12: 9) to one of these examples. With this method, one is able to receive individual data. Then, one could mimic the situation which is discussed here (page 15):

"Where the distribution of individuals lost to follow-up over-time unquestionably differs between the arms, for example a high number of early censoring in one arm versus late censoring in the other arm, this may indicate the dependence of these censoring events. Differences in early censoring are especially relevant here because they can, in most

situations, be more easily associated with missing follow-up data than "end-of study censoring"."

In example 1 (figure 2), I would suggest to classify the early censored data within 7 days (as marked in figure) as "missing participant outcome data". And then apply the procedure as proposed by the authors and provide a demonstration of "5. How censoring participants with missing follow-up data may affect the results of the Study." This would be pragmatic and convincing.

A recent example of this method is also given here: Lambert, J et al. Infectious disease consultation for candidaemia. The Lancet Infectious Diseases, 2020, Volume 20, Issue 2, 164 – 165

> Again, we want to thank the peer reviewer for suggesting the approach, which we gladly followed. Given the clarity of the survival curve for example 1, we were able to reconstruct outcome event and censoring time points directly from the available survival curve. We compared the hazard ratio and confidence intervals resulting from our directly reconstructed dataset with the hazard ratio and confidence intervals calculated for a dataset we reconstructed following the approach by Guyot et al. and found a closer correspondence to the original estimates with our manually extracted data. Furthermore, since the approach by Guyot et al. assumes independent censoring, we found that an extraction where we were able to include the majority of censoring time points without further assumption is preferable for our cause. For these reasons, we finally chose the manually extracted dataset for the imputations suggested by the reviewer. In accordance with the reviewer's suggestion we then imputed events for all participants which were censored prior to seven months in order to illustrate the uncertainty that is added by early censoring to survival analyses. We included a scenario to the manuscript where all participants censored within the first seven months of follow-up experience the event of interest one month after the censoring time-point. We sincerely hope that our approach and the resulting changes to our manuscript comply with the reviewer's ideas.

The following sections have been added to the manuscript and the appendix to comply with the reviewer's suggestions:

5.3. Illustration of the uncertainty introduced through early dependent censoring to comparisons

In order to illustrate the impact of early depended censoring on survival analyses, we reconstructed individual participant data from the analysis of overall survival in a study by Denis et al. (32) (see also section 6.1). In this study example the number of censored participants was different between the groups, particularly in the beginning of follow-up. Given the transparent reporting of outcome and censoring events in the available survival curve (Figure 2), we were able to reconstruct event and censoring time points for the individuals in each group (see Appendix A3). Box 1 provides a detailed description of the study example and Appendix A3 provides a summary of our proceeding to reconstruct survival data. We verified the consistency of our reconstructed dataset with the approach presented by Guyot et al. (33), that allows recreating individual participant level data from published survival curves, and recalculated hazard ratios and Kaplan-Meier survival curves.

To demonstrate the impact of early censoring on results, we considered a hypothetical scenario in which all participants who were censored prior to seven months of follow-up experience the event one month after censoring, i.e. these data are no longer censored but are counted as events. This assumption represents the extreme case of a very large positive correlation between early censoring and the experience of the event of interest.

Appendix A4 figures 1 and 2 show the Kaplan-Meier survival curves for the reconstructed dataset and the hypothetical scenario. The original hazard ratio resulting from the authors' analysis is 0.32 (95% confidence interval (CI) 0.15 to 0.67). The hazard ratio resulting for the data we reconstructed from the published survival curve was 0.32 (95% CI 0.15 to 0.65) showing that our reconstructed data set is nearly identical to the original one. The original analysis indicates a substantial

survival advantage for participants in the experimental arm under the questionable assumption of independent censoring.

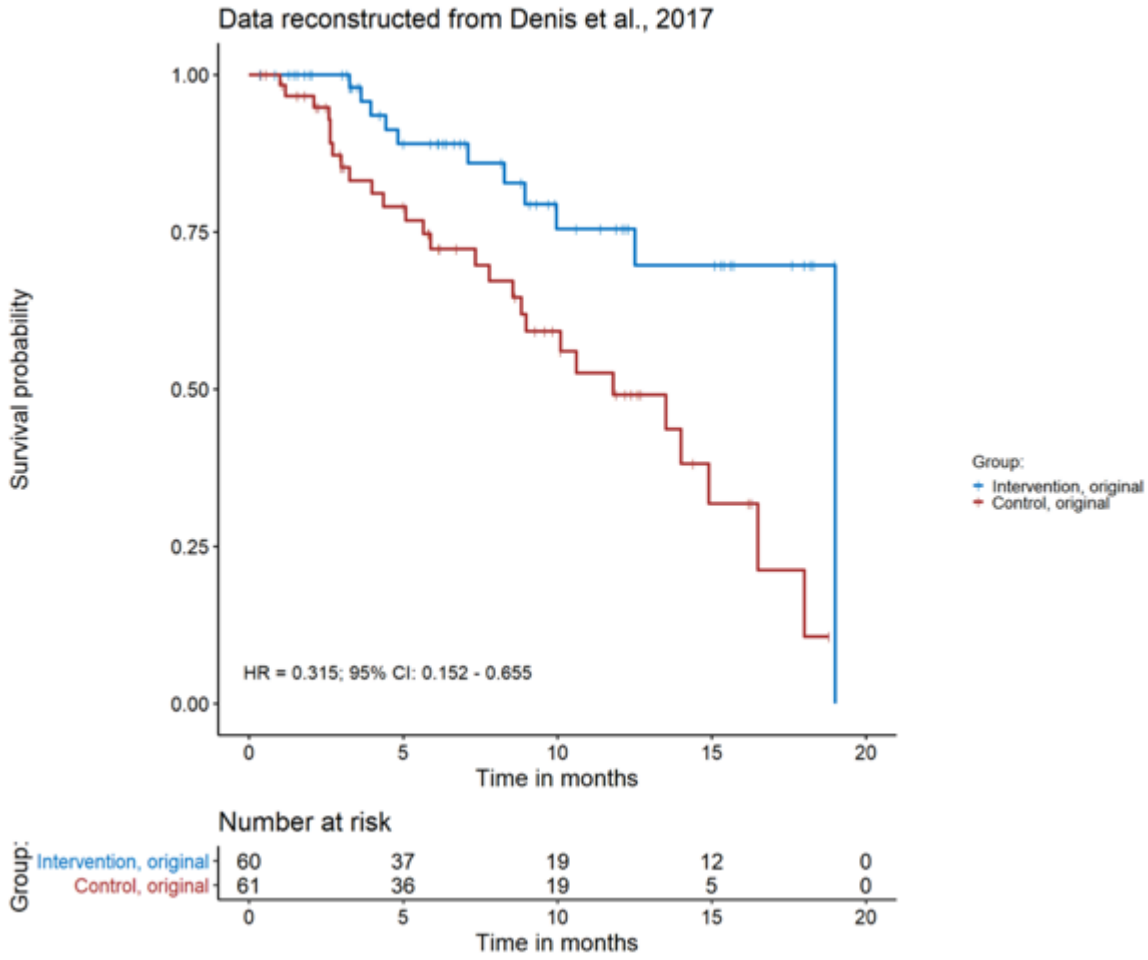
Appendix A4 figures 1 and 2 illustrate that a positive correlation between early censoring and the experience of the event of interest leads to an overestimation of the survival probability in both study arms. As more participants in the intervention arm are censored prior to seven months compared to the control arm (26 participants versus 19 participants), the hazard ratio increases to 0.69 (95% CI 0.44 to 1.07) in the hypothetical scenario. This illustrates that the effect estimation is biased if there is a positive correlation between early censoring and the experience of the event of interest and additionally a higher proportion of censored participants in the intervention arm. Therefore, there is a loss of certainty in the results of survival analyses in the case of substantial censoring, particularly throughout the early periods of follow-up and where no information is available on the reasons for censoring.

Appendix A3. Reconstruction of survival data to illustrate the impact of early dependent censoring

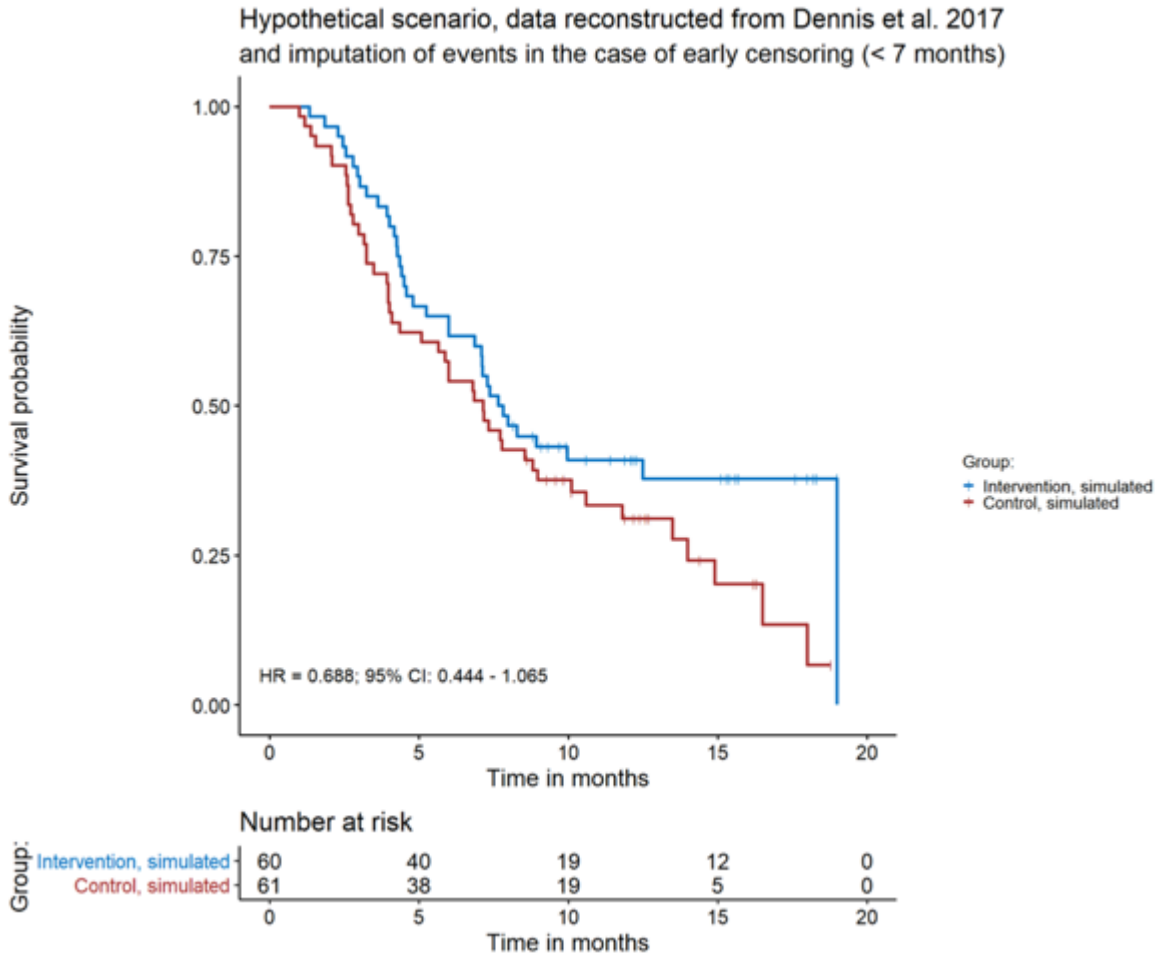
To illustrate the impact of early dependent censoring on comparisons, we reconstructed individual participant data from the survival curves published for the analysis of overall survival in the article by Denis et al. (32). The study shows an unbalanced number of censored participants particularly during early follow-up, with more censored participants in the intervention arm compared to the control arm. Given the clear reporting in the survival curves, we were able to reconstruct outcome event and censoring time points for the individuals in each of the compared groups. We verified our proceeding with the algorithm presented Guyot et al. (33) that allows to reconstruct individual participant level data from published survival curves. The algorithm attributes a constant rate of censoring to intervals in between outcome events and time-points for which a number of individuals at risk is reported. It therefore works optimal assuming independent censoring. Under the objective of our illustration, we decided not to directly use the dataset resulting from the algorithm

proposed by Guyot and colleagues but to work with individual patient data that we reconstructed directly from the published survival curve. Nevertheless, we used the data set produced under application of the algorithm to confirm the consistency of our manually extracted data by comparing the data points retrieved through both approaches.

We extracted data with the software DigitizeIt (www.digitizeit.de), which allows to assign each point on the survival curve a corresponding time-point on the x-axis. We marked all declines of the curve as outcome event and all crosses as censoring time-points. The reported curve for the experimental arm was unclear for two censoring events in the first interval (0 to 5 months) and the last interval (over 15 months) respectively, which were not directly identifiable on the curve, but must have occurred in these intervals as indicated by the number of individuals at risk. Similarly, for the curve representing survival in the control arm, two censoring events were not identifiable within the first interval (0 to 5 months). For all scenarios we assumed the missing censoring events to have happened on the last possible time-point of this interval (4.99 and 18.99 months). In the so retrieved dataset, we modified the survival data of participants censored within the first seven months of follow-up to illustrate the impact of early dependent censoring. We present a hypothetical scenario where all participants censored prior to seven months of follow-up experience the outcome event one month after the original censoring. Subsequently, we calculated hazard ratios with the Cox proportional hazards model and present Kaplan-Meier survival curves. All statistical analyses were performed using the software R (56). We want to point out that our imputation does not claim to compare a difference in treatment effects, but to illustrate the loss of certainty that is introduced to survival analyses through a high degree of censoring particularly during the early period of follow-up.



Appendix-figure 1: Kaplan-Meier survival curves calculated from the individual participant level data reconstructed from the analysis of overall survival in Denis et al. (32). (figures in higher resolution are included in the submitted manuscript file)



Appendix-figure 2: Kaplan-Meier survival curve calculated from the individual participant level data reconstructed from the analysis of overall survival in Denis et al. (32). Participants who were censored prior to seven months of follow-up in both study arms were set to experience the outcome event one month after original censoring. (figures in higher resolution are included in the submitted manuscript file)

GRADE ~~Guideline~~guidelines:

29. Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with missing data in intervention studies

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Abstract

Objective: To provide Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidance for the consideration of study limitations (risk of bias) due to missing participant outcome data for time-to-event outcomes in intervention studies.

Study Design and Setting: We developed this guidance through an iterative process that included membership consultation, feedback, presentation and iterative discussion at meetings of the GRADE Working Group.

Results: The GRADE working group has published guidance on how to account for missing participant outcome data in binary and continuous outcomes. When analysing time-to-event outcomes (e.g. overall survival, time-to-treatment failure) data of participants for whom the outcome of interest (e.g. death, relapse) has not been observed are dealt with through censoring. To do so, standard methods require that censored individuals are representative for those remaining in the study. Two types of censoring can be distinguished, end of study censoring and censoring because of missing data, commonly named loss to follow-up censoring. However, both types are not distinguishable with the usual information on censoring available to review authors. Dealing with individuals for whom data is missing during follow-up in the same way as individuals for whom full follow-up is available at the end of the study increases the risk of bias. Considerable differences in the treatment arms in the distribution of censoring over time (early versus late censoring), the overall degree of missing follow-up data and the reasons why individuals were lost to follow-up may reduce the certainty in study results. With often only very limited data available, review and guideline authors are required to make transparent and well-considered judgements when judging risk of bias of individual studies and then come to an overall grading decision for the entire body of evidence.

Conclusion: Concern for risk of bias resulting from censoring of participants for whom follow-up data is missing in the underlying studies of a body of evidence can be expressed in the study limitations (risk of bias) domain of the GRADE approach.

Keywords

GRADE; Certainty of the evidence; Time-to-event outcomes; Survival analysis; Risk of bias; Loss to follow-up; Censoring missing data.

What is new

Key findings

- Analysis methods for time-to-event outcomes deal with participants for whom outcome data is unavailable through censoring. Two types of censoring, end of study censoring and censoring because of missing data (commonly named loss to follow-up censoring), have to be differentiated.
- Censoring of individuals with missing follow-up data ~~may~~is likely to violate the assumption of independence of censoring and increases the risk ~~for~~of biased results.
- The magnitude of bias resulting from censoring of participants with missing data depends on several factors. An increasing degree of dependent censored observations and difference among the study arms, increases the risk of ~~biased results~~bias.

What are the implications and what should be changed?

- Often ~~the~~, reasons why individuals in studies were censored and the time-points of censoring are ~~not available~~unavailable to systematic review and guideline authors. ~~Systematic review and guideline authors~~ who therefore have to make risk of bias judgements for primary studies based on the distribution of censoring over time or the degree ~~and reasons~~of missing participant follow-up data ~~is missing~~.
- Systematic review and guideline authors need to make GRADE judgements across the body of evidence for study limitations resulting from censoring of participants with missing data considering all available information, including the possibility of carrying out sensitivity ~~analyses~~analysis by ~~temporarily removing studies with~~assessing whether studies at high risk of bias or studies ~~where~~in which there are ~~some~~ concerns yield different results.

1. Introduction:

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group has defined domains that can limit the certainty in a body of evidence (1-6). Within its study limitations domain (i.e., risk of bias), the GRADE approach has issued guidance on how to account for missing participant outcome data for binary and continuous outcomes (6, 7). That guidance proposes conducting sensitivity meta-analyses making assumptions about the outcomes of participants with missing data, to test the robustness of the findings of the primary meta-analysis (7, 8).

~~While~~Although the basic principles for ~~the assessment of a~~assessing risk of bias associated with missing participant outcome data in binary outcome analysis ~~are applicable~~also apply to time-to-event analysis ~~as well~~, there are ~~certain conceptual discrepancies that result in a different assessment and detection of a potential bias in~~issues uniquely applicable to time-to-event outcomes. In contrast to binary data analysis, time-to-event studies, which assess not only whether an event of interest occurs~~,~~ but also ~~the time taken for that event to occur~~when it occurs, typically follow patients for varying periods of time. Because time-to-event analyses ~~allow to~~ include data from individuals with variable lengths of follow-up, those for whom follow-up data becomes absent during the study interval are typically treated in the same way as those with regular follow-up until the end of the analysis (i.e. they provided complete data). Therefore, we here refer to missing follow-up data to ~~describe that~~characterize the situation when information for an individual becomes absent at a time~~ ~~-point within the intended and pre-specified observation period. This article discusses GRADE rating of study limitations associated with missing follow-up data when dealing with time-to-event analysis.

2. Background

2.1. Time-to-event analysis and censoring

Time-to-event analysis is also often referred to as survival analysis, in which the "survival time" describes the time until an event such as death occurs. The most prominent methods to analyse time-to-event outcomes include Kaplan-Meier curves along with the log-rank test and the Cox proportional hazards regression model (9, 10). Time-to-event outcomes are often described by survival rates, defined as the probability that an individual will not have experienced an event (e.g. "survived") up to a certain time point, or hazard rates, which can be interpreted as instantaneous failure rates, meaning an individual's likelihood of experiencing an event (e.g. "death") at a certain time point given that the event has not occurred up to this time point.

The most prominently applied relative effect measure is the hazard ratio, which is the ratio of hazards between two groups. It is commonly obtained from the Cox proportional hazards regression model, which adjusts for relevant covariates and confounders. ~~A univariate~~An unadjusted hazard ratio can also be derived indirectly using other analytical techniques, like the Kaplan-Meier method or the log-rank test (10, 11).

A core feature of time-to-event analysis is the consideration of "censoring" which occurs when ~~a particular patient completes his/her~~patients complete their follow-up period without having experienced the event of interest. Censored observations are included in analyses to optimize the efficiency that time-to-event analysis provides over ~~simple~~ binary data analysis ~~(12)~~(12). If the time to an event and censoring are not included in the calculation of the (log) hazard ratio, it equals the (log) relative risk.

To include censored observations in time-to-event analyses, general methods of survival analysis require an assumption of non-informative and independent censoring. Violations of this assumption introduce risk of bias. ~~For interested readers we provide~~Appendix A1 provides a short review of the definition of non-informative censoring and its relation to independent censoring ~~in the appendix (Appendix A.1).~~. In accordance with established

training resources for time-to-event analysts ~~(13)~~(13), we will use the concept of independent and dependent censoring to describe situations under which censoring may lead to distortion of analysis results.

Independent censoring ~~assumes that~~occurs when censored participants and those remaining under observation have the same probability of experiencing the event of interest, as if the censored individuals were "randomly drawn" during the course of follow-up ~~(13, 14)~~(13, 14). An example for censoring mechanisms independent from the survival time (and also non-informative) is administrational closure of a study. Differences in the observation times of participants then are solely a result of the staggered study entry times and the fixed study closure time ~~as visible in~~ (figure 1) (13, 15).

Figure 1: Types of censoring: For participant 1 the occurrence of the outcome event is observable. Participants 2 and 3 are censored because of the administrational closure of the study. The variation in their duration of follow-up and the differing censoring time~~-~~ points result from the staggered recruiting phase of the study. Participant 4 is lost from the observation before the administrational ending of the study and censored for a different reason.

When individuals are censored because of missing follow-up data, this assumption is likely to be violated. Examples of such situations which may bias results include:

- Participants withdraw consent due to physical or mental side effects of an intervention;
- Participants are withdrawn from the observation and censored following switching treatment as a result of progressive disease;
- Investigators fail to locate study participants.

2.2. Reporting ~~of~~ time-to-event data and censoring in primary studies

~~The overall~~Flaws in reporting ~~of~~ time-to-event analyses may ~~be particularly flawed, which complicates~~complicate their adequate appraisal by systematic review authors including ~~the assessment of a~~assessing risk of bias resulting from censoring of individuals with missing follow-up data (16-19). ~~Insufficient~~Suboptimal reporting ~~relates~~includes but is not limited to outcome definitions, the extent and duration of follow-up, precision measures such as the number of participants at risk at certain time points, and details of statistical model building. ~~Precise definitions of~~Authors often fail to precisely define censoring mechanisms ~~and~~, omit the number of censored participants ~~are likewise often omitted and it is often not known~~, and fail to state why individual study participants were censored (16-19).

~~Other methodological research has shown that even studies~~Studies published in leading medical journals are not immune to reporting ~~errors as~~limitations: for instance, one methodological study found inconsistency between the number of participants reported in the text/tables as 'lost before the end of the study' and those assessed from Kaplan-Meier curves ~~(20)~~(20). Prior work has specified minimal reporting items for time-to-event analyses and survival curves (17, 18, 21, 22). Appendix ~~A.2~~A2 outlines ~~specific~~ reporting requirements that allow systematic review and guideline authors to assess ~~the suitability~~possible risk of bias resulting from informative censoring.

3. Methods

This guidance was developed by members of the GRADE working group. They included methodologists, clinical epidemiologists and biostatisticians with experience in systematic reviews and/or guideline development. The group developed the guidance based on iterative discussions by email, on conference calls and at a GRADE working group meeting in Manchester, UK, in October 2018. The final draft of the guidance was presented during the GRADE working group meeting in Hamilton in June 2019 and was approved following the group's standard approval process.

4. Scope

This guidance aims to support systematic review and guideline authors in the assessment of ~~the~~ study limitations (risk of bias) due to missing follow-up data for time-to-event outcomes in intervention studies. ~~Therefore, we here~~We describe an approach ~~to the issue from~~that takes a systematic reviewer perspective ~~that relies~~relying on information that one could typically obtain from only the trial report and its accompanying records ~~only~~. To comply with well-known resources for systematic review authors to assess the risk of bias in individual studies and with reference to previous GRADE guidance for rating the certainty of the evidence with focus on study limitations (risk of bias), we refer to missing follow-up data as the unavailability of follow-up data for individuals during the study interval (6, 23, 24). This includes all types of missing data and situations in which the outcome status of study participants becomes unavailable during the study period irrespective of the reason (e.g., patients not available or inappropriately excluded) ~~(24, 25).~~(25, 26).

The concerning risk of bias arises, for example, when investigators censor individuals for whom data is missing ~~dependently~~ and include them in the computation of effect measures in the same way as participants with independent censoring (e.g., those whose follow-up ended appropriately at the end of the data collection period). Systematic review and guideline authors seldom have ~~the possibility of knowing~~information regarding the reasons for censoring for each participant in every eligible study. Consistent with well-known instructions for systematic review authors, we therefore provide guidance that is primarily aimed at detecting a potential bias in individual studies ~~(23). Judgements on study level are then used to inform the risk of bias assessment for an overall body of evidence for one specific~~(23, 24). Judgements on study level then inform the risk of bias assessment for an overall body of evidence separately for each outcome.

In accordance with ~~the~~ previous GRADE guideline for missing participant outcome data for binary and continuous outcomes, we ~~give~~provide guidance for systematic review and guideline authors who assess comparative clinical trials based on aggregated data ~~(7)~~(7). ~~Similar to this guideline we~~We differentiate the issue of adequately accounting for loss to follow-up from that of adherence to the intention to treat (ITT) principle, which relates to analyzing study participants with known data in the groups to which they were allocated (7, ~~26~~27).

We focus on risk of bias in the outputs of the "standard" methods of survival analysis and the Cox model hazard ratio as the single comparative relative effect size measure (16-19). Within the context of this guidance we assume that the primary study investigators and subsequently the authors of meta-analyses have chosen the correct method for analysing competing events for the intended research question.

5. How censoring participants with missing follow-up data may affect the results of the study

5.1. Censoring of participants leading to over- and under estimation of the survival probability

Similar to binary outcome analysis, the distortion of the outcome probability of the group under study depends on the outcome probability of those for whom data is missing. ~~In case data for~~When individuals who are more likely to experience the (negative) event of interest (e.g~~.~~,. death) are also more likely to be missing (positive correlation between the occurrence of the event and missingness of data), e.g. because they are more likely to be lost to follow-up, the true survival probability of a study group will inevitably be overestimated (12, 23). This means that the corresponding true risk of the (negative) event occurrence will be underestimated. Such an association may occur, for example, if participants with treatment-

related adverse events are no longer followed-up and are censored at the time of loss to follow-up.

On the other hand, in case of a negative correlation between the occurrence of the event and the probability of being censored, the true survival probability for a study group may be underestimated (and the corresponding true event risk overestimated) ~~(23)~~(23). ~~An~~For example ~~for this situation might happen~~, underestimation of the event-free survival probability will occur if ~~time-to-treatment failure is assessed~~ in a study comparing the impact of psychiatric interventions ~~and~~ on time-to-treatment failure participants in one arm ~~profit~~benefit so substantially that they fail to return and are therefore lost from the study.

5.2. Effect of censoring of participants with missing follow-up data on the hazard ratio

Factors that might result in a biased hazard ratio are the frequency of the outcome event of interest, the treatment effect in terms of the distribution of the outcome event between the study arms, and the frequency and distribution of censoring because of missing data (e.g. effect of intervention on the frequency of loss to follow-up). As the impact of dependent censoring on the hazard ratio cannot be determined based on the observed data (because the true outcome of censored individuals is not observable~~))~~), quantifications of the associated bias are difficult ~~(15)~~(15).

Nevertheless, the potential bias resulting from censoring of missing follow-up data can be substantial, especially when the outcome probability for those ~~for whom data is~~with missing data is considerably increased. In studies evaluating antiretroviral treatment programmes for HIV in settings with limited resources ~~the~~, loss to follow-up rates are ~~considerably~~typically high. Performing a systematic review and meta-analysis of studies ~~where~~of such programmes in which individuals lost to follow-up ~~in studies evaluating such programs~~ were actively traced~~, for example~~ by telephone calls or social networks, Brinkhof et al. ~~(27) found that the~~

~~mortality among patients lost to follow-up in such studies was considerably increased as well. In a subsequent study Brinkhof et al.~~ (28) found that the mortality among patients lost to follow-up was considerably increased. In a subsequent study, Brinkhof et al. (~~28~~29) then used the mortality estimates from their previous systematic review to impute representative mortality data for individuals lost to follow-up in an evaluation of five antiretroviral treatment programmes in sub-Saharan Africa~~. This study~~ and found that survival analysis ignoring increased mortality among participants lost to follow-up greatly underestimated overall mortality and leads to a biased ~~the~~ evaluation of the ~~programme~~programmes.

In most situations, however, the reasons for censoring and the associated prognosis ~~to experience the event of interest will not~~will be ~~available~~unavailable to systematic review and guideline authors. Therefore, similar to assessments of a risk of bias in binary data analysis, one has to rely on the simplified principle~~,~~ that the higher the frequency of dependent censoring of participants ~~for whom (follow-up) data is missing~~ in relation to the event rates and the greater the difference between the groups, the higher the potential for biased results (6). Simulations of single arm studies show that the degree of bias is more strongly influenced by the overall proportion of participants that are censored with an increased/decreased risk ~~to experience the outcome, and thus dependently, rather than the differences in the hazard among study participants who are remaining at risk until the end of the observation period (29). In between-group comparisons~~of experiencing the outcome, rather than the difference in the hazard of study participants who are remaining at risk until the end of the observation period and those who are censored (30). Between-group comparison simulations show that the degree of bias in settings with proportional hazards in Cox models is mainly enhanced by the overall degree and the early time~~-~~ points of censoring for any reason (~~30~~31).

5.3. Illustration of the uncertainty introduced through early dependent censoring to comparisons

In order to illustrate the impact of early depended censoring on survival analyses, we reconstructed individual participant data from the analysis of overall survival in a study by Denis et al. (32) (see also section 6.1). In this study example, the number of censored participants was different between the groups, particularly in the beginning of follow-up. Given the transparent reporting of outcome and censoring events in the available survival curve (Figure 2), we were able to reconstruct event and censoring time points for the individuals in each group (see Appendix A3). Box 1 provides a detailed description of the study example and Appendix A3 provides a summary of our proceeding to reconstruct survival data. We verified the consistency of our reconstructed dataset with the approach presented by Guyot et al. (33), that allows recreating individual participant level data from published survival curves by assuming constant censoring within a given time interval, and recalculated hazard ratios and Kaplan-Meier survival curves.

To demonstrate the impact of early censoring on results, we considered a hypothetical scenario in which all participants who were censored prior to seven months of follow-up experience the event one month after censoring, i.e. these data are no longer censored but are counted as events. This assumption represents the extreme case of a very large positive correlation between early censoring and the experience of the event of interest.

Appendix A4 figures 1 and 2 show the Kaplan-Meier survival curves for the reconstructed dataset and the hypothetical scenario. The original hazard ratio resulting from the authors' analysis is 0.32 (95% confidence interval (CI) 0.15 to 0.67). The hazard ratio resulting for the data we reconstructed from the published survival curve was 0.32 (95% CI 0.15 to 0.65) showing that our reconstructed data set is nearly identical to the original one. The original analysis indicates a substantial survival advantage for participants in the experimental arm under the questionable assumption of independent censoring.

Appendix A4 figures 1 and 2 illustrate that a positive correlation between early censoring and the experience of the event of interest leads to an overestimation of the survival probability in both study arms. As more participants in the intervention arm are censored prior to seven months compared to the control arm (26 participants versus 19 participants), the hazard ratio increases to 0.69 (95% CI 0.44 to 1.07) in the hypothetical scenario. This illustrates that the effect estimation is biased if there is a positive correlation between early censoring and the experience of the event of interest and additionally a higher proportion of censored participants in the intervention arm. Therefore, there is a loss of certainty in the results of survival analyses in the case of substantial censoring, particularly throughout the early periods of follow-up and where no information is available on the reasons for censoring.

6. Suggestions to assess risk of bias resulting from censoring in an individual study

6.1. Identifying risk of bias due to censoring in individual studies

To appropriately assess the potential bias for study results emerging from dependent censoring of participants for whom follow-up data is missing, reasons why individual participants were censored for each outcome would be ~~informative. Where~~helpful. When information ~~on~~regarding the number of censored individuals with reasons together with the time- point of censoring ~~is~~are available, imputation procedures based on assumptions, similar to those described in the GRADE guidance paper for missing outcome data within binary data analysis, could be applied to assess the robustness of effect measures to loss to follow-up ~~(7)~~(7).

Unfortunately, it is unlikely that review authors will be able to obtain data on the reasons and time~~-points for censoring for study participants and the reporting of information on missing data such as the mechanisms of missingness in RCTs is shown to be flawed (31). Before assessing a potential bias, it is recommended to gather all available information on possible~~

~~mechanisms for censoring, occasionally from the primary study investigators themselves.~~ points for censoring for study participants and the reporting of information on missing data (34). Nevertheless, before assessing a potential bias, gathering all available information on possible mechanisms for censoring, if possible from the primary study investigators themselves, is likely to be helpful.

For an informed judgement of risk of bias resulting from censoring of participants because of missing follow-up data, both the degree and the distribution of censoring among the study groups over time should be available. In randomized trials with a valid randomization process, censoring events resulting from treatment independent covariates (independent censoring) should have a similar distribution over time in both treatment arms. ~~Where~~An unequivocal difference in the distribution of individuals lost to follow-up over-time ~~unquestionably differs between the arms~~, for example a high number of early censoring in one arm versus late censoring in the other ~~arm, this may~~, is likely to indicate ~~the~~ dependence of these censoring events.

Differences in early censoring are especially relevant ~~here~~ because they can~~, in most situations,~~ be more easily associated with missing follow-up data than "end-of study censoring". In the absence of individual patient data, investigators ~~may~~will need to rely on information about the study participants throughout the course of the study that is available from reports. Most informative are survival curves and the number of reported individuals at risk to experience the outcome event across the study period.

It is good practice, even though not consistently done, to indicate in the survival curves the time points ~~where~~at which individuals were censored ~~in the survival curves~~ (16, 22). This is often done by study authors by marking censoring time~~-~~ points on the survival curves, e.g. as vertical lines, or as number of participants censored between given time points displayed along the number of participants at risk for these time points. This information then allows an

assessment of whether censoring happened early or late throughout the observation period and to assess differences in this distribution between study arms. ~~For~~

Figure 2 presents an example ~~please see figure 2 where~~in which considerably more participants are censored in the intervention arm during the first months of the study as indicated by the vertical lines crossing the survival curves of the treatment arms. Box 1 presents a detailed description of the example~~.~~ (see also section 5.3).

Figure 2: Kaplan-Meier curve for the outcome overall survival from the study Denis et al (32). The vertical lines crossing the curves mark censored events. The elliptical form indicates that the number of early censored individuals is higher in the experimental arm compared to the control arm. The rectangular form shows that the number of participants at risk to experience the event for certain time points is reported below the curves for each study arm and are similar for both groups at 5 and 10 months of follow-up, despite a more favourable survival probability in the experimental arm. (32). Adapted from "Randomized Trial Comparing a Web-Mediated Follow-up With Routine Surveillance in Lung Cancer Patients" by Denis et al., 2017, Journal of the National Cancer Institute, 109(9), p. 6. Copyright 2017 by Oxford University Press. Adapted with permission.

Box 1: example 1: Denis et al. (32):

In a randomized trial comparing a web mediated follow-up strategy with routine surveillance for participants suffering from lung cancer, *the primary end point was overall survival (OS) defined from random assignment to death or to the last assessment of patient's status when the patient was censored.* A hazard ratio between groups was calculated using a Cox proportional hazards model. A total of 133 participants were randomized, and after exclusions of participants found after randomization to be ineligible, 60 and 61 participants were included in the modified intention-to-treat analyses in the intervention and the control arms respectively. The number of reported deaths per arm was 11 versus 26 and the number of relapses 34 versus 36. The study was closed early at an interim analysis by recommendation of the independent data monitoring board.

The degree of censoring was not reported throughout the study publication. However, an assessment of the presented survival curve (figure 2) shows substantially more censoring of participants in the experimental arm, particularly during early follow-up. Despite the visible survival benefits and the statistically significant hazard ratio in favour of the intervention group, the number of patients at risk is similar for both treatment arms at months 5 and 10. This suggests that a similar number of individuals who died in the control arm must have been censored in the intervention arm. This severe imbalance, despite randomization of the participants, introduces high risk to bias due to censoring of participants with missing follow-up data. In a hypothetical scenario, where individuals lost to follow-up are more likely than those who were not lost to follow up to die shortly after censoring, the survival benefit shown by the hazard ratio in the study is likely inflated and possibly inexistent. Here we would suspect a high risk of bias and, in a situation where only one study is included in the body of evidence or other included studies have similar imbalances , we would consider rating down due to study limitations for overall survival.

If only a survival curve and the number at risk for particular time- points are available and direct information on the distribution of censoring is not presented (e.g. no censoring marks on the curves) or assessable (e.g. single marks for censoring not distinguishable on the curve due to high degree of censoring), it is sometimes possible to estimate the degree of participants censored for a certain time point from the given information by comparing the visible survival benefits in the curves and the number at risk for the reported time points (20).(20). In figure 2, for example, at five and ten months of follow-up, the same or a similar number of participants at risk are reported in both treatment arms (5 months: 37 versus 36; 10 months: 19 versus 19). Comparing this information with the visible differences in survival probabilities in the curves, noticeably favoring the experimental arm, allows the conclusion that substantially more participants have been lost to follow-up in the experimental than in the control arm. This is because after five and ten months of follow-up, approximately the same number of individuals that experienced the event (death) in the control arm must have been lost to follow-up in the experimental arm. ForBox 1 presents a detailed description of the example see box 1.

In situations whereWhen authors report the number of individuals for several time- points is reported together with the survival curves, established methods to reconstruct summary time-to-event data also allow to approximateapproximations of the number of individuals censored within certain time intervals (11, 3335). Where. When authors provide the number of individuals at risk is given for a sufficient number of time points in the primary study report, such procedures may also be conclusively used and can support an assessment of the distribution of censoring in the study arms over time. Considerable variation in the overall difference and a difference in the distribution in terms of early versus late censoring between arms can then confirm a high risk of bias and a critical limitation to the effect estimator of a time-to-event outcome of an individual study. We encourage review and allowing guideline

authors to carefully and transparently justify their decisions. ~~An~~Box 2 and figure 3 provide an additional illustrative example~~ and the associated survival curve are given in box 2 and figure 3.~~ .

Figure 3: Kaplan-Meier curve for the outcome invasive disease-free survival from the study Martin et al (~~34~~36) (see Box 2). The number of individuals censored up to the respective time-points of follow-up are reported along the number of individuals at risk to experience the outcome at this time point. The number of censored individuals is substantially higher in the neratinib arm throughout the follow-up period. The number of individuals at risk (excluding those who experienced the event or were censored) in the placebo arm is substantially higher than the number of individuals at risk in the neratinib arm. Nonetheless, the neratinib arm is shown to be beneficial by the HR (<1). Adapted from "Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial" by Martin et al., 2017, The Lancet Oncology, 18(12), p. 1694. Copyright 2017 by Elsevier. Reprinted with permission.

Box 2: Example 2: Martin et al. (~~34~~36)

The randomised, double blind, placebo-controlled ExteNET study compared adjuvant neratinib and placebo in patients with HER2-positive breast cancer after standard locoregional treatment, trastuzumab, and chemotherapy. The five-year analysis of the primary endpoint invasive disease-free survival which was defined as time from randomisation to first occurrence of invasive disease and recurrences or all cause death showed a significant benefit for the intervention. Hazard ratios were derived from a Cox proportional hazards model and individuals were censored for the primary end-point when they did not re-consent for additional follow-up at the date of their last physical examination, if disease recurrence did not occur within the 2 years of follow-up in this study or if they did not have a disease-free survival event within the relevant time-frame (5.6 months). In each treatment arm 1420 participants were randomized and included in the intention-to-treat analysis.

While the study publication did not specify the proportion of censored individuals and the respective reasons for censoring, the survival curve for the primary outcome (figure 3) shows severe imbalances in the number of censored individuals. The number of censored participants between the time-points is reported together with the number of participants at risk to experience the event for certain time points below the curves and for each study arm respectively. The percentages present the proportion of participants who are event-free for the respective time-points. The number of censored individuals in the experimental arm is substantially higher than in the placebo arm, especially in the early observational period. This results in a lower number of individuals is at risk, excluding those who have experienced the event of interest or were censored, at any time point thereafter in the favored experimental arm. Assessing the times for the beginning of accrual (July 9, 2009), the ending of accrual (October 24, 2011) and the end of the five year follow-up (March 1, 2017) one can be certain that the early censoring events were due to loss to follow-up, and not to "*end-of-follow-up*", because the minimum complete observation time was at least 5.4 years (from Oct 24, 2011 - March 1, 2017). Given the information outlined above, a judgement of high risk of bias for this study due to censoring of participants because of missing follow-up data is justifiable. In a hypothetical situation, where a body of evidence for a certain outcome consists solely of this example, we would consider rating down for study limitations.

6.2 What to do when individual studies do not provide the distribution of censoring over time ~~is not known in individual studies~~

Review authors often find themselves in situations ~~where the~~in which they must assess potential risk of bias through censoring of participants because of missing follow-up data ~~must be made~~ based on only very limited information (16-19). When the distribution of censoring over time in individual studies is not clear, but there are serious imbalances in the number of individuals for whom data is missing (e.g. individuals lost to follow-up summarized in a study flow-diagram) in the study arms or the reasons for the absence of follow-up data differ among arms (e.g. provided in a study flow-diagram), we suggest, in accordance with the Risk of Bias 2.0 tool, concern for a high risk of bias ("probably yes") for an individual study outcome~~.~~ (23, 24). To derive a decision, the instructions for risk of bias due to loss to follow-up in binary data analysis from the GRADE guideline on study limitations (risk of bias) should be considered (6). For time-to-event analyses from individual studies that do not report information regarding the distribution of censoring over time, its degree, and reasons, we suggest ~~to~~ explicitly ~~state~~stating that a judgement was not possible because the required information was absent.

6.3. Individual participant data would be desirable to assess the risk of bias

Within-study sensitivity analyses for censoring, such as best/worst-case scenarios and other imputation procedures, require individual participant data. If data on individual failure and censoring times and reasons are available, individual patient data meta-analyses for time-to-event outcomes would allow for a more elaborate assessment of the sensitivity of results to missing data issues. ~~So, for~~

For example, such analyses may be possible when data for individuals lost to follow-up can be imputed based on plausible assumptions for individuals for whom data is missing ~~(7)~~(7).

Significant changes in the estimates could then lead to decisions to rate down the certainty of evidence. Available statistical tests for the independence assumption also require additional data ~~(35). However, they~~(37) and are usually impossible to perform, when conducting a standard systematic review. Simple quantification measures for the completeness of follow-up in survival analyses also exist, but are usually not included in study reports.

6.4. Rating the risk of bias resulting from censoring of participants because of missing follow-up data and deriving an overall judgement for an individual study

Indicators	**Considerations for the risk of bias through censoring of participants with missing follow-up data assessment in individual studies**
Time point of censoring considerably different in both arms (early versus late censoring)	Critical concern for high risk of bias as early censoring is more likely to be due to missing data (e.g. loss to follow-up) as opposed to end of study censoring.
Censoring degree among arms diverging (Overall number of censored patients reported, but distribution over time not known)	~~A high risk of bias is more likely as a different degree and differing reasons for censoring are contradicting with a valid randomization process and thus imply that missingness may depend on the received intervention (23)~~ A high risk of bias is more likely as a different degree and differing reasons for censoring are contradicting with a valid randomization process and thus imply that missingness may depend on the received intervention (23)
If reasons for censoring are reported (e.g. summarised in a study flow diagram): Different reasons why data for individuals was missing (e.g. were lost to follow-up) and different degree between arms.	

Table 1: Decision support for judgements of a risk of bias though inappropriate censoring in an individual study

A judgment on the risk of bias associated with missing data for time-to-event outcomes within GRADE should be based on the principles outlined in previous guidelines for rating the quality of the evidence addressing study limitations (GRADE guideline 4), particularly with regard to the risk of bias associated with missing participant outcome data in a body of

evidence for both binary and continuous outcomes (GRADE guideline 17) (6, 7). The assessment criteria specified in this guidance allow ~~to integrate~~integration of time-to-event specific differences (e.g. censoring of individuals for whom data is missing and those who ended follow-up appropriately) and to support a decision on the presence of a risk of bias.

Table 1 provides considerations that reviewers can ~~be used~~use to estimate the extent of the risk of bias introduced by censoring of participants because of missing data in an individual study. To derive a decision on the impact of missing follow-up data on the overall risk of bias for an outcome in an individual study reviewers must consider all other potential study limitations~~, for example the~~ including lack of allocation concealment~~,~~ or the lack of blinding ~~and selective outcome reporting, within a body of evidence for a particular time-to-event outcome must be considered. A rating can then be made~~ following ~~the~~which they can judge risk of bias can following usual GRADE principles ~~of the GRADE approach~~ (6). ~~Accordingly, a~~A crucial limitation in one risk of bias criterion, which may include substantial differences in the degree and distribution in the amount of early and late censoring, or several criteria with some limitations, which may include considerable difference in the overall degree of censoring, ~~that are~~may be sufficient to ~~lower ones confidence in an effect would allow~~merit a judgement of a serious limitation. ~~In case there is a~~A crucial limitation for one or more criteria ~~which are sufficient to substantially lower the confidence in an effect estimate, this~~ would result in a judgement of a very serious limitation for the outcome of an individual study (6). These judgements should then inform an overall rating of the GRADE risk of bias domain for a body of evidence.

7. Making an overall judgement for a body of evidence

To derive a judgment for the risk of bias domain across studies in a body of evidence, reviewers should apply the usual GRADE principles for study imitations ~~have to be applied~~ (6): no serious limitations (do not rate down), if ~~the outweighing information is contributed~~

~~by~~evidence comes largely from studies ~~of~~at low risk of bias; serious limitations (rate down one level), if ~~the outweighing information is contributed by~~evidence comes largely from studies at ~~moderate~~high risk of bias; very serious limitations (rate down two levels), if ~~the outweighing information contributed by~~evidence comes largely from studies at very high risk of bias. ~~Depending on the individual situations one may also consider to exclude~~

If studies ~~with very serious limitations from the body~~vary in their risk of bias, and results differ in high and low risk of ~~evidence~~ bias studies, reviewers may base best evidence summaries on the lower risk of bias studies (6).

In particular, in an appropriately large set of studies, when the potential risk of bias due to censoring of participants with missing lost to follow-up data differs across studies, ~~sensitivity analyses excluding studies with a high risk of bias or studies where there are some concerns should be performed. Review and guideline authors are encouraged to integrate these results into their overall judgements. In case of substantial changes, including a change of direction of the pooled effect estimate, systematic review or guideline authors should consider rating down the certainty of the evidence for study imitations (risk of bias).~~reviewers can conduct sensitivity analysis to determine whether results differ in high and low risk of bias studies. When results differ, reviewers should present best estimates from only low risk of bias studies.

8. Discussion and further guidance for the assessment of time-to-event evidence

For this guide we chose the prior outlined definitions and concepts, but they are not unassailable. Well-known resources for the conduct of systematic reviews focus on the hazard ratio as relative effect measure to include time-to-event data in meta-analyses ~~(36). Therefore, our guidance focuses on the hazard ratio as~~(38). Therefore, our guidance focuses on the hazard ratio as the relative effect measure for time-to-event analysis. In time-to-event analysis

certain competing risk analyses require censoring of competing events, meaning single or multiple events precluding the occurrence of the event of interest~~, by default (13, 37). Nevertheless, such analyses are likewise susceptible to bias due to censoring of participants because of missing follow-up data, when individuals are excluded from follow-up and censored for other reasons. An exception is~~ (13, 39).

Nevertheless, such analyses remain susceptible to bias due to censoring of participants because of missing follow-up data when individuals are excluded from follow-up and censored for other reasons. An exception occurs when study authors applied competing risk analysis methods to account for the particular reasons data is absent, e.g. loss to follow-up, in their primary analysis.

To illustrate the issues outlined in this guidance we present examples from randomized trials; some considerations are, however, also applicable ~~also~~ to non-randomized studies with control arms. In the absence of randomization, confounders may introduce bias because of an association between censoring time and the outcome of interest and the control of such confounders plays a critical role (~~38~~40). We acknowledge ~~the changeability~~possible subsequent progress of the field and will adapt this guidance as necessary.

~~There is a~~A great variety of additional approaches to analyze time-to-event data~~, which are applied~~ apply less frequently for primary analyses and rarely find their way into meta-analyses. ~~Numerous~~Investigators have proposed numerous analytic techniques to test the sensitivity of single trial results to the dependence of censoring ~~have been proposed. Several,~~ several of the ~~methods~~which are based on multiple imputation and account for the dependence of follow-up, taking the distribution of survival events into account.

These approaches are not solely ~~aiming at~~applicable to the Cox model, but address Kaplan-Meier estimators, parametric proportional hazards models and other analysis techniques.

Practical applications of the methods show substantial bias when the survival expectation of the censored individuals alters in a negative or positive manner from the expectation of the individuals remaining on study (~~39-47~~41-49). Computationally more advanced methods, including approaches that explicitly allow for adjustment of dependent censoring are based on strict assumptions, require ~~a~~ detailed data, and are currently used only for exploratory purposes ~~only. In situations where~~. When the results of such procedures are available they can support a judgement on the consequences of censoring~~, if properly applied~~ (~~48-~~50-52).

~~Censoring is an important threat to the validity of safety analyses, because~~Because the occurrence of adverse events is usually carried out as binary data analysis in contingency tables~~.~~, censoring is an important threat to the validity of safety analyses. However, when comparing adverse events among ~~different studies~~study arms, all individuals should be observed for a similar time-period to allow a fair comparison of interventions. Censoring of participants from individual study arms, for example because of competing events such as ~~censoring at~~switching treatment ~~switching~~ after disease progression, results in varying observation times among participants and subsequently in diverging average times at risk for adverse events ~~in comparisons between study arms. Bender et al. (51) pointed out specific situations where~~. Bender et al. (53) pointed out specific situations in which the risk of bias due to inadequate analysis of adverse events led to significant reductions of the certainty in the evidence in evaluations to inform reimbursement decisions for new drugs by ~~the~~ relevant authorities in Germany as “greater harm could not be excluded with sufficient certainty”. Analysis of safety endpoints by means of appropriate time-to-event analysis techniques ~~is required and~~ should be common practice ~~(52).~~(54).

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All authors are members of the GRADE Working Group

CRediT authorship contribution statement

Marius Goldkuhle: Writing - original draft, Methodology, Writing - review & editing, Conceptualization, Project administration. **Ralf Bender:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Elie A. Akl:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Elvira C. van Dalen:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Sarah Nevitt:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Reem A. Mustafa:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Gordon H. Guyatt:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Marialene Trivella:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Benjamin Djulbegovic:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Holger Schünemann:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Michela Cinquini:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Nina Kreuzberger:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization~~.~~, statistical analysis. **Nicole Skoetz:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization, Supervision.

Article history

Slides presented at GRADE meetings in Bogota (2018), Manchester (2018) and Hamilton (2019)

Declarations of interest:

None

Appendix

Appendix ~~A.1~~A1: Independent and non-informative censoring

Non-informative censoring, as described by ~~Lagakos (15)~~Lagakos (15), requires *"that the time-point of a censoring event holds no information about an individual's likelihood to experience the event of interest* (its survival time)". This means that the true distribution of the survival time, where no individual is lost from observation and individuals are observed until the event occurs, and the true censoring distribution, where the study ends before all subjects experience the event and censored individuals do not experience the event prior to the end of study, provide no information for each other. Informative censoring is sometimes referred to as a type of selection bias under the reasoning that loss to follow-up or withdrawal in randomized trials leads to selection after randomization, when certain participants due to certain measured or unmeasured characteristics or conditions may be less likely or more likely to be censored and as well less likely or more likely to experience the event of interest. In other words, the association of the risk of being censored and the risk of experiencing the event results from a common source of both risks (~~38~~40). The definition of independent censoring is not equivalent to non-informative censoring and ~~Lagakos (15)~~Lagakos (15) shows that dependent censoring is a special form of informative censoring, however, in most situations where the assumption of independent censoring is violated, the assumption of non-informative censoring is too ~~(13)~~(13).

Appendix ~~A.2~~A2: Reporting requirements for survival analysis that allow to assess the risk of bias due to censoring

In order to assess the suitability of the independent censoring assumption by users, including systematic review and guideline authors, the methods in a primary study report should ideally provide detailed definitions of the assessed outcomes including the event(s) of interest, the time of origin and all conditions leading to censoring despite end-of observation (e.g. absence of the event at study closure, loss to follow-up or withdrawal due to competing events) (17, 18). Standardized outcome definitions would here be highly preferable ~~(19)~~(19). With regard to the applied analysis methods we would demand that it is explicitly reported why the assumption of dependent censoring is feasible. When outcomes which include competing risks are assessed, we would require the application and reporting of appropriate methods, which will be outlined in a future guidance. The result section should hold the total events of interest and number of censored individuals in each of the study arms and the number of participants censored separately of those before the end the observational period including the individual reasons (17, 18). It is highly desirable that Kaplan-Meier curves, if feasible, are given for each of the assessed outcomes. In the curves, the time-points of censored events should be indicated as well as the number at risk below the curves for appropriate time-points ~~(22)~~(22). The number of censored individuals for certain time-points with an indication of censoring reasons is an option to enhance transparency. Lastly, the duration of follow-up for each study arm should be given and the calculation method should be clearly stated (~~53~~55).

Appendix A3. Reconstruction of survival data to illustrate the impact of early dependent censoring

To illustrate the impact of early dependent censoring on comparisons, we reconstructed individual participant data from the survival curves published for the analysis of overall survival in the article by Denis et al. (32). The study shows an unbalanced number of censored participants particularly during early follow-up, with more censored participants in the intervention arm compared to the control arm. Given the clear reporting in the survival curves, we were able to reconstruct outcome event and censoring time points for the individuals in each of the compared groups. We verified our proceeding with the algorithm presented Guyot et al. (33) that allows to reconstruct individual participant level data from published survival curves. The algorithm attributes a constant rate of censoring to intervals in between outcome events and time-points for which a number of individuals at risk is reported. It therefore works optimal assuming independent censoring. Under the objective of our illustration, we decided not to directly use the dataset resulting from the algorithm proposed by Guyot and colleagues but to work with individual patient data that we reconstructed directly from the published survival curve. Nevertheless, we used the data set produced under application of the algorithm to confirm the consistency of our manually extracted data by comparing the data points retrieved through both approaches.

We extracted data with the software DigitizeIt (www.digitizeit.de), which allows to assign each point on the survival curve a corresponding time-point on the x-axis. We marked all declines of the curve as outcome event and all crosses as censoring time-points. The reported curve for the experimental arm was unclear for two censoring events in the first interval (0 to 5 months) and the last interval (over 15 months) respectively, which were not directly identifiable on the curve, but must have occurred in these intervals as indicated by the number of individuals at risk. Similarly, for the curve representing survival in the control arm, two

censoring events were not identifiable within the first interval (0 to 5 months). For all scenarios we assumed the missing censoring events to have happened on the last possible time-point of this interval (4.99 and 18.99 months). In the so retrieved dataset, we modified the survival data of participants censored within the first seven months of follow-up to illustrate the impact of early dependent censoring. We present a hypothetical scenario where all participants censored prior to seven months of follow-up experience the outcome event one month after the original censoring. Subsequently, we calculated hazard ratios with the Cox proportional hazards model and present Kaplan-Meier survival curves. All statistical analyses were performed using the software R (56). We want to point out that our imputation does not claim to compare a difference in treatment effects, but to illustrate the loss of certainty that is introduced to survival analyses through a high degree of censoring particularly during the early period of follow-up.

Appendix A4. Reconstructed survival curves

Appendix-figure 1: Kaplan-Meier survival curves calculated from the individual participant level data reconstructed from the analysis of overall survival in Denis et al. (32).

Appendix-figure 2: Kaplan-Meier survival curve calculated from the individual participant level data reconstructed from the analysis of overall survival in Denis et al. (32). Participants who were censored prior to seven months of follow-up in both study arms were set to experience the outcome event one month after original censoring.

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GRADE Guideline:
Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with missing data in intervention studies

What is new

Key findings

- Analysis methods for time-to-event outcomes deal with participants for whom outcome data is unavailable through censoring. Two types of censoring, end of study censoring and censoring because of missing data (commonly named loss to follow-up censoring), have to be differentiated.
- Censoring of individuals with missing follow-up data is likely to violate the assumption of independence of censoring and increases the risk of biased results.
- The magnitude of bias resulting from censoring of participants with missing data depends on several factors. An increasing degree of dependent censored observations and difference among the study arms, increases the risk of bias.

What are the implications and what should be changed?

- Often, reasons why individuals in studies were censored and the time-points of censoring are unavailable to systematic review and guideline authors who therefore have to make risk of bias judgements for primary studies based on the distribution of censoring over time or the degree of missing participant follow-up data.
- Systematic review and guideline authors need to make GRADE judgements across the body of evidence for study limitations resulting from censoring of participants with missing data considering all available information, including the possibility of carrying out sensitivity analysis by assessing whether studies at high risk of bias or studies in which there are concerns yield different results.

GRADE guidelines:

29. Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with missing data in intervention studies

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Abstract

Objective: To provide Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidance for the consideration of study limitations (risk of bias) due to missing participant outcome data for time-to-event outcomes in intervention studies.

Study Design and Setting: We developed this guidance through an iterative process that included membership consultation, feedback, presentation and iterative discussion at meetings of the GRADE Working Group.

Results: The GRADE working group has published guidance on how to account for missing participant outcome data in binary and continuous outcomes. When analysing time-to-event outcomes (e.g. overall survival, time-to-treatment failure) data of participants for whom the outcome of interest (e.g. death, relapse) has not been observed are dealt with through censoring. To do so, standard methods require that censored individuals are representative for those remaining in the study. Two types of censoring can be distinguished, end of study censoring and censoring because of missing data, commonly named loss to follow-up censoring. However, both types are not distinguishable with the usual information on censoring available to review authors. Dealing with individuals for whom data is missing during follow-up in the same way as individuals for whom full follow-up is available at the end of the study increases the risk of bias. Considerable differences in the treatment arms in the distribution of censoring over time (early versus late censoring), the overall degree of missing follow-up data and the reasons why individuals were lost to follow-up may reduce the certainty in study results. With often only very limited data available, review and guideline authors are required to make transparent and well-considered judgements when judging risk of bias of individual studies and then come to an overall grading decision for the entire body of evidence.

Conclusion: Concern for risk of bias resulting from censoring of participants for whom follow-up data is missing in the underlying studies of a body of evidence can be expressed in the study limitations (risk of bias) domain of the GRADE approach.

Keywords

GRADE; Certainty of the evidence; Time-to-event outcomes; Survival analysis; Risk of bias; Loss to follow-up; Censoring missing data.

What is new

Key findings

- Analysis methods for time-to-event outcomes deal with participants for whom outcome data is unavailable through censoring. Two types of censoring, end of study censoring and censoring because of missing data (commonly named loss to follow-up censoring), have to be differentiated.
- Censoring of individuals with missing follow-up data is likely to violate the assumption of independence of censoring and increases the risk of biased results.
- The magnitude of bias resulting from censoring of participants with missing data depends on several factors. An increasing degree of dependent censored observations and difference among the study arms, increases the risk of bias.

What are the implications and what should be changed?

- Often, reasons why individuals in studies were censored and the time-points of censoring are unavailable to systematic review and guideline authors who therefore have to make risk of bias judgements for primary studies based on the distribution of censoring over time or the degree of missing participant follow-up data.
- Systematic review and guideline authors need to make GRADE judgements across the body of evidence for study limitations resulting from censoring of participants with missing data considering all available information, including the possibility of carrying out sensitivity analysis by assessing whether studies at high risk of bias or studies in which there are concerns yield different results.

1. Introduction:

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group has defined domains that can limit the certainty in a body of evidence (1-6). Within its study limitations domain (i.e., risk of bias), the GRADE approach has issued guidance on how to account for missing participant outcome data for binary and continuous outcomes (6, 7). That guidance proposes conducting sensitivity meta-analyses making assumptions about the outcomes of participants with missing data, to test the robustness of the findings of the primary meta-analysis (7, 8).

Although the basic principles for assessing risk of bias associated with missing participant outcome data in binary outcome analysis also apply to time-to-event analysis, there are issues uniquely applicable to time-to-event outcomes. In contrast to binary data analysis, time-to-event studies, which assess not only whether an event of interest occurs but also when it occurs, typically follow patients for varying periods of time. Because time-to-event analyses include data from individuals with variable lengths of follow-up, those for whom follow-up data becomes absent during the study interval are typically treated in the same way as those with regular follow-up until the end of the analysis (i.e. they provided complete data). Therefore, we here refer to missing follow-up data to characterize the situation when information for an individual becomes absent at a time-point within the intended and pre-specified observation period. This article discusses GRADE rating of study limitations associated with missing follow-up data when dealing with time-to-event analysis.

2. Background

2.1. Time-to-event analysis and censoring

Time-to-event analysis is also often referred to as survival analysis, in which the "survival time" describes the time until an event such as death occurs. The most prominent methods to

analyse time-to-event outcomes include Kaplan-Meier curves along with the log-rank test and the Cox proportional hazards regression model (9, 10). Time-to-event outcomes are often described by survival rates, defined as the probability that an individual will not have experienced an event (e.g. “survived”) up to a certain time point, or hazard rates, which can be interpreted as instantaneous failure rates, meaning an individual’s likelihood of experiencing an event (e.g. “death”) at a certain time point given that the event has not occurred up to this time point.

The most prominently applied relative effect measure is the hazard ratio, which is the ratio of hazards between two groups. It is commonly obtained from the Cox proportional hazards regression model, which adjusts for relevant covariates and confounders. An unadjusted hazard ratio can also be derived indirectly using other analytical techniques, like the Kaplan-Meier method or the log-rank test (10, 11).

A core feature of time-to-event analysis is the consideration of “censoring” which occurs when patients complete their follow-up period without having experienced the event of interest. Censored observations are included in analyses to optimize the efficiency that time-to-event analysis provides over binary data analysis (12). If the time to an event and censoring are not included in the calculation of the (log) hazard ratio, it equals the (log) relative risk.

To include censored observations in time-to-event analyses, general methods of survival analysis require an assumption of non-informative and independent censoring. Violations of this assumption introduce risk of bias. Appendix A1 provides a short review of the definition of non-informative censoring and its relation to independent censoring. In accordance with established training resources for time-to-event analysts (13), we will use the concept of independent and dependent censoring to describe situations under which censoring may lead to distortion of analysis results.

Independent censoring occurs when censored participants and those remaining under observation have the same probability of experiencing the event of interest, as if the censored individuals were "randomly drawn" during the course of follow-up (13, 14). An example for censoring mechanisms independent from the survival time (and also non-informative) is administrational closure of a study. Differences in the observation times of participants then are solely a result of the staggered study entry times and the fixed study closure time (figure 1) (13, 15).

Figure 1: Types of censoring: For participant 1 the occurrence of the outcome event is observable. Participants 2 and 3 are censored because of the administrational closure of the study. The variation in their duration of follow-up and the differing censoring time points result from the staggered recruiting phase of the study. Participant 4 is lost from the observation before the administrational ending of the study and censored for a different reason.

When individuals are censored because of missing follow-up data, this assumption is likely to be violated. Examples of such situations which may bias results include:

- Participants withdraw consent due to physical or mental side effects of an intervention;
- Participants are withdrawn from the observation and censored following switching treatment as a result of progressive disease;
- Investigators fail to locate study participants.

2.2. Reporting time-to-event data and censoring in primary studies

Flaws in reporting time-to-event analyses may complicate their adequate appraisal by systematic review authors including assessing risk of bias resulting from censoring of individuals with missing follow-up data (16-19). Suboptimal reporting includes but is not limited to outcome definitions, the extent and duration of follow-up, precision measures such

as the number of participants at risk at certain time points, and details of statistical model building. Authors often fail to precisely define censoring mechanisms, omit the number of censored participants, and fail to state why individual study participants were censored (16-19).

Studies published in leading medical journals are not immune to reporting limitations: for instance, one methodological study found inconsistency between the number of participants reported in the text/tables as 'lost before the end of the study' and those assessed from Kaplan-Meier curves (20). Prior work has specified minimal reporting items for time-to-event analyses and survival curves (17, 18, 21, 22). Appendix A2 outlines reporting requirements that allow systematic review and guideline authors to assess possible risk of bias resulting from informative censoring.

3. Methods

This guidance was developed by members of the GRADE working group. They included methodologists, clinical epidemiologists and biostatisticians with experience in systematic reviews and/or guideline development. The group developed the guidance based on iterative discussions by email, on conference calls and at a GRADE working group meeting in Manchester, UK, in October 2018. The final draft of the guidance was presented during the GRADE working group meeting in Hamilton in June 2019 and was approved following the group's standard approval process.

4. Scope

This guidance aims to support systematic review and guideline authors in the assessment of study limitations (risk of bias) due to missing follow-up data for time-to-event outcomes in intervention studies. We describe an approach that takes a systematic reviewer perspective relying on information that one could typically obtain from only the trial report and its

accompanying records. To comply with well-known resources for systematic review authors to assess the risk of bias in individual studies and with reference to previous GRADE guidance for rating the certainty of the evidence with focus on study limitations (risk of bias), we refer to missing follow-up data as the unavailability of follow-up data for individuals during the study interval (6, 23, 24). This includes all types of missing data and situations in which the outcome status of study participants becomes unavailable during the study period irrespective of the reason (e.g., patients not available or inappropriately excluded) (25, 26).

The concerning risk of bias arises, for example, when investigators censor individuals for whom data is missing and include them in the computation of effect measures in the same way as participants with independent censoring (e.g., those whose follow-up ended appropriately at the end of the data collection period). Systematic review and guideline authors seldom have information regarding the reasons for censoring for each participant in every eligible study. Consistent with well-known instructions for systematic review authors, we therefore provide guidance that is primarily aimed at detecting a potential bias in individual studies (23, 24). Judgements on study level then inform the risk of bias assessment for an overall body of evidence separately for each outcome.

In accordance with previous GRADE guideline for missing participant outcome data for binary and continuous outcomes, we provide guidance for systematic review and guideline authors who assess comparative clinical trials based on aggregated data (7). We differentiate the issue of adequately accounting for loss to follow-up from that of adherence to the intention to treat (ITT) principle, which relates to analyzing study participants with known data in the groups to which they were allocated (7, 27).

We focus on risk of bias in the outputs of the "standard" methods of survival analysis and the Cox model hazard ratio as the single comparative relative effect size measure (16-19). Within the context of this guidance we assume that the primary study investigators and subsequently

the authors of meta-analyses have chosen the correct method for analysing competing events for the intended research question.

5. How censoring participants with missing follow-up data may affect the results of the study

5.1. Censoring of participants leading to over- and under estimation of the survival probability

Similar to binary outcome analysis, the distortion of the outcome probability of the group under study depends on the outcome probability of those for whom data is missing. When individuals who are more likely to experience the (negative) event of interest (e.g. death) are also more likely to be missing (positive correlation between the occurrence of the event and missingness of data), e.g. because they are more likely to be lost to follow-up, the true survival probability of a study group will inevitably be overestimated (12, 23). This means that the corresponding true risk of the (negative) event occurrence will be underestimated. Such an association may occur, for example, if participants with treatment-related adverse events are no longer followed-up and are censored at the time of loss to follow-up.

On the other hand, in case of a negative correlation between the occurrence of the event and the probability of being censored, the true survival probability for a study group may be underestimated (and the corresponding true event risk overestimated) (23). For example, underestimation of the event-free survival probability will occur if in a study comparing the impact of psychiatric interventions on time-to-treatment failure participants in one arm benefit so substantially that they fail to return and are therefore lost from the study.

5.2. Effect of censoring of participants with missing follow-up data on the hazard ratio

Factors that might result in a biased hazard ratio are the frequency of the outcome event of interest, the treatment effect in terms of the distribution of the outcome event between the study arms, and the frequency and distribution of censoring because of missing data (e.g.

effect of intervention on the frequency of loss to follow-up). As the impact of dependent censoring on the hazard ratio cannot be determined based on the observed data (because the true outcome of censored individuals is not observable), quantifications of the associated bias are difficult (15).

Nevertheless, the potential bias resulting from censoring of missing follow-up data can be substantial, especially when the outcome probability for those with missing data is considerably increased. In studies evaluating antiretroviral treatment programmes for HIV in settings with limited resources, loss to follow-up rates are typically high. Performing a systematic review and meta-analysis of studies of such programmes in which individuals lost to follow-up were actively traced by telephone calls or social networks, Brinkhof et al. (28) found that the mortality among patients lost to follow-up was considerably increased. In a subsequent study, Brinkhof et al. (29) then used the mortality estimates from their previous systematic review to impute representative mortality data for individuals lost to follow-up in an evaluation of five antiretroviral treatment programmes in sub-Saharan Africa and found that survival analysis ignoring increased mortality among participants lost to follow-up greatly underestimated overall mortality and leads to a biased evaluation of the programmes.

In most situations, however, the reasons for censoring and the associated prognosis will be unavailable to systematic review and guideline authors. Therefore, similar to assessments of a risk of bias in binary data analysis, one has to rely on the simplified principle that the higher the frequency of dependent censoring of participants in relation to the event rates and the greater the difference between the groups, the higher the potential for biased results (6). Simulations of single arm studies show that the degree of bias is more strongly influenced by the overall proportion of participants that are censored with an increased/decreased risk of experiencing the outcome, rather than the difference in the hazard of study participants who are remaining at risk until the end of the observation period and those who are censored (30).

Between-group comparison simulations show that the degree of bias in settings with proportional hazards in Cox models is mainly enhanced by the overall degree and the early time points of censoring for any reason (31).

5.3. Illustration of the uncertainty introduced through early dependent censoring to comparisons

In order to illustrate the impact of early depended censoring on survival analyses, we reconstructed individual participant data from the analysis of overall survival in a study by Denis et al. (32) (see also section 6.1). In this study example, the number of censored participants was different between the groups, particularly in the beginning of follow-up. Given the transparent reporting of outcome and censoring events in the available survival curve (Figure 2), we were able to reconstruct event and censoring time points for the individuals in each group (see Appendix A3). Box 1 provides a detailed description of the study example and Appendix A3 provides a summary of our proceeding to reconstruct survival data. We verified the consistency of our reconstructed dataset with the approach presented by Guyot et al. (33), that allows recreating individual participant level data from published survival curves by assuming constant censoring within a given time interval, and recalculated hazard ratios and Kaplan-Meier survival curves.

To demonstrate the impact of early censoring on results, we considered a hypothetical scenario in which all participants who were censored prior to seven months of follow-up experience the event one month after censoring, i.e. these data are no longer censored but are counted as events. This assumption represents the extreme case of a very large positive correlation between early censoring and the experience of the event of interest.

Appendix A4 figures 1 and 2 show the Kaplan-Meier survival curves for the reconstructed dataset and the hypothetical scenario. The original hazard ratio resulting from the authors'

analysis is 0.32 (95% confidence interval (CI) 0.15 to 0.67). The hazard ratio resulting for the data we reconstructed from the published survival curve was 0.32 (95% CI 0.15 to 0.65) showing that our reconstructed data set is nearly identical to the original one. The original analysis indicates a substantial survival advantage for participants in the experimental arm under the questionable assumption of independent censoring.

Appendix A4 figures 1 and 2 illustrate that a positive correlation between early censoring and the experience of the event of interest leads to an overestimation of the survival probability in both study arms. As more participants in the intervention arm are censored prior to seven months compared to the control arm (26 participants versus 19 participants), the hazard ratio increases to 0.69 (95% CI 0.44 to 1.07) in the hypothetical scenario. This illustrates that the effect estimation is biased if there is a positive correlation between early censoring and the experience of the event of interest and additionally a higher proportion of censored participants in the intervention arm. Therefore, there is a loss of certainty in the results of survival analyses in the case of substantial censoring, particularly throughout the early periods of follow-up and where no information is available on the reasons for censoring.

6. Suggestions to assess risk of bias resulting from censoring in an individual study

6.1. Identifying risk of bias due to censoring in individual studies

To appropriately assess the potential bias for study results emerging from dependent censoring of participants for whom follow-up data is missing, reasons why individual participants were censored for each outcome would be helpful. When information regarding the number of censored individuals with reasons together with the time point of censoring are available, imputation procedures based on assumptions, similar to those described in the GRADE guidance paper for missing outcome data within binary data analysis, could be applied to assess the robustness of effect measures to loss to follow-up (7).

Unfortunately, it is unlikely that review authors will be able to obtain data on the reasons and time points for censoring for study participants and the reporting of information on missing data (34). Nevertheless, before assessing a potential bias, gathering all available information on possible mechanisms for censoring, if possible from the primary study investigators themselves, is likely to be helpful.

For an informed judgement of risk of bias resulting from censoring of participants because of missing follow-up data, both the degree and the distribution of censoring among the study groups over time should be available. In randomized trials with a valid randomization process, censoring events resulting from treatment independent covariates (independent censoring) should have a similar distribution over time in both treatment arms. An unequivocal difference in the distribution of individuals lost to follow-up over-time, for example a high number of early censoring in one arm versus late censoring in the other, is likely to indicate dependence of these censoring events.

Differences in early censoring are especially relevant because they can be more easily associated with missing follow-up data than "end-of study censoring". In the absence of individual patient data, investigators will need to rely on information about the study participants throughout the course of the study that is available from reports. Most informative are survival curves and the number of reported individuals at risk to experience the outcome event across the study period.

It is good practice, even though not consistently done, to indicate in the survival curves the time points at which individuals were censored (16, 22). This is often done by study authors by marking censoring time points on the survival curves, e.g. as vertical lines, or as number of participants censored between given time points displayed along the number of participants at risk for these time points. This information then allows an assessment of whether censoring

happened early or late throughout the observation period and to assess differences in this distribution between study arms.

Figure 2 presents an example in which considerably more participants are censored in the intervention arm during the first months of the study as indicated by the vertical lines crossing the survival curves of the treatment arms. Box 1 presents a detailed description of the example (see also section 5.3).

Figure 2: Kaplan-Meier curve for the outcome overall survival from the study Denis et al (32). The vertical lines crossing the curves mark censored events. The elliptical form indicates that the number of early censored individuals is higher in the experimental arm compared to the control arm. The rectangular form shows that the number of participants at risk to experience the event for certain time points is reported below the curves for each study arm and are similar for both groups at 5 and 10 months of follow-up, despite a more favourable survival probability in the experimental arm. (32). Adapted from "Randomized Trial Comparing a Web-Mediated Follow-up With Routine Surveillance in Lung Cancer Patients" by Denis et al., 2017, Journal of the National Cancer Institute, 109(9), p. 6. Copyright 2017 by Oxford University Press. Adapted with permission.

Box 1: example 1: Denis et al. (32):

In a randomized trial comparing a web mediated follow-up strategy with routine surveillance for participants suffering from lung cancer, *the primary end point was overall survival (OS) defined from random assignment to death or to the last assessment of patient's status when the patient was censored.* A hazard ratio between groups was calculated using a Cox proportional hazards model. A total of 133 participants were randomized, and after exclusions of participants found after randomization to be ineligible, 60 and 61 participants were included in the modified intention-to-treat analyses in the intervention and the control arms respectively. The number of reported deaths per arm was 11 versus 26 and the number of relapses 34 versus 36. The study was closed early at an interim analysis by recommendation of the independent data monitoring board.

The degree of censoring was not reported throughout the study publication. However, an assessment of the presented survival curve (figure 2) shows substantially more censoring of participants in the experimental arm, particularly during early follow-up. Despite the visible survival benefits and the statistically significant hazard ratio in favour of the intervention group, the number of patients at risk is similar for both treatment arms at months 5 and 10. This suggests that a similar number of individuals who died in the control arm must have been censored in the intervention arm. This severe imbalance, despite randomization of the participants, introduces high risk to bias due to censoring of participants with missing follow-up data. In a hypothetical scenario, where individuals lost to follow-up are more likely than those who were not lost to follow up to die shortly after censoring, the survival benefit shown by the hazard ratio in the study is likely inflated and possibly inexistent. Here we would suspect a high risk of bias and, in a situation where only one study is included in the body of evidence or other included studies have similar imbalances , we would consider rating down due to study limitations for overall survival.

If only a survival curve and the number at risk for particular time points are available and direct information on the distribution of censoring is not presented (e.g. no censoring marks on the curves) or assessable (e.g. single marks for censoring not distinguishable on the curve due to high degree of censoring), it is sometimes possible to estimate the degree of participants censored for a certain time point by comparing the visible survival benefits in the curves and the number at risk for the reported time points (20). In figure 2, for example, at five and ten months of follow-up the same or a similar number of participants at risk are reported in both treatment arms (5 months: 37 versus 36; 10 months: 19 versus 19). Comparing this information with the visible differences in survival probabilities in the curves, noticeably favoring the experimental arm, allows the conclusion that substantially more participants have been lost to follow-up in the experimental than in the control arm. This is because after five and ten months of follow-up, approximately the same number of individuals that experienced the event (death) in the control arm must have been lost to follow-up in the experimental arm. Box 1 presents a detailed description of the example.

When authors report the number of individuals for several time points together with the survival curves, established methods to reconstruct summary time-to-event data also allow approximations of the number of individuals censored within certain time intervals (11, 35). When authors provide the number of individuals at risk for a sufficient number of time points, such procedures may also conclusively support an assessment of the distribution of censoring in the study arms over time. Considerable variation in the overall difference and a difference in the distribution in terms of early versus late censoring between arms can then confirm a high risk of bias and a critical limitation to the effect estimator of a time-to-event outcome of an individual study allowing guideline authors to carefully and transparently justify their decisions. Box 2 and figure 3 provide an additional illustrative example.

Figure 3: Kaplan-Meier curve for the outcome invasive disease-free survival from the study Martin et al (36) (see Box 2). The number of individuals censored up to the respective time-points of follow-up are reported along the number of individuals at risk to experience the outcome at this time point. The number of censored individuals is substantially higher in the neratinib arm throughout the follow-up period. The number of individuals at risk (excluding those who experienced the event or were censored) in the placebo arm is substantially higher than the number of individuals at risk in the neratinib arm. Nonetheless, the neratinib arm is shown to be beneficial by the HR (<1). Adapted from "Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial" by Martin et al., 2017, The Lancet Oncology, 18(12), p. 1694. Copyright 2017 by Elsevier. Reprinted with permission.

Box 2: Example 2: Martin et al. (36)

The randomised, double blind, placebo-controlled ExteNET study compared adjuvant neratinib and placebo in patients with HER2-positive breast cancer after standard locoregional treatment, trastuzumab, and chemotherapy. The five-year analysis of the primary endpoint invasive disease-free survival which was defined as time from randomisation to first occurrence of invasive disease and recurrences or all cause death showed a significant benefit for the intervention. Hazard ratios were derived from a Cox proportional hazards model and individuals were censored for the primary end-point when they did not re-consent for additional follow-up at the date of their last physical examination, if disease recurrence did not occur within the 2 years of follow-up in this study or if they did not have a disease-free survival event within the relevant time-frame (5.6 months). In each treatment arm 1420 participants were randomized and included in the intention-to-treat analysis.

While the study publication did not specify the proportion of censored individuals and the respective reasons for censoring, the survival curve for the primary outcome (figure 3) shows severe imbalances in the number of censored individuals. The number of censored participants between the time-points is reported together with the number of participants at risk to experience the event for certain time points below the curves and for each study arm respectively. The percentages present the proportion of participants who are event-free for the respective time-points. The number of censored individuals in the experimental arm is substantially higher than in the placebo arm, especially in the early observational period. This results in a lower number of individuals is at risk, excluding those who have experienced the event of interest or were censored, at any time point thereafter in the favored experimental arm. Assessing the times for the beginning of accrual (July 9, 2009), the ending of accrual (October 24, 2011) and the end of the five year follow-up (March 1, 2017) one can be certain that the early censoring events were due to loss to follow-up, and not to "*end-of-follow-up*", because the minimum complete observation time was at least 5.4 years (from Oct 24, 2011 - March 1, 2017). Given the information outlined above, a judgement of high risk of bias for this study due to censoring of participants because of missing follow-up data is justifiable. In a hypothetical situation, where a body of evidence for a certain outcome consists solely of this example, we would consider rating down for study limitations.

6.2 What to do when individual studies do not provide the distribution of censoring over time

Review authors often find themselves in situations in which they must assess potential risk of bias through censoring of participants because of missing follow-up data based on only very limited information (16-19). When the distribution of censoring over time in individual studies is not clear, but there are serious imbalances in the number of individuals for whom data is missing (e.g. individuals lost to follow-up summarized in a study flow-diagram) in the study arms or the reasons for the absence of follow-up data differ among arms (e.g. provided in a study flow-diagram), we suggest, in accordance with the Risk of Bias 2.0 tool, concern for a high risk of bias ("probably yes") for an individual study outcome (23, 24). To derive a decision, the instructions for risk of bias due to loss to follow-up in binary data analysis from the GRADE guideline on study limitations (risk of bias) should be considered (6). For time-to-event analyses from individual studies that do not report information regarding the distribution of censoring over time, its degree, and reasons, we suggest explicitly stating that a judgement was not possible because the required information was absent.

6.3. Individual participant data would be desirable to assess the risk of bias

Within-study sensitivity analyses for censoring, such as best/worst-case scenarios and other imputation procedures, require individual participant data. If data on individual failure and censoring times and reasons are available, individual patient data meta-analyses for time-to-event outcomes would allow for a more elaborate assessment of the sensitivity of results to missing data issues.

For example, such analyses may be possible when data for individuals lost to follow-up can be imputed based on plausible assumptions for individuals for whom data is missing (7). Significant changes in the estimates could then lead to decisions to rate down the certainty of evidence. Available statistical tests for the independence assumption also require additional

data (37) and are usually impossible to perform, when conducting a standard systematic review. Simple quantification measures for the completeness of follow-up in survival analyses also exist, but are usually not included in study reports.

6.4. Rating the risk of bias resulting from censoring of participants because of missing follow-up data and deriving an overall judgement for an individual study

Indicators	**Considerations for the risk of bias through censoring of participants with missing follow-up data assessment in individual studies**
Time point of censoring considerably different in both arms (early versus late censoring)	Critical concern for high risk of bias as early censoring is more likely to be due to missing data (e.g. loss to follow-up) as opposed to end of study censoring.
Censoring degree among arms diverging (Overall number of censored patients reported, but distribution over time not known)	A high risk of bias is more likely as a different degree and differing reasons for censoring are contradicting with a valid randomization process and thus imply that missingness may depend on the received intervention (23)
If reasons for censoring are reported (e.g. summarised in a study flow diagram): Different reasons why data for individuals was missing (e.g. were lost to follow-up) and different degree between arms.	

Table 1: Decision support for judgements of a risk of bias though inappropriate censoring in an individual study

A judgment on the risk of bias associated with missing data for time-to-event outcomes within GRADE should be based on the principles outlined in previous guidelines for rating the quality of the evidence addressing study limitations (GRADE guideline 4), particularly with regard to the risk of bias associated with missing participant outcome data in a body of evidence for both binary and continuous outcomes (GRADE guideline 17) (6, 7). The assessment criteria specified in this guidance allow integration of time-to-event specific

differences (e.g. censoring of individuals for whom data is missing and those who ended follow-up appropriately) and to support a decision on the presence of a risk of bias.

Table 1 provides considerations that reviewers can use to estimate the extent of the risk of bias introduced by censoring of participants because of missing data in an individual study. To derive a decision on the impact of missing follow-up data on the overall risk of bias for an outcome in an individual study reviewers must consider all other potential study limitations including lack of allocation concealment or the lack of blinding following which they can judge risk of bias can following usual GRADE principles (6). A crucial limitation in one risk of bias criterion, which may include substantial differences in the degree and distribution in the amount of early and late censoring, or several criteria with some limitations, which may include considerable difference in the overall degree of censoring, may be sufficient to merit a judgement of a serious limitation. A crucial limitation for one or more criteria would result in a judgement of a very serious limitation for the outcome of an individual study (6). These judgements should then inform an overall rating of the GRADE risk of bias domain for a body of evidence.

7. Making an overall judgement for a body of evidence

To derive a judgment for the risk of bias domain across studies in a body of evidence, reviewers should apply the usual GRADE principles for study imitations (6): no serious limitations (do not rate down), if evidence comes largely from studies at low risk of bias; serious limitations (rate down one level), if evidence comes largely from studies at high risk of bias; very serious limitations (rate down two levels), if evidence comes largely from studies at very high risk of bias.

If studies vary in their risk of bias, and results differ in high and low risk of bias studies, reviewers may base best evidence summaries on the lower risk of bias studies (6). In

particular, in an appropriately large set of studies, when the potential risk of bias due to censoring of participants with missing lost to follow-up data differs across studies, reviewers can conduct sensitivity analysis to determine whether results differ in high and low risk of bias studies. When results differ, reviewers should present best estimates from only low risk of bias studies.

8. Discussion and further guidance for the assessment of time-to-event evidence

For this guide we chose the prior outlined definitions and concepts, but they are not unassailable. Well-known resources for the conduct of systematic reviews focus on the hazard ratio as relative effect measure to include time-to-event data in meta-analyses (38). Therefore, our guidance focuses on the hazard ratio as the relative effect measure for time-to-event analysis. In time-to-event analysis certain competing risk analyses require censoring of competing events, meaning single or multiple events precluding the occurrence of the event of interest (13, 39).

Nevertheless, such analyses remain susceptible to bias due to censoring of participants because of missing follow-up data when individuals are excluded from follow-up and censored for other reasons. An exception occurs when study authors applied competing risk analysis methods to account for the particular reasons data is absent, e.g. loss to follow-up, in their primary analysis.

To illustrate the issues outlined in this guidance we present examples from randomized trials; some considerations are, however, also applicable to non-randomized studies with control arms. In the absence of randomization, confounders may introduce bias because of an association between censoring time and the outcome of interest and the control of such confounders plays a critical role (40). We acknowledge possible subsequent progress of the field and will adapt this guidance as necessary.

A great variety of additional approaches to analyze time-to-event data apply less frequently for primary analyses and rarely find their way into meta-analyses. Investigators have proposed numerous analytic techniques to test the sensitivity of single trial results to the dependence of censoring, several of the which are based on multiple imputation and account for the dependence of follow-up, taking the distribution of survival events into account.

These approaches are not solely applicable to the Cox model, but address Kaplan-Meier estimators, parametric proportional hazards models and other analysis techniques. Practical applications of the methods show substantial bias when the survival expectation of the censored individuals alters in a negative or positive manner from the expectation of the individuals remaining on study (41-49). Computationally more advanced methods, including approaches that explicitly allow for adjustment of dependent censoring are based on strict assumptions, require detailed data, and are currently used only for exploratory purposes. When the results of such procedures are available they can support a judgement on the consequences of censoring (50-52).

Because the occurrence of adverse events is usually carried out as binary data analysis in contingency tables, censoring is an important threat to the validity of safety analyses. However, when comparing adverse events among study arms, all individuals should be observed for a similar time-period to allow a fair comparison of interventions. Censoring of participants from individual study arms, for example because of competing events such as switching treatment after disease progression, results in varying observation times among participants and subsequently in diverging average times at risk for adverse events. Bender et al. (53) pointed out specific situations in which the risk of bias due to inadequate analysis of adverse events led to significant reductions of the certainty in the evidence in evaluations to inform reimbursement decisions for new drugs by relevant authorities in Germany as “greater

harm could not be excluded with sufficient certainty". Analysis of safety endpoints by means of appropriate time-to-event analysis techniques should be common practice (54).

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None

Appendix

Appendix A1: Independent and non-informative censoring

Non-informative censoring, as described by Lagakos (15), requires *"that the time-point of a censoring event holds no information about an individual's likelihood to experience the event of interest* (its survival time)". This means that the true distribution of the survival time, where no individual is lost from observation and individuals are observed until the event occurs, and the true censoring distribution, where the study ends before all subjects experience the event and censored individuals do not experience the event prior to the end of study, provide no information for each other. Informative censoring is sometimes referred to as a type of selection bias under the reasoning that loss to follow-up or withdrawal in randomized trials leads to selection after randomization, when certain participants due to certain measured or unmeasured characteristics or conditions may be less likely or more likely to be censored and as well less likely or more likely to experience the event of interest. In other words, the association of the risk of being censored and the risk of experiencing the event results from a common source of both risks (40). The definition of independent censoring is not equivalent to non-informative censoring and Lagakos (15) shows that dependent censoring is a special form of informative censoring, however, in most situations where the assumption of independent censoring is violated, the assumption of non-informative censoring is too (13).

Appendix A2: Reporting requirements for survival analysis that allow to assess the risk of bias due to censoring

In order to assess the suitability of the independent censoring assumption by users, including systematic review and guideline authors, the methods in a primary study report should ideally provide detailed definitions of the assessed outcomes including the event(s) of interest, the time of origin and all conditions leading to censoring despite end-of observation (e.g. absence of the event at study closure, loss to follow-up or withdrawal due to competing events) (17, 18). Standardized outcome definitions would here be highly preferable (19). With regard to the applied analysis methods we would demand that it is explicitly reported why the assumption of dependent censoring is feasible. When outcomes which include competing risks are assessed, we would require the application and reporting of appropriate methods, which will be outlined in a future guidance. The result section should hold the total events of interest and number of censored individuals in each of the study arms and the number of participants censored separately of those before the end the observational period including the individual reasons (17, 18). It is highly desirable that Kaplan-Meier curves, if feasible, are given for each of the assessed outcomes. In the curves, the time-points of censored events should be indicated as well as the number at risk below the curves for appropriate time-points (22). The number of censored individuals for certain time-points with an indication of censoring reasons is an option to enhance transparency. Lastly, the duration of follow-up for each study arm should be given and the calculation method should be clearly stated (55).

Appendix A3. Reconstruction of survival data to illustrate the impact of early dependent censoring

To illustrate the impact of early dependent censoring on comparisons, we reconstructed individual participant data from the survival curves published for the analysis of overall survival in the article by Denis et al. (32). The study shows an unbalanced number of censored participants particularly during early follow-up, with more censored participants in the intervention arm compared to the control arm. Given the clear reporting in the survival curves, we were able to reconstruct outcome event and censoring time points for the individuals in each of the compared groups. We verified our proceeding with the algorithm presented Guyot et al. (33) that allows to reconstruct individual participant level data from published survival curves. The algorithm attributes a constant rate of censoring to intervals in between outcome events and time-points for which a number of individuals at risk is reported. It therefore works optimal assuming independent censoring. Under the objective of our illustration, we decided not to directly use the dataset resulting from the algorithm proposed by Guyot and colleagues but to work with individual patient data that we reconstructed directly from the published survival curve. Nevertheless, we used the data set produced under application of the algorithm to confirm the consistency of our manually extracted data by comparing the data points retrieved through both approaches.

We extracted data with the software DigitizeIt (www.digitizeit.de), which allows to assign each point on the survival curve a corresponding time-point on the x-axis. We marked all declines of the curve as outcome event and all crosses as censoring time-points. The reported curve for the experimental arm was unclear for two censoring events in the first interval (0 to 5 months) and the last interval (over 15 months) respectively, which were not directly identifiable on the curve, but must have occurred in these intervals as indicated by the number of individuals at risk. Similarly, for the curve representing survival in the control arm, two

censoring events were not identifiable within the first interval (0 to 5 months). For all scenarios we assumed the missing censoring events to have happened on the last possible time-point of this interval (4.99 and 18.99 months). In the so retrieved dataset, we modified the survival data of participants censored within the first seven months of follow-up to illustrate the impact of early dependent censoring. We present a hypothetical scenario where all participants censored prior to seven months of follow-up experience the outcome event one month after the original censoring. Subsequently, we calculated hazard ratios with the Cox proportional hazards model and present Kaplan-Meier survival curves. All statistical analyses were performed using the software R (56). We want to point out that our imputation does not claim to compare a difference in treatment effects, but to illustrate the loss of certainty that is introduced to survival analyses through a high degree of censoring particularly during the early period of follow-up.

Appendix A4. Reconstructed survival curves

Appendix-figure 1: Kaplan-Meier survival curves calculated from the individual participant level data reconstructed from the analysis of overall survival in Denis et al. (32).

Appendix-figure 2: Kaplan-Meier survival curve calculated from the individual participant level data reconstructed from the analysis of overall survival in Denis et al. (32). Participants who were censored prior to seven months of follow-up in both study arms were set to experience the outcome event one month after original censoring.

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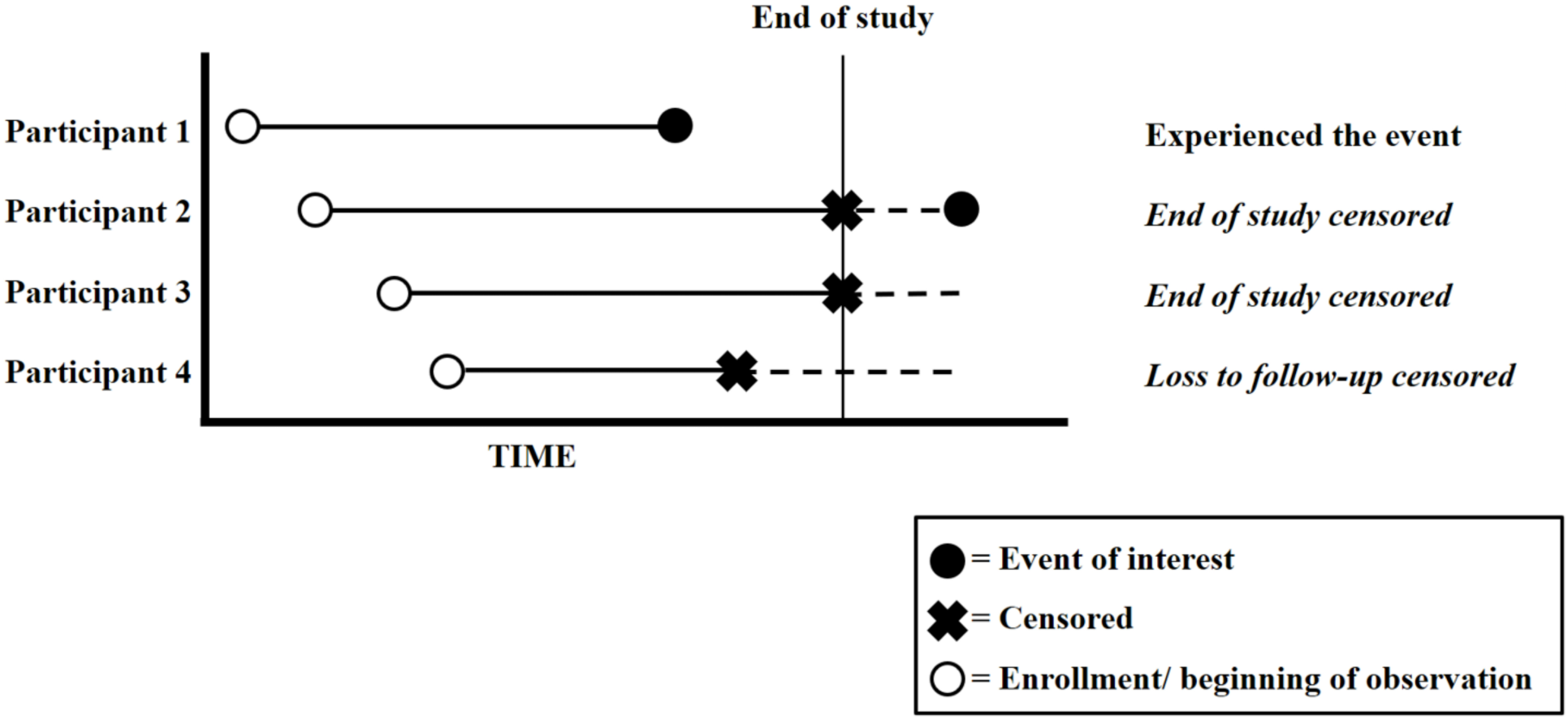
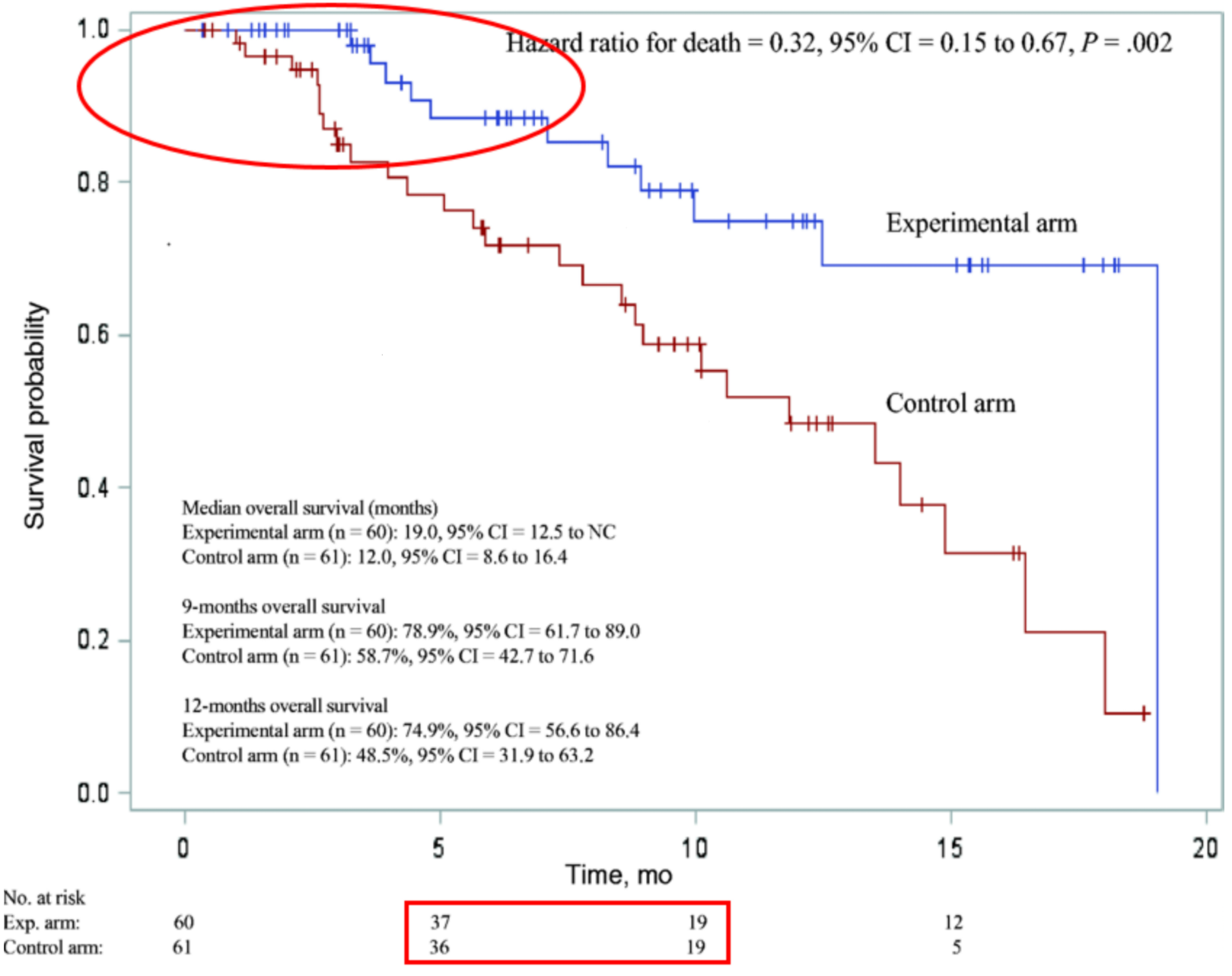
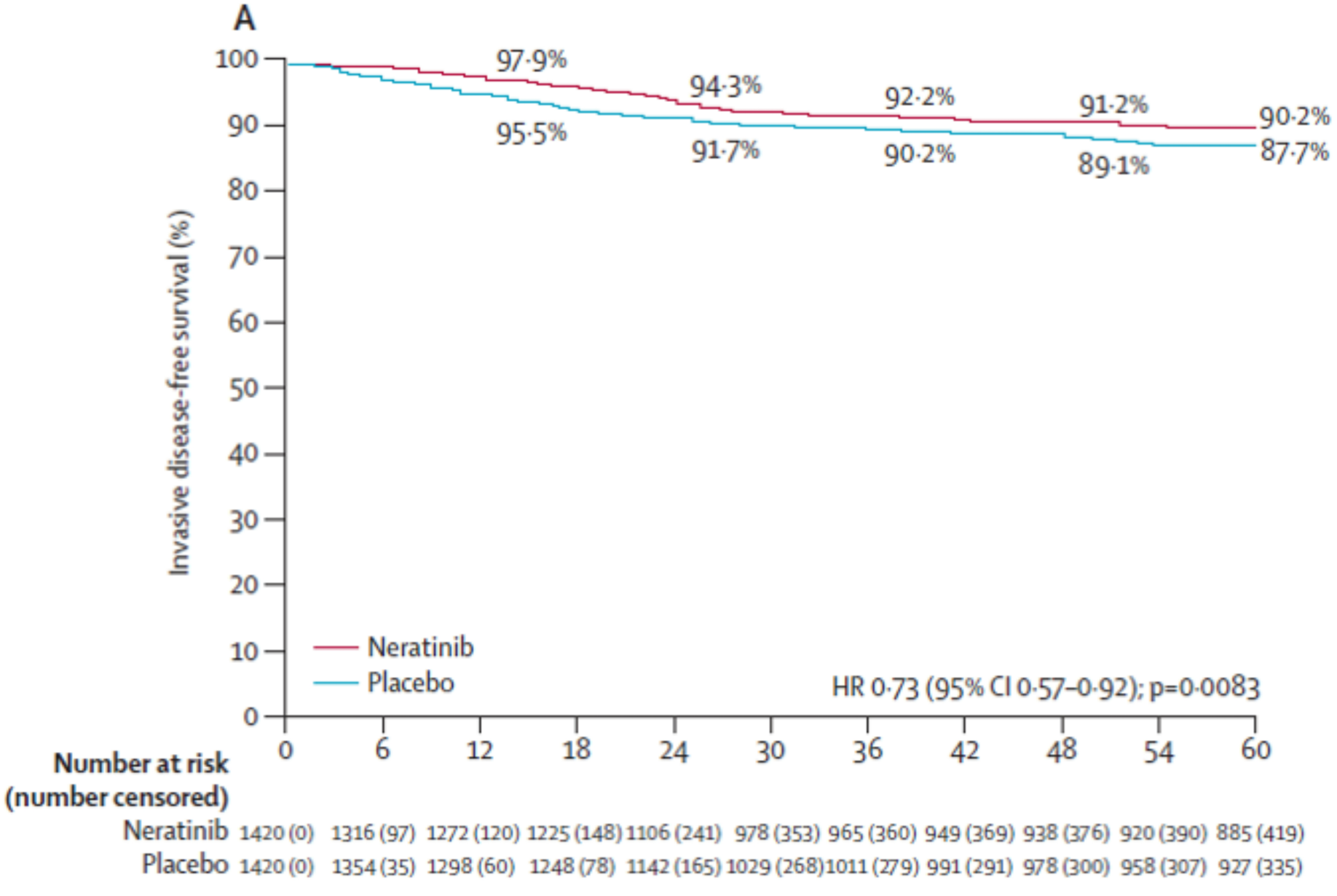
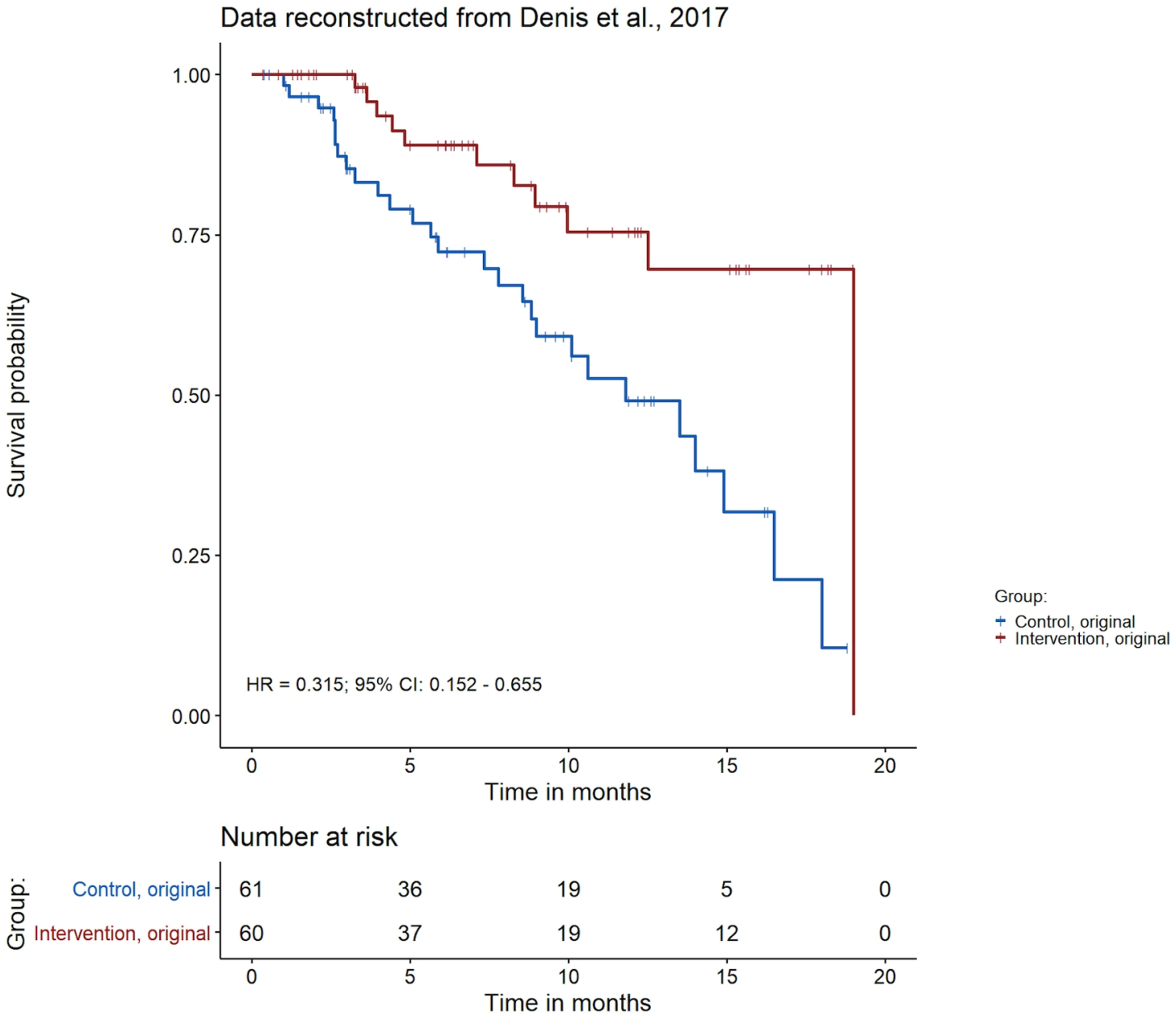
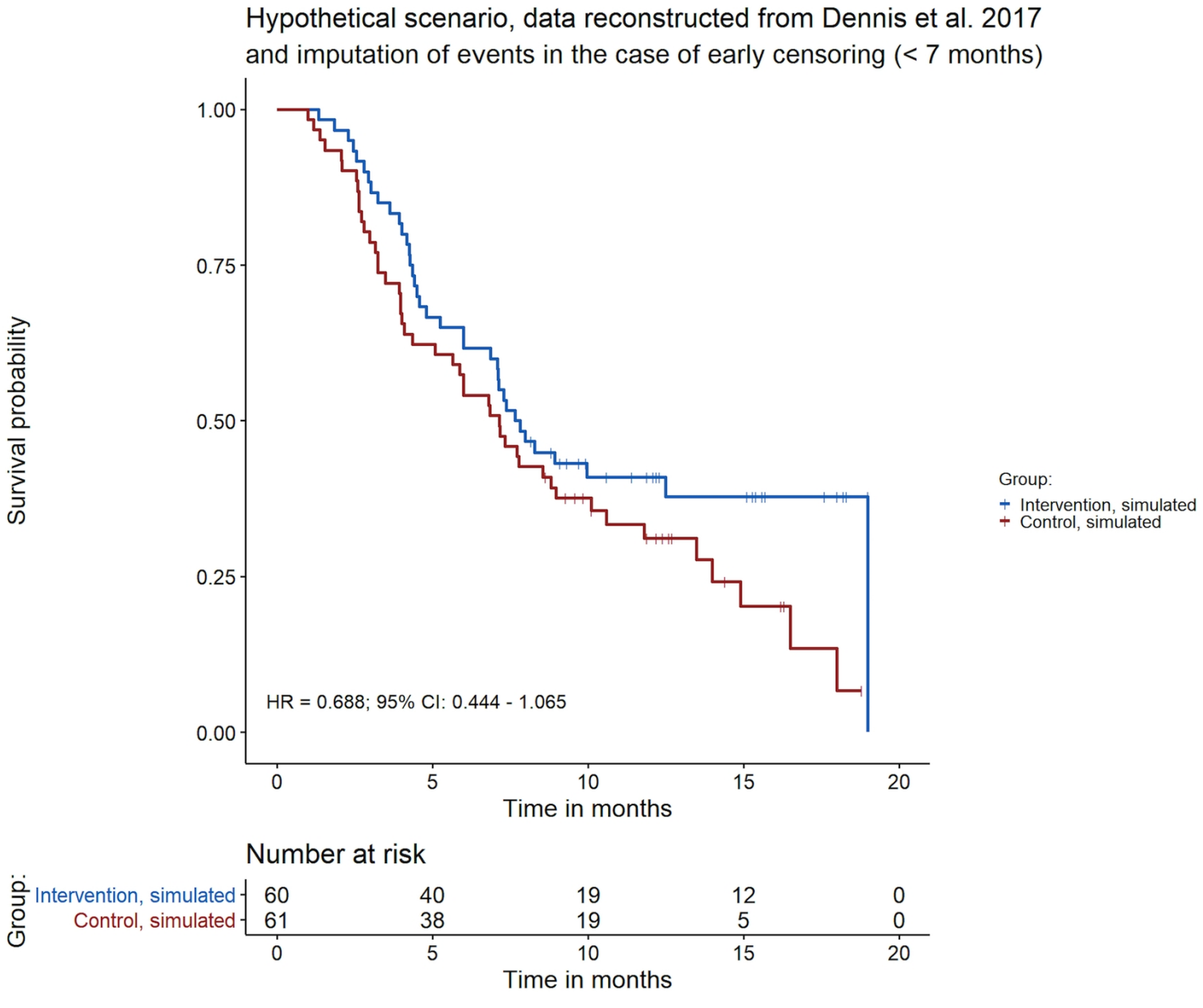

End of study
Participant 1
Participant 2
Participant 3
Participant 4
TIME
Experienced the event
End of study censored
End of study censored
Loss to follow-up censored
= Event of interest
= Censored
= Enrollment/ beginning of observation


Hazard ratio for death = 0.32, 95% CI = 0.15 to 0.67, P = .002
Experimental arm
Control arm
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
Median overall survival (months)
Experimental arm (n = 60): 19.0, 95% CI = 12.5 to NC
Control arm (n = 61): 12.0, 95% CI = 8.6 to 16.4
9-months overall survival
Experimental arm (n = 60): 78.9%, 95% CI = 61.7 to 89.0
Control arm (n = 61): 58.7%, 95% CI = 42.7 to 71.6
12-months overall survival
Experimental arm (n = 60): 74.9%, 95% CI = 56.6 to 86.4
Control arm (n = 61): 48.5%, 95% CI = 31.9 to 63.2
0
5
10
15
20
Time, mo
No. at risk
Exp. arm: 60 37 19 12
Control arm: 61 36 19 5


A
100
90
80
70
60
50
40
30
20
10
0
Invasive disease-free survival (%)
97·9%
94·3%
92·2%
91·2%
90·2%
95·5%
91·7%
90·2%
89·1%
87·7%
Neratinib
Placebo
HR 0·73 (95% CI 0·57–0·92); p=0·0083
0
6
12
18
24
30
36
42
48
54
60
Number at risk
(number censored)
Neratinib 1420 (0) 1316 (97) 1272 (120) 1225 (148) 1106 (241) 978 (353) 965 (360) 949 (369) 938 (376) 920 (390) 885 (419)
Placebo 1420 (0) 1354 (35) 1298 (60) 1248 (78) 1142 (165) 1029 (268) 1011 (279) 991 (291) 978 (300) 958 (307) 927 (335)


Data reconstructed from Denis et al., 2017
Survival probability
1.00
0.75
0.50
0.25
0.00
HR = 0.315; 95% CI: 0.152 - 0.655
0
5
10
15
20
Time in months
Group:
Control, original
Intervention, original
Number at risk
Group:
Control, original
Intervention, original
61
36
19
5
0
60
37
19
12
0
0
5
10
15
20
Time in months


Hypothetical scenario, data reconstructed from Dennis et al. 2017
and imputation of events in the case of early censoring (< 7 months)
Survival probability
1.00
0.75
0.50
0.25
0.00
HR = 0.688; 95% CI: 0.444 - 1.065
0
5
10
15
20
Time in months
Group:
Intervention, simulated
Control, simulated
Number at risk
Group:
Intervention, simulated 60 40 19 12 0
Control, simulated 61 38 19 5 0
0
5
10
15
20
Time in months

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5. Manuscript Title: GRADE Guideline: Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with

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Section 1. Identifying Information

1. Given Name (First Name): Marialena
2. Surname (Last Name): Trivella
3. Date: 1/13/2020

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title: GRADE Guideline: Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with

6. Manuscript Identifying Number (if you know it)

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 1. Identifying Information

1. Given Name (First Name): Nina
2. Surname (Last Name): Kreuzberger
3. Date: 1/24/2020

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title: Censoring of participants with missing data in intervention studies

6. Manuscript Identifying Number (if you know it)

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Section 1. Identifying Information

1. Given Name (First Name): Nicole
2. Surname (Last Name): Skoetz
3. Date: 1/30/2020

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title: GRADE Guideline: Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with

6. Manuscript Identifying Number (if you know it)

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Section 4. Intellectual Property -- Patents & Copyrights

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Ralf
2. Surname (Last Name): Bender
3. Date: 1/14/2020

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title

Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with missing data in

6. Manuscript Identifying Number (if you know it)

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Section 1. Identifying Information

1. Given Name (First Name) | 2. Surname (Last Name) | 3. Date

Reem | Mustafa | 1/20/2020

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title

GRADE guidance: Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with

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Sarah | Nevitt | 1/13/2020

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Benjamin | Djulbegovic | 1/13/2020

4. Are you the corresponding author? ☐ Yes ☐ No

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Elie | Akl | 1/21/2020

4. Are you the corresponding author? ☐ Yes ☑ No

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Elvira C | van Dalen | 1/13/2020

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title

GRADE guideline Rating the certainty in time-to-event outcomes – Study limitations due to censoring of participants with

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CRediT authorship contribution statement

Marius Goldkuhle: Writing - original draft, Methodology, Writing - review & editing, Conceptualization, Project administration. **Ralf Bender:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Elie A. Akl:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Elvira C. van Dalen:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Sarah Nevitt:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Reem A. Mustafa:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Gordon H. Guyatt:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Marialene Trivella:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Benjamin Djulbegovic:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Holger Schünemann:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Michela Cinquini:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Nina Kreuzberger:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization. **Nicole Skoetz:** Writing - original draft, Writing - review & editing, Methodology, Conceptualization, Supervision.