Author's response to reviews

Title: Calculation of NNTs in RCTs with time-to-event outcomes: A literature review

Authors:

Mandy Hildebrandt (Mandy.Hildebrandt@iqwig.de)
Elke Vervoelgyi (Elke.Vervoelgyi@iqwig.de)
Ralf Bender (Ralf.Bender@iqwig.de)

Version: 2 Date: 30 April 2008

Author's response to reviews: see over
Response to the Reviewers

30.04.2008

General response to the editor and all reviewers:

During the preparation process of table 3 and the discussion of the helpful comments of Reviewer 1 (J. Lubsen) we realized that a few articles had been classified to the wrong group of articles. This explains the slight differences in the presented article numbers compared to the first submission.

We thank the five reviewers for their useful comments which improved the manuscript in our opinion. Additionally, we thank the editor for extending the deadline for the submission of the revised manuscript.

Response to Reviewer 1 (Jacobus Lubsen):

1) We defined exactly what we mean by NNT in the Background, namely the usual effect measure to quantify the impact of a treatment in terms of patient numbers that have to be treated to avoid one event (regardless of the treatment duration).

2) We explained in detail that the arguments of reviewer 1 that in the case of chronic disease and continuous treatment the NNT "has to be derived from the underlying hazards" do not hold for the common NNT definition we use. The reviewer equates by mistake follow-up time with treatment duration. We agree that in the case of continuous treatments one should be careful if a cost-effectiveness analysis should be made on the basis of NNTs. The treatment costs depend on the duration of treatment and this is shorter than the follow-up time for patients having an event before the end of the study. Thus, simple NNTs are insufficient for cost-effectiveness analyses in the case of chronic diseases and continuous treatments. If the duration of treatment is important, more complicated methods are required, e.g. survival techniques for time dependent covariates. However, these methods are not considered in this paper because the problem of treatment duration is independent from the type of outcome (binary or time-to-event data) and independent from the effect measure (NNT, risk difference, odds ratio, hazard ratio).

3) We explained in detail that the reciprocal of a hazard difference and the reciprocal of a risk difference are different effect measures. Only in the case of exponential survival times and rare events the hazard difference can be used to approximate the risk difference. Thus, only in the situation of exponential survival times and rare events NNTs (as defined above) can be approximated by inverting hazard differences.
Response to Reviewer 2 (Jorgen Nexoe):

1) We changed the words "literature survey" to "literature review". In the revised version we explain and discuss the different methods for calculating NNTs with time-to-event outcomes. Thus, we did not change the other part of the title, because we think that it appropriately fits with the content of our revised manuscript.

2) We added a number of references concerning the highly controversial discussion in the literature about the usefulness of NNTs.

3) We do not think that the frequent use of inappropriate calculation methods for NNTs in the case of survival times indicates that the NNT itself is difficult to understand. Would the reviewer conclude from the fact that often the Wald method is inappropriately used to calculate confidence intervals for risks close to 0 or 1 that the concept of confidence intervals is difficult to understand? Our result that frequently inappropriate methods for NNT calculation are used in the case of survival times underlines the requirement to point out that special methods based on survival time techniques have to be used in this situation as described in the Discussion.

4) See point 2)

5) A detailed discussion about the usefulness of NNTs to present the results of RCTs is beyond the scope of the paper.

Response to Reviewer 3 (Dirk Stengel):

1) We deleted the former Table 1. We added a flow chart according to the QUOROM statement to describe the trial selection procedure.

2) We described details about the 35 studies presenting NNTs for time-to-event outcomes in the new Appendix.

3) We added the information about the published and recalculated NNTs for the studies using inappropriate calculation methods (where possible).

Response to Reviewer 4 (Islay Gemmel):

1) changed

2) changed

3) changed

Response to Reviewer 5 (Andy Grieve):

1) The four leading medical journals we used for our review are frequently considered in literature reviews. We added a statement in the Discussion that it can be expected that a broader review containing also medical journals of lower rank would lead to even a higher proportion of papers with inadequate NNT calculation.

2) We deleted the statement from the Conclusion.
3) We added a number of references concerning the highly controversial discussion in the literature about the usefulness of NNTs.

4) We deleted the percentages from the Tables.

5) We extended the references concerning interval estimation of NNTs. We did not repeat the corresponding discussion as this is published in the statistical as well as in the medical literature.