natamycin was associated with a three-line improvement in BSCVA at 3 months (logMAR −0.29, 95%CI −0.50 to −0.08) and reduced odds of perforation/TPK (OR = 0.35, 95%CI 0.15 to 0.82). Results were robust to multiple sensitivity analyses, including flexible functional forms of visual acuity and restricting the analysis to narrower bandwidths around the cutoff (20/400).

Conclusions

While RD and RCT results were similar, the RD effect was larger, although not significantly so (P = 0.52 for BSCVA). These results suggest that the use of threshold rule in an RD design may be useful for estimation of causal effects under conditions where trials are not possible, or for replication of trial results.

O11

Evaluation of failure time surrogate endpoints in individual patient data meta-analyses of randomized clinical trials. A poisson approach

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Surrogate endpoints are often used in randomized clinical trials instead of well-established hard endpoints for practical convenience: they are usually cheaper, more rapid, or less invasive to measure. The meta-analytic approach relies on two measures of individual level surrogacy (R_indiv^2) and trial level surrogacy (R_trial^2) [1]. This approach was extended to the survival data case [2], with a first step using copulas to measure individual level surrogacy in terms of Kendall's tau and a ?A3B2 show $132#?>second step using weighted regression to compute R_trial^2. Despite being the reference method for survival data today, this approach can suffer from convergence problems in the second step, which is the one which computes R_trial^2. In the present work, we considered a bivariate survival model with (i) an individual random effect shared between the two endpoints to measure individual level surrogacy (Kendall's tau) and (ii) correlated treatment-by-trial interactions to measure R_trial^2. We used auxiliary mixed Poisson models to jointly estimate the parameters of such model with piecewise constant baseline hazards. To reduce the computational complexity, we also considered reduced Poisson models, accounting for only individual- or only trial-level surrogacy. We studied via simulations the operating characteristics of this mixed Poisson approach as compared to the two-step copula approach, with Clayton, Plackett and Hougaard copulas and with or without adjustment of the second-step regression for measurement error. The Clayton copula model was the most robust and reliable of the copula models compared; the Poisson model with both individual- and trial-level random effects outperformed its reduced equivalents. We also applied the methods to an individual patient data meta-analysis in advanced/recurrent gastric cancer (4069 patients from 20 randomized trials). As the convergence rate and the estimation results may vary substantially between models, we encourage the user to carefully evaluate the convergence of each alternative approach and to report the results of different models. We implemented the methods presented here in the R package surrosurv (https://cran.r-project.org/package=surrosurv).

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O12

Influence of peer review on the reporting of primary outcome(s) and statistical analyses of randomised trials

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Objective

Selective reporting of outcomes in clinical trials is a serious problem. We aimed to investigate the influence of the peer review process within biomedical journals on the reporting of primary outcome(s) and statistical analyses of reports of randomised trials.

Methods

Each month, we searched PubMed (between May 2014 and April 2015) to identify primary reports of randomised trials published in six high impact general and 12 high impact specialty journals. The corresponding author of each trial publication was then contacted by email asking them to complete an online survey investigating changes made to their manuscript as part of the peer review process. Our main outcome was the nature and extent of changes made to manuscripts by authors as part of the peer review process, in relation to reporting of the primary outcome(s) and/or primary statistical analysis. We also assessed how often authors follow these requests and whether this was influenced by specific journal or trial characteristics.

Results

Nine hundred eighty-three corresponding authors were invited to take part in the online survey, of which 258 (29%) responded. The majority of trials were multicentre ($n = 191$; 74%), parallel group ($n = 225$; 86.5%); median sample size = 325 (IQR 138 to 1010). Half assessed drug interventions ($n = 127$; 49%), over half were non-industry funded ($n = 159$; 62%) and the primary outcome was clearly defined in 92% ($n = 238$), of which the direction of treatment effect was statistically significant in 48%.

The majority of authors responded (1–10 Likert scale) they were satisfied with the overall handling (mean 8.6, SD 1.5) and quality of peer review (mean 8.5, SD 1.5) of their manuscript by the journal. Only 3% ($n = 8$) said the editor or peer reviewers asked them to change or clarify the trial's primary outcome. However, 27% ($n = 69$) reported they were asked to change or clarify the statistical analysis of the primary outcome; most responded they fulfilled the request, the main motivation being to improve the statistical methods ($n = 38$; 55%) or avoid rejection ($n = 30$; 43.5%). Overall there was no difference between authors being asked to make this change and the type of journal, intervention, significance of the primary outcome or funding source. 36% ($n = 94$) responded that they were asked to include additional analyses that had not been included in the original manuscript; in 77% ($n = 72$) these were not pre-specified in the protocol. 23% ($n = 60$) were asked to modify their overall conclusion, in most cases ($n = 53$; 88%) to provide a more cautious interpretation.

Conclusion

Overall there was little evidence of a negative impact of the peer review process in terms of selective reporting of the primary outcome. Most changes requested resulted in improvements to the manuscript, improving clarity of statistical methods used, and providing more cautious conclusions. However, some changes requested by peer reviewers were deemed inappropriate and could have a negative impact on reporting of the final publication, such as the adding of unplanned additional analyses.