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A Novel Framework to Assess Non-Inferiority in National Institute for Health and Care Excellence (NICE) Cost-Comparison Evaluations (CCEs) where Network Meta-Analyses (NMAs) Report Non-Statistically Significant Differences

Ben Burgess, PhD; Sophie Ip, PhD; Nicole Downes, BSc (Hons); Archie Walters, MSc; Clare Dadswell, PhD; Steven J. Edwards, DPhil

Introduction

- In 2017, the National Institute for Health and Care Excellence (NICE) introduced the cost-comparison evaluation (CCE) pathway which comprises simpler comparisons of costs and resources compared to standard technology appraisals.[1]
- However, the CCE pathway is only appropriate when the new treatment is equivalent, or non-inferior, in terms of clinical effectiveness, relative to relevant comparators.[1]
- Despite this fundamental assumption, recent systematic literature reviews (SLRs) have reported that clinical equivalence, or non-inferiority, is not consistently appraised across CCEs.[2,3]
- Accordingly, there is a lack of clarity for NICE committees, External Assessment Groups (EAGs), and pharmaceutical companies regarding how equivalence, or non-inferiority, should be assessed within CCEs.[2-4]
- This lack of clarity is particularly important where the results of indirect treatment comparisons (e.g., network meta-analyses [NMAs]) are statistically non-significant. In such scenarios, there is limited guidance on how to assess whether a new treatment may be considered non-inferior relative to a comparator.[2,3]
- Likewise, it has previously been noted that no clear visualisations exist to assess non-inferiority in NICE CCEs.[2]

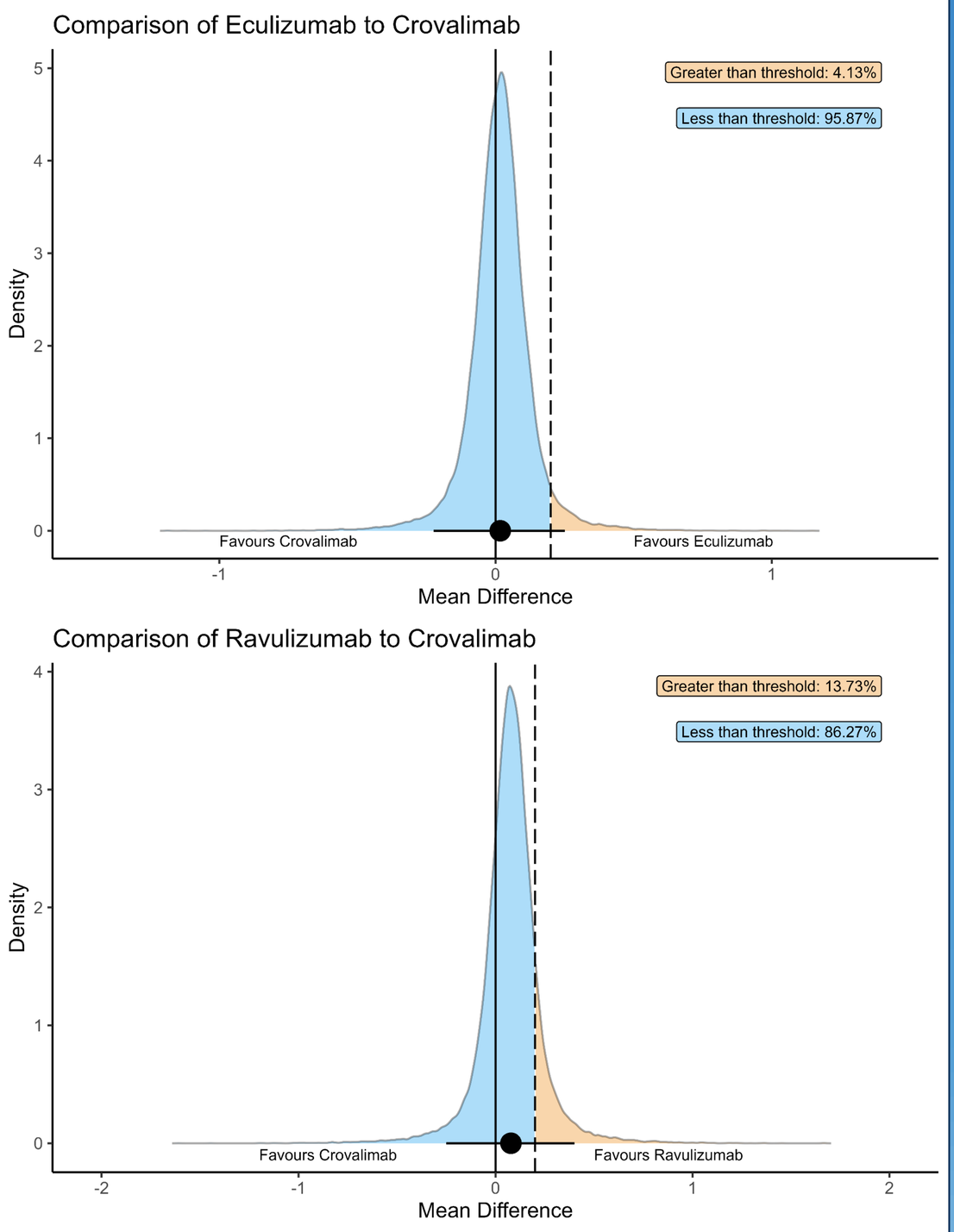
Methods

- A new framework was developed as an 'add-on' to a typical Bayesian NMA, which uses empirical cumulative density functions to calculate the probability that a treatment is non-inferior to a comparator using a non-inferiority margin (NIM).
- The framework produces a 'point-and-density plot' that showcases the point estimate and 95% credible intervals (CrIs) of a treatment comparison as well as the distribution of Bayesian iterations, and the probability of non-inferiority.
- Although arbitrary, it is suggested that a 95% probability threshold may be a sufficiently 'high-bar' to assess non-inferiority.
- This framework was applied to a recent NICE CCE (TA1019)[5] for crovalimab to treat paroxysmal nocturnal haemoglobinuria (PNH) by conducting an NMA for the co-primary endpoint of transfusion avoidance, for which the NMA results were statistically non-significant.

Results

- The point estimates reported in this case study align with those reported in TA1019 and are shown in Figure 1. However, the 95% CrIs calculated in this case study are wider than those reported in TA1019. This is likely due to the use of informative Bayesian priors in TA1019 that were not reported (and so not incorporated into the case study NMA).
- Within TA1019, a NIM of 0.20 was reported, which was used in this case study comparing crovalimab to eculizumab and ravulizumab.
- For crovalimab vs eculizumab and crovalimab vs ravulizumab, the point estimates did not favour crovalimab, and the 95% CrIs for both comparisons overlapped both 0 and the NIM. However, the point-and-density plots indicate a 95.87% and an 86.27% probability that crovalimab was non-inferior relative to eculizumab and ravulizumab, respectively.
- Based on the 95% probability threshold, there is evidence to suggest that crovalimab is non-inferior relative to eculizumab, but not to ravulizumab.

Figure 1. Point-and-density plots for the comparison of crovalimab to eculizumab (upper panel) and ravulizumab (lower panel) for the endpoint of transfusion avoidance.



The threshold for traditional hypothesis testing is shown by the solid line, while the dashed line indicates the non-inferiority margin. The pooled estimate and 95% Credible Intervals are shown by the black circle and error bars.

Objective

- This research aimed to develop a new framework to allow NICE committees to determine whether a new treatment is non-inferior to an existing comparator when faced with statistically non-significant NMA results.

Conclusions

- The framework addresses a known challenge with evaluating CCEs, namely, how to assess clinical similarity when the results of an NMA indicate that there is no evidence for a statistically significant difference.
- Through the use of a case study of a recent NICE CCE, the framework is shown to allow easily interpretable assessments of non-inferiority to be made through the use of dedicated outputs.

References

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