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Comparing Ophthalmology Treatments via the Integration of IPD and Aggregate-level Data: **Which Matching Adjusted Indirect Comparison (MAIC) Approach is Best?**

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Objectives

Indirect Treatment Comparison (ITC) methods aim to estimate the comparative effectiveness of treatments, often in the absence of direct evidence from head-to-head RCTs. However, naive ITCs can lead to biased comparisons, especially in situations where baseline patient characteristics (e.g. age, disease severity) that are predictive of efficacy outcomes, or confounded with treatment, differ between studies.

Matching adjusted indirect comparison (MAIC) approaches are extremely useful in this setting, as they can reduce baseline imbalances between studies. These MAIC approaches typically seek to re-weight Individual Patient Data (IPD) in a study such that the distribution(s) of key baseline characteristics match those of the aggregate-level characteristics from another study (typically a study published by a competitor). Essentially, we can then address important questions such as "What efficacy response would we have observed in our clinical trial had we enrolled similar patients to our competitor?"

The aim of our analysis was to use an ophthalmologic case study to investigate the overall performance of three MAIC methods: Signorovitch (SV)[1], Entropy Balancing (EB)[2], and Polynomial Weighting (PW)[3].

Methods

Each of the three MAIC methods were applied to IPD collected in phase 3 RCTs, whose main objective was to investigate the relative efficacy anti-VEGF therapies in the treatment of visual impairment due to diabetic macular edema. The IPD comprised of n=368 patients whose important baseline characteristics, namely best corrected visual acuity (BCVA) and central retinal thickness (CRT), differed from the 'target' patient population (n=572)[3].

The goal of the analysis was to re-weight each patient in the IPD such that the weighted summary statistics (mean, SDs) for baseline BCVA and CRT matched those in the target population.

We calculated the Effective Sample Size (ESS) for each method, which is a measure of the spread of the estimated weights across the patients. The closer the weights are to a value of one, then the higher the ESS will be. Importantly, a higher ESS will result in more precise estimates of comparative effectiveness. In addition, we assessed each MAIC method on its ability to 'minimise' large weights (i.e. avoiding certain patients having undue influence on the results). The Pearson correlation 'r' was used to assess the pairwise agreement between each of the three methods. Finally, each method was evaluated on other important aspects such as flexibility, transparency, ease of implementation, industry acceptability and popularity.

Table 1: Overall MAIC performance characteristics

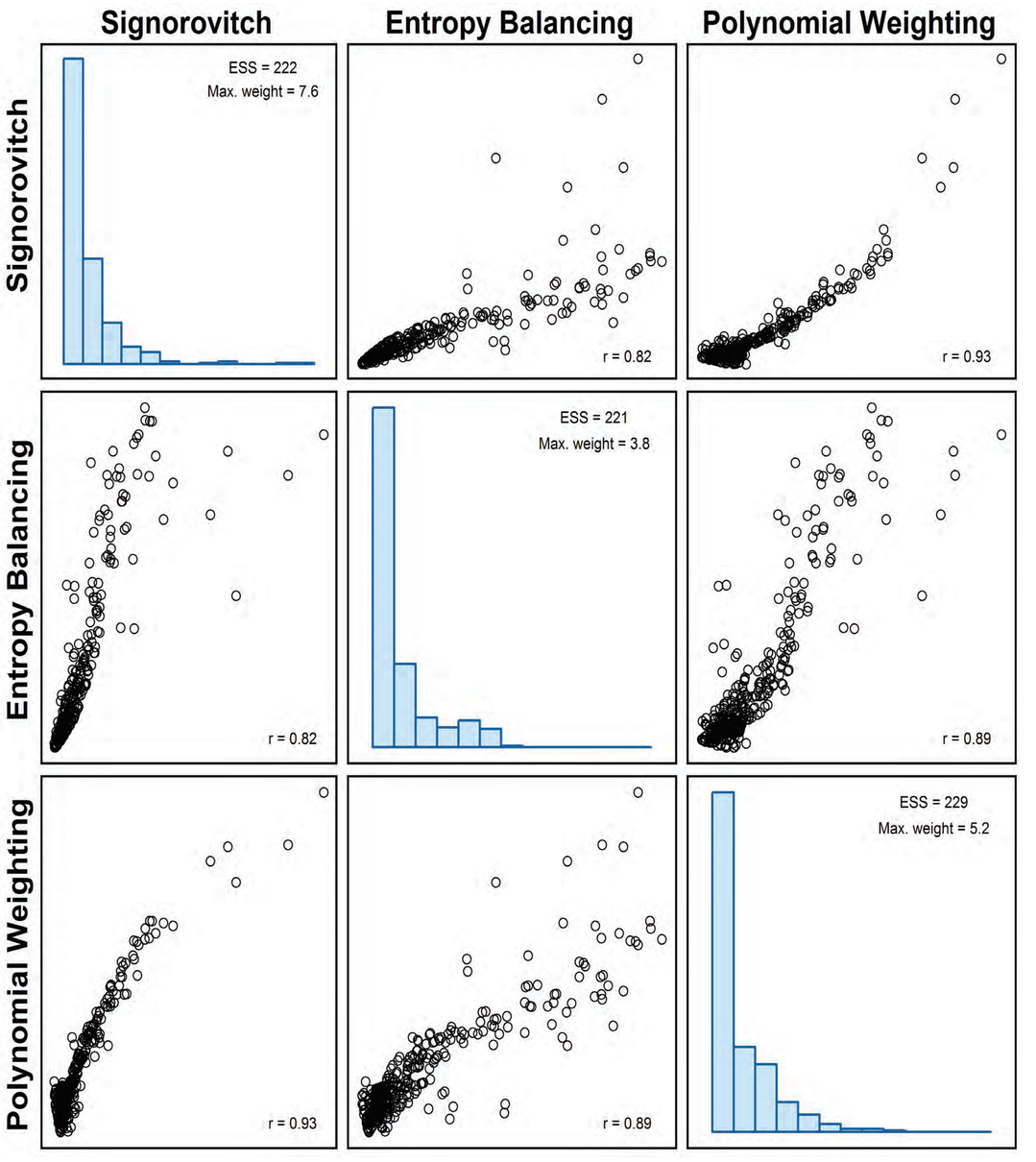
Characteristic	Signorovitch (SV)	Entropy Balancing (EB)	Polynomial Weighting (PW)
Central moment matching[a]	🙂	🙂	🙂
Non-central moment matching[b]	☹️	☹️	🙂
ESS maximisation[c]	☹️	☹️	🙂
Low maximum weights	☹️	🙂	😐
Established methodology	🙂	🙂	😐
Pharma industry use	🙂	☹️	☹️
Simplicity	😐	☹️	🙂
Ease of implementation	🙂	😐	😐
Software / code availability[d]	🙂	🙂	☹️

[a] Anecdotal evidence suggests possible convergence issues with the SV method in small samples.
[b] SV & EB methods do not explicitly allow for matching against non-central moments, e.g. percentiles.
[c] ESS maximisation is a claimed benefit of the EB method.
[d] SAS & R code for the PW method are available from the authors upon request.

Results

All three MAIC methods were able to match the target, aggregate-level data (both means and SDs). Each method estimated IPD weights that were broadly in line with one another. The strongest correlation was observed between the SV and PW methods (Figure 1). The PW method outperformed the other methods in terms of maximising the ESS. However, the EB method estimated the lowest of the maximum weights.

Figure 1: Comparison of IPD weights as estimated by three MAIC methods



Results (cont.)

The EB method was the most challenging to implement - use of the R package 'ebal'[4] appears to require the user to simulate target IPD. The SV method (fitted using amended R code from NICE[5]) was the simplest. The PW method appears to provide the greatest flexibility to the user, given its ability to match against both 'central' moments (e.g. mean, SD) as well as 'non-central' ones (e.g. median, IQR). This method is arguably also the simplest for non-statisticians to understand, helped by the transparency in its workings. There appears to be wide-spread industry acceptance of the SV method, while the other two methods remain relatively unknown/unused. The availability of published case studies and statistical code reflect this.

Conclusions

Whilst the Signorovitch method has become almost synonymous with MAIC, the Entropy Balancing and Polynomial Weighting methods offer potentially superior performance. In particular, the Polynomial Weighting method provides greater flexibility, transparency, and simplicity.

In the absence of head-to-head trial data, these new MAIC approaches should provide less biased and more precise estimates of comparative effectiveness – ultimately leading to better decision making by regulators and payers.

References

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