A Novel ITC Approach: Matching Patient-Level Data to Study-Level Summary Means and Variances

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#1 Objectives
Indirect Treatment Comparisons (ITCs) are used to contrast the effectiveness of two or more treatments, and are usually undertaken in the absence of head-to-head information. However, these ITCs are less accurate in situations where baseline patient characteristics that are predictive of efficacy outcomes (e.g., age, disease duration) differ between studies. Any clinically meaningful variation in these characteristics between the studies should be adjusted for in the statistical analyses in order to arrive at more reliable estimates of treatment differences.

At present, many ITCs use a comparison of a sponsor’s Individual Patient Data (IPD) with aggregate data (weighted means and standard deviations) from their competitors’ studies. Various methods currently exist which allow for the matching of the means of these baseline characteristics between IPD and aggregate data, but crucially not their variances as well. Any differences in variation will lead to biased ITC p-values, heightening the risk of a false conclusion on relative efficacy.

#2 Methods
Our method matches both means and standard deviations (SDs) across multiple baseline patient characteristics between IPD and aggregate data.

The Weighted-IPD method runs as follows:
1. For each baseline characteristic, obtain a weight value for each patient in the IPD via a polynomial with randomly chosen coefficients (a, b, c), e.g. \( f_{\text{age}} = a + b \times \text{age} + c \times \text{age}^2 \)
2. Using the weights in step one, calculate a single weight for each individual patient as the product of all the weights for that patient, e.g. \( w_{\text{patient}} = f_{\text{age}} \times f_{\text{disease severity}} \)
3. Using the weights obtained in step 2, calculate the weighted means and SDs of each of the baseline characteristics in the IPD
4. Compare the weighted means and SDs in the IPD with the aggregate means and SDs and calculate a suitable loss function, e.g. sum of squared differences
5. Repeat steps 1-4 thousands of times
6. Identify the optimal weights such that the differences in means and SDs between the weighted IPD vs. aggregate data are as small as possible
7. Run the standard ITC analysis, but using the set of weights identified in step 6 to re-weight the IPD.

#3 Results
Table 1 shows the differences in the two baseline characteristics between the original IPD and aggregate data under each of the two treatment types (anti-VEGF & laser). The results of the Weighted-IPD method are shown in the final column under each treatment.

Table 1. Baseline BCVA and CRT for the Sponsor (IPD) and Competitor (Aggregate) Studies

<table>
<thead>
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<th>Characteristic</th>
<th>Sponsor (IPD)</th>
<th>Competitor (Aggregate)</th>
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<tbody>
<tr>
<td>BCVA (letters) Mean</td>
<td>64.1</td>
<td>60.2</td>
</tr>
<tr>
<td>SD</td>
<td>10.3</td>
<td>12.8</td>
</tr>
<tr>
<td>CRT (μm)</td>
<td>435</td>
<td>509</td>
</tr>
<tr>
<td>SD</td>
<td>126</td>
<td>151</td>
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RBCVA: best corrected visual acuity; CRT: central retinal thickness; SD: standard deviation; VEGF: vascular endothelial growth factor.

As can be seen in Table 1, our newly developed Weighted-IPD method was extremely successful in matching both the means and SDs across these two predictors of treatment efficacy.

Any subsequent statistical analysis comparing the efficacy outcomes between these two treatments could then easily incorporate these weights. Essentially, we can then address important questions such as:

“What efficacy response would we have observed in our clinical trial if we had enrolled similar patients to our competitor?”

#4 Conclusions
The ability to match both location (means) & spread (SDs) between IPD and aggregate/study-level data is critical in order to reliably estimate the statistical significance of indirect treatment comparisons.

Current comparative effectiveness methods fail to match both location and spread – our novel approach provides a solution to this problem.

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Figure 1: Weighted-IPD Method

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#2 Methods (cont.)
The Weighted-IPD method is depicted visually in Figure 1.

We highlight this method here with a case study of anti-VEGF therapies in the treatment of visual impairment due to diabetic macular edema. Our aim was to re-weight the IPD such that the baseline visual acuity (BCVA) and retinal thickness (CRT) matched the aggregate data. The studies included in the IPD and aggregate data all contained laser as their standard therapy. Our ultimate goal was to make a more accurate efficacy comparison of the two anti-VEGF treatments arms (IPD vs. aggregate).

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