Outcome Reporting Bias in Randomised Controlled Trials: An assessment using Multivariate Meta-Analysis

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Abstract

- Selective outcome reporting occurs when a subset of the originally recorded outcomes in a trial are selectively reported in a publication based on their results.
- We assessed 21 systematic reviews that considered treatments for rheumatoid arthritis. We analysed the impact of Outcome Reporting Bias (ORB).
- For the example of Auranofin, high risk of ORB were awarded to at least one trial for tender joints count, pain, physician global and acute phase reactant.
- Findings of our analysis show that multivariate meta-analysis offers one such sensitivity analysis to adjust for ORB when there is missing trial data for many review outcomes.

Materials and Methods

- Systematic reviews published by the Cochrane Musculoskeletal Group that considered treatment of rheumatoid arthritis were identified.
- Reviews were assessed for Outcome Reporting Bias (ORB) in relation to an established core set of eight outcomes for rheumatoid arthritis (Table 1). A nine-point classification system previously developed was used to assess the potential risk of ORB2 (Table 2).
- The impact of ORB was assessed by comparing estimates from a univariate and multivariate meta-analysis for both fixed and random effects models3.
- To calculate covariances4 to be used in the Multivariate random effects model we considered within-study correlations between the core outcomes which were obtained from analysis of individual patient data conducted by a previous study.

Table 1 Core outcomes set for assessment of rheumatoid arthritis1

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<tbody>
<tr>
<td>Acute Phase Reactants (ESR) or C-reactive Protein (CRP) (APR)</td>
<td>Radiological Damage (RD)</td>
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Table 2 ORBIT Classification System

| A | Analysed p<0.05 (High Risk) |
| B | Analysed p≥0.05 (Low Risk) |
| C | Analysed but insufficient for MA (Low Risk) |
| D | Analysed but no results reported (High Risk) |

Clear that the outcome was measured and analysed

E | Measured but not necessarily analysed (High Risk) |
F | Measured but not necessarily analysed (Low Risk) |
G | Not mentioned – LIKELY measured (High Risk) |
H | Not mentioned – UNLIKELY measured (Low Risk) |
I | Unknown whether the outcome was measured |
J | Outcome NOT measured (No Risk) |

Flow Chart of the Systematic Reviews assessed

Number of rheumatoid arthritis reviews identified on the Cochrane Library

<table>
<thead>
<tr>
<th>Number of trials a=122</th>
<th>b=DIAS</th>
<th>c=DMARDs</th>
<th>d=Biologics</th>
<th>e=Biologics</th>
<th>f=Glucocorticoids</th>
</tr>
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<tbody>
<tr>
<td>Reviews requiring an further assessment: n=6</td>
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Number of trials a=212 | b=DIAS | c=DMARDs | d=Biologics | e=Biologics | f=Glucocorticoids |

Could not assess trial reports further: n=17 |

Trials assessed: n=155 |

Trials fully reporting all core outcomes: n=21 |

Not fully reporting on all core outcomes: n=52 |

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Figure 1 Overall missing data and missing data as result of high ORB classification (%)

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Figure 2 Multivariate Random effects Meta-analysis (REML) (Auranofin vs. placebo)

Results

- We assessed 21 SRs. In particular we assessed 155 clinical trials (94 disease modifying anti-rheumatic drugs DMARDs, 45 biologics and 16 glucocorticoids) (Flow Chart).
- The current analysis of the 21 SRs assessed (Figure 1) has demonstrated a high percentage of missing data for some outcomes (Pain, Patient global and Physician Global).
- Some outcomes considered are highly correlated (Pain and Pat.Global, 91%) other outcomes are low correlated (APR and SJC 17%).

- When we applied the multivariate random effects meta-analysis for a systematic review of Auranofin versus placebo (Figure 2), we found that some outcomes (TJC, Pain) the shift towards the null suggests that ORB could be a problem because the univariate result overestimates the treatment effect.

Conclusion

- Multivariate meta-analysis offers a solution to adjust for the impact of missing data and ORB.
- In the review showed in this poster, the summary treatment effect estimates and their statistical significance changed importantly when multivariate meta-analysis was used to reduce ORB through additional information from correlated outcomes.

References