How is rescue medication defined, reported, and adjusted for in randomised controlled trials?

A systematic review

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Objectives

- Estimate the proportion of articles that define and report the use of rescue medication.
- Evaluate the statistical methods used to adjust for rescue medication use on the primary outcome.
- Estimate the change in treatment effect after adjustment for rescue medication.

Methods

- Phase II/III randomised controlled trials that evaluate the efficacy of a set of pre-established monoclonal antibodies in patients with chronic asthma or chronic eczema were eligible for this review.

Results

- 60 RCTs were identified of which all allowed use of rescue medication in the trial.
- 28 reported rescue medication use in the primary publication; 27 summarised rescue use by arm.
- 9 trials undertook a rescue-adjusted analysis on the primary outcome.
- 1 trial used an optimal method of analysis.

<table>
<thead>
<tr>
<th>Methods of rescue-adjusted analysis</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>ANCOVA model setting efficacy data to missing after rescue medication use (or dropout) and LOCF method used to impute missing values</td>
<td>4 (44)</td>
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<tr>
<td>CMH test specifying participants as non-responders at rescue medication initiation (or study withdrawal)</td>
<td>4 (44)</td>
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<td>Mixed model excluding assessments from the FAS if they were obtained at scheduled visits that were preceded by a limited subset of medications that could confound interpretation (Inc. rescue medication).</td>
<td>1 (11)</td>
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<td>Total</td>
<td>9 (100)</td>
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Conclusions

- Rescue medication is frequently permitted in trials but is not routinely reported.
- Despite evidence of imbalance in rescue use between arms, few articles showed interest in isolating the treatment effect in order to obtain rescue-adjusted treatment effect.
- Trials that did aim to obtain a rescue-adjusted treatment effect frequently employed methods that are highly vulnerable to introducing bias into the estimate.