SWAR 35: Impact of adjustment of baseline factors on meta-analysis of randomised trials

Objective of this SWAR
To explore the impact of adjustment for known prognostic factors in trials when prognostic characteristics are (a) imbalanced or (b) balanced across randomised groups.

Study area: Analysis
Sample type: Randomised trials
Estimated funding level needed: Low

Background
This Study Within a Review (SWAR) [1] will run in parallel with an individual participant data (IPD) meta-analysis of more than 20 randomised trials with more than 50,000 eligible participants investigating predictors of treatment response to inhaled corticosteroids (ICS) in chronic pulmonary obstructive disease (COPD) (PROSPERO: CRD42024508286).

We will explore the impact of adjusting for established prognostic factors on the results of the IPD meta-analysis. Tools for assessing risk of bias in reports based on aggregate data consider that if the baseline characteristics between groups appear balanced or if the observed imbalances are compatible with chance ($p>0.05$), then the likelihood of significantly biased results due to treatment heterogeneity is adequately reduced. However, concerns have been raised that the impact of established prognostic factors may be significant even if the baseline characteristics appear balanced between the randomised groups [2-5]. As a result, the European Medicines Agency (EMA) in the “ICH-E9: Statistical practice for clinical trials guidelines”, recommends that trials should “identify covariates likely to have an important impact on the primary outcome and adjust for them” and has developed guidelines on adjustment for baseline covariates in clinical trials [6,7]. Similarly, the CONSORT statement recommends adjustments for variables that are thought to be prognostic but highlights that decisions to conduct adjusted analyses should not be guided by statistically significant baseline differences [8].

In COPD, there are baseline factors that are known to be associated with the risk of various outcomes independently of the intervention. For example, patients with a history of frequent exacerbations or high blood eosinophils are likely to experience more exacerbations during follow-up. For our meta-analysis, there are also baseline factors that are predictors of heterogeneous treatment response, such as blood eosinophil count (which is associated with response to ICS) and current smoking status (which is associated with lack of response to ICS).

In this SWAR, we will explore differences between the results of unadjusted versus adjusted analyses when the baseline characteristics are imbalanced or balanced.

Interventions and Comparators
Intervention 1: Adjustment for known, prospectively selected prognostic factors (as per the main IPD meta-analysis).

Index Type: Full Review; Adjustment for baseline variables

Method for Allocating to Intervention or Comparator:
N/A

Outcome Measures
Impact on meta-analysis results of accounting for known prognostic factors on the outcomes and treatment-covariate interactions.

Analysis Plans
We will assess the impact of adjusting for established confounding factors, using those prospectively selected for the main IPD meta-analysis. For each outcome, we will compare unadjusted estimates with (a) analyses accounting for established risk factors known to affect the

baseline risk or value of an outcome (age, baseline exacerbations rate, baseline spirometric severity, concomitant COPD treatments), and (b) analyses additionally accounting for treatment interactions with predictors of heterogeneous treatment response (identified in our IPD meta-analysis). We will examine changes in statistical significance ($p<0.05$) and differences in effect estimates and confidence intervals. We will use the GRADE partially contextualised approach for defining thresholds of trivial, small, moderate or large differences for the selected outcomes [9], and use those thresholds for assessing differences in the effect estimates between adjusted versus unadjusted analyses. Thresholds will be informed by the literature and consensus among health professionals with relevant expertise (members of the ICS-RECODE study group) and patient representatives, for each outcome assessed. The following outcomes will be considered: exacerbations, mortality, quality of life, and pneumonia.

The findings will be presented narratively, in tabulated format and in forest plots, to demonstrate differences between analyses.

Possible Problems in Implementing This SWAR

We have already gained access to the IPD of most relevant trials. Therefore, we do not anticipate any problems in completing these analyses.

References

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5. Yang S, Starks MA, Hernandez AF, et al. Corrigendum to "Impact of baseline covariate imbalance on bias in treatment effect estimation in cluster randomized trials: Race as an example" [Contemporary Clinical Trials 2020;88:105775]. Contemporary Clinical Trials 2021;103:106298.
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8. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
9. Schunemann HJ, Neumann I, Hultcrantz M, et al. GRADE guidance 35: update on rating imprecision for assessing contextualized certainty of evidence and making decisions. Journal of Clinical Epidemiology 2022;150:225-42.

Publications or presentations of this SWAR design

Examples of the implementation of this SWAR

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