SWAR 36: Impact of pre-randomisation withdrawal of a patient's treatment on the results of a meta-analysis of randomised trials

Objective of this SWAR
To explore the impact of any effects on outcomes and treatment-covariate interactions of discontinuing a patient's main treatments before randomisation into the trial.

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 on outcomes and treatment-covariate interactions of withdrawing a patient from a main treatment before they are randomised into the trial. It has been proposed that discontinuation of ICS is associated with a significant withdrawal effect, with an increased risk of exacerbations after discontinuation [2]. We will quantify this effect and explore whether the other assessed interventions (long-acting muscarinic antagonist (LAMA) or a long-acting β2-agonist (LABA)) exhibit similar effects. We aim to determine whether such withdrawal effects influence the observed treatment effects and covariate interactions in trials where these treatments are discontinued.

Interventions and Comparators
Intervention 1: Impact on trial outcomes of potential withdrawal effects from discontinuation of the main maintenance treatments of COPD (LABA, LAMA or ICS) before the patient is randomised.

Index Type: Full Review; Methods evaluation within an IPD meta-analysis

Method for Allocating to Intervention or Comparator:
N/A

Outcome Measures
Impact of withdrawal effects on outcomes and treatment-covariate interactions.

Analysis Plans
Our analyses will follow the main IPD analysis. Outcomes of interest for this analysis will be exacerbations rate, time-to-first exacerbation, time-to-pneumonia, mortality, quality of life, serious adverse events, and discontinuation of the randomised treatment.

We will assess withdrawal effects of LABA, LAMA, and ICS in trial groups where the index drug class (e.g., ICS) was not administered during the trial. We will compare selected outcomes in patients who were or were not receiving the index drug class at baseline. Differences in effect estimates, treatment-covariate interactions, or marginal effects will indicate significant withdrawal effects. We will estimate withdrawal duration by comparing monthly exacerbation rates between groups and present them visually.

In trials with at least 12 months of follow-up, we will compare treatment effects in the early versus late follow-up periods (likely the first versus second six months, informed by identified withdrawal effects and data availability) in participants who were receiving the index drug class before recruitment, and either continued or discontinued it during the trial. We will also explore differences in treatment-covariate interactions and marginal effects of preselected prognostic factors.

We will examine changes in 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 (Schunemann et al., 2022), and we will use those thresholds for assessing identified differences. 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 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

1. Devane D, Burke NN, Treweek S, et al. Study within a review (SWAR). Journal of Evidence Based Medicine 2022;15(4):328-32.

2. Vestbo J, Anderson JA, Calverley PM, et al. Bias due to withdrawal in long-term randomised trials in COPD: evidence from the TORCH study. Clinical Respiratory Journal 2011;5:44-9.

3. Schunemann, H. J., Neumann, I., Hultcrantz, M., BRIGNARDELLO-PETERSEN, R., ZENG, L., MURAD, M. H., IZCOVICH, A., MORGANO, G. P., BALDEH, T., SANTESSO, N., CUELLO, C. G., MBUAGBAW, L., GUYATT, G., WIERCIOCH, W., PIGGOTT, T., DE BEER, H., VINCETI, M., MATHIOUDAKIS, A. G., MAYER, M. G., MUSTAFA, R., FILIPPINI, T., IORIO, A., NIEUWLAAT, R., MARCUCCI, M., COELLO, P. A., BONOVAS, S., PIOVANI, D., TOMLINSON, G., AKL, E. A. & GROUP, G. W. 2022. GRADE guidance 35: update on rating imprecision for assessing contextualized certainty of evidence and making decisions. J Clin Epidemiol, 150, 225-242.

Publications or presentations of this SWAR design

Examples of the implementation of this SWAR

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