SWAT 237: Comparison of the outcomes of pneumonia versus Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with COPD

Objective of this SWAT
This study uses data from a series of randomised trials to meet the following objectives:
(a) To compare the outcomes of severe pneumonia (requiring hospital admission) versus severe COPD exacerbations (requiring hospital admission) in patients with Chronic Obstructive Pulmonary Disease (COPD).
(b) To assess the impact of concomitant inhaled corticosteroids (ICS) use on the outcomes of severe pneumonia and severe exacerbations.
(c) To explore the interaction of baseline blood eosinophil count (BEC), baseline neutrophils, and other prespecified clinical markers, measured prior to the acute event, with the outcomes of severe pneumonia and severe COPD exacerbations.
(d) To explore the outcomes of severe pneumonia versus severe exacerbations classified according to their treatments (only systemic corticosteroids, only antibiotics, or both) and their predictors (as described above).

Additional SWAT Details
Primary Study Area: Analysis
Secondary Study Area:
Who does the SWAT intervention target: Participants; Patients
Estimated resources needed to conduct the SWAT: Medium
Estimated cost of the SWAT (£): 30,000

Findings from Implementation of this SWAT
Reference(s) to publications of these findings:
Primary Outcome Findings:
Cost:

Background
Inhaled corticosteroids (ICS) are one of the mainstay treatments of chronic obstructive pulmonary disease (COPD) [1]. In selected patients with enhanced airway eosinophilic inflammation, ICS can reduce the frequency of exacerbations, improve quality of life, decelerate lung function decline and might prolong survival [1-4]. However, these benefits come at the expense of an increased risk of pneumonia and other serious side effects [5].

The ICS-RECODE research programme is a secondary analysis of individual participant data from randomised trials evaluating the addition of ICS to other usual care treatments for COPD and aims to identify predictors and develop predictive models of treatment response to ICS in COPD [6]. As described, ICS have a protective role against exacerbations but increase the risk of pneumonia. Therefore, to make informed decisions around ICS use, it is crucial to understand the relative clinical burden of these two disease entities, among patients with COPD.
In this analysis, we will leverage high quality data from a series of randomised trials to compare the outcomes of severe (hospitalised) pneumonia versus severe (hospitalised) COPD exacerbation in patients with COPD and to assess how ICS treatment affects those outcomes.

Host Trial Population: Adults
Host Trial Condition Area: Respiratory Conditions

Interventions and Comparators
Intervention 1: Outcomes of severe pneumonia
Intervention 2: Outcomes of severe COPD exacerbation

Method for Allocating to Intervention or Comparator: Randomisation

Outcome Measures
Primary Outcomes: 1. Time to death from the event of interest (exacerbation or pneumonia)
2. Time to next severe respiratory event (severe COPD exacerbation or severe pneumonia) or death
Secondary Outcomes: 1. Time to next event (COPD exacerbation or pneumonia) or death
2. Time to major adverse cardiovascular events.
3. Duration of hospital stay

Analysis Plans
This analysis will be conducted within the ICS-RECODE dataset, consisting of 22 randomised trials assessing the addition of ICS to other usual treatments of COPD (such as short- or long-acting bronchodilators). Details of the main ICS-RECODE dataset eligibility have been reported previously [6]. In addition to those criteria, we will select trials with a follow-up duration of at least 48 weeks, that report on at least 40 cases of severe (hospitalised) pneumonia during the trial period. We will exclude participants with a diagnosis of alpha-1 antitrypsin deficiency and those receiving maintenance systemic corticosteroids or biologic treatments for their airway diseases. We will perform a two-stage meta-analysis, meaning that we will first analyse data at the level of each trial and we will pool all results in a meta-analysis. We will follow standard methodology described in the IPD handbook to conduct this IPD meta-analysis [7] and will report it in accordance with the PRISMA statement [8].

We will use the ROBINS-I for assessing RoB [9]. While our analysis is conducted in randomised trials, it is not focused on the efficacy of interventions, and therefore, the Cochrane RoB or RoB-2 tools are not appropriate here. ROBINS-I is primarily focused for interventions, but it is accepted to use it for non-randomised studies where exposures, rather than treatments are compared. In this case, the exposures are pneumonia and COPD exacerbation events. We will particularly focus on assessing the representativeness of the study population of each of the included studies. We will use GRADE for appraising the certainty of the available evidence [10, 11]. We will use the ICEMAN tool for assessing the credibility of potential treatment-covariate interactions [12].

Patients with at least one eligible event (severe pneumonia or severe COPD exacerbation) during the first 6 months of the trial period will be considered eligible for this analysis. The first severe acute respiratory event (pneumonia requiring hospitalisation or COPD exacerbation requiring hospitalisation) will be defined as the index event. We will include all patients with a severe pneumonia as index event and we will perform 1:3 or (if possible) 1:4 propensity matching with patients with an index event of severe exacerbation. Participants will be matched for age, gender, history of exacerbations and baseline FEV1. We will use Cox proportional hazard analysis for evaluating time-to-event outcomes provided the proportional hazards assumptions is reasonably met (based on Schoenfeld residuals) and no significant competing risks are present. Studies with a significant lack of proportionality, will be excluded. We will use generalised linear models for comparing continuous variables. All our analyses will be adjusted for concomitant use of ICS, LABA and/or LAMA, BEC at baseline, smoking status and comorbidities (number of body systems affected). We will explore potential treatment-covariate interactions with baseline BEC, baseline neutrophils, concurrent ICS use, smoking status and gender.

In the second stage, random-effect meta-analyses will be fitted using a restricted maximum likelihood estimation. The Hartung-Knapp-Sidik-Jonkmak approach will be used for calculating confidence intervals. Heterogeneity in all meta-analyses will be summarised by the estimate of between-trial variance of true effects.

In a sensitivity analysis we will only include trials where the presence of consolidation in the index event was confirmed by an experienced radiologist.

Possible Problems in Implementing This SWAT
We do not anticipate any significant problems. Data access has already been confirmed and we have the time, resources and expertise required to complete these analyses.

References Cited in This Outline

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References to This SWAT

TBC

Source of This SWAT

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