Manchester University
NHS Foundation Trust

ICS-RECODE:

Predictors of treatment REsponse to inhaled corticosteroids (ICS) in COPD: randomised COntrolled trials individual participant Data re-Evaluation.

Study protocol

Protocol – Version Control	
Version Number	1.0.
Version Date	30 January 2024

FUNDED BY
NIHR | National Institute for Health and Care Research

Full/Long Title Of The Study

ICS-RECODE: Predictors of treatment REsponse to inhaled corticosteroids (ICS) in COPD: randomised COntrolled trials individual participant Data re-Evaluation.

Short Study Title/Acronym

The ICS-RECODE study: Predictors of treatment response to inhaled corticosteroids in COPD.

Protocol Version Number And Date

Version 1.0.

Amendment History

Amendment No.	Protocol Version and date	Details of Changes Made
0	v.1.0, 30 January 2024	Original version of the protocol

Research Reference Numbers

IRAS Number	320000
Sponsor Reference	B01942
Funder Reference	NIHR152516

This protocol has regard for the HRA guidance.

This project will be conducted in accordance with the study protocol and the ethical principles outlined by Good Clinical Practice (GCP) and the Declaration of Helsinki in its most current version

Signature Page

The sponsor signature on the IRAS form, acts as documented acceptance that the sponsor approves the protocol.

The Chief Investigator should sign below to confirm the following:

The Chief Investigator confirms the protocol has been agreed and accepted and agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Dr Alexander G. Mathioudakis

30 – January – 2024

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1. Key Study Contacts

Insert full details of the key study contacts including the following

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2. Lay English Summary

COPD is short for Chronic Obstructive Pulmonary Disease. It's a lung problem that makes it hard for people to breathe because their lungs are damaged. It affects over 3 million people in the UK. COPD patients may have times where their symptoms are worse. These are called flare ups. They may have increased cough, struggle to catch their breath or produce too much mucus (phlegm). These can lead to hospital visits, reduce quality of life, and could even cause early death.

"Inhaled steroids" are a type of medicine given in an inhaler. Some COPD patients take this medication to reduce their symptoms including swelling of the airways. This helps their breathing and can prevent flare-ups. But they can also cause side effects like pneumonia, a severe chest infection. It's important to give inhaled steroids only to people who will benefit the most and have fewer side effects.

Aim: Our goal is to figure out what tests can tell doctors and nurses about who will benefit the most from inhaled steroids.

Design: Many projects have tested if inhaled steroids are safe and helpful for COPD patients. But most aren't big enough to show us who will benefit the most from this medicine. We'll bring information from these projects together to combine the results. This will help us find tests that can identify patients who will benefit from inhaled steroids. We won't collect any names or private information.

We have already found the projects that looked at COPD patients taking inhaled steroids. We have asked for information about these projects, including the results, by using a process that drug companies follow. Once we get the data, we will check them, make sure they are in a similar format, and combine the results.

We'll use a ground-breaking method to analyse the data called "Individual Patient Data (IPD) meta-analysis". This method will help us understand the data better. This is vital as we'll use this information to find the tests that can help target inhaled steroid use to the right patients.

Combining and studying all the data is hard work. The studies include more than 55,000 people with COPD. It needs dedication, time, and skills to get the right answer. We have gathered experts in COPD, clinical trials, statistics, and IPD meta-analyses to do it. The project will take 2 years.

Patient and Public Involvement (PPI): People with COPD are vital to our project. We have two patient representatives and our hospital's PPI lead on our team. We will also involve more COPD patients in

focus groups. Their opinions will be heard and used throughout the study. They will help us decide the best ways to test which patients would benefit from inhaled steroids. They will also help us decide, what tests are acceptable in normal doctor appointments, how to share our findings and plan future research.

3. Study Summary

In selected patients with chronic obstructive pulmonary disease (COPD), inhaled corticosteroids (ICS) reduce the risk of exacerbations, improve health status, pulmonary function and, possibly, survival. These benefits come at a risk of severe side effects, such as pneumonia. In clinical practice, blood eosinophils are used to identify people likely to benefit from ICS. However, the National Institute of Health and Care Excellence (NICE), after formally evaluating all available data, concluded that the overall evidence supporting the use of eosinophils or other biomarkers to guide ICS use is still weak. Hence, a clinical recommendation could not be supported, and research recommendations were issued instead.

Objective: This project addresses the important problem of more reliably identifying those patients with COPD most likely to benefit from the administration of ICS, at the lowest risk of side effects. We will conduct an individual participant data (IPD) meta-analysis of randomised controlled trials (RCTs) to identify and validate predictive clinical biomarkers and predictive models of treatment response to ICS.

Data: We have identified 27 RCTs totalling >65,000 eligible participants and our data access applications for 21 of these RCTs with >52,000 eligible participants have already been approved. The remaining applications are under review.

Methods: Based on a prospective analysis plan:

- We will re-analyse data from all included trials with the aim to standardise the definition and evaluation of outcomes and covariates of interest (predictors of treatment response).

- We will conduct a two-stage IPD meta-analysis to assess the safety and efficacy of ICS for COPD, accounting for various potential prognostic factors (i.e. effect modifiers).

- We will then explore potential treatment-covariate interactions with selected covariates, aiming to identify and/or validate predictors of treatment response to ICS.

- Finally, we will develop and validate prediction models of treatment response, using both hypothesis-driven and data-driven methods. We will compare their performance characteristics in independent patient samples.

Study Design	Individual Participant Data Meta-Analysis
Study Participants	Patients with COPD included in previously completed clinical trials evaluating the addition of inhaled corticosteroids (ICS) to other established treatments for COPD such as short- or long-acting bronchodilators.
Planned Size of Sample	We have identified and requested access to 27 eligible randomised controlled trials (RCTs) totalling >65,000 eligible participants. To date our data access applications for 21 of these RCTs, totalling >52,000 eligible participants have already been approved.
Overall Study Duration	2 years
Research Question/Aim(s)	This project aims to address the important problem of more reliably identifying patients with COPD likely to benefit most from the administration of ICS, at the lowest risk of side effects. We will conduct an individual participant data (IPD) meta-analysis of randomised controlled trials (RCTs) to identify and validate predictive clinical biomarkers and predictive models of treatment response to ICS.
Study objectives	- To standardise the definition and evaluation of outcomes and covariates of interest (predictors of treatment response). - To assess the safety and efficacy of ICS for COPD, accounting for various potential prognostic factors (i.e. effect modifiers). - To explore potential treatment-covariate interactions with selected covariates, aiming to identify and/or validate predictors of treatment response to ICS.

	- To develop and validate prediction models of treatment response, using both hypothesis-driven and data-driven methods. We will compare their performance characteristics in independent patient samples.
Primary Outcome Measure	**Primary Endpoint**
Severe exacerbations rate	Severe exacerbations rate
Moderate or severe exacerbations rate	Moderate or severe exacerbations rate
Secondary Outcome Measure(s)	**Secondary Endpoint(s)**
Mortality	Number of deaths and time-to-death
Time-to-first exacerbation	Time-to-first severe exacerbation; Time-to-first moderate or severe exacerbation; Time-to-first exacerbation of any severity
Rate of exacerbations of any severity	Rate of exacerbations of any severity
Pulmonary function	Forced expiratory volume in 1 second (FEV_1), change from baseline; Forced vital capacity (FVC), change from baseline
Health related quality of life	St George's Respiratory Questionnaire, COPD Assessment Test, or any other instrument that the included studies may have used. Assessed as change from baseline

Exercise capacity	6-minutes walking test, incremental shuttle walk test, or any other instruments that the included studies may have used. Assessed as change from baseline
Pneumonia (safety)	Time-to-first episode of pneumonia
Serious adverse events (safety)	Number of participants that experienced at least one serious adverse event and the time-to-first serious adverse event.

4. Funding and Support in Kind

Funder(s)	**Financial And Non-Financial Support Given**
National Institute for Health and Care Research (NIHR)	£206,143.34
NIHR Manchester Biomedical Research Centre (BRC)	Non-financial support. The NIHR Manchester BRC provides clinical, research and PPI expertise that is crucial to the design and delivery of this project.
AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Mundipharma, Novartis	Non-financial support. These pharmaceutical companies kindly agreed to offer us access to the individual participant data of their eligible trials.

5. Role of Study Sponsor and Funder

Manchester University NHS Foundation Trust is acting as sponsor for this study and is assuming overall responsibility for the initiation and management of the study. The Trust will provide permission to conduct the research and monitor the progress of that research. The research team all hold substantive or honorary contracts with the Trust and therefore the sponsor has influence over all aspects of the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results which are the responsibility of the research team.

National Institute for Health and Care Research (NIHR) is funding this study through the Health Technology Assessment (HTA) programme. The funder will receive progress updates and the final study report in line with the NIHR requirements. The funder will not have influence over any aspect of the study design, conduct, data analysis and interpretation, manuscript writing, or dissemination of the results.

AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Mundipharma, Novartis will offer non-financial support. More specifically, they will offer us access to the individual participant data of their eligible trials. In line with our data sharing agreements, the study investigators will be responsible for the study design, conduct, data analysis and interpretation, manuscript writing and dissemination of the results. Representatives of the pharmaceutical companies will be invited to join the independent advisory group and will be able to share their views and suggestions in the conduct, analysis and interpretation, manuscript writing and dissemination. However, the investigators will have no obligation to implement any of the pharmaceutical industry suggestions. The investigators will only be obliged to remove any confidential information from the manuscript for which the pharmaceutical companies may request deletion. The results of the analyses that are described in this protocol will not be considered confidential information under any circumstances.

6. Roles and Responsibilities of Study Management Committees/Groups & Individuals

The CI (Dr Alexander G. Mathioudakis) will have the overall responsibility for delivery of this study to the specified objectives, to time and within budget.

A **Study Management Group** consisting of the named investigators, including two patient representatives, and our research manager will meet at least twice a year and will monitor study conduct, progress, and adherence to the study protocol.

A **Study Steering Committee** will provide overall supervision for the project on behalf of the Project Sponsor and Project Funder and will ensure the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

We will also set up an international **Independent Advisory Group** that will provide independent clinical and methodological advice and will allow meaningful engagement of patients and relevant stakeholders to this research project. We will enlist health professionals with expertise in COPD, representing both primary and secondary care, as well as investigators from the original trials steering committees and from the trial sponsors. We will also invite a representative from NICE (confirmed) and the Asthma + Lung UK (TBC) in the advisory group.

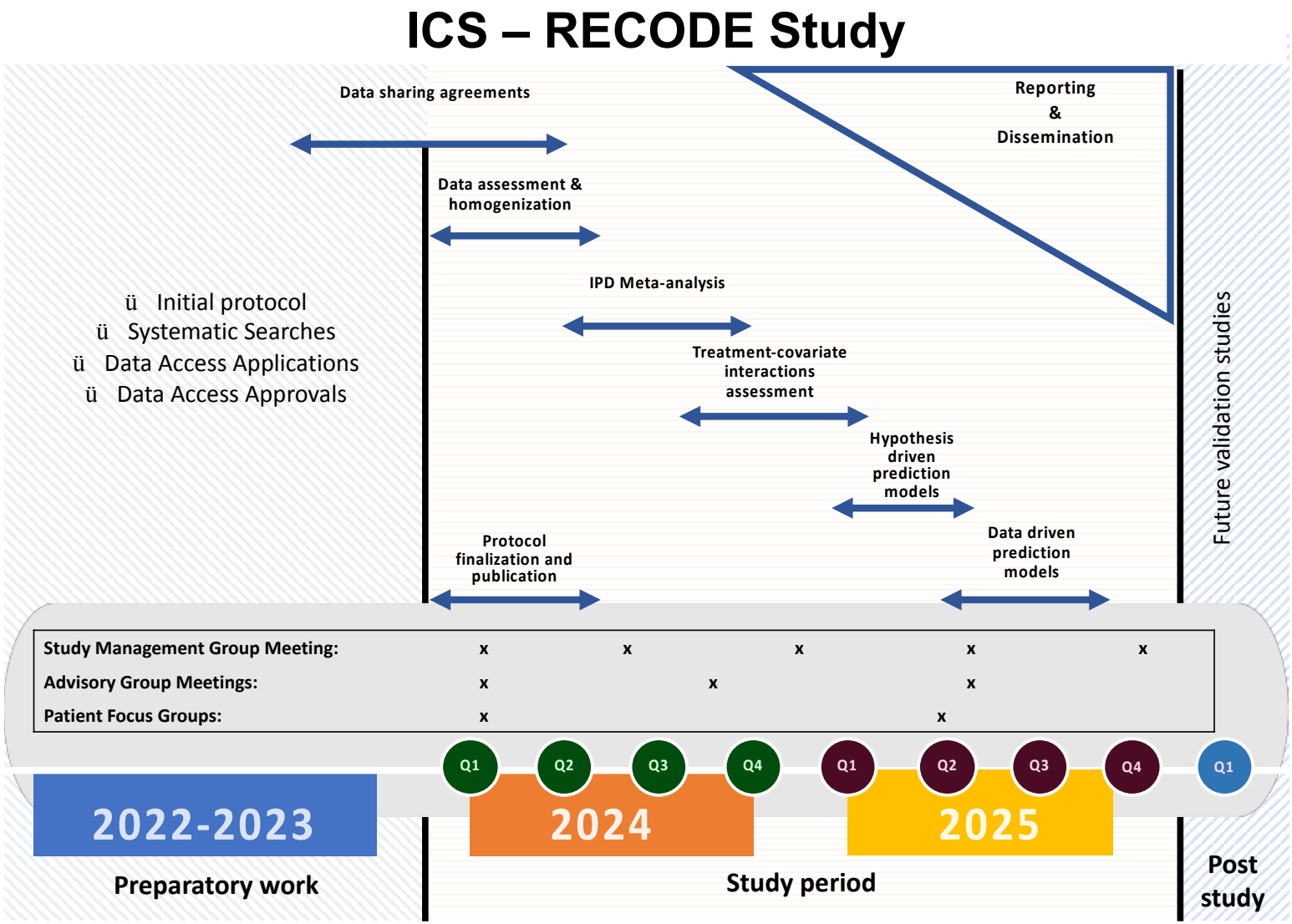
Finally, we will set up a **group of public contributors** and we will conduct two focus groups to capture patient views around outcomes and their prioritisation, acceptability of capturing the variables that will be included in the models, as well as prioritising future research building on this project's findings. Our PPI group will also contribute to the preparation and review of lay English reports and co-develop a strategy for disseminating our findings to the public, to ensure we engage with a diverse population.

Key Words: Chronic Obstructive Pulmonary Disease; COPD; Inhaled Corticosteroids; ICS; Personalised Medicine; Individual Participant Data; Meta-analysis; Biomarkers; Prediction Models of Treatment Response; Treatment Response.

Abbreviations

Abbreviation	Definition
COPD	Chronic Obstructive Pulmonary Disease
EOS	Blood eosinophils
FEV_1	Forced Expiratory Volume in 1 second
HRA	Health Research Authority
ICS	Inhaled Corticosteroids
IPD	Individual Participant Data
MFT	Manchester University NHS Foundation Trust
PPI	Patient and Public Involvement
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
RoB	Risk of Bias
SWAR	Study Within A Review
TMF	Trial Master File

7. Study Flow Chart



8. Background

8.1. Problem assessed.

This project addresses the important problem of identifying patients with chronic obstructive pulmonary disease (COPD) that will gain most benefit from the administration of inhaled corticosteroids (ICS), at the lowest risk of severe side effects. This issue will be addressed through an individual participant data (IPD) meta-analysis of eligible randomised controlled trials (RCTs). We have identified 27 eligible RCTs totalling >65,000 participants and we have applied for data access. Our data access applications for 25 eligible RCTs totalling >55,000 participants randomised to eligible treatment arms have already been approved. The remaining applications are still under review, and we fully expect them to be successful.

COPD affects over three million people in the UK, represents the third leading cause of death globally and is associated with significant morbidity and disability [1,2]. Global Burden of Disease Study estimates COPD remains the third leading cause of disability adjusted life years among people over the age of 50 years [3].

ICS can reduce the frequency of exacerbations, improve quality of life, decelerate lung function decline, and possibly reduce mortality in patients with COPD [4-6]. However, these benefits come at the expense of side effects that include a significant increase in the risk of pneumonia [7,8]. This is a concerning risk, since the 6-month mortality rate after a hospital admission for pneumonia versus exacerbation without pneumonia was recently estimated to be 20% and 3%, respectively, among patients with COPD [9].

Being characterised by marked heterogeneity in both clinical manifestations and underlying mechanisms, COPD represents a prime target for the introduction of precision medicine interventions [10]. ICS treatment effects are heterogeneous across COPD patients, and various biomarkers have been proposed to guide their administration[2]. However, the accuracy of these biomarkers has not been established, leading the National Institute for Health and Care Excellence (NICE) to prioritise relevant research, in recent COPD guidelines [11]. Our proposal will explore and validate predictive clinical biomarkers and prediction models of treatment response to ICS by re-analysing ample, high-quality IPD from up to 27 RCTs (N>65,000) assessing ICS for COPD.

8.2. Review of the existing evidence.

Our review revealed only one predictive model of treatment response to ICS, which has significant limitations, while formal evaluation of the evidence by ATS and NICE using GRADE revealed low certainty around the use of eosinophils for guiding ICS administration.

More specifically, we systematically searched PubMed for studies assessing predictors or predictive models of ICS treatment response in COPD (searches: up to October 2022). Our findings were consistent with the rigorous systematic review that informed the relevant NICE COPD recommendation [11]. We only identified one prediction model based on routinely collected data, which is limited by the small number of accessible variables and attrition [12]. We found numerous studies assessing various biomarkers of treatment response both in RCTs and observational studies. However, apart from blood EOS, these analyses did not yield strong and consistent associations with treatment response. Ample evidence from pre-specified or post-hoc RCT analyses suggest a positive association between blood EOS and treatment response to ICS [13-16], leading the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the ERS guidelines on ICS withdrawal to recommend the use of blood EOS to guide clinical decisions around the use of ICS [2,17]. Blood EOS is used as a surrogate of airway eosinophilia, the trait that is targeted by ICS, therefore confirming the biological plausibility of this biomarker [18,19].

However, formal evaluation using the GRADE methodology in NICE and ATS COPD guidelines revealed that the overall body of evidence around the use of blood EOS is still weak and cannot guide the decision to step up from dual bronchodilator therapy that includes a long-acting beta 2 agonist (LABA) and a long-acting muscarinic antagonist (LAMA) to triple therapy containing LABA+LAMA+ICS: “it is currently unclear whether they (EOS) should be used to initiate triple therapy (with ICS) or what the cut off level should be” [11,20]. Data from ETHOS that have been published since then do not fully address this issue either, since the addition of ICS appeared to decrease the exacerbation rate both amongst patients with higher EOS and, to a lesser extent, among those with lower EOS. In parallel, several studies, have revealed weaknesses of blood EOS as a therapeutic biomarker. First of all, our post-hoc analyses of the ISOLDE and FLAME trials raised concerns around the indiscriminate use of eosinophils measured while patients are or are not receiving ICS for guiding the administration of ICS (see previous section) [21,22]. These concerns are further substantiated by the poor association that was noted between blood EOS and ICS response in large observational studies that used the different EOS measures (on or off ICS) interchangeably [23-25].

Overall, treatment response to ICS is clearly heterogeneous in COPD, but currently used biomarkers to guide ICS administration are suboptimal and supported by weak evidence. There is an urgent need for rigorous data to inform clinical practice.

9. Rationale

It has been demonstrated that ICS can significantly improve disease outcomes in carefully selected patients with COPD, while others do not gain much benefit, but are still exposed to an increased risk of side effects such as pneumonia, which is also associated with substantial morbidity and mortality in patients with COPD [1,2]. Therefore, the identification and validation of biomarkers or combination thereof in prediction models that could target ICS administration to people likely to experience a better benefit-to-risk ratio could lead to improved clinical outcomes and reduce health expenditure and the burden of polypharmacy in patients with COPD. Importantly, optimal use of ICS could significantly reduce the risk of exacerbation and pneumonia, also reducing hospitalisations, thus benefitting the NHS that is currently facing a dire bed crisis. Since COPD is responsible for one in eight emergency hospital admissions in the UK [26], the potential benefits are very significant.

Recommendations for research on this area have been issued by NICE and the American Thoracic Society (ATS) [20] COPD guidelines, and by an international multi-stakeholder panel, endorsed by the European Respiratory Society (ERS) and ATS [27]. Personalised care is also prioritised in the NHS Long Term Plan [28]. Prevention of exacerbations was prioritised in a recent James Lind Alliance research prioritisation for COPD exacerbations (highest priority, ranked 1st) [29]. Tackling polypharmacy was highlighted as a priority in the NHS Patient Safety Strategy [30]. Personalised care including targeted use of ICS, exacerbations prevention, and reduction of polypharmacy have also been prioritised in two PPI focus group meetings with patients with COPD that were conducted in our department. Asthma and Lung UK also confirms that patients with COPD communicate with them concerns around potential long-term side effects of steroids (see attached support letter).

At present, blood eosinophils (EOS) are broadly used to guide the initiation and discontinuation of ICS for COPD, despite the absence of adequate available evidence. Based on the best available evidence at the time, the 2020 ERS guidelines on ICS withdrawal in COPD issued a strong recommendation for continuing ICS in patients with high blood EOS and a weak recommendation for discontinuing ICS in those with low blood EOS [17]. However, steroids are known to suppress blood EOS [31] and, for this reason, our group conducted two post-hoc analyses of the ISOLDE and FLAME trials to assess whether blood

EOS measured while patients are receiving ICS could guide future treatment decisions [21,22]. Both studies found that in patients who respond to ICS, EOS were suppressed after the initiation of ICS. On the contrary, in approximately 20% of patients, blood EOS rise in response to ICS administration and this rise is associated with a deleterious effect of ICS characterised by increased frequency of exacerbations and accelerated lung function decline. Discontinuation of ICS is based on blood EOS measured during ICS treatment and our findings suggest that the indication for discontinuation of ICS should be higher, rather than lower EOS measured while patients are receiving ICS. Therefore, the current ERS guidelines on ICS withdrawal and established clinical practice may be incorrect. This is a very concerning observation calling for urgent research to conclusively confirm or refute this hypothesis, to inform the guidelines and ensure patients receive the best available care. Addressing this issue is a central objective of the proposed study.

10.Research Question/Aim(s)

The ICS-RECODE study will address NICE COPD Guidelines (NG 115) research recommendation 4 [11]: What features predict ICS responsiveness most accurately in people with COPD?

Our overarching objective is to use rich datasets of completed RCTs assessing the safety and efficacy of ICS for COPD, to identify predictors of treatment response to ICS by means of an individual participant data (IPD) meta-analysis.

10.1. Specific Objectives

(i) We will conduct an IPD meta-analysis to assess the safety and efficacy of ICS for COPD accounting for potential prognostic variables of treatment response.

(ii) We will explore potential treatment-covariate interactions aiming to identify/validate potential predictors of treatment response (i.e. effect modifiers).

(iii) We will develop and validate prediction models of treatment response.

This study will be powered to identify an interaction between the primary outcomes and blood EOS, the most frequently used biomarker in clinical practice.

10.2. Outcomes and covariates of interest

The final outcomes, their hierarchy and the selected covariates will be further informed by patient focus groups.

10.2.1. Primary Outcome

- Exacerbations: Rate of severe exacerbations; Rate of moderate or severe exacerbations. For the purposes of this work, moderate exacerbations are those treated with systemic corticosteroids and/or antibiotics, but do not require hospital admission. Severe exacerbations are those necessitating hospital admission.

10.2.2. Secondary Outcomes

- Mortality: Number of deaths and time-to-death.
- Exacerbations: Rate of exacerbations of any severity; Time-to-first severe exacerbation; Time-to-first moderate or severe exacerbation; Time-to-first exacerbation of any severity.
- Pulmonary Function: Forced expiratory volume in 1 second (FEV_1), change from baseline; Forced vital capacity (FVC), change from baseline.
- Health related quality of life: St George's Respiratory Questionnaire, COPD Assessment Test, or any other instrument that the included studies may have used. Assessed as change from baseline.
- Exercise capacity: 6-minute walking test, incremental shuttle walk test, or any other instruments that the included studies may have used. Assessed as change from baseline.
- Pneumonia: Time-to-first pneumonia.
- Serious adverse events: Number of participants that experienced at least one serious adverse event and time-to-first serious adverse event.

10.2.3. Pre-selected covariates for treatment covariate interactions

- Blood EOS
- Blood EOS measured while patients were receiving ICS
- Blood EOS measured while patients were not receiving ICS
- ICS dose

- Current or previous diagnosis of asthma or atopy
- Reversibility of airflow limitation
- FEV_1 variability
- Diurnal peak expiratory flow rate (PEFR) variation
- Asthma features as described in NICE COPD guidelines
- Smoking status
- Types of exacerbations (treated with antibiotics, systemic corticosteroids, or their combination).
- Selection of these covariates was informed by our systematic review. None of the continuous covariates will be dichotomised.

10.2.4. Additional prognostic factors to be considered

- Age
- Gender
- Treatment adherence
- Baseline exacerbations rate
- Baseline symptoms severity (mMRC/CAT)
- Baseline spirometric severity
- Concomitant COPD treatments
- Predominance of chronic bronchitis versus emphysema
- Main comorbidities.

11. Study Design and Methods of Data Collection

11.1. Study Design

We will (i) conduct an individual participant data meta-analysis and (ii) develop prediction models of treatment response to inhaled corticosteroids in COPD, using individual participant data from completed eligible RCTs.

11.2. Search strategies

We searched the Cochrane Central Register of Controlled Trials and the Cochrane Airways Trials Register, that capture RCTs and systematic reviews from all major online libraries, including (but not limited to) Medline, EMBASE, CINAHL, and the World Health Organisation Clinical Trials Register. We used a structured search strategy (box 1), that yielded 3,924 titles. This search strategy was developed by the CI (AGM) and was cross-checked by the co-applicants who have extensive relevant clinical and methodological expertise.

Box 1. Search Strategy.

(((Pulmonary Disease, Chronic Obstructive [MH]) or (Lung Diseases, Obstructive [MH:noexp]) or (Emphysema [MH]) or (Bronchitis, Chronic [MH]) or (COPD [tiab]) or (emphysema [tiab]) or (chronic bronchitis [tiab]) or (obstructive [ti] and ((pulmonary [ti]) or (respiratory [ti]) or (airway* [ti]) or (airflow [ti]) or (lung [ti]))))**)**

and

(((Beclomethasone [MH]) or (Budesonide [MH]) or (Fluticasone [MH]) or (Mometasone Furoate [MH]) or (Triamcinolone [MH]) or (Beclomethasone [tiab]) or (Beclometasone [tiab]) or (Budesonide [tiab]) or (Fluticasone [tiab]) or (Ciclesonide [tiab]) or (Mometasone [tiab]) or (Flunisolide [tiab]) or (Triamcinolone [tiab]) or (ICS [tiab]) or (Trimbow [tiab]) or (Trelegy [tiab]) or (Trixeo [tiab]) or (Symbicort [tiab]) or (Dulera [tiab]) or (Breo [tiab]) or (Airduo [tiab]) or (Advair [tiab]) or (Seretide [tiab]) or (Duoresp [tiab]) or (Flutiform [tiab]) or (Fostair [tiab]) or (Relvar [tiab]) or (Sirdupla [tiab]) or (Viani [tiab]) or (Qvar [tiab]) or (Flovent [tiab]) or (Alvesco [tiab]) or (Asmanex [tiab]) or (Flixotide [tiab]) or (Arnuity [tiab]) or (Pulmicort [tiab]) or (Aerospan [tiab]) or (Aerobid [tiab]) or (Beclovent [tiab]) or (AmronAir [tiab]))**) not**

(((Child [MH]) not (adult [MH]))**)**

11.3. Systematic review strategy

Two investigators independently assessed all identified studies for eligibility at a title/abstract level, followed by a full-text evaluation of all potentially eligible studies. Disagreement in this and the

following steps were / will be resolved through discussion and, if needed, adjudication by a more experienced researcher. We captured eligible ongoing and completed RCTs, as well as relevant systematic reviews. The reference lists of the latter were also screened. We found 27 eligible studies totalling >65,000 participants and another 8 potentially eligible studies that will be further assessed for eligibility upon data access approval (table 1).

All eligible RCTs were sponsored by the pharmaceutical industry and IPD are available upon request either in one of the following databases: vivli.org; clinicalstudydatarequest.com; or the sponsor's internal databases. We have already applied for access to IPD from all eligible and potentially eligible studies, and we have gained approval to access 21 eligible RCTs totalling over 52,000 potentially eligible randomised participants. AstraZeneca could not share data from 6 RCTs due to ongoing regulatory activities and involvement of those studies in another analysis. We will re-apply to access these data by the end of 2023, and we hope we might be able to access those studies as well. Data sharing agreements are currently being developed between the trust and the data owners. Our group has previously applied for, accessed and analysed IPD RCT data and data sharing agreements are in place with GSK and Novartis (for previous projects). Moreover, Jørgen Vestbo and Dave Singh have strong collaborations with all sponsors and have served as steering committee members or chairs for several of the eligible trials. Overall, we are confident that we will gain access to the data of most eligible RCTs.

Risk of bias will be assessed using the RoB-2 tool[32], and judgements will be informed by trial protocols, reports and individual participant data as recommended in the IPD meta-analysis handbook (e.g. assessment of the random sequence, treatment deviations and missing outcome data)[33]. Risk of bias will be appraised by two investigators independently.

Table 1: Eligible and potentially eligible studies. Potentially eligible are studies that did not clearly report whether baseline exacerbation rate (prior to recruitment) was captured or not, and some studies stating that "baseline exacerbation rate was captured in a subgroup of participants", without determining the number of participants where this variable was captured. All GSK potentially eligible studies belong to the latter category. Potentially eligible studies will be further assessed for inclusion once IPD are available, or once the sponsors provide additional information.

Trial sponsor	Trial IDs. Access approved: - Eligible: Green	Participants randomised in relevant	Eligible participants with	Status

	- Potentially eligible: Orange Access declined	study arms (N)	confirmed EOS availability	
Glaxo Smith Kline	n= 11 NCsT02164513 (IMPACT), NCT01313676 (SUMMIT), SFCB3024 (TRISTAN), NCT00268216 (TORCH), NCT01054885, NCT01053988, NCT02105974, NCT01009463, NCT01017952, NCT01110200, Kardos AJRCCM 2006 n= 5 FLTA3025, SFCA3007, NCT00115492, NCT00144911, SFCA3006	N= 39,152 N= 3,633	N= 13,195 (6 RCTs)	**Data access acquired**
AstraZeneca (Symbicort)	n= 2 NCT00419744, NCT02157935 n= 1 NCT01069289 n = 4 NCT00206154 (SHINE), NCT00206167, NCT02766608 (TELOS), NCT02727660 (SOPHOS)	N= 2,438 N = 1,293 N = 6,792	N= 2,438 (2 RCTs) N = 6,792 (4 RCTs)	**Data access acquired for three RCTs** **Access to the remaining trials was declined, as consents did not include provision for data sharing**

				outside AZ.
AstraZeneca (Trixeo studies)	n= 2 NCT02465567 (ETHOS), NCT02497001 (KRONOS)	N= 7,704	N= 7,704 (2 RCTs)	**Data access declined at present due to ongoing regulatory activities and involvement in another analysis. We will re-apply in one year's time.**
Chiesi	n= 3 NCT02579850 (TRIBUTE), NCT00476099, NCT00929851 (FORWARD)	N= 3,436	N=3,436 (3 RCTs)	**Data access approved**
Boehringer Ingelheim	n= 1 NCT00975195 (WISDOM)	N= 2,488	N= 2,488 (1 RCT)	**Data access acquired**
MSD - Organon	n= 1 NCT00383721	N= 1,125		**Data access approved***
Mundipharma	n= 1 EudraCT 2012–004162–17 (EFFECT)	N= 1,765	N= 1,765 (1 RCT)	**Data access acquired**
Novartis	n= 2 NCT02603393 (SUNSET), NCT01555138 (INSTEAD)	N= 1,634	N= 1,634 (2 RCTs)	**Data access acquired**

* Two additional MSD trials were previously listed as potentially eligible. However, after discussion with the company, we can confirm that these did not meet our inclusion criteria.

11.4. Data access

We have submitted applications to access the patient level data of all eligible or potentially eligible trials. Most of our applications were approved, as seen in table 1. Anonymised data will be uploaded to secure servers for analysis. For each trial we will use the server of the original sponsor's preference. We expect that most original sponsors will ask us to access the data through their secure servers, using a VPN connection. However, if some of the sponsors choose to send the data over to us, we will save them in a secure network (see section 19).

11.5. Eligibility Criteria

All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation.

11.5.1. Inclusion Criteria (all inclusion criteria are at a trial level)

- Trials evaluating maintenance management in COPD of any severity.
- COPD diagnosis based on consistent clinical symptoms with fixed airflow limitation demonstrated in spirometry.
- Studies evaluating ICS as a maintenance treatment for COPD. We will accept studies assessing ICS administered as a monocomponent, or as part of an established combination of inhaled medications (such as LABA/ICS or LABA/LAMA/ICS). We will accept studies comparing ICS with placebo or no control, and those evaluating ICS-containing versus no-ICS-containing combinations (i.e.: LABA/LAMA/ICS versus LABA/LAMA and LABA/ICS versus LABA).
- The administration of any other established COPD treatments will be permitted, provided that they are not part of the randomised intervention.
- Studies with an overall, relevant study population of at least 500 participants, to allow for the assessment of treatment-covariate interactions.
- Studies reporting on baseline spirometric COPD severity and exacerbations history.

11.5.2. Trial Level Exclusion Criteria

- Studies that do not assess any of the outcomes of interests.
- Studies that do not report on the baseline exacerbation rate prior in the year to recruitment

11.5.3. Patient Level Exclusion Criteria

- Patients with a diagnosis of alpha-1 antitrypsin deficiency.
- Patients receiving biologic treatments for their airway diseases.

12. Statistics and Analysis

12.1. IPD database

A data dictionary with detailed standardised definitions of all variables to be used (baseline characteristics, outcome data and other covariates) will be developed to effectively establish the structure of the IPD database. The specifications of the data dictionary will be based on the CDISC nomenclature and the dictionary will be locked prior to conducting any meta-analysis. Data from the various included trials will be reformatted and re-coded in line with the dictionary. Although IPD will already be cleaned, we will still check the validity, range, and consistency of the variables, alongside assessing for potential risk of bias to inform RoB-2 assessments.

12.2. Missing data

We will assume data are missing at random. Multiple imputations at the level of each trial will be used for addressing sporadically missing values, to avoid borrowing information across trials. To deal with data systematically missing in some trials, we will use multivariate meta-analysis of partially and fully adjusted results.

12.3. IPD meta-analysis

We will conduct a two-stage IPD meta-analysis because (i) it is anticipated that data will be accessed through the online registry databases, therefore we will not be able to pool the IPD from all RCTs in a single dataset; (ii) in the second stage, it utilizes well known meta-analysis and reporting methods, that the readers will be more familiar with, while it performs at least as well as the one-stage method; (iii) it allows us to avoid aggregation bias by ensuring that only within-trial information is used in the first stage of the analysis, minimising potential analytical bias; and (iv) two-stage approaches are stronger for assessing treatment-covariate interactions[33].

In the first stage of the meta-analysis, we will re-analyse all outcomes in each of the included studies, using consistent methodology and accounting for the previously described predefined confounding factors. Specifically, we will conduct modified intention-to-treat analyses including all participants that fulfil the eligibility criteria and have sufficient analysable data.

We will use regression models for analysing our continuous outcomes (FEV_1, quality of life, respiratory symptoms, and exercise capacity), and we will adjust for the outcomes' baseline values, in addition to the predefined parameters. Negative binomial models will be used for assessing the rate of severe and of moderate or severe exacerbations and serious adverse events. Logistic regression will be used for assessing binary data (mortality, pneumonia). Finally, for time-to-event outcomes, including time-to-first exacerbation and time-to-death, we will use cox regression, provided the hazards are reasonably proportional and there are no significant competing risks.

In the second stage, random-effect meta-analysis 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, and we will also report a 95% prediction interval for the potential treatment in a new trial.

12.4. Treatment-covariate interactions

We will explore interactions between the administration of ICS and any of the predefined covariates, using a two-stage approach to avoid aggregation bias. For each covariate, we will repeat all previously described analyses for each of the outcomes, accounting for preselected covariates (excluding those associated with the index variable), but also including a treatment-covariate interaction term. In the second stage, the interaction terms of individual trials will be pooled in a random effects meta-analysis model, as described previously. We will report an overall estimate of the predictive value of covariates, along with their confidence intervals. We will be using the methods suggested by Riley chapter 7[33].

12.5. Prediction models of treatment response

ICS for COPD represents an ideal candidate for developing prediction models based on the criteria of the PATH statement and IPD meta-analysis of multiple, large RCTs represents an ideal substrate for such analyses[34]. Models will be constructed for the following outcomes: exacerbation rate, pneumonia, mortality rate and FEV_1, following methodology recommended in the PATH statement. Trials will be aggregated in groups according to the sponsor (as the trials from various sponsors are anticipated to be deposited in different databases). Treatment response models will be constructed in the two larger

groups of studies using appropriate penalised regression analyses, followed by data driven models (causal forests)[35], with trial-level intercepts, on a one-stage approach. For the data-driven models, beyond the prespecified variables, we will also consider other frequently evaluated variables across the included trials baseline characteristics. Penalisation and structural risk minimisation will be used to prevent overfitting in the multivariable and machine learning models, respectively. Models will undergo internal-external cross-validation, followed by external validation in the remaining datasets (studies conducted by other sponsors). In addition, in the remaining datasets we will also compare the performance of all available models assessing each of the selected outcomes, including our hypothesis-driven and data-driven models, predictive univariate models based on our previous analysis, and already existing models. The performance of each model will be tested using a version of the C-statistic that is adapted for evaluating treatment effect prediction, per PATH [34]. The optimal model will be selected; its performance characteristics will be tested in each of the included trials and will be pooled.

12.6. Potential bias in IPD meta-analysis results:

We will report on the number and characteristics of eligible trials that we will not be able to acquire IPD data from. We will also use funnel plots to explore for potential publication or small study bias. Moreover, in a sensitivity meta-analysis, we will explore whether the addition of the aggregate data from trials whose IPD may not be available to us change the overall results of our meta-analyses.

In additional sensitivity/ subgroup analyses we will:

(a) Only include data from trials of low risk of bias,

(b) Exclude patients with a history of asthma or confirmed airway reversibility. Asthma as a disease is responsive to ICS and we would like to ensure the inclusion of patients with concomitant asthma does not modify/weaken our findings.

(c) Assess separately patients that were receiving ICS at baseline, prior to recruitment, and were therefore randomised to continue receiving or withdraw from ICS, and patients that were not receiving ICS at baseline, and were therefore randomised to start or not start ICS. This subgroup analysis was selected to address the short-term increase in the risk of exacerbations and other adverse outcomes that has been observed in some studies following ICS withdrawal[36].

(d) Only include studies evaluating a fixed triple combination (LABA + LAMA + ICS) versus the respective dual bronchodilators (LABA + LAMA). In these studies, the treatment regimens are more standardised,

while the impact on ICS is tested in the currently recommended treatment step (as an add-on treatment two dual bronchodilator).

12.7. Certainty of the body of evidence

We will use the ICEMAN (Instrument for assessing the credibility of effect modification analyses) tool for assessing the credibility of treatment-covariate interactions[37] and GRADE methodology for evaluating the certainty of prediction models of treatment response[38].

12.8. Power calculations

Initial power calculations were based on eligible RCTs that captured the main outcomes and at least a single blood eosinophil count (19 trials, n=39,452). Based on 1000 simulations, the power to detect an interaction between ICS administration and blood EOS was >99.9% for an alpha of 5% for the one-year rate of severe and of moderate or severe exacerbations. In our simulations, blood EOS was simulated to have similar characteristics to the Copenhagen General Population Study[39] and the estimated exacerbations rate was sourced from a previous post-hoc analysis of three eligible RCTs[15]. Based on these assumptions, we targeted 25% heterogeneity with a study-level random parameter.

Our data access applications for 15 trials totalling 24,956 participants with available EOS data have already been approved. In repeat power calculations only considering these 15 RCTs, the power to detect an interaction between ICS and EOS remained >99.9%.

13. Study within a review (SWAR). RoB assessment: Comparing judgements of aggregate or individual-participant data

13.1. Background

The RoB-2 tool for randomised controlled trials was developed to address limitations identified in the original RoB tool[32]. The revised tool employs signalling questions to address a broader range of RoB issues. The refined RoB tool (RoB-2) is more lenient compared to RoB-1 and it is therefore anticipated that a greater proportion of trials will be assessed as low instead of unclear RoB[32]. Applying RoB-2 is believed to be more time consuming than applying RoB-1.

A modified version of RoB-2 is currently being developed for assessing RoB in IPD meta-analyses by Tierney and colleagues. IPD and the additional trial documentation that we will access for this project can better inform RoB judgements. In the included studies, we will compare RoB judgements using the RoB-1 and RoB-2 tools based on aggregate, followed by individual participant data. We will specifically

explore whether detailed assessment of the IPD reduces uncertainty in RoB assessment, or reveals any RoB that is missed when assessing aggregate data using either the RoB-1 or RoB-2 tool. In parallel, we will pilot the modified RoB-2 tool for IPD meta-analyses that is being developed.

In addition, we will further explore the impact of adjusting for established prognostic factors on the results. Both RoB-1 and RoB-2 tools consider that if the baseline characteristics between groups appear balanced or if the observed imbalances are compatible with lack, 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 study groups or when "observed imbalances are compatible with lack"[40-43]. As a result, the 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"[44] and has developed guidelines on adjustment for baseline covariates in clinical trials[45]. Similarly, the revised CONSORT statement recommends adjustments for variables that are thought to be prognostic. It is highlighted that the decisions for adjusted analyses should not be guided by statistically significant baseline differences[46]. In our meta-analysis, there are well-established factors associated with the baseline risk of various outcomes occurring (e.g. independently of the intervention, patients with a history of frequent exacerbations or high blood eosinophils are likely to experience more exacerbations during follow-up), and predictors of heterogeneous treatment response (such as blood eosinophil count that is known to be associated with treatment response to inhaled corticosteroids, or current smoking status, that is associated with lack of ICS response). We will explore differences in the results of unadjusted versus adjusted analyses when the baseline characteristics are imbalanced or balanced.

We anticipate that our findings could potentially inform the RoB-2 tools for aggregate or IPD meta-analyses[32], or the CONSORT statement (if RoB is not properly reported in the trial publications)[46].

13.2. SWAR Objectives

The objectives of this Study within the Review (SWAR) are:

To compare the impact of applying RoB-1 and RoB-2 to the body of evidence (in terms of the proportion of trials/ data assessed as at low, high, or unclear risk of bias and time taken to apply each tool).

To assess if and how examination of individual participant data from included studies impacts on RoB assessment (in terms of the proportion of trials/data assessed as at low, high or unclear risk of bias and time taken to apply each tool).

To pilot test the modified version of RoB-2 for IPD meta-analyses (RoB-2 for IPD meta-analyses currently in development).

To explore the impact of adjustment for known prognostic factors in trials when prognostic characteristics are imbalanced at baseline and in trials where prognostic characteristics are balanced across arms at baseline.

13.3. SWAR Methods

Using RoB-1 and RoB-2 tools and based on published aggregate data, two experienced investigators will assess the RoB per outcome for each of the studies included in this systematic review. All outcomes selected for the IPD will be considered, including severe exacerbations rate; moderate or severe exacerbations rate; mortality; time-to-first severe exacerbation; time-to-first moderate or severe exacerbation; FEV_1; quality of life; exercise capacity; pneumonia; serious adverse events. The included studies will be evenly split into two groups. One researcher will initially evaluate RoB-1 for the first group and RoB-2 for the second group, while the other researcher will assess these tools in reverse order. The duration required to complete each tool will be recorded. They will also record whether informant data were located in the main trial publications or in the supplementary documentation. Disagreements will be resolved by consensus and discussion with an experienced adjudicator.

We will then assess the RoB using information from all available study documents and the IPD. In a random order, we will assess RoB following (i) the guidance described in the IPD Handbook (Riley, Tierney, Stewart)[33] and (ii) the modified RoB-2 tool for IPD meta-analyses (in development). The time needed to complete each tool will be recorded.

In addition, we will explore the impact of adjusting for established confounding factors on the results (among those covariates that will be considered for the main study). 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 established predictors of heterogeneous treatment response (Blood EOS, current or previous diagnosis of asthma or atopy or FEV_1 variability, reversibility of airflow limitation).

The findings of this methodological study will be presented narratively and in tabulated format. We will describe differences in RoB judgements using RoB-1 and RoB-2 in aggregate data/ published reports, in IPD data and all available trial documents. We will report on the time needed to complete each tool. For each RoB domain, we will explain the reasons for the observed differences. In addition, we will describe the time required to complete the RoB-2 tool for IPD data and explore potential challenges in its use. Differences across various unadjusted or adjusted models will be presented descriptively.

The SWAR work will be reported as an additional methodological publication.

14. Ethical and Regulatory Considerations

This is a secondary analysis of anonymous patient level data from completed trials conducted by the pharmaceutical industry. No new data will be collected and the investigators will not have access to any patient identifiable data. Therefore, no Research Ethics Committee review will be required. Our study protocol will be submitted to the Health Research Authority (HRA) for approval. The study will not be commenced until the protocol is approved by the HRA.

15. Amendments

Any amendments to the study shall be reviewed by the Sponsorship Team prior to submission. Any non-substantial amendments shall be notified to the HRA and any substantial amendments, along with amended documentation, shall be approved by the HRA, prior to implementation as per nationally agreed guidelines. The Chief Investigator or designee will work with the R&I department to put the necessary arrangements in place to implement the amendment and to confirm their support for the study as amended.

16. Peer Review

The scientific quality of this research project has been assessed by:

- Members of the research group, including world leading experts in COPD, clinical trials methods, biostatistics, systematic reviews and meta-analyses, including individual participant data meta-analyses from the University of Manchester, Manchester University NHS Foundation Trust, University of York and St. George's University.

- Two patient representatives and our PPI lead that have also joined our Study Management Group.

- A number independent expert boards that assessed the importance of the question and methodological rigour on behalf of the pharmaceutical companies who will provide access to their data. All these boards approved this study and recommended the companies provide us with access to their data.

- Independent peer reviewers appointed by the NIHR and by the NIHR HTA panel, who recommended funding for this study.

17. Patient & Public Involvement

17.1. Patients, service users, carers, and public involvement in developing this study

Overview:

• Focus groups and interviews with ICS users informed conceptualisation and design.

• PPI lead (EH) and two patient representatives (JL and AP) were involved in drafting the proposal.

• Asthma + Lung UK and COPD Foundation support this work and will facilitate PPI engagement.

• Proposal aligns with James Lind Alliance top priorities for COPD exacerbations.

Our research group, supported by the Manchester University NHS Foundation Trust Patient and Public Involvement and Engagement specialist team (Vocal), has a strong ethos for involving patients and the public in the prioritisation of research questions, study design, delivery, and interpretation.

The concept for this proposal started from priorities identified in two focus groups involving a total of 21 people living with COPD or caring for people living with COPD. These focus groups also prioritised

the outcomes of our meta-analysis. More recently, the PI discussed this research with 8 ICS users; all considered this research a priority. They reviewed the plain English summary and further influenced the selection of outcomes and main covariates. For example, they proposed exercise capacity as an outcome.

Two patient representatives with lived experience of COPD have joined our group as lay researchers and will provide patient perspective throughout this study. Aided by the co-PIs and EH (PPI lead), they have contributed to the preparation of the plain English summary and provided input in the selection of outcomes and main variables. JL is an experienced patient advocate from the USA and represents the COPD Foundation. He has previous experience of contributing to the steering committees of a number of studies, including RCTs. He has been a PPI co-author on peer review papers indexed in PubMed. AP is a COPD patient and lay representative from Manchester who has contributed to research studies as a participant or as PPI representative in focus groups. In view of their different exposure to the research environment, the two representatives bring different perspectives, both of which are crucial to our work. JL brings an international perspective that is based on his personal experience, his engagement the COPD Foundation and his prior involvement in research oversight. AP brings a local, “fresher” patient perspective, while he also has extensive experience of the UK National Health Service (NHS) as a patient and could provide insight on the anticipated burden and applicability of our proposed predictive models of treatment response.

The applicants have also worked with Asthma + Lung UK (A+L UK), the leading national charity with a mission to improve lung health for all, and the COPD Foundation, the largest organisation of patients with COPD globally (support letters attached). The research and innovation teams of both organisations reviewed the plain language protocol and offered their support to this proposal, as it aligns with their strategic goals. Both organisations recognised the importance of our project and highlighted the significant anticipated patient benefits. Asthma + Lung UK agreed to facilitate patient involvement through their Expert Patient Panel, while the COPD Foundation will be represented by JL. Both organisations committed to support future involvement and dissemination opportunities.

Our work aspires to inform the top James Lind Alliance research priority for COPD exacerbations: “What can prevent exacerbations of COPD”.

17.2. Patients, service users, carers, and public involvement in the delivery, interpretation, reporting, and dissemination of this research study

Overview:

- Patient representatives and PPI lead will join the Study Management Group.
- Two focus groups will run during the project with the following aims:

1st: Protocol refinement, including outcomes hierarchy.

2nd: Acceptability & interpretation of results & future research.

- Input from Asthma + Lung UK expert patients' panel.
- Multidisciplinary advisory group will meet every 9 months.

Two named patient representatives (see previous question) and the PPI lead will join the Study Management Group with the specific responsibility to capture and contribute patient perspectives to inform research decisions. JL and AP will receive tailored training and will have a strategic role in study oversight, being involved in all decisions and offering patients' perspective. They will co-author all public facing reports.

Moreover, patient perspectives will be captured through two focus groups involving diverse patients and their carers. We will recruit participants through the NIHR BEAT Respiratory Campaign (see support letter). These patients/carers will receive tailored training around the study protocol and terminology. We will invite the same public contributors to both focus groups to give people with lived experience the opportunity to have longitudinal impact on the study.

The first focus group (month 1) will aim to finalise the selection of outcomes and variables that will be tested for treatment-covariate interactions. This will involve exploring whether additional outcomes considered important by patients should be included in the individual participant data meta-analysis. Moreover, we will develop a hierarchy for the outcomes, to inform the development and interpretation of the multivariable models of treatment response to ICS. In parallel, we will explore the acceptability of the covariates/tests that are proposed as potential predictors of treatment response to ICS.

The second focus group (to be held once early results of the data driven analyses are available), will explore the acceptability of capturing the proposed variables for guiding ICS use. The data-driven models may indicate the need for more than one assessment visit, induced sputum, or other diagnostic procedures for guiding ICS treatment. It will be important to assess the acceptability of these procedures by patients, given the trade-off. Patients will also be involved in the interpretation of the results and the development of a strategy for disseminating our findings to the public. Finally, patient views around future research building upon the findings of this project will also be assessed. Specifically, we will explore the value of a prospective trial to validate the predictors and prediction models of treatment response to ICS and -if this is considered a priority by patients- the potential design of such a trial.

The topics addressed in these focus groups, along with the main emerging themes will be further discussed within the A+L UK expert patient panel. This nationally representative panel is committed to understanding and promoting the preferences and needs of patients, whilst having extensive experience of the NHS structure and function from a patients' perspective.

Patients (AP+JL), health professionals and other stakeholders, including representatives from NICE and from the included trial sponsors/steering committees will be engaged through an advisory group that will meet virtually every nine months, to discuss the progress and next steps.

18. Protocol Compliance

The research team will be vigilant for protocol deviations and will record them on a study specific deviation log which will be regularly assessed by the CI.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach and should also be reported to the sponsor without delay.

19. Data Protection and Participant Confidentiality

We will only receive anonymised individual participant data from the eligible or potentially eligible RCTs. Anonymised data will be uploaded to secure servers for analysis. For each trial, we will use the server of the sponsor's preference. We expect that most of the original clinical trial sponsors will ask us to access the data through their secure servers using a password protected VPN connection. In such

cases, we will accept responsibility for accessing the servers responsibly and the clinical trial sponsors will be responsible for ensuring that the servers adhere to the required security protocols. If some clinical trial sponsors choose to send the data over to us, we will save them in a secure and password protected network hosted either by the University of Manchester, or Manchester University NHS Foundation trust, and only named study investigators will have access. In this server we will also save securely all data that we will create and extract from each study (e.g. our codes, the results of our analyses and RoB assessments) and we will perform the 2nd stage of the IPD meta-analysis.

Only named investigators from our research group will have access to the servers and passwords will not be shared. In addition, we will not make any effort to extract individual participant data from the secure servers. Data will be analysed in the secure servers and we will only extract the results of our analyses (summary figures).

Data sharing agreements with clauses that are in line with this protocol will be signed with all data contributors, to ensure we have a common understanding and agreement around data protection practices, as well as management of foreground IP and dissemination of results.

20. Monitoring

The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust in line with applicable MFT SOPs and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the research team.

21. Access to the Final Study Dataset

To ensure data protection and in line with our data sharing agreements with the data owners, only researchers directly involved in the analysis of the data will have access to the full dataset. Specifically, the CI and lead study statistician will have access to the full dataset. Additional researchers may have access to the full dataset upon agreement with the data owners and as needed for the purposes of completing the analysis.

In line with our data sharing agreements, upon completion of this research, our access to the individual participant data of the included studies will be ceased. Any individual participant data that may be stored in our servers will be deleted.

MFT will not have ownership of the complete datasets from each trial and we will not be able to share them with other researchers. Data sharing applications should be directed to the RCT sponsors who own the data. Our group would be delighted to share with other researchers the statistical codes that will be used for cleaning and standardising the trial data and for performing the analyses. These codes will be available upon request. We may be required to remove sections that reveal information regarding the data that are considered confidential by the data owners.

22. Dissemination and Impact

22.1. What does this research intend to produce?

Using the best available evidence and rigorous methodology, this work will reveal (a) predictors of treatment response to ICS in COPD; (b) predictive models of treatment response to ICS in COPD; and (c) will establish the optimal strategy for guiding the administration (initiation or discontinuation) of ICS for patients with COPD. This strategy may be based on a single variable (e.g. blood eosinophils) or a multivariate model and will optimise the ICS risk-benefit ratio.

If our results confirm that blood eosinophils (or blood eosinophils measured while patients are not receiving ICS) can accurately predict treatment response to ICS, then, in view of the existing evidence, they could be used to support strong clinical recommendations and to drive clinical practice. Other predictors or predictive models will likely need to be further validated and/or calibrated before being able to drive clinical practice.

In parallel, we anticipate publishing three major publications (IPD meta-analysis with blood eosinophils as a predictor of treatment response; the hypothesis-driven univariate and multi-variate models; the data-driven multivariate prediction models). The results will also be presented in national/ international conferences. Last but not least, we will produce technical and lay summaries of our findings and these will be distributed to clinicians and patients through their respective organisations and relevant stakeholders, including NICE, the British Thoracic, European Respiratory and other relevant societies, as well as the Global Initiative for Chronic Obstructive Lung Disease (GOLD COPD) panel. AGM, JV, DS and RF hold leadership posts in many of these organisations and will facilitate dissemination. As described, we anticipate the results of this work will inform COPD guidelines and clinical practice.

22.2. How will patients, services users, NHS, social care organisations and the wider population be informed about and engaged in this work?

We will engage with patients, clinicians, and other relevant stakeholders throughout this work.

Patients: Two patient representatives (Alan Preston and John Linnell) will join the study management group and provide patient perspective throughout this study, supported by the chief investigator and Sinduja Manohar, our PPI lead. Moreover, the patient representatives and patient lead will be responsible to capture patient perspectives and feed them to the Study Management Group. We will recruit additional patients through the NIHR BEAT respiratory diseases campaign and we will conduct two focus groups, to capture patient views around outcomes and their prioritisation, acceptability of capturing the variables that will be included in the models, as well as prioritising future research building on this project's findings. Patients will also contribute to the preparation of lay English reports and of a strategy for disseminating our findings to the public.
Our PPI groups will also contribute to the preparation and review of lay English reports and co-develop a strategy for disseminating our findings to the public to ensure we engage with a diverse population.

The lay English report will be shared with partner patient organisations (Asthma + Lung UK and COPD Foundation). In addition, we will share this report with other collaborating patient organisations, including all European respiratory patients' organisations that we will reach through the European Lung Foundation (ELF, our group has a strong collaboration with this organisation). Based on this report, we will also produce blogs, podcasts, pictures and/or infographics, that will be hosted at the NIHR Manchester Biomedical Research Centre website and will be disseminated through the Social Media of the investigators and of the partner organisations, that have a broad reach including clinical academics, patients, and lay people, but they are also frequently picked up by the media and medical blogs. In collaboration with the NIHR Manchester BRC dissemination team, we will aim to attract national media coverage, given the prevalence and burden of disease and importance of this research question.

Other stakeholders: We will also set-up an international advisory group, that will provide clinical and methodological expertise. We will enlist health professionals with expertise in COPD, representing both primary and secondary care, as well as investigators from the original trials and from the trial sponsors. We will also involve a representative from NICE (confirmed) and the Asthma + Lung UK (TBC) in this advisory group. This group will provide independent advice and expertise and will allow meaningful engagement of patients and relevant stakeholders to this research project.

Finally, we will actively use social media and university blogs to disseminate our progress and research findings to a wider audience.

22.3. How will the outputs enter the health and care system?

The study protocol and results of this study will be published open access in peer review journals. We anticipate publishing four major publications (IPD meta-analysis with blood eosinophils as a predictor of treatment response; the hypothesis-driven univariable and multivariable models; the data-driven multivariable prediction models; the results of the risk of bias SWAR). In addition, we will present our results at two national conferences such as the British Thoracic Society and the UK Primary Care Respiratory Society Conferences, to reach both primary and secondary care healthcare professionals with interest in respiratory medicine. We will also present our results at two international conferences, such as the European Respiratory Society and American Thoracic Society International Conferences, to maximise geographic impact.

Our plans to disseminate findings to patients and the public are summarised in section 5.2.

At a later stage, once our models have been further validated and calibrated in real-life patient populations and receive appropriate regulatory approvals, we will produce educational resources, including a website with an online calculator for the model. We may liaise with other websites such as the mdcalc.com to ensure our model will be included in their website (future work).

We fully anticipate the results of this project will inform future COPD clinical practice guidelines and will be the main indicator of successful dissemination and impact. NICE has issued a recommendation for research around optimising the administration of inhaled corticosteroids for patients with COPD and we are working with NICE to ensure our output will meet their criteria and will be used in future guidelines. In parallel, the findings will be disseminated to relevant national and international organisations producing clinical guidelines, including the BTS, ERS, ATS and GOLD. AGM, JV, DS and RF hold leadership posts in many of these organisations and will facilitate the dissemination and consideration for future guidelines.

If the use of predictors or predictive models is proved to be of significant benefit, our group will advocate for the introduction of financial incentives for primary and secondary care to adopt them. The strength of financial incentives has been demonstrated. For example, a financial incentive led to an absolute increase in the use of the COPD Discharge Bundle by 20% within two years [47].

Our group has strong links with the NIHR Manchester Applied Research Centre (ARC). Dissemination and implementation of our findings will be supported by the Implementation theme of the NIHR Manchester ARC.

22.4. What further funding or support will be required if this research is successful?

This project will identify predictors and predictive models of treatment response to ICS using ample, high-quality data from RCTs. However, the eligibility criteria of the majority of included trials is relatively restrictive, meaning that the results will need to be further validated and the predictive models will perhaps need to be further calibrated in real-life patient populations. Depending on the variables that will be identified and/or included in the model, this could be achieved using routinely collected clinical data (e.g. from the Clinical Practice Research Datalink – CPRD) or an existing cohort study, such as the ECLIPSE, SPIROMICS or COPDGene cohorts. Funding will be needed for this validation project to cover the statistician's time and data access, likely from NIHR or another funder.

Moreover, the resulting novel predictors or predictive models will need to be validated prospectively in a pragmatic RCT that will assess both the effectiveness and cost-effectiveness of their use. Taking advantage of novel technologies, such as the use of routinely collected clinical data for identifying potentially eligible patients and for capturing outcome data could limit the resources needed for completing such a trial. Still, substantive funding will be needed, likely from the HTA programme.

22.5. What are the possible barriers for further research, development, adoption, and implementation?

There is a chance that the variables that will be included in our predictive models may not be available in routinely collected datasets or large patient cohorts. In such a case, the validation and calibration of the prognostic models will need to be prospective. However, this is unlikely given the large number of available real-life cohorts that could potentially be used.

In addition, measurement of the variables included in the data-driven predictive models may be expensive or inconvenient, to the extent that the intervention may not be considered cost-effective or acceptable by patients. To address this issue, we will present more than one models, along with the potential benefits and risks of using them. We will also test the acceptability of various variables with patients and our advisory board. While a formal economic analysis is beyond the scope of this work, we will ask our experienced advisors to consider the costs of the proposed interventions as well. Finally,

evaluation of all the preselected variables that will be considered in the hypothesis-driven models are simple to capture and inexpensive.

22.6. What will be the impact of this research and for whom

This work will result in high quality evidence that will optimise the personalisation of the use of ICS for COPD. It is anticipated that the resulting treatment strategy will limit the use of ICS to approximately 40% of patients that still experience exacerbations despite receiving dual bronchodilator therapy with a long-acting beta 2 agonist and a long-acting muscarinic antagonist. Data from ETHOS and IMPACT trials suggest that when addition of ICS is indicated, it is associated with a significant decrease in the rate of moderate or severe exacerbations (ETHOS: Hazard Ratio 0.67, 95% Confidence Intervals [0.60, 0.76], IMPACT: Rate ratio 0.67 [0.58, 0.79]), with similar effect on the frequency of severe exacerbations [5,48]. In addition, beneficial effects are observed in pulmonary function and health status, while the addition of ICS could perhaps prevent mortality [5,48].

In line with previous data, our post-hoc analysis of the ISOLDE trial, suggests that ICS have significant undesirable effects in non-responders, that include an increased risk of pneumonia and infective exacerbations, and an accelerated lung function decline [21]. Our post-hoc analysis of the FLAME trial showed that the excess risk of pneumonia is concentrated in non-responders [22]. Therefore, omission of ICS will protect patients from significant side effects.

ICS are currently significantly overused [49]. Targeting of ICS administration will also have beneficial impact by reducing avoidable polypharmacy, which is known to be associated with adverse outcomes, especially among older people [50].

Beyond the significant effects to patients, optimisation of ICS use for COPD will also benefit the NHS that is currently facing a dire bed crisis and shortage of health professionals. In the UK, it is estimated that COPD is responsible for one in eight emergency admissions to hospital [26]. ICS are currently significantly overused increasing the risk of pneumonia, while in the absence of adequately validated clinical biomarkers to guide their use, they may be withheld from people that could have gained significant benefits, such as a decrease in their exacerbation rates. Therefore, optimal ICS use could significantly decrease hospital admissions due to COPD exacerbations and pneumonia.

Finally, our results will increase our understanding around COPD subtypes (steroid responsive versus non-responsive). We anticipate that they will lead future research aiming to disentangle the heterogeneity that characterises COPD and its underlying inflammation and mechanisms and to identify novel therapeutic targets.

23. Authorship Eligibility Guidelines

The main report will be authored by the Chief Investigators and other researchers with substantial contribution to the project, who fulfil the International Committee of Medical Journal Editors (ICMJE) criteria for authorship. We do not intend to use professional medical writers. The final decision regarding manuscript authorship will lie with the Chief Investigators.

24. Intellectual property

24.1. Background IP

Background IP includes the individual participant data from eligible clinical trials that our pharmaceutical industry collaborators will share with us. Manchester University NHS Foundation Trust and our Academic collaborators/ co-applicants will not contribute any background IP to this project. Management of the background IP will be clearly defined in the data sharing agreements. The pharmaceutical companies (data contributors) will maintain ownership of their background IP throughout the project's duration and beyond. Strict access control measures will be implemented to safeguard background IP. More specifically, only named investigators will have access to the datasets, which will be stored in a secure server. Most pharmaceutical industry collaborators work with their own secure online servers and will provide secure access to the investigators. In case some of the pharmaceutical industry collaborators prefer us to manage their data, these will be securely saved at the Manchester University NHS Foundation Trust's or University of Manchester's secure network and access will only be provided to named investigators. Our collaborators data will only be used for performing the pre-planned and approved analyses and -if required- we will request approval before performing any additional analyses. In addition, we commit to acknowledging our collaborators individual participant data contributions and respecting their IP rights in any project publications, presentations, or other dissemination efforts.

By fostering a collaborative and transparent environment, we aim to build a strong foundation of trust and cooperation, ultimately maximizing the project's potential for success.

24.2. Foreground IP

Foreground IP will include the findings of our IPD meta-analysis and the models of treatment response to inhaled corticosteroids. All new intellectual property will be the sole property of Manchester

University NHS Foundation Trust. Our pharmaceutical industry collaborators request a perpetual, non-exclusive, fully paid-up, royalty-free, irrevocable, worldwide, unrestricted license to utilise any New Intellectual Property, with the right to sublicense through multiple tiers. This request is included in the vivli (vivli.org) platform's data sharing agreement that is the result of extensive negotiation between the platform and the organisations that contribute data to vivli, and as such, is non-negotiable. Other pharmaceutical industry partners not working with vivli have independently shared similar requests. The request for this license is fully justified given that our analyses will be based on our pharmaceutical industry collaborators data. Granting unrestricted license to our pharmaceutical collaborators will also contribute to the dissemination of our results. Given that the resulting models will require validation and calibration in real life study populations before being used in clinical practice and given that our pharmaceutical industry collaborators would have represented our primary target market, we do not foresee the development of marketable IP as part of this project. Therefore, all foreground IP will be made freely and publicly available.

25. Archiving

We will follow MFT's SOP for Archiving.

Archiving will be authorised by the Sponsor following submission of the end of study report. The sponsor will be responsible for archiving all study documents. Our access to anonymised individual participant data from the included trials, along with the original trial documents will cease upon submission of the end of study report (and we will delete any individual participant data that may be stored in MFT or University of Manchester secure servers). Our analysis plans, codes, results and any other material produced in the course of this research, that belong to the investigators and MFT will be securely stored for at least 15 years at the MFT Servers and a back-up will be stored separately. Destruction of any essential documents will require authorisation from the Sponsor.

All archived documents will be stored in a digital format. We will not keep any printed documents.

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