Methodology and feasibility of randomised controlled trials evaluating precision medicine interventions for acute exacerbations of chronic obstructive pulmonary disease (COPD)

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Contents

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List of abbreviations

ADL	Activities of Daily Living
BODE	Body mass index, airflow Obstruction, Dyspnea and Exercise score
BRC	Biomedical Research Network
CARS	COPD Activity Rating Scale
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
CDLM	Capacity of Daily Living during the Morning
CERQual	Confidence in the Evidence from Reviews of Qualitative research
CRQ	Chronic Respiratory Questionnaire
COPD	Chronic Obstructive Pulmonary Disease
COMET	The Core Outcome Measures in Effectiveness Trials
COS	Core Outcome Set
COS-AECOPD	Core Outcome Set for clinical trials evaluating the management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease
COS-STAD	Core Outcome Set - STAndards for Development
COS-STAP	Core Outcome Set - STAndardised Protocol Items
COS-STAR	Core Outcome Set - STAndards for Reporting
COSMIN	COnsensus-based Standards for the selection of health status Measurement Instruments
CRF	Clinical Research Facility
CRN	Clinical Research Network
CT	Computed tomography
DECODE-NET	DisEntangling Chronic Obstructive pulmonary Disease Exacerbations: An international clinical trials NETwork
ELF	European Lung Foundation
EOS	Blood Eosinophil Count
ERS	European Respiratory Society
EXACT-PRO	Exacerbation of Chronic Obstructive pulmonary disease tool - Patient Reported Outcome
FDA	Food and Drug Administration
FIM	Functional Independence Measure

GDPR	General Data Protection Regulation
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation.
HR	Hazard Ratio
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
LCOPD	Living with COPD Questionnaire
LMICs	Low-to-Middle Income Countries
MD	Mean Difference
mMRC	Modified Medical Research Council Dyspnoea Index
MRADL	Manchester Respiratory Activities of Daily Living Questionnaire
NIV	Non-invasive ventilation
OMERACT	Outcome Measures in Rheumatology
OR	Odds Ratio
PCT	Procalcitonin
PICO	Population, Interventions, Comparators, Outcomes
PFSS-11	Pulmonary Functional Status Scale
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement
RCTs	Randomised Controlled Trials
RR	Relative Risk
RSV	Respiratory Syncytial Virus
SGRQ	Saint George's Respiratory Questionnaire
SRs	Systematic Reviews
SYNESIS	Safety and clinical effectiveness of withholding SYstemic corticosteroids in Non-EoSInophilic chronic obstructive pulmonary disease exacerbationS. The SYNESIS randomised controlled trial by the DECODE-NET.
TRACE-COPD	Characterisation and targeted TReatment of ACute Exacerbations of Chronic Obstructive Pulmonary Disease

Abstract

Exacerbations are responsible for a significant part of the burden and mortality from COPD. They are treated uniformly with bronchodilators, systemic corticosteroids, and often antibiotics. However, systemic steroids and antibiotics are only effective in 30-50% and 50% of exacerbations that are associated with airway eosinophilic inflammation and bacterial infection, respectively. Therefore, both treatments are overused, posing risks to patients and the community. Moreover, >30% of exacerbations are triggered by viruses and are not treated aetiologically. Consequently, there is a timely opportunity to evaluate the utility of precision medicine interventions for COPD exacerbations. My overarching objective was to lay the clinical and methodological groundwork for the conduct of rigorous precision medicine RCTs.

The TRACE-COPD is a six-month, open-label pilot RCT involving 135 patients. It aims to assess the feasibility, acceptability, and safety of using procalcitonin and blood eosinophils to guide the administration of both antibiotics and systemic steroids for COPD exacerbations. TRACE has not been completed yet due to the pandemic. However, it has already revealed feasibility issues that were addressed in a revised protocol and will inform the design of future RCTs.

To improve the quality and comparability of future RCTs of COPD exacerbations management, I brought together a global, multi-stakeholder panel that developed a core outcome set. COPD exacerbations outcomes were identified through methodological systematic reviews and qualitative research. The most critical outcomes were prioritised through a two-round Delphi survey that was completed by 256 patients, 488 health professionals and 319 researchers, from 88 countries. The core outcome set, and core outcome measurement instruments were finalised in two global, multistakeholder consensus meetings and were endorsed by four international respiratory societies.

By means of a meta-analysis, the prevalence of respiratory viruses in stable COPD and exacerbations was quantified, to inform future diagnostic, therapeutic and public health interventions. We found 93 eligible studies assessing 2963 patents during stable disease state and 18956 exacerbations. The prevalence of respiratory viruses in unselected patients with stable COPD was 10.2% [95% CI: 6.9%-14.0%] and in exacerbations 36.6% [33.6%-39.6%]. The most prevalent viruses were rhinovirus, respiratory syncytial virus, and influenza.

The outputs of this work could inform the design and interventions of future RCTs of COPD exacerbations management.

Lay abstract

Chronic Obstructive Pulmonary Disease (COPD) is a burdensome, long-term lung disease, causing persistent respiratory symptoms and poor quality of life. It is frequent, affecting more than 10% of people aged over forty. Patients often experience exacerbations, which are symptom flare-ups causing poor health and are responsible for 1 in 8 hospital admissions.

There are different types of exacerbations. Some are caused by bacteria (bugs) and should be treated with antibiotics. Other are caused by inflammation of the airways with eosinophils (which are specific cells of the immune system) and respond to oral steroids. And some are caused by viruses and require antiviral treatments. However, we do not have accurate tests to distinguish different types of exacerbations. As a result, all exacerbations are treated the same with inhaled medications called bronchodilators to open-up the airways, steroids to treat inflammation, and often antibiotics to treat infections. Therefore, both antibiotics and steroids are massively overused and can cause side effects, or the development of super-bugs. Moreover, exacerbations triggered by viruses are not treated properly.

The aim of my work was to lay the groundwork for high-quality clinical trials that will test novel personalised treatments for COPD flare-ups. I set up a clinical trial to preliminary assess whether personalised treatments for flare-ups are safe. More importantly, I wanted to look for potential challenges that need to be looked at before setting up larger trials. This pilot trial has not been completed due to COVID-19 pandemic. However, we have already found and resolved several problems, to ensure both this and future trials will be completed successfully.

I also looked at the measures (outcomes) that researchers use to test if new treatments work and whether they are safe. Trials should test outcomes that are important to patients, but this is not always the case. For this reason, I brought together a global team of experts and patients that agreed on the most critical outcomes to be tested in all future trials of COPD flare-ups treatment. To achieve that, we completed systematic reviews, interviews with patients, a two-stage online survey and two meetings with international representation. We involved patients, health professionals and researchers. The agreed outcomes are endorsed by four international respiratory societies.

Finally, through a systematic review we found how frequently people with COPD and COPD flare-ups suffer from infections by different viruses.

These findings will inform the design of trials of novel personalised treatments for flare ups.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning

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Dedication

To my wife Victoria, who is the source of my inspiration…

To my parents George and Efstathia and my brother Dimitris…

…for their love, understanding and for their continuous guidance and emotional support.

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I am deeply grateful to my main Supervisor, Professor Jørgen Vestbo, for his continuous invaluable guidance, support, and mentorship that has a crucial impact on my development as a clinician and researcher. He is a true inspiration and without his input I would have not been able to complete this work.

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Finally, I am grateful to all the staff from North West Lung Centre and Research and Innovation Directorate at Manchester University NHS Foundation Trust, NIHR Manchester Biomedical Research Centre (BRC), Manchester Clinical Research Facility (CRF), and Manchester Clinical Research Network (CRN), that supported this work.

Contribution statement

Alexander G. Mathioudakis had a leading role in the design, conduct and reporting of all the work presented in this thesis. Details are described below.

Chapter 2: AGM and JV conceived and designed this study. AGM, with input from JV and other academics from the North West Lung Centre, prepared the funding and ethics applications and the study protocol, drafted this manuscript, set up the study and has started recruited patients.

Chapter 3: AGM conceived this study with input from JV. AGM designed the study with input from PAC and JV. AGM prepared and conducted the systematic searches, assessed all studies for eligibility, performed data extraction and assessed risk of bias of all included studies. MM and JJ also performed the previous tasks, independently, in line with Cochrane guidance. AGM drafted the manuscript.

Chapters 4-5: AGM, JV and J-UJ conceived this study. AGM designed the study with input from JY, PW, JV, and J-UJ. AGM led the conduct of all methodological systematic reviews that were conducted as part of this project. AGM co-ordinated the qualitative work globally and delivered the UK component of this work. AGM designed, conducted, analysed and reported the Delphi survey with input from PRW, JV and J-UJ. AGM along with PRW, JV and J-UJ planned and conducted the consensus meetings. AGM drafted the manusctips.

Chapter 6: AGM, AB and JV conceived this work. AGM designed the study protocol with input from AB and JV. AGM prepared and conducted the systematic searches, assessed all studies for eligibility, performed data extraction and assessed risk of bias of all included studies. AGM, AMK, GSA, RF, PK, MJM also performed the previous tasks, independently [work was shared among them], in line with Cochrane guidance. AGM conducted the analyses. AGM drafted the manuscript with input from JV.

The author

Alexandros Mathioudakis is a Clinical Research Fellow and Honorary Lecturer in Respiratory Medicine, at the University of Manchester and Manchester University NHS Foundation Trust. His research focuses on Airway Diseases phenotypes and personalized medicine, as well as clinical research methodology and evidence-based medicine.

He graduated from the Medical School of the National and Kapodistrian University of Athens (Greece, 2011) and started his clinical training in Respiratory and General Internal Medicine in Health Education North West. He undertook a Fellowship in Guidelines Methodology at Cochrane Iberoamerica and NICE (European Respiratory Society, ERS 2016), followed by an Academic Clinical Fellowship in Respiratory Medicine at the University of Manchester (NIHR, 2016-2018 and a PhD Studentship by the NIHR Manchester Biomedical Research Centre (BRC, 2018-2022).

He has published >85 peer reviewed publications and has an h-index of 25 in Google Scholar. He has contributed to the development of the 2019 update of the British Guideline on the Management of Asthma (SIGN/BTS, 2019) and of the ERS Guidelines on Sarcoidosis Management (2021). He is also involved in the development of the ERS Guidelines on Pulmonary Alveolar Proteinosis (ongoing) and three methodological guidelines by GRADE, on the conduct of systematic reviews. He has received research funding for investigator-initiated studies by the European Respiratory Society, the North West Lung Charity, and Boehringer-Ingelheim.

He is actively involved with the ERS. He is currently the Secretary of ERS Group 5.1 (Airway Pharmacology & Treatment) and has previously served in the Early Career Members Committee, as a representative of Assembly 5 (Airway Diseases), a member of the Guidelines Working Group, of the Long-Range planning committee of Assembly 5, and of the College of Experts. Moreover, he has served as a co-chair of two and member of another three ERS task forces. He has been a member of the British Thoracic Society Standards of Care Committee, an Early Career Co-chair of the DECODE-NET (DisEntangling Chronic Obstructive pulmonary Disease Exacerbations: An international clinical trials NETwork), and a member of the Steering Committee of the Pediatric Asthma in Real Life (PeARL) think tank.

He is an Editor at Cochrane Airways (Cochrane Database of Systematic Reviews, 2019-, IF: 9.3), Section Editor in Breathe (ERS, 2020-) and Folia Medica (2017-2020), Academic Editor in

Disease Markers (Hindawi, IF: 3.4, 2021-), Associate Editor in Frontiers in Drug Safety and Regulation (2021-), Guest Editor in Biomedicines (MDPI, IF: 6.1, 2022), and a member of the editorial board in Population Medicine, Frontiers in Allergy, Asthma Research and Practice and Archives of Hellenic Medicine. He periodically reviews grant proposals for National Institute for Health Research (NIHR-UK), Health Research Board (HRB-Ireland), the Netherlands Organization for Health Research and Development (ZonMw), and the European Respiratory Society (ERS). He regularly reviews manuscripts for the British Medical Journal, European Respiratory Journal, American Journal of Respiratory and Critical Care Medicine, and other leading journals.

Selected Publications

Original publications linked to this thesis

1. Mathioudakis AG, Abroug F, Agusti A, Ananth S, Bakke P, Bartziokas K, Beghe B, Bikov A, Bradbury T, Brusselle G, Cadus C, Coleman C, Contoli M, Corlateanu A, Corlateanu O, Criner GJ, Csoma B, Emelyanov A, Faner R, Fernandez-Romero G, Hammouda Z, Horváth P, Huerta Garcia A, Jacobs M, Jenkins C, Joos G, Kharevich O, Kostikas K, Lapteva E, Lazar Z, Leuppi JD, Liddle C, Linnell J, López-Giraldo A, McDonald VM, Nielsen R, Papi A, Saraiva I, Sergeeva G, Sioutkou A, Sivapalan P, Stovold E, Wang H, Wen F, Yorke J, Williamson PR, Vestbo J, Jensen JU, on behalf of the DECODE-NET. *ERS Statement: A core outcome set for clinical trials evaluating the management of chronic obstructive pulmonary disease (COPD) exacerbations.* **Eur Respir J 2021**: 2102006. (IF: 16.7)

2. Mathioudakis AG, Ananth S, Bradbury T, Csoma B, Sivapalan P, Stovold E, Fernandez-Romero G, Lazar Z, Criner GJ, Jenkins C, Papi A, Jensen JU, Vestbo J, on behalf of the DECODE-NET. *Assessing treatment success or failure as an outcome in randomised clinical trials of COPD exacerbations. A meta-epidemiological Study.* **Biomedicines 2021**; 9(12), 1837. (IF: 6.1)

3. Mathioudakis AG, Janner J, Moberg M, Alonso-Coello P, Vestbo J. *A systematic evaluation of the diagnostic criteria for COPD and exacerbations used in randomised controlled trials on the management of COPD exacerbations.* **ERJ Open Res 2019**;5(4):00136-2019.

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6. Mathioudakis AG, Abroug F, Agusti A, Bakke P, Bartziokas K, Beghe B, Bikov A, Bradbury T, Brusselle G, Cadus C, et al. *Core Outcome Set for the management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease. The COS-AECOPD ERS Task Force study protocol.* **ERJ Open Res. 2020**;6(3):00193-2020.

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7. Mathioudakis AG, Bikov A, Foden P, Lahousse L, Brusselle G, Singh D, Vestbo J. *Change in blood eosinophils following treatment with inhaled corticosteroids may predict long-term clinical responses in COPD.* **Eur Respir J 2020**;55(5):1902119. (IF: 16.7)

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22. Mathioudakis AG, Janssens W, Sivapalan P, Singanayagam A, Dransfield MT, Jensen JU, Vestbo J. *Acute exacerbations of chronic obstructive pulmonary disease: In search of diagnostic biomarkers and treatable traits*. **Thorax 2020**; 75(6):520-527. (IF: 10.8)

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1. Introduction

1.1. Rationale

Chronic Obstructive Pulmonary Disease (COPD), a chronic and debilitating disease, affect more than 1.2 million people in the UK and over 174 million globally, and is responsible for more than 5% of deaths nationally[1-3]. Acute exacerbations punctuate the natural history of COPD, impacting on disease morbidity, mortality, and progression[2-4]. Typically, one in six patients admitted with an acute exacerbation die within 90 days of presentation, and exacerbations are responsible for one in eight emergency hospital admissions, costing the NHS over £253 million every year[2-4]. Patients consider exacerbations and hospitalizations due to exacerbations to be the most important and debilitating effect of COPD, according to a systematic review of 217 quantitative studies evaluating how patients with COPD value the outcomes of their disease[5]. Despite the burden that COPD exacerbations pose to patients, healthcare systems and the society, our clinical approach and management of exacerbations remain suboptimal and unchanged for decades[6]. Therefore, exacerbations represent a major, unaddressed, global health need.

Therapeutically, COPD exacerbations are approached as a single disease entity and treated uniformly with bronchodilators, systemic corticosteroids and commonly with antibiotics[3,4,6]. However, only exacerbations associated with airway eosinophilic inflammation (30-50% of all exacerbations) appear to respond to systemic corticosteroids and only those with bacterial infection present (50%) respond to antibiotics. Therefore, both antibiotics and steroids are significantly overused, posing risks to patients and the community. Moreover, up to 30% are attributed to viral infections and are currently not treated aetiologically[7-9]. COPD exacerbations triggered by viruses are associated with increased morbidity and prolonged hospitalisation, while overlapping viral and bacterial infections are also associated with increased mortality[10-12]. Timely administration of antiviral agents may improve their outcomes[13]. Unfortunately, in clinical practice, viral infections are underdiagnosed and undertreated in the context of COPD exacerbations[11,12].

Consequently, there is an urgent need and timely opportunity to investigate the utility of a precision medicine approach for the treatment of COPD exacerbations *(figure 1)*. Emerging data indicate that procalcitonin and blood eosinophil count (EOS) could potentially identify exacerbations associated with bacterial infection and airway eosinophilic inflammation

respectively, and safely guide the administration of antibiotics and systemic corticosteroids[7-9,14]. The combination of these, and perhaps other biomarkers, could revolutionise the management of exacerbations and should be tested systematically for safety and clinical effectiveness.

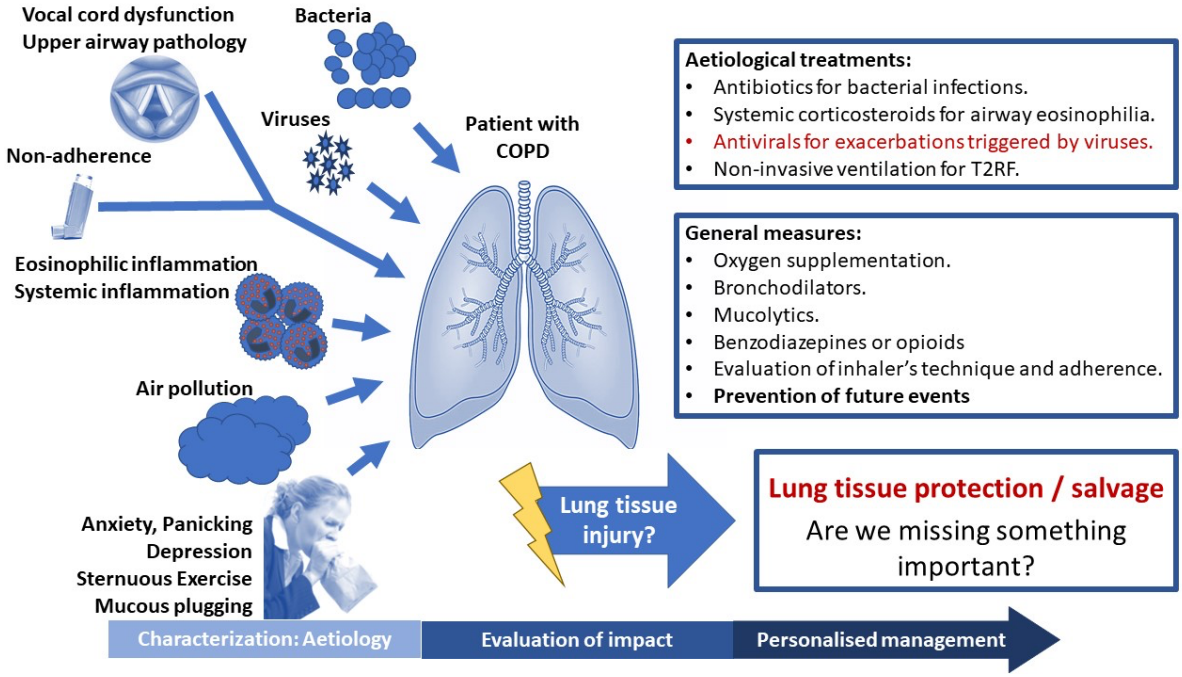


Figure 1. *Characterisation and aetiological treatment of acute exacerbations of chronic obstructive pulmonary disease. Reproduced from Mathioudakis et al, Thorax 2020[15].*

1.2. Objectives

The overarching objective of my project was to lay the clinical and methodological groundwork for the conduct of high-quality clinical and cost effectiveness randomised controlled trials (RCTs) for evaluating precision medicine interventions for acute exacerbations of COPD.

More specifically, my aims were:

(i) To conduct the TRACE-COPD (Characterisation and targeted TReatment of ACute Exacerbation of Chronic Obstructive Pulmonary Disease), a pilot randomised controlled trial (RCT), to test the feasibility and acceptability of conducting a large scale, pragmatic clinical and cost effectiveness RCT, to assess precision medicine interventions for the management of COPD exacerbations. A secondary objective

of the TRACE-COPD trial is to preliminary explore the clinical effectiveness and safety of a biomarker-guided intervention using procalcitonin and blood eosinophils to guide the administration of antibiotics and systemic corticosteroids, respectively.

(ii) To develop a core outcome set (COS) and core outcome measurement instruments for controlled clinical trials assessing the management of COPD exacerbations. These could improve the clinical value, interpretability, and comparability of RCTs.

(iii) To evaluate by means of a systematic review and meta-analysis the prevalence of respiratory viruses in stable COPD and COPD exacerbations. These epidemiological data could be used to inform the development of future precision medicine interventions for exacerbations triggered by viruses, a prevalent treatable trait.

1.3. Importance

Introduction of precision medicine practices is an NHS priority[16] and COPD exacerbations represent an important target. The need to characterize COPD exacerbations and to personalise their management were considered top research priorities by patients and health professionals alike in a recent study endorsed by the James Lind Alliance[17].

Safe antibiotic avoidance is crucial for patients with COPD who frequently receive unneeded treatments for their exacerbations, while their airways become colonised by bacteria that are progressively more resistant to available antibiotics[18,19]. The suggested biomarker-guided intervention has the potential to lead to significant net benefits to global health; i.e., targeting antibiotic use in COPD exacerbations will lead to a significant decrease in overall antibiotic prescription rates and will contribute to the limitation of antibiotic resistance across the UK (and globally). Preserving the effectiveness of available antibiotics is a strategic target of the NIHR and the Department of Health, highlighted in the RAND document[20,21].

Limitation of polypharmacy is another research priority. Safe avoidance of unneeded administration of systemic steroids can reduce the burden of their side effects and polypharmacy among patients with COPD who are usually aged and multimorbid. For exacerbations triggered by bacteria or viruses, steroid avoidance is crucial, as they exert immunosuppressive effects leading to worse outcomes[22].

Targeted treatment has the potential to decrease treatment costs, even though procalcitonin measurement is still expensive. Firstly, this intervention will limit current over-prescription of unneeded antibiotics and systemic steroids and the burden of their side effects. Moreover, our meta-analysis showed that procalcitonin guidance could safely reduce the length of hospitalization for exacerbations[7]. Procalcitonin is more specific to bacterial infections compared to other biomarkers that can also effectively reduce antibiotic administration in COPD exacerbations, such as sputum purulence or C-reactive protein, thus further limiting antibiotic administration[15].

Viral infections in the context of COPD exacerbations represent a missed opportunity for potentially effective precision medicine interventions since timely administration of antiviral agents, that are already commercially available, could improve their outcomes[13]. Therefore, better characterisation of the epidemiological and clinical characteristics of this treatable trait could facilitate the identification of appropriate diagnostic and therapeutic interventions that could be formally assessed in future RCTs.

From a methodological perspective, clinical research studies need to consistently evaluate outcomes that are relevant and important to key stakeholders including patients, healthcare professionals, and policy makers. Therefore, the development of a core outcome set and core outcome measurement instruments for evaluating the management of COPD exacerbations will improve the quality, comparability, and usability of future clinical research, including randomised controlled trials, and will contribute to the limitation of research waste.

Overall, this research is anticipated to facilitate the introduction of precision medicine interventions in the management of COPD exacerbations and to improve the quality and comparability of future relevant clinical research, with direct benefits for individual patients, the society and healthcare services (figure 2).

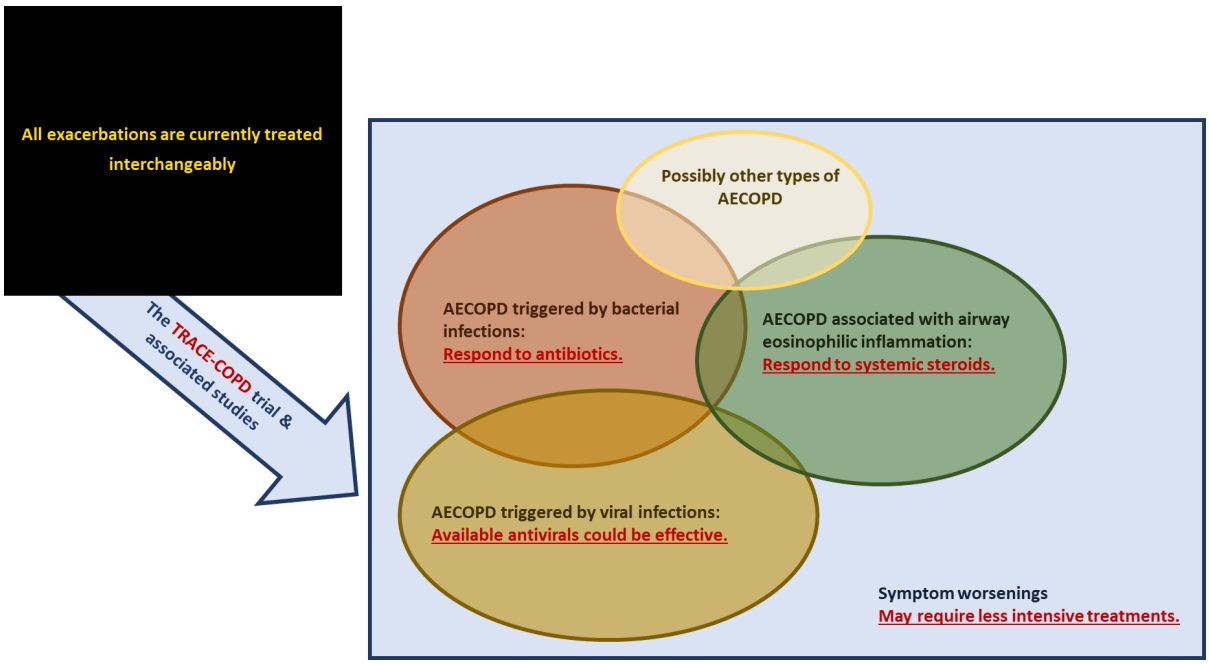


Figure 2. *All exacerbations are currently treated interchangeably with the administration of bronchodilators, systemic corticosteroids and almost invariably antibiotics. My vision is to contribute to the introduction of a precision medicine approach towards the management of COPD exacerbations, which should be thoroughly characterised and treated aetiologically.*

1.4. Existing evidence

1.4.1. Precision medicine interventions for COPD exacerbations

While COPD exacerbations are heterogeneous, they are still treated interchangeably, in the absence of clinically validated biomarkers to differentiate them[2-4,6]. To evaluate existing evidence, a series of systematic reviews (SRs) and meta-analyses were conducted, using standard guidance by Cochrane Collaboration and GRADE Working Group[23,24].

Firstly, we systematically searched for validated biomarkers used in interventional studies to guide the management of exacerbations. No biomarker guided interventions were identified for exacerbations triggered by viruses. We found studies evaluating procalcitonin[7], c-reactive protein (CRP)[25,26], sputum or naso-/oro-pharyngeal respiratory viral PCR[27], or sputum purulence[28] to guide antibiotic administration, and blood eosinophils (EOS) to guide systemic corticosteroid administration[8]. Sputum-purulence, currently recommended by NICE, is recognised as inaccurate[2,3,6]. CRP has poor specificity for exacerbations triggered by bacteria, as it is also raised in viral infections, or inflammatory states of other aetiology[25,26].

Characteristically, the C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations (PACE) and the CRP-guided antibiotic treatment in acute exacerbations of COPD in hospital admissions (CATCH) RCTs that used CRP to guide the administration of antibiotics for moderate and severe exacerbations, only achieved modest absolute decrease of 20.4% and 15.5% in antibiotic use, respectively[25,26]. On the other hand, for respiratory viral PCR we usually use upper respiratory samples that may not reflect the viral composition of the lower airways[10], while some exacerbations that are triggered by a co-infection with bacteria and viruses may be associated with worse outcomes and require treatment with antibiotics[29-33]. Finally, while sputum or blood bacterial cultures are often considered appropriate tests for confirming bacterial aetiology, their sensitivity is limited, while the presence of bacteria in the sputum does not necessarily imply bacterial aetiology of the exacerbation, since the airways of patients with COPD are often colonised by bacteria. Moreover, their long processing time means their results will not be available to facilitate treatment decisions in the acute setting[34]. Therefore, we further assessed procalcitonin and EOS.

1.4.1.1. Procalcitonin to guide the administration of antibiotics

Procalcitonin originates from the CALC genes and is produced consistently in response to bacterial infections[35]. More specifically, its production is triggered by endotoxin or by mediators released in response to bacterial infection, including interleukin 1β, 6, and tumour necrosis factor α[35]. On the contrary, interferon γ, a cytokine that has a central role in antiviral immune response, inhibits the production of procalcitonin[36]. As a result, procalcitonin is raised in bacterial infections, but not in viral infection or other types of inflammation not associated with bacterial infection[37].

Use of antibiotics for the management of unselected COPD exacerbations has been assessed in a recent Cochrane systematic review that included data from 19 RCTs totalling 2,663 study participants[38]. In moderate exacerbations, antibiotics were found to decrease the risk of treatment failure (relative risk, RR 0.72, 95% confidence intervals [0.56-0.94], absolute decrease by 8.3%), without significantly affecting all-cause mortality (RR 1.27 [0.49-3.30]). In severe exacerbations, antibiotics did not improve treatment failure rate (RR 0.65 [0.38-1.12]), length of hospital stay (mean difference, MD 0.09 [-0.79, 0.96]), or all-cause mortality (odds ratio, OR 2.48 [0.94-6.55]). On the contrary, antibiotics improved the outcomes of critical exacerbations, that were treated in the intensive care unit (ICU), including treatment failure

rate (OR 0.19 [0.08-0.45]), length of hospital stay (MD -9.60 [-12.84, -6.34]) and all-cause mortality (OR: 0.21 [0.06-0.72]). Overall, antibiotics were not associated with increased risk of any adverse events (OR 1.20 [0.89-1.63]), or diarrhoea (OR: 1.68 [0.92-3.07]). The overall certainty in these findings was low due to inadequate data and methodological limitations. Potential beneficial effects of antibiotics in exacerbations triggered by bacteria might have been diluted or missed due to the lack of efficacy in non-bacterial exacerbations.

Based on a prospectively registered protocol, we conducted a meta-analysis to assess the safety and clinical effectiveness of procalcitonin to guide antibiotic administration for moderate or severe (but not critical) COPD exacerbations[7]. Eight completed studies evaluated procalcitonin guidance versus standard care in 1,061 episodes of exacerbations. Antibiotic administration was recommended for procalcitonin >0.25mcg/L in the intervention arm of all included trials. This meta-analysis suggested procalcitonin-guidance can decrease antibiotic prescription rate by 36% (relative risk RR= 0.64 [0.52,0.78], risk difference RD= -0.28 [-0.40,-0.16]) compared with standard care, without adversely affecting clinical outcomes such as the rate of treatment failure (RR= 0.81 [0.62,1.06]), length of hospitalisation (mean difference MD= -0.76 [-1.95,0.43]), exacerbation recurrence (RR= 0.96 [0.69,1.35]) or mortality (RR= 0.99 [0.58,1.69]). While GRADE quality of evidence was low-to-moderate due to limited overall study population and methodological limitations, all outcomes supported the intervention and all studies presented consistent results. The main methodological limitation was the relatively limited adherence to procalcitonin guidance (which ranged between 61-98% in the included trials). However, the results remained robust in a subgroup analysis only including studies with high adherence to procalcitonin protocols (adherence >80%). An additional RCT conducted in China that was not included in our systematic review due to differences in the study population and compared administrating versus withholding antibiotics in 194 patients with a COPD exacerbation and procalcitonin levels below 0.1 ng/ml reported a high adherence rate (>80%) and did not reveal any between-group difference in the main efficacy outcomes[39].

Updated searches (January 2022) revealed two further eligible RCTs that have been completed after our previous searches[40,41]. Both trials recruited patients with a lower respiratory tract infection. The ProACT trial recruited patients presenting to the emergency department, while the other trial only accepted hospitalised patients. Both studies presented subgroup data of a total of 581 patients with COPD exacerbation and found that procalcitonin

protocols were non-inferior to standard care, although adherence to the procalcitonin protocols was low, limiting our confidence on these findings.

Critical COPD exacerbations (treated in the ICU) were excluded from our systematic review, as we considered this group very different (characteristically, the previously mentioned Cochrane review suggested that antibiotics are very effective in this setting). Daubin and colleagues tested procalcitonin guidance in this setting (patients with COPD exacerbations admitted to the ICU), in an open-label RCT[42]. In their study, procalcitonin-guidance was associated with a trend over increased 3-month mortality compared to standard care (adjusted difference of 6.6% [-0.3%, 13.5%]). Moreover, in a subgroup analysis only including patients that did not receive antibiotics, mortality was higher in the procalcitonin arm (19/61 versus 7/58 patients, p=0.015). However, this last finding might have been driven by indication bias. It is likely that more severely ill patients, who were less likely to survive, received antibiotics in the control group even in the absence of signs of a bacterial infection, leading to an apparent decrease in the mortality rate in the subgroup of patients who did not receive antibiotics in the control treatment arm. However, that does not mean that the excess antibiotic administration improved the overall patients' outcomes. Overall, use of procalcitonin in the critical setting needs to be further evaluated.

These observations strongly support the safety of procalcitonin guidance for non-critical exacerbations and highlight the need to be tested in pragmatic, high-quality, adequately powered confirmatory trials.

Over recent years, some observational studies have noted significant discrepancies between procalcitonin levels and bacteriological results in patients presenting with exacerbations and doubted the ability of procalcitonin to guide the administration of antibiotics for these patients[43-45]. However, this study design is inappropriate to assess procalcitonin as a biomarker because the sputum cultures are not the gold standard test for identifying COPD exacerbations triggered by bacteria. The airways of patients with COPD are frequently colonised with bacteria, which may lead to false positive results[46], while sterile sputum cultures cannot exclude a bacterial infection[47].

It has been proposed that strict antibiotic stewardship strategies based on clinical characteristics could effectively reduce antibiotic administration in COPD exacerbations[48]. However, extensive campaigns against inappropriate antibiotic prescribing in respiratory

infections have had modest impact[48,49]. Moreover, a secondary analysis of the European COPD Audit (which evaluated 16,000 exacerbations), reported that 61.4% of all hospitalized exacerbations fulfilled strict stewardship criteria for antibiotic administration and 86% received antibiotics[50]. In our meta-analysis, only 45.6% of hospitalised exacerbations received antibiotics following procalcitonin-based protocols, suggesting that procalcitonin guidance could decrease antibiotic administration by 40% compared with current practice and it can confer an additional 15% decrease compared with effective stewardship.

At present, use of procalcitonin to guide antibiotic administration for COPD exacerbations is being evaluated in another RCT in China (NCT04682899, PI: Bin Cao) that intends to recruit 500 patients with severe COPD exacerbations. Participants will be randomised to receive biomarker guided or standard care. Biomarker guidance will be based on a combination of procalcitonin and sputum purulence. More specifically, antibiotics will be strongly discouraged, discouraged, encouraged, or strongly encouraged for patients with procalcitonin levels <0.1 ng/ml, between 0.1-0.25 ng/ml without sputum purulence, between 0.1-0.25 with sputum purulence, and >0.25 ng/ml.

1.4.1.2. Blood eosinophils to guide the administration of systemic corticosteroids

COPD is predominantly characterised by neutrophilic inflammation in the airways[51]. However, eosinophilic inflammation has been observed in the airways of 20-40% of patients with COPD, both during stable disease state and exacerbations, and it is associated with an increased risk of future exacerbations[51,52]. Eosinophilic inflammation represents an established target of corticosteroid activity[53,54], while neutrophils appear to be less responsive[55]. While it is challenging to assess eosinophilic inflammation in the airways, it has been demonstrated that blood eosinophils represent a good surrogate biomarker[51]. For this reason, blood eosinophils have been assessed as a marker of response to treatment with corticosteroids both in stable COPD and exacerbations[14,56,57].

The role of systemic corticosteroids on the management of unselected COPD exacerbations, compared to placebo, has been evaluated in 16 RCTs, totalling 1,787 participants, as summarized in a Cochrane systematic review[58]. Systemic corticosteroids were found to limit the risk of treatment failure (OR 0.48, 95% confidence intervals [0.35-0.67], absolute decrease by 12.2%), risk of relapse in one month (hazard ratio, HR 0.78 [0.63, 0.97]) and length of hospitalization (MD -1.22 days [-2.26, -0.18]), and to modestly reduce breathlessness, at a cost of a significantly increased rate of participants experiencing any adverse event (OR 2.33

[1.59-3.43], absolute increase of 19.6%), and hyperglycaemia (OR 2.79 [1.86-4.19], absolute increase of 15.8%]). Interestingly, the administration of systemic corticosteroids was not associated with a survival benefit (mortality: OR 1.0 [0.6-1.7], no difference). Systemic corticosteroids are associated with numerous side effects[59,60], especially among those receiving prolonged or multiple courses every year, due to frequent exacerbations[61]. Owing to their immunosuppressive effects, they are associated with secondary bacterial, viral, or fungal infections, including pneumonia and sepsis[61,62]. They induce or deteriorate the control of diabetes and hypertension[63]. Moreover, they cause osteoporosis, fractures, and muscle wasting that could very adversely impact the quality of life and outcomes of patients with COPD[64].

Consequently, several RCTs have evaluated interventions aimed at limiting unneeded administration of systemic corticosteroids. Firstly, shortening the duration of systemic corticosteroids was evaluated in eight trials[65]. The REDUCE trial, a double-blinded trial based on 314 patients, demonstrated that shorter courses were not inferior to longer courses (5 versus 14 days) of systemic corticosteroid for COPD exacerbations leading to an emergency presentation[66]. These findings have informed therapeutic guidelines, which now recommend shorter courses of systemic corticosteroids[61]. The ongoing RECUT trial explores the safety of further reducing the duration of systemic corticosteroid courses to 3 days, for moderate exacerbations, not requiring a hospital admission[67].

Another systematic review based on a pre-registered protocol was conducted to identify clinical trials assessing whether blood eosinophils can be used to drive the administration of systemic corticosteroids for COPD exacerbations. Searches were updated in November 2021. Two eligible RCTs were identified. In a double-blind RCT involving 166 patients with moderate AECOPD, Bafadhel and colleagues showed that omitting systemic corticosteroids in cases with blood eosinophil count of ≤2% was not associated with worse outcomes (however, only 81 cases with EOS ≤2% were included in this trial)[8]. In the CORTICO-COP trial, after an initial dose of methylprednisolone was administered to all 318 participants with severe (hospitalized) COPD exacerbations, further doses during the subsequent four days were guided on a day-by-day basis by the blood eosinophil count in the intervention group[14]. In the eosinophil-guided group, EOS were measured daily and each day systemic steroids were only administered for EOS $\geq 0.3*10^9$ cells per litre. In the control group, all participants received a complete five-day course of systemic corticosteroids. Using this approach, the median

duration of systemic steroid administration was halved in the eosinophil-guided group (2 versus 5 days). No significant differences were observed in clinically important outcomes, such as the days alive and out of hospital within 14 days, mortality, re-exacerbation, and re-hospitalisation.

Eosinophil-guided administration of systemic corticosteroids was also evaluated in a post-hoc analysis of three RCTs involving 243 unselected patients with COPD exacerbation. These trials compared systemic corticosteroids versus placebo. The post-hoc analysis revealed that systemic corticosteroids significantly decreased the risk of treatment failure among exacerbations with EOS >2% (MD= 55% [38%,73%]), but not among those with EOS ≤2% (MD= 6% [-9%,27%])[9]. These results suggest EOS guidance could safely target systemic steroid administration in exacerbations.

At present, blood eosinophil guidance is currently evaluated in three other RCTs:

The Eo-Drive double-blind RCT (NCT04234360, PI: Arnaud Bourdin) intends to recruit 600 patients with severe COPD exacerbations, including 300 with low blood eosinophils (≤2%) and 300 with high eosinophils (>2%). Each of these eosinophil guided groups will be randomised to receive systemic corticosteroids versus no systemic corticosteroids.

The STAR2 double-blinded RCT (NCT04458636, PI: Mona Bafadhel) intends to recruit 203 patients with moderate COPD exacerbations irrespectively of the blood eosinophil count. All patients with high blood eosinophils (>2%) will receive systemic corticosteroids, while those with low eosinophils will receive either systemic corticosteroid or placebo.

The EoPred-ICU open-label RCT (NCT03981081, PI: Fekri Abroug) intends to recruit 192 patients admitted to the intensive care unit due to an AECOPD. In the intervention group, patients will only receive systemic corticosteroids if their blood eosinophil count exceeds 2%, while all patients in the control group will receive systemic corticosteroids.

Our systematic reviews did not yield completed or ongoing trials evaluating the combination of procalcitonin and EOS to safely target and reduce the administration of both antibiotics and systemic steroids in COPD exacerbations. Given the potential net benefits, we decided to launch a series of trials to test this intervention (figure 2). The biomarker cut-points will be 0.25mcg/L for procalcitonin and 2% of total white cells for EOS. Both cut points were validated by previous trials and post-hoc analyses[6-9]. We decided to start by conducting a pilot trial (the

TRACE-COPD trial) for several reasons: (i) Procalcitonin guidance has not been tested in the UK, where strict antibiotic stewardship policies are in place, and its efficacy needs to be confirmed in this context. (ii) Some participants will test negative for both biomarkers and will receive neither antibiotics, nor systemic steroids; the safety and acceptability of this intervention by the participants have not been previously assessed. (iii) Recruiting patients for an RCT in the acute setting is often associated with unexpected challenges and could be resource intensive; for this reason, we would like to explore the feasibility and required resources; (iv) Both patients and clinicians are used to treating exacerbations with antibiotics and systemic corticosteroids and -therefore- we wanted to test the acceptability of and adherence to the intervention. Adherence to procalcitonin guidance was limited in some of the preceding trials, in the absence of adequate safety data. As safety data has been accumulated, we will now try to maximise adherence to the treatment protocol.

In preparation of the TRACE-COPD trial, we conducted an exploratory study to assess COPD exacerbations distribution across the biomarker defined groups in 42 patients hospitalised with COPD exacerbations [non-published data]. Among the participants, 27(64.3%) tested positive for EOS (>2%) and 23 (54.8%) for procalcitonin (>0.25mcg/L). 16 (38.1%) and 8 (19.0%) tested positive and negative for both biomarkers, respectively. While the small study population limits the accuracy of the proportions, this analysis confirms that there is a sizeable proportion of exacerbations testing negative for both biomarkers. These cases might represent COPD exacerbations of a different aetiology (e.g., viral infections). Such patients will receive neither antibiotics nor systemic corticosteroids based on our biomarker-guided treatment protocol. The safety of the intervention should be carefully evaluated in this group of patients, and we anticipate gathering some preliminary safety data from TRACE, before launching a larger, confirmatory RCT.

1.4.2. Outcomes of clinical trials on COPD exacerbations management

RCTs represent the gold standard design for research studies evaluating the safety, efficacy and clinical effectiveness of novel treatments[68]. Properly done, random allocation of patients can achieve sufficient control over confounding factors to deliver an accurate comparison of the treatments studied[68]. The first and most crucial step in designing an RCT is the definition of the key elements that are captured in the PICO (Population, Interventions, Comparators, and Outcomes) question[69]. Selection of outcomes that are more relevant to patients and clinicians to be evaluated in a clinical trial is often the most challenging methodological

component[70]. Suboptimal outcomes may limit the clinical value, interpretability, and comparability of the findings of a clinical trial, leading to avoidable research waste[70].

In the context of a trial, only a limited number of outcomes can be evaluated. Trialists often prioritize outcomes that require fewer resources, are easier to measure, and are more likely to favour one intervention over the other(s), or answer specific questions that may be of limited importance to patients, health professionals or the regulatory authorities[71]. As a result, crucial information on potential beneficial or harmful effects of interventions are often missed. This limits the interpretability, comparability and clinical value of clinical trials, whose primary objective is to inform evidence-based recommendations and clinical practice. Moreover, properly pooling the results of different trials in the context of a meta-analysis is only possible if the same outcomes are measured, ideally using the same instruments.

The outcomes of clinical trials evaluating the management of COPD exacerbations are particularly heterogeneous. As a result, several recent rigorous systematic reviews, including those evaluating the most established and thoroughly evaluated treatments of COPD exacerbations (such as antibiotics and systemic corticosteroids) report limited confidence on the body of evidence due to this variability in the evaluated outcomes[34,38,58,72]. Therefore, there is an urgent need to develop consensus on the most critical outcomes to be assessed in all future relevant clinical trials.

Over recent years, methodology has been developed by the COMET initiative (Core Outcome Measures in Effectiveness Trials) to facilitate the identification of the most pertinent outcomes to be tested in RCTs. A core outcome set is an agreed minimum set of critically important outcomes that should be evaluated in all future trials in a specific area of health care, aiming to improve their quality and comparability[70]. A core outcome set should be based on evidence-informed, international and multistakeholder consensus. The views of patients, health professionals, clinical trialists and guideline developers should be strongly represented in this consensus, to ensure the most critical outcomes are prioritized and to facilitate uptake of the core outcome set in future trials[73]. In addition, the COMET in collaboration with the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) initiative, developed methodology for selecting a single, optimal instrument for measuring each outcome, to promote consistency and facilitate comparing and pooling the findings of different RCTs.

Exhaustive searches of the COMET database, Medline and EMBASE did not yield any published or ongoing methodological studies focusing on the development of a Core Outcomes Set for clinical trials of COPD exacerbations management. For this reason, we developed a globally representative multi-stakeholder group, to develop both a core outcome set, along with core outcome measurement instruments for such trials.

1.4.3. Respiratory viruses in stable COPD and exacerbations

Respiratory viruses are detected in 30-50% of all exacerbations[15,31,74-76], while they are also present in over 10% of all patients with stable COPD at any given time[76-78]. Interestingly, viral infections represent the only trigger that has conclusively been proven to have a direct causal link with COPD exacerbations, through experimental viral challenge studies[79,80].

The effect respiratory viruses have on the outcomes of COPD has not been rigorously evaluated, but it appears they pose an additional burden both in stable COPD and exacerbations[77,78]. Findings from the East London COPD cohort suggest that the detection of any virus in patients with stable COPD is predictive of an increased frequency of exacerbations, and in exacerbating patients it is predictive of prolonged and more severe symptoms[78]. However, a lower mortality rate is observed in exacerbations associated with viruses, compared to those testing positive for bacteria[81]. Not surprisingly, exacerbations characterised by concomitant viral and bacterial infections are associated with more severe symptoms burden, longer hospitalisations, and increased mortality[33].

As a result, prevention and treatment of exacerbations triggered by viruses could significantly improve the outcomes of patients with COPD. Characteristically, influenza vaccination has been proven to decrease the frequency of exacerbations[82,83] and is currently recommended for all patients suffering from COPD[84]. However, there are still significant, unaddressed clinical needs. While the effectiveness of neuraminidase inhibitors for treating influenza is well-established, influenza-triggered exacerbations are underdiagnosed and undertreated in clinical practice[85,86]. Moreover, commercially available antivirals against RSV that are of limited benefit to people without underlying respiratory conditions[87], might confer significant benefits to patients with underlying COPD, who experience more burdensome viral infections. However, their use in RCTs or clinical practice is limited due to the lack of accurate diagnostic biomarkers for exacerbations triggered by viruses.

The cost of molecular techniques that allow rapid identification of several respiratory viruses remains prohibitive, while the detection of a virus cannot establish viral aetiology of an exacerbation, since viruses are often present in stable COPD as well. In parallel, the sensitivity and specificity of the presence of upper respiratory or common cold symptoms that often concur or precede virally induced exacerbations are limited[74,76].

Various viruses are identified in the upper and lower respiratory samples of patients with stable COPD and exacerbations and may exert distinct clinical characteristics and outcomes. Further data on the prevalence and burden of different respiratory viruses are needed to drive the development of targeted diagnostic, preventive, and therapeutic interventions. To date though, most studies assess the presence of any virus and more specific data are only available for the most common viruses: rhinovirus, influenza, and respiratory syncytial virus[31,75,77,78].

The prevalence of different respiratory viruses has been evaluated in numerous observational studies. However, available data are very heterogeneous due to the seasonality of respiratory viruses, differences in patients' characteristics (e.g., proportion of patients receiving inhaled and/or systemic corticosteroids during sampling) and in the study designs. Existing systematic reviews and meta-analyses, that could have provided a better insight, are incomplete and characterized by methodological flaws[88,89]. Characteristically, there is limited overlap in the studies that are included in these reviews suggesting the searches were inadequate, while the quality appraisal of the included studies is lacking.

As a crucial first step to tackle this prevalent, burdensome, but potentially preventable and treatable trait, we decided to quantify the prevalence of various respiratory viruses in stable COPD and exacerbations by means of a rigorous systematic review and meta-analysis.

2. Characterisation and targeted TReatment of ACute Exacerbations of Chronic Obstructive Pulmonary Disease. Protocol and first findings from the TRACE-COPD, an open-label, pilot RCT.

Authors: Alexander G. Mathioudakis, Dave Singh, Jørgen Vestbo

Status of this work: *This is a draft paper, that has not been submitted for publication yet.*

Author contribution: *AGM and JV conceived and designed this study. AGM, guided by JV and other academics from the North West Lung Centre, prepared the funding and ethics applications, drafted this manuscript, set up the study and has started recruiting patients, supported by the NIHR Manchester CRF and BRC.*

2.1. Abstract

Background: Pharmacological treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD) consists of bronchodilators, antibiotics, and systemic corticosteroids. In the absence of clinically validated therapeutic biomarkers, both antibiotics and systemic steroids are significantly overused, posing significant threats to individual patients and the society. Blood eosinophil count and procalcitonin appear promising biomarkers, able to guide systemic corticosteroid and antibiotic administration, respectively. It is anticipated that the combination of these biomarkers would facilitate stratification and targeted treatment of COPD exacerbations, but it has not been tested in a randomised controlled trial (RCT).

Methods: The TRACE-COPD is a six-month, parallel-group, open-label, pilot RCT comparing a biomarker guided treatment protocol, based on procalcitonin and blood eosinophils, versus standard care, for COPD exacerbations. The TRACE-COPD study will involve 135 patients presenting with a COPD exacerbation, who will be randomised in a 2:1 ratio to the intervention or control groups. In the intervention group, a course of antibiotics is only given if procalcitonin is above 0.25mcg/L at presentation and a course of systemic corticosteroids only if blood eosinophil count exceeds 2% of total white cell count, at presentation. The primary outcomes will be reduction in the proportion of patients receiving antibiotics and/or systemic steroids for the index exacerbations, the acceptability of the intervention by patients and clinicians and the feasibility and resources required for the conduct of a larger, confirmatory trial. Secondary outcomes will include additional safety and feasibility outcomes.

Feasibility results: Recruitment of the TRACE-COPD trial is paused at present, due to the COVID-19 pandemic. During the first year of recruitment, feasibility issues were identified and addressed. First, due to recent changes in NICE guidelines, rescue packs with systemic antibiotics had been prescribed to all patients at risk of exacerbations; therefore, most patients presenting with an exacerbation had already received systemic treatments. Since the selection of treatment naïve patients was not feasible or pragmatic, we broadened the eligibility criteria.

Moreover, we found out that the local research infrastructure could not support unscheduled recruitment of acutely ill patients presenting with exacerbations. This issue was resolved since

we allowed patients to receive the first treatments in the emergency department prior to recruitment. Consequently, recruitment could be planned within up to 24 hours of presentation. In parallel, our centre is currently developing infrastructure to facilitate the delivery of acute respiratory care trials.

Conclusion: The TRACE-COPD has already revealed challenges in the design and delivery of trials of COPD exacerbations management. These challenges have been addressed and we are confident that TRACE will be completed after the pandemic. In addition, our feasibility findings will inform the design and conduct of future clinical trials of COPD exacerbations management.

2.2. Introduction

Acute exacerbations, being the main culprit of the debilitating burden and clinical outcomes of chronic obstructive pulmonary disease (COPD), represent a major unaddressed global health need[2,90]. Their pharmacological treatment, consisting of bronchodilators, antibiotics, and systemic corticosteroids, is only partly effective and remains unchanged for over a decade[6].

It has been demonstrated that acute exacerbations are heterogeneous and require a precision medicine approach in their treatment[31,75]. Antibiotics are only useful in exacerbations caused by bacteria, representing approximately 50% of all COPD exacerbations, while systemic corticosteroids are only effective in 30-50% of all exacerbations, that are characterized by enhanced eosinophilic inflammation in the airways[7,8,14,31,75]. However, in the absence of biomarkers that could accurately and timely identify the causes of exacerbations, both antibiotics and systemic steroids are significantly overused, posing significant risks to individual patients and the society[50]. Systemic corticosteroids are associated with frequent side effects that include an increased risk of pneumonia, osteoporosis and fractures, development of diabetes or deterioration of its control, venous thromboembolism, and adrenal insufficiency[59,91,92]. On the other hand, unnecessary use of antibiotics disrupts the existing microbial balance, promoting the generation and selection of resistant strains, that could cause the development of antibiotic-resistant infections, as well as their spread in the community[93]. Safe antibiotic avoidance is crucial for people with COPD who frequently receive unneeded treatments for their exacerbations, while their airways become colonised by bacteria that are progressively more resistant to available antibiotics[18,19].

As a result, several randomised controlled trials (RCTs) have evaluated precision medicine interventions for the management of COPD exacerbations. A recent systematic review based on data from 8 RCTs totalling 1062 participants suggested that use of procalcitonin to guide the administration of antibiotics could halve antibiotic administration without impacting clinical outcomes[7]. Similarly, two RCTs evaluating 484 exacerbations demonstrated that use of blood eosinophils could safely halve the administration of systemic corticosteroids[14]. The body of evidence supporting the use of these biomarkers is still relatively weak, due to a limited overall study population of the available trials, and due to methodological limitations.

The TRACE-COPD trial is a pilot randomised controlled trial aiming to preliminary evaluate for the first time the feasibility, safety, and clinical effectiveness of using procalcitonin and blood eosinophil count to guide the administration of both antibiotics and systemic corticosteroids for COPD exacerbations. The TRACE-COPD and a future confirmatory trial will expand the existing evidence on the safety and clinical effectiveness of both procalcitonin and blood eosinophils as therapeutic biomarkers and will introduce a basic level of characterisation of COPD exacerbations that could be further enriched in the future as novel biomarkers are developed and validated. They will also evaluate the safety of the intervention specifically among patients who will test negative for both biomarkers and the acceptability of the intervention by patients and clinicians alike. Importantly, we aim to address methodological limitations of previously conducted studies, such as the poor adherence to the biomarker-guided protocols.

2.3. Methods

2.3.1. Study design

The TRACE-COPD is a six-month, parallel-group, open-label, pilot RCT comparing a biomarker guided treatment protocol, based on procalcitonin and blood eosinophils, versus standard care, for COPD exacerbations. The protocol of this trial has been approved by the Greater Manchester East Research Ethics Committee (Research Authority, reference: 18/NW/0710, November 13th, 2018), and has been prospectively registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN, number: ISRCTN85620156). The trial is carried out in accordance with this protocol, the International Conference on Harmonisation Good Clinical Practice Guideline[94], the Helsinki Declaration[95] and it will be reported following the CONSORT guideline[96]. The main study characteristics are summarized in figure 3.

The main objective of the TRACE-COPD trial is to evaluate the acceptability of the biomarker guided treatment protocol by patients and clinicians, the feasibility and resources required for the conduct of a larger, confirmatory trial in the future. In parallel, it will provide a preliminary evaluation of the safety and clinical effectiveness of the intervention. We intend to recruit 135 patients with a background of COPD, presenting with a moderate or severe acute exacerbation. We define severe, exacerbations requiring hospitalization and moderate,

those requiring antibiotics and/or systemic corticosteroids, but not hospitalisation, according to the judgement of a clinician, who is unaware of the treatment allocation, procalcitonin and eosinophil levels of the participants and who is advised to follow the NICE criteria for deciding whether the participant requires hospitalization[3]. Detailed inclusion and exclusion criteria are presented in table 1.

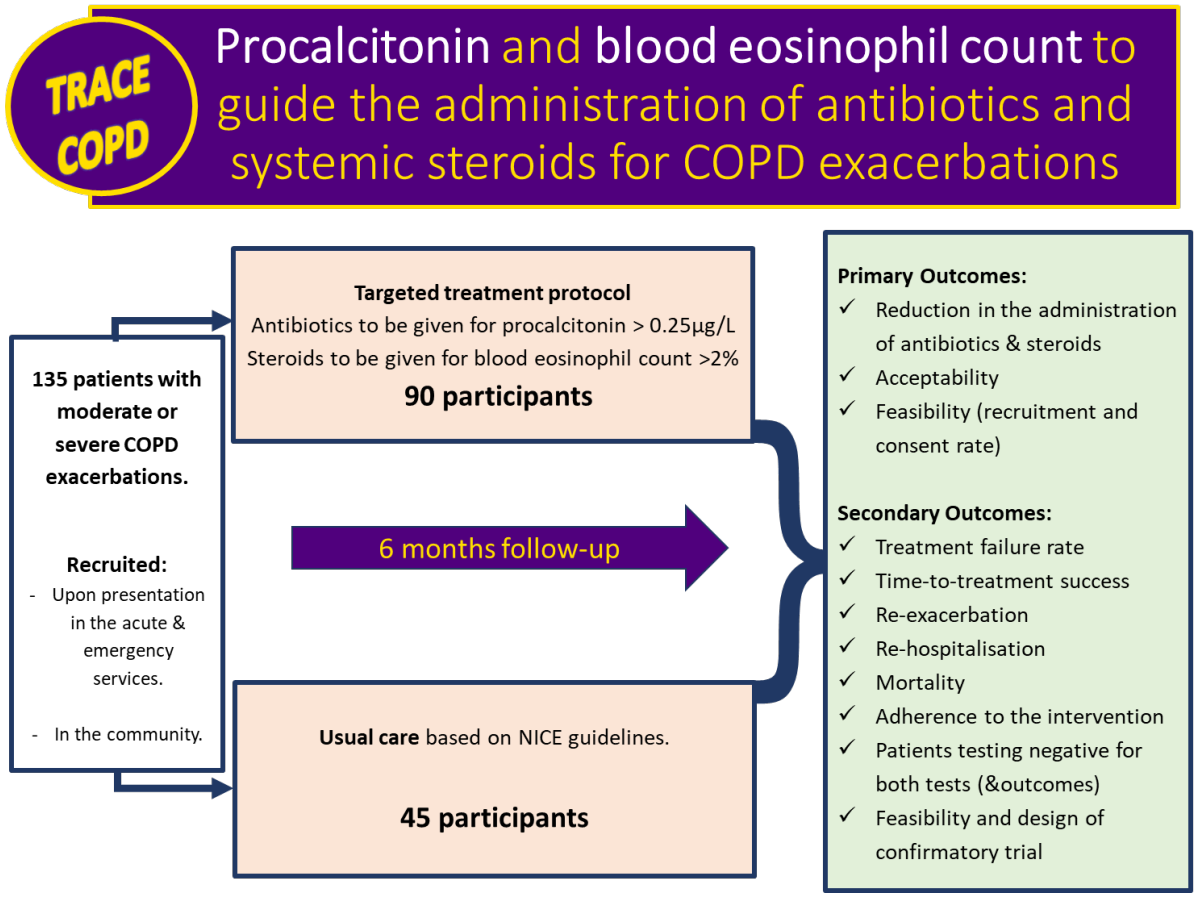


Figure 3. *The TRACE-COPD trial: Main study characteristics.*

Inclusion criteria	***Exclusion criteria***
Male or female aged over 40 years.	Primary diagnosis of pneumonia.
Current or ex-smokers with a smoking history of at least 10 pack years.	Suspected or confirmed decompensated hypercapnic respiratory failure.
Previous clinical diagnosis of COPD.	Current diagnosis of asthma.
Moderate or severe COPD exacerbation, with a significant deterioration of at least two of the following symptoms during the	Known immunodeficiency, cystic fibrosis, active tuberculosis, clinically significant

last 2-7 days: (i) Sputum volume; (ii) Sputum purulence; (iii) Breathlessness; (iv) Wheeze.	bronchiectasis. Life expectancy of <1 year due to medical problems other than COPD.
Not having received more than five days' worth of antibiotics and/or systemic corticosteroids during the preceding two weeks.	Known allergy, sensitivity, or absolute contraindication to the administration of doxycycline and/or prednisolone.
Capable and willing to consent.	Pregnant or lactating.
Willing to allow his/her general practitioner to be notified of their participation in the study.	Having participated in active clinical trials during the last 6 months or currently participating in any other research project on COPD exacerbations.

Table 1. Inclusion and exclusion criteria of the TRACE-COPD trial

Participants are recruited within 24 hours from presentation either from the emergency or acute medical departments of the participating hospitals, or participating primary care surgeries, or by the community COPD teams of these hospitals, during home visits, in response to patients' phone calls complaining of symptoms consistent with an exacerbation. This allows us to include both patients with moderate and severe exacerbations, but also to evaluate the feasibility of hospital and community recruitment and the required resources.

After signing an informed consent, eligible participants are randomised to the biomarker guided treatment or standard care in a 2:1 treatment allocation. A 2:1 treatment allocation was selected to allow for a thorough evaluation of the safety and acceptability of the intervention within the biomarker defined subgroups and specifically among participants who test negative for both biomarkers. A block randomization sequence, with a block size of nine, was generated using STATA Statistical Software version 15 (StataCorp 2017). The sequence was stratified according to site and recruitment source (emergency/acute medical department or the community COPD team). The allocation sequence is only known to the Biostatistics Department in Wythenshawe Hospital, Manchester University NHS Foundation Trust, and is concealed using sealed, opaque envelopes, which are only unsealed after enrolment of a participant.

2.3.2. Interventions

The TRACE-COPD trial compares whether the use of two biomarkers, procalcitonin and blood eosinophil count, could safely guide the administration of both antibiotics and systemic steroids for acute exacerbations of COPD.

In the biomarker guided treatment (intervention) group, participants only receive a course of antibiotics if their procalcitonin exceeds 0.25mcg/L at presentation. In addition, they only receive a course of systemic corticosteroids if their blood eosinophil count exceeds 2% of the total white cell count. For patients who will have already received systemic corticosteroids prior to recruitment and present with low EOS, systemic steroids will be discontinued, but the need for further systemic corticosteroids will be re-evaluated during the first follow-up visit (day 1-3) based on a repeat EOS count.

In the control group, participants receive standard care according to the NICE guidelines[3]. More specifically, a course of oral corticosteroids is administered to all exacerbations requiring hospital admission and to moderate exacerbations characterised by significantly increased breathlessness. A course of antibiotics is administered for exacerbations characterised by increased sputum purulence, compared to the stable state.

All participants, in both study arms receive inhaled and/or nebulised bronchodilators. The responsible clinicians are also encouraged to administer additional treatments, such as mucolytics and/or supplemental oxygen based on the clinical need and following national guidelines.

When indicated in each group, antibiotics will comprise a course of doxycycline for a duration of seven days. The first dose will be 200mg, followed by daily doses of 100mg. While still unaware of the treatment allocation and procalcitonin measurement, a treating clinician may consider intravenous antibiotics are required. In these cases, intravenous antibiotics are administered, following local antimicrobial policies, for participants allocated to the control group and for those allocated to the intervention group that have a raised procalcitonin (>0.25 mcg/L). The total duration of antibiotic courses remains seven days and the antibiotics are switched to oral doxycycline as soon as this is deemed clinically appropriate.

When systemic corticosteroids are indicated, then these include a five-day course of prednisolone, at a dose of 30mg.

2.3.3. Outcomes

The primary outcomes of the TRACE-COPD trial are: (i) the proportion of participants receiving antibiotics for the index exacerbation; (ii) the proportion of participants receiving systemic corticosteroids for the index exacerbation; (iii) the acceptability of the intervention by patients and clinicians; and (iv) the recruitment and consent rate.

Secondary outcomes include: (i) treatment failure rate at day 14 and at day 30[1]; (ii) time to treatment success; (iii) re-exacerbation and re-hospitalisation at 6 months; (iv) mortality during the index exacerbation and at 6 months; (v) adverse events and serious adverse events at day 14; (vi) increased length of admission or readmission due to side effects to study medications; (vii) adherence to the intervention; (viii) the proportion of patients testing negative for both biomarkers and the safety of the intervention in this subgroup; (ix) sample estimate for the confirmatory trial; (x) feasibility and challenges of recruitment of patients with a COPD exacerbation in the emergency department and/or the community; (xi) resources required for the confirmatory trial; (xii) identification of potential weaknesses of the study protocol, based on researchers' and participants' feedback on the study experience, challenges in the conduct of the study and in capturing the selected outcomes. Any weaknesses will be addressed with modifications of the protocol for the future, confirmatory trial. Finally, in additional exploratory analyses we will evaluate the diagnostic, prognostic, and therapeutic potential of inflammatory and extracellular matrix biomarkers.

For the purposes of the TRACE-COPD trial, we define the first day of the exacerbation as the recruitment day, when the participants seek medical attention for their symptoms[97]. The last day of the exacerbation is defined as the first day of three consecutive days while patients report having returned to their normal health state or the first of seven consecutive days in which patients only report minor increase in symptoms compared to baseline, without fever or altered sputum colour. Treatment failure is defined as a persistence of symptoms beyond day 14 from presentation, a significant deterioration leading to unplanned healthcare utilization, or the clinical need for administration of additional antibiotics and/or systemic corticosteroids, or death[97]. We will also evaluate treatment failure at day 30. Time-to-

[1] See next paragraphs for the definitions of treatment success and treatment failure.

treatment success will be defined as the number of days between presentation and the last day of the exacerbation, provided that the participants will not experience treatment failure.

2.3.4. Procedures

Detailed procedures are presented in figure 4. Potentially eligible patients, seeking medical attention for an acute exacerbation of their COPD are approached by members of our clinical research team. Consenting patients are recruited after confirmation of their eligibility. During the recruitment visit, details on the medical, medications history and findings from physical examination are recorded and biological samples are collected. The responsible clinician, based on the clinical assessment and while unaware of the treatment allocation, procalcitonin and blood eosinophil values of the participant, documents whether antibiotics and/or systemic corticosteroids and/or hospitalization are indicated, according to current NICE guidelines. Randomization envelops are then opened and participants are treated according to their treatment allocation. Apart from antibiotics and systemic corticosteroids, there are no other limitations in the treatment of the participants. Clinicians are encouraged to consider the administration of inhaled or nebulized short-acting bronchodilators, controlled oxygen therapy, mucolytics, to check the inhaler's technique and adherence, and to optimize the maintenance treatment of the participants. Participants are required to complete symptom questionnaires daily until confirmation of treatment success, and then monthly for six months. Specifically, an extended version of the COPD assessment test (CAT)[98], that additionally enquires about sputum purulence and wheeze, is completed. Participants are asked to respond describing their symptoms since the last iteration of the questionnaire. Participants receive automated text messages or phone calls reminding them to complete the questionnaires at the same time every day.

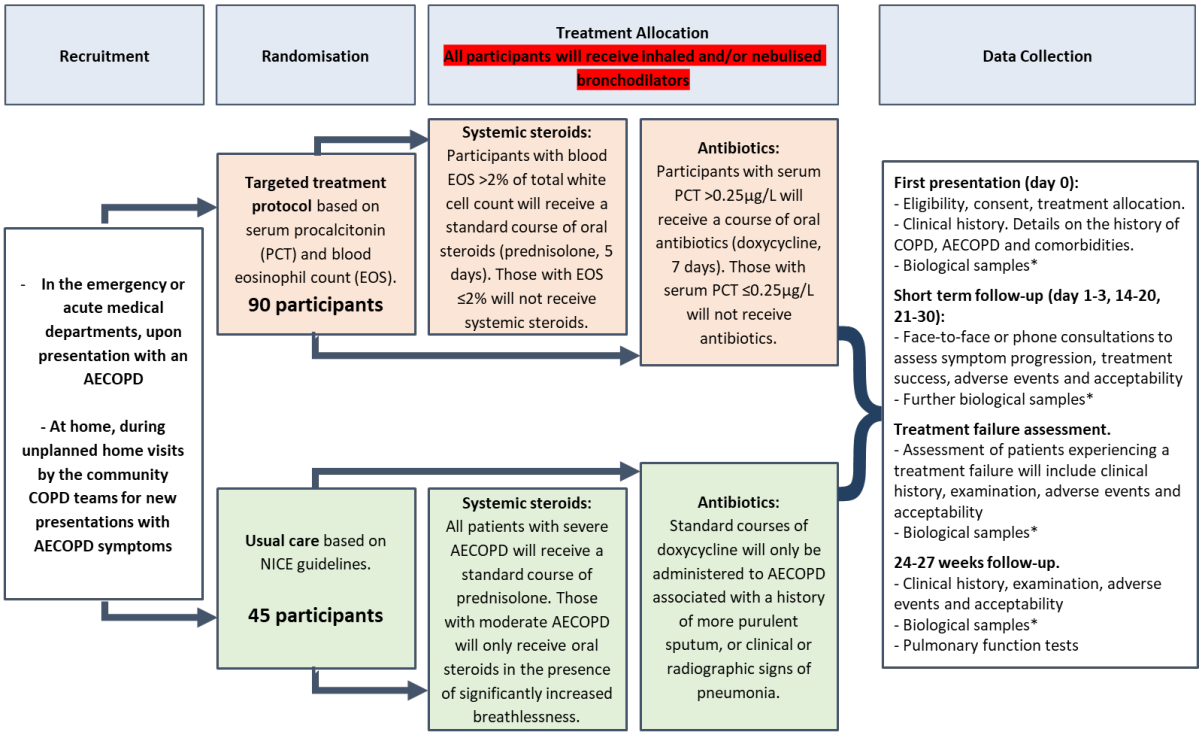


Figure 4. *The TRACE-COPD study design and procedures.*

Follow-up visits are scheduled for 1-3 days, 14-20 days and 24-27 weeks after recruitment. An additional visit is planned in case of treatment failure. A phone call could replace the second follow-up visit if treatment success is confirmed. An additional phone call is scheduled 30 days from presentation. During every face-to-face visit or phone call, patients are enquired on their symptoms, medications history, adherence to the treatment protocols, adverse events, and acceptability of the intervention. In addition, biological samples are collected during every face-to-face visit. Post-bronchodilation spirometry during clinically stable disease is obtained during the last follow-up visit.

Biological samples include blood samples, that will be used for inflammatory and extracellular matrix profiling, sputum samples and nasal swabs to quantify the presence of bacteria and viruses. Optional measurements will include volatile organic compounds and lung sound recordings, for exploratory analyses. Procalcitonin and blood eosinophil count are measured instantly, using validated point-of-care devices (BRAHMS Direct for procalcitonin[99] and the HemoCue WBC Diff System for blood eosinophils[100]). All point-of-care devices undergo quality controls in accordance with the developers' recommendations. Results of the point-of-care devices will be compared with standard automated laboratory measurements.

2.3.5. Safety

Participants experiencing treatment failure receive standard care by experienced clinicians. These include all participants who are still symptomatic 14 days after recruitment, and those experiencing a significant deterioration of their symptoms, requiring additional treatments, during their exacerbation. Participants are encouraged to seek medical advice in case of significant symptoms deterioration.

Blood cultures are not collected routinely, but in case of a positive blood culture, patients will receive antibiotics irrespective of their treatment allocation. In response to positive sputum cultures, all participants in the control group will receive antibiotics, as per standard practice; participants in the intervention group with high procalcitonin at presentation, will receive antibiotics according to the microbial sensitivities. Upon receipt of a positive sputum culture for a patient in the intervention group with low procalcitonin at presentation, we will repeat procalcitonin measurement. If it is still negative, we will consider the positive culture to represent colonisation; if positive, we will administer antibiotics. Change of antibiotics based on blood or sputum cultures and sensitivities in patients already receiving antibiotics will not be considered treatment failure in any case, in contrast to the delayed initiation of antibiotics.

2.3.6. Statistical analysis

Baseline characteristics of the participants will be presented in a tabulated format. Feasibility outcomes will be presented narratively and using descriptive statistics. Antibiotic and systemic corticosteroid exposure will be analysed on (i) an intention-to-treat basis and (ii) overall exposure rate. We will analyse time to treatment success using Kaplan-Meier curves and the log-rank test. All remaining analyses will be performed on an intention-to-treat basis using chi-squared, two-sampled t-test or Mann-Whitney U test. We will perform further analyses to take into account differences in the outcomes of moderate versus severe exacerbations (Cox proportional model for time to treatment success and generalised linear models for the remaining outcomes). In sensitivity analyses, we will analyse the impact of blood eosinophil count as a therapeutic biomarker on the outcomes separately, accounting for co-administration of antibiotics. Similarly, we will evaluate separately the impact of procalcitonin guided antibiotic administration, accounting for co-administration of systemic corticosteroids.

Based on the results of a recent meta-analysis evaluating procalcitonin-guided administration of antibiotics for COPD exacerbations[7], the TRACE-COPD trial is powered to demonstrate a

28% absolute decrease in antibiotics administration for the index exacerbation (antibiotic administration of 47% and 75% for the treatment and control arms respectively). The study power is 80%, at a 2-sided 5% significance level, with continuity correction and allowing for a drop-out rate of 10%. This population will also suffice to demonstrate a 40% decrease in the administration of systemic corticosteroids for the index exacerbation[8] and to assess recruitment and consent rates in two different centres, in the hospital and community settings. Since the TRACE-COPD is a pilot trial, it is not powered to demonstrate non-inferiority in the safety outcomes, however, potential safety signals would be captured. For the same reason, we did not adjust for multiplicity.

2.3.7. Trial oversight, funding, and support

The TRACE-COPD study is being guided by a Trial Management Group consisting of the Chief Investigator (Professor Jørgen Vestbo), the Principal Investigators in each study centre (Dr. Alexander G. Mathioudakis [Wythenshawe Hospital], Prof Richard Body [Manchester Royal Infirmary], and Dr. Abdul Ashish [Wigan Hospital]), a biostatistician, a member of the pharmacy team, a Clinical Trials Manager from the Manchester Clinical Research Facility, the Lead Research Nurse, two independent researchers (Prof. Dave Singh and Dr. Timothy Felton) and a patient representative. The trial management group is responsible for the day-to-day running and management of the trial, but also acts as a Trial Steering Committee and monitors the safety of participants.

This investigator-initiated trial was funded by Boehringer Ingelheim. It is Sponsored by the Manchester University NHS Foundation Trust and supported by the NIHR Manchester Biomedical Research Centre (BRC) and the NIHR Manchester Clinical Research Facility (CRF). It is also adopted in the NIHR Clinical Research Network (CRN) study portfolio.

Neither the funder, nor the organisations supporting this study had/will have any role in the study design, preparation of the protocol, data collection, data analysis, data interpretation or preparation of the study report. The study protocol was developed by AGM and JV, with input from other members of the Trial Management Group.

2.4. Preliminary Feasibility Findings and Potential Solutions

The TRACE-COPD trial has not been completed, largely due to the COVID-19 pandemic. At present, recruitment is paused. There are plans to restart recruitment once the pandemic is

over and the NIHR Manchester Biomedical Research Centre (BRC) 2 is expected to be set up, as it will include infrastructure support for clinical trials focusing on acute respiratory diseases, that will enable the delivery of this trial.

Recruitment was open in one site for almost one year prior to the pandemic. Unfortunately, we were only able to recruit four patients during this period (see CONSORT diagram, figure 5). However, we had the opportunity to observe challenges in recruitment that led us to amend the study protocol and we are confident that we will be able to complete the trial smoothly at a later stage.

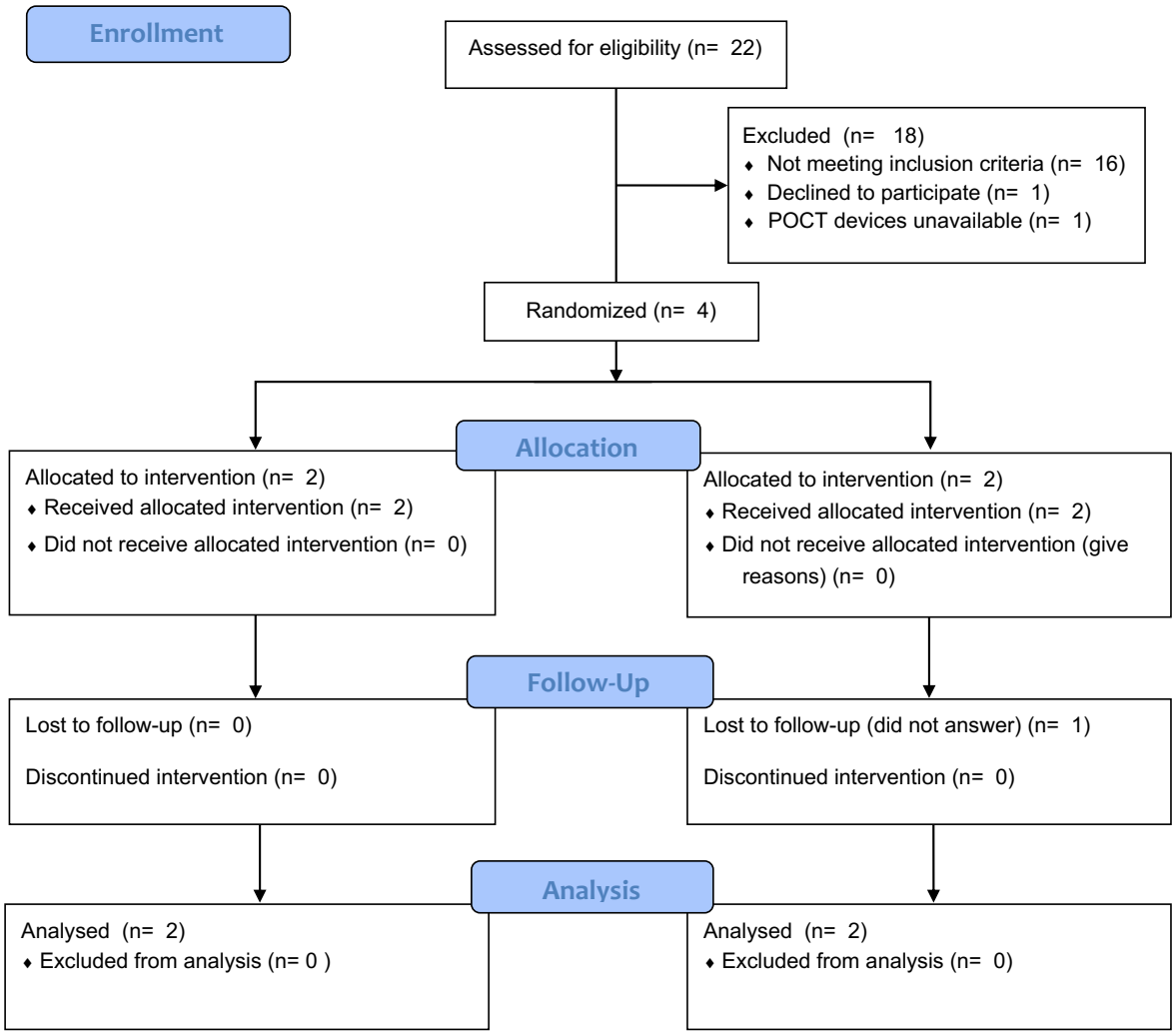


Figure 5. *The TRACE-COPD trial CONSORT diagram (version 1). Only patients who were/ were believed to be treatment naïve for the index exacerbation were assessed for eligibility.*

2.4.1. Eligibility criteria – Treatment naivety

Initially, we planned to recruit patients who were treatment naïve for the presenting exacerbation, meaning that they should have not received any antibiotics or systemic

corticosteroids within the preceding two weeks. Indeed, our aim was to use biomarkers to guide the initiation, rather than discontinuation of antibiotics and/or systemic steroids. However, we found this approach is not pragmatic. Characteristically, during October-November 2019, around 4-8 patients attended the Emergency Department at Wythenshawe Hospital with a COPD exacerbations daily, during recruitment hours (8am-6pm). However, we only identified 2-4 potentially eligible patients per month, as the vast majority had already received rescue packs with antibiotics and/or systemic corticosteroids at presentation. The situation was different 2-3 years previously, when a recruitment pilot was conducted at Salford Royal Infirmary and found that approximately 40% of those attending the Emergency Department were treatment naïve for the index exacerbation. However, the 2018 version of the NICE COPD guidelines included a new self-management section with a recommendation to administer rescue packs to all patients with a history of at least one exacerbation who remain at risk of further exacerbations[3]. This recommendation probably led to increased prescription of rescue packs in primary care and altered the characteristics of patients presenting to the emergency department.

Therefore, inclusion of patients who are not treatment naïve as well may be a more pragmatic approach. Based on several previous randomised controlled trials in patients with lower respiratory tract infections, but also in patients with COPD exacerbations, we are confident that procalcitonin could guide the discontinuation of antibiotics, for patients already receiving them[34,101].

It is somewhat less clear whether a single measurement of blood eosinophil count could guide the discontinuation of oral corticosteroids. In the CORTICO-COP trial, systemic corticosteroids appeared to suppress blood eosinophils[14]. More specifically, it was observed that the administration of systemic corticosteroids often led to the suppression of blood eosinophils the following day, leading researchers to withhold them, but the eosinophil count often rose again 24 hours later (and systemic corticosteroids were restarted, in accordance with the study protocol). The safety of this approach was confirmed in the CORTICO-COP trial, which was a non-inferiority trial involving 318 patients presenting with severe COPD exacerbations. For this reason, we decided to follow a similar approach in the TRACE-COPD trial. More specifically, in patients who have already received systemic corticosteroids for the index exacerbation and have low blood EOS at presentation (≤2%), we will stop systemic

corticosteroids, but the need for this treatment will be re-evaluated during the first follow-up visit, based on a repeat EOS count.

Inclusion of patients who are not treatment naïve for the index exacerbation has two important benefits: (i) this approach is more pragmatic, and (ii) it will accelerate study recruitment. Since the TRACE-COPD trial is a pilot trial and its main objective is to evaluate the safety and feasibility of conducting a larger scale pragmatic trial to evaluate biomarker-guided treatments for COPD exacerbations, this was considered an appropriate amendment. Moreover, the initial power calculations are still considered valid for this pilot trial.

We still aim to include a subgroup of treatment naïve participants. This subgroup of patients will be evaluated separately. For this reason, we also changed our recruitment strategy, to facilitate recruitment of treatment naïve patients. More specifically, we will allow recruitment of participants from general practice surgeries and via the community COPD team, during home visits. Participants seeking input from these groups are more likely to be steroid naïve. Patients will also be approached during stable disease state and will be asked to contact our research team in case of future exacerbations (during recruitment hours).

2.4.2. Recruitment in the acute setting

It is a great privilege for Clinical Academics in the UK that the National Institute for Health Research (NIHR) has infrastructure in place to support RCTs. More specifically, the TRACE-COPD trial is supported by the NIHR Clinical Research Facility (CRF), NIHR Clinical Research Network (CRN) and the NIHR Manchester Biomedical Research Centre (BRC). However, we observed that it is very challenging and resource intensive process for these units to support the recruitment of acutely ill patients at presentation. These units need to manage their resources (staff, laboratory spaces, etc) to accommodate a large number of clinical studies. Therefore, it is not cost-effective to have staff members stand-by to anticipate the unscheduled presentation of potentially eligible patients. As a result of this issue, Salford Royal and Wigan Infirmaries were not able to contribute to the trial, despite the strong interest of the clinical teams in both sites.

There are several potential solutions for this issue. The simplest solution, employed in many trials (including the CORTICO-COP trial[14]) is to allow the administration of routine clinical care at hospital presentation and recruit potential participants later, perhaps before the second treatment dose. This approach allows to plan recruitment at a specific time every day.

Potential criticism of this approach is that even a single dose of antibiotics and/or systemic corticosteroids might alter patients' outcomes, thus introducing confounding in the trial findings. This might not be such an issue for the TRACE-COPD trial anymore, since most participants recruited in the hospital setting are anticipated to have already received some doses of systemic treatments (see previous section).

The development of centres of expertise in acute respiratory care trials with appropriately organised staff and infrastructure is another solution. While it is not possible to occupy staff to anticipate the presentation of potentially eligible patients for a single, small trial, it might be cost-effective to develop a strong team that could support the conduct of multiple, large acute respiratory care trials. Such a model was successfully employed during COVID-19 pandemic for the RECOVERY and other therapeutic RCTs throughout the UK[102,103]. Given the importance and challenges of acute respiratory care trials, our centre aspires to develop into a centre of expertise for such RCTs. Both the NIHR Manchester BRC and CRF aim to develop relevant infrastructure and resources.

Active involvement of the clinical staff in such trials could also facilitate recruitment. Non-academically oriented staff will need both training and incentives to contribute to the recruitment in addition to their busy clinical work[104]. However, good clinical practice training and exposure to clinical research studies could be a valuable opportunity for trainees to develop new skills and enrich their curriculum vitae, while it might also foster an ethos for research across NHS with beneficial repercussions. NIHR advocates for embedding a research culture within the NHS. Over the last two years, numerous clinicians have been involved in COVID-19 trials; therefore, after the pandemic, clinical staff may be more receptive to contributing to clinical trials.

Finally, another option would be to develop hybrid teams with both clinical and research roles. For example, the community respiratory team at Wythenshawe hospital, that offers seven-day cover and represent the first point of contact for many patients with COPD in case of exacerbations, has expressed an interest in being involved in TRACE-COPD trial. However, unfortunately, the team is currently overwhelmed by clinical work. Perhaps, the addition of one or two staff members funded by academic budgets would allow the group to successfully fulfil their clinical duties and facilitate the conduct of clinical research studies such as TRACE.

2.5. Discussion

The TRACE-COPD is the first RCT to evaluate a precision medicine treatment algorithm using two biomarkers to guide the administration of both antibiotics and systemic corticosteroids for the management of acute exacerbations of COPD. This approach could prevent the unnecessary administration of both medications and – consequently – adverse events, risks associated with polypharmacy, and the development of antimicrobial resistance. Moreover, early stratification of exacerbations, at presentation, will likely allow the introduction of additional targeted treatments in the future.

Both procalcitonin and blood eosinophil count were selected after systematic evaluation of the literature. They have been previously assessed individually in RCTs as potential therapeutic biomarkers for exacerbations, with very promising results. In the majority of several trials assessing procalcitonin guided therapy in COPD exacerbations[7] or other acute respiratory tract infections[105], therapeutic protocols only suggest the use of procalcitonin as adjunctive to clinical presentation. These protocols strongly recommend, recommend, recommend against, and strongly recommend against antibiotic therapy for procalcitonin values of >0.5 mcg/L, 0.25-0.5 mcg/L, 0.1-0.25 mcg/L and <0.1 mcg/L, respectively. This approach results in limited adherence to biomarker-led recommendations, which has been reported to be <50% in some RCTs[7,105,106]. These RCTs provide limited insight into the accuracy of procalcitonin as a therapeutic biomarker. This approach was used to guarantee patients' safety in the initial trials. The enlarging evidence base supporting procalcitonin's accuracy allows for stricter therapeutic protocols to better evaluate the biomarker. For this reason, in the TRACE-COPD trial, antibiotics are prescribed for procalcitonin >0.25 mcg/L, but not for lower concentrations. Clinicians are advised to deviate from the biomarkers protocol in case of treatment failure.

The optimal cut-point value for blood eosinophil counts has been extensively discussed in stable disease[107-110] and exacerbations[8,14]. We chose a cut-point of 2% of total white cells. The trial led by Mona Bafadhel, that was the only reported trial at the time when the TRACE-COPD trial was designed, used the same cut-point[8]. More recently, the CORTICO-COP trial used a cut point of $0.3*10^9$ cells/L[14]. However, by using the percentage of total white cells, it is less likely for participants presenting with bacterial infections, whose neutrophils are usually raised, to fulfil the criteria for receiving systemic corticosteroids. For instance, a patient with

a white cell count of $20*10^9$/L, will only receive systemic corticosteroids if their EOS is $>0.4*10^9$/L. This was considered a safe approach.

The TRACE-COPD trial was designed before the development of the COPD Exacerbations Core Outcome Set[111]. Given the significant variability in the outcomes tested in COPD exacerbation trials, which limits their interpretability and comparability[112,113], outcome selection of the TRACE-COPD trial was informed by a methodological systematic review evaluating the endpoints selected by all exacerbations trials that were conducted during the last decade[112,113], a focus group discussion and face-to-face interviews with a total of 27 patients with COPD and a history of exacerbations. Prior to re-launching recruitment, we will update the outcomes to include the core outcome set.

Time-to-treatment success was considered more sensitive in identifying treatment effects, compared to treatment failure rate, which only evaluates the proportion of participants who are still symptomatic at a specific timepoint. Importantly, lead-time bias is avoided (lead-time bias: impact of deaths early during the study period, on outcome measures of duration, such as the duration of hospitalisation). Days alive and out of hospital within 14 days after recruitment, the primary outcome of the CORTICO-COP trial, is very similar to time-to-treatment success[14]. However, the latter focuses on symptoms resolution, rather than discharge from hospital. It was chosen because TRACE will also recruit patients with moderate exacerbations, that are not hospitalised. In addition, the timing of hospital discharge is significantly affected by social circumstances of the patients, availability of hospital beds, administrative delays, as well as the availability of community support services, such as the short-term administration of nebulisers at home, or follow-up visits at home by the community COPD teams[114-116].

The TRACE-COPD trial is now paused due to the COVID-19 pandemic. However, during the first year of recruitment we were able to identify feasibility challenges that have now been resolved. As a result, the study protocol has been amended and we fully expect a smooth recruitment both for the TRACE-COPD and the future confirmatory trial. In parallel, we discussed our challenges with several colleagues nationally and internationally with expertise in COPD exacerbations trials and we found that we all face similar challenges. As a result, we launched the DECODE-NET (DisEntangling Chronic Obstructive pulmonary Disease Exacerbations: a global clinical trials NETwork), to promote collaboration, the development of expertise and -most importantly- the conduct of multicentre, collaborative, high-quality

RCTs of COPD exacerbations management[117]. DECODE-NET now includes over 50 centres from Africa, America, Asia, Europe, and Oceania, that have already demonstrated the feasibility of their collaboration and intend to launch the first collaborative RCT.

Despite being a pilot study, the TRACE-COPD trial provides an opportunity to preliminary evaluate the safety and clinical effectiveness of the intervention in the overall population, but also in biomarker defined subgroups of the population, and this will be used to inform the design of the confirmatory trial. Other strengths of the study include the stricter protocol of biomarker guided treatments, that is anticipated to lead to higher adherence, the evaluation of the recruitment feasibility and resource requirements both in the community and hospital settings and its multicentre nature.

Overall, it is anticipated that this series of trials could lead to the introduction of a precision medicine approach to the management of COPD exacerbations, that will limit unnecessary administration of antibiotics and systemic corticosteroids. They will also allow for the introduction of additional targeted treatments, which represent our best hope for improving their outcomes.

3. Clinical trials on COPD exacerbations management: A systematic evaluation of outcome measures and diagnostic criteria of COPD and exacerbations.

Status of this work: *This work has been published in the following two parts:*

- *Mathioudakis AG, Moberg M, Janner J, Alonso-Coello P, Vestbo J.* Outcomes reported on the management of COPD exacerbations: a systematic survey of randomised controlled trials. ***ERJ Open Res 2019****; 5(2). pii: 00072-2019.*
- *Mathioudakis AG, Janner J, Moberg M, Alonso-Coello P, Vestbo J.* A systematic evaluation of the diagnostic criteria for COPD and exacerbations used in randomised controlled trials on the management of COPD exacerbations. ***ERJ Open Res 2019****; 5(4):00136-2019.*

Author contribution: *Study conception: AGM, with input from JV. Methodology and systematic searches: AGM, with input from PAC and JV. Study selection, data extraction, risk of bias assessment: AGM, MM, JJ. Supervision: JV. Manuscript preparation: AGM. Revision and approval: All authors.*

3.1. Abstract

Introduction: Randomised controlled trials evaluating COPD exacerbations management adopt diverging designs that render their results incomparable, complicating their translation into clinical practice and policy. Characteristically, they report heterogeneous outcome measures, while there is significant variability in the diagnostic criteria used for COPD and exacerbations. As a first step in the development of a core outcome set, that will aim to homogenize outcome measures in future RCTs, we assessed the outcomes reported in recent relevant RCTs and systematic reviews (SRs).

Methods: We conducted a methodological SR (registration number: CRD42016052437) of RCTs and SRs on COPD exacerbations management published in Medline and PubMed during the last decade. We evaluated their methodology, specifically focusing on the reported outcome measures and diagnostic criteria for COPD and exacerbations.

Results: Based on 123 RCTs and 38 SRs, we found significant methodological variability. Spirometric confirmation of COPD is unattainable during exacerbations, so most trials recruit patients with previously confirmed diagnosis or adopt a pragmatic approach, recruiting all patients with compatible history; these approaches are more appropriate for efficacy or effectiveness trials, respectively. Diagnostic criteria for exacerbations vary significantly; stricter diagnostic criteria can successfully exclude mimics. Mortality, which was assessed in 82% of the included trials, was the most frequently assessed outcome, followed by the rate of treatment success or failure (63%), adverse events (59%), health status, symptoms and quality of life (59%), lung function (47%), and duration of exacerbations (42%).

Conclusion: The significant heterogeneity in the selection and definition of diagnostic criteria and outcome measures by RCTs and SRs limits the interpretability and comparability of their results and warrants homogenization through methodological research, including the development of a core outcome set for COPD exacerbations management.

Take home message: Comparability of RCTs evaluating the management of COPD exacerbations is limited by heterogeneity in their design. Standardisation of outcome measures and diagnostic criteria for COPD and exacerbations would help researchers to compare, contrast and synthesise them.

3.2. Introduction

Chronic obstructive pulmonary disease (COPD), affecting more than 10% of people aged over 40 years, is a leading cause of death and disability globally[2,6,118]. Acute exacerbations punctuate the natural history of COPD, representing a major determinant of disease morbidity, mortality and progression, health care utilization and costs[2,6,118]. Their management is currently based on treatments that are only partially effective and almost unchanged for over a decade[2,6]. On the contrary, our understanding of the exacerbations pathogenesis and underlying mechanisms is growing rapidly[6,75]; therefore, we anticipate that novel, targeted treatments will be introduced and trialed in the near future.

Researchers conducting randomised controlled trials (RCTs) on the management of COPD exacerbations face important challenges. Firstly, the study population selection is complicated by limitations in the diagnosis of COPD and of exacerbations. More specifically, spirometric confirmation of the diagnosis and staging of COPD is unattainable upon recruitment to a trial during an exacerbation, as patients are often unable to perform good quality spirometry, due to acute breathlessness. In addition, the diagnosis and severity assessment of exacerbations are currently based solely on clinical presentation[2,6], with inherent limitations in diagnostic threshold[2,119] and severity grading[120,121].

The definition and consistent use of relevant and comparable outcomes, including patient important outcomes is currently lacking. Characteristically, there is no universal measure for treatment success or failure in COPD exacerbations, and simple to measure outcomes such as symptom burden and duration are not easily agreed on (figure 6). In the absence of consensus, the outcomes reported in published randomised controlled trials vary significantly. This complicates comparing, synthesizing, and interpreting trial results, leading several recent Cochrane reviews on COPD exacerbations to report limited confidence on the body of evidence due to this variability[38,58].

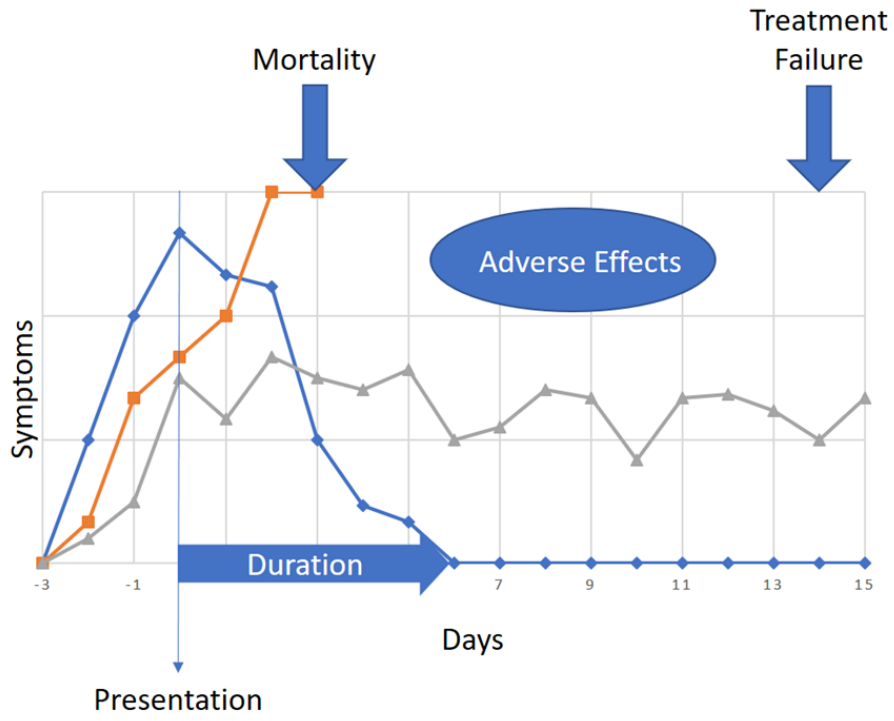


Figure 6. Hypothetical exacerbations with different outcomes. Important outcomes include the duration of symptoms from presentation, treatment failure rate, mortality, and adverse effects of the interventions. Standardization of their measurement is required.

The development of a core set of outcomes, representing the minimum that should be measured and reported in all relevant clinical trials, could remedy this issue. Following methodology developed by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative[70], we conducted a methodological systematic review to evaluate the outcomes reported in trials on COPD exacerbations, as a first step in the development of a core outcome set. In addition, we specifically assessed the extent to which these trials report patient-important outcomes. Simultaneously, we investigated the diagnostic criteria used for COPD and exacerbations, which also need to be homogenized.

3.3. Methods

This systematic review is based on a prospectively registered protocol (PROSPERO register, ID: CRD42016052437)[122].

3.3.1. Study selection & Data extraction

Eligible studies were randomised controlled trials (RCTs) and systematic reviews (SRs) of RCTs studying interventions aimed to treat COPD exacerbations. Medline and PubMed were

searched on October 2018 for eligible studies published between 2006-2018. Detailed search strategy is available in figure 7.

Search results were screened for eligibility by 2 reviewers independently (among AGM, JJ, MM) in two steps, which included an initial screening of the titles and abstracts, followed by detailed assessment of the full text reports of potentially relevant articles. Selection process is described in a PRISMA flowchart (figure 8). Details of the included studies are presented in Appendix 8.2.1. Studies which were deemed potentially eligible during the screening of titles and abstracts but were excluded at a later stage, as well as the reason for their exclusion are presented in the online appendix of the original publication. Relevant study characteristics, diagnostic criteria for COPD and COPD exacerbations and all the outcomes evaluated in each included study were independently extracted in a standardized form by 2 reviewers (AGM, JJ, MM). When it was deemed appropriate, further data were sought from published trial protocols. Disagreement in each of these stages was resolved by consensus among the three reviewers. Results are presented narratively.

3.3.1. Outcome Classification

All outcomes reported in the included studies were classified into the following three categories by the three reviewers who were working independently and in a blinded fashion. Disagreement was resolved by consensus among all authors.

Patient-important outcomes: Outcomes that reflect how patients feel, function, or survive[123,124]. These include mortality, morbidity, measures of health status and quality of life.

Surrogate outcomes: Early outcomes that may indicate disease progression and increased risk of patient-important outcomes, such as oxygen saturation which could predict treatment success or duration of hospitalization in patients requiring supplemental oxygen[7,125].

Physiological and Laboratory Outcomes: Outcomes assessing response of physiological or laboratory measures, without direct, tangible effects on patients[125].

Chronic Obstructive Pulmonary Disease	#1	Chronic Obstructive Pulmonary Disease [MH]
	#2	Lung Diseases, Obstructive [MH:NOEXP]
	#3	Emphysema [MH]
	#4	Chronic Bronchitis [MH]
	#5	COPD [tiab]
	#6	COAD [tiab]
	#7	“Chronic Bronchitis” [tiab]
	#8	Emphysema [tiab]
	#9	Obstructive[ti]
	#10	(Pulmonary OR Respiratory OR Airway OR Airflow OR Lung)[ti]
	#11	#9 AND #10
	#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #11
Exacerbation	#13	Disease Exacerbation [MH]
	#14	Exacerbation [tiab]
	#15	Exacerbation* [tiab]
	#16	#13 OR #14 OR #15
RCT Filter	#17	randomized controlled trial [pt]
	#18	controlled clinical trial [pt]
	#19	randomized [tiab]
	#20	placebo [tiab]
	#21	clinical trials as topic [mesh: noexp]
	#22	randomly [tiab]
	#23	trial [ti]
	#24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
SR Filter	#25	Medline[tiab]
	#26	Systematic[tiab] and (review[tiab])
	#27	Meta analysis[publication type]
	#28	Meta-analysis[tiab]
	#29	Metaanalysis[tiab]
	#30	#25 OR #26 OR #27 OR #28 OR #29
Final selection	#31	Search ("2006"[Date - Publication] : "2017"[Date - Publication])
	#32	animals [mh] NOT humans [mh]
	#33	#12 AND #16 AND #31 AND (#24 OR #30)
	#34	#33 NOT #32

Figure 7. *Search strategy*

3.4. Results

3.4.1. Description of the Included Studies

Details of the search results and study selection process are provided in a PRISMA flowchart (figure 8). Briefly, our search strategy yielded 1,796 results, among which we selected 173 eligible manuscripts, reporting on 38 systematic reviews and 123 randomised controlled trials. References of all included studies are available in appendix 8.2.1.

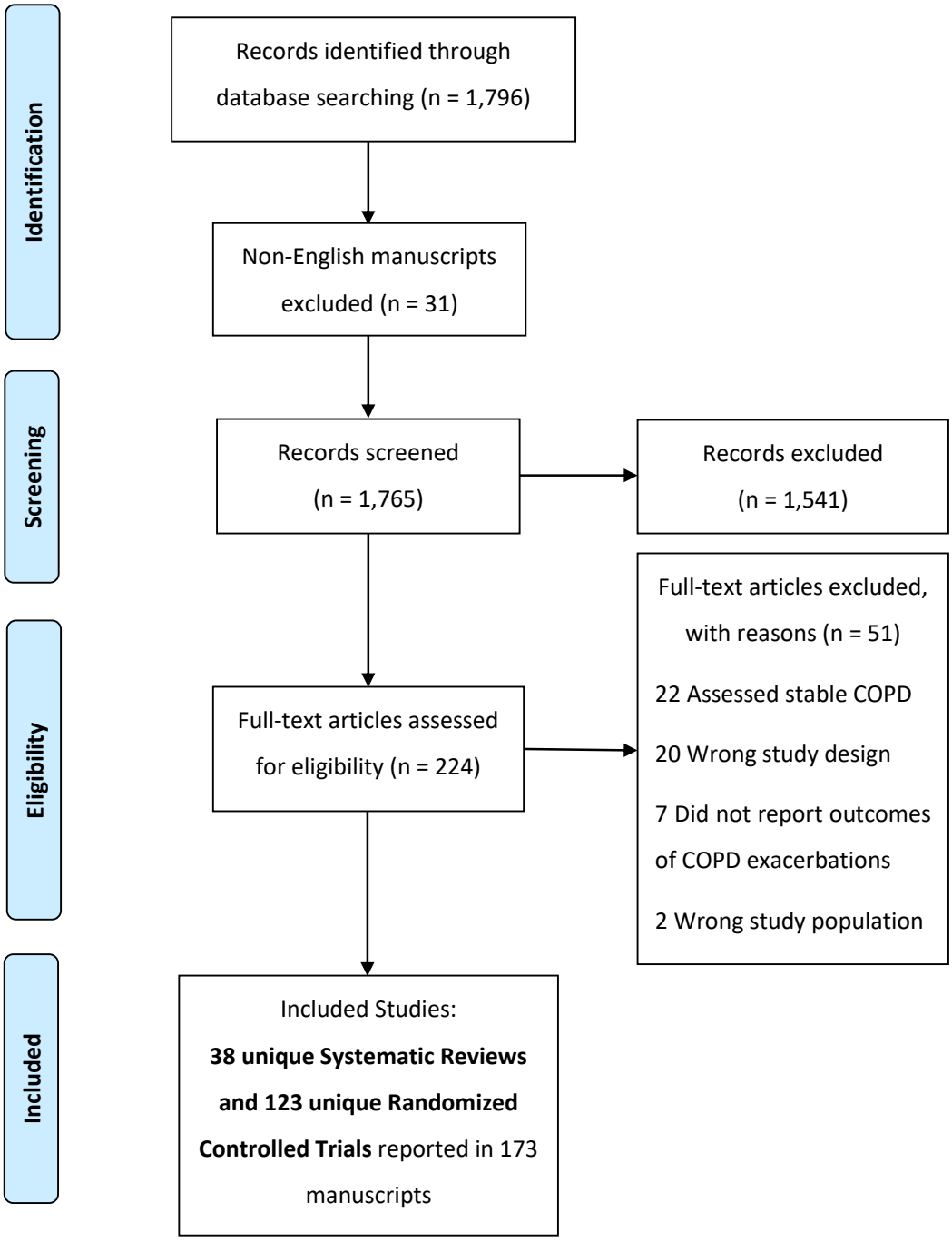


Figure 8. *PRISMA Flowchart*

Most of the included studies focused on the use of antibiotics (14 SRs; 34 RCTs), corticosteroids (8; 13), physiotherapy and rehabilitation (2; 18), oxygen therapy and ventilation (6;15), bronchodilators (1; 9), self-management and telehealth (2; 5), and complementary medicine (3; 8). Study populations of the included trials ranged between 9 and 980 participants and follow-up period between 45 minutes and 2 years. With regards to blinding, 45, 21 and 57 trials were double-blind, single-blind and open-label, respectively. Investigators were blinded to the intervention in 15 of the single-blind trials, with patients blinded in the remaining single-blind studies. Fifty-five (45%) of the included trials were multi-centre and 23 (19%) were sponsored by a pharmaceutical company.

A prospectively registered protocol was only available for 67/123 (55%) of trials and 9/38 (24%) of SRs. There was an upward trend for trials, as 60%, 54%, 92%, 86% and 100% of the trials published in 2014, 2015, 2016, 2017 and 2018, respectively, reported a prospective protocol. Unfortunately, SRs did not follow a similar pattern and almost exclusively SRs published by the Cochrane Collaboration reported a prospective protocol.

Primary and secondary outcomes were clearly and separately defined in 84 (68%) of the trials and 19 (50%) of the included SRs.

3.4.2. Diagnosis of COPD

It is recommended that a COPD diagnosis should be based on a compatible clinical history and spirometric evidence of persistent airflow limitation during stable clinical disease[2]. This is unattainable during an acute respiratory condition when the specificity of spirometry is limited[126]. RCTs evaluating the management of exacerbations implement different methods to overcome this issue.

In our systematic review, four (3%) of the included RCTs recruited patients during clinically stable disease, succeeding in acquiring a formal diagnosis of COPD prior to the exacerbation. A previous clinical diagnosis of COPD confirmed by spirometry was a prerequisite in 40 trials (33%), a previous clinical diagnosis alone was acceptable in 23% of the studies, and a typical history of chronic bronchitis at the time of recruitment was accepted in 24%. Finally, the diagnostic criteria for COPD were not reported or were unclear in 18% of the included studies. In order to confirm the diagnosis of COPD, several studies excluded patients with a diagnosis of asthma and/or atopy (19%), bronchiectasis (11%), or any other known respiratory diseases (6%).

3.4.3. Diagnosis of exacerbations

In the absence of accurate biomarkers, the diagnosis of COPD exacerbations is still based on clinical presentation. However, the clinical characteristics of COPD exacerbations are non-specific and can result from many other acute cardiorespiratory diseases. Different diagnostic criteria have been proposed[2,127], which are more or less stringent and classify acute respiratory events differently.

The criteria proposed by Anthonisen and colleagues, which require an acute deterioration of at least two symptoms among sputum volume, sputum purulence and breathlessness[127], were most frequently used in the evaluated trials (24%), followed by those adopted by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (13%). GOLD defines exacerbation as an acute sustained deterioration of the patients' condition that is beyond the normal day-to-day variation and necessitates the administration of additional medications[2]. Three other trials (2%) used modified Anthonisen criteria, which required the presence of either two of the previously mentioned symptoms (major symptoms), or at least one major and one minor symptom, which included cough, wheeze, nasal discharge, sore throat or pyrexia[128]. Other combinations of specific symptoms (including any of the previously mentioned symptoms, tachypnoea, or tachycardia) and biomarkers (parameters of the arterial blood gases, white cell count, neutrophil count, or c-reactive protein) were considered as diagnostic in 23% of the trials, while 38% did not describe specific diagnostic criteria but mostly required a diagnosis by a clinician. Almost half of the trials (46%) recruited only hospitalized (severe) exacerbations. Reporting of the diagnostic criteria was poor in these studies, likely because a hospital diagnosis of COPD exacerbation per se is considered more accurate.

Several studies specifically mentioned the exclusion of COPD mimics, such as pneumonia (33%), acute heart failure (19%), pneumothorax (3%) or pulmonary embolism (2%). To eliminate acute decompensation of left ventricular failure, some studies excluded patients with pre-existing cardiac failure, while others excluded presentations which were considered likely to represent decompensated cardiac failure by a senior physician. However, the acquisition of an echocardiogram or a CT-pulmonary angiography to exclude mimics at presentation was not described in any of the trials. Finally, 22% of the studies only recruited patients who were symptomatic for at least 24-72 hours and/or for a maximum of 10-14 days

before presentation, as the probability of exacerbation mimics is considered to be increased in shorter or longer periods of symptoms, respectively.

3.4.4. Outcome measures of randomised controlled trials

3.4.4.1. Patient-Important Outcomes

Mortality: Mortality at longest follow-up was evaluated in 101 of the included trials (82%). It was the primary outcome of 6 RCTs (5%).

Clinical treatment success or failure: Treatment success or failure rates were evaluated in 77 trials (63%). More specifically, 21 studies (17%) reported data on both treatment success and failure rates, while 27 (22%) and 29 (24%) studies only reported on treatment failure or treatment success, respectively. Treatment success or failure were evaluated at variable time-points, between 3 and 90 days from presentation (table 2).

Timepoint of assessment	Number of studies
End of treatment	11
1-6 days from presentation	6
7-10 days from presentation	22
12-15 days from presentation	22
16-30 days from presentation	13
>30 days from presentation	7

Table 2. Treatment success or failure evaluation time-points. Some studies evaluated this outcome at more than one time-points.

Treatment failure was defined in the majority of studies (n=24) as a composite outcome including several of the following components: death, intensive care unit admission, requirement of additional treatment (usually systemic corticosteroids or antibiotics for respiratory reasons), need for hospitalization or re-admission, significant symptom deterioration or, infrequently, diagnosis of a new exacerbation after complete symptom resolution. Fourteen studies defined treatment failure as lack of complete symptom resolution or lack of improvement in the symptoms at a specific time point, and ten studies as the need for treatment intensification.

Most trials (n=37) defined treatments success as complete resolution or significant improvement of the clinical symptoms associated with the exacerbation. Some evaluated both “cure”, defined as complete resolution of the signs and symptoms of an exacerbation

and “improvement”, usually defined as complete resolution of the fever, with incomplete resolution of other signs and symptoms and without clinical need for additional treatments. Four trials considered treatment success as discharge from hospital, two discharge from intensive care unit, and seven as successful withdrawal of ventilation or supplementary oxygen administration (depending on the intervention and study setting).

Adverse effects: 73 RCTs (59%) reported on the adverse effects of the study interventions. Most evaluated all adverse effects, severe adverse effects and mortality or presented the most frequent adverse effects. Some trials focused on specific known side effects of the study drugs or interventions and others also evaluated the impact of study drugs on vital signs, electrolytes, acid-base balance, or specific biochemical tests.

Health status, quality of life and symptoms: Changes in symptoms, quality of life and/or health status of the participants was evaluated in 73/123 trials (59%). 41 (33%) assessed symptom progression using simple symptom scores, such as visual analogue scales or Likert scales. Breathlessness was the most frequently evaluated symptom, followed by phlegm volume. Other symptoms included cough, phlegm colour and fatigue.

Thirty-four other studies (28%) utilized more comprehensive health status and quality of life questionnaires, mostly the COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ). Other questionnaires included Saint George Respiratory Questionnaire (SGRQ), Chronic Respiratory Questionnaire (CRQ), EXAcerbation of Chronic Pulmonary disease Tool (EXACT), EuroQol-5D (EQ5D), Short Form 36 Health Survey (SF-36) and the Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity index (BODE).

Two of the trials evaluating health status did not report adequate details on the methodology utilized.

Duration of the exacerbation: Duration of the index exacerbation was reported in 42 RCTs (34%).

(i) Time to treatment success: All three studies (3%) reporting time to treatment success were based on symptom questionnaires. Two studies used the same, well-defined criteria, based on daily symptom diaries evaluating the Anthonisen criteria. The first day of the exacerbation was defined as the day the patient sought medical advice. The last day was defined as the first of three consecutive days when the patient had returned to his normal health state or

the first of seven consecutive days in which the patient only reported minor increase in symptoms compared to baseline, without fever or altered sputum colour.

(ii) Length of hospital or intensive care stay: Length of hospital or intensive care stay was reported in 39 of the included RCTs (32%): 33 studies reported on the length of hospitalization, 10 on the length of stay in the intensive care unit, and 10 on the length of ventilation.

Re-exacerbation, re-hospitalization, and health care utilization: Time-to-next exacerbation or hospitalization, re-exacerbation, re-hospitalization, or number of exacerbations during follow up were reported in 33 trials (27%). More specifically, 28 (23%) reported on further exacerbations and 14 (11%) on further hospitalizations.

Fourteen studies (11%) assessed health care utilization during follow-up. From this outcome we excluded those studies that only evaluated length of hospital or intensive care stay or ventilation during the initial presentation, as this was described separately. These 14 studies evaluated hospital admissions (number and duration), emergency room visits, emergency outpatient visits, telephone calls with the physicians and/or consultations with primary care physicians.

Exercise Capacity: Only 14 studies (11%) reported on the rate of improvement in exercise capacity. Most (n=11) utilized 6-minute walking test, while two used 3-minute walking test, one the incremental shuttle walk test and one used 2-minute step in place.

Anxiety and Depression: Change in the levels of anxiety and depression was evaluated in 6 studies (5%). Four studies utilized the Hospital Anxiety and Depression Scale (HADS), one used a visual analogue scale, and one used the Geriatric Depression Scale.

3.4.4.2. Surrogate Outcomes

Arterial blood gases and oxygen saturation: These outcomes were mostly reported in trials evaluating oxygen therapy, ventilation, or chest physiotherapy. More specifically, 40 RCTs (33%) reported on arterial blood gases (pH, pO_2, pCO_2, SpO_2) and 5 additional studies reported on oxygen saturation measured by pulse oximetry.

Microbiological response: Microbiological response (which was assessed based on serial sputum cultures) at various time-points was assessed in 16 RCTs (13%). All studies used similar definitions for success or failure. For patients with a positive sputum culture at presentation,

bacteriological eradication was defined as the absence of the original causative organism in subsequent sputum cultures; presumed bacteriological eradication was defined as the absence of appropriate culture material, because the patient had clinically improved and was unable to produce phlegm. The presence of the original causative organism in repeat sputum cultures was defined as persistence and the isolation of a new organism, as superinfection. Patients with persistent clinical symptoms (clinical treatment failure), who were unable to produce phlegm, were categorized as presumed bacteriological persistence. Bacteriological relapse and eradication with re-infection were also defined in some of the trials.

Medication use: 18 trials (145%) reported on the use of medications during follow up, including use of reliever therapy, duration of antibiotic and/or systemic steroid courses or the administration of additional courses of the above.

Outcomes	Frequency of reporting	
	RCTs n (%)	**SRs n (%)**
Patient important Outcomes		
Mortality	101 (82%)	29 (76%)
Treatment success or failure	77 (63%)	29 (76%)
Adverse effects	73 (59%)	26 (68%)
Health status, symptoms & quality of life	73 (59%)	17 (45%)
Duration of exacerbations	42 (34%)	20 (53%)
Re-exacerbation, re-hospitalization	33 (27%)	16 (42%)
Exercise capacity	14 (11%)	1 (3%)
Anxiety and depression	6 (5%)	1 (3%)
Surrogate, Physiological and Laboratory Outcomes		
Lung function	58 (47%)	18 (47%)
Arterial blood gases and oxygen saturation	40 (33%)	5 (13%)
Microbiological response	16 (13%)	7 (18%)
Biomarkers	32 (26%)	2 (5%)
Medication use	18 (15%)	3 (8%)

Table 3. Frequency that different outcome measures were reported in the 123 RCTs and 38 SRs included in this methodological review.

3.4.4.3. Physiological and Laboratory Outcomes

Pulmonary function: Rate of pulmonary function improvement over time was the most frequently evaluated physiological outcome (58/123 trials, 47%). Forced expiratory volume in 1 second (FEV1) was the most frequently assessed parameter, followed by forced vital capacity (FVC) and peak expiratory flow rate (PEFR).

Biomarkers: Thirty-two trials reported on the impact of the interventions on various biomarkers. C-reactive protein was the most frequently reported marker (18 trials, 15%). Other biomarkers included white cell count, several interleukins, tumour necrosis factors, interferons, leukotrienes, procalcitonin, alpha$_1$-antitrypsin and other biomarkers specific to the interventions evaluated.

3.4.5. Outcomes of systematic reviews

Outcomes reported in SRs were similar to those reported in primary studies. Details are available in table 3.

3.5. Discussion

This methodological study, evaluating 38 SRs and 123 RCTs conducted during the last decade, identified variability in the diagnostic criteria for COPD and COPD exacerbations. Moreover, we found significant heterogeneity in the selection and definition of outcome measures. These limitations might render the findings of RCTs and SRs focusing on the management of COPD exacerbations incomparable and hinder the production of evidence-based syntheses and recommendations.

We included both RCTs and SRs of RCTs as the latter are based on methodology independently developed by the systematic reviewers, who select pragmatic inclusion criteria, and primary and secondary outcome measures that are pertinent to patients and clinicians and not necessarily the same as the primary studies they evaluate.

Only half of the identified trials and less than 20% of the SRs were based on a prospectively registered protocol. Prospective publication of an RCT or SR protocol could limit the phenomenon of selective reporting of trial results, as well as the impact of publication bias on SRs and guidelines. For this reason, International Committee of Medical Journal Editors (ICMJE) introduced a requirement for a prospective protocol for all clinical trials published in

participating journals, already from 2004[129]. Since then, the proportion of RCTs which were based on a prospectively registered protocol has been consistently increasing. Unfortunately, a similar requirement for the publication of SRs is still lacking, but the Cochrane Collaboration has been advocating for it.

3.5.1. Diagnostic criteria

For the diagnosis of COPD, more stringent diagnostic criteria, requiring at least a previous clinical diagnosis of COPD, confirmed by post-bronchodilator spirometry during clinically stable disease may be more appropriate for efficacy trials, that require a more homogenous study sample. Effectiveness trials, which must reflect real-life, could adopt more pragmatic criteria, such as a previous clinical diagnosis, a history of chronic bronchitis or the presence of radiographic signs of emphysema, in a patient exposed to risk factors, such as cigarette smoking. The authors believe all participants of such trials should complete spirometry subsequently during clinically stable state. In addition, planned sensitivity analyses should include an analysis consisting solely of participants with prospective spirometric confirmation of COPD diagnosis. While recruitment during clinically stable disease would allow a formal diagnosis of COPD prior to the exacerbation, it is limited by the resulting substantial increase in the costs and follow-up period, as well as by the unavoidable selection of patients with frequent exacerbations.

It has been demonstrated that the selection of different diagnostic criteria for COPD exacerbations can significantly affect trial outcomes[6]. Thus, there is an urgent need for standardized diagnostic criteria, that should be used and clearly reported in such trials.

For the diagnosis of exacerbations, the GOLD criteria have poor specificity and for this reason many trials adopted the Anthonisen criteria, which are more specific[127]. However, these were developed to identify infective exacerbations[127] and lack sensitivity to non-infective exacerbations, which are not characterized by increased sputum volume or purulence. The previously described modified Anthonisen criteria, which also include cough, wheeze, nasal discharge, sore throat and pyrexia, were developed to address this concern[128].

The list of COPD exacerbation mimics is sizable and should be actively sought in COPD exacerbation trials. Thorough clinical history and examination should be complemented by a chest radiograph, although this may not be possible in community recruitment. The role of cardiopulmonary ultrasound should also be explored. As described, symptom duration

emerges as an important discriminatory parameter, since short periods of symptoms may represent a day-to-day variability in the symptoms of stable COPD[2]. However, this is not always practical (e.g., when trialing new ways of early reduction of inflammation). Similarly, the probability of having an exacerbation mimic is increased in patients who have been symptomatic for a long period before presentation (>10-14 days).

A critical issue that was only indirectly addressed by a small number of trials is the heterogeneity in the aetiology, underlying mechanisms, outcomes, and response to treatment of exacerbations. Distinct acute disease entities that affect patients with COPD, such as bacterial infections, viral infections or events triggered by enhanced eosinophilic inflammation[7,31], are currently grouped under a single umbrella term. However, it is not clear if this is appropriate, especially for the purposes of interventional clinical studies. It is anticipated that exacerbations respond differently to treatments, according to their aetiology. For example, only exacerbations triggered by bacteria would respond to antibiotics[7].

3.5.2. Outcomes

A significant methodological limitation of the included studies was the lack of a clear separation between primary (powered) and secondary outcomes. Specifically, 32% of the included trials and 57% of the SRs did not clearly distinguish primary and secondary outcomes, complicating the interpretation of their results.

RCTs and SRs of COPD exacerbations management evaluate a variety of outcomes, including several patient-important outcomes. Frequently reported outcomes include mortality, clinical success or failure, adverse effects, improvement in health status, symptoms and quality of life, spirometry, duration of exacerbation and re-exacerbation. Advantages and disadvantages of these outcomes are summarized in table 4. Only mortality and adverse effects were assessed and reported in a standardized manner that allows comparability.

Outcome	Advantages	Disadvantages
Mortality	Widely accepted; consistently defined, universally available in trials, observational studies, and registries.	Insensitive to small or medium treatment effects, those improving symptoms or accelerating recovery.
Clinical treatment success or failure	Frequently evaluated and reported in exacerbations trials. A crude measure of treatment effect.	Significant variability in the definition that limits comparability.
Improvement in health status or symptoms	Easy to complete questionnaires, frequently self-administered. Some are designed to evaluate multiple features of an exacerbation.	Significant variability in the utilized measures, which are of untested and doubtful validity. Often have complex results that are challenging to interpret.
Length of hospitalization	Easy to define and widely accepted outcome. Universally available in trials, observational studies, and registries.	Cannot be used for moderate (non-hospitalised) exacerbations. Also, its accuracy is limited by (a) the availability and extent of community COPD care, (b) non-medical delays in discharge as well as social care, (c) the lack of consistent criteria to guide timing of hospital discharge.
Time-to-treatment success	May be more sensitive to small or medium treatment effects; especially, acceleration of recovery.	Infrequently reported. May be limited by the subjectivity of patient-reported outcomes.
Microbiological response	Easily and consistently defined.	Lack of sensitivity and specificity of sputum cultures in COPD exacerbations.
Spirometry	Consistently defined and universally available test.	A substantial proportion of patients are unable to perform acceptable spirometry, during exacerbation. Lack of repeatability during an exacerbation.

Table 4. Advantages and disadvantages of the main outcome measures.

Clinical success or failure represents one of the most important outcomes of a COPD exacerbation. Unfortunately, there is significant variability in the definitions of this outcome across different trials. The most frequently reported is the simplest of the definitions used. This classifies complete resolution of all signs and symptoms as cure, incomplete resolution of signs and symptoms with resolution of fever as improvement and the persistence or deterioration of symptoms as treatment failure. The selection of timepoints to evaluate this outcome (and other exacerbation outcomes) is of utmost importance, given the dynamic nature of exacerbations. Previous studies estimated the length of symptoms duration of COPD exacerbation and found median durations of 11-13 days from symptoms onset[130] or 7-10 days after seeking medical advice[7,125]. While logically an exacerbation starts with symptoms onset, identification of that timepoint is often impractical and it is simpler to define as onset the day when patient seeks medical advice. This timepoint has the additional advantage that it usually coincides with the onset of the intervention. Therefore, evaluation of the treatment failure rate between 1-2 weeks after presentation could provide meaningful results.

Many studies evaluated improvement of health status, quality of life or symptoms over time. The numerous distinct measures of these outcomes and use of diverse timepoints significantly limit comparability. Time from presentation to treatment success (defined as the reversion of symptoms back to the patient's baseline level, prior to the exacerbation) has been assessed by a surprisingly limited number of studies, but it is a simple to capture and comparable outcome. It would also be very sensitive, as it could reveal small effects that could be missed by more crude measures such as treatment success or failure rate. While the three identified trials used the Anthonisen criteria to confirm symptom resolution, other, non-interventional, studies have used other symptom scores, such as EXACT[131] or the London COPD cohort diary card scores[132], which are more comprehensive.

Time to treatment success is a more accurate outcome than the length of hospitalization, which can be affected by comorbidities, social circumstances, the clinician's perception of patients' symptoms or even the hospital's structure, availability of hospital beds and delays in administrative processes[114-116]. It is also not limited to hospitalized exacerbations, in contrast to the length of hospitalization.

Some treatments of COPD exacerbations do not only aim to treat the acute episode, but also to delay further events. Time-to-next exacerbation or frequency of exacerbations during follow-up represent simple measures of this outcome that have been consistently evaluated.

3.5.1. Strengths and limitations

Our systematic review has several strengths. It is the first study evaluating the methodology and outcome measures of RCTs and SRs comparing interventions aimed at treating COPD exacerbations. Our findings are based on all randomised controlled trials (n=123) and systematic reviews (n=38) published during the last decade. All stages of our systematic review, which was based on a prospectively registered protocol, were conducted by two authors independently and the strong reproducibility of the investigators' judgements strengthen the validity of our findings.

A limitation of our review is that we only searched Medline and PubMed for published RCTs and SRs; we did not screen other publication databases or registries. However, we included a very large number of high-quality studies, and we are confident that our findings are complete and representative of the available work. Our review is also limited by inherent limitations of the included studies. Most importantly, study protocols were not prospectively registered or available online for half of the included trials and most SRs. Therefore, we extracted our data from the published manuscripts, and we cannot exclude the possibility of selective outcome reporting by some studies. Finally, we do not report intervention specific, infrequently reported outcomes, such as muscle strength (outcome of some physiotherapy related interventions) or adherence to the intervention, as they were not considered relevant to the aims of this report.

3.5.2. Conclusions

In conclusion, our study revealed significant methodological limitations and heterogeneity in the diagnostic criteria of COPD and exacerbations, as well as in the selection and definition of outcomes in trials on COPD exacerbations, that hinder repeatability and comparability of their findings. This could be remedied by the development of a core outcomes set for trials on exacerbations' management and by the development of consensus in the definition of COPD and exacerbations in the context of such RCTs.

As stated in our introduction, COPD exacerbations are frequent and burdensome events. Yet, their treatment has seen little changes over many years and the intervention research does

not in any way match the size of the problem. Other medical emergencies have seen vast progress[98,133] and the respiratory community needs to address how to catch up. Defining a Core Outcome Set is a first step. Subsequently, collaborative efforts are needed and societies such as the ERS ought to take a leading role here.

4. Core Outcome Set for the management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease. The COS-AECOPD ERS Task Force study protocol.

Status of this work: *Published. Some data from the online appendix of the main COS-AECOPD publication (Chapter 5), are also included in this chapter.*

- Mathioudakis AG, Abroug F, Agusti A, Bakke P, Bartziokas K, Beghe B, Bikov A, Bradbury T, Brusselle G, Cadus C, Coleman C, Contoli M, Corlateanu A, Corlateanu O, Criner G, Csoma B, Emelyanov A, Faner R, Fernandez-Romero G, Hammouda Z, Horvath P, Huerta Garcia A, Jacobs M, Jenkins C, Joos G, Kharevich O, Kostikas K, Lapteva E, Lazar Z, Leuppi JD, Liddle C, Lopez-Giraldo A, McDonald VM, Nielsen R, Papi A, Saraiva I, Sergeeva G, Sioutkou A, Sivapalan P, Stovold E, Wang H, Wen F, Yorke J, Williamson PR, Vestbo J, Jensen J-U. *Core Outcome Set for the management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease. The COS-AECOPD ERS Task Force study protocol.* **ERJ Open Res 2020**;6(3):00193-2020.

Author contribution: Study conception: AGM, JV, J-UJ. Methodology: AGM, with input from JY, PW, JV, and J-UJ. Supervision: JV. Manuscript preparation: AGM. Revision and approval: All authors.

4.1. Abstract

Introduction: Randomised controlled trials (RCTs) on the management of chronic obstructive pulmonary disease (COPD) exacerbations evaluate heterogeneous outcomes, often omitting those that are clinically important and patient relevant. This limits their usability and comparability. A core outcome set (COS) is a consensus-based minimum set of clinically important outcomes that should be evaluated in all RCTs in specific areas of health care. We present the study protocol of the COS-AECOPD ERS Task Force, that developed a COS for COPD exacerbations management, to remedy these limitations.

Methods: For the development of this COS, we followed standard methodology recommended by the COMET initiative. A comprehensive list of outcomes was assembled through a methodological systematic review of the outcomes reported in relevant RCTs. Qualitative research with patients with COPD was also conducted, aiming to identify additional outcomes that may be important to patients, but are not currently addressed in clinical research studies. Prioritization of the core outcomes was facilitated through an extensive, multi-stakeholder Delphi survey with a global reach. Selection was finalised in an international, multi-stakeholder meeting. For every core outcome, we recommended a specific measurement instrument and standardized timepoints for evaluation. Selection of instruments was based on evidence-informed consensus.

Conclusion: We aspire that our work will improve the quality, usability, and comparability of future RCTs on the management of COPD exacerbations and, ultimately, the care of patients with COPD. Multi-stakeholder engagement and societal support by the ERS will raise awareness and promote implementation of the COS.

Protocol Registration: COMET database ID: 1325

Take home message: The COS-AECOPD ERS Task Force developed a core outcome set (COS) for COPD exacerbations' management. COS is an agreed minimum set of clinically important outcomes to be evaluated in all RCTs and can improve their usability and comparability.

4.2. Introduction

Chronic obstructive pulmonary disease (COPD), the third leading cause of death globally, has a growing prevalence and currently affects over 174 million people[1,2,134]. Acute exacerbations punctuate the natural history of COPD, determining disease morbidity, mortality, and progression[2,4,12]. Every year, up to 40% of patients diagnosed with COPD have at least one moderate or severe exacerbation, while 9-16% experience more[135,136]. As a result, exacerbations are responsible for a significant proportion of all hospital admissions (one in eight in the UK), while the 90-day mortality rate of an admission for an exacerbation exceeds 15%[3,6,118]. Exacerbations are also associated with a substantial socioeconomic burden[2,6].

While our understanding of the pathogenesis and underlying mechanisms of exacerbations is growing rapidly[12,31,75], their management remains only partly effective and almost unchanged for decades[2,3,6]. Standard treatment still consists of three main components: bronchodilators, antibiotics, and corticosteroids. Therefore, novel treatments are to be expected, and an increasing number of clinical research studies will be conducted in the coming years. These will include randomised controlled trials (RCTs) that can provide conclusive evidence of the safety and effectiveness of an intervention, by minimizing potential biases[137,138]. Clinical trials seek to evaluate the safety, efficacy and/or clinical effectiveness of interventions by comparing their effects on outcomes. Only a limited number of outcomes can be evaluated in each trial. Researchers often select outcomes that are easier to measure, require fewer resources, are more likely to favour one intervention over the other(s), or address specific hypotheses, which may be of limited importance to patients, clinicians, or the regulatory authorities[71]. Consequently, crucial data on potential beneficial or harmful effects of interventions are often missed. This hampers the interpretability and potential value of RCTs, whose main aim is to inform clinical guidelines and practice. Moreover, the use of different instruments to evaluate the same outcome is likely to limit comparability.

Particularly in trials evaluating the management of COPD exacerbations, the definition of outcomes is still vague and heterogeneous, while consistent use of relevant, comparable, patient important outcomes is lacking. In a recent methodological systematic review[112,113], we found significant heterogeneity in the outcomes assessed and reported by trials on the management of COPD exacerbations (table 3). Only 63% of all RCTs conducted during the last decade assessed the proportion of patients whose exacerbations were successfully treated or experience treatment failure, while less than 35% evaluated duration of the exacerbation

as an outcome (either the duration of a hospital admission or symptoms). Finally, there was significant heterogeneity in the definition of outcomes and in the instruments used to evaluate them. This lack of standardization complicates interpreting, comparing, contrasting, and synthesising the results of RCTs. As a result, several recent meta-analyses on the management of COPD exacerbations have reported limited certainty in the available evidence[7,38,58].

We report the study protocol of the COS-AECOPD study, that was conducted to address these limitations. We aimed to develop a Core Outcome Set (COS) and core outcome measurement instruments to be used for RCTs evaluating the management of COPD exacerbations. The aim of a COS was to develop global, multi-stakeholder consensus on a minimum number of outcomes that future, relevant RCTs should measure and report on, while core measurement instruments represent consensus on the way these outcomes will be assessed in future, relevant RCTs. It has been demonstrated that when COS and measurement instruments are implemented, they homogenize the design of RCTs, increase their usability and comparability[139,140]. Additionally, a COS for COPD exacerbations will improve the possibilities for meaningful and statistically sound meta-analyses, helping to inform future clinical practice guidelines.

This project was supported by the European Respiratory Society (ERS Task Force 2019-12) and the European Lung Foundation (ELF). It was also supported by the DECODE-NET (DisEntangling Chronic Obstructive pulmonary Disease Exacerbations clinical trials NETwork), an emerging clinical trials network involving over 30 centres in Africa, Asia, Australia, Europe and America[141]. The DECODE-NET intends to use the resulting COS in planned and future trials.

4.3. Methods

The Core Outcome Measures in Effectiveness Trials (COMET), an initiative aiming to bring together people interested in the development and application of COS, has developed explicit methodology for the development of COS. For the development and reporting of this COS, we followed explicit methodology suggested by the COMET initiative (the COMET handbook), Core Outcome Set - STAndards for Development (COS-STAD), Core Outcome Set (STAndards for Reporting (COS-STAR) and Core Outcome Set - STAndardised Protocol Items (COS-STAP)

documents (table 5)[70,73,142,143], which had already been implemented successfully in several high-quality COS projects[144-146]. For the selection of the core outcome measurement instruments, we used a pragmatic, modified version of the methodology proposed by the COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN)[147].

For the development of a COS, COMET recommends the development of a comprehensive list of relevant outcomes followed by a prioritization process, aimed at selecting the most important (core) outcomes. The long list of outcomes was formed by a methodological systematic review evaluating outcomes measured and reported in relevant RCTs[113]; the methodology and findings are presented in Chapter 3. It is recommended that the list of outcomes should also be informed by qualitative research aiming to elicit factors that are considered relevant and important to patients and their caregivers, that may not be evaluated in clinical research studies. Prioritization of the core outcomes is facilitated by a Delphi survey involving multiple stakeholders, with a global reach, and at least two consensus meetings with similar characteristics.

Domain	Standard	COS-AECOPD
Scope	Setting	Clinical research, focusing on RCTs
	Condition	Treatment of acute exacerbations of COPD
	Population	Adults with COPD exacerbations of any severity
	Interventions	Any intervention
Stakeholder involvement	Users	Clinical researchers, trialists, guideline developers, policy makers, regulators, research funders, and the pharmaceutical industry (with global representation)
	Healthcare professionals	Doctors, nurses, physiotherapists with expertise in COPD (Global representation)
	Patients	Patients with COPD and their carers (with global representation)
Consensus process	Initial list of outcomes to be informed by patients' and health professionals' views	Patients' and healthcare professionals' views will be identified through methodological systematic reviews and an extensive Delphi study. Patients' views will also be captured through qualitative studies.

	A priori scoring process and consensus definition	See Methods: Delphi survey
	A priori criteria for including, dropping, or adding outcomes.	See Methods: Delphi survey
	Avoid ambiguity of language used in the list of outcomes	The phrasing of the outcomes will be reviewed by the COS panel and the patients participating in the COS focus groups.

Table 5. Compliance of the COS-AECOPD with the COS-STAD standards for COS development.

4.3.1. Study oversight

This study was conducted by the COS-AECOPD ERS Task Force. This Task Force was co-chaired by Alexander G. Mathioudakis and Jens-Ulrik Jensen. A steering committee was formed consisting of Alexander G. Mathioudakis, Jens-Ulrik Jensen, Jørgen Vestbo (clinical researchers with expertise in trials focusing on COPD exacerbations), Carol Liddle and Isabel Saraiva (patient representatives) and Paula Williamson (chair of the COMET initiative). The steering committee was responsible for the management and co-ordination of the study. The steering committee met regularly, every 3 months (face-to-face or via teleconference), to review the study progress, ensure the study complies with good clinical practice principles, relevant regulations and adheres to the study protocol. Feedback from the ERS Task Force panel (consisting of clinical researchers with expertise in the management of COPD exacerbations, methodologists, and patient representatives; the authors of the main COS-AECOPD report) was sought regularly via email. The recommendations about the core outcomes and their measurement instruments were finalized in two or more face-to-face or virtual consensus meetings that were attended by panel members and additional patient representatives.

4.3.2. Development of the Core Outcome Set

4.3.2.1. Identification of the COPD exacerbations outcomes

For the development of this core outcome set, in line with recommendations by the COMET initiative, we first developed a comprehensive list of all outcomes related to COPD exacerbations. This list was informed by (i) a methodological systematic review to capture the outcomes evaluated in randomised controlled trials (RCTs) and systematic reviews on the management of COPD exacerbations, (ii) a focused systematic review of qualitative studies

exploring outcomes considered important by patients and their caregivers, and (iii) qualitative research consisting of a focus group and individual interviews with patients with COPD from several countries globally.

4.3.2.2. Systematic review of outcomes evaluated in RCTs and SRs on COPD exacerbations management

This methodological systematic review has been reported in Chapter 3[113,148]. In brief, we searched Medline/ PubMed for RCTs and systematic reviews of RCTs evaluating pharmacological and non-pharmacological interventions for the management of COPD exacerbations, published between 2006-2018. Two authors screened the titles and abstracts of all studies yielded by the search and the full text of all potentially eligible studies based on the initial screening. Main characteristics of the included studies and details about the outcomes evaluated and measurement instruments used were extracted in a structured excel form by one author and cross-checked by a second author. In each step of this process, disagreement was resolved by consensus among the authors. The methodology and findings of this methodological systematic review are presented in Chapter 3.

4.3.2.3. Qualitative research

We conducted a focus group discussion, followed by semi-structured interviews, aiming to identify outcomes that patients with COPD consider important. We involved geographically spread participants with different disease severity, age, cultural and socioeconomic backgrounds. More specifically, participants included male and female adults suffering from COPD, who had a history of at least one hospitalized exacerbation or frequent moderate exacerbations (treated in the community), or an exacerbation with concomitant hypercapnic respiratory failure requiring non-invasive ventilation, during the preceding year. Some participants were approached while recovering from an exacerbation, and others during stable disease state. Members of our team recruited and interviewed patients in several countries with different socioeconomic characteristics, across the globe (we plan to recruit patients from Africa, Americas, Asia, Australia, and Europe). Each participant was only able to attend either one interview or the focus group meeting.

Preselected open-ended questions were used to elicit participants' expectations and concerns regarding COPD exacerbations and their views on the outcomes of exacerbations. These questions were developed by academic and lay members (patients diagnosed with COPD) of our research team, with input from a qualitative researcher (JY), the COMET

initiative chair (PW) and the COMET qualitative research team. They are summarized in table 6. At the end of the interview, some of the participants were also invited to contribute to the development of plain language descriptions of the identified outcomes. Think-aloud techniques were used to evaluate how they interpret the outcomes[149]. Qualitative studies were conducted in the language spoken in each participating country. All investigators who contributed to the interviews received relevant material and/or a short introductory training presentation, to strengthen relevant skills and ensure consistency across the different study sites.

Preselected open-ended questions
Ask about the experience of having a COPD exacerbation. "How has your experience of your last exacerbation/flare-up been?" "Can you tell me about your experience of having a flare-up of your COPD?" "How did your last exacerbation affect you?"
Ask about the impact of exacerbations on patients' health and well-being: "What have been the challenges from COPD exacerbations/flare-ups to your health and wellbeing?" Prompt specifically about physical/ mental/ social wellbeing. "When you have a flare-up of your COPD, how does this impact your life? "How is your life different while your COPD is stable compared to when you have a flare-up?"
Ask about the treatments that are offered for COPD exacerbations. "During your previous exacerbations, when did you decide that you needed treatment?" "What treatments were you offered / did you use for your recent exacerbations?" "When was the last time you had a discussion with a doctor or nurse about the treatments you receive for exacerbations? What factors did you consider when deciding to try or not try a treatment?"
Ask about their expectations from treatments of COPD exacerbations. Ask specifically about pharmacotherapy and non-invasive ventilation (for patients who have used it). "To what extent the effects of treatments you had for your exacerbations matched your expectations?" "What specifically have you hoped for from the treatments for your COPD exacerbations?" Prompt specifically about physical/ mental/ social wellbeing.
Ask about the effects that COPD exacerbations treatments have: "How medicines for your flare-ups make you feel?". Also ask for NIV.

"What do you consider to be the most beneficial effects of treatments?

"What are the most concerning effects (called side effects) of medications for your exacerbations, for you?"

Prompt for specific areas such as physical/ mental/ social impact.

Ask about concerns for future COPD exacerbations:

"What concerns do you have about your future COPD exacerbations/flare-ups?"

"What are the most concerning effects of exacerbations in your life?"

"If a new treatment became available, what specific effects would you like it to have on you?"

Prompt for details on physical/ mental/ social impact. "Cure" is not an acceptable response here.

After making sure the participants understand what an outcome is, ask explicitly which outcomes they think are important to be evaluated.

Plain English Language definition of outcomes:

To help patients, doctors and other health professionals make decisions about treatments, we need evidence about what works best. Treatments are developed and tested by researchers to make sure they work and are safe. To do this, researchers need to look at the effects those treatments have on patients. Researchers do this by measuring an 'outcome'. For example, in a study of how well a new asthma treatment works, 'outcomes' might include:

Night-time wheeze

Quality of life measures

(Can describe instead outcomes of COPD exacerbations that the patients have already mentioned)

"Which outcomes do you think are important to be evaluated?" Prompt for details on outcomes related to physical/ mental/ social wellbeing.

Ask why they think those outcomes are more important (and document participants' quotes):

"You 've said X outcome is important, what makes you think that?"

Avoid "why" questions as those can make people feel put on the spot.

Ask whether they think their perspective on what is important has changed over time.

"Do you think anything has altered your perspective regarding your exacerbations and their outcomes?"

"Were there any outcomes that you considered important previously that were not mentioned during this interview?"

Plain language version of the outcomes: Discuss each of the outcomes described in the following table. Ask patients to describe them in their own language. Do they understand the outcomes correctly? At the end, ask again the patients if they think any other important outcomes are missing from our list. You should clearly highlight outcomes that were volunteered by patients earlier, compared to the outcomes that were discussed by the interviewer later.
Ask about the impact of exacerbations on patients' health and well-being: "What have been the challenges from COPD exacerbations/flare-ups to your health and wellbeing?" Prompt specifically about physical/ mental/ social wellbeing. "When you have a flare-up of your COPD, how does this impact your life? "How is your life different while your COPD is stable compared to when you have a flare-up?"

Table 6. Preselected questions that were used to facilitate the focus group and semi-structured interviews.

The focus group and all interviews were audio recorded and anonymized. All outcomes described directly or indirectly by participants were extracted verbatim, grouped, and translated in the English language. The frequency that every outcome was volunteered by participants is presented as a relative measure of importance of the outcome. In addition, we undertook thematic analysis with a framework approach to data organization[150], aiming to identify participants' hopes and concerns regarding COPD exacerbations and their treatment. We explored differences in the responses of participants from different geographic and socio-economic backgrounds.

4.3.2.4. Delphi survey

Prioritization of the most critical outcomes for inclusion in the core outcome set was facilitated by an online, two-stage, global, multistakeholder, modified Delphi survey and two consensus meetings involving patient representatives, clinicians, clinical researchers and other relevant stakeholders with relevant expertise and global representation.

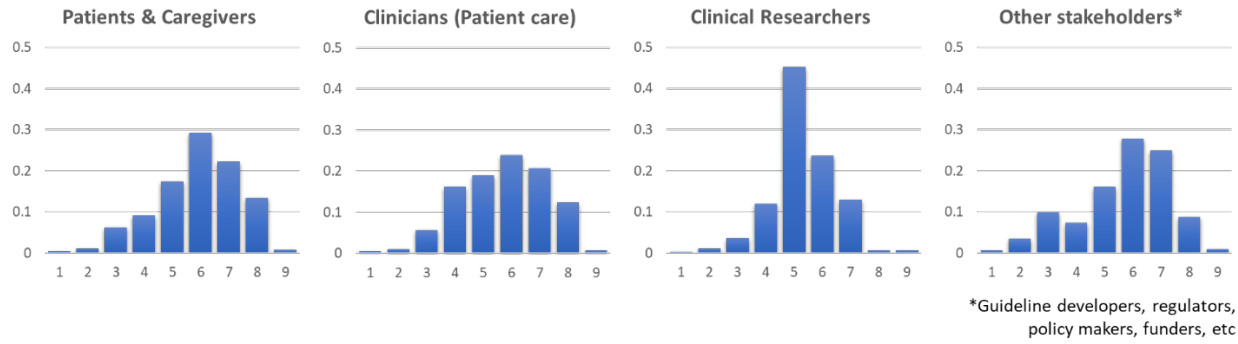
A Delphi survey is a widely used method for developing consensus. The modified Delphi survey, along with detailed instructions and description of the research project were prepared in plain language with input from the European Lung Foundation (ELF) and lay members of the ELF's COPD Patient Advisory Group. It was translated in 10 languages (Chinese simplified, Danish, English, German, Greek, Hungarian, Italian, Portuguese, Russian, Spanish).

Translations were validated using two-way translations by native speakers. The survey was conducted using the DelphiManager, a secure, online software developed by the COMET initiative[151].

Four stakeholder groups were invited to participate in the survey: (a) Patients diagnosed with COPD, with lived experience of COPD exacerbations, caregivers of such patients, or representatives of such patients (e.g. patient organizations); (b) Health professionals caring for patients (doctors, nurses, physiotherapists, etc); (c) Clinician researchers (health professionals who care for patients but are also involved in designing research studies); (d) Other stakeholders, including regulators, policymakers, funders, guideline developers, or those working in health technology assessment organizations.

We used a modified Delphi approach proposed by the COMET initiative, involving two Delphi rounds to minimize attrition[152]. In the first round of the Delphi survey, after completing their baseline characteristics and declaring potential conflicts of interest, participants were presented with a list of all unique outcomes identified through the previously described systematic reviews and qualitative research studies. Participants were asked to rate the importance of each outcome for clinical decision making on a scale from 1 to 9, following the Grading of Recommendations, Assessment and Evaluation (GRADE) guidance[23,153]. Scores between 1-3, 4-6 and 7-9 will signified outcomes of limited importance, important but not critical, and critical outcomes, respectively. Finally, respondents were encouraged to suggest additional outcomes they may consider important in addition to those included in the survey.

Only participants who completed the first round of the survey by providing ratings for at least 80% of the outcomes were included in the analyses and were invited to participate in the second round. In the second survey round, participants were presented with graphical displays of the distribution of the scores that had been submitted from each stakeholder group during the first round of the survey (figure 9). The outcomes list was supplemented by additional, new outcomes identified during the first survey round. Respondents were asked to re-consider their ratings taking into account how the different stakeholder groups rated each of the outcomes, clarifying that they should not feel under any pressure to change their ratings if they do not want to.



Outcome	Score									
	Limited importance			Important – Not critical			Critical			
	1	2	3	4	5	6	7	8	9	Unable to score
Outcome #1	O	O	O	O	O	O	O	O	O	O

Figure 9. *Delphi round 2. Respondents were provided with the score distributions from the first Delphi round, stratified by stakeholder category. Their previous scoring was also highlighted (here: the respondent's score for this outcome was 8). Respondents were asked to reconsider their scoring, based on the available data. They were under no pressure to change their scores.*

After the second Delphi round, consensus was assessed using data from respondents who completed the second round by providing ratings for at least 80% of the outcomes. Outcomes that were rated critical (between 7-9) by at least 70% in all three stakeholder groups, and of limited importance (between 1-3) by less than 15% of all participants, in all stakeholder groups, were included in the core outcome set. In parallel, we were planning on excluding outcomes that were rated between 7-9 (critical) by ≤50% of all participants in each stakeholder group, while the remaining outcomes were selected for further evaluation during the consensus meeting.

We have conducted extensive preparatory work to achieve a global reach of the survey. The survey was disseminated broadly, to health professionals, members of the ERS with a documented interest in airway diseases, as well as members of other national and international scientific societies. It was also disseminated to patients with COPD and their caregivers through the ELF's network of local, national, and international organisations representing patients across the world. Moreover, we were planning on sharing the survey with clinical researchers, policy makers, guideline developers, regulators, research funders

and industry representatives from all continents who have published on COPD exacerbations during the last decade and their emails were identified through extensive literature searches (>5,000 unique emails; we finally decided not to use these emails due to privacy concerns). Finally, the survey was publicized through social media (Twitter and Facebook); it was shared by the panel members and the previously mentioned professional and patient organizations. For all these stakeholders, we have developed invitations that were compliant with the General Data Protection Regulation (GDPR) and e-Privacy regulations.

4.3.2.5. Consensus meeting

At least two face-to-face or virtual consensus meetings were organized as part of this project. The Core Outcome Set was finalized during the first meeting, while the second was devoted to the selection of the optimal measurement instrument for each of the core outcomes. To empower patients, who had an active role in both meetings, we offered training about the research project rationale, aims and methods and their role during the consensus meetings. The active involvement of patient representatives necessitated that the two meetings were moderated by experienced and impartial facilitators. These facilitators ensured relevant data were presented objectively and in a plain language, and that all participants had the opportunity to share their views and cast a well-informed and independent vote. Geographic and socio-economic diversity was considered in the selection of participants.

During the first consensus meeting, the results of the Delphi survey were presented and the inclusion or exclusion of outcomes that had reached the respective thresholds in the Delphi survey was confirmed. The remaining outcomes were discussed in detail. Thorough discussion where both health professionals/ researchers and patients were invited to share their views about the level of importance of each of these outcomes was followed by a poll. Each participant was asked to re-rate the outcomes considering their previous ratings, the Delphi survey results and the preceding discussion. Participants were classified in two groups (a) health professionals, researchers, and policy makers and (b) patients diagnosed with COPD and patient representatives. Only outcomes that were rated as critical by at least 70% of the participants in both groups were added to the core outcome set.

4.3.3. Selection of core outcome measurement instruments

The aim of this component of our study was to select and recommend a single, optimal instrument to measure every core outcome, to ensure consistency and comparability across

clinical trials. This was achieved through evidence-informed consensus, during the second consensus meeting of our task force.

Outcome measurement instruments refer to the specific methodology used to evaluate the impact of an intervention on an outcome. More specifically, while outcomes answer the question "What to measure?", instruments refer to the question "How to measure it?". For example, Saint George's Respiratory Questionnaire or the Clinical COPD Questionnaire (CCQ) are both instruments that assess the outcome health status in COPD[113]. Often, different instruments are used for evaluating the same outcome, limiting the comparability of the RCT results. For this reason, we recommend a specific instrument for each of the selected core outcomes.

The COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN) recommends a thorough methodology for in-depth evaluation and selection of outcome instruments[147]. However, such extensive methodological studies were beyond the scope and resources of the COS-AECOPD study. For this reason, we followed a more pragmatic approach. Our aim during this process was to select methodologically sound outcome measurement instruments, while promoting consistency. For this reason, we first identified instruments that are already in use through our methodological systematic review[113]. For outcomes that are often evaluated by the same instrument (in >40% of trials evaluating that outcome), this instrument was considered established and was preselected for prioritization, unless important methodological issues were raised by any of the panel members during the second consensus meeting. In case members of the panel raised such concerns, we were planning on further evaluating instruments used to measure the specific outcome by means of a focused literature review (see next paragraph), with the aim to develop consensus in a follow-up meeting.

4.3.3.1. Focused literature reviews

For other outcomes, not consistently measured using the same instrument, we conducted focused literature searches of Medline/ PubMed and the COSMIN database. We used a standardized filter for studies evaluating COPD exacerbations (see chapter 3), terms describing the core outcome of interest and terms describing the term "outcome" or "endpoint". At first, we searched for systematic reviews evaluating the quality and measurement properties of different instruments. In the absence of high-quality methodological systematic reviews, we searched for primary methodological studies formally

assessing measurement properties. Alternatively, we looked for previous position or consensus documents or studies of any design that could inform the panel's decision. These literature searches were launched after the first round of the Delphi survey and initially focused on the outcomes which were clearly considered critical by the respondents already from that stage.

4.3.3.2. Second consensus meeting.

The objective of the second consensus meeting was to select and recommend a single measurement instrument for every core outcome, to ensure consistency and comparability across clinical trials. Each of the outcomes was discussed during the consensus meeting. The panel reviewed available evidence, which had been circulated in advance via email (after the first consensus meeting, when the selection of the core outcomes was finalized) and developed consensus on a simple instrument for each outcome after considering (a) the frequency with which each instrument is used in clinical trials; (b) the time and resources required to use each instrument; and (c) available data on their measurement properties, as described by COSMIN recommendations (reliability, responsiveness, interpretability and variability)[147]. After discussion, a single instrument was selected for every core outcome and participants were asked to vote. Due to the more technical nature of this assignment, only two patients and a representative of the ELF with previous experience in COPD research joined the consensus meeting. Therefore, the voting was not be stratified by stakeholder group. Voting options included: (a) a strong recommendation, (b) an interim recommendation along with research agenda, (c) a research agenda without a recommendation, or (d) a request to develop an alternative recommendation or for additional data to make an informed decision. A strong recommendation for a specific instrument was issued if at least 70% of the participants voted for that option. If less than 70% considered a strong recommendation appropriate but at least 70% voted for the first or second options, then an interim recommendation was issued, along with a recommendation for further research for this core outcome measurement instrument. The prespecified threshold for making a research recommendation without an interim instrument was also set at 70%; in any other case we were planning on re-voting in a follow-up consensus meeting, after further data acquisition and discussion.

Timing of outcomes evaluation is also crucial as COPD exacerbations are acute, dynamic events. Minimum timepoints for follow-up evaluation were provisionally selected based on

consensus among the panel members and in consultation with European Lung Foundation's COPD Patient Advisory Group. To reach an informed consensus, the task force members reviewed the timings of outcome evaluation in previous trials and the impact of timing on the results.

Feedback was sought from the participants of all consensus meetings to explore whether they considered that they had been offered the opportunity to share their views and that they were able to cast well-informed votes.

Potential changes from the prospectively registered protocol were summarized and justified.

4.3.4. Sample size

We did not conduct formal power calculations for this study, as there are no strict recommendations on the number of participants in a qualitative study or Delphi survey. In the first stage (qualitative research), we decided to interview at least seventy patients, and to continue until we were confident that saturation had been achieved and potential socio-economic and geographic differences had been captured.

For the Delphi survey, we developed a thorough strategy for recruiting members of each stakeholder category and we aimed to engage as many participants as possible, to develop global, multi-stakeholder consensus, while also raising awareness about the issue and our COS. We anticipated a study population at the range of hundreds.

4.3.5. Protocol registration

The study protocol of the COS-AECOPD ERS Task Force was registered prospectively with the COMET database (COMET ID: 1325).

4.4. Discussion

Comparability - and occasionally interpretability - of RCTs on COPD exacerbation management is particularly problematic[113]. The COS-AECOPD ERS Task Force aimed to remedy these limitations by developing a COS for the management of COPD exacerbations, that will promote standardization of the outcomes reported in future RCTs and their measurement instruments.

COMET suggests that a qualitative systematic synthesis could occasionally replace patient interviews. Our qualitative systematic review (unpublished data) yielded data from one previous systematic review and three primary studies. Fatigue and psychological well-being emerged as outcomes of importance to patients that are rarely tested in RCTs and systematic reviews and were included in the longlist of outcomes. However, confidence on the findings, evaluated using CERQual methodology[154], was low, because of concerns regarding the adequacy and relevance of the available data. Adequate understanding of patients' needs and priorities is crucial for the development of high quality COS. Characteristically, qualitative studies conducted by the OMERACT (Outcome Measures in Rheumatology) almost two decades ago identified fatigue as a crucial outcome of rheumatoid arthritis[155]. Fatigue, which was previously not evaluated in RCTs, is currently one of the most frequently reported and informative outcomes in that field. For these reasons, we decided to conduct additional, original qualitative research to inform the COS-AECOPD.

For outcomes prioritization, we decided to use the modified Delphi approach proposed by COMET. Instead of asking the respondents to identify potential outcomes, we fed the survey with outcomes identified through intensive methodological and qualitative research and this ensured that the longlist of outcomes was more complete. Respondents were also encouraged to suggest additional relevant outcomes. Moreover, we limited the number of Delphi rounds to two, to limit attrition. While two rounds may not be adequate to reach consensus for many of the outcomes, the results were fed to a multi-stakeholder consensus group meeting for finalisation. This approach has been successfully utilised in previous high-quality COS[144-146].

A potential limitation of this study is our pragmatic approach towards the selection of outcome instruments and the follow-up timing, which did not fully adhere to the COSMIN recommendations. This is very unlikely to have affected the selection of instruments for simple, objective outcomes (such as mortality). It might have affected the selection of measures of composite or patient reported outcomes. However, selection of instruments was informed (i) by focused literature searches of studies evaluating the measurement properties of the instruments, (ii) by current standard research practice, as our aim is to enhance homogeneity across different RCTs, and (iii) by the experience of several principal investigators and methodologists involved in COPD exacerbations trials, who were involved in this task force. Moreover, while researchers are strongly encouraged to use the core

outcomes and associated measurement instruments in all future RCTs, they are also encouraged to assess other outcomes, that may be relevant to their interventions, RCTs or interests but may also include methodological evaluation of alternative instruments.

High resource requirements for the evaluation of certain outcomes included in COS may limit their implementation, especially in pilot or early phase studies. However, most of the outcomes identified through our systematic reviews are simple and inexpensive to measure and can be captured after a relatively short follow-up period[113]. In addition, costs and resource requirements will be considered by the panel when selecting the measurement instruments. Finally, it would not be expected that early phase studies would include the COS necessarily, however it may be important that they include some of the core outcomes, to gather data that would help power the later phase studies.

The outcomes suggested by different regulatory bodies may not be included in the COS-AECOPD. In this case, investigators would be advised to evaluate both the outcomes required by the regulatory authorities and the additional outcomes that will be proposed by this COS, which was informed by a global, multi-stakeholder agreement. It is anticipated that regulatory authorities are likely to start endorsing high-quality COS in the near future. For example, the Food and Drug Administration (FDA) is currently developing three COS in a pilot project (for other diseases)[156].

A major strength of the COS-AECOPD study is the strong design, which is based on a thorough methodological systematic review and extensive qualitative research to develop a longlist of clinically relevant outcomes and an extensive Delphi survey, aiming to develop consensus. Moreover, the global reach and involvement of all relevant stakeholders, following an exhaustive strategy to recruit and engage them, has facilitated the development of international consensus, improved awareness of the methodological issues, and will enhance the COS implementation in future research studies. Societal support by the ERS will also promote awareness and implementation.

The need for high-quality research on COPD exacerbations is prioritized by the ERS. Apart from this Task Force, the Society is also supporting the CICERO (Collaboration In COPD ExaceRbatiOns) ERS Clinical Research Collaboration, aiming to set up a pan-European, prospective observational cohort study of patients hospitalised with COPD exacerbations, to evaluate their clinical and mechanistic characteristics[157]. As part of this project the CICERO

team is developing relevant methodology, including a comprehensive data collection plan for such studies. The two projects have been developed in a collaborative fashion, where pertinent interim data of each project were shared and used to inform the following steps of each project.

Overall, it is our strong belief that the development of a COS for the management of COPD exacerbations will improve the quality, comparability, and usability of future RCTs and will consequently have a positive impact on the management of COPD exacerbations, clinical practice guidelines and the care of patients with COPD.

5. ERS Statement: A core outcome set for clinical trials evaluating the management of chronic obstructive pulmonary disease (COPD) exacerbations.

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5.1. Abstract

Clinical trials evaluating the management of acute exacerbations of COPD assess heterogeneous outcomes, often omitting those that are clinically relevant or more important to patients. We have developed a core outcome set, a consensus-based minimum set of important outcomes that we recommend are evaluated in all future clinical trials on exacerbations management, to improve their quality and comparability.

COPD exacerbations outcomes were identified through methodological systematic reviews and qualitative interviews with 86 patients from 11 countries globally. The most critical outcomes were prioritized for inclusion in the core outcome set through a two-round Delphi survey that was completed by 1,063 participants (256 patients, 488 health professionals and 319 clinical academics) from 88 countries in 5 continents. Two global, multi-stakeholder, virtual consensus meetings were conducted to (i) finalize the core outcome set and (ii) prioritize a single measurement instrument to be used for evaluating each of the prioritized outcomes. Consensus was informed by rigorous methodological systematic reviews. The views of patients with COPD were accounted for in all stages of the project.

Survival, treatment success, breathlessness, quality of life, activities of daily living, need for higher level of care, arterial blood gases, disease progression, future exacerbations and hospital admissions, treatment safety and adherence were all included in the core outcome set. Focused methodological research was recommended to further validate and optimize some of the selected measurement instruments. The panel did not consider the prioritized set of outcomes and associated measurement instruments burdensome for patients and health professionals to use.

Take home message: A core outcome set and outcome measurement instruments for clinical trials evaluating COPD exacerbations management was developed, based on evidence-informed, global, multi-stakeholder consensus.

5.2. Background

Acute exacerbations punctuate the natural history of chronic obstructive pulmonary disease (COPD) and are largely responsible for the adverse disease outcomes[4,12,84]. Every year, approximately a third of those diagnosed with COPD experience at least one moderate or severe exacerbation, while 9-16% experience these events even more frequently[135,136,158,159]. More importantly, every year, one in twenty unselected patients with COPD and one in four of those monitored in secondary care for their COPD experience severe exacerbations[158], which are associated with a ninety-day mortality that approximates 15%[6,160,161].

While novel maintenance treatments have reduced the occurrence of exacerbations[162], their management remains suboptimal and has not changed for decades[6,163,164]. However, over recent years, the complexity and heterogeneity of exacerbations, as well as their underlying mechanisms are increasingly being understood[10-12,31,75]. In addition, the clinical validation of promising biomarkers paves the way for the introduction of precision medicine interventions, that could revolutionize the approaches to managing exacerbations[7,14,25,165]. Therefore, it is anticipated that an increased number of clinical trials will be conducted in the coming years, to evaluate novel treatments, including precision medicine interventions.

However, the design and conduct of clinical trials on managing COPD exacerbations are complicated by methodological and practical challenges[141]. Selection and consistent use of relevant, comparable, well-defined, and patient-important outcomes represent a critical challenge. A recent meta-epidemiological study revealed remarkable heterogeneity in the outcomes evaluated and reported in COPD exacerbation trials, as well as the definition of these outcomes and instruments used to assess them[113,148]. This has led recent relevant systematic reviews and meta-analyses to report limited certainty in the available evidence[7,38,72].

To address this issue, the European Respiratory Society (ERS) formed this task force:

- **To develop a core outcome set for clinical trials evaluating the management of COPD exacerbations.** A core outcome set is an agreed minimum set of critically important outcomes that should be evaluated in all future trials in a specific area of health care, aiming to improve their quality and comparability [70].

- **To prioritize a single instrument for measuring each of the core outcomes.** The core outcome measurement instruments describe how each of the core outcomes should be evaluated in clinical trials [166].

The outputs of this project were based on global, multi-stakeholder consensus.

5.3. Methods

Detailed methodology of the COS-AECOPD (Core outcome set for the management of acute exacerbations of chronic obstructive pulmonary disease) ERS Task Force was prospectively registered with the COMET database (www.comet-initiative.com; ID: 1325) and published (Chapter 4)[167]. Changes from the prospectively registered protocol were summarized and justified.

This study was conducted and reported following the methodology recommended by the COMET initiative (the COMET handbook)[70], the Core Outcome Set STAndards for Development (COS-STAD)[73] and STAndards for Reporting (COS-STAR)[142].

In brief, this project consisted of three components. First, we developed a comprehensive list of all outcomes related to COPD exacerbations. Through a methodological systematic review, we identified outcomes that were evaluated in 123 randomised controlled trials and 38 systematic reviews on the management of COPD exacerbations (Chapter 3)[113,148]. This list was enriched with additional outcomes considered important by patients, that have not been evaluated in trials so far. These were identified through a focused systematic review of qualitative studies [5,168-170], complemented by a focus group and individual interviews with a total of 86 patients from 11 countries globally. After removing duplicate entries, the list included 47 unique outcomes. This list was further enriched by the respondents of the subsequent Delphi survey.

Next, prioritization of the most critical outcomes for inclusion in the core outcome set was facilitated by a Delphi survey and a consensus panel. An online, two-stage, global, multistakeholder Delphi survey was employed, that was developed in plain language and was available in 10 languages, to facilitate global participation[151]. Three stakeholder groups were invited to participate in the survey: (a) Patients diagnosed with COPD, who had experienced exacerbations, and personal caregivers or representatives of such patients (e.g., patient

organisations); (b) Health professionals caring for patients (e.g., doctors, nurses, or physiotherapists); and (c) Clinical researchers (health professionals who care for patients but are also involved in designing research studies). After the second round of the survey, consensus was assessed based on prospectively selected thresholds for inclusion or exclusion, considering responses of the three stakeholder groups separately and using data from respondents who completed both survey rounds. More specifically, outcomes rated critical (between 7-9) by at least 70% of participants in all three stakeholder groups, and of limited importance (between 1-3) by less than 15% of all participants, in all stakeholder groups, were included in the core outcome set. Outcomes that were not prioritized by any of the stakeholder groups (based on the previous criteria), were excluded, while those that were prioritized by some but not all groups were selected for further evaluation during the consensus meeting.

Prioritization was finalized during the first consensus meeting (April 21st, 2021). Outcomes with an inconclusive survey result, that were prioritized for inclusion in the core outcome set by at least one, but not all stakeholder groups were discussed in detail. Participants were classified in two groups (a) health professionals or researchers and (b) patients diagnosed with COPD and their representatives. Thorough discussion where both groups were invited to share their views about the importance of each of these outcomes was followed by polls. Only outcomes that were rated as critical by at least 70% of the participants in both groups were added to the core outcome set.

The final component of this project consisted of the selection of a single, optimal instrument for measuring every core outcome, to ensure consistency and comparability across trials (methodology described in figure 10). Evidence-informed consensus was achieved during a second panel meeting (April 28th, 2021), where a pragmatic methodology was followed for prioritizing measurement instruments. Instruments that are already in use were identified through our methodological systematic review [113]. Since our aim was to promote consistency, for outcomes that are often evaluated by the same instrument, that instrument was considered for prioritization during the consensus meeting, upon evaluating its strengths and methodological limitations. For other outcomes, including all patient reported outcomes, we conducted focused literature searches of Medline/PubMed and the COSMIN database, to identify studies evaluating the quality and measurement properties of the different instruments. The panel reviewed available evidence, which was circulated in advance of the

consensus meeting via email and developed consensus on a simple instrument for each outcome considering (a) the frequency that each instrument is used in clinical trials; (b) the time and resources required to use each instrument; and (c) available data on their measurement properties, as described by COSMIN recommendations [147]. After discussion, a single instrument was selected for every core outcome and participants were asked to vote for (a) a strong recommendation, (b) an interim recommendation along with research agenda, (c) a research agenda without a recommendation, or (d) for an alternative recommendation or the need for additional data to make an informed decision. Due to the more technical nature of this assignment, only two patients with COPD and a representative of the European Lung Foundation (ELF), with previous experience in COPD research, joined the consensus meeting, and therefore, the voting was not stratified by stakeholder group. Prespecified voting thresholds are described in the protocol (chapter 4).

Feedback was sought by all participants of the consensus meetings to explore whether they felt they were offered the opportunity to share their views and that they were able to cast well-informed votes.

5.3.1. Management of the conflicts of interest

Potential conflicts of interest of the panel members and all consensus meeting participants were reported and managed in line with the ERS policies (available here: https://www.ersnet.org/science-and-research/development-programme/). None of the panel members or consensus meeting participants reported any conflicts directly related to this project, but in the event such conflicts had been reported, our plan was to ask members with such conflicts to abstain from the respective polls.

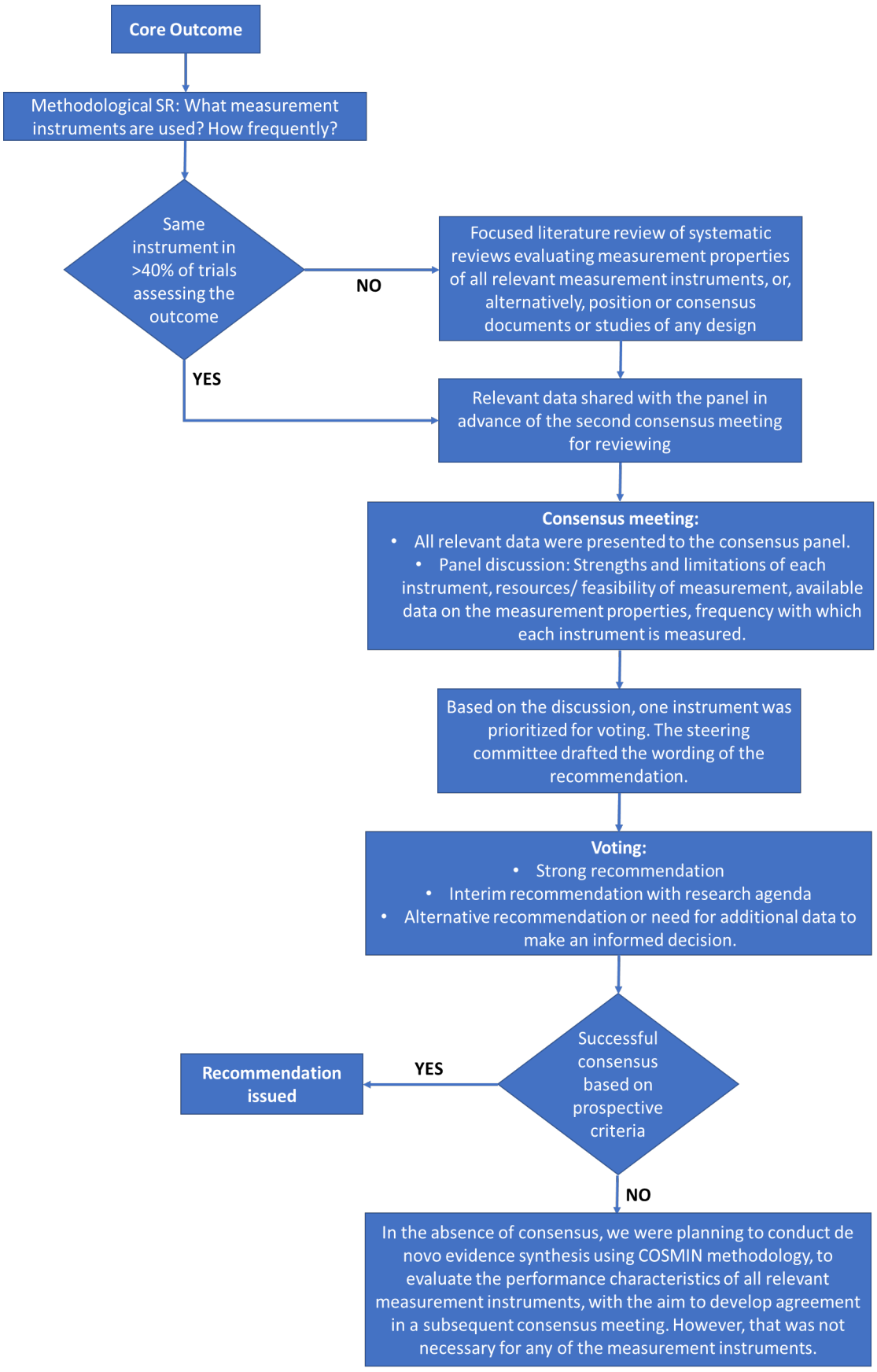

Figure 10. *Flowchart summarizing the methodology used for selecting core outcome measurement instruments.*

5.4. Results

The core outcome set development process is summarized in figure 11.

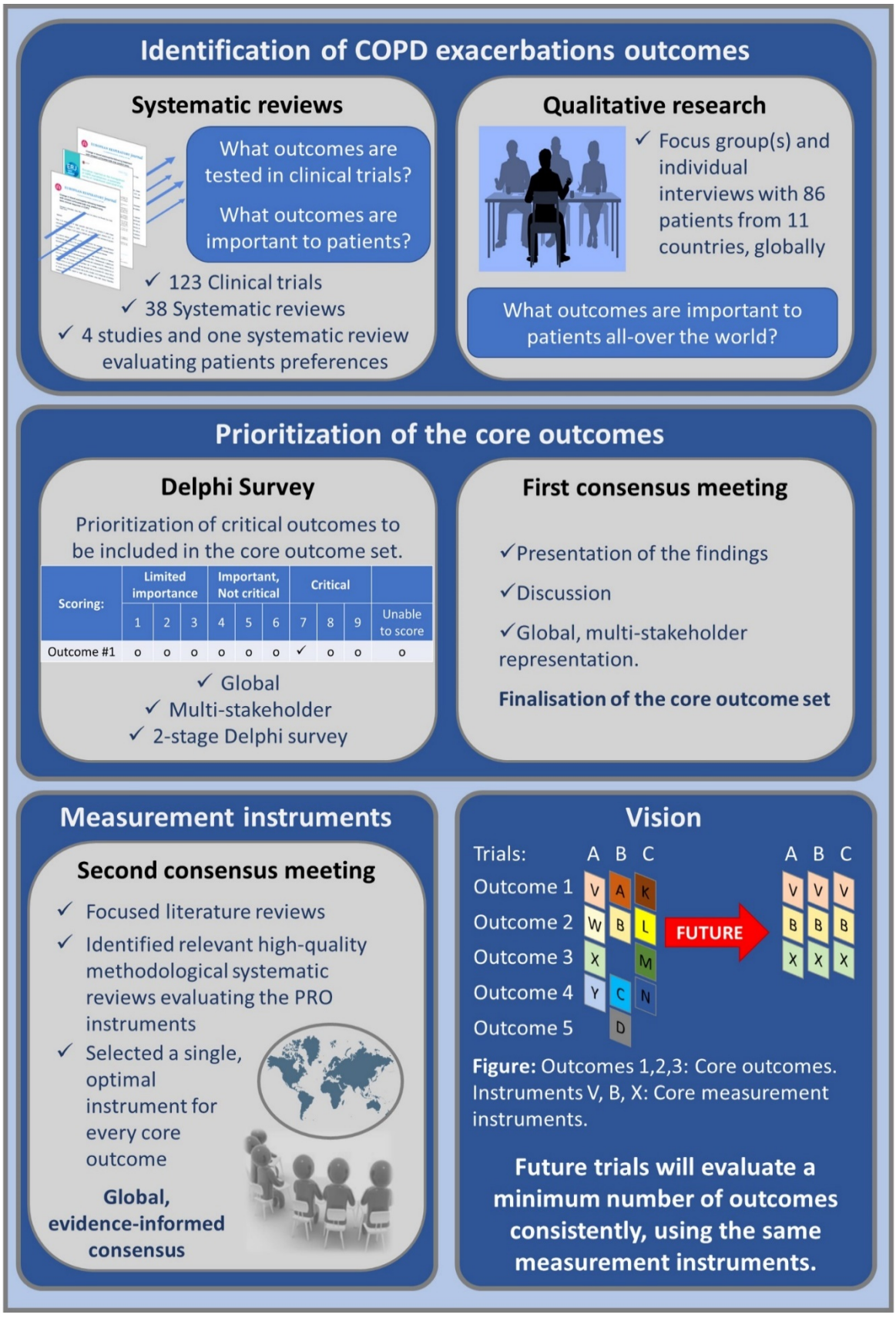

Figure 11. *Study flowchart summarizing the main steps of the COS development process.*

5.4.1. Systematic review of qualitative studies

To enrich the longlist of COPD exacerbation outcomes, we conducted a systematic review aiming to identify qualitative studies evaluating the experiences, views, and preferences of patients with COPD and their caregivers around the management of COPD exacerbations. We searched Medline/ PubMed using a filter for qualitative studies on the outcomes of diseases that was developed by the COMET group[171]. Detailed search strategy and the PRISMA flowchart are presented in appendix 8.3.3. Titles and abstracts and -when required- full texts were screened by two authors independently for eligibility. One author identified all outcomes of COPD exacerbations that were described in the included studies and a second author cross-checked for accuracy. Disagreement was resolved by consensus among the authors.

One systematic review[5] and three primary qualitative research studies[168-170] were selected for inclusion. Overall, this review yielded two additional outcomes that were incorporated in the longlist: (i) Anxiety and (ii) Fatigue.

5.4.2. Qualitative research

To further complement the longlist of outcomes of COPD exacerbations, we conducted qualitative research to identify outcomes that patients deem important that might have not been captured by our systematic reviews. We conducted a focus group (n=8 participants, UK) and individual interviews with a total of 86 purposefully selected patients with COPD from 11 countries globally (Australia, Belarus, China, Denmark, Greece, Hungary, Moldova, Russia, Spain, Tunisia, and the United Kingdom). We involved patients with a history of a recent hospitalised exacerbation, patients with frequent moderate exacerbations (treated in the community) and patients with a history of exacerbations with concomitant type 2 respiratory failure, requiring non-invasive ventilation. We included both male and female patients and sought to involve different age groups, geographic, cultural, and socioeconomic backgrounds. A detailed list of the preselected open-ended questions that were used to elicit patients' views around COPD exacerbations outcomes is available in chapter 4.

Six additional outcomes were identified and added to our longlist of COPD exacerbations outcomes: (i) Appetite, (ii) Sleep quality, (iii) Early morning symptoms, (iv) Night-time symptoms, (v) Disease progression, and (iv) Social engagement / isolation. Additional details on the interviews will be reported separately.

5.4.3. Finalization of the longlist of outcomes

After deduplication, the longlist of outcomes of COPD exacerbations management included 47 unique outcomes. Of these, 39 originated from the first methodological systematic review, two from the systematic review of qualitative research studies and six from the qualitative research that we conducted. This list was further enriched by the respondents of the Delphi survey, as described in the next section.

Following the COMET taxonomy, all identified outcomes were grouped in five areas: Mortality or Survival outcomes, Physiological or Clinical, Life Impact, Resource Use, and Adverse Events or Adverse Effects outcomes[172].

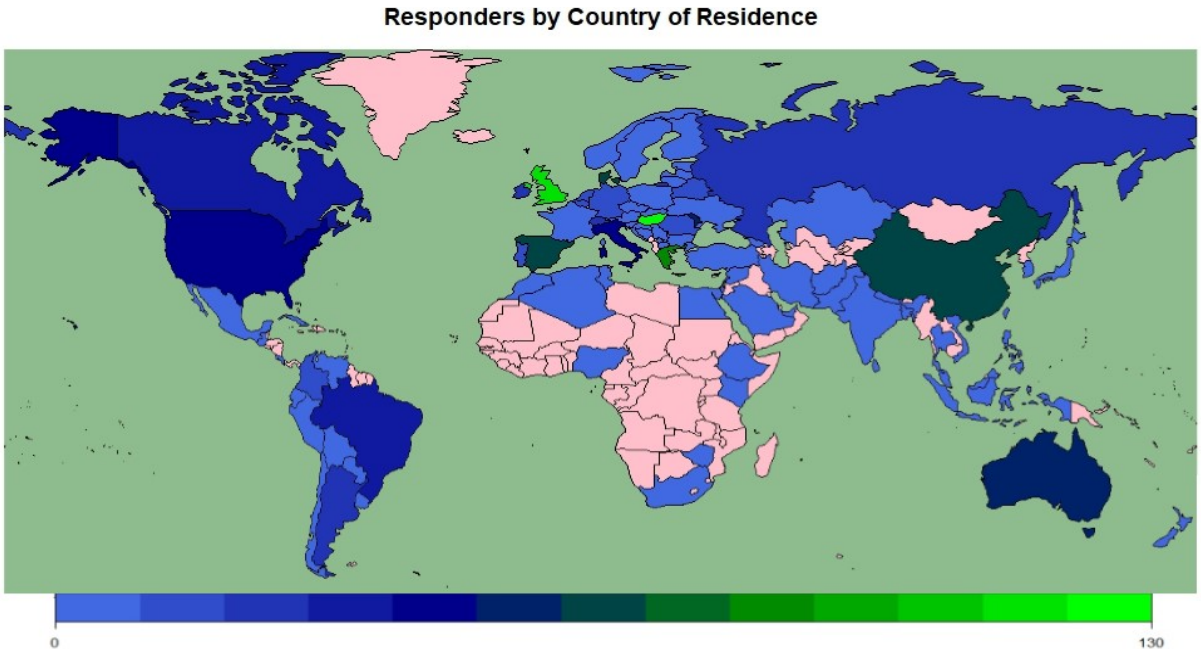

Figure 12. *Geographic distribution of the Delphi survey participants. The colour of each country represents the number of participants (see colour scheme).*

5.4.4. Delphi survey

The first round of the Delphi survey was available online between May 2nd and June 27th, 2020, and the second round between July 21st and October 30th. Of 1,201 individuals who started a registration at the Delphi survey website, 1,063 (88.5%) from 88 countries in Africa, Americas, Asia, Europe, and Oceania (figure 12) completed the first round of the survey and comprised our study population. These included 256 (24.1%) patients or patient representatives, 488 (45.9%) health professionals and 319 (30.0%) researchers. Baseline - characteristics of the participants are described in tables 7-9. Six unique, additional outcomes

were proposed by the respondents during the first round of the Delphi survey and were introduced in the second round (table 10).

Neof	Patients & Representatives	Health Professionals (HP)	Researchers
Study participants	**256** Patients: 229 Caregivers: 22 Representatives: 5	**488** Doctors: 399 Nurses: 53 Physiotherapists: 17 Other HP: 19	**319** Doctors: 230 Nurses: 13 Physiotherapists: 34 Other HP: 7 Others*: 35
Completed 2nd round	197 (77.0%)	398 (81.6%)	291 (91.2%)
Declared potential conflicts of interest	3 (1.2%)	13 (2.7%)	17 (5.3%)
Age (years):			
21 - 30	4 (1.6%)	74 (15.2%)	31 (9.7%)
31 - 40	10 (3.9%)	132 (27.0%)	91 (28.5%)
41 - 50	17 (6.6%)	109 (22.3%)	82 (25.8%)
51 - 60	56 (21.9%)	97 (19.9%)	64 (20.1%)
61 - 70	93 (36.3%)	62 (12.7%)	45 (14.1%)
71 - 80	66 (25.8%)	12 (2.5%)	6 (1.9%)
81 - 90	9 (3.5%)	2 (0.4%)	0 (0.0%)
>90	1 (0.4%)	0 (0.0%)	0 (0.0%)
Female (%)	112 (43.8%)	277 (56.8%)	140 (43.9%)
Continent:			
Africa	1 (0.4%)	6 (1.2%)	12 (3.8%)
Americas	44 (17.2%)	78 (16.0%)	51 (16.0%)
Asia	14 (5.5%)	68 (13.9%)	32 (10.0%)
Europe	175 (68.4%)	325 (66.6%)	201 (63.0%)
Oceania	22 (8.6%)	11 (2.3%)	23 (7.2%)
Economy:**			

Low	0 (0.0%)	1 (0.2%)	3 (0.9%)
Lower middle	12 (4.7%)	59 (12.1%)	19 (6.0%)
Upper middle	20 (7.8%)	125 (25.6%)	57 (17.9%)
High	170 (66.4%)	246 (50.4%)	175 (54.9%)
Conducting Research	2 (0.8%)	187 (38.3%)	283 (88.7%)
Designing Research studies	0 (0.0%)	0 (0.0%)	319 (100%)
Predominantly working on research	0 (0.0%)	21 (4.3%)	59 (18.5%)
Development of Guidelines	0 (0.0%)	95 (19.5%)	161 (50.5%)

*Others: Researchers and not health professionals; policy makers; regulators. HP: Health professionals. ** Economy of the participants' country, according to the World Bank Classification 2021.

Table 7. Baseline characteristics of the Delphi Survey Participants. Reported as N (% of the participants in the corresponding stakeholder group).

Highest level of Education	
Primary education	23 (10.0%)
Secondary education	111 (48.5%)
University education	82 (35.8%)
Not reported	13 (5.7%)
Employment status	
Currently studying	1 (0.4%)
Currently working	45 (19.7%)
Currently unemployed	13 (5.7%)
Early retirement	45 (19.7%)
Retirement	117 (51.1%)
Not reported	8 (3.5%)
Years since COPD diagnosis	

Up to 5	66 (28.8%)	
6-10	68 (29.7%)	
11-15	43 (18.8%)	
16-20	28 (12.2%)	
Over 20	15 (6.6%)	
Not reported	9 (3.9%)	
Exacerbations' history	**Any exacerbation**	**Severe (hospitalized) exacerbation**
None	55 (24.0%)	163 (71.2%)
1	49 (21.4%)	34 (14.8%)
2	36 (15.7%)	18 (7.9%)
3	31 (13.5%)	6 (2.6%)
4	12 (5.2%)	2 (0.9%)
More than 4	41 (17.9%)	2 (0.9%)
Not reported	5 (2.2%)	4 (1.7%)
Previous NIV use or ICU admission		
Yes / No / Not reported	43 (18.8%) / 182 (79.5%) / 4 (1.7%)	

Table 8. Additional baseline characteristics of patients with COPD who completed the Delphi survey.

Among all participants, 896 (84.3%) also completed the second survey round. Visual inspection of the distribution of first-round participant average outcome rating did not reveal differences between those who did or did not complete the second round of the survey. After the second round of the survey, 15 and 29 outcomes met the thresholds for inclusion in and exclusion from the core outcome set, respectively, while the ratings of 9 outcomes were inconclusive. These nine outcomes were further considered during the first consensus meeting. The results of the Delphi survey are presented in detail in appendix 8.3.5 and summarized in table 10. Only a minority of the participants (3.1%) reported relevant conflicts of interest and the exclusion of their responses did not alter the survey results.

Visualisation of the responses of participants from (a) low or lower-middle (LMICs), (b) upper-middle, and (c) high income countries did not reveal any difference in the ratings among these groups. Moreover, for every outcome, the average (median) ratings of each of these groups were very similar (maximum difference = 1).

	Doctors	Nurses	Physiotherapists	Other health professionals	Researchers and not health professionals
Study participants	629	66	51	26	30
Completed 2nd round	522	63	50	23	27
Declared potential conflicts of interest	20 (3.2%)	1 (1.5%)	0 (0.0%)	5 (19.2%)	4 (13.3%)
Primary employment setting:					
Primary care	60 (9.5%)	5 (7.6%)	5 (9.8%)	4 (15.4%)	0 (0.0%)
Secondary hospital	121 (19.2%)	14 (21.2%)	2 (3.9%)	0 (0.0%)	0 (0.0%)
Tertiary/University hospital	348 (55.3%)	17 (25.8%)	30 (58.8%)	9 (34.6%)	2 (6.7%)
Clinical trials, methodology or epidemiology unit	1 (0.2%)	3 (4.5%)	0 (0.0%)	1 (3.8%)	1 (3.3%)
Health technology Assessment or guidelines development organization	3 (0.5%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	2 (6.7%)
Governmental Organization	2 (0.3%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (3.3%)
Research funding organization/Charity	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
Patients' organization	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (3.8%)	0 (0.0%)
Pharmaceutical industry	4 (0.6%)	0 (0.0%)	0 (0.0%)	4 (15.4%)	0 (0.0%)
Other	26 (4.1%)	3 (4.5%)	7 (13.7%)	1 (3.8%)	7 (23.3%)
Not reported	63 (10.0%)	24 (36.4%)	4 (7.8%)	5 (19.2%)	16 (53.3%)
COPD patients assessed during the previous year					

None	16 (2.5%)	4 (6.1%)	6 (11.8%)	5 (19.2%)	5 (16.7%)
1-250	283 (45.0%)	25 (37.9%)	29 (56.9%)	15 (57.7%)	2 (6.7%)
251-500	154 (24.5%)	8 (12.1%)	10 (19.6%)	0 (0.0%)	0 (0.0%)
501-750	58 (9.2%)	3 (4.5%)	4 (7.8%)	1 (3.8%)	0 (0.0%)
751-1000	30 (4.8%)	1 (1.5%)	1 (2.0%)	0(0.0%)	0 (0.0%)
>1000	35 (5.6%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not reported	53 (8.4%)	24 (36.4%)	1 (2.0%)	5 (19.2%)	23 (76.7%)
Research activity:					
Involved in conducting research	369 (58.7%)	29 (43.9%)	40 (78.4%)	16 (61.5%)	13 (43.3%)
Involved in designing research	230 (36.6%)	13 (19.7%)	34 (66.7%)	9 (34.6%)	11 (36.7%)
Devote >50% of their working time to research	45 (7.2%)	11 (16.7%)	11 (21.6%)	6 (23.1%)	7 (23.3%)
Involved in developing guidelines	210 (33.4%)	18 (27.3%)	17 (33.3%)	5 (19.2%)	5 (16.7%)

Table 9. Additional baseline characteristics of expert respondents (health professionals and researchers) of the Delphi survey.

COPD exacerbations outcomes considered		Delphi Survey Results			Consensus meeting	
Sources of outcomes Methodological SRs Qualitative interviews Delphi survey (Round 1)	**Outcomes' selection results** Included Inconclusive Excluded	Patients & Patient representatives	Health professionals	Researchers	Patients & Patient representatives	Health professionals & Researchers
Death outcomes						
Death from COPD Exacerbation		81.8%	94.5%	96.9%		
Death from any cause		68.5%	74.8%	84.0%	100%	100%
Clinical and Physiological Outcomes						
Anxiety		35.5%	27.0%	28.3%		
Breathlessness		79.3%	93.3%	94.9%		
Chest discomfort		15.8%	5.8%	8.2%		
Fatigue		54.2%	46.3%	44.7%		
Cough		49.3%	54.3%	53.6%		
Coughing up blood (haemoptysis)		62.1%	58.3%	46.8%		
Production of dark-coloured sputum		56.7%	58.5%	53.6%		
Sputum amount		38.4%	42.0%	35.5%		

Sputum thickness (ease of expectoration)	40.4%	41.8%	29.0%		
Wheeze	39.4%	46.8%	35.2%		
Appetite	24.6%	17.5%	14.0%		
Change in weight	33.5%	25.8%	23.9%		
Respiratory muscle strength	65.5%	58.8%	47.8%		
Low mood/ depression	41.9%	35.5%	40.6%		
Sleep quality	51.7%	38.3%	35.5%		
Early morning symptoms	36.5%	32.0%	25.6%		
Night time symptoms	45.8%	50.3%	41.3%		
Treatment success (or failure)	80.3%	87.8%	89.1%		
Worsening of symptoms after the initial treatment	71.9%	78.5%	77.1%		
Disease progression	83.7%	88.8%	86.7%		
Future exacerbations	75.9%	89.3%	90.4%		
Lung function during and immediately after the exacerbation	71.4%	54.3%	43.0%	7.7%	11.1%
Permanent deterioration in lung function	87.7%	88.5%	82.3%		
Levels of oxygen and carbon dioxide in the blood (arterial blood gases)	76.4%	80.3%	75.4%		
Development of pneumonia	76.4%	86.8%	83.6%		
Development of resistant bacteria	73.4%	80.8%	70.6%		
Damage of lung cells and lung tissue	81.3%	71.5%	57.3%	38.5%	22.2%
Infection by bacteria (bugs) or viruses	72.4%	68.0%	64.8%	92.9%	68.4%

Inflammation in the lungs/airways	73.4%	61.5%	49.1%	50.0%	27.8%
Adverse event outcomes					
Adverse events of treatments	60.6%	58.3%	65.9%		
Serious adverse events from treatments	76.8%	89.5%	93.5%		
Development and/or progression of other diseases (e.g. heart attack)	67.5%	69.5%	69.6%		
Resources use outcomes					
Need for hospital admission for the presenting exacerbation	69.0%	84.6%	90.8%	100%	100%
Length of hospital stay for the exacerbation	45.3%	62.3%	68.3%		
Future hospital admissions	52.2%	70.5%	76.5%	71.4%	77.8%
Need for non-invasive ventilation (NIV) use for the exacerbation	64.0%	83.5%	81.9%	61.5%	78.6%
Length of non-invasive ventilation (NIV) use for the exacerbation	58.1%	60.25%	57.0%		
Need for admission to the intensive care unit for the exacerbation	71.9%	86.8%	88.7%		
Length of stay in the intensive care unit for the exacerbation	63.1%	72.8%	71.0%	38.5%	50%
Need for additional medications to achieve symptoms control	64.5%	59.5%	57.3%		
Need for long-term administration of supplemental oxygen after the exacerbation	58.6%	62.8%	66.9%		
Need for long-term use of non-invasive ventilation (NIV) after the exacerbation	55.7%	69.5%	65.5%		

Life impact outcomes					
Ability to exercise	57.6%	51.0%	60.4%		
Physical strength	48.8%	38.3%	35.5%		
Walking distance	57.6%	67.3%	68.3%		
Activities of daily living	70.4%	82.5%	84.6%		
Health related quality of life	75.4%	82.5%	87.7%		
Social engagement/ isolation	54.2%	50.5%	50.5%		
Treatment adherence	72.4%	83.8%	84.6%		
Impact of family members and caregivers	56.7%	50.3%	47.4%		
Impact on sexual function	36.0%	36.3%	37.5%		

Table 10. Summary of the selection process of the core outcomes from the longlist. Percentages refer to the proportion of participants that consider a particular outcome critical. Background colour coding: First column: Grey, blue, purple colours signify outcomes identified through the methodological systematic reviews, qualitative interviews, or the Delphi survey, respectively. In the remaining columns, background colour refers to the results of the outcome selection process at each stage; green, yellow and red colours signify inclusion, inconclusive result or exclusion of the respective outcome.

5.4.5. Consensus meetings

The first consensus meeting was attended by a global panel including 17 patients or patient representatives, 22 health professionals and/or clinical researchers with relevant expertise, and two methodologists with expertise in core outcomes development (Appendix 8.3.8). The methodologists did not vote in the polls but provided methodological input during the discussion. Nine outcomes with inconclusive ratings in the Delphi survey were discussed during the consensus meeting and three of them were prioritized for inclusion in the core outcome set (table 10).

The second meeting was attended by a global panel involving two patients and a patient representative (ELF), 21 health professionals and/or clinical researchers with relevant expertise, and one methodologist with expertise in core outcomes development (Appendix 8.3.8). Due to the more technical nature of this assignment, we involved a smaller number of patients and patient representatives who had previous experience in COPD research. During this consensus meeting, the structure of the core outcome set was finalized (Table 11). Permanent deterioration in lung function was originally prioritized as a core outcome in the Delphi survey. However, during the consensus process, it became clear that this is a way of measuring the outcome disease progression and was, therefore, reclassified. For each of the core outcomes, a single, optimal measurement instrument was prioritized and recommended (table 12). Strong recommendations were issued for only four of the core outcomes, while for the remaining outcomes an interim instrument was recommended, along with a call for relevant methodological research (table 13).

Feedback was collected from all consensus meeting participants. All participants felt that their views were heard, and the consensus was well-informed.

The COPD Exacerbations Core Outcome Set

1. **Death**
    a. **Death from any cause**
    b. **Death from a COPD exacerbation**
2. **Treatment success**
3. **Need for higher level of care**
    a. **Need for hospital admission for the presenting exacerbation**

b. Need for admission to the intensive care unit for the exacerbation
4. Levels of oxygen and carbon dioxide in the blood (arterial blood gases)
5. **Patient reported outcomes** **a. Breathlessness** **b. Health related quality of life** **c. Activities of daily living** **d. Worsening of symptoms after the initial treatment**
6. **Future Impact** **a. Disease progression** **b. Future exacerbations** **c. Future hospital admissions**
7. **Safety** **a. Serious adverse events from treatments** **b. Development of resistant bacteria** **c. Development of pneumonia**
8. Treatment adherence

Table 11. Core Outcome Set for Clinical Trials Evaluating the Management of COPD Exacerbations.

Death from any cause. Death from any cause during study period. Record date of death.
Death from COPD exacerbation. Consider the immediate cause of death as documented in the death summary. In cases of death due to an immediate complication of an exacerbation, such as a ventricular arrhythmia, massive pulmonary embolism, or myocardial infarction, the exacerbation should be considered the cause of death. Ideally, cause of death will need to be confirmed by a blinded adjudication committee. However, this may not always be feasible.
Treatment success.

Treatment success defined as sufficient improvement of the signs and symptoms of the exacerbation that no additional systemic treatments (antibiotics or systemic corticosteroids) are required.
Need for hospital admission for the presenting exacerbation. A clinical need to admit a patient to the hospital, or equivalent intensification of the monitoring or care that may be provided in other settings (including patients' home). Admissions for social reasons should be reported separately. For evaluating this outcome investigators should record whether a patient required admission at any timepoint and whether they still required hospital admission at a specific follow-up timepoint.
Need for admission to the intensive care unit (ICU) for the presenting exacerbation. Need for ICU admission should be evaluated on the basis of the need for invasive mechanical ventilation, defined as (i) persistent or deteriorating respiratory acidosis despite optimized medical treatment and delivery of non-invasive ventilation (NIV); (ii) persistent or deteriorating respiratory acidosis despite optimized medical treatment and a contra-indication for the use of NIV, for example due to severe facial deformity where fitting a mask is impossible, upper airway obstruction, or facial burns; (iii) respiratory arrest or peri-arrest situations unless there is a rapid recovery from manual ventilation or provision of NIV. For evaluating this outcome investigators should record whether a patient required admission at any timepoint and whether they still require ICU admission at a specific follow-up timepoint.
Levels of oxygen and carbon dioxide in the blood (arterial blood gases). A setting and intervention specific outcome. A baseline and at least one follow-up measurement are required with a clear indication of whether or not the patient was receiving oxygen at the time of the measurement, and if yes, how much. It may not be feasible for studies evaluating outpatients.
Breathlessness. Breathlessness should be evaluated using the modified Borg's scale. It should be measured at approximately the same time every day. It can be self-completed.

Health related quality of life. The COPD Assessment Test (CAT) should be used for assessing health related quality of life.
Activities of daily living. The Capacity of Daily Living in the Morning Questionnaire (CDLM) should be used for evaluating basic activities of daily living during the exacerbation. The Manchester Activities of Daily Living Questionnaire (MRADL) should be used for evaluating basic and instrumental activities of daily living, during recovery (long-term impact of the exacerbation).
Worsening of symptoms after the initial treatment. The modified Borg's scale and the COPD assessment test (CAT) should be used to detect symptoms worsening after the initial treatment.
Disease progression. Permanent deterioration in lung function should be used to evaluate the impact of exacerbations on disease progression. Two pulmonary function tests during stable clinical condition are needed: One within 6 months prior to the index exacerbation, and one within 2-6 months afterwards. Change from baseline in forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio should be noted. The number of exacerbations experienced between the two measurements should be noted. Ideally, only the index exacerbation should be included between the two measurements. Disease progression as a core outcome is only relevant for longer-term studies that recruit participants during stable disease state, in anticipation of an exacerbation.
Future exacerbations. Future exacerbations, noting whether they are moderate or severe, after treatment success is confirmed.
Future hospital admissions. Future hospital admissions for any medical reason, or equivalent intensification of the monitoring or care that may be provided in other settings, after treatment success is confirmed.
Serious adverse events from treatments.

Following the definition of the International Council for Harmonisation. Serious adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment, that fulfils any of the following: (a) Results in death; (b) Is life threatening; (c) Requires inpatient hospitalisation or prolongation of existing hospitalisation; (d) Results in persistent or significant disability / incapacity; (e) Is a congenital anomaly or birth defect. Suspected unexpected serious adverse reactions (SUSARs) should also be reported.			
Development of resistant bacteria. Trials evaluating antimicrobials, antimicrobial stewardship strategies, novel immune modifiers or other interventions that may affect bacterial resistance should evaluate bacterial resistance to the administered antibiotics in spontaneous sputum. As a minimum, resistance should be evaluated at baseline and within a week after treatment completion. Sputum induction may provide additional information. However, in each study, researchers should consider the balance between the added value compared to the risk, participants discomfort and required resources.			
Development of pneumonia. Pneumonia confirmed by the presence of new consolidation in the chest x-ray or other imaging modalities of the chest, in the presence of consistent clinical signs and symptoms. When possible, chest imaging should be acquired at baseline, to assess for the presence of pneumonia. This may not be possible for trials recruiting patients outside the hospital setting. Follow-up chest imaging should be driven by clinical need.			
Treatment adherence. An intervention specific outcome. Methods for assessing treatment adherence should be clearly reported.			
	Strong recommendation		**Interim recommendation, with research agenda**

Table 12. Outcome measurement instrument recommendations. Green and yellow background colours signify a strong recommendation and an interim recommendation with associated research agenda, respectively.

Death from COPD exacerbation. - Development and implementation of standardized methodology for determining the cause of death during an acute event, such as an acute exacerbation.
Treatment success. - Development of objective and accurate methods for confirming treatment success. - Development of objective and accurate methods for confirming cure. - Quantification of the duration of exacerbations and identification of timepoints when the evaluation of treatment success is sensitive to treatment effect.
Need for hospital admission for the presenting exacerbation. - There is a need for novel instruments that could consistently capture the need for monitoring or care intensification that is traditionally offered in a hospital setting.
Need for admission to the intensive care unit for the presenting exacerbation. - Standardization of the indications and contra-indications for (i) admission to the intensive care unit, and (ii) mechanical ventilation, of patients with COPD exacerbations.
Levels of oxygen and carbon dioxide in the blood (arterial blood gases). - Development of instruments that will allow for comparison of the levels of oxygen and carbon dioxide in the blood of patients receiving different levels of supplemental oxygen. - Development and validation of non-invasive methods for estimating the levels of carbon dioxide in the blood.
Breathlessness. - Formal evaluation/ comparison of measurement properties of instruments used to evaluate breathlessness during COPD exacerbations.
Health related quality of life. - Formal evaluation/ comparison of measurement properties of instruments used to evaluate quality of life during COPD exacerbations.
Activities of daily living. - Formal evaluation/ validation of the properties of instruments used to measure activities of daily living during and after a COPD exacerbation, using the COSMIN methodology. - The Capacity of Daily Living in the Morning (CDLM) questionnaire focuses on morning activities. Evaluation of other tools evaluating activities throughout the day.

- Development of validated translations of the selected instruments and confirmation of cross- cultural validity.
Worsening of symptoms after the initial treatment. - Formal evaluation of the measurement properties of tools that could be used to identify worsening of symptoms after the initial treatment (such as the EXACT-PRO [173]).
Disease progression. - Development novel and simple methods for evaluating the impact of exacerbations on disease progression. - Evaluation of the role of other pulmonary function parameters in evaluating the impact of exacerbations on disease progression (e.g., lung volumes, diffusion capacity). - Could change in the computed tomography (CT) of the chest compared to baseline reveal the impact of the exacerbation on disease progression (e.g., the extent of emphysema quantified by loss of lung density, or changes in the diameter of the pulmonary artery).
Future exacerbations. - Development of consistent methods for differentiating a prolonged exacerbation from the onset of a new exacerbation. - Development and validation of methodology for differentiating different types of COPD exacerbations.
Future hospital admissions. See: Need for hospital admission for the index exacerbation.
Development of resistant bacteria. - Assessment of the additional information offered by conducting sputum induction to assess for bacterial resistance in patients recovering from a COPD exacerbation. - Evaluation of the sensitivity of different types of samples (respiratory or non-respiratory) in evaluating bacterial resistance.

Table 13. Outcome measurement instruments: Research agenda

5.4.6. Considerations around the selection of outcome measurement instruments

The recommended outcome measurement instruments and relevant research recommendations are summarized in table 12-13. Table 14 describes the voting results for each of the selected measurement instruments. In the following paragraphs, we describe the

relevant data and pertinent discussion points that were considered by the panel when selecting the measurement instruments. For each instrument we describe: (i) the findings from our original methodological SR (Chapter 3); (ii) the findings of the additional focused literature reviews that were conducted (the search strategies that were used and search results for each of these reviews are presented in Appendix 8.3.6); (iii) pertinent discussion points during the consensus meeting; and (iv) the recommendations.

Voting responses				
Outcome	**Strong**	**Interim, with Research agenda**	**Research agenda only**	**Other instrument or further data needed**
Death from any cause	100%	0%	0%	0%
Death from a COPD exacerbation	55%	39%	6%	0%
Treatment success	0%	88%	6%	6%
Need for hospital admission for the presenting exacerbation	22%	78%	0%	0%
Need for admission to the intensive care unit for the presenting exacerbation	18%	82%	0%	0%
Levels of oxygen and carbon dioxide in the blood (arterial blood gases)	47%	47%	0%	6%
Breathlessness	28%	66%	6%	0%
Health related quality of life	65%	35%	0%	0%
Activities of daily living	0%	76%	0%	24%
Worsening of symptoms after the initial treatment	0%	100%	0%	0%
Disease progression	7%	80%	13%	0%
Future exacerbations	50%	44%	6%	0%
Future hospital admissions	53%	33%	7%	7%
Serious adverse events from treatments	86%	7%	7%	0%

Development of resistant bacteria	64%	22%	14%	0%
Development of pneumonia	71%	29%	0%	0%
Treatment adherence	100%	0%	0%	0%

Table 14. Second consensus meeting: Voting results

5.4.6.1. Death from any cause

Methodological SR (Chapter 3)[113]: Mortality was evaluated in 101 (82%) of all included RCTs. 100/101 studies evaluated number of deaths in each treatment group during a specific follow-up period, or during hospital or ICU stay.

Literature review: Not performed since this outcome is evaluated consistently.

Panel discussion summary: Death from any cause is the most frequently evaluated mortality outcome in clinical trials and it is evaluated consistently. The panel agreed to adopt this approach.

Recommendation: Death from any cause should be measured as the number of deceased patients in each treatment group by a specific timepoint (**Strong Recommendation**).

5.4.6.2. Death from a COPD exacerbation

Methodological SR[113]: Only one trial evaluated death from COPD exacerbation as an outcome. The methodology used to determine the cause of death and whether a death was caused by an exacerbation was not described.

Literature review: We did not identify methodological studies evaluating outcome measurement instruments for assessing this outcome in COPD exacerbation trials. Three studies described the rules used for determining the cause of death in TORCH and UPLIFT, two clinical trials evaluating the management of stable COPD[174-176]. Both adjudication committees described that if the final illness was precipitated by a recent COPD exacerbation, then the final cause of death should be considered COPD exacerbation, regardless of the subsequent fatal events, such as pneumonia, sepsis, respiratory, renal, or multi-organ failure, myocardial infarction. Both adjudication committees also highlighted inconsistency between

the cause of death described in the death certificate and issued by the adjudication committee.

Panel discussion summary: Death from COPD exacerbation is rarely evaluated in exacerbation trials. COPD exacerbations are often complicated by events such as ventricular arrhythmia, massive pulmonary embolism, acute myocardial infarction, or pneumonia[177]. As a result, the determination of the cause of death during an exacerbation is complex and often inconsistent across different centres and countries. The panel agreed that if a death is caused by an immediate complication of the exacerbation, then the exacerbation should be considered the cause of death. Given the inconsistencies observed in the determination of the cause of death, the panel agreed that ideally, cause of death should be confirmed by a well-informed and blinded adjudication committee. However, such committees are resource intensive and may not always be feasible. For this reason, a pragmatic approach based on the documented primary cause registered in the death certificate was adopted by the panel.

Recommendation: Consider the immediate cause of death as documented in the death summary. In cases of death due to an immediate complication of an exacerbation, such as a ventricular arrhythmia, massive pulmonary embolism, or myocardial infarction, the exacerbation should be considered the cause of death.

Ideally, cause of death will need to be confirmed by a blinded adjudication committee. However, this may not always be feasible. (**Interim Recommendation with research agenda**).

5.4.6.3. Treatment success

Methodological SR[113]: Treatment success or treatment failure was evaluated in 77 (63%) of the trials included in our systematic review. More specifically, 21 (17%) studies reported data on both treatment success and failure rates, while 27 (22%) and 29 (24%) studies only reported on treatment failure, or treatment success, respectively. The instruments used to evaluate this outcome varied significantly.

Literature review: The focused literature review did not reveal any methodological studies evaluating the measurement properties of different instruments used to assess treatment success or cure of a COPD exacerbation. In the absence of existing methodological studies to inform our decision-making process, we conducted a meta-epidemiological study aimed to

systematically evaluate the measurement instruments used for assessing treatment success or failure, to explore how effective they are, and which timepoints are more sensitive.

The methodology of this systematic review was prospectively registered (PROSPERO ID: CRD42020222287) and further details on the methods and findings are described in Appendix 8.3.7. In brief, we systematically searched Medline/PubMed, the Cochrane Airways Trials Register and the COSMIN database on 12th November 2020, to identify ongoing and completed trials testing pharmacological and non-pharmacological interventions for the management of COPD exacerbations, reported in the English language during the last 15 years. We also looked for methodological studies evaluating the performance characteristics of different instruments for assessing treatment success or failure in clinical trials on COPD exacerbations.

We did not identify any eligible methodological studies evaluating the performance characteristics of instruments used to assess treatment success or failure in COPD exacerbations trials. We identified 176 ongoing or completed RCTs evaluating pharmacological or non-pharmacological interventions for the management of COPD exacerbations, of which 54 (30.7%) assessed the overall outcome of the index exacerbation. This was selected as the primary outcome in 35 (64.8%) and as a secondary outcome in 19 (35.2%) of these trials. Timepoints of evaluation of this outcome varied from 2 hours to 1 year after recruitment across the included trials.

Composite endpoints consisting of several undesirable outcomes of an exacerbation.

Instruments consisting of several undesirable outcomes of an exacerbation (e.g., death; need for treatment intensification; admission to the intensive care; or hospital admission), together defining an overall unfavourable outcome were defined as composite instruments. Twenty-three RCTs included 27 composite measurement instruments [8,14,178-198]. Most of these RCTs were at high or unclear risk of methodological bias. High risk of performance or detection bias was observed in 12/23 (52.2%) and 11/23 (47.8%) RCTs, respectively. Only six RCTs were deemed to be of an overall low risk of bias (table 15).

	Sequence	Allocation	Performance	Detection	Attrition	Reporting	Other
Aaron 2013	Low	Low	Low	Low	Low	Low	Low
Aggarwal 2011	Low	Unclear	High	High	Low	Unclear	Unclear
Bafadhel 2012	Low	Low	Low	Low	Low	Low	Low
Carrera 2009	Low	Low	Low	Low	High	Unclear	Low
Corrado 2009	Low	Low	High	High	Low	Unclear	Unclear
Daniels 2010	Low	Low	Low	Low	Low	High	Low
de Jong 2007	Low	Unclear	Low	Low	Low	Low	Low
Goossens 2013	Low	Low	High	High	Low	Low	Low
Hua 2020	Low	Low	High	High			
Jolliet 2016	Low	Unclear	High	Low	Low	Low	Low
Nicolini 2014	Low	Low	High	High	Low	Low	Low
Nouira 2010	Low	Low	Low	Low	Low	Low	Low
Papalampidou 2020	Low	High	High	High			
Prasad 2020	Low	Low	High	High	Low	Low	High
Sehgal 2019	Low	Low	High	High	Low	Low	Low
Sivapalan 2019	Low	Low	High	High	Low	Low	Low
Strambu 2019	Low	Low	Low	Low	Low	Low	Low
Tajamul 2020	Low	Low	High	High	Low	Low	Low
Urueta-Robledo 2006	Unclear	Unclear	Low	Low	High	Unclear	Unclear
van Velzen 2017	Low	Low	Low	Low	Low	Low	Low
van Zanten 2007	Unclear	Unclear	High	High	Low	Unclear	Low
Vermeersch 2019	Low	Low	Low	Low	Low	Low	Low
Wilson 2015	Unclear	Unclear	Low	Low	High	Low	Low
Woodruff 2011	Unclear	Unclear	Low	Low	High	Low	High

Table 15. Risk of bias of RCTs reporting composite outcome measurement instruments.

Each composite instrument included a median of 3 (range 2-5) components. These components described different undesirable events and if any of these events was fulfilled then participants were considered to have experienced treatment failure. The most frequently used components were death (n=16, 59.3% of the outcomes), need for hospital admission or re-admission (14, 51.9%), and treatment intensification (14, 51.9%). More details are presented in table 16.

Components of the composite outcome definitions	N (%)
Death	16 (59.3%)
Need for hospital admission / re-admission	14 (51.9%)
Need for treatment intensification	14 (51.9%)
Need for endotracheal intubation/ mechanical ventilation	10 (37.0%)

Persistent or deteriorating symptoms and signs	8 (29.6%)
Need for non-invasive ventilation	3 (11.1%)
Need for urgent outpatient or emergency room visit	3 (11.1%)
New infection	3 (11.1%)
Need for higher level of hospital care	2 (7.4%)
Deteriorated arterial blood gases	1 (3.7%)
Hemodynamic instability	1 (3.7%)
Need for ICU admission	1 (3.7%)
Prolonged hospital stay	1 (3.7%)
Reduced level of consciousness	1 (3.7%)
Treatment intolerance	1 (3.7%)

Table 16. Undesirable outcomes included in the composite treatment failure instruments, along with the frequency they were utilised.

Qualitative or semi-quantitative descriptions of the participants' clinical status.

Descriptive instruments define treatment success or failure based on qualitative or semi-quantitative descriptions of the patients' clinical status with regards to the exacerbation at a specific time point. The following states are often defined: cure, marked improvement, improvement, or treatment failure. Thirty-four RCTs included 45 descriptive instruments [26,125,196-227]. All but three trials were deemed to be at high risk of methodological bias. A high risk of performance or detection bias was revealed in 16 (47.1%) and 13 (38.2%) of the 34 studies, respectively (table 17).

Four states were defined: Cure, marked improvement, improvement, treatment failure. The definitions of these states differed across the included trials (table 18). Moreover, the definition of clinical effectiveness varied. While in most trials, cure of the exacerbation or the absence of treatment failure was defined as treatment success, other trials accepted marked improvement, or, less frequently, improvement as an indicator of effectiveness (table 18). The previous terms were used in many of the included trials. The instruments described in the remaining trials were matched to the most appropriate states by consensus among the investigators.

	Sequence	Allocation	Performance	Detection	Attrition	Reporting	Other
Alvarez-Sala 2006	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Andre-Alves 2007	Unclear	Unclear	High	High	Low	Unclear	High
Blasi 2013	Unclear	Unclear	High	High	Low	Low	Unclear
Blasi 2013 B	Low	Low	Low	Low	Low	Unclear	High
Brusse-Keizer 2014	Low	Low	Low	Low	Low	Low	High
Ceviker 2014	Low	Low	High	Low	High	Unclear	Unclear
Chatterjee 2011	Low	Low	High	Low	Low	Unclear	Unclear
Daniels 2010	Low	Low	Low	Low	Low	High	Low
Gao 2019	Unclear	Unclear	High	High	Low	Unclear	Low
Giusti 2016	Low	Low	Low	Low	Low	Low	Low
Gotfried 2007	Unclear	Unclear	High	High	Low	Low	Low
Jiang 2017	Low	Unclear	High	High	Low	Unclear	Low
Li 2010	Low	Unclear	High	High	High	Unclear	Low
Llor 2009	Unclear	Low	Low	Low	Low	Unclear	Low
Llor 2012	Low	Unclear	Low	Low	Low	Low	Low
Nouira 2010	Low	Low	Low	Low	Low	Low	Low
Park 2017	Unclear	Low	Low	Low	Low	Unclear	High
Petitpretz 2007	Unclear	Unclear	High	High	High	Unclear	Unclear
Prins 2019	Low	Low	High	High	Low	Low	Low
Rhee 2015	Low	Low	Low	Low	High	High	High
Ritchie 2019	Low	Low	Low	Low	Low	Low	Low
Roede 2007	Low	Low	Low	Low	Low	Unclear	High
Rohde 2015	Unclear	Unclear	Low	Low			
Stallberg 2009	Unclear	Low	Low	Low	Low	Low	Low
Stolz 2007	Unclear	Unclear	High	High	Low	Low	Low
Urueta-Robledo 2006	Unclear	Unclear	Low	Low	High	Unclear	Unclear
van den Broek 2008	Low	Low	Low	Low	Low	Unclear	Unclear
van Zanten 2007	Unclear	Unclear	High	High	Low	Unclear	Low
Verduri 2015	Low	Low	High	High	Low	Low	Low
Wang 2010	Unclear	Low	Low	Low	Low	High	Unclear
Xie 2019	Low	Low	High	Low			
Yoon 2013	Low	Low	High	High	Low	Unclear	Unclear
Zervos 2007	Unclear	Unclear	High	High	Low	Unclear	High
Zhang 2019	Low	Low	Low	Low			

Table 17. Risk of bias of RCTs reporting descriptive instruments.

COPD exacerbation states described	N
Cure or Resolution	
Complete resolution of all signs and symptoms of the exacerbation.	8
Sufficient improvement of the signs and symptoms such that no additional systemic treatments were prescribed.	5
Anthonisen Respiratory Symptoms Score <5 [204].	2

Three consecutive days when patients' symptoms are back at their baseline, or seven consecutive days in which the patient only reported a "minor increase" in symptoms compared to baseline, without fever or change in sputum colour.	2
Resolution of symptoms, signs, and laboratory findings.	1
Resolution of symptoms, signs, laboratory findings and eradication of the causative organism.	1
Remission (not further described)	4
Marked improvement	
Resolution of all signs and symptoms of the exacerbation, or reduction of at least 3 points in a non-validated score, compared to baseline.	2
Only one of the following parameters remains abnormal: Clinical symptoms, signs, laboratory findings, causative pathogen [not eradicated].	1
Major symptoms including cough, exacerbation and dyspnoea almost disappeared and the chest imaging is significantly improved.	1
Significantly improved symptoms, signs, and laboratory tests. Effectiveness index between 60-90% (based on a non-validated scale).	1
Improvement	
Improved signs and symptoms, without any new signs or symptoms.	4
Improved symptoms as evaluated by clinical scores: Anthonisen Respiratory Symptoms Score between 6-10; 30% improvement in the Bronchitis Severity Score (BSS); Reduction of 1-3 points in a non-validated score.	3
Improved, but more than one of the following parameters remain abnormal: Clinical symptoms, signs, laboratory findings, causative pathogen (not eradicated).	1
Improved symptoms, signs, and laboratory tests. Effectiveness index between 30-60% (based on a non-validated scale).	1
Resolution of at least 50% of symptoms back to the baseline level.	1
Resolution of fever with incomplete resolution of signs and symptoms, without the need for additional antibiotics.	1

Resolution or reduction of the symptoms and signs without new symptoms and signs associated with the infection.	1
Improvement (not further described)	4
Treatment failure	
Lack of resolution of signs and symptoms, requiring additional treatment, (or death).	8
Persistence or worsening of signs and symptoms, or death.	7
Lack of resolution of signs and symptoms or need for further treatment.	4
Persistence or worsening of signs, symptoms, or laboratory tests	1
Worsening of at least one symptom, or no change in the symptoms, or reduction of less than 3 points in a non-validated score, compared to baseline.	1
Ineffective treatment (no further described)	3

Table 18. Definitions of various COPD exacerbations states within descriptive instruments.

Proportion of participants experiencing treatment success or failure over time.

Treatment success or failure is a time-sensitive outcome. Too early or too late during the exacerbation, nearly none or all the participants will have fulfilled the criteria of success or failure respectively, limiting the ability of the outcome to detect between group differences in clinical trials. For this reason, we explored the proportion of participants fulfilling the outcomes of interest at different timepoints.

Figure 13 depicts the proportion of study participants in treatment arms treated with guideline recommended treatments (usual care) that experienced treatment failure as judged by composite outcome measurement endpoints (defined based on several undesirable outcomes of an exacerbation). This outcome was assessed at different timepoints, mostly within a month from recruitment, although in some trials it was tested at up to three months follow-up (and in one case at 9 months; not included in figure 13).

The proportion of participants experiencing treatment failure based on these outcomes increases over time, as all participants fulfilling the criteria of treatment failure at any time

until the selected timepoint are considered to have experienced the outcome (treatment failure). Importantly, treatment failure assessed at a later follow-up usually also includes patients experiencing a re-exacerbation. As anticipated, treatment failure rates and slopes over time are higher among people admitted to the hospital or treated in the intensive care unit (ICU). When assessed between one and two weeks from recruitment the median (range) of the treatment failure rates across the included studies were 8.3% (6%-10.6%) in the emergency setting, 6.5% (1.5%-13.5%) in the hospital setting, and 19.3% (15.3%-34.2%) in the ICU setting. At three months follow-up, in studies conducted in the hospital setting, over half of the participants are identified as having experienced treatment failure. Moreover, 40% of participants treated in the community and 30% of those assessed in the emergency department are also anticipated to have experienced treatment failure at three months.

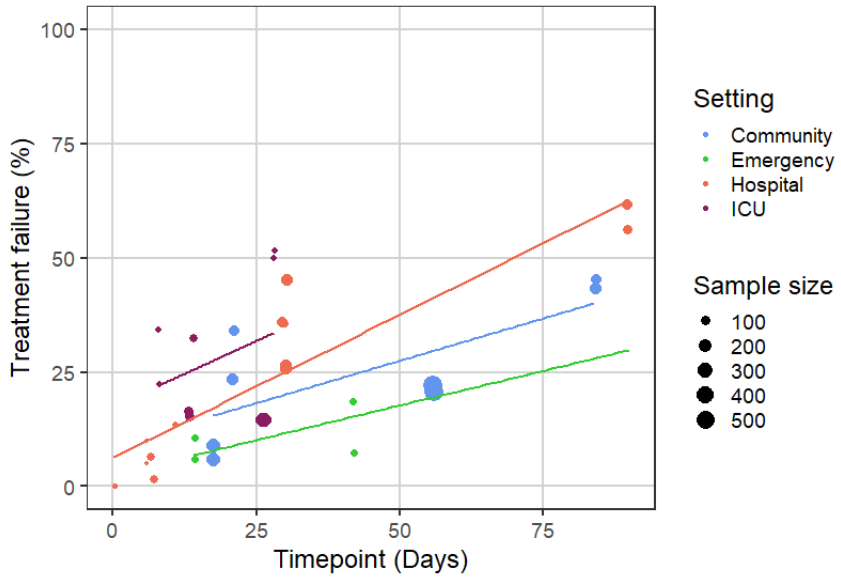

Figure 13. *Treatment failure rates assessed using composite measurement instruments among participants in arms of the included trials that received treatments/interventions that are consistent with current clinical practice guidelines (i.e., study arms with experimental interventions that are not consistent with current clinical practice were excluded from this analysis).*

The proportions of study participants fulfilling descriptive criteria for (a) cure, (b) marked improvement, (c) improvement, or (d) treatment failure, at different timepoints, are summarised in figure 14. These states were evaluated at different timepoints, up to one

month from recruitment, except for two studies that assessed cure or treatment failure at three months (not depicted in figure 14).

When assessed between one and two weeks from recruitment, the median (range) of cure rates across the included studies were 74.5% (0% - 96.5%) in the community setting, 30.6% (30.5%-30.7%) in the emergency setting, 36.4% (12.5%-67.2%) at the hospital setting, and 30.2% (18.6%-41.9%) in the NIV setting. The median (range) for marked improvement were 85.0% (28.9%-96.9%) in the hospital and 45.1% (34.1%-56.1%) in the NIV setting. The respective figures for improvement were 85.1% (64.9%-92.8%) in the community, 81% (80.6%-81.5%) in the emergency, 84.6% (68.6%-100%) in the hospital, and 79.1% (65.9%-90.2%) in the NIV settings. Finally, treatment failure rates were 10.0% (1.8%-22.0%) in the community, 8.0% (7.7%-8.3%) in the emergency, 15.4% (0%-24.4%) in the hospital, and 20.9% (9.8%, 34.1%) in the NIV settings.

Overall, the proportion of participants experiencing cure or marked improvement varied significantly during the first two weeks of follow-up, largely due to the significant variability in the outcome definitions. Stricter instruments, such as those requiring a complete resolution of all signs and symptoms associated with the exacerbation to confirm cure yielded lower cure rates, while higher rates were observed with more lenient definitions. Most of the included studies assessed patients treated in the community, or in the hospital for their exacerbation. As anticipated, cure rates were generally higher among participants treated in the community compared to those hospitalised, for any given follow-up timepoint.

The proportion of participants experiencing improvement or treatment failure varied less across the included studies and was less dependent on the instruments or timepoints of evaluation.

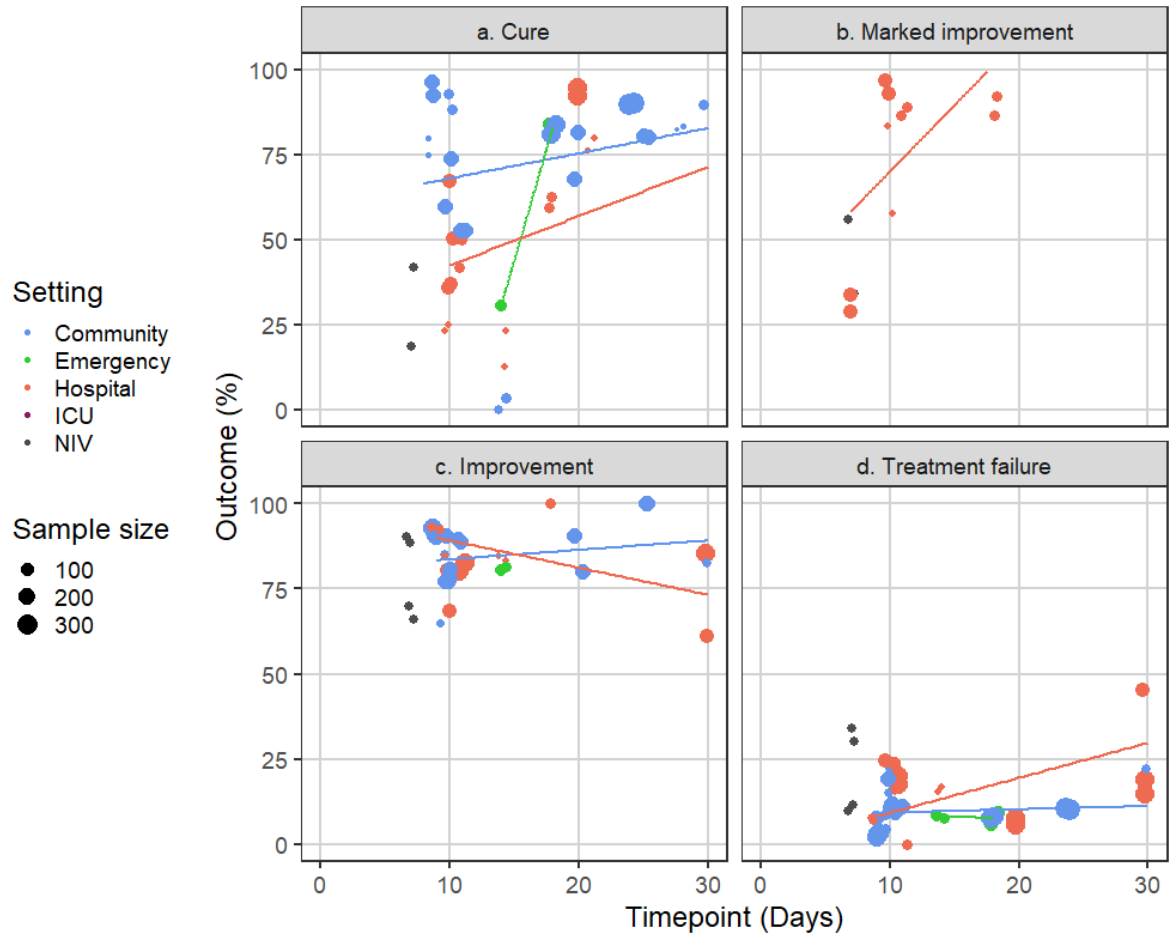

Figure 14. *(a) cure, (b) marked improvement, (c) improvement, or (d) treatment failure assessed using descriptive measurement instruments among participants in arms of the included trials that received treatments/interventions that are consistent with current clinical practice guidelines (i.e., study arms with experimental interventions that are not consistent with current clinical practice were excluded from this analysis).*

Measurement timepoints and treatment effects.

We also explored which instrument and timepoints are more effective in revealing potential treatment effects. However, we were not able to draw strong conclusions due to limitations in the adequacy and quality of available data (details are available in the appendix 8.3.7.2).

Panel discussion summary: Our systematic reviews revealed significant variability in the definitions and/or instruments used to evaluate treatment success or failure. Some trials used composite endpoints consisting of several adverse outcomes of an exacerbation, such as

death, need for treatment intensification, or need for hospital admission, together defining an overall unfavourable outcome. However, these include components that have very different impact (utility) on patients, such as death versus the need of supplemental oxygen[5]. Importantly, the relative frequency of these outcomes may vary across the different exacerbation subtypes, thus limiting the interpretability of the results. For example, exacerbations caused by a bacterial infection are associated with higher mortality, while an increased re-hospitalization rate is observed in exacerbations characterised by enhanced eosinophilic inflammation[15,228]. Moreover, our meta-epidemiological assessment suggests that composite instruments may be less sensitive in identifying treatment effect compared to descriptive instruments, as fewer studies using composite instruments identified a statistically significant effect in trials evaluating interventions that the investigators hypothesised were superior to the control treatments. While this finding is indirect and based on a small number of observations, it may reflect a limited sensitivity of these instruments. Moreover, most of these components are included as independent outcomes in the core outcome set, anyway. For these reasons, the panel did not consider that the evaluation of such composite endpoints would add value to the trials.

More trials used descriptive instruments for assessing the overall outcome of exacerbations. These instruments are limited by the subjectivity of assessing the severity of the clinical conditions by patients and clinicians alike. As a result, these instruments may be susceptible to performance and detection bias. A similar limitation is accepted in the methodology used to classify exacerbations by severity, depending on the clinicians' judgement around the need for systemic treatments or hospital admission[148,229]. These problems spring from the significant heterogeneity that characterizes acute exacerbations of COPD and from the lack of clinically validated biomarkers or objective indices, that could facilitate severity assessment or confirmation of cure.

Upon consideration of the strengths and limitations of the two groups of instruments, the panel favoured descriptive instruments. The most frequently used descriptive instrument defined cure as complete resolution of all signs and symptoms of an exacerbation. However, this instrument was not adopted in the core outcome set due to limitations that may have limited its usability. Firstly, large observational studies have demonstrated that the recovery

period of an exacerbation varies and may be very prolonged [230,231]. It has been suggested that one in four patients experience persistent symptoms compared to their pre-exacerbation status in excess of 25-35 days after the exacerbation's onset [230,231], while recovery of the patients' pre-exacerbation exercise capacity or activities of daily living may further delay [232,233]. Moreover, acute exacerbations expedite the progression of COPD. As a result, the clinical condition of patients after recovery from an exacerbations may be characterised by a greater symptomatic burden compared to the previous baseline [233]. Therefore, anticipating the complete resolution of all signs and symptoms caused by the exacerbation may not be appropriate; in addition, this outcome may be more susceptible to subjectivity in the assessment of potentially limited and clinically insignificant remaining symptoms during recovery.

The second most frequently used definition of treatment success "Sufficient improvement of the signs and symptoms, such that no additional systemic treatments were prescribed" was considered more pragmatic and was endorsed by the panel as an interim instrument. While still subjective, the decision of the clinician to prescribe additional systemic treatments better reflects daily clinical practice and it is often used in trials.

Another interesting instrument defined treatment success as the first of three days while patients' symptoms are back at their baseline, or the first of seven days in which patients only report a minor increase in symptoms compared to baseline, without fever or change in sputum colour. This instrument has only been used in a limited number of trials and is not adequately validated, while it may require additional resources for measuring it. For these reasons it was not adopted by the core outcome set panel. However, this instrument may provide more consistency and allow trialists to measure more accurately time-to-treatment success. Therefore, it may be worth being further validated in future trials.

Treatment success or failure is frequently evaluated as an outcome in other acute respiratory diseases as well, including community, hospital-acquired or ventilator-associated pneumonia, COVID-19, and acute asthma [234,235] [unpublished data]. Trialists face similar challenges in the selection of appropriate instruments for evaluating this outcome in these acute respiratory diseases [234] [unpublished data]. We were not able to identify any other methodological

studies evaluating instruments for measuring treatment success or failure in any acute respiratory diseases.

Recommendation: Treatment success defined as sufficient improvement of the signs and symptoms of the exacerbation that no additional systemic treatments (antibiotics or systemic corticosteroids) are required (**Interim Recommendation with research agenda**).

5.4.6.4. Need for hospital admission for the presenting exacerbation

Methodological SR[113]: This outcome has two components: whether a patient required hospital admission at any timepoint and whether they still required hospital admission at a specific follow-up timepoint. The former and latter components are more relevant for RCTs evaluating moderate and severe exacerbations, respectively. In our methodological systematic review, 33 (27%) studies evaluated length of hospital stay and three studies need for hospital admission for the index exacerbation. This outcome was assessed consistently by recording whether a participant was admitted to the hospital (at a specific timepoint or daily until discharge).

Literature review: Not performed since this outcome is evaluated consistently.

Panel discussion summary: Hospital at home and telemonitoring options introduce heterogeneity in the criteria for hospital admission and length of stay [232]. This outcome is also impacted by non-clinical factors, such as social reasons, discharge planning delays [236], the availability of hospital beds, or travel distance. These issues should be accounted for when evaluating duration of hospital stay.

Recommendation: A clinical need to admit a patient to the hospital, or equivalent intensification of the monitoring or care that may be provided in other settings (including patients' home). Admissions for social reasons should be reported separately.

For evaluating this outcome investigators should record whether a patient required admission at any timepoint and whether they still require hospital admission at a specific follow-up timepoint (**Interim Recommendation with research agenda**).

5.4.6.5. Need for admission to the intensive care unit (ICU) for the presenting exacerbation.

Methodological SR[113]: Similar to the outcome need for hospital admission, this outcome has two components: whether a patient required admission to the ICU at any timepoint and whether they still required ICU admission at a specific follow-up timepoint. The former and latter components are more relevant for RCTs evaluating severe (hospitalized) and critical (admitted to the ICU) exacerbations, respectively. In our methodological systematic review, 10 (8%) studies evaluated length of ICU admission, 10 (8%) length of invasive mechanical ventilation, two the need for ICU admission and two the need for invasive mechanical ventilation. As described in the following section, invasive mechanical ventilation could be used as a measure of the need for ICU admission. This outcome was assessed consistently by recording whether a participant was admitted to the ICU or were invasively ventilated (at a specific timepoint or daily until discharge).

Literature review: Not performed since this outcome is evaluated consistently.

Panel discussion summary: Indications for admission to the ICU vary significantly. Characteristically, while in most centres non-invasive ventilation is now delivered in a respiratory ward or a high dependency unit, in some centres it is still delivered in the ICU[237]. Availability of ICU beds may also impact the decision to admit, and the duration of ICU stay. On the other hand, patients with COPD with poor functional status and underlying multi-morbidity are often not offered an ICU admission or invasive mechanical ventilation, due to futility[238]. The criteria used to support such decisions vary across centres and countries, according to local policies and availability of resources.

Acknowledging that the main, consistent indication for ICU admission in this group of patients is the need for invasive mechanical ventilation, the panel recommended that trials should record the need for invasive mechanical ventilation. A clear definition for the need for invasive mechanical ventilation for adult patients with acute hypercapnic respiratory failure was identified in the BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults (see next section; a focused literature review did not reveal any other recent guidelines addressing indications for invasive ventilation in this patient group)[238].

The decision to focus on the need for invasive mechanical ventilation rather than the receipt of ventilation was based on the earlier observation that often, while these criteria are fulfilled, patients are not offered invasive ventilation, due to futility.

Recommendation: Need for ICU admission should be evaluated on the basis of the need for invasive mechanical ventilation, defined as (i) persistent or deteriorating respiratory acidosis despite optimized medical treatment and delivery of non-invasive ventilation (NIV); (ii) persistent or deteriorating respiratory acidosis despite optimized medical treatment and a contra-indication for the use of NIV, for example due to severe facial deformity where fitting a mask is impossible, upper airway obstruction, or facial burns; (iii) respiratory arrest or peri-arrest situations unless there is a rapid recovery from manual ventilation or provision of NIV.

For evaluating this outcome investigators should record whether a patient required admission at any timepoint and whether they still require ICU admission at a specific follow-up timepoint (**Interim Recommendation with research agenda**).

5.4.6.6. Levels of oxygen and carbon dioxide in the blood (arterial blood gases).

Methodological SR[113]: Forty (33%) RCTs reported on arterial blood gases (pH, oxygen tension, carbon dioxide tension, and/or oxygen saturation measured by pulse oximetry). In all studies, arterial blood was sampled for evaluating blood gases.

Literature review: Not performed since this outcome is evaluated consistently.

Panel discussion summary: This was considered a setting and intervention specific outcome. Firstly, it may not be feasible to be assessed in studies recruiting in an outpatient clinic. The panel agreed that the value of measuring blood levels of oxygen and carbon dioxide in this setting may be limited.

On the other hand, evaluating arterial (and not venous) blood gases as an outcome in hospitalized patients is crucial both for clinical purposes, but also as a research outcome. While a single measurement might be sufficient in clinical practice, at least two measurements are required in the context of a research study, to evaluate the magnitude of change from baseline in response to treatment. For this reason, the panel recommends that a baseline and at least one follow-up measurement are required. However, more intensive

monitoring of the arterial blood gases may be required for specific interventions, such as non-invasive ventilation or modes of oxygen delivery.

Recommendation: A setting and intervention specific outcome. A baseline and at least one follow-up measurement are required with a clear indication of whether or not the patient was receiving oxygen at the time of the measurement, and if yes, how much. It may not be feasible for studies evaluating outpatients (**Interim Recommendation with research agenda**).

5.4.6.7. Breathlessness

Methodological SR[113]: Breathlessness was evaluated using the Borg's scale in 13 (11%) of the included studies, the modified Medical Research Council (mMRC) Dyspnoea Scale in 6 (5%) trials, the Baseline and Transitional Dyspnoea Index in 1 trial and other, non-validated Scales in 11 (9%) trials. Moreover, it was assessed as part of multidimensional symptoms/ severity scores, mainly the COPD Assessment Test (CAT). Other scores evaluated less frequently included the EXAcerbation of Chronic Obstructive pulmonary disease tool – Patient Reported Outcome (EXACT-PRO), the Clinical COPD questionnaire (CCQ), Chronic Respiratory Questionnaire (CRQ) and the BODE index.

Literature review: Our focused literature review revealed three methodological systematic reviews evaluating the performance characteristics of instruments used to evaluate breathlessness. Oliveira and Marques only included studies focusing on the measurement properties of instruments used to assess breathlessness specifically during pulmonary rehabilitation in patients with acute exacerbations, therefore, it was not informed by adequate data[239]. Jadad and colleagues did not formally evaluate measurement properties of the identified instruments[240]. For these reasons the panel discussion was mainly informed by the review conducted by Dorman and colleagues, that focused on the evaluation of breathlessness in palliative care, with a specific focus on COPD and the identified measurement properties were considered applicable to our work (although indirect)[241].

Panel discussion summary: The mMRC Scale does not directly assess breathlessness, as it is a measure of activity limitation due to breathlessness. Moreover, use of the mMRC during an exacerbation was considered by the panel less sensitive, since most patients with moderate or severe exacerbations would cluster in Grade 4 ("Too breathless to leave the house or

breathless when dressing or undressing"), thus limiting the discriminant validity of the scale in this context. CAT is a multidimensional tool measuring several symptoms and health status and therefore does not provide a focus on breathlessness[98]. CAT will be captured anyway, as it is recommended for evaluating health-related quality of life.

The modified Borg Scale is easy to complete, and broadly used in clinical practice and research. Clinically validated translations are available in many languages. Its measurement properties have been thoroughly and positively assessed [241] (table 19). As a result, the modified Borg Scale was recommended by the panel.

Psychometric characteristics	Confirmation
Face validity	Confirmed
Content validity	-
Factor analysis	N/A
Construct validity	Confirmed
Discriminant validity	Confirmed
Test-retest	? Variability identified
Internal consistency	N/A
Responsiveness	No data*
Acceptability	Confirmed
Time to complete	Confirmed – Very quick

Table 19. Psychometric properties of the Borg's Scale (Data source: [241]).

*Responsiveness was not confirmed in this methodological SR, that was not specific to COPD exacerbations. However, numerous trials using the scale as an outcome for COPD exacerbations demonstrate treatment response, suggesting good responsiveness.

Recommendation: Breathlessness should be evaluated using the modified Borg's scale. It should be measured at approximately the same time every day. It can be self-completed (**Interim Recommendation with research agenda**).

5.4.6.8. Health-related quality of life.

Methodological SR[113]: Comprehensive health status and quality of life questionnaires were used in 34 (28%) of the included studies. COPD assessment test (CAT) was used in 11 (9%) studies, the Saint George's Respiratory Questionnaire in 8 studies, the Clinical COPD Questionnaire (CCQ) in 6 studies, the Chronic Respiratory Questionnaire (CCQ), the Euroqol-5D and the 36-Item Short Form Survey in 5 studies each (some studies assessed more than one instruments). Other instruments were used less frequently.

Literature review: Our focused literature review revealed two methodological systematic reviews evaluating the performance characteristics of instruments used to evaluate health related quality of life in COPD. Oliveira and Marques only included studies focusing on the measurement properties of instruments used to assess quality of life specifically during pulmonary rehabilitation in patients with acute exacerbations, therefore, it was not informed by adequate data[239]. As a result, the panel discussion was mainly informed by Weldam and colleagues, a systematic review that evaluated the performance characteristics of quality of life instruments for use in COPD[242]. While this methodological systematic review was not specifically focused on COPD exacerbations, it was considered appropriate for informing out work. Further information about CAT and the CCQ were sourced by two other systematic reviews by Gupta et al[243] and Zhou et al[244], focusing on the performance characteristics of these tools, respectively.

Panel discussion summary:

CAT is the most frequently used validated tool for assessing health related quality of life in trials on the management of exacerbations, followed by the Saint George's Respiratory Questionnaire (SGRQ) and the Chronic COPD Questionnaire (CCQ) [113]. A systematic review using the COSMIN methodology for evaluating the measurement properties of 23 instruments used to assess quality of life in COPD recommended the use of CAT, Chronic Respiratory Questionnaire (CRQ), the Saint George's Respiratory Questionnaire (SGRQ) or the

Living with Chronic Obstructive Pulmonary Disease (LCOPD) Questionnaire [242]. While CAT, CRQ and SGRQ have similar measurement properties (summarized in table 20), CAT can be completed within 1-3 minutes while the other tools are more complex and time consuming. Given that CAT is already the most frequently used tool for evaluating health-related quality of life, it was recommended by the panel. A comparison with a baseline estimate of the health-related quality of life prior to the exacerbation would be beneficial, but in larger randomised studies, balance in the baseline characteristics of participants in the study groups can usually be trusted to randomization.

	CAT	CRQ	SGRQ	LCOPD	CCQ
Disease specific	Yes	Yes	Yes	Yes	Yes
Content validity	Excellent +	Excellent +		Excellent +	
Criterion validity					
Structural validity	Excellent +	Excellent +	Excellent +		
Cross-cultural validity		Poor +	Poor ?	Poor ?	Poor ?
Internal consistency	Excellent +	Excellent +	Good +	Good +	Poor +
Reliability	Good +	Good +	Excellent +	Good +	Good +
Measurement error					
Responsiveness	Good +	Good +	Good +		Good +
Ease of completion	1-3 mins	15-25 mins	25 mins	10 mins	1-3 mins

Table 20. Measurement properties of instruments used to assess quality of life in COPD. Summary of the (i) judgements on the quality of the available methodological studies and (ii) their findings around whether the instruments fulfil each criterion. Judgement of the methodological quality was based on the study with the best methodological quality, among those concluding more favourable properties for each of the instruments. Scale: Poor, Fair, Good, Excellent. Findings: Sufficient (+), Indeterminate (?), Insufficient (-). (Data source: [242])

Recommendation: The COPD Assessment Test (CAT) should be used for assessing health related quality of life (Interim Recommendation with research agenda).

5.4.6.9. Activities of daily living (ADL)

Methodological SR[113]: Activities of daily living as an outcome is rarely evaluated in COPD exacerbations trials. More specifically only two of the included studies evaluated this outcome. One used the Activity of Daily Living Dyspnoea Scale (ADL-D scale) and the other the Barthel's index.

Literature review: This focused systematic review revealed three methodological systematic reviews evaluating the performance characteristics of instruments used to evaluate activities of daily living in COPD. Oliveira and Marques only included studies focusing on the measurement properties of instruments used specifically during pulmonary rehabilitation in patients with acute exacerbations, therefore, it was not informed by adequate data[239]. Two systematic reviews by Janaudis-Ferreira[245] and by Liu[246] assessed ADL in COPD. While they were not focused specifically on exacerbations, they were considered appropriate for informing our work.

Panel discussion summary:

This outcome is rarely evaluated in exacerbation trials. ADL are classified as basic and instrumental[247]. Basic ADL are simple activities that are essential for independent life, such as self-care (showering, dressing, or grooming) and basic mobility, while instrumental ADL encapsulate more complex activities, requiring higher functioning, such as preparing meals, home maintenance, shopping, handling finances, and travelling alone[245]. Instrumental ADL are less relevant during an exacerbation, especially during severe exacerbations, while patients are admitted in the hospital and may not be able to undertake such complex activities; but they are pertinent to quantify the overall impact of an exacerbation on a patient's ADL. For this reason, the panel decided to recommend a tool focusing on basic ADL, to be evaluated during the exacerbation and a second tool, assessing both basic and instrumental ADL for longer-term follow-up.

The psychometric properties of instruments used to quantify ADL in patients with COPD have been evaluated in two methodological systematic reviews[245,246]. Five of the identified

instruments focused on basic ADL, of which the Katz Activities of Daily Living Scale, the Barthel index and the motor subscale of the functional independence measure (FIM) were not disease specific and included domains that are less relevant to COPD patients (e.g., control of bladder and bowels). While the Glittre index is disease specific, it focuses on exercise capacity and includes a simple exercise component, which many patients may find challenging to complete during an exacerbation. Finally, the Capacity of Daily Living during the Morning (CDLM) Questionnaire[248] is a simple, disease specific questionnaire, whose measurement properties have been adequately evaluated with favourable findings (table 21). For this reason, the CDLM tool was recommended for quantifying basic ADL during an exacerbation.

The identified methodological reviews revealed eight disease-specific tools assessing a combination of instrumental and basic ADL[245,246]. Responsiveness to change in a patient's clinical condition, a crucial characteristic required for evaluating the impact of exacerbation on ADL, has only been confirmed for three of these tools: the Manchester Respiratory Activities of Daily Living Questionnaire (MRADL)[249], the COPD Activity Rating Scale (CARS)[250], and the 11-items Pulmonary Functional Status Scale (PFSS-11)[251]. While all three tools were considered valid options, the performance characteristics of the MRADL questionnaire were more thoroughly validated compared to CARS, while it was also considered simpler to complete, compared to the PFSS-11 tool (table 21). For promoting consistency, the panel recommends that the MRADL questionnaire be used to evaluate both basic and instrumental ADL at recovery from COPD exacerbations. A comparison with a baseline estimate of the ADL prior to the exacerbation would be beneficial and could potentially be captured retrospectively during recruitment. Recall bias is anticipated to be limited, since in most cases, the duration of the acute event at recruitment would rarely exceed a week and the questions refer to some of the most critical activities of daily living.

	CDLM	Glittre	MRADL	CARS	PFSS-11
Disease specific	YES	YES	YES	YES	YES
Content validity	Good (+)	Poor (?)	Fair (+)	Poor (?)	Fair (?)
Criterion validity					

Structural validity				Fair (+)	Good (+)
Hypothesis testing	Fair (+)	Fair (-)	Good (+)	Fair (+)	Fair (+)
Cross-cultural validity					
Internal consistency	Poor (?)		Good (+)	Fair (+)	Good (+)
Reliability	Fair (+)	Good (+)	Good (+)		Poor (?)
Measurement error					
Responsiveness	Fair (?)	Fair (?)	Fair (+)		Fair (+)
Interpretability	X				
Ease of completion	Yes	Not during AECOPD	X	X	X

Table 21. Measurement properties of instruments used to assess activities of daily living in COPD. Summary of the (i) judgements on the quality of the available methodological studies and (ii) their findings around whether the instruments fulfil each criterion. Judgement of the methodological quality was based on the study with the best methodological quality, among those concluding more favourable properties for each of the instruments. Scale: Poor, Fair, Good, Excellent. Findings: Sufficient (+), Indeterminate (?), Insufficient (-). (Data source: [245,246]).

Recommendation: The Capacity of Daily Living in the Morning Questionnaire (CDLM) should be used for evaluating basic activities of daily living during the exacerbation (**Interim Recommendation with research agenda**).

The Manchester Activities of Daily Living Questionnaire (MRADL) should be used for evaluating basic and instrumental activities of daily living, during recovery (long-term impact of the exacerbation) (**Interim Recommendation with research agenda**).

5.4.6.10. Worsening of symptoms after the initial treatment

Methodological SR[113]: Changes in symptoms was evaluated using symptom scores and scales, quality of life and/or health status instruments in 73 (59%) trials. 41 (33%) of the studies

assessed symptoms progression using simple symptom scores, such as visual analogue scales or Likert scales. 34 (28%) of the studies utilized comprehensive health status and quality of life questionnaires, mostly the COPD assessment test (CAT), the Saint George's Respiratory Symptoms Questionnaire and the Clinical COPD questionnaire (CCQ).

Literature review: Not performed. The discussion for this instrument was informed by the focused systematic reviews conducted for the outcomes (i) Breathlessness and (ii) Quality of Life.

Panel discussion summary: The panel considered that this outcome can be evaluated using the Borg's scale and CAT test, that have already been recommended as measures of breathlessness and health related quality of life, respectively. Moreover, it was highlighted that three PROs have already been recommended for regular assessment during the exacerbation (Borg's scale, CAT test and the CDLM scale). There were concerns that a recommendation for additional daily PROs could limit the feasibility and uptake of the core outcome set.

Recommendation: The modified Borg's scale and the COPD assessment test (CAT) should be used to detect symptoms worsening after the initial treatment (**Interim Recommendation with research agenda**).

5.4.6.11. Disease progression

Methodological SR[113]: The definition of this outcome is available in the panel discussion summary section. Four studies recruited patients at stable clinical disease and could therefore capture their baseline status. However, only two of them attempted to evaluate disease progression by comparing forced expiratory volume in 1 second (FEV_1) before and after the exacerbation. No other studies evaluated disease progression.

Literature review: We did not identify methodological systematic reviews or studies evaluating the measurement properties of instruments used to evaluate disease progression in COPD. Such studies would be challenging and resource intense to conduct, as large study populations and prolonged follow-up would be needed to formally assess instruments for evaluating disease progression. We identified one consensus document attempting to define disease progression as an outcome[252] and several studies aiming to identify variables that

could be used to assess this outcome[253-265]. The consensus document described several instruments for evaluating disease progression: Decline in FEV_1, exercise capacity, or health status, assessment of progression by CT scanning, increase in healthcare utilization and costs. The list of studies aiming to identify variables that could be used to assess disease progression is not exhaustive, since the search strategy aimed to identify methodological studies. These studies assessed the association of numerous laboratory tests and biomarkers as predictors of disease progression. Interestingly, they used decline in FEV_1 and progression by CT scanning as gold-standards for evaluating disease progression.

Panel discussion summary: This outcome was suggested by patients during the qualitative research studies that preceded the Delphi survey. Acute exacerbations are known to accelerate disease progression in patients with COPD[233,266,267]. Several parameters have been used as potential measures of disease progression, including symptom burden, health status, exercise capacity, blood biomarkers, pulmonary function decline, or radiologic progression revealed in computed tomography (CT) of the chest[252,265,267-269].

There was agreement within the panel that evaluation of disease progression as an outcome in exacerbation trials is only meaningful as change from baseline; therefore, a baseline measurement is required. To achieve that, participants would have to be recruited while the disease is stable, in anticipation of developing an exacerbation. However, such a study design requires significantly more resources and prolonged follow-up periods or a patient database with recent measurements taken during periods of clinical stability.

Not surprisingly, disease progression is only rarely evaluated as an outcome in exacerbation trials using objective tests[113]. Change from baseline in pulmonary function was only assessed in two of the trials included in the methodological systematic review, while imaging was not used in any of the studies as an estimate of disease progression. Symptoms and quality of life are evaluated frequently, but not as change from baseline (see respective outcomes).

Change in FEV_1 over time is the most established instrument for evaluating COPD progression in clinical trials and observational studies evaluating the management of disease longitudinally and for this reason, the panel recommends that it should also be used for evaluating the impact of exacerbations on disease progression. Acknowledging the limitations

of this study design, the panel recommends that this outcome only be considered core for long-term studies where baseline values can be captured.

Recommendation: Permanent deterioration in lung function should be used to evaluate the impact of exacerbations on disease progression. Two pulmonary function tests during stable clinical condition are needed: One within 6 months prior to the index exacerbation, and one within 2-6 months afterwards. Change from baseline in forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio should be noted. The number of exacerbations experienced between the two measurements should be noted. Ideally, only the index exacerbation should be included between the two measurements.

Disease progression as a core outcome is only relevant for longer-term studies that recruit participants during stable disease state, in anticipation of an exacerbation (**Interim Recommendation with research agenda**).

5.4.6.12. Future exacerbations

Methodological SR[113]: Future exacerbations were evaluated in 28 (23%) clinical trials. Exacerbations during follow-up were noted and many trials also noted whether these were moderate or severe. Analytical methodology varied (number of patients with at least one exacerbation, mean/median number of exacerbations, time to next exacerbation). However, analytical methodology is beyond the scope of this document.

Literature review: Not performed since this outcome is evaluated consistently.

Panel discussion: It is crucial that treatment success or cure of the index exacerbation should be clearly defined, to allow for the distinction between prolonged symptoms due to a single exacerbation and new exacerbations.

Recommendation: The number of future exacerbations during follow-up should be recorded, noting whether they are moderate or severe (**Interim Recommendation with research agenda**).

5.4.6.13. Future hospital admissions

Methodological SR[113]: Future hospital admissions were evaluated in 14 (11%) clinical trials. All trials evaluating this outcome noted hospitalisations for any reason during follow-up.

Literature review: Not performed since this outcome is evaluated consistently.

Panel discussion summary: Similar to the outcome need for admission for the presenting exacerbation, concerns were raised regarding (i) social admissions and (ii) the variability in the indications for future hospital admission, for example due to hospital-at-home and telemonitoring options. For this reason, it was decided that the outcome "Future hospital admission" should incorporate equivalent intensification of the monitoring or care that may be provided in another setting. Trialists need to prospectively record available hospital-at-home and telemonitoring options and the thresholds for considering "equivalent intensification of the monitoring or care" in their setting. Hospital admissions for social reasons should not be counted.

Recommendation: Future hospital admissions for any medical reason, or equivalent intensification of the monitoring or care that may be provided in other settings, after treatment success is confirmed (**Interim Recommendation with research agenda**).

5.4.6.14. Serious adverse events

Methodological SR[113]: Serious adverse events were captured in 73 (59%) of the included studies. This outcome is consistently captured following the definition and methodology proposed by the International Council for Harmonisation[270].

Literature review: Not performed since this outcome is evaluated consistently.

Panel discussion summary: This outcome is consistently evaluated universally following the definition and methodology proposed by the International Council for Harmonisation.

Recommendation: Following the definition of the International Council for Harmonisation. Serious adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment, that fulfils any of the following: (a) Results in death; (b) Is life threatening; (c) Requires inpatient hospitalisation or prolongation of existing hospitalisation; (d) Results in persistent or significant disability / incapacity; (e) Is a congenital anomaly or birth defect. Suspected unexpected serious adverse reactions (SUSARs) should also be reported. **(Strong recommendation)**.

5.4.6.15. Development of resistant bacteria

Methodological SR[113]: Bacterial resistance was evaluated as part of the composite outcome microbiological response in 16 (13%) RCTs. Other trials reported the presence of new bacterial resistance as an adverse event. None of the included studies reported performing sputum induction and bacterial resistance results are based on spontaneous sputum.

Literature review: Not performed since this outcome is evaluated consistently.

Panel discussion summary: Antimicrobial resistance is often explored as part of a composite microbiological response outcome or as adverse event in trials involving antibiotics as interventions. Bacterial growth and resistance are usually evaluated in spontaneous sputum, while in the absence of sputum, bacterial eradication is presumed and is not further assessed. The panel adopts this approach. Moreover, it was discussed that bacterial resistance may not be a relevant outcome for all interventions, but only for antimicrobials, antimicrobial stewardship strategies, novel immune modifiers, or other interventions that may affect bacterial resistance.

Recommendation: Trials evaluating antimicrobials, antimicrobial stewardship strategies, novel immune modifiers or other interventions that may affect bacterial resistance should evaluate bacterial resistance to the administered antibiotics in spontaneous sputum. As a minimum, resistance should be evaluated at baseline and within a week after treatment completion.

Sputum induction may provide additional information. However, in each study, researchers should consider the balance between the added value compared to the risk, participants discomfort and required resources (**Interim Recommendation with research agenda**).

5.4.6.16. Development of pneumonia

Methodological SR[113]: Development of pneumonia is captured as an adverse event. Adverse events were captured in 73 (59%) of the included studies. Most of these studies described the frequency of the most prevalent adverse events, including pneumonia. Pneumonia was diagnosed by the presence of new consolidation in a chest X-ray or CT chest that was performed in response to consistent clinical signs and symptoms. Not surprisingly, none of the trials described asymptomatic screening for pneumonia during the follow-up.

Literature review: Not performed since this outcome is evaluated consistently.

Panel discussion summary: Development of pneumonia as a safety outcome is often evaluated in exacerbation trials. Methodology is consistent and was adopted by this task force. Pneumonia should be confirmed by the presence of new consolidation in the chest X-ray or other imaging modalities of the chest, in the presence of consistent clinical signs and symptoms. A baseline chest x-ray would be helpful, but it may not be feasible for trials recruiting patients outside the hospital setting.

Recommendation: Pneumonia confirmed by the presence of new consolidation in the chest x-ray or other imaging modalities of the chest, in the presence of consistent clinical signs and symptoms. When possible, chest imaging should be acquired at baseline, to assess for the presence of pneumonia. This may not be possible for trials recruiting patients outside the hospital setting. Follow-up chest imaging should be driven by clinical need. **(Strong recommendation)**.

5.4.6.17. Treatment adherence

Methodological SR[113]: Adherence was evaluated in 7 (6%) of the included trials. Methodology varied according to the intervention.

Literature review: Not performed since assessment of this outcome is treatment specific.

Panel discussion summary: This is an intervention specific outcome. Trialists should describe transparently the methodology used for evaluating treatment adherence.

Recommendation: his outcome was considered intervention specific. Methods for assessing treatment adherence should be clearly reported **(Strong recommendation)**.

5.4.7. Deviations from the study protocol

5.4.7.1. Delphi survey stakeholder groups.

We were planning on including a fourth stakeholder group in the Delphi survey, consisting of regulators, policy makers, guideline methodologists or those working in health technology assessment organizations. However, we did not manage to attract adequate responses in order to consider them independently. This stakeholder group was represented in the consensus meetings.

5.4.7.2. Change in the threshold for excluding outcomes based on the Delphi survey results.

When interpreting the Delphi survey results, we were planning to exclude outcomes that were considered non-critical by at least 50% of the Delphi survey participants from each stakeholder group. However, due to the coronavirus disease 19 (COVID-19) pandemic, we had to switch our planned face-to-face consensus meeting to two virtual meetings. Conducting virtual multi-stakeholder consensus meetings involving lay participants is challenging and time-consuming. Drawing on the experience amassed by the COMET initiative while facilitating similar, virtual consensus meetings during the pandemic, we decided to further consider during the consensus meetings only outcomes that had been rated as critical by at least one stakeholder group. This approach allowed a more thorough and constructive discussion and more confident consensus decisions for the outcomes that were considered. In parallel, reassurance was offered by our methodologist that based on the initiative's prior experience selection of outcomes that have not been prioritized by any stakeholder groups within the Delphi survey for inclusion in the core outcome set is unlikely.

5.5. Discussion

Based on a rigorous methodology, recommended by the COMET initiative, this task force developed a core outcome set for clinical trials assessing pharmacological and non-pharmacological interventions in COPD exacerbations. In addition, it recommended a single optimal measurement instrument for evaluating each core outcome and prioritized methodological research for further optimizing some of these instruments in the future. This work was informed by systematic reviews, qualitative research involving 86 patients from 11 countries globally, an extensive, multi-stakeholder two-stage Delphi survey that was completed by 1,063 participants from 88 countries and two multi-stakeholder consensus meetings with global representation.

A key objective of the panel was to develop a pragmatic core outcome set, that would not require excessive resource commitment and would be feasible to be evaluated in all clinical trials, to promote implementation. While the final core outcome set includes more outcomes

than some of the other sets, most of the selected outcomes are simple to assess, routinely collected, and do not require excessive resources. Moreover, when possible, the panel favoured the selection of simple and pragmatic measurement instruments, taking into consideration the time and resources required for capturing them. Recognizing that disease progression can only be evaluated in trials of a longer-term and resource intensive design, the panel recommended that this outcome should only be assessed in this subgroup of trials. However, the importance of disease progression as an outcome should not be underestimated, and trialists are encouraged to consider appropriate study designs to capture it.

Several of the prioritized outcomes are currently only evaluated infrequently in relevant clinical trials [113]. Moreover, variability was observed in the instruments used to measure many of the core outcomes. These observations confirm that this work was indeed needed and can improve the consistency, quality, and comparability of clinical trials on the management of exacerbations. While the panel was able to recommend one optimal instrument for consistently evaluating each of the core outcomes, most of these were considered interim recommendations, paired with a research agenda. Due to the variability in the instruments used in trials by now, adequate validation and information on the measurement properties of the instruments in the context of exacerbation trials to support strong recommendations was lacking. However, the recommendations of measurement instruments were based on currently available evidence, including data on the frequency that each instrument is used in exacerbation trials, but also previously conducted rigorous systematic reviews evaluating the measurement properties of all recommended patient reported outcomes[241,242,245,246]. Still, trialists are encouraged to embed in their trials methodological research studies that could facilitate further optimization of the measurement instruments. Similar challenges with the selection of outcomes and measurement instruments to be used have been identified in trials assessing the management of other acute respiratory events, including pneumonia, acute bronchitis, and the coronavirus disease 2019 (COVID-19)[234,235,271]. Crosstalk among these fields could be beneficial.

COPD exacerbations represent an acute condition that can be successfully managed. Therefore, the timing of outcomes evaluation is a crucial parameter that should be optimized

and standardized. This is especially so for the precise time when the overall treatment outcome (treatment success) is assessed. However, our meta-epidemiological study did not conclude on the optimal measurement timepoint due to significant clinical and methodological heterogeneity of the included studies[113]. Consequently, further data is needed to inform the optimal timepoint for evaluating treatment success and our panel was not able to produce informed recommendations. Moreover, the duration of follow-up is trial specific, and the panel opted not to recommend a minimum duration of follow-up. However, to promote consistency and comparability, it is suggested that longer-term outcomes should be evaluated at three and six months from recruitment if the selected follow-up duration includes one or both timepoints. Moreover, it is suggested that the outcomes should be evaluated at specific timepoints, rather than at discharge or at symptom relief, since such "mobile" timepoints might introduce bias.

5.5.1. Comparison with other outcome prioritization initiatives

While this is the first formal core outcome set for COPD exacerbations trials, COPD exacerbations outcomes have been prioritized by two other initiatives. First, COPD exacerbations outcomes have also been assessed and prioritized by the eo-Drive trial group (Eosinophil-driven corticotherapy for patients hospitalized for COPD Exacerbations, NCT04234360). Consensus was developed through a Delphi survey involving 21 French clinical academics with expertise in COPD exacerbation trials[272]. In general, the outcomes that were selected by that group were consistent with our core outcome set. Our panel included additional safety outcomes (serious adverse events and development of bacterial resistance), which may have been considered of less importance for the eo-Drive trial as the safety profile of systemic corticosteroids has been thoroughly evaluated in previous studies. Moreover, disease progression, activities of daily living and quality of life were not prioritized for evaluation in the eo-Drive study either. The lack of validated instruments for assessing some of these outcomes in the context of an exacerbation trial may have discouraged the eo-Drive group. Moreover, the eo-Drive trial will recruit participants upon presentation with an exacerbation; therefore, assessment of disease progression is not possible. On the other hand, the multi-stakeholder involvement and rigorous methodological research may have

allowed our panel to identify additional outcomes that may be more relevant to patients. For example, ADL were not captured in the longlist of outcomes assessed by the French group.

While this core outcome set and measurement instruments were developed for clinical trials on the management of COPD exacerbations, it would be important to be captured in relevant systematic reviews, meta-analyses and, also, observational studies. Their adoption in observational studies would enhance the comparability with trial results and interpretability of the complete body of available evidence. Finally, well-conducted observational studies could facilitate the validation and optimization of the measurement instruments recommended for each outcome. The Collaboration In COPD ExaceRbatiOns (CICERO) ERS Clinical Research Collaboration has recently developed standards for clinical assessment, management and follow-up of acute hospitalised exacerbations of COPD[273]. These also include research recommendations, about outcomes that should be measured in relevant observational studies[273]. These largely overlap with the core outcomes that were prioritized by this panel. The CICERO panel also recommended the evaluation of new or worsening comorbidities following the index exacerbation event (such as diabetes or osteoporosis) and increase in short-acting inhaled therapy. On the other hand, activities of daily living, disease progression, development of resistant bacteria and development of pneumonia were not considered by that initiative. There was agreement between the two groups in all other outcomes. These differences may result from the different scope of the two projects as the COS-AECOPD ERS Task Force developed a core outcome set for clinical trials evaluating the management of COPD exacerbations, while CICERO developed standards for clinical practice evaluating the management of severe (hospitalised) COPD exacerbations, that were also recommended to be captured in clinical research studies.

Moreover, CICERO did not recommend measurement instruments; therefore, adopting recommendations from this task force, could improve comparability across the spectrum of clinical research on COPD exacerbations. However, CICERO did recommend the use of mMRC dyspnoea index and COPD assessment test for assessing symptoms during a hospitalized exacerbation. Our panel recommended the Borg's scale instead. mMRC was not considered sensitive in this setting, since most patients, especially those with severe exacerbations,

would cluster in Grade 4 ("Too breathless to leave the house or breathless when dressing or undressing").

Overall, while this core outcome set is broader than the outputs of the previous initiatives, most of the previously prioritized outcomes are included in our core outcome set and that could further promote consistency.

5.5.2. Other challenges in the design of COPD exacerbations RCTs.

Selection and measurement of outcomes are not the only challenges researchers face when designing clinical research on the management of COPD exacerbations. The diagnostic, classification and severity grading criteria of exacerbations remain ill-defined, subjective, and suboptimal, revealing an urgent unaddressed research need [127,148,229]. More specifically, it is increasingly understood that exacerbations of different aetiology or characteristics (e.g., those caused by bacterial or viral infections, triggered by eosinophilic inflammation, or associated with type 2 respiratory failure), represent distinct clinical entities with different outcomes, that require personalized management [7,12,31,75]. These distinctions should be made both in clinical practice and trials, however, adequately validated diagnostic tests are still lacking. Extensive, well-designed studies and international collaboration are needed to address these issues.

5.5.3. Strengths and limitations

A potential limitation of this work is that it did not fully follow the methodology proposed by the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) recommendations for selecting the recommended outcome measurement instruments. COSMIN recommends de novo conduct of methodological systematic reviews to evaluate the measurement properties of all available instruments that could be used to assess an outcome and is particularly relevant for patient reported outcomes. While it was not feasible to complete these as part of an ERS Task Force, we identified relevant high-quality methodological systematic reviews, evaluating the available instruments for all patient reported outcomes that were included in the core outcome set, which were used to inform our recommendations. Despite our best effort, the Delphi survey was somewhat limited by

the lack of respondents from low-income countries. Lack of access or engagement represent a recognized problem, limiting the participation of people from low-income countries to such online surveys [274]. Given the wide geographic distribution and multi-stakeholder involvement of our sample, and the similar responses across low-/lower-middle, upper-middle, and high-income countries, we do not believe that significantly limits the generalizability of our findings. The prospectively published, transparent protocol represent a major strength of this study. Unfortunately, we had to deviate from the protocol on two occasions. While we were planning on including a fourth stakeholder group in the Delphi survey, consisting of regulators, policymakers, guideline methodologists or those working in health technology assessment organizations, we did not manage to attract adequate responses to consider this group independently. However, this stakeholder group was represented in the consensus meetings. In addition, we had to change the threshold for excluding outcomes based on the results of the Delphi survey. Initially, we had planned on excluding outcomes that were considered non-critical by at least 50% of the Delphi survey participants from each stakeholder group. However, due to the coronavirus disease 19 (COVID-19) pandemic, we had to switch our planned face-to-face consensus meeting to two virtual meetings. Conducting virtual multi-stakeholder consensus meetings involving lay participants is challenging and time-consuming. Drawing on the experience amassed by the COMET initiative while facilitating similar, virtual consensus meetings during the pandemic, we decided to further consider during the consensus meetings only outcomes that had been rated as critical by at least one stakeholder group. This approach allowed a more thorough and constructive discussion and more confident consensus decisions for the outcomes that were considered. Moreover, none of the consensus meeting participants suggested that any of the other outcomes should have been considered.

5.5.4. Dissemination strategy

Uptake in future, relevant clinical trials is a crucial challenge for core outcome sets and for this reason, we have developed an implementation strategy. Firstly, we attempted to engage in the development of this core set all relevant stakeholders globally, through the Delphi survey and the consensus meetings. Moreover, the resulting set is currently endorsed by four international societies (European Respiratory Society, American Thoracic Society, Latino-

American Thoracic Society and Pan-African Thoracic Society), adopted by the DECODE-NET (DisEntangling Chronic Obstructive pulmonary Disease Exacerbations – an international clinical trials NETwork) [141], and registered with the COMET Initiative. We intend to disseminate this document to clinical researchers with similar research interests and sponsors of COPD exacerbations trials, that completed the Delphi survey, or were identified through our methodological systematic reviews. The document will also be disseminated to relevant professional organizations, health technology assessment and guideline development groups, policymakers, and regulators. Finally, a plain English description of this document will be shared with patient organizations and the lay participants of the Delphi survey and consensus group meetings.

5.6. Conclusion

In summary, this task force developed a core outcome set for trials in acute exacerbations of COPD and recommended an optimal instrument for measuring each of the core outcomes, aiming to improve the consistency, quality, and comparability of future relevant clinical trials.

6. Prevalence of respiratory viruses in stable chronic obstructive pulmonary disease (COPD) and exacerbations: A systematic review and meta-analysis.

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***Status of this work:** This is a draft paper, that has not been submitted for publication yet.*

***Author contribution:** Study conception: AGM, AB, JV. Study design: AGM, with input from AB and JV. Methodological expertise: AGM, RF. Study screening: AGM, AMK, GSA, RF, PK, MJM. Data extraction: AGM, AMK, GSA, VCG, RF. Analysis: AGM. Manuscript preparation: AGM, with input from JV. Contribution of additional, unpublished data from original epidemiological studies: MA, JB, SF, TJ. Critical revision of the manuscript for intellectual content: All authors.*

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6.1. Abstract

Introduction: Respiratory viruses represent a prevalent, burdensome, preventable, and treatable trait both in stable COPD and disease exacerbations. Yet, they are poorly addressed in clinical practice. This meta-analysis aimed to quantify the prevalence of respiratory viruses in COPD.

Methods: Based on a prospectively registered protocol, we searched three online databases for studies of any design, evaluating the prevalence of respiratory viruses in unselected patients with COPD during stable disease state or exacerbations, using molecular diagnostic techniques. Methodological quality was appraised using a prevalence study specific tool. We performed random-effects meta-analysis using the inverse variance method and the Freeman-Tukey transformation.

Results: We found 93 eligible studies of which 21 assessed the prevalence of respiratory viruses in 2963 patients with stable COPD and 90 focused on exacerbations, totalling 18956 acute events. At any given time, 10.2% [95% confidence intervals: 6.9%-14.0%] of unselected patients with stable COPD test positive for viruses. Rhinovirus (3.7%), respiratory syncytial virus (RSV-3.7%) and influenza (1.4%) are most frequently identified. Viruses are detected in 36.6% [33.6%-39.6%] of all exacerbations, with a numerically higher prevalence in moderate exacerbations (44% versus 36%). The most prevalent viruses in exacerbations are rhinovirus (13.0%), influenza (8.0%) and RSV (5.6%). Lower respiratory tract samples appear more sensitive to viral infection during exacerbations, as they yield a significantly higher prevalence (39.6% versus 32.6%).

Conclusion: This rigorous meta-analysis presents the best available information on the prevalence of respiratory viruses in COPD and is anticipated to inform diagnostic, therapeutic and public health interventions.

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6.2. Introduction

Chronic obstructive pulmonary disease (COPD), a leading cause of death and disability globally[1,134], is characterised by chronic debilitating respiratory symptoms and acute exacerbations that drive the adverse disease outcomes[84]. Respiratory viruses represent a prevalent, burdensome, preventable, and treatable trait, both in stable COPD and disease exacerbations[11,15,275]. It is estimated that viruses are detected in the respiratory tract in approximately 10% of all patients with COPD at any given time[76-78] and in 30-50% of all exacerbations[15,31,74-76]. The presence of respiratory viruses in stable COPD is linked with an increased frequency of exacerbations, while in exacerbations, it is predictive of prolonged and more severe symptoms[78]. Not surprisingly, exacerbations characterised by concomitant viral and bacterial infections are associated with the highest symptomatic burden and mortality[33].

As a result, the prevention and treatment of viral infections in COPD could significantly improve patient outcomes. Indeed, influenza vaccination has been proved to decrease the frequency of exacerbations[82,83] and is currently recommended for all patients suffering from COPD[84]. However, there are still significant, unaddressed needs. While the effectiveness of neuraminidase inhibitors for treating influenza is well-established, exacerbations triggered by influenza are under-detected and undertreated in clinical practice[86]. Moreover, commercially available antiviral treatments against the respiratory syncytial virus (RSV), that are of limited benefit to people without underlying chronic respiratory conditions[87], might confer significant benefits to patients with underlying COPD, who experience more burdensome viral infections. The development of personalised diagnostic and therapeutic interventions to target viruses as a treatable trait in COPD represent a pertinent unaddressed clinical need.

Rigorous evaluation of viral epidemiology in COPD could facilitate the prioritisation of targets and the development of precision medicine interventions. However, there is an astonishing imbalance between the ample published studies evaluating the prevalence of respiratory viral prevalence both in stable COPD and exacerbations, which are mostly based on relatively small study cohorts, and our overall limited certainty around the prevalence of various viruses.

Therefore, this systematic review and meta-analysis aimed at quantifying the prevalence of respiratory viruses, detected using molecular techniques, in the respiratory tract of

unselected patients with stable COPD or exacerbations. Moreover, by means of meta-regression analysis it explores factors impacting this prevalence.

6.3. Methods

For conducting and reporting this meta-analysis, we followed standard methodology recommended by the Cochrane Collaboration[276], and the Preferred Reporting Items for Systematic Reviews (PRISMA) statement[277]. The study protocol was prospectively registered with the International Prospective Register for Systematic Reviews (PROSPERO, ID: CRD42019147658) and published[10].

We included studies of any design evaluating the prevalence of one or more viruses in the respiratory tract of unselected patients with COPD during stable disease state or exacerbation, using molecular techniques. Studies based on enriched populations, such as retrospective studies assessing viral samples requested based on clinical suspicion were excluded. We also excluded studies conducted during the coronavirus disease 2019 (COVID-19) pandemic to avoid confounding, as changes in the daily lives of patients with COPD, such as shielding, and use of face masks have significantly affected their clinical characteristics and viral exposures[278]. The prevalence of respiratory viruses in patients with pneumonia was beyond the scope of this manuscript. However, many of the exacerbations' cohorts did not exclude patients with pneumonia. We did not exclude these studies, but, when possible, we sourced data from the subgroup of participants that did not have radiological infiltrates.

A sensitive search strategy that is available in Appendix 8.4.1, was implemented to identify relevant studies in three electronic databases (Medline/PubMed, EMBASE and the Cochrane CENTRAL), as well as the WHO International Clinical Trials Registry Platform. All databases were searched from inception to 6 October 2021, without language restrictions. The reference lists of all included studies were also screened. Eligibility of all studies that were identified by the searches was evaluated by two authors independently at a title and abstract level followed by a full-text assessment of all potentially eligible studies. Relevant data were extracted in a structured and pilot tested data form. Details about the main characteristics of the included studies and their participants were extracted by one and cross-checked by a

second author, while outcome data were extracted by two authors independently. To avoid publication bias, we searched for all viruses that were screened in each included study (e.g., all viruses that were tested by the assay that was used), not only those that were reported in the results, as viruses that were not detected in any study participants were often omitted.

Methodological quality was assessed by two authors independently using a risk of bias tool for prevalence studies that was developed by Hoy and colleagues[279]. This tool allows for rigorous assessment of the representativeness of the study sample, through the evaluation of the eligibility criteria and baseline characteristics of study participants of each included study, as well as the methodology used to select potential participants for inclusion (e.g., random selection or census) and the likelihood of non-response bias. Data collection process, case-definitions, outcome measurement instruments and the appropriateness of the numerators and denominators that were used in the final prevalence estimates are also scrutinised.

Throughout study selection, data abstraction, and critical appraisal of the included studies, disagreement between the investigators was resolved by discussion or, when necessary, adjudication by a third investigator. When required, additional data were requested from the original study investigators by email.

We only accepted as stable samples those that were taken at least one month after the last exacerbation. Moreover, for longitudinal studies assessing the prevalence of respiratory viruses in stable COPD, we preferably accepted one sample per season (every three months). The only exception was that we included data from a well conducted cohort study by Falsey and colleagues that sampled patients with stable COPD every two months but clarified that none of the participants tested positive for the same virus in sequential visits[280]. For analysing exacerbations, we considered exacerbation as the unit of analysis, and therefore accepted the inclusion of more than one event per participant.

For the purposes of this review, we defined as severe those exacerbations leading to hospitalisation; as moderate those requiring systemic treatment with antibiotics or systemic corticosteroids, or an emergency visit; and as mild, exacerbations not requiring any systemic treatments or unscheduled healthcare visits. The outcome ‘prevalence of any virus’ was

defined as the proportion of patients that tested positive for at least one virus and was only considered valid if the study participants were screened at least for the three most prevalent viruses: rhinovirus, influenza, and respiratory syncytial virus (RSV).

Our main analyses evaluated the prevalence of viral positivity (any virus) and of the various respiratory viruses in (a) stable disease state, (b) exacerbations of any severity, (c) moderate exacerbations, and (d) severe exacerbations. Study heterogeneity was evaluated using the I^2 statistic. Substantial heterogeneity (I^2 >50%) is reported and explored by prespecified meta-regression analyses. In anticipation of significant clinical and methodological heterogeneity, meta-analyses of proportions were conducted using the random-effects model, the inverse variance method, and the Freeman-Tukey (double arcsine) transformation[281,282]. For assessing publication bias, we used funnel plots with sample size as the measure of accuracy, which are more appropriate for meta-analyses of proportions[283].

Several sensitivity analyses were conducted to explore for potential confounding in our study design. First, we excluded studies of exacerbations that did not exclude patients with concomitant pneumonia. Second, we analysed separately studies using upper versus lower respiratory tract samples to test for respiratory viruses. Third, we only accepted data from a single stable and/or a single exacerbation visit per participant. Fourth, we only included studies of low risk of bias. Finally, we repeated all meta-analyses using the logit instead of the Freeman-Tukey transformation.

Finally, heterogeneity of the primary meta-analyses was investigated by means of several meta-regression analyses. In univariate meta-regression analyses we explored the impact of several factors on the prevalence of viruses: spirometric disease severity (forced expiratory volume in one second, FEV_1 % predicted), use of inhaled corticosteroids, proportion of patients that were sampled during the influenza season (between October and May), type of sample tested (upper or lower respiratory tract sample), influenza vaccination during the preceding year, age, gender, use of maintenance systemic corticosteroids, the last year of sample collection. The significant missingness across the potential effect modifiers that were tested did not allow us to conduct stepwise meta-regression. However, we tested in

multivariate meta-regression analyses the first five of the previously described factors, that were deemed most clinically relevant by the study team.

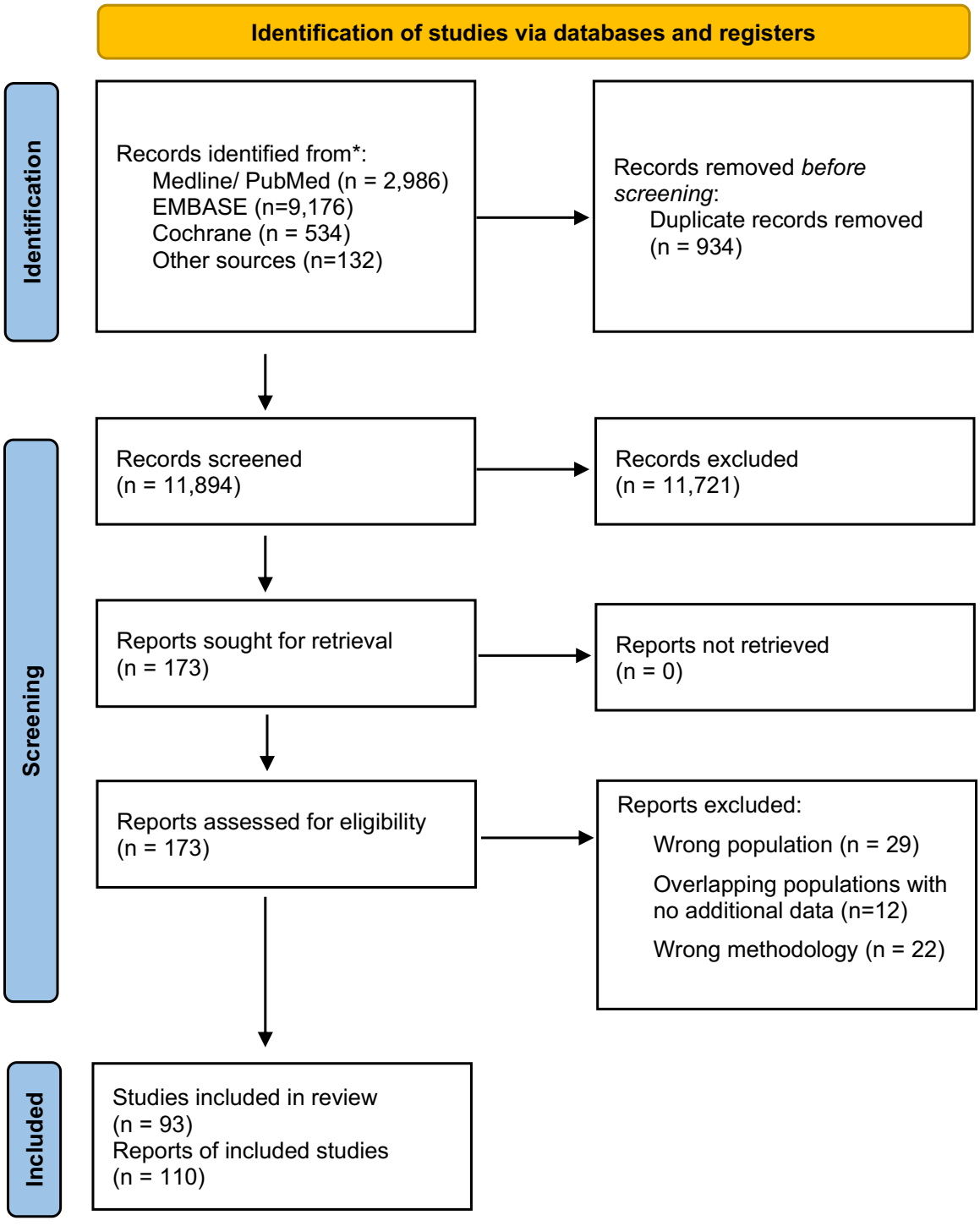

Figure 15. *PRISMA Flowchart summarising the study selection process.*

6.4. Results

Among 11894 unique titles that were screened, we identified 93 eligible studies. Detailed description of the selection process is summarised in a PRISMA flowchart (figure 15). The prevalence of respiratory viruses during stable disease state was evaluated in 31 studies involving 2963 patients [31,75,77,78,280,284-309] and during exacerbations in 90 studies totalling 18956 acute events[29-31,33,43,44,47,75,77,78,81,280,286-363]. Most of the included studies were observational, while four sourced data from populations included in randomised controlled trials. The main characteristics of the included studies are summarized in tables 22 and 23. Data collection was prospective in most included studies with two notable exceptions of retrospective studies that were conducted in centres that consistently screen for respiratory viruses all patients presenting with a COPD exacerbation as confirmed in the manuscript[81], or by the lead investigator[354].

All but two studies were deemed of an overall low or moderate risk of bias (tables 24, 25). However, most studies did not adequately report on the measures taken to ensure the study sample was random and on non-response bias, thus limiting our confidence on the representativeness of their samples. The definition of COPD, exacerbations, as well as the baseline characteristics of the participants were loosely described in studies evaluating broader study populations (e.g., lower respiratory tract infections), where subgroup data of patients with COPD were available. Several studies also introduced potential bias by assessing participants at multiple acute episodes and/or multiple stable disease timepoints.

The prevalence of respiratory viruses (any virus) among unselected patients with COPD during stable disease state was estimated to be 10.18% with 95% confidence intervals of [6.92%, 13.99%] based on data from 17 studies and 3380 participants. During exacerbations, our meta-analysis revealed a significantly higher prevalence of 36.57% [33.58%, 39.60%], based on 60 studies totalling 8442 participants. Viruses were detected more frequently in moderate (44.07% [37.66%, 50.59%]) compared to severe (36.21% [31.12%, 41.46%]) exacerbations, although between group difference did not reach statistical significance (p=0.07).

The most frequently identified viruses in stable disease state were rhinovirus (3.73% [1.71%, 6.50%]), respiratory syncytial virus (3.67% [1.26%, 7.27%]) and influenza (1.43% [0.50%,

2.83%]). In exacerbations, rhinovirus was also the most prevalent virus (13.04% [9.95%, 16.48%]), followed by influenza (7.96% [4.8%, 11.83%]) and respiratory syncytial virus (5.29% [3.92%, 6.87%]). The overall estimates of the prevalence of all respiratory viruses during stable disease state and exacerbations are summarized in figure 16. Forest plots of the meta-analyses of the most prevalent viruses are available in Appendices 8.4.2, 8.4.3.

Significant differences were observed in the prevalence of respiratory viruses when evaluated in upper respiratory tract samples, such as nasopharyngeal swabs or aspirates, compared to lower respiratory tract samples, such as sputum or bronchoalveolar lavage. More specifically, the prevalence of any virus in COPD exacerbations was significantly higher when assessed using lower (39.64% [34.81%, 44.58%]), compared to upper respiratory tract samples (32.61% [28.56%, 36.8%], between group difference = 0.04). This difference is driven by a significantly higher detection of rhinovirus in lower respiratory tract samples (18.42% [15.09%, 21.99%] versus 9.02% [6.98%, 11.29%], between group difference: $p<0.001$). A similar observation was noted for adenovirus (2.05% versus 0.57%, between group difference: $p=0.004$). These findings were not driven by the severity of exacerbations across the included studies. The prevalence of respiratory viruses in stable COPD did not significantly differ between studies evaluating upper or lower respiratory tract samples. However, numerically, the prevalence of respiratory viruses was higher in upper respiratory samples (11.58% [5.04%, 20.35%], versus 6.33% [2.88%, 11.01%]). The prevalence of rhinovirus, influenza, coronavirus and metapneumovirus were numerically higher in upper respiratory samples, while the opposite was observed for respiratory syncytial virus (Appendix 8.4.4).

The remaining sensitivity analyses did not significantly alter the findings of our meta-analysis. Since two factors (lower respiratory samples and moderate severity of exacerbations) were associated with increased viral prevalence in the context of exacerbations, we explored whether any of these observations was secondary and explained by the other correlation. However, this hypothesis was refuted.

Most of our analyses were limited by substantial heterogeneity across the included studies. This heterogeneity was not resolved in univariate meta-regression analyses accounting for various characteristics of the included studies (see methods). The exclusion of studies that

accepted patients with concomitant pneumonia did not resolve the heterogeneity in meta-analyses evaluating exacerbations either. In our exploratory multivariate meta-regression analyses, assessing the detection of any virus in stable COPD, heterogeneity was explained by differences in spirometric severity and the use of inhaled corticosteroids. The heterogeneity of the assessment of the prevalence of any respiratory virus in exacerbations was resolved after accounting for spirometric severity, influenza vaccination during the preceding year, use of inhaled corticosteroids and the type of sample tested (upper versus lower respiratory tract). However, these findings were not corroborated in multivariate meta-regression analyses of the prevalence of individual viruses. Interestingly, in the subgroup analyses of upper versus lower respiratory samples, heterogeneity was resolved in most meta-analyses by accounting for FEV_1, use of inhaled corticosteroids and/or influenza vaccination during the preceding year.

The funnel plots of all meta-analyses were inspected for publication bias. The funnel plots of influenza, influenza A, and influenza B prevalence in exacerbations were notable for the asymmetry caused by the largest cohort[344] that reported a significantly higher prevalence of influenza compared to the remaining studies. Data for this study were sourced from an extensive surveillance cohort in Canada that recruited pyrexic patients with severe (hospitalized) exacerbations. Influenza was significantly more prevalent in this group of patients. As a result of the use of random effect models, the exclusion of this study did not significantly impact the overall prevalence estimates for influenza (7.47% [6.02%, 8.94%], influenza A (7.70% [5.29%, 10.51%]), or influenza B (1.84% [0.12%, 2.66%]). All other funnel plots were symmetrical and therefore, all our meta-analyses were at low risk of publication bias.

Study ID	Continent	N	Age	Gender (Male%)	Smoking history (Ex / Current / Never)	Sampled between October-May (%)	FEV1 (% pred)	Exacerbations Frequency	Influenza Vaccination	ICS (%)	OCS (%)
Bafadhel 2011	Europe	145	69 (R: 43-88)	69.7%	69%/ 29%/ 2.1%		52 (2)	3 (0.2)		86.0%	6.0%
Borg 2003	Europe	46	69 (R: 43-81)								
Bouquet 2020	Europe & North America	133	65.5 (R:50-93)	65.0%	61.3%/ 28.3%/ 10.4%	100%	38 (R: 13-85)	1.4 (0-12.1)			
Contoli 2017	Europe	60	70.6 (0.9)	80.0%		52.90%	63.9 (0.9)	0.91 (0.09)		50.0%	0%
De Serres 2009	North America	25	~73			100%					
Du 2017	Asia	50	75 (10)	66.0%			57 (11)				
Falsey 2006	North America	112	72 (10)	49.0%	88.4%/ 11.6%/ 0%		44 (19)		97.0%	67.0%	20.0%
Gandhi 2012	North America	127	72 (10)	49.0%	88.4%/ 11.6%/ 0%		44 (19)		97.0%	67.0%	20.0%
Hilzendeger 2016	Europe	51	62 (10)	64.7%	51%/ 49%/ 0%		59 (20)			65.0%	12.0%
Hosseini 2015	Asia	96	63 (9.1)	55.2%		~78%	49.4 (24.3)				
Ilvan 2013	Asia	21	66.0 (8.4)	100.0%	81%/ 19%/ 0%		55.6 (21.6)			33.3%	

Johnston 2013	North America	80	67.4 (R: 44-89)	49.4%	69.6%/ 30.4%/ 0%		48.2 (7.7)			81.0%	2.5%
Kherad 2010	Europe	86	71 (9)	64.0%	NR / 38%/ NR	~85%		1.1 (1.4)	74.4%		
Ko 2019	Asia	80	73.2 (7.4)	97.5%	NR / 22.5%/ NR		46.7 (17.6)		41.2%	85.0%	
Kokturk 2015	Asia	18	66.9 (9.47)	96.3%	59.3%/ 37%/ 3.7%		43.8 (16.9)			73.1%	0.0%
Liao 2014	Asia	525	65.8 (7.3)	86.5%							
Lopez Caro 2019	Europe	55	73.3 (10.3)	76.4%	76.4%/ 16.4%/ 7.3%	NR	53.7 (14.4)	1.75 (1.66)			
McManus 2008	Europe	68	66.3(9.4)	44.1%	44.1%/ 55.9%/ 0%		48 (22)			77.9%	8.8%
Papakonstantinou 2015	Europe	53	67.9 (R: 48-81)	60.3%	71.7%/ 28.3%/ 0%		50.3 (21.5)			76.0%	34.0%
Papi 2006	Europe	64	70.6 (2.5)	87.5%	95.3%/ 4.7%/ 0%		49.5 (2.3)			97.0%	
Ringshausen 2009a	Europe	66	65 (11)	83.3%	59.1%/ 31.8%/ 9.1%		42.9 (R: 19.4-77.3)			69.7%	63.6%
Ringshausen 2009b	Europe	68	65.3 (10.8)	53.8%	60.3%/ 30.9%/ 8.3%		43.4 (R: 19.4-77.3)			70.6%	61.8%
Rohde 2003	Europe	42	67.5 (R: 45–86)	90.5%	54.8%/ 28.6%/ 16.7%		55.5 (R: 18.1-74.7)	1 (0–8)		55.0%	54.8%

Rohde 2005	Europe	65	66 (R: 45-81)				44.2 (R: 22.0-93.7)				
Rohde 2008	Europe	20	69 (R: 52-77)	90.0%	50%/ 25%/ 25%		57 (R: 22.7-74.7)	0 (0-5)			
Seemungal 2001	Europe	83	66.6 (7.1)	71.1%	NR / 33.7%/ NR		19.8 (0.51)		74.0%	97.6%	
Stolz 2019	Europe	450	66.9 (9.4)	67.4%	64.9%/ 35.1%/ 0%		54.5 (16.9)	1.13 ± 0.84		72.4%	
Vanspauwen 2012	Europe	109	66 (R: 42-85)	52.3%	71.6%/ 28.4%/ 0%			200.0%			
Wilkinson 2006b	Europe	74	67.4 (IQR: 62.2-71.4)	60.8%		~85%	39.2 (IQR: 29.6-57.8)	2.51 (IQR: 1.28-3.83)	100.0%	100.0%	
Xie 2021	Asia	91	71 (8)	94.5%	NR / 36.3%/ NR					79.1%	

Table 22. Baseline characteristics of the studies assessing the prevalence of respiratory viruses in Stable COPD

Study ID	Continent	N	Age	Gender (Male%)	Smoking history (Ex / Current / Never)	Sampled between October-May (%)	FEV1 (% pred)	Exacerbations Severity (Inclusion)	Pneumonia Excluded	Influenza Vaccination (%)	ICS (%)	OCS (%)
Aaron 2001	North America	14	71.6 (7.7)	78.6%	100% / 0% / 0%		39 (12.7)		Yes			
Almansa 2011	Europe	40	73.1 (9.1)	95.0%	NR / 20% / NR	100%		Severe	Unclear			
Almansa 2012	Europe	57	71.1 (10.0)	82.5%		~85%		Severe	No			
Alotaibi 2019	North America	72	65.8 (11.5)	63.9%	NR / 61.1 % / NR		46.6 (16.7)	Severe	Unclear		70.8%	
Aronen 2016	Europe	67	80.1 (62)	77.6%	61.3% / 30.6% / 8.1%			Severe	Yes	45.5%	59%	48%
Bafadhel 2011	Europe	182	69 (R: 43-88)	69.7%	69% / 29% / 2.1%		52 (2)	Any	Yes		86%	6%
Beckham 2005	North America	194	63.1 (9.2)	49.0%	49% / 35% / 16%			Moderate, Severe	Unclear	73%		
Belongia 2018	North America	481				100%		Moderate, Severe	No			
Boixeda 2012	Europe	132	72.9 (8.6)	97.7%	76.5% / 23.5% / 0%	~80%	41.3 (15)	Severe	Yes	68.9%		

Borg 2003	Europe	79	69 (R: 43-81)					Severe	Yes			
Bouquet 2020	Europe & North America	296	65.5 (R: 50-93)	65.0%	61.3% / 28.3% / 10.4%		38 (R: 13-85)	Moderate, Severe	Unclear			
Camargo 2008	North America	76	72 (9)	68.4%	71.1% / 28.9% / 0%	100%		Moderate, Severe	Yes	85%	47.4%	30.3%
Cameron 2006	Oceania	107	68 (10.9)	49 %	NR / 50% / NR	~80%		Critical	No			
Chang 2015	Asia	72	75.2 (7.9)	100.0%	54.2% / 45.8% / 0%		40.1 (15.7)	Moderate, Severe	Yes		80.6%	19.4%
Clark 2014	Europe	304	70 (IQR: 62-77)	46.0%	NR / 35.0% / NR	100%		Severe	Yes	72%		
Contoli 2017	Europe	50	70.6 (0.9)	80.0%		52.9%	63.9 (0.9)	Moderate	Yes		44%	0%
Dai 2015	Asia	81	71 (10)	75.0%	NR. / 12% / NR		54 (26.8)	Severe	Unclear			
Daubin 2008	Europe	39	62 (15)	67.0%	NR / 28.2% / NR			Critical	Yes		59%	
De Serres 2009	North America	108	~73	54.6%	79.6% / 17.6% / 2.8%	100%		Moderate, Severe	Unclear	82.4%	66.7%	30.6%
Dimopoulos 2015	Europe	247	69.3 (IQR 9.5)	77.3%		~70.5%	44.6 (16.7)	Severe	No	45.3%	63.2%	

Djamin 2015	Europe	136						Moderate, Severe	Unclear	84.1%		
Drago 2009	Europe	30	R: 55-85	66.7%	40.0% / 60% / 0%			Moderate, Severe	Yes		66.7%	
Du 2017	Asia	80	75 (8)	71.3%			56 (11)	Severe	Unclear			
Falsey 2006	North America	92	72 (10)	49 %	88.4% / 11.6% / 0%		44 (19)	Moderate, Severe	No	97.0%	67%	20%
Falsey 2012	North America	184	66.7 (12.6)	52.7%	NR / NR / 0%	100%		Severe	Yes	71.7%	58.2%	19.6%
Feng 2021	Asia	347	48.5 (7.5)	55.6 %	26.8% / 40.9% / 32.3%			Severe	Unclear			
Gallego 2016	Europe	265	69.5 (8.2)		89% / 11% / 0%	~77.4%	34 (11)	Moderate, Severe	Yes	89.0%	100%	0%
Gandhi 2012	North America	102	72 (10)	49 %	88.4% / 11.6% / 0%		44 (19)	Moderate, Severe	Yes	97.0%	67%	20%
Gorse 2009	North America	715	67.7 (7.9)	92.9%	NR / 32.6% / NR	100%	41.2 (15.5)	Moderate, Severe	Unclear	100.0%		18.3%
Hamelin 2005	North America	111		N/A				Moderate, Severe	No			
He 2017	Asia	7		60.7%				Critical	Yes			

Hosseini 2015	Asia	170	66 (8.9)	54.7%		~76%	40 (22.7)	Moderate, Severe	Unclear			
Huerta 2015	Europe	310	70.7 (8.7)	62.0%	68% / 31% / 0%	N/A	50.1 (16.5)	Any	No	100.0%		
Hutchinson 2009	Oceania	148	72	63.0%	78% / 22% / 0%			Any	Unclear	100.0%		
Ilvan 2013	Asia	45	64.3 (9.0)	84.4%	68.9% / 24.4% / 6.7%		43.4 (11.2)	Moderate, Severe	Unclear		53.3%	
Jahan 2021	Asia	74	65.5 (10.4)	87.8%				Moderate, Severe	Yes			
Jiang 2015	Asia	255							No			
Johnston 2010	North America	110	63.2 (IQR: 13.7)	42.2%	67.7% / 32.3% / 0%	100%	61.6 (15.4)	Any	Unclear		95%	12.7%
Johnston 2013	North America	191	67.4 (R: 44-89)	49.4%	69.6% / 30.4% / 0%	~78%	48.2 (7.7)	Any	Unclear		81.0%	2.5%
Jubinville 2018	North America	8	66.2 (4.2)	33.3%	22.2% / 77.8% / 0%		52.0 (19.3)	Moderate	Yes			
Kan-O 2021	Asia	44	76.6 (7.2)	84.1%	NR / 27.3% / NR			Moderate	Yes		52.3%	4.5%
Kawamatawong 2017	Asia	62	79.2 (5)	88.7%		N/A	37.0 (12.5)	Moderate, Severe	Unclear	3.2%	83.8%	
Kherad 2010	Europe	86	71 (9)	64 %	NR / 38% / NR	~70%		Moderate, Severe	Yes	74.4%		

Kim 2016	Asia	241	71.1 (9.5)	83.4%	NR / NR / 13.7%	68%	47.6 (20.3)	Severe or critical	Yes			14%
Ko 2007	Asia	262	75.7 (7.7)	81.6%	82.1% / 16.8% / 1%	~73%	39.6 (18.9)	Severe	Yes	40.3%	52%	
Ko 2019	Asia	402	77.4 (8.6)	91.3%	NR / 16.9% / NR		45.8 (20.5)	Severe	Unclear	37.3%	78.9%	
Kokturk 2015	Asia	27	66.9 (9.47)	96.3%	59.3% / 37% / 3.7%		38.2 (17.5)	Severe	Yes		73.1%	0%
Koul 2015	Asia	498		62.0%	NR / 12.8% / NR	~85%		Severe	Unclear	8.0%		
Koul 2017	Asia	233		65.2%	NR / 12.9% / NR	~78.1%		Severe	Unclear	3.0%		1.3%
Kwak 2016	Asia	278	69.2 (11.0)	65.7%	NR / 26.3% / NR	~71.9%	44.7 (20.9)	Severe	Yes	58.3%	33.3%	0%
Liao 2014	Asia	114		83.3%					Unclear			
Lopez Caro 2019	Europe	55	73.3 (10.3)	76.4%	76.4% / 16.4% / 7.3%	NR	53.7 (14.4)	Moderate, Severe	Unclear			
Mallia 2018	Europe	27	67 (2.6)	69.0%			62.4 (5.1)		Unclear		53%	
McManus 2008	Europe	136	70.2 (9.4)	47.1%	55.9% / 44.1% / 0%		39 (20)	Severe	Unclear		69.1%	6.6%
Messous 2021	Africa	84	67.8 (10)	92.9%		100%		Severe	Yes			
Mohan 2015	Asia	137	62.3 (11.4)	78.8%	NR / NR / 19%			Severe	Unclear	0.0%	54%	
Mulpuru 2019	North America	4755	~70	49.2%	NR / 29.2% / NR	100%		Severe	Unclear	66.4%		

Nolen 2020	North America	129				100%		Severe	No			
Ostby 2013	Europe	13						Critical	Yes			
Pang 2021	Asia	239						Severe	Yes			
Pant 2009	Oceania	24	69 (R: 49-80)	54.2%	41.7% / 58.3% / 0%	100%	35 (R: 17-104)	Moderate, Severe	Yes			
Papakonstantinou 2015	Europe	44	69.5 (R: 46-86)	56.8%	70.5% / 29.5% / 0%		48.0 (15.9)	Moderate, Severe	No		77%	44%
Papi 2006	Europe	64	70.6 (2.5)	87.5%	95.3% / 4.7% / 0%		49.5 (2.3)	Severe	Yes	100.0%	97%	
Perotin 2013	Europe	45	63.1 (8.2)	82.4%	NR / 31.4% / NR	68.9%	43.7 (11.3)	Any	Unclear	70.6%	88.2%	
Prasad 2021	Oceania	1542				100%		Severe	No			
Ramirez 2018	North America	328						Severe	Yes			
Reina 2020	Europe	187		79.0%		100%		Moderate, Severe	Unclear			
Ringshausen 2009a	Europe	123	68 (9)	77.2%	57.7% / 26% / 16.3%		44.3 (R: 18.5-78.9)		Yes		65%	69.1%
Ringshausen 2009b	Europe	134	67.8 (8.7)	78.4%	58.2% / 23.9% / 17.9%		45.2 (R: 18.5-78.9)	Severe	Yes		64.9%	69.4%

Rohde 2003	Europe	85	70 (R: 43–83)	80.0%	49.4% / 37.7% / 12.9%		37.9 (R: 16.8-79.5)	Severe	Yes		65%	57.7%
Rohde 2005	Europe	130	66 (R: 41-80)				35.2 (R: 18.7-74.1)	Severe	Yes			
Rohde 2008	Europe	36	70.5 (R: 43-83)	75.0%	44.4% / 44.4% / 11.1%		41.4 (R: 22.4-661)	Severe	Yes			
Roland 2001	Europe	22	68.2 (7.8)		NR / 37% / NR		39.8 (17.0)	Any	No	100.0%	92%	
Saldias 2012	South America	120	68.6 (7.7)	53.0%	100% / 0% / 0%		46 (17)	Moderate	Unclear	83.5%	66.7%	
Sanz 2015	Europe	195	63.9 (13.1)	69.7%				Severe	Unclear			
Seemungal 2001	Europe	168	66.6 (7.1)	71.1%	NR / 33.7% / NR		19.8 (0.51)	Moderate	No	74.0%	97.6%	
Shimizu 2015	Asia	50	76 (8.6)	93.5%	NR / 8.7% / NR	~82%	54.7 (18.1)	Moderate, Severe	No	78.3%		
Stolz 2019	Europe	187	66.9 (9.4)	67.4%	64.9% / 35.1% / 0%		54.5 (16.9)	Any	Yes		72.4%	
Tan 2003	Asia	15	71 (11)	87.0%	73% / 27% / 0%		44 (7)	Severe	Unclear		53%	0%
van Rijn 2019	Europe	88	63.5 (R: 46-75)	64.0%	NR / NR / 0%		49 (R: 23-74)	Any	Unclear		79%	
Vanspauwen 2012	Europe	74	66 (R: 42-85)	52.3%	71.6% / 28.4% / 0%			Any	Yes			

Wang 2017	Asia	204						Severe	No			
Wark 2013	Oceania	121	70.3 (11.4)	48.5%	72.8% / 22.3% / 4.9%		36.6 (14.8)	Moderate, Severe	Unclear			
Wilkinson 2006	Europe	56	68.8 (6.9)	60.0%	NR / 23.0% / NR		40.6 (15.6)	Any	No	100.0%	100%	
Wilkinson 2017	Europe	324	66.8 (8.6)	53.5%	57.5% / 42.5% / 0%	60.6%	46.4 (15.2)	Any	No	89.8%	89%	
Xie 2021	Asia	91	71 (8)	94.5%	NR / 36.3% / NR			Severe	Unclear		79.1%	
Yin 2017	Asia	264	75 (8)	74.6%	56.0% / 44.0% / 0%		41.1 (2.7)	Severe	No			
Zakharkina 2011	Europe	29	70.7 (8.05)	62.1 %	79.3% / 13.8% / 6.9%	100%	39.4 (11.4)	Moderate, Severe	Unclear			
Zhao 2018	Asia	99							Unclear			
Zheng 2017	Asia	100	70.4 (11.8)	62.0%	59.0% / 38.0% / 3%	86%		Severe	Unclear	41.0%		

Table 23. Baseline characteristics of the studies assessing the prevalence of respiratory viruses in COPD Exacerbations

Study ID	Inclusion criteria	Baseline characteristics	Random selection	Non-response bias	Indirect data collection	Case definition	PCR reliability	Consistent data collection mode	Appropriate numerator, denominator	Overall
Bafadhel 2011	Low	Low	High	High	Low	Low	Low	Low	Low	LOW
Borg 2003	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Bouquet 2020	Low	Low	Low	High	Low	Low	Low	Low	Low	LOW
Contoli 2017	High	High	Low	High	Low	Low	Low	Low	High	MODERATE
De Serres 2009	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Du 2017	Low	Low	High	High	Low	Low	Low	Low	Low	LOW
Falsey 2006	Low	Low	High	High	Low	Low	Low	Low	High	MODERATE
Gandhi 2012	Low	Low	High	High	Low	Low	Low	Low	High	MODERATE
Hilzendeger 2016	Low	Low	Low	High	Low	Low	High	Low	Low	LOW
Hosseini 2015	High	High	High	High	Low	Low	High	Low	Low	MODERATE
Ilvan 2013	High	High	High	High	Low	Low	High	Low	Low	MODERATE
Johnston 2013	Low	Low	High	High	Low	Low	High	Low	Low	LOW
Kherad 2010	High	Low	High	High	Low	Low	Low	Low	Low	LOW
Ko 2019	Low	Low	Low	High	Low	Low	Low	Low	Low	LOW
Kokturk 2015	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Liao 2014	High	High	High	High	Low	Low	High	Low	High	MODERATE
Lopez Caro 2019	Low	Low	Low	High	Low	Low	Low	Low	Low	Low
McManus 2008	High	Low	High	High	Low	Low	Low	Low	Low	LOW
Papakonstantinou 2015	High	Low	High	High	Low	Low	Low	Low	Low	LOW
Papi 2006	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Ringshausen 2009a	Low	High	High	High	Low	Low	Low	Low	Low	LOW

Ringshausen 2009b	Low	High	High	High	Low	Low	Low	Low	Low	MODERATE
Rohde 2003	Low	High	High	High	Low	Low	Low	Low	Low	LOW
Rohde 2005	Low	High	High	High	Low	Low	Low	Low	Low	LOW
Rohde 2008	Low	High	High	High	Low	Low	Low	Low	Low	LOW
Seemungal 2001	Low	Low	High	High	Low	Low	High	Low	Low	LOW
Stolz 2019	Low	Low	High	High	Low	Low	Low	Low	High	LOW
Vanspauwen 2012	Low	Low	High	High	Low	Low	High	Low	Low	LOW
Wilkinson 2006b	Low	High	High	High	Low	Low	Low	Low	High	MODERATE
Wilkinson 2017	High	Low	High	High	Low	Low	Low	Low	Low	LOW
Xie 2021	Low	Low	Low	High	Low	Low	Low	Low	Low	LOW

Table 24. Risk of bias of studies evaluating the prevalence of respiratory viruses in stable COPD.

Study ID	Inclusion criteria	Baseline characteristics	Random selection	Non-response bias	Indirect data collection	Case definition	PCR reliability	Consistent data collection mode	Appropriate numerator, denominator	Overall
Aaron 2001	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Almansa 2011	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Almansa 2012	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Alotaibi 2019	High	Low	High	High	Low	Low	Low	Low	Low	LOW
Aronen 2016	Low	High	Low	High	Low	Low	Low	Low	High	LOW
Bafadhel 2011	Low	Low	High	High	Low	Low	Low	Low	High	LOW
Beckham 2005	High	High	High	High	Low	Low	Low	Low	High	MODERATE
Belongia 2018	Low	Low	High	High	Low	High	Low	Low	High	MODERATE
Boixeda 2012	Low	Low	High	High	Low	Low	Low	Low	Low	LOW
Borg 2003	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Bouquet 2020	Low	Low	Low	High	Low	Low	Low	Low	High	LOW
Camargo 2008	Low	Low	High	High	Low	Low	Low	Low	Low	LOW
Cameron 2006	Low	High	Low	Low	Low	Low	High	Low	High	LOW
Chang 2015	High	High	High	High	Low	Low	High	Low	Low	MODERATE
Clark 2014	Low	High	Low	High	Low	High	Low	Low	Low	LOW
Contoli 2017	Low	Low	Low	Low	Low	Low	Low	Low	High	LOW
Dai 2015	Low	Low	Low	High	Low	Low	Low	Low	Low	LOW
Daubin 2008	Low	Low	Low	Low	Low	Low	Low	Low	Low	LOW
De Serres 2009	Low	Low	Low	High	Low	Low	Low	Low	Low	LOW
Dimopoulos 2015	Low	Low	Low	High	Low	Low	Low	Low	High	LOW

Djamin 2015	High	High	High	High	Low	Low	Low	High	High	MODERATE
Drago 2009	High	High	High	High	Low	High	High	Low	High	HIGH
Du 2017	Low	Low	High	High	Low	Low	Low	Low	High	LOW
Falsey 2006	Low	Low	High	High	Low	Low	Low	Low	High	MODERATE
Falsey 2012	High	High	High	High	Low	Low	Low	Low	High	MODERATE
Feng 2021	Low	Low	High	High	Low	Low	Low	Low	High	LOW
Gallego 2016	Low	High	Low	High	Low	Low	High	Low	High	MODERATE
Gandhi 2012	Low	Low	High	High	Low	Low	Low	Low	High	MODERATE
Gorse 2009	High	High	Low	High	Low	Low	Low	High	Low	MODERATE
Hamelin 2005	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
He 2017	High	Low	Low	High	Low	Low	Low	Low	Low	LOW
Hosseini 2015	High	High	High	High	Low	Low	High	Low	High	MODERATE
Huerta 2015	High	High	High	High	Low	Low	Low	Low	High	MODERATE
Hutchinson 2009	High	High	High	High	Low	Low	High	Low	High	MODERATE
Ilvan 2013	High	High	High	High	Low	Low	High	Low	Low	MODERATE
Jahan 2021	Low	Low	High	High	Low	Low	Low	Low	High	LOW
Jiang 2015	High	High	Low	Low	Low	Low	High	Low	High	MODERATE
Johnston 2010	Low	Low	High	High	Low	Low	High	High	High	MODERATE
Johnston 2013	Low	Low	High	High	Low	Low	High	High	Low	MODERATE
Jubinville 2018	Low	Low	High	High	Low	Low	Low	Low	Low	LOW
Kan-O 2021	Low	Low	High	High	Low	Low	Low	Low	Low	LOW
Kawamatawong 2017	Low	Low	High	High	Low	Low	Low	Low	High	LOW
Kherad 2010	High	Low	High	High	Low	Low	Low	Low	Low	LOW
Kim 2016	Low	Low	Low	High	Low	Low	Low	Low	Low	LOW
Ko 2007	Low	Low	Low	Low	Low	Low	Low	Low	Low	LOW
Ko 2019	Low	Low	Low	High	Low	Low	Low	Low	Low	LOW
Kokturk 2015	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Koul 2015	Low	High	Low	High	Low	Low	High	Low	Low	LOW

Koul 2017	Low	High	Low	High	Low	Low	High	Low	Low	LOW
Kwak 2016	Low	Low	Low	High	Low	Low	Low	Low	High	LOW
Liao 2014	High	High	High	High	Low	Low	High	Low	High	MODERATE
Lopez Caro 2019	Low	Low	Low	High	Low	Low	Low	Low	Low	Low
MacDonald 2021	High	Low	High	Low	Low	Low	High	Low	Low	LOW
Mallia 2018	High	High	High	High	Low	High	Low	High	High	HIGH
McManus 2008	High	Low	High	High	Low	Low	Low	Low	High	LOW
Messous 2021	Low	Low	Low	Low	Low	Low	Low	Low	High	LOW
Mohan 2015	Low	High	High	High	Low	Low	High	Low	High	MODERATE
Mulpuru 2019	Low	Low	High	High	Low	Low	Low	Low	Low	LOW
Nolen 2020	High	High	High	High	Low	High	Low	Low	High	MODERATE
Ostby 2013	Low	Low	Low	Low	Low	High	High	Low	Low	LOW
Pang 2021	High	High	High	High	Low	High	Low	Low	High	MODERATE
Pant 2009	Low	Low	Low	Low	Low	Low	Low	Low	Low	LOW
Papakonstantinou 2015	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Papi 2006	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Perotin 2013	Low	Low	Low	High	Low	Low	Low	Low	High	LOW
Prasad 2021	High	High	High	High	Low	High	Low	Low	High	MODERATE
Ramirez 2018	High	High	High	High	Low	Low	Low	Low	High	MODERATE
Reina 2020	Low	High	Low	High	Low	Low	Low	Low	High	LOW
Ringshausen 2009a	Low	High	High	High	Low	Low	Low	Low	Low	LOW
Ringshausen 2009b	Low	High	High	High	Low	Low	Low	Low	Low	MODERATE
Rohde 2003	Low	High	High	High	Low	Low	Low	Low	Low	LOW
Rohde 2005	Low	High	High	High	Low	Low	Low	Low	Low	LOW
Rohde 2008	Low	High	High	High	Low	Low	Low	Low	Low	LOW
Roland 2001	High	High	High	High	Low	Low	Low	Low	High	MODERATE
Saldias 2012	Low	Low	High	High	Low	Low	High	Low	High	MODERATE

Seemungal 2001	Low	Low	High	Low	Low	Low	High	Low	High	LOW
Shimizu 2015	Low	Low	Low	High	Low	Low	Low	Low	High	LOW
Stolz 2019	Low	Low	High	High	Low	Low	Low	Low	High	LOW
Tan 2003	High	High	High	High	Low	Low	Low	Low	Low	LOW
van Rijn 2019	Low	Low	High	High	low	Low	Low	Low	Low	LOW
Vanspauwen 2012	Low	Low	High	High	Low	Low	High	Low	Low	LOW
Wang 2017	High	High	High	High	Low	High	High	Low	High	HIGH
Wark 2013	Low	High	High	High	Low	Low	High	Low	High	MODERATE
Wilkinson 2006	Low	High	High	High	Low	Low	Low	Low	High	MODERATE
Wilkinson 2017	High	Low	Low	High	Low	Low	Low	Low	High	LOW
Xie 2021	Low	Low	Low	High	Low	Low	Low	Low	Low	LOW
Yin 2017	Low	Low	Low	High	Low	Low	Low	Low	Low	LOW
Zakharkina 2011	High	High	High	High	Low	Low	Low	Low	Low	MODERATE
Zhao 2018	Low	High	Low	High	Low	Low	Low	Low	High	LOW
Zheng 2017	High	Low	Low	High	Low	Low	Low	Low	Low	LOW

Table 25. Risk of bias of studies evaluating the prevalence of respiratory viruses in COPD exacerbations

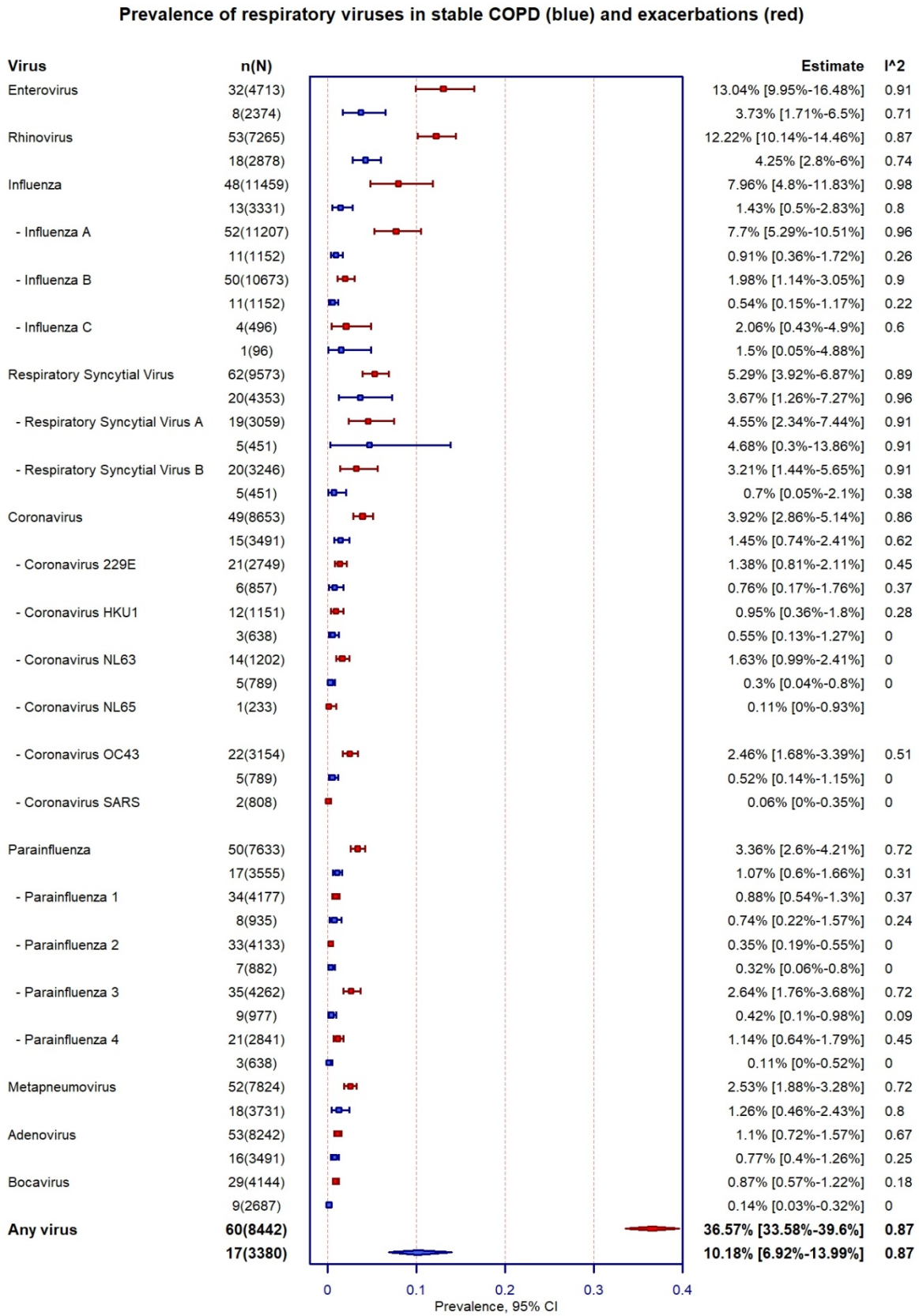

Figure 16. *Prevalence of respiratory viruses in COPD during stable disease state (blue) and during exacerbations (red). n: Number of included studies. N: Overall study population. CI: Confidence intervals. I^2: Heterogeneity (I^2)*

6.5. Discussion

Based on data from 93 studies, identified through rigorous systematic evaluation of the literature, this comprehensive systematic review and meta-analysis quantified the prevalence of respiratory viruses in unselected patients with stable COPD, moderate and severe COPD exacerbations. We demonstrated that during exacerbations, lower respiratory tract samples are more sensitive to the detection of rhinovirus and adenovirus. Meta-regression analyses revealed factors potentially associated with the prevalence of respiratory viruses, such as spirometric disease severity, use of inhaled corticosteroids, and influenza vaccination during the preceding year. There was no indication that the prevalence of respiratory viruses differs between pneumonic and non-pneumonic COPD exacerbations.

The proportion of moderate exacerbations that were triggered by viruses was numerically higher compared to severe exacerbations (44.1% versus 36.2%). This observation suggests exacerbations caused by viruses tend to be less severe compared to other types of exacerbations, such as those triggered by bacteria. This is consistent with the observed association of procalcitonin, an accurate biomarker of bacterial infections, with worse COPD exacerbations outcomes[364-366]. Further studies are needed to inform prognostication of exacerbations of different aetiology, as well as the clinical characteristics and outcomes of exacerbations triggered by different types of viruses.

Samples sourced from the lower respiratory tract, such as sputum or bronchoalveolar lavage yielded a significantly higher prevalence of viral infections, mainly rhinovirus, in COPD exacerbations. An observational study comparing the use of different samples for detecting respiratory viruses during exacerbations also reported several cases where viruses identified in lower but not in the upper respiratory samples[301].There is a chance that the better quality and larger quantity of the lower respiratory samples may have driven this difference. However, this is not supported by the opposite trends that were observed in stable disease state samples, where the prevalence of any virus and of rhinovirus were numerically lower in lower respiratory samples. It is more likely that to trigger a COPD exacerbation, rhinovirus or other viruses need to infect the lower and not necessary the upper respiratory tract. This is supported by the lack of temporal association between upper respiratory tract infections and exacerbations that was observed in the PREVENT trial[367]. On the other hand, Mallia et al. reported successful provocation of signs and symptoms consistent with a COPD exacerbation after inoculation of rhinovirus in both nostrils of 11/13 patients with COPD[368]. However, the study sample was limited, and the methodology inadequately described. Characteristically, rhinovirus was inoculated using an atomizer,

which might have delivered the virus to both upper and lower airways. Moreover, these findings have not been replicated by other groups.

Our findings highlighted crucial, unaddressed research questions. Data are needed around the seasonal distribution of various respiratory viruses in COPD exacerbations, as well as the seasonal variability of the exacerbations' aetiology. The clinical characteristics of acute exacerbations associated with viruses identified in the upper and/or lower respiratory tract need to be explored, and, also, the clinical characteristics and outcomes of exacerbations associated with different respiratory viruses. These can either be addressed in extensive, thoroughly characterised cohorts that are currently lacking, or perhaps by means of an individual participant data meta-analysis of the existing studies that will allow for more rigorous data handling and evaluation.

There are no validated tools for assessing the overall certainty in a body of evidence around prevalence. Overall, the confidence in our findings is limited by the moderate risk of methodological bias that characterised about 40% of the included studies and by the inconsistency (heterogeneity) of the individual study results, that was probably driven by differences in the study populations across the different cohorts, including the severity of COPD, use of inhaled corticosteroids, influenza vaccination history, seasonal variability and local epidemics affecting the prevalence of the viruses. The sensitivity and specificity of various molecular assays, especially in older studies, may have also contributed to some extent to this heterogeneity. Unfortunately, inadequate information around some variables known to be associated with viral prevalence, such as the seasonal distribution of the samples collected in each study, prevented us from fully explaining the heterogeneity across the included studies. On the other hand, our analysis is informed by numerous studies evaluating unselected patients with stable COPD or exacerbations (and there are no concerns around indirectness), totalling large study populations that yielded precise results. Moreover, funnel plots with the sample size as the measure of accuracy, which are optimal for assessing publication bias in meta-analyses of proportions[283] did not reveal significant publication bias.

Some deviations from our initial protocol limit our study. First, we excluded conference abstracts. Due to word limitations, abstracts often presented incomplete viral data, usually highlighting only information considered to be most clinically pertinent or unusual, that may have introduced bias and led to an overestimation of the respiratory viral prevalence of some viruses. Quality appraisal of abstracts was also impossible due to the limited description of the methods. Finally, it was not possible to avoid data duplication since several groups reported preliminary results from incomplete study cohorts, often in

multiple conference abstracts. Second, while we were planning on using a logit transformation for conducting our meta-analysis, we finally opted to use the Freeman-Tukey double arcsine transformation as it addresses variance instability, as well as the problem of confidence intervals falling outside the 0-1 range, both important issues in meta-analyses of the less prevalent viruses[282]. Third, while we were originally planning on including a single measurement per patient during stable disease and during exacerbations, we finally accepted a sample every three months (every season) during stable disease state and one sample per exacerbation. This paradigm was followed by many studies that presented aggregate data including multiple measurements per patient. Including multiple exacerbations per participant is justified by recent findings from the Acute Exacerbation and Respiratory InfectionS in COPD (AERIS) cohort[369] suggesting a predisposition to recurrent bacterial or eosinophilic but not viral exacerbations among patients with COPD. More specifically, after a bacterial or eosinophilic exacerbation patients were more likely to experience further exacerbations of the same type. This tendency was not observed in exacerbations triggered by viruses and therefore it is unlikely that our revised approach has introduced bias. Similarly, several studies evaluating viruses longitudinally during stable disease state failed to demonstrate prolonged infections or colonisation[280,307,367]. The only exception is respiratory syncytial virus; it has been postulated it may sometimes colonise chronically patients with COPD causing accelerated FEV_1 decline. Our findings remained robust to sensitivity analyses implementing the logit transformation or only accepting a single measurement per study participant.

Another limitation is that this meta-analysis did not consider severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or its impact on the broader viral epidemiology in COPD. However, such evaluation is not possible in the midst of the pandemic, due to the huge, imbalanced impact of SARS-CoV-2 both on population viral epidemiology, but also in the daily lives of people. Patients with COPD have been particularly affected, since they were shielding for a prolonged period of time, which was followed by a period of consistent use of face masks and limited social activities[278,370,371]. Moreover, it remains unclear whether SARS-CoV-2 can trigger COPD exacerbations, as most cases of lower respiratory tract involvement in COPD are associated with bilateral viral pneumonia, a distinct clinical entity.

This is the first meta-analysis to assess the prevalence of respiratory viruses in stable disease state. Their prevalence during COPD exacerbations has been investigated in three previous meta-analyses each including between 8-27 original studies[88,89,372]. Our meta-analysis was based on 93 studies, including previously unpublished data from four original studies. Important strengths of our work included the rigorous systematic review of the literature and adherence to full systematic review methods, including

dual study screening and selection, extraction of relevant data and quality appraisal, as well as the lack of limitation by language.

Overall, our comprehensive systematic review and meta-analysis provides the best available information on the prevalence of respiratory viruses in stable COPD and acute exacerbations. Our findings suggest respiratory viral infection represent a prevalent, potentially treatable trait in COPD exacerbations, highlighting an urgent unmet clinical research and public health need.

7. Overall Discussion

7.1. Summary of findings

The aim of this work was to lay the clinical and methodological groundwork for the conduct of high-quality clinical and cost-effectiveness RCTs for evaluating precision medicine interventions for acute exacerbations of COPD.

The preparation of the TRACE-COPD trial, which was not completed due to the COVID-19 pandemic, revealed significant challenges in the design and conduct of RCTs of COPD exacerbations management. While designing the trial, we faced challenges in the selection of the outcomes that are most pertinent to patients and health professionals, an issue that has now been resolved with the development of a core outcome set and outcome measurement instruments for clinical trials of COPD exacerbations management. The TRACE-COPD trial set-up demonstrated the need for more pragmatic, broader eligibility criteria and more rigorous recruitment strategies that are already addressed in the revised protocol and will inform future trials as well. These challenges also led to the development of the DECODE-NET, an international clinical trials network to facilitate RCTs on the management of COPD exacerbations.

The ERS COPD exacerbations core outcome set, and outcome measurement instruments will facilitate the selection of the most clinically pertinent outcomes for assessment in clinical trials of COPD exacerbations management. It will improve the quality and comparability of future RCTs, that will better inform systematic reviews, meta-analyses, clinical practice guidelines, and, ultimately, clinical practice. In parallel, it will also reduce research waste. The multi-stakeholder and global representation of the panellists and Delphi survey respondents, involvement of well informed and trained patients, the rigorous methodology that was implemented, the endorsement by four international respiratory societies (European Respiratory Society, American Thoracic Society, Latino-American Thoracic Society and Pan-African Thoracic Society), and the adoption by the DECODE-NET are anticipated to guarantee high uptake. Plans are in place to further disseminate the document and seek further endorsement.

Finally, the prevalence of respiratory viruses in stable COPD and acute exacerbations was quantified by means of a rigorous systematic review and meta-analysis, sourcing data from 93 original studies, mostly of low or moderate risk of bias. Moreover, this work demonstrated that lower respiratory samples, such as sputum or bronchoalveolar lavage are more sensitive for detecting viral infections in the context of COPD exacerbations. These findings could inform future diagnostic, therapeutic and public health interventions.

Overall, it is aspired that these findings will inform and optimise the design and interventions of future RCTs of COPD exacerbations management.

7.2. The DECODE-NET

While setting up the TRACE-COPD trial, it became very clear that the design and delivery of trials of COPD exacerbation management is very challenging. First, there was little international consensus around the main characteristics of trials, such as the selection of clinically relevant outcomes, or the definition of study populations. In addition, the actual delivery is complicated by the acute nature of exacerbations that require recruitment during unscheduled healthcare visits. We discussed these challenges with colleagues nationally and internationally with expertise in COPD exacerbations trials and found that they all face similar challenges. Therefore, we decided to launch the DECODE-NET, an international clinical trials network aiming to facilitate the conduct of the large, high-quality RCTs that are needed to improve the outcomes of COPD exacerbations[117]. Our Network now includes over 50 centres from Africa, America, Asia, Europe, and Oceania.

Through the development of the core outcome set, we have already demonstrated the feasibility of our collaboration and the strength of our Network, and we now intend to launch the first collaborative RCT. The SYNESIS (Safety and clinical effectiveness of withholding SYstemic corticosteroids in Non-EoSInophilic chronic obstructive pulmonary disease exacerbationS) will be a pragmatic RCT and will compare the administration of systemic corticosteroids versus placebo for patients with moderate or severe COPD exacerbations and low blood eosinophils. We plan to recruit 605 study participants across 25-30 study centres, to demonstrate the non-inferiority of withholding systemic corticosteroids for this group of patients.

Successful set-up and onset of recruitment to the SYNESIS trial will further confirm the ability of our Network to deliver collaborative RCTs and our ultimate aim is to acquire competitive international funding that will allow us to set up a platform trial to test various precision medicine diagnostic and therapeutic interventions. Both SYNESIS and the future confirmatory trial design will be informed by the findings of all the projects described in this thesis, as well as the experience of all the global experts that have joined the DECODE-NET.

7.3. Future research directions

7.3.1. Precision medicine platform RCT

COPD exacerbations are complex and heterogeneous and require novel, precision medicine interventions. Accumulating data on exacerbations mechanisms and the clinical validation of promising biomarkers over recent years pave the way for the introduction of novel precision medicine interventions that will need to be tested in RCTs. Therefore, once the trial design and feasibility of COPD exacerbations trials have been optimised, it is only logical that a platform trial should be launched, to enable the assessment of multiple diagnostic and therapeutic interventions and accelerate the introduction of novel treatments to clinical practice. This is the main objective of the DECODE-NET.

Given the challenges in the delivery of RCTs of COPD exacerbation management, it is crucial to develop centres of expertise in the conduct of such trials. To this direction, the next phase of NIHR Manchester BRC and CRF will both aim to develop infrastructure locally to facilitate acute respiratory care trials. In addition, the DECODE-NET will offer peer-support in the development of expertise across all participating centres.

7.3.2. Considerations on the design of COPD exacerbations trials

The ERS COPD Exacerbations Core Outcome Set is anticipated to improve the quality and comparability of future RCTs, that will better inform systematic reviews, meta-analyses, clinical practice guidelines, and, ultimately, clinical practice. However, several of the selected measurement instruments were only recommended for interim use in the absence of adequate data on their performance characteristics, or in the absence of adequate validation in the context of COPD exacerbations. It is crucial that methodological research will be prioritised to optimise these instruments. Such studies could be embedded in COPD exacerbations trials and the DECODE-NET is fully committed to that. Such studies may lead to full adoption or revision of the selected measurement instruments.

Beyond outcomes selection, optimization and international consensus is needed for other critical components of COPD exacerbation trials design. Importantly, the definitions and diagnostic criteria of COPD and acute exacerbations in the context of RCTs are lacking and trialists adopt heterogeneous approaches. We have preliminary explored this issue in our methodological systematic review (Chapter 3)[148]. Further methodological work is under way, led by Dr Thomas Bradbury at the George Institute of Global Health, University of Sydney, in collaboration with our group. The Exacerbation Definitions used In COPD Trials (EDICT) meta-epidemiological study explores how different definitions of COPD exacerbations

may impact trial outcomes. It is hoped that the results of this study will inform international consensus on the definition of COPD exacerbations.

Moreover, it is crucial that the heterogeneity of exacerbations will also be consistently addressed both in clinical research and practice. It is now clear that the mechanisms, clinical characteristics, and outcomes of exacerbations of different aetiology (e.g., bacterial, viral, eosinophilic) vary[15,31,75]. These differences need to be accounted for both in clinical research and practice. Therefore, consensus is needed on an accurate characterisation process, possibly based on a combination of biomarkers. This is another priority of the DECODE-NET.

Another challenge trialists face is developing pragmatic strategies for excluding mimics of COPD exacerbations, such as pneumonia, pulmonary embolism, or decompensated heart failure. In our methodological systematic reviews (Chapter 3), we found that eligibility criteria of many RCTs require a review by a senior physician and/or a chest x-ray to exclude mimics at presentation. While none of the included studies enlisted ultrasound, a combination of thoracic and cardiac ultrasound could be further explored in future trials, especially given the expanding thoracic ultrasound expertise among respiratory physicians and the expanding basic thoracic and cardiac ultrasound expertise across the emergency services throughout the UK. The accuracy and feasibility of thoracic and cardiac ultrasound in this context will need to be tested prospectively.

7.3.3. COPD exacerbations triggered by viruses

Respiratory viruses represent a prevalent, burdensome, but preventable and treatable trait of stable COPD and exacerbations. Our meta-analysis quantified the prevalence of viral infections in the context of stable COPD and acute exacerbations, as well as the frequency of individual viruses and our findings could be used to inform the development of diagnostic, therapeutic and public health interventions.

Further research is needed to assess the seasonal distribution of each respiratory virus. More importantly, data are needed around the clinical characteristics and burden of individual viruses. These questions could possibly be addressed by means of an individual participant data meta-analyses, perhaps with a network component to assess the outcomes of exacerbations triggered by various respiratory viruses.

The development of accurate but affordable diagnostic biomarkers should also be prioritised. Unfortunately, the cutting-edge respiratory viral panels that can detect all clinically relevant viruses and quantify their loads are not yet cost-effective for use in clinical practice.

The safety, clinical and cost-effectiveness of preventive and therapeutic precision medicine interventions targeted to specific burdensome respiratory viral infections should be tested in future RCTs as they could potentially improve the quality of life and outcomes of patients with COPD.

7.4. Conclusion

The management of COPD exacerbations remains suboptimal and unchanged for decades. Progress has been hindered by the complexity and heterogeneity of COPD exacerbations, as well as the complexity and challenges of designing and conducting of clinical trials of COPD exacerbations management. This work focused on addressing some of these challenges and its outputs are anticipated to facilitate the design and delivery of future precision medicine RCTs of COPD exacerbations management. Moreover, it led to the development of local infrastructure and global collaboration, that will reinforce the delivery of such trials with the ultimate aim to improve the management and outcomes of patients with acute COPD exacerbations.

8. Appendices

8.1. Chapter 2: Protocol of the TRACE-COPD trial

Study Title:	A Randomised Controlled Trial to evaluate whether serum procalcitonin and blood eosinophil count can guide and limit the administration of antibiotics and systemic steroids in patients presenting with moderate or severe acute exacerbations of chronic obstructive pulmonary disease, compared to standard care.
Protocol Short Title/Acronym:	Characterisation and targeted **TR**eatment of **AC**ute **E**xacerbations of **C**hronic **O**bstructive **P**ulmonary **D**isease. The **TRACE-COPD** Randomised Controlled Trial.
IRAS Number:	*248241*
ISRCTN Number:	*ISRCTN85620156*
Sponsor's Reference Number:	*B00292*
Version No and Date:	*Version 4..* *Date: 16/12/2019*
Chief Investigator:	*Professor Jørgen Vestbo DMSc, FRCP, FERS, FMedSci*
Principal Investigators:	*Dr. Alexander G. Mathioudakis MD, MRCP(UK)* *Dr Abdul Ashish, MBBS, MD, FRCP*
Sponsor:	*Research and Innovation Division, Manchester Foundation Trust*
Funder (if applicable):	*Boehringer Ingelheim.*

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, the Sponsoring Trust's R&D Office (or a regulatory authority, and members of the Health Research Authority or Local Research Network).

Amendment History

Superseded Version	Reason for Change
Version 1. 01/10/2018	
Version 2. 14/02/2019	*See IRAS amendment form:* *1. Professional background of the research team members* *2. Timing of follow-up visits.* *3. Physical examination at follow-up visits.* *4. Lung sound recording* *5. Exhaled volatile organic compounds sampling during the recruitment visit.* *6. Visit schedule - Day 21 visit* *7. Exclusion criteria amendment.* *8. Symptom questionnaires.*
Version 3. 21/03/2019	1. Trial registration updated: ISRCTN85620156 2. Data sharing plans updated.
Version 4. 16/12/2019	See IRAS Amendment form: 1. Change in the eligibility criteria (allow the inclusion of patients who have already received antibiotics and/or systemic corticosteroids for the index exacerbation). For patients receiving antibiotics and/or systemic corticosteroids at baseline, procalcitonin and/or blood eosinophils will be used to guide discontinuation of these medications 2. Recruitment strategy (recruitment in general practice surgeries) 3. Allow the use of intravenous antibiotics instead of doxycycline, when clinically indicated 4. Update in the devices used 5. Updated study timelines

Key Trial Contacts

Insert full details of the key trial contacts including the following

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Signature page

The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

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 clinical 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.

For and on behalf of the Study Sponsor:

Signature: Date:

..... 16/12/2019

Dr Lynne Webster

Position: Head of Research Office

Research and Development Directorate

Manchester University NHS Foundation Trust

Chief Investigator:

Signature: Date:

..... 16/12/2019

Professor Jørgen Vestbo DMSc, FRCP, FERS, FMedSci.

8.1.1. Trial Summary

Title:	A randomised controlled trial to evaluate whether serum procalcitonin and blood eosinophil count can guide and limit the administration of antibiotics and systemic steroids in patients presenting with moderate or severe acute exacerbations of chronic obstructive pulmonary disease, compared to standard care.
Short title/ACRONYMN:	Chracterisation and targeted **TR**eatment of **AC**ute **E**xacerbations of **C**hronic **O**bstructive **P**ulmonary **D**isease. The **TRACE-COPD** Randomised Controlled Trial.
Trial medications:	We will use serum procalcitonin and blood eosinophil count (EOS) to guide the administration of antibiotics (doxycycline or intravenous antibiotics, according to the local antimicrobial policies) and systemic steroids (prednisolone). These medications are administered to patients presenting with AECOPD as part of their standard care.
Objectives:	The primary objectives of the TRACE-COPD trial will be to evaluate whether use of serum procalcitonin and blood eosinophil count can decrease the administration of antibiotics and systemic corticosteroids among patients presenting with moderate or severe AECOPD, compared to standard care. In addition, we will evaluate the acceptability of the intervention, consent and retention rate, as we plan to conduct a multi-centre, confirmatory, pragmatic trial in the future. Secondary objectives of the TRACE-COPD trial will be to assess treatment failure rate, time-to-treatment success, re-exacerbation and re-hospitalisation rate, mortality, adverse events and severe adverse events, increased length of admission or re-admission due to side effects to study medications,

	adherence to the intervention, the proportion of patients testing negative for both biomarkers and the safety of intervention in this population, sample size for the future, confirmatory trial, further feasibility outcomes and data to support the design of the confirmatory trial. In the study population of the TRACE-COPD trial we will also evaluate several biomarkers, aiming to further characterise exacerbation clusters.
Type of trial:	Parallel group, open-label randomised controlled trial
Trial Participants:	Patients presenting with moderate or severe COPD exacerbations
Trial design and methods:	Patients will be recruited upon presentation with a moderate or severe AECOPD in the acute medical or emergency services of the participating hospitals or upon contacting the community COPD or pulmonary rehabilitation teams of the participating hospitals with the same presentation (moderate or severe AECOPD). Patients will also be recruited from participating general practice surgeries. Upon recruitment and consent, patients will be randomised in a 2:1 allocation, either to the biomarkers or standard care arms. Participants allocated to the biomarkers arm will only receive antibiotics (doxycycline, standard course, or intravenous antibiotics, according to the local antimicrobial policies) and/or systemic corticosteroids (prednisolone, standard course) if their serum procalcitonin is > 0.25 mcg/L and/or their blood eosinophil count > 2% of total white cell count, respectively. For patients who will have already received systemic corticosteroids for the index exacerbation, before recruitment, and present with low blood eosinophils (≤2%), these will be repeated 1-3 days later, and systemic corticosteroids will be administered in case repeat

	blood eosinophils are >2%. In the standard care arm, antibiotics and systemic steroids will be administered per NICE guidelines. Participants will be asked to complete daily symptom scores until confirmation of treatment success and they will be reviewed face-to-face or via a phone call at day 1-3, 14-20 and - if deemed necessary to confirm treatment success - at day 21-30 after presentation. They will also be reviewed by the research team in case of treatment failure. Finally, all participants will be followed-up in the outpatient clinic 24-27 weeks after their initial presentation. Biological samples, including blood and spontaneous sputum samples, nasal swabs and will be collected at all face-to-face follow-up visits. Exhaled volatile organic compounds (VOCs) and lung sound recordings may also be collected. Spirometry will be conducted at 6-months follow-up.
Planned Sample Size:	135 participants
Trial duration per participant:	6 months
Estimated total trial duration:	1 year, 31 days
Planned trial sites:	Manchester University NHS Foundation Trust (Wythenshawe Hospital and possibly the Manchester Royal Infirmary). Wigan and Leigh NHS Foundation Trust (Wigan Hospital) Selected general practice surgeries (see IRAS form)
Total number of participants planned:	135 patients: Approximately 65 to be recruited from the community (via the community COPD teams of the participating hospitals or via the participating general practice surgeries); and

	70 will be recruited from the participating hospitals' acute medical and emergency services
Main inclusion/exclusion criteria:	We will include patients aged >40 years with a smoking history of ≥10 pack-years with a previous clinical diagnosis of COPD, presenting with an acute exacerbation of COPD.
Statistical methodology and analysis:	Baseline characteristics & imbalances will be presented. Descriptive statistics will be used for feasibility outcomes. Antibiotic and steroid exposure will be analysed on (i) an intention-to-treat basis and (ii) overall exposure rate. All remaining outcomes will be analysed on an intention-to-treat basis. We will first analyse results by treatment allocation. In additional analyses we will consider differences in the outcomes of moderate vs severe exacerbations and the outcomes of patients who are treatment naïve for the index exacerbation, versus those who have already received antibiotics and/or systemic steroids.

8.1.2. Plain English Summary

Acute exacerbations of COPD (AECOPD) are symptom flare-ups causing poor health, hospitalisation or death and they are responsible for 1:8 hospital admissions in the UK. AECOPD are managed by inhaled drugs to open-up the airways, systemic steroids to treat inflammation and almost invariably antibiotics to treat bacterial infections. However, only 50% of AECOPD that are caused by bacteria (bugs) respond to antibiotics and only 30-50% that are caused by inflammation of the airways with eosinophils respond to systemic steroids. Therefore, both medications are currently overused, posing unnecessary risks to patients with COPD. For instance, steroids can cause infections, fractures or muscle wasting, while overuse of antibiotics can lead to the development of super-bugs.

Previous studies have suggested that a biomarker in the blood, procalcitonin (PCT), can point out AECOPD responding to antibiotics and a subgroup of white blood cells, the blood

eosinophil count (EOS), can identify those responding to systemic steroids. This provides a potential opportunity to personalise the management of AECOPD, which could lead to improved use of healthcare resources and reduction in the frequency of side effects and antibiotic burden (the development of super-bugs).

We will set up a controlled clinical trial to assess whether the combination of procalcitonin and EOS can identify moderate or severe AECOPD associated with bacterial infection or EOS airway inflammation and can safely and effectively decrease and target the administration of antibiotics and/or steroids. Approximately half of the participants will be recruited in the hospital and the remaining in the community. All participants will be monitored for six months after the AECOPD.

As this is the first trial assessing this biomarker combination, we will only recruit 135 participants to get an insight into the effects of the intervention and information that we need to launch a larger, confirmatory trial in the future.

8.1.3. Background, Rationale, Risks and Benefits

8.1.3.1. Background

COPD affects more than 174 million people worldwide and 1.2 million people in the UK, being responsible for >5% of all deaths nationally[1-3]. Acute exacerbations (AECOPD) punctuate the natural history of COPD, representing a major determinant of disease morbidity, mortality, healthcare utilisation and costs[2-4]. Characteristically, 1 in 6 of those admitted with AECOPD die within 90 days from presentation, while exacerbations are responsible for 1 in 8 of all hospital admissions, at a cost to the NHS of more than £253millions per year[2-4].

AECOPD management is only partly effective and almost unchanged for over a decade[2,6]. Importantly, while AECOPD are approached as a single disease entity and treated uniformly with bronchodilators, systemic steroids and frequently antibiotics[2-4,6], in fact they represent a spectrum of heterogeneous disease entities with diverging underlying mechanisms, outcomes and treatment needs[31,75]. More specifically, only AECOPD associated with airway eosinophilic inflammation (30-50%) appear to respond to systemic corticosteroids and those with bacterial infection (50%) to antibiotics[8,9,34]; up to 30% are attributed to viral infections

and could benefit from antivirals[31,75]. In addition, only some exacerbations are associated with long-term sequelae in patients' health status and adverse outcomes and the mechanism is largely unknown[373].

Consequently, there is an urgent need to develop methods to better characterise AECOPD and to introduce precision medicine. Based on a series of systematic reviews, we identified serum procalcitonin and blood eosinophil count (EOS) as potentially effective biomarkers that could identify AECOPD associated with bacterial infection and airway EOS inflammation and safely guide the administration of antibiotics and systemic steroids in AECOPD, respectively, significantly reducing the prescription rate of both treatments (50% each, in severe AECOPD).

The TRACE-COPD will be the first trial to assess the safety and efficacy of a biomarker-driven treatment protocol using the combination of these biomarkers to guide the administration of both antibiotics and systemic steroids in AECOPD. It will evaluate the feasibility, challenges and costs of a future precision medicine, pragmatic trial to confirm safety, clinical and cost effectiveness of biomarker-led treatments for AECOPD. We will evaluate several inflammatory biomarkers and the viral loads of prevalent respiratory viruses, aiming to further characterise different AECOPD types (those triggered by bacterial or viral infection or enhanced airway eosinophilic inflammation or other types). We will also store fully anonymised clinical data and biological samples from the well-characterised study population of the TRACE-COPD study, as we plan to conduct further mechanistic studies to explore the immunopathology of different AECOPD studies (future studies, not covered by this ethical application; we intend to use anonymised clinical data and biological samples that will be collected during the trial and will be safely stored in the NIHR Research Facility at Manchester University NHS Foundation Trust – Wythenshawe Hospital).

Existing evidence

While AECOPD are heterogeneous, they are still treated interchangeably, due to the lack of clinically validated biomarkers to differentiate them[2-4,6]. To address this issue, we conducted a series of systematic reviews and meta-analyses, using standard guidance by Cochrane and GRADE Working Group, to identify validated relevant biomarkers and to evaluate whether they can safely guide AECOPD treatment. Details of these systematic reviews are presented in section 1.4.

Rationale

AECOPD are frequent, deadly, burdensome and sub-optimally managed. Most importantly, AECOPD represent a heterogeneous group of disease entities that require characterisation and targeted treatment. The TRACE-COPD trial and planned future mechanistic studies aim to deliver a set of biomarkers that will be able to accurately diagnose, characterise AECOPD and guide pharmacotherapy.

The TRACE-COPD will be an exploratory trial as such a trial is required to precede the confirmatory trial of the proposed targeted treatment protocol for several reasons: (i) Procalcitonin guidance has not been tested in the UK, where strict antibiotic stewardship policies are in place, and its efficacy needs to be confirmed in this context. (ii) Adherence to procalcitonin guidance was optional in previous trials, in the absence of adequate safety data; as safety data has been accumulated, we will now seek to maximise adherence to the treatment protocol for the first time and its safety needs to be assessed in an exploratory trial. (iii) Some participants will test negative for both biomarkers and will receive neither antibiotics, nor systemic steroids; the safety and acceptability of this intervention by the participants have not been previously assessed.

The proposed research is anticipated to lead to significant advances in AECOPD management, with direct benefits for individual patients, the society and healthcare services, within five years of its completion.

Introduction of precision medicine is an NHS priority[16] and AECOPD present a prime target. Safe antibiotic avoidance is of utmost importance, especially for patients with COPD who frequently receive unneeded antibiotics, while their airways are colonised by bacteria that progressively become less sensitive to available antibiotics[18,19]. The suggested intervention will lead to significant net benefits to global health given the prevalence of AECOPD; i.e., targeting antibiotic use in AECOPD will lead to a significant decrease in overall antibiotic prescription rates across the UK (and globally) and will contribute to the limitation of antibiotic resistance in the community. Preserving the effectiveness of available antibiotics is a strategic target of the Department of Health[20] and UK Healthcare Stakeholders [RAND document][21]. Safe avoidance of unneeded administration of systemic steroids is also crucial, especially during exacerbations caused by bacterial infections, as steroids exert

immunosuppressive effects. It is also important for patients with COPD in general, who are usually aged and multimorbid, as it can reduce the significant burden of their side effects and polypharmacy, another research priority[25]. Characterisation of different AECOPD types will unavoidably lead to the introduction of new, targeted treatments, such as novel, potent anti-inflammatory treatments.

We expect that targeted treatment will decrease treatment costs, even though procalcitonin measurement is still expensive. Firstly, this intervention will limit current over-prescription of unneeded antibiotics and systemic steroids and the burden of their side effects. Moreover, our meta-analyses suggested that procalcitonin guidance could safely reduce the length of hospitalisation for AECOPD.

In addition, we will conduct mechanistic (biomarker) studies, that will seek to further characterise different AECOPD types, specifically aiming to develop accurate diagnostic and prognostic biomarkers. Firstly, we will evaluate the underlying inflammatory processes in different types. In addition, we will assess bacterial and viral presence and load in the airways of the participants (using sputum samples and nasal swabs, respectively). AECOPD triggered by viruses have poor outcomes and are not currently treated aetiologically, due to lack of accurate diagnostic biomarkers. Therefore, our studies could lead the development of diagnostic biomarkers and -consequently- to immediate introduction of commercially available antiviral treatments for the management of these AECOPD. We will also save fully anonymized samples and clinical data that may be used in future mechanistic/translational studies.

Overall, this project has the potential to improve the management of AECOPD and, thus, the health status, quality of life and survival of COPD patients. We fully intend to also evaluate the cost-effectiveness of these interventions and biomarkers in our future confirmatory trial.

8.1.3.2. Risk and benefits

The recruiting investigator will discuss potential risks and benefits with patients prior to trial entry. Risks and benefits will also be outlined in the participants information sheet.

Potential Risks

Safety of patients who will test negative for both biomarkers (serum procalcitonin and EOS): As described, ample direct and indirect data support the safety of procalcitonin and EOS to guide the administration of antibiotics and systemic steroids in AECOPD. However, in the TRACE-COPD trial, we will test whether the combination of these biomarkers can guide the administration of both antibiotics and systemic steroids. This intervention might result in some participants testing negative for both biomarkers and these patients will receive neither antibiotics, nor systemic steroids. The safety and acceptability of this intervention by the participants have not been previously assessed. We strongly believe that the intervention will be safe because:

Each of the biomarkers has been thoroughly evaluated and there were no safety signals.

Antibiotics and systemic corticosteroids have different therapeutic targets. Antibiotic administration cannot impact the outcomes of AECOPD that are not associated with acute bacterial infection. Similarly, steroid administration cannot improve the outcomes of AECOPD that are not associated with eosinophilic airway inflammation (on the contrary, it could adversely affect the outcomes of AECOPD associated with an acute bacterial infection). Therefore, it will be safe to omit both antibiotics and systemic steroids in AECOPD testing negative for both biomarkers, which are therefore not associated neither with infection, nor with eosinophilic airway inflammation. These AECOPD might either reflect viral infections or episodes of symptom worsening as part of COPD day-to-day symptom variability (pauci-inflammatory[6]).

All participants will receive inhaled and/or nebulised bronchodilators, and oxygen if required.

In any case, patients' safety is our first priority and we have developed a detailed protocol to ensure the safety of the TRACE-COPD participants. More specifically, participants experiencing treatment failure will receive standard care by experienced clinicians or community COPD nurses. These will include all participants who will still be symptomatic at day 14-20 and those with significant symptoms deterioration during the AECOPD (symptoms deterioration will be captured by daily quantitative symptom questionnaires or will be reported by the patient, clinicians or investigators). Participants will be encouraged to seek medical advice in case of significant symptoms deterioration. Blood cultures will not be

collected routinely, but in case of a positive blood culture, patients will receive antibiotics irrespective of their treatment allocation.

Potential Benefits

Avoidance of the unneeded administration of systemic steroids could protect patients from their numerous side effects, which include (but not limited to) an increased risk of infections including pneumonia, osteoporosis, diabetes, muscle atrophy and weakness (including respiratory muscle weakness), increased appetite and weight gain, insomnia, cataracts or glaucoma.

Avoidance of the unneeded administration of antibiotics could protect from the development of antibiotic resistant bacteria, a rapidly evolving threat to global health.

Future benefits of patients with COPD will also include accurate diagnosis of AECOPD and the identification of other AECOPD types (i.e. AECOPD triggered by viruses) and development of targeted, effective treatments.

4.4. Change in the inclusion criteria

Initially, we planned to recruit patients presenting before receiving any antibiotics and/or systemic corticosteroids within two weeks from presentation. However, over the first months of recruitment, we found this is not pragmatic. More specifically, during October-November 2019, around 4-8 patients attended the Emergency Department at Wythenshawe Hospital every day, during recruitment hours. However, we only identified 2-5 potentially eligible patients each month, through the initial screening by the clinical team, as the vast majority of patients had already received treatments for their exacerbations. This was surprising, as the situation was not similar 2-3 years ago, when a recruitment pilot study was conducted at Salford hospital, and found that approximately 40% of patients that was attending the Emergency Department were treatment naïve for the index exacerbation.

These issues were discussed during the TRACE-COPD Trial Management Group meeting dated 27/11/2019. All participants agreed that these observations suggest that the eligibility criteria were not pragmatic, as most patients receive rescue packs with antibiotics and/or systemic corticosteroids before contacting our clinical teams. Since the TRACE-COPD trial aspires to be

pragmatic, we decided to change the eligibility criteria and accept those who have previously received antibiotics and/or systemic corticosteroids for the index exacerbation.

Based on several previous randomized controlled trials in patients with lower respiratory tract infections, but also in patients with COPD exacerbations, we are confident that procalcitonin could guide the discontinuation of antibiotics, for patients already receiving them[34,101].

It is somewhat less clear whether a single measurement of blood eosinophil count could guide the discontinuation of oral corticosteroids. In the CORTICO-COP trial, it appeared that systemic corticosteroids could suppress blood eosinophils. It was observed the administration of systemic corticosteroids often led to the suppression of blood eosinophils the following day, leading researchers to withhold systemic corticosteroids, but the eosinophil count was often again raised the next day (and systemic corticosteroids were restarted, in accordance with the study protocol). The safety of this approach was confirmed in the CORTICO-COP trial, which was a non-inferiority trial involving 318 patients presenting with severe COPD exacerbations. For this reason, we decided to follow a similar approach in the TRACE-COPD trial. More specifically, in patients who have already received systemic corcicosteroids for the index exacerbation, and have low blood eosinophils at presentation (≤2%), we will stop systemic corticosteroids, but we will also repeat blood EOS during the follow-up visit (1-3 days from presentation) and re-assess the need for steroids.

Inclusion of patients who are not treatment naïve for the index exacerbation has two important benefits: (i) this approach is more pragmatic, and (ii) it will accelerate study recruitment. Since the TRACE-COPD trial is a pilot trial and its main objective is to evaluate the safety and feasibility of conducting a larger scale trial to evaluate biomarker-guided treatments for COPD exacerbations, this was considered an appropriate amendment. Moreover, the initial power calculations are still considered valid for this pilot trial.

We still aim to include a subgroup of treatment naïve participants. This subgroup of patients will be evaluated separately. For this reason, we also changed our recruitment strategy, to facilitate recruitment of treatment naïve patients. More specifically, we will allow recruitment of participants from general practice surgeries, as participants seeking input from a general practitioner are more likely to be steroid naïve. Patients will also be approached during stable

disease state and will be asked to contact our research team in case of future exacerbations (during recruitment hours).

8.1.4. Trial Objectives and Design

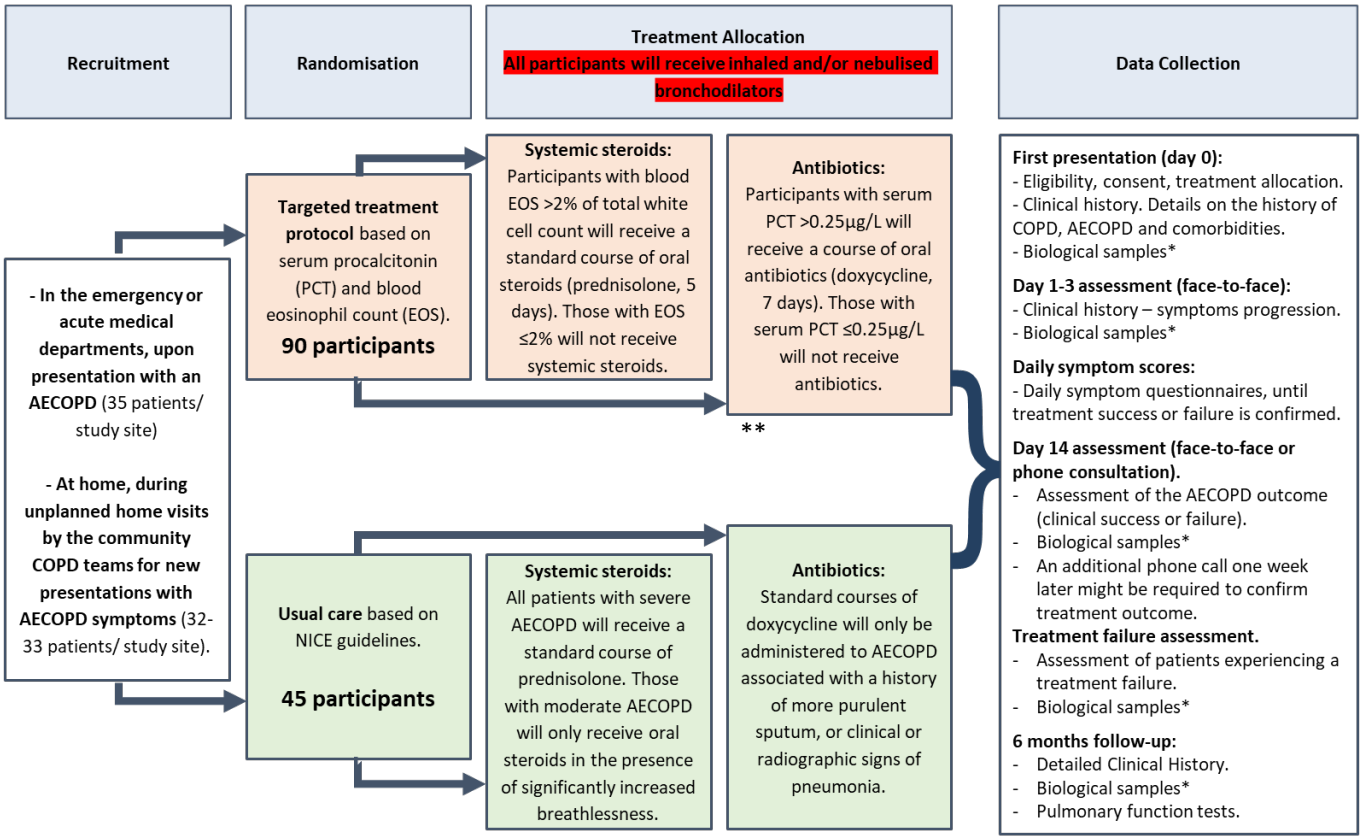
8.1.4.1. Trial Short Description

The TRACE-COPD trial will be a parallel group, open-label, randomised controlled trial. Participants will be recruited upon presentation with a moderate or severe AECOPD and they will be randomised to a biomarker group versus standard care. In the biomarker group, serum procalcitonin and blood eosinophil count will be used to guide the administration of antibiotics and systemic corticosteroids, respectively. More specifically, only patients with serum procalcitonin >0.25mcg/L will receive antibiotics and only those with EOS > 2% of total white cell count will receive oral corticosteroids. For participants who have already received antibiotics for the index exacerbation, prior to recruitment, the same cut-point of 0.25mcg/L will be used to guide the discontinuation of antibiotics (i.e. if procalcitonin is lower than 0.25mcg/L in patients who have already received antibiotics, these will be discontinued). For participants who have already received systemic corticosteroids for the index exacerbation, these will be discontinued at presentation if EOS ≤2%. However, EOS will also be measured in the first follow-up visit 1-3 days after presentation and if they are raised (>2%), then systemic corticosteroids will be restarted for a total duration of 5 days. This follow-up visit [1-3 days after presentation], will be timed at least 48 hours from the last dose of systemic corticosteroids - to avoid false negative measurements due to suppression of EOS by the previous steroids doses.

Standard care group will be managed per NICE guidelines: Oral corticosteroids will be administered to all patients presenting with severe exacerbations and to patients with moderate AECOPD characterised by significantly increased breathlessness, while antibiotics will be administered to patients presenting with AECOPD associated with a history of more purulent sputum, or clinical or radiologic signs of pneumonia, in accordance with the judgement of the responsible clinician (for the purposes of the TRACE-COPD trial, we will consider responsible clinician any member of the clinical team that regularly assess and manage patients with COPD exacerbations or any appropriately trained and delegated member of our research team).Participants will receive treatment (antibiotics and/or

systemic steroids) for 7/5 days and they will be followed for 6 months (24-27 weeks). After the recruitment visit, patients will be reviewed face-to-face or via a phone call three or four times (1-3 days after recruitment [this will be a face-to-face visit], 14-20 days after recruitment, 6 months (24-27 weeks) after recruitment, with an additional visit if required at 21-30 days after recruitment to confirm treatment success and an additional visit to assess participants in case of treatment failure). In addition, participants will be invited in a focus-group meeting to evaluate acceptability of the intervention and patients' experience throughout the TRACE-COPD trial.

8.1.4.2. Trial Flow chart/Schema



* Biological samples will include blood samples, spontaneous sputum samples, nasal swabs and optionally exhaled volatile organic compounds. Lung sound recordings may also be collected in every face-to-face visit. ** For patients who had already received corticosteroids before presentation, and have low baseline EOS, systemic corticosteroids will be discontinued, but EOS will be repeated 1-3 days after recruitment to confirm discontinuation.

8.1.4.3. Trial Objectives

The overarching objective of the TRACE-COPD trial is to contribute to the characterisation of distinct AECOPD types and the introduction of targeted treatments.

The main objective of the TRACE-COPD trial will be to compare the use of serum procalcitonin and EOS to guide the administration of antibiotics and systemic steroids for moderate-to-severe AECOPD versus standard care. Specifically, whether biomarker guidance can significantly decrease the administration of both antibiotics and systemic steroids, without adversely affecting the main patient-important outcomes of an exacerbation, such as rate of and time to treatment success, mortality, re-exacerbation and (re-)hospitalisation rate.

In addition, the TRACE-COPD study will evaluate whether it is safe and feasible to conduct a larger, multi-centre, confirmatory trial to evaluate biomarker-guided treatment for AECOPD, in the near future.

Finally, we will conduct mechanistic (biomarker) studies, aiming to evaluate the mechanisms that underlie different AECOPD types, specifically aiming to develop accurate diagnostic and prognostic biomarkers.

Primary objectives

The primary objectives of the TRACE-COPD trial are:

- To test whether the use of serum procalcitonin and blood eosinophil count to guide the administration of antibiotics and systemic steroids for patients presenting with a moderate or severe AECOPD can decrease the proportion of patients receiving antibiotics for the index exacerbation by 28% (absolute decrease) and the proportion of patients receiving systemic steroids by 40% (absolute decrease), compared to standard care.
- In addition, to test acceptability of the intervention, recruitment and consent rate in the acute and emergency hospital settings as well as in the community, in order to assess feasibility of a future non-inferiority, multi-centre pragmatic precision medicine trial to confirm the safety and effectiveness of different biomarker-led treatments for AECOPD.

Secondary objectives

The secondary objectives of the TRACE-COPD trial will be:

- To evaluate the safety of the intervention. More specifically, to evaluate whether use of the proposed biomarkers might adversely affect patient-important outcomes of AECOPD, such as rate of and time to treatment success, re-exacerbation and (re-)hospitalisation rate, mortality and adverse events. Importantly, to estimate the proportion of patients testing negative to both biomarkers and the safety of the intervention in this subgroup.
- To evaluate the adherence of clinicians and patients to the biomarker-guided treatment protocol.
- To assess the feasibility and challenges of recruitment of AECOPD in two different settings (acute and emergency hospital services and the community), the resources required for a future confirmatory trial and modifications to the protocol of the future, confirmatory trial in order to improve patients' experience and capture of the outcomes.
- To evaluate differences in systemic and exhaled inflammatory biomarkers, as well as the presence and load of bacteria and viruses in different AECOPD types.

Primary endpoints/outcomes

- Reduction in the proportion of patients receiving antibiotics for the index exacerbation (from recruitment, until confirmation of treatment success or after treatment failure).
- Reduction in the proportion of patients receiving systemic steroids for the index exacerbation (from recruitment, until confirmation of treatment success or after treatment failure).
- Acceptability of the intervention, recruitment and consent rate, in order to assess feasibility of a future, confirmatory trial. Acceptability will be evaluated in a qualitative manner, in focus-group meetings.

Secondary endpoints/outcomes

- Treatment failure rate at day 14 from recruitment. Treatment failure will be defined as lack of treatment success, significant symptoms deterioration leading to unplanned healthcare utilisation, or the clinical need for administration of additional antibiotics and/or systemic corticosteroids [e.g. positive blood cultures], or death, by day 14).
- Time-to-treatment success (treatment success: last day of the AECOPD will be defined as the first of three consecutive days when the patient will have returned to his normal health state or the first of seven consecutive days in which the patient will only report minor increase in symptoms compared to baseline, without fever or altered sputum colour).
- Re-exacerbation and re-hospitalisation at 6 months.
- Mortality during the index AECOPD (before treatment success) and at 6 months.
- Adverse events and serious adverse events at day 14.
- Increased length of admission or (re-)admission due to side effects to study medications
- Adherence to the intervention by clinicians and patients.
- The proportion of patients testing negative to both biomarkers and the safety of the intervention in this subgroup (secondary outcomes i-vii).
- Sample size for the future platform trial.
- Feasibility and challenges of community recruitment of AECOPD
- Resources required for the future trial, including clinic rooms, time investment in the programme by the study clinicians.
- To modify the protocol for the confirmatory trial based on researchers' and participants' feedback on the study experience, challenges in the conduction of the study and selected outcomes, thus aiming to provide a patient-centred, pragmatic RCT.
- Differences in systemic and exhaled inflammatory biomarkers in different AECOPD clusters
- Bacterial and viral presence and load in different AECOPD clusters.

8.1.4.4. Trial Design

The TRACE-COPD trial will be a parallel group, open-label, randomised controlled trial. It is designed to demonstrate the superiority of biomarker-guided treatment of AECOPD, with regards to the proportion of patients with AECOPD who will receive antibiotics and/or systemic steroids.

Study Setting

The TRACE-COPD trial will be conducted in two centres: Manchester University NHS Foundation Trust (Wythenshawe Hospital and possibly the Manchester Royal Infirmary) and Wrightington, Wigan and Leigh NHS Foundation Trust (Wigan Hospital). In addition, patients will be recruited from participating general Practices (see IRAS form). Approximately half of the participants will be recruited via the emergency or acute medical services of the participating hospitals, while the remaining will be recruited in the community, in walk-in clinics at the participating hospitals, in general practice surgeries or during home visits in response to patients' phone calls to the community COPD teams or participating general practitioners, reporting symptoms suggestive of AECOPD.

The study interventions will be performed by appropriately trained, delegated members of the research team.

End of trial

The end of TRACE-COPD trial is defined as the date of the last visit of the last patient undergoing the trial.

8.1.5. Trial Medications

Investigational Medicinal Product

Not applicable. The TRACE-COPD trial will not involve investigational medicinal products.

Non-investigational medicinal products guided by the study biomarkers

a. Doxycycline. Doxycycline is a tetracycline (antibiotic), routinely used in the treatment of different types of bacterial infections. It is licensed for AECOPD.

b. Prednisolone. Prednisolone is a corticosteroid, used to treat several types of allergic, inflammatory or autoimmune disorders. It is used as standard care in the management of AECOPD (licensed).

The aim of the TRACE-COPD trial is not to evaluate the efficacy and/or safety of these medications, but the efficacy and safety of biomarker guidance for AECOPD treatment (procalcitonin to guide the administration of doxycycline and EOS to guide the administration of prednisolone).

8.1.5.1. Legal status of the drug

All drugs used in the TRACE-COPD trial are non-investigational medicinal products, already having a marketing authorisation for use in AECOPD.

8.1.5.2. Reference safety information and known drug reactions

Reference safety information

The reference documents for the study drugs (doxycycline and prednisolone) will be the Summary of Product Characteristics available in the electronic Medicines Compendium (www.medicines.org.uk, eMC) and the British National Formulary (bnf.nice.org.uk, BNF, NICE). Both doxycycline and prednisolone are used in routine clinical care for decades and their safety profiles have been evaluated very thoroughly.

Known drug reactions and interaction with other therapies

Doxycycline and prednisolone are non-investigational medicinal products that will be used in the TRACE-COPD trial. Known drug reactions and interactions of doxycycline and prednisolone are described in the eMC and BNF (NICE). In brief, main drug reactions and interactions identified in the eMC and BNF are summarised below.

a. Doxycycline

Side effects:

Rare side effects: Anaphylaxis, angioedema, blood disorders (haemolytic anaemia, thrombocytopenia, porphyria and eosinophilia), exfoliative dermatitis, hepatotoxicity,

hypersensitivity reactions, pancreatitis, pericarditis, photosensitivity, rash, Steven-Johnson syndrome, urticaria.

Frequency not known: Antibiotic-associated colitis, anorexia, anxiety, benign intracranial hypertension, diarrhoea, dry mouth, dysphagia, flushing, fungal superinfection, headache, nausea, oesophageal irritation, tinnitus, visual disturbances, vomiting.

Special precautions:

Pregnancy: Tetracyclines should not be given to pregnant women

Breast feeding: Tetracyclines should not be given to women who are breast-feeding

Hepatic impairment: Tetracyclines should be avoided or used with caution in patients with hepatic impairment.

Renal impairment: Tetracyclines should be used with caution (avoid excessive doses).

Drug interactions:

Doxycycline might react with the following drugs (details are available in the BNF): Acenocoumarol, Acitretin, Alcohol (beverage), Alectinib, Alitretinoin, Aluminium hydroxide, Asparaginase, Atorvastatin, Calcium carbonate, Carbamazepine, Clavulanic acid, Crisantaspase, Daclizumab, Dactinomycin, Dantrolene, Demeclocycline, Didanosine, Enzalutamide, Ferric maltol, Ferrous fumarate, Ferrous gluconate, Ferrous sulfate, Flucloxacillin, Fluconazole, Fluvastatin, Fosphenytoin, Isoniazid, Isotretinoin, Itraconazole, Kaolin, Lanthanum, Leflunomide, Lenalidomide, Lomitapide, Lymecycline, Magnesium carbonate, Magnesium trisilicate, Mercaptopurine, Methotrexate, Micafungin, Minocycline, Mitotane, Oxytetracycline, Paracetamol, Pegaspargase, Phenobarbital, Phenytoin, Polysaccharide-iron complex, Pravastatin, Primidone, Rifampicin, Rosuvastatin, Simvastatin, Sodium feredetate, Sulfasalazine, Tetracycline, Tigecycline, Trabectedin, Tretinoin, Valproate, Vincristine, Warfarin, Zinc

b. Prednisolone

Side effects:

Frequency not known: Abdominal distension, acute pancreatitis, aggravation of epilepsy, aggravation of schizophrenia, amenorrhoea, anaphylaxis (in children), bruising, candidiasis, congestive heart failure, corneal thinning, Cushing's syndrome (with moon face, striae and acne), dyspepsia, ecchymoses, exacerbation of ophthalmic fungal disease, exacerbation of ophthalmic viral disease, exophthalmos, facial erythema, glaucoma, headache, hiccups, hirsutism, hypercholesterolaemia, hyperglycaemia, hyperhidrosis, hyperlipidaemia, hypersensitivity reactions (in children), impaired healing, increased appetite, increased intra-ocular pressure, increased intracranial pressure with papilloedema (usually after withdrawal) (in children), increased susceptibility to and severity of infection, leucocytosis, long bone fractures, malaise, menstrual irregularities, muscle weakness, myocardial rupture following recent myocardial infarction, nausea, negative calcium balance, negative nitrogen balance, oesophageal ulceration, papilloedema (in adults), petechiae, posterior subcapsular cataracts, potassium loss, psychiatric reactions (including euphoria, nightmares, insomnia, irritability, mood lability, suicidal thoughts, psychotic reactions and mood disturbances), psychological dependence, reactivation of dormant tuberculosis, scleral thinning, skin atrophy, sodium retention, suppression of growth (in children), telangiectasia, tendon rupture, thromboembolism, urticaria, vertebral fractures, vertigo, water retention, weight gain.

Special precautions:

Breast feeding: The benefit of treatment with corticosteroids during breast-feeding outweighs the risk.

Hepatic impairment: The plasma drug concentration may be increased. Oral and parenteral use should be undertaken with caution.

Renal impairment: Use by oral and injectable routes should be undertaken with caution.

Treatment cessation: Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension or death. A prolonged period is defined as more than 40 mg

prednisolone daily for more than 1 week, recently received repeated courses, or receipt of more than 3 weeks treatment.

Drug interactions:

Prednisolone might react with the following drugs (details are available in the BNF): Aceclofenac, Acemetacin, Acenocoumarol, Amifampridine, Aminophylline, Amiodarone, Amisulpride, Amphotericin, Anagrelide, Apomorphine, Arsenic trioxide, Artemether, Artenimol, Aspirin, Atazanavir, Atezolizumab, Atracurium, Bacillus Calmette-Guérin vaccine, Bambuterol, Beclometasone, Bedaquiline, Bendroflumethiazide, Benzydamine, Betamethasone, Bosutinib, Bromfenac, Budesonide, Bumetanide, Cabozantinib, Carbamazepine, Celecoxib, Ceritinib, Chlorothiazide, Chlorpromazine, Chlortalidone, Choline salicylate, Cisatracurium, Citalopram, Clarithromycin, Clomipramine, Clopamide, Cobicistat, Crizotinib, Cyclopenthiazide, Darunavir, Dasatinib, Deferasirox, Deflazacort, Delamanid, Dexamethasone, Dexibuprofen, Dexketoprofen, Diclofenac, Digoxin, Disopyramide, Dronedarone, Droperidol, Efavirenz, Enzalutamide, Eribulin, Erlotinib, Erythromycin, Escitalopram, Etodolac, Etoricoxib, Felbinac, Fenoprofen, Flecainide, Fluconazole, Fludrocortisone, Fluphenazine, Flurbiprofen, Formoterol, Fosamprenavir, Fosphenytoin, Furosemide, Glycerol phenylbutyrate, Haloperidol, Hydrochlorothiazide, Hydrocortisone, Hydroflumethiazide, Hydroxyzine, Ibuprofen, Idelalisib, Indacaterol, Indapamide, Indometacin, Influenza vaccine (live), Inotuzumab ozogamicin, Ipilimumab, Itraconazole, Ketoconazole, Ketoprofen, Ketorolac, Lapatinib, Levomepromazine, Lithium, Lofexidine, Lopinavir, Measles, mumps and rubella vaccine (live), Mefenamic acid, Meloxicam, Methadone, Methylprednisolone, Metolazone, Mifamurtide, Mifepristone, Mitotane, Mivacurium, Moxifloxacin, Nabumetone, Naproxen, Nepafenac, Nicorandil, Nilotinib, Nivolumab, Olodaterol, Ondansetron, Osimertinib, Paliperidone, Pancuronium, Panobinostat, Parecoxib, Pasireotide, Pazopanib, Pembrolizumab, Phenindione, Phenobarbital, Phenytoin, Pimozide, Piroxicam, Primidone, Quinine, Ranolazine, Ribociclib, Rifampicin, Risperidone, Ritonavir, Rocuronium, Rotavirus vaccine, Salbutamol, Salmeterol, Saquinavir, Sildenafil, Sodium phenylbutyrate, Somatropin, Sorafenib, Sotalol, Sulindac, Sulpiride, Sunitinib, Suxamethonium, Telavancin, Tenoxicam, Terbutaline, Tetrabenazine, Theophylline,

Tiaprofenic acid, Tipranavir, Tizanidine, Tolfenamic acid, Tolterodine, Torasemide, Toremifene, Triamcinolone, Typhoid vaccine (oral), Vandetanib, Vardenafil, Varicella-zoster vaccine, Vecuronium, Vemurafenib, Venlafaxine, Vilanterol, Vinflunine, Voriconazole, Warfarin, Xipamide, Yellow fever vaccine (live), Zuclopenthixol.

8.1.5.3. Dosing Regimen

a. Doxycycline: Doxycycline will be administered once a day, orally, for seven days. The first dose will be 200mg and subsequent dose will be 100mg. The first dose will be administered after randomization and following doses will be administered the following mornings, as per standard care. The responsible clinician could choose to administer intravenous antibiotics instead of oral doxycycline on the basis of severe infective/sepsis symptoms. In the biomarker group, the decision to administer antibiotics will be based on procalcitonin results, but if procalcitonin is raised, it will be in the discretion of the responsible clinician to choose the administration of intravenous antibiotics instead of doxycycline, based on clinical presentation/severity.

b. Prednisolone: 30mg prednisolone will be administered once a day, orally for five days. The first dose will be administered after randomization and following doses will be administered the following mornings as per standard care.

8.1.5.4. Drug storage, supply and accountability

Study drugs (doxycycline and prednisolone) will be stored in the hospital pharmacies and supplied, as per usual care. No special plans are required for drug storage, supply and accountability.

8.1.5.5. Subject Compliance

All participants will receive daily reminders to receive their medications (either by the nursing staff, when they are admitted to the hospital, or by mobile phone messages/calls, when they are not admitted or after being discharged). Compliance will be measured in daily, self-administered diary cards. In addition, patients will be enquired regarding compliance and regarding any remaining tablets at day 14 follow-up visit or phone call. Finally, compliance will be assessed in treatment failure assessments.

8.1.5.6. Trial restrictions

There will be no restrictions in the medications or dietary requirements or any other restrictions for the study participants. The only exceptions will be:

- Patients will be advised not to use their inhalers for 12 hours prior to their pulmonary function tests, unless they need them for symptoms control.
- Patients will be asked not to eat or drink anything apart from still water for 2 hours prior to exhaled volatile organic compounds sampling (optional test).
- Patients will be asked to avoid strenuous exercise for 2 hours prior to their pulmonary function tests or exhaled volatile organic compounds sampling.

8.1.5.7. Concomitant Medication

Participants will generally continue to receive all their established, long-term medications. These will include any medications that participants receive for medical problems other than COPD, as well as medications received for their COPD, including inhaled medications (short- or long-acting beta-2 agonists, short- or long-acting antimuscarinic agents or inhaled corticosteroids and their combinations), mucolytics, methylxanthines or phosphodiesterase-4 inhibitors. Responsible clinicians will be able to withhold or discontinue any of these medications if that is considered clinically appropriate. In addition, responsible clinicians will be able to introduce any new medications for medical problems other than COPD at any time-point during the study period. Responsible clinicians will be encouraged to optimize COPD treatment of all patients, following NICE and GOLD guidelines, upon presentation with an AECOPD.

Apart from the study drugs (doxycycline and prednisolone), all participants will receive additional inhaled and/or nebulized short-acting beta-2 agonists and short-acting antimuscarinic agents as per standard care. They will also receive controlled oxygen therapy aiming for oxygen saturation of 88-92%, if their pCO2 is above 5.5 kPa at presentation, or aiming for oxygen saturation of 94-98%, if their pCO2 is 5.5 or less at presentation. Participants may also receive mucolytics (carbocisteine and/or nebulized normal saline), if that is considered appropriate by the responsible clinician. Hospitalised patients might also receive deep venous thrombosis prophylaxis (low molecular weight heparins), per usual care.

8.1.6. Biomarkers

In the TRACE-COPD trial, we will use serum procalcitonin and blood eosinophil count to guide the administration of antibiotics and systemic steroids, respectively. We will use validated, near-patient assays to measure both biomarkers at home. Near-patient assays will allow real-time decisions to administer or withhold antibiotics and/or systemic steroids (in the intervention group), both in the hospital and community settings. For blood eosinophil count measured in the hospital we will either use the near-patient assay, or the hospital's analyser.

For procalcitonin we will use IB BRAHMS PCT, or BRAHMS PCT Direct, which are rapid point-of-care immunoassays for in vitro quantitative determination of procalcitonin in EDTA whole blood, or the Abbott hospital laboratory immunoassay. IB BRAHMS PCT has a measuring range of 0.08-10mcg/L, a lower detection limit of 0.08 mcg/L and a lower limit of quantification of 0.12mcg/L. BRAHMS PCT Direct has a lower limit of quantification of 0.22mcg/L. The Abbott system has a lower limit of quantification of 0.01mcg/L. The processing time for all assays is 20 minutes. Our cut-point will be 0.25mcg/L, which has been validated by numerous previous trials evaluating AECOPD as well as many other infections (see "Background"). Validation studies are available from:

IB BRAHMS PCT:

http://oml.bistravoda.ro/wp-content/uploads/PDF/samsung_ib_brahms_pct.pdf.

BRAHMS PCT Direct:

https://www.procalcitonin.com/pct-assays/pct-direct.html#correlation

The Abbott System:

https://www.corelaboratory.abbott/us/en/offerings/segments/sepsis

For blood eosinophil count, we will use the HemoCue WBC Diff NPT device, which stains white cells, receive several pictures and uses image analysis to quantify total white cells and a differential cell count including neutrophil, lympthocyte, monocyte, eosinophil and basophil counts. Its displayed range for total white cell count is 0.3-40*10^9/L. Lower limit of detection

has been determined to be $0.3*10^9$ cells/L for total white cell count and $0.1*10^9$ cells/L for blood eosinophil count. Validation studies are available from:

https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0ahUKEwjflO-Z-Y7cAhUrCMAKHZyEBmkQFgg5MAE&url=http%3A%2F%2Fwww.pathology.health.nsw.gov.au%2FArticleDocuments%2F239%2FHemoCue%2520WBC%2520Diff_Operating%2520Manual.pdf.aspx&usg=AOvVaw00VIrSzz-IKwGKmj6pnmxK. The HemoCue WBC Diff NPT device has also been validated for the quantification of EOS in patients with AECOPD[100].

For eosinophils our cut-point will be 2% of total white cell count. This cut-point has been validated, as it was used in the two previous studies evaluating EOS to guide the administration of systemic steroids in AECOPD (See "Background").

8.1.7. Selection and Withdrawal of Subjects

8.1.7.1. Informed consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person with delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki (2013 amendment). More specifically, all delegated members of the research team will receive relevant training and their capability to participate in the informed consent process will be evaluated by the PI.

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with stand routine care at the participating site (including the collection of identifiable participant data). Potential participants will receive verbal information about the project and a written patient information sheet (consent form and patient information sheet are available in the appendix). All their questions will be answered in detail. Their right to refuse participation without giving reasons will be respected. Since we will not allow delays in the administration of aetiological treatment to patients with AECOPD, patients will have limited time to think about the trial and decide whether they will consent to participate or not. However, patients will be able to withdraw consent at any time-point and if they choose to do so, they will receive standard

care, delivered by experienced respiratory clinicians. They will have the choice either to withdraw from treatment, but to allow the research team to follow their outcomes or to discontinue follow-up measurements as well.

Recruitment at presentation with an exacerbation may be challenging, as patients are symptomatic and might not be interested in considering a trial. However, we consider it important to randomise patients before the administration of any doses of antibiotics or systemic steroids. For this reason, we plan to evaluate recruitment rate using this approach for the first month of recruitment. In case of suboptimal recruitment rate during the first month, then we will allow the administration of standard care upon presentation with an exacerbation (among patients presenting to the hospital) and in this case, we will recruit within 12 hours from presentation, before the administration of a second dose.

We do not plan to seek consent from vulnerable groups. The PI takes responsibility for ensuring that all participants are protected and participate voluntarily in an environment free from coercion or undue influence. Patients who are unable to consent for themselves will be excluded from the TRACE-COPD trial. Participants who have given informed consent but lose their capacity to consent during the study will be withdrawn from the study. No further data or tissue would be collected, or any other research procedures carried out on or in relation to the participant. A person will be assumed to have the mental capacity to make an informed decision unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to make a decision for him or herself because of impairment or a disturbance in the functioning of their mind or brain. If mental capacity is doubtful, it will be evaluated by the member of the research team who is responsible for receiving an informed consent. A capable person will:

- understand the purpose and nature of the research
- understand what the research involves, its benefits (or lack of benefits), risks and burdens
- understand the alternatives to taking part
- be able to retain the information long enough to make an effective decision.
- be able to make a free choice

- be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)

Where participants are capable of consenting for themselves but are particularly susceptible to coercion, then they will be provided with adequate time and balanced information to allow them to make an informed, independent consent. If that is doubted, then patients will be excluded.

The participants will remain free to withdraw consent at any time without giving reasons and without prejudicing their further treatment and will be provided with a contact point where they may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner (although we do not expect the need for re-consent or provision of new information in the TRACE-COPD study).

In cases of persons who might not adequately understand verbal explanations or written information given in English, hospital interpreters will be sought, provided that this will not delay the initiation of AECOPD treatment. Otherwise, patients will be excluded from the study. If an interpreter is used, then back translation will be used to confirm the accuracy of translation.

8.1.7.2. Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Additional biological samples, including blood, sputum and nasal swabs for viral screening, and optionally recordings of the participants' lung sounds will be received at multiple timepoints (during every face-to-face visit) and will be stored in the NIHR Research Facility at Manchester University NHS Foundation Trust (Wythenshawe Hospital) for future use. These samples may be used in future exploratory mechanistic studies that will aim to further characterise different AECOPD types and to identify diagnostic and prognostic biomarkers for COPD. All data and samples that will be stored in the NIHR Research Facility at Manchester University NHS Foundation Trust (Wythenshawe Hospital) will be fully anonymised.

Participants of the TRACE-COPD trial will be given the option to opt out from the future mechanistic studies. If participants choose to withdraw their consent to collect samples for future mechanistic studies, they will be offered the option to allow or not allow the research team to use the material provided up to that point.

8.1.7.3. Inclusion and exclusion criteria

Inclusion Criteria

We will include:

- Males or females aged >40 years
- With a smoking history of at least 10 pack-years
- A previous clinical diagnosis of COPD
- Seeking medical advice for a moderate or severe AECOPD- Capable of giving an informed consent
- Subjects who are willing to allow his/her general practitioner, to be notified of their participation in the study.

We will define severe exacerbations as those requiring hospitalisation, based on NICE criteria and moderate as those requiring antibiotics and/or systemic steroids, but not hospitalisation, according to the judgement of the responsible clinician who will be unaware of procalcitonin and EOS levels (following NICE guidelines).

Exclusion Criteria

We will exclude:

- Those presenting with decompensated type 2 respiratory failure, requiring non-invasive ventilation and those admitted to the intensive care unit upon presentation.
- Patients with a primary diagnosis of pneumonia.
- Patients with a current diagnosis of asthma.
- Patients with known immunodeficiencies, cystic fibrosis, active tuberculosis, clinically significant bronchiectasis and those receiving long-term antibiotics
- Patients with concomitant diseases limiting their life expectancy to less than a year. People not able or keen to provide an informed consent for the study.
- Female participants who are pregnant or lactating.

- Patients diagnosed with medullary thyroid carcinoma (as this secretes procalcitonin).
- Participants in active clinical trials of investigational medicinal products (IMP) or people who participated in clinical trials of IMP during the preceding 6 months. We will not recruit patients participating in any trial on COPD exacerbations.
- Patients with known allergy or sensitivity to doxycycline or prednisolone or an absolute contra-indication to their use.
- Patients in active clinical trials of investigational medicinal products (IMP) or people who participated in clinical trials of IMP during the preceding 6 months.
- Patients participating in any trial on COPD exacerbations

8.1.7.4. Screening and Eligibility Assessment

Posters informing the patients about the TRACE-COPD trial and about the possibility that they might be approached by members of the research team for recruitment if their presentation is consistent with an AECOPD will be displayed in the Emergency and Acute Medical Departments of the participating hospitals and in the participating general practice surgeries. Patients identified after calling the community COPD teams reporting respiratory symptoms, consistent with an AECOPD, will be informed over the phone that there is an ongoing research project and they might receive further information and an invitation to participate during the home visit.

Potentially eligible patients will be identified upon presentation to the Acute or Emergency services of the participating hospitals or to the participating general practice surgeries, by the nursing or medical staff. Potentially eligible patients will be those aged >40 years, current or previous smokers, with a known history of COPD, presenting with symptoms consistent with an AECOPD. Such patients will be approached and assessed by delegated members of the research team, they will receive verbal and written information about the study and they will be asked to consent. After signing an informed consent, they will be screened for eligibility in more detail (all inclusion and exclusion criteria).

For potentially eligible patients who will not consent to participate or will not finally meet the eligibility criteria, we will ask verbal consent to collect limited, fully anonymized data. More specifically, these will include their age, gender, ethnicity, severity of AECOPD, whether they

attended the hospital or emergency services or sought help by the community COPD teams, the reason they were not eligible or the reason they declined participation. These data will be collated for Consolidated Standards of Reporting Trials (CONSORT), for assessing and reporting the generalisability of results.

Since we will not allow delays in the administration of aetiological treatment of patients with AECOPD, patients will have limited time to think about the trial and decide whether they will consent to participate or not (time from presentation to the administration of study treatment should be less than four hours, which is the national target for antibiotic administration for acute infections).

8.1.7.5. Identification and selection of Participants

Successive patients presenting with a moderate or severe AECOPD and accessing routine acute or emergency care at Manchester University NHS Foundation Trust (Wythenshawe Hospital and possibly the Manchester Royal Infirmary) or Wigan and Leigh NHS Foundation Trust (Wigan Hospital) or seeking help from the community COPD teams of these hospitals or participating general practice surgeries (see IRAS form) will be identified and approached for screening. More specifically, potential patients will be identified from the Emergency Departments triage teams or from the Acute Medical Unit Co-ordinating teams or by the medical and nursing staff of the participating general practice surgeries. In addition, the community COPD teams will identify patients who are contacting them by phone, as per routine care.

8.1.7.6. Randomisation Procedure

Randomisation

We will use validated software (nQuery 8, or newer versions), which will be managed by our in-house biostatisticians, independently. Patients will be stratified according to the recruiting hospital and setting. Stratified randomisation will be provided as separate lists for every stratification factor. Randomisation lists will be delivered to a person not otherwise involved in the TRACE-COPD trial, who will produce randomisation envelopes for each separate list, so that patients' allocation be concealed until assignment irreversibly occurs.

Patients will be allocated in a 2:1 ratio to the biomarker-guided treatment versus standard care, as this will allow more thorough evaluation of the safety of the intervention, especially among patients testing negative for both biomarkers.

Method of implementing the allocation sequence

For randomisation, we will use validated software (nQuery 8 or newer version), which will be managed independently by our in-house biostatisticians. The research team will receive separate, numbered and sealed randomisation envelops for every stratification factor (four groups of envelopes: one for each participating emergency/acute medicine department and one for each community COPD team). Only after acquisition of the patients' informed consent and confirmation of the eligibility, delegated members of the research team will open the envelopes (therefore, patient allocation will be concealed until assignment irreversibly occurs).

Blinding

The TRACE-COPD will be an open-label trial. However, the technicians conducting lung function testing will be blinded to the treatment allocation of the participants. In addition, members of the Trial's Management Group will also be blinded to patients' treatment allocation when considering AE/SAE. Self-administered, ordinally scaled symptom questionnaires will be completed by the participants and analysed objectively. All remaining efficacy and safety measures will be evaluated by objective measures (mostly objective proportions – e.g. mortality, or proportion of patients who received antibiotics for the index exacerbation).

Withdrawal of Subjects

All patients will be followed for six months, except from patients choosing to withdraw their consent. In cases or treatment failure or severe reactions to study drugs, patients will receive standard care by experienced respiratory clinicians, but they will continue to be part of the trial.

Adherence to study drugs (doxycycline and prednisolone) will be monitored and encouraged, but lack of adherence will not lead to withdrawal of the subject.

Expected Duration of Trial

The initiation of the trial will be defined as the recruitment of the first participant and the end of the trial as the last visit of the last patient (6-months follow up visit, which will take place between 24-27 weeks after recruitment). Each patient will participate in the trial for six months, while the total duration of the trial conduct will be one year and one month.

8.1.8. Trial Procedures

8.1.8.1. Visit details

a. Baseline visit: Participants will be recruited upon presentation in the acute medical or emergency services of the participating hospitals with an AECOPD or at their homes, during a home visit for an AECOPD, by delegated members of the research team. During the baseline visit, patients will sign an informed consent, assessed for eligibility, randomised and receive the initial study drug treatment. During this visit participants will be enquired on their medical history, they will complete symptom scores and they will undergo a physical examination. Blood samples, spontaneous sputum sample and nasal swabs will also be collected. Exhaled volatile organic compounds and lung sound recordings may also be collected.

b. Day 1-3 visit: Participants will be reviewed 1-3 days after recruitment. During this visit, medical history will be confirmed and further data on current patients' symptoms will be collected. Patients will undergo a physical examination if that is deemed necessary for clinical reasons, by the investigators. Self-administered daily symptom questionnaires that patients will be collecting will be reviewed. Adherence to study drugs will be evaluated and reinforced. Further blood samples, spontaneous sputum samples and nasal swabs will be collected. Exhaled volatile organic compounds and lung sound recordings may also be collected. This will be a face-to-face visit. Patients will be reviewed in the hospital if they are admitted or if they can easily attend an outpatient appointment. Otherwise, this could also be a home visit.

c. Day 14-20 follow-up: Participants will be reviewed either face-to-face or via phone call 14-20 days after recruitment. The aim of this follow-up visit/phone call will be to document adherence to study drugs and to assess treatment failure/ treatment success. Treatment success will be defined as the first of three consecutive days in which the patient will have returned to his/her normal health state or the first of seven consecutive days in which the

patient will only report minor increase in symptoms compared to baseline, without fever or altered sputum colour. Treatment failure will be defined as lack of treatment success, significant symptoms deterioration leading to unplanned healthcare utilisation, or the clinical need for administration of additional antibiotics and/or systemic corticosteroids, or death, by day 14. Additional blood, spontaneous sputum and exhaled volatile organic compounds samples, nasal swabs and lung sound recordings may be collected from patients who will be reviewed face-to-face at 14 days.

d. Day 21-30 follow-up: An additional phone call might be required to confirm treatment success or treatment failure.

e. Treatment failure assessment: Participants experiencing treatment failure will be reviewed within four days by the research group, either in one of the participating hospitals, or in their homes. If patients are admitted to a non-participating hospital, the research team will also visit the patients or liaise with the responsible clinicians in order to collect the appropriate data and samples. During this visit, treatment failure will be confirmed, adherence to study drugs will be reviewed, medical history will be assessed, patients will undergo physical examination if that is deemed necessary for clinical reasons, by the investigators, any remaining symptom questionnaires will be collected, and further biological samples will be collected, including blood samples, spontaneous sputum samples and nasal swabs. Exhaled volatile organic compounds and lung sound recordings may also be collected.

f. 6 months visit: Participants will be reviewed 24-27 weeks after recruitment. During this visit, medical history will be updated, and patients will undergo a physical examination. Any remaining symptom questionnaires will be collected, and further biological samples will be collected. These will include blood samples, spontaneous sputum samples and nasal swabs. Exhaled volatile organic compounds and lung sound recordings may also be collected. Finally, a spirometry will be performed. All participants will attend an outpatient appointment.

g. Focus group meeting: Participants will be invited to participate in focus group meetings (optional participation), to provide feedback on the acceptability of the intervention and the study experience. Also, to contribute to the design of a future, patient focused, confirmatory trial.

Procedures

Clinical history: Confirmation of the diagnosis of COPD; duration of COPD; exacerbations history; baseline symptom scores; quality of life; smoking history; COPD medications; non-drug treatments for COPD; cardiac problems; other medical problems; other long-term medications. With regards to the acute presenting complaint, we will collect exhaustive history on symptoms nature and duration, aiming to carefully screen for AECOPD mimics.

Symptom scores: Patients will be asked to complete daily symptom questionnaires until confirmation of treatment success. Then they will be asked to complete weekly symptom scores and also to complete symptom scores in case of recurrent respiratory symptoms. Moreover, at presentation patients will be asked to complete symptom scores reflecting their baseline symptoms (before the exacerbation). Patients will receive SMS/phone reminders to complete their daily and weekly symptom questionnaires which will be completed in printed forms. We may also produce an equivalent anonymized online form and in this case, participants will be able to choose either the printed or online version. The symptom scores will include the COPD Assessment Test (CAT) and two additional symptoms, namely wheeze and sputum purulence, to be rated between 0-5. At presentation, patients will be asked to grade their AECOPD on a 0-4 scale of perceived severity. The same severity scoring will be completing by the clinician first examining the patient.

Physical examination: Full physical examination, including detailed respiratory and cardiac examination.

Chest radiograph: A chest X-ray will be requested as part of the routine care of all patients presenting to the hospital. Patients recruited at home will only be referred for an X-ray in cases where pneumonia, pneumothorax or other lung pathologies are clinically suspected (as per clinical care).

Blood sampling: Venous blood sampling will be performed using a standard technique detailed in the SRM. Blood will be used for routine haematological (FBC) and biochemical (U&E, LFTs, CRP) screening and measurement of inflammatory biomarkers which will include procalcitonin. Remaining blood will be fully anonymized and stored in the NIHR Research Facility at MFT for future analyses of additional biomarkers.

Spontaneous sputum sampling: Spontaneous sputum samples will be performed using a standard technique detailed in the SRM. Sputum samples will be used for differential cell counting, bacterial and viral load assessment and soluble biomarker analysis. Remaining sputum samples will be fully anonymized and stored in the NIHR Research Facility at MFT for future analyses of additional biomarkers.

Nasal swabs: Nasal swabs will be collected using a standard technique detailed in the SRM. Nasal swabs will be used for the evaluation of viral presence and load. Remaining samples will be fully anonymized and stored in the NIHR Research Facility at MFT for future analyses of additional biomarkers.

Lung sound recordings: Lung sounds will be recorded using a Littmann stethoscope with an attached CE marked recording device (eKuore One: https://www.ekuore.com/en/electronic-digital-stethoscope/) during all face-to-face visits. Recordings will be analysed using neural network technology by a collaborating group, that will only have access to fully anonymised data. Our aim will be to evaluate whether different biomarker defined types of exacerbations are associated with distinct lung sound profiles.

Exhaled volatile organic compounds (VOCs) sampling: Exhaled VOCs may be collected. If so collection will occur with the Owlstone Medical sampling device. The samples will then be analysed with gas chromatography mass-spectometry at Manchester Institute of Biotechnology (fully anonymized samples).

Pulmonary function testing: Pulmonary function testing will include a spirometry before and after the administration of a bronchodilator (400mcg of salbutamol). DLCO (Diffusing capacity of the lung for carbon monoxide) may also be evaluated. Pulmonary function tests will be conducted using a standard technique detailed in the SRM.

8.1.8.2. Visit schedule

	Recruitment	**Treatment Phase**				**Follow Up**	**Qualitative**
Visits	1	2	3	4	5	6	7
	Recruitment visit	Day 1-3	Day 14-20	Day 21-30 (if required)	Treatment failure visit	6 months follow up.	Focus Group after completion of the study

Face-to-face (FTF) versus phone visits	FTF	FTF	FTF or phone	phone	FTF	FTF	FTF
Informed Consent	X						
Medical History	X	X			X	X	
Physical exam	X	Optional			Optional	X	
Vital Signs	X	X			X	X	
Eligibility assessment	X						
Randomisation	X						
Administration of study drugs (doxycycline &	X	X					
Assessment of treatment response (antibiotics &		X	X		X		
Adverse Events review		X	X	X	X	X	
Concomitant Medication review	X		X		X	X	
Evaluation of symptom scores	X	X	X	X	X	X	
Biological samples*	X	X	X		X	X	
Lung sound recordings	X**	X**	X**		X**	X**	
Spirometry						X	

Acceptability of the intervention, study experience.		X	X	X	X	X	X

* Biological samples will include blood samples, sputum samples and nasal swabs. They may also include exhaled volatile organic compounds. ** Optional

Table 26. TRACE-COPD Visit Schedule

8.1.8.3. Positive bacterial cultures

Blood cultures will not be routinely collected. In cases of positive blood cultures in patients not receiving doxycycline, we will administer appropriate antibiotics and will consider such cases as treatment failures. However, in patients who will have received antibiotics upon enrolment, we will not consider treatment failure the need to change the antibiotics in response to the presence of bacteria resistant to doxycycline in blood or sputum cultures. In case of a positive bacterial sputum culture in patients not receiving doxycycline, we will repeat procalcitonin measurement: If that is positive, then patient will receive appropriate antibiotics and we will consider that treatment failure; if procalcitonin is persistently negative, we will consider that the identified bacteria are colonising the airways of the patient but not causing active infection - therefore, we will not introduce antibiotics or consider that a treatment failure.

8.1.8.4. Analysis of samples

Samples will be collected as described previously during all face-to-face meetings with patients. Samples will include blood, sputum samples, nasal swabs and exhaled volatile organic compounds, using standard techniques detailed in the SRM.

Whole blood will be used for routine haematological (FBC) and biochemical (U&E, LFTs, CRP) tests, and measurement of various inflammatory biomarkers which will include procalcitonin. Remaining, fully anonymized samples will be stored at -80^{o}C in the NIHR Research Facility at Manchester University NHS Foundation trust, for future analyses.

Sputum samples will be sent to the microbiological laboratories of the participating hospitals for M,C&S. Remaining fully anonymized samples will be stored at -80^{o}C in the NIHR Research Facility at Manchester University NHS Foundation trust, for future analyses.

Nasal swabs will be used to evaluate the presence and viral load of prevalent respiratory viruses. Remaining fully anonymized samples will be stored at -80^{o}C in the NIHR Research Facility at Manchester University NHS Foundation Trust, for future analyses.

Exhaled VOCs samples will be analysed with gas chromatography mass-spectometry at Manchester Institute of Biotechnology (anonymized samples).

All samples that will be stored in the NIHR Research Facility at Manchester University NHS Foundation Trust will be fully anonymized after the completion of the TRACE-COPD study. They will be used in future mechanistic studies. Separate ethical application will be sought in the future for additional analyses, not covered by this application.

It will be the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the General Data Protection Regulation 2018. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

8.1.8.5. Qualitative assessments – Nested studies

All TRACE-COPD participants will be invited to participate in focus group meetings. These will aim to aid dissemination of the results of the TRACE-COPD study to the public, as well as the design and conduct of the future, confirmatory trial. Specific areas that will be evaluated include:

- The plain English report of the TRACE-COPD trial
- The acceptability of the intervention by patients, including relevant barriers and facilitators.
- Patients experience during the trial and ways of improving that.
- Primary and secondary endpoints for the confirmatory trial
- How should potential participants be approached for the recruitment
- The patient information sheet

Finally, these focus group meetings will aim to develop a vivid group of COPD patients and care-providers who will be interested in being actively involved in future research projects.

Analysis: We will identify and group themes reported in the focus groups and we will describe our findings narratively and using tabulated summaries.

8.1.9. Assessment of Efficacy

8.1.9.1. Primary Efficacy Parameters

The primary efficacy parameters of the TRACE-COPD trial will be:

- Reduction in the proportion of patients receiving antibiotics for the index exacerbation by 28% (absolute decrease).
- Reduction in the proportion of patients receiving systemic steroids for the index exacerbations by 40% (absolute decrease).

In this proportions, we will include patients who received antibiotics and/or steroids because they tested positive for the respective biomarkers, but also those who tested negative for the biomarkers but received treatment anyway, either due to treatment failure or due to lack of adherence to the treatment by the clinician or patient.

8.1.9.2. Secondary Efficacy Parameters

The secondary efficacy parameters of the TRACE-COPD trial will be:

- Treatment failure rate at day 14. Treatment failure will be defined as lack of treatment success, significant symptoms deterioration leading to unplanned healthcare utilisation, or the clinical need for administration of additional antibiotics and/or systemic corticosteroids [e.g. positive blood cultures in patients not receiving doxycycline], or death, by day 14.
- Time-to-treatment success. Time-to-treatment success will be measured in days from presentation with an AECOPD (baseline visit) to the last day of the exacerbation. Last day of the AECOPD will be defined as the first of three consecutive days when the patient will have returned to his normal health state or the first of seven consecutive days in which the patient will only report minor increase in symptoms compared to baseline, without fever or altered sputum colour.
- Re-exacerbation and (re-)hospitalisation at 6 months

- Mortality (during the index exacerbation and at six months) will be considered both an efficacy and safety outcome for the purposes of the TRACE-COPD trial.

8.1.10. Assessment of Safety

For assessment of safety, we will follow MFT SOP for Safety Reporting for CTIMPs conducted at MFT (event though the TRACE-COPD will not be a CTIMP).

8.1.10.1. Safety reporting

Definition of Adverse Events for the trial

In the TRACE-COPD trial we will follow the definitions of adverse events recommended by the MHRA GCP guide.

Adverse events (AE): An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.

- Signs, symptoms or clinical sequelae of a suspected interaction

- Signs, symptoms or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported a nonserious ADR/SAE).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to the hospital).

- Anticipated day-to-day fluctuations of the pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Adverse Drug Reaction (ADR): Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, for which there is a reasonable possibility that the untoward occurrence is causally related to the medicinal product. ADRs are a subject of AEs for a given medicinal product.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as a non-serious ADR or SAE.

Serious Adverse Event (SAE): A serious adverse event is any untoward medical occurrence that, at any dose:

- Results in death.

- Is life-threatening (events in which the subject was at risk of death at the time of t he event. It does not refer to an event, which hypothetically might have caused death, if it was more severe).

- Requires hospitalisation or prolongation of existing hospitalisation (In general, hospitalisation signifies that the subject has been detained [usually involving at least an overnight stay] at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs, unless they prolong hospitalisation or fulfil any other serious criteria - when AE are serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered AE.

- Results in disability/incapacity (Disability: substantial disruption of a person's ability to conduct normal life functions)

- Is a congenital anomaly/ birth defect.

- Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm that do not result in hospitalisation, or development of drug dependency or drug abuse.

TERM	**DEFINITION**
Adverse Event (AE)	Any **untoward medical occurrence** in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any **untoward and unintended response in a subject to an investigational medicinal product** which is related to any dose administered to that subject
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any **adverse event or adverse reaction** that: - **Results in death** - **Is life-threatening** - **Requires hospitalisation or prolongation of existing hospitalisation** - **Results in persistent or significant disability or incapacity** - **Consists of a congenital anomaly or birth defect.**

	Important medical events may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences. The term life-threatening in the definition of serious refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Suspected unexpected serious adverse reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is **not consistent with the information about the medicinal product** in question set out in the summary of product characteristics for that product.
Reference safety information	The information used for assessing whether an adverse reaction is expected. This is contained in either the **investigator's brochure** or the **summary of product characteristics**.

Table 27. Summary of the definitions of adverse events in the TRACE-COPD trials.

As the TRACE-COPD is not a drug trial but a study of how biomarkers can guide treatments and both doxycycline and prednisolone are licenced drugs (non-investigational medicinal products) that have been used for more than 25 years in the NHS, the principal investigators will review adverse events within 1 month and the Trial's Management Group every 3 months. SAE and SUSAR, with the exception of treatment failure and pneumonia, will be reported to the sponsor after every meeting of the Trial's Management Group. Treatment failure and pneumonia will only be reported in case of significant, unexpected imbalances between the randomised groups.

Expected Serious Adverse Events not requiring reporting

Treatment failure and pneumonia will be considered expected serious adverse events of the trial and they will not be considered to be SUSAR. Treatment failures and/or pneumonias will only be reported to the sponsor if there is a significant, unexpected difference in the rate of treatment failure or pneumonias across randomised groups.

Recording and reporting of SAEs AND SUSARs

All SAEs/SUSARs (apart from treatment failure and pneumonia) occurring from the start of trial treatment until the 14-days follow-up meeting will be recorded on a standard SAE/SUSAR form and will be evaluated for duration and intensity according to MedDRA (Medical Dictionary for Regulatory Activities). SAE/SUSAR forms must be faxed to the sponsor after every meeting of the Trial's Management Group (see paragraph 11.1.3 for further details). Once all resulting queries have been resolved the original form should also be posted to the Sponsor and a copy to be retained on site.

- The standard SAE/SUSAR form will include the following information:
- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. related to trial drug/investigation), in the opinion of the investigator
- Whether the event would be considered expected or unexpected.

Responsibilities for safety reporting

The Principal Investigator (PI) and delegated research staff are responsible for:

- Checking for AEs and ARs when participants attend for treatment/follow-up.
- For using medical judgement in assigning seriousness, causality and expectedness using the Reference Safety Information approved for the trail.
- Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Trial's Management Group and provide further follow-up information to the Trial's Management Group as soon as available.
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) coding to all SAEs and SARs.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

The Chief Investigator (CI) is responsible for reviewing:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning expectedness.
- Review of safety signal analysis and SAE trends in accordance with the MFT SOP for Safety Monitoring for MFT sponsored CTIMPs and the Risk Management Plan for MFT Sponsored CTIMPs.
- Reporting of SUSARs to the Competent Authority (MHRA) and REC within one week after every meeting of the Trial's Management Group.
- Checking for (every 3 months) and notifying PIs of updates of the Reference Safety Information for the trial.
- Reporting safety information to the Sponsor oversight committees identified by the trial (Trial Management Committee), according to the Risk Management Plan for MFT Sponsored CTIMPs.
- All the safety data for the trial and complete the relevant sections of the Safety Monitoring report which is submitted to Sponsor Oversight Committee, on a monthly basis.

The CI should regularly review the SAE log to conduct regular safety signal analysis to determine the continued safety of the drug within the study. The CI should conduct regular trend analyses to determine the continued safety of the drug within the study.

The sponsor is responsible for central data collection and verification of all reported SAEs, SARs and SUSARs onto a database.

Trial Management Group (TMG), in accordance with the trials terms of reference, periodically reviews overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual basis.

Out of hours contact arrangements

Participants will not be able to contact the research team out of hours. They will be advised to seek routine medical input out of hours. More specifically, they will be encouraged to contact the COPD outreach team or general practitioners, or attend the hospital emergency departments, in cases of significant deterioration of their symptoms or presentation of significant new symptoms out of hours. Participants will, however, be asked to contact the research team as soon as possible after such an event.

We do not consider it necessary for patients to be able to contact the research team out of hours as the drugs used in this study (doxycycline and prednisolone) have been used for decades and their safety profiles are well characterised.

8.1.10.2. The type and duration of the follow-up of subjects after adverse events.

Subjects experiencing a serious adverse event will be followed-up with daily phone calls until complete resolution of the SAE.

Any SUSAR related to the study drugs will need to be reported to the Sponsor irrespective of how long after study drug administration the reaction has occurred.

8.1.10.3. Reporting urgent safety measures

We will follow the MFT SOP for Urgent Safety Measures.

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

8.1.10.4. Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the study medications, or an unrelated event.

8.1.10.5. Overdose

In case overdoses with doxycycline and/or prednisolone are observed (from drug charts or patient comments), it will be the responsibility of the PI to use their clinical judgement to decide whether the study treatment will need to be stopped or continued. If a SAE is associated with the overdose, PIs should ensure that the overdose is fully described in the SAE report form.

8.1.10.6. Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Trial's Management Group.

If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

Responsible clinicians will have the option to discontinue individual participants from the TRACE-COPD study if the individual patients' circumstances change (e.g. in case of acute decompensated hypercapnic respiratory failure, when non-invasive ventilation is indicated, and antibiotic administration is of proved value.

8.1.10.7. Development safety update reports

We will follow MFT SOP for Development Safety Update Reporting

8.1.10.8. 11.8 Signal review and trend analysis

Safety signal review

MFT SOP for Safety monitoring for MFT Sponsored CTIMPs will be followed.

Ongoing safety signal detection: In general, safety will be evaluated during the scheduled visits with the investigator via monitoring signs and symptoms of known adverse events (AEs), and by identifying new AEs from physical examinations and clinical laboratory assessments as per the protocol, from reviewing the participants medical records and from asking the participant.

Review of safety signals for emerging risks: The CI or a delegated representative will obtain additional information on any newly identified or potential safety signal every three months by reviewing where relevant: Scientific literature, patients individual AE log, the data present for the study drugs in different clinical trials, product complaints and the Medicines Information database (pharmacy), digital media, previous awareness (SmPC) or patient leaflets, non-interventional studies, safety monitoring reports, spontaneous reports or regulatory communications.

The CI or their delegated representative will analyse the potential safety signal to determine if an adverse effect is associated with a study drug, quantitative strength of the association, consistency of the data, exposure response relationship, biological plausibility, experimental findings, possible analogies and the nature and quality of the data will be taken into account. The analysis may contain:

- strength of evidence for a causal effect; i.e., number of reports, exposure, temporal association, plausible mechanism, de/re-challenge, alternative explanation/ confounders
- seriousness and severity of the reaction and its outcome
- novelty of the reaction
- drug-drug interactions
- reactions occurring in special populations

The CI or their delegated representative will determine the timeline by which further activities should be undertaken, including any changes to the protocol/ risk mitigations for the trial.

The CI or their delegated representative is responsible for informing all sites of any relevant updates in relation to safety information.

Trend analysis of adverse events

MFT SOP for Safety monitoring for MFT Sponsored CTIMPs will be followed.

The CI, in conjunction with the PIs, Clinical Trials Manager and the Study Lead Research Nurse will conduct regular trend analyses on the incidents in the SAE log to determine the continued safety of the study. Trend analysis will include:

- Clinical review of all life threatening or SAEs resulting in death as soon as possible
- Clinical review of all other SAEs on a monthly basis including total numbers of SAEs to determine if there are more than would be expected.
- Clinical review of clinically significant AEs or recurring AEs on a 3 monthly basis

8.1.11. Data Handling

8.1.11.1. Types of data

We will collect longitudinal quantitative and qualitative data, including clinical measurements such as patient questionnaires, lung function measurements, biomarker levels. Tissue samples will also be collected for biomarker quantification.

8.1.11.2. Format and scale of the data

The raw data will be collected onto case record forms and also transcribed onto anonymized excel spreadsheets. Data will be arranged in a long format (i.e. single row per subject per study time point) for the purposes of longitudinal modelling (General Estimating Equations). Data will be transferred to SPSS version 22.0 (IBM) or alternative statistical package for analysis. The TRACE-COPD trial will consist of 135 records, including up to 6 timepoints per subject, respectively. Using these common software packages and data formats will facilitate data sharing.

8.1.11.3. Methodologies for data collection / generation

All data in this study will be collected to the highest standards guided by the European Directive on Good Clinical Practice in Clinical Trials, the General Data Protection Regulation, the MRC Guidelines for Good Clinical Practice in Clinical Trials, the MRC guidance on Good Research Practice: Principles and Guidelines, the MRC guidance on Personal Information in Medical Research and also by MFT SOP for Data Management. Confidentiality of patient data will be maintained by adherence to NHS confidentiality code of practice and the Caldicott Principles. As such identifiable data will not be contained within patient record forms or databases; unique patient identifier numbers will instead be used.

8.1.11.4. Data quality and standards

The consistency of data will be controlled by the use of validated methods and SOPs to ensure procedures are performed correctly, consistently and equipment is calibrated/performance checked regularly. Data entry into spreadsheets will be validated by 100% checks for accuracy.

8.1.11.5. Managing, storing and curating data.

In this study, clinical data will be collected into case record forms, spreadsheets and statistical databases. Crude data will be backed up by transcription onto anonymized spreadsheets and transfer into a database stored on a password protected data server hosted by the University

of Manchester and only accessible to delegated members of the research team and IT support. These data servers will be managed by our onsite Information Technology support services and responsibility for curating of the data rests with the Chief Investigator.

8.1.11.6. Metadata standards and data documentation

The methods used to collect data will all be documented in detail in our team and departmental SOPs with supplemental information about data collection such as equipment used stored in study logs and file notes. Detailed descriptions of spreadsheet and database variables will be entered where possible into the database software itself, but otherwise kept in supplementary files. The study protocol will also supplement the database.

8.1.11.7. Data preservation strategy and standards

Only anonymised data will be retained for long-term storage, to be used for future research and data sharing.

8.1.11.8. Data sharing

All subjects participating in the TRACE-COPD study will be consented specifically for sharing of anonymised study data and samples. Fully anonymised data, tissue samples and lung sound recording will be shared with academic and industrial collaborators who will contribute to this study, who may be based outside the UK but within the EU. After completion of the TRACE-COPD trial, we will facilitate sharing of anonymized clinical data and samples with other researchers, who may be affiliated with the Academia or the pharmaceutical industry, following a 3-year period of exclusivity. We will only consider sharing tissue samples and lung recordings with researchers and industrial partners who will be based in the EU. We will also consider sharing anonymised research data with researchers and/or industrial partners who may be based outside tf the EU. The exclusivity period will allow those contributing to make full use of the data. In accordance with MFT policies, sharing of research samples with other institutions and industrial collaborators will be regulated by appropriate agreements.

Details of the data repository available for sharing will be included on the COPD research team pages of the Centre for Respiratory and Allergy Research website, which is located in the University of Manchester website. Moreover, this information will be included in all relevant scientific publications.

Our data repository will have a Steering Committee comprising the Head of the Division of Infection, Immunity and Respiratory Medicine (Professor Angela Simpson), Chief Investigator of the COPD team (Professor Jørgen Vestbo), a Research and Development Manager and a Biostatistician. The Steering Committee will meet quarterly to oversee policy, to consider applications for access to data, and to discuss data management issues.

Anonymised safety data related to drugs produced by Boehringer Ingelheim will be shared with the funder.

8.1.11.9. What to record in patients' medical records

The MFT SOP for Study conduct will be followed. We will clearly document about all patients who have been spoken to about the TRACE-COPD trial, whether they consented to participate, whether they deemed eligible or non-eligible or whether they have chosen not to participate in the trial.

We will document all visit dates, visit numbers, patients' treatment allocation and adherence and relevant clinical data (medical history, drug history, allergies, study medications, changes in their treatment, relevant clinical examination, adverse events or adverse reactions, details of any SAE/SUSAR when relevant, date of the next visit).

8.1.12. Archiving

We will follow MFT 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 trial documents. Personal data of the patients will be stored for 6-12 months after completion of the study. Fully anonymized research data generated by the study will be stored for 15 years. Destruction of any essential documents will require authorisation from the Sponsor. Anonymized data will be boxed and archived off site.

8.1.13. Statistics and data analysis

8.1.13.1. Sample size calculation

The TRACE-COPD trial is powered to demonstrate an absolute 28% decrease in antibiotics administration for the index AECOPD (antibiotic administration of 47% and 75% for treatment and control arms respectively, based on results of our meta-analysis, 2-sided equality, power:

80%, type 1 error risk: 5%, drop-out rate: 10%, continuity correction factor, n=135). This population will also suffice to demonstrate a 40% decrease in systemic steroids administration for the index exacerbation and to assess recruitment and consent rates in two different centres, in the hospital and community settings (30 participants per hospital, per setting). As an exploratory, the TRACE-COPD will not be powered to demonstrate non-inferiority in the safety outcomes, however, potential safety signals would be captured.

8.1.13.2. Randomisation

For randomisation, we will use secured software (nQuery 8 or newer version), that will be managed independently by our in-house biostatisticians. Patients will be stratified according to the recruiting hospital and setting and will be allocated in a 2:1 ratio to the biomarkers or standard care arms. While the TRACE-COPD is an open label trial, treatment allocation will be concealed, until assignment irreversibly occurs.

8.1.13.3. Planned recruitment rate

Wythenshawe and Salford Royal Hospitals admit 1,000 and 700 patients with AECOPD per year, respectively. As expected, significantly more patients with AECOPD are admitted during the winter months. Moreover, the community COPD teams of the hospitals conduct 500-700 home visits every year. A recruitment pilot in Salford Royal Hospital concluded that we can recruit 30 patients presenting to the Acute Medical or Emergency Hospital services of either site, per month, during winter (eligible patients, prepared to consent). Therefore, we estimate that four months would suffice to recruit 135 patients presenting to the hospital. However, given that we will not recruit out-of-hours or during weekends, we decided to allow for six months of recruitment from both sites and both settings.

8.1.13.4. Statistical analysis plan

Patient characteristics and baseline imbalances will be presented narratively. Descriptive statistics will be used for feasibility outcomes. Antibiotic and steroid exposure rates will be analysed on (i) an intention-to-treat basis and (ii) overall exposure rate. We will use x2 statistic to compare exposure rates. Time-to-treatment success will be analysed by Kaplan-Meier curves and by log-rank test. All remaining analyses will be performed on an intention-to-treat basis by x2, two-sampled t-test or Mann-Whitney U test. We will perform further analyses to consider differences in the outcomes of moderate versus severe AECOPD (Cox proportional

hazards model for time to treatment success and generalised linear models for the remaining outcomes). In further analyses we will also take into account exacerbations history, baseline symptoms severity during stable COPD, smoking status and adherence to study treatments.

We will make every effort to follow all participants till the end of the 6 months period. Missing values will not be imputed for any of the primary or secondary endpoints.

8.1.14. Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator and Primary Investigators, a biostatistician, a member of the pharmacy team, a Clinical Trials Manager from the Manchester Clinical Research Facility and the Lead Research Nurse. As the TRACE-COPD trial is of limited size, the TMG will be responsible for the day-to-day running and management of the trial but will also act as a Trial Steering Committee and for this reason, it will also include two independent researchers (Prof. Dave Singh and Dr. Timothy Felton) and two patient representatives (TBC). The TMG role will include the following:

- Supervise the conduct and progress of the study, and adherence to the study protocol.
- Assess the safety and efficacy of the interventions during the study.
- Evaluate the quality of the study data.
- Review relevant information from other sources (e.g. related studies).
- Ensure patient safety is not being compromised.
- Ensure the study is being conducted in accordance with Good Clinical Practice (GCP) and the UK Clinical Trial Regulations.
- Escalate any issues for concern to the Sponsor, specifically where the issue could compromise patient safety or the integrity of the study or quality of the study data.

Decisions about continuation or termination of the study or suggested substantial amendments to the protocol will be the responsibility of the TMG, and the TMG will provide information and advice to the Sponsor and Funder in this regard.

The TMG will meet 4 times a year or more frequently, if that is deemed necessary by the Chief Investigator.

8.1.15. Peer review

The study protocol has been reviewed by world-leading researchers with relevant research expertise within the research team and within the North West Lung Centre and the University of Manchester (Prof. Jørgen Vestbo, Dr. Nawar Bakerly, Prof. Jaclyn Smith, Prof. Paul Dark). The protocol has also been peer reviewed by external experts: Prof. Richard Emsley (Manchester CTU), Prof. Julia Brown (Leeds CTU) and Prof Gordon Guyatt (McMaster's Department of Health Research Methods, Evidence and Impact, Canada). In addition, it has been reviewed by Boehringer Ingelheim R&D and Corporate Departments. All reviewers agreed that the study is timely, builds on previously published, peer-reviewed work, it is feasible, and its results could lead to improvement in the management of patients with COPD.

8.1.16. Public and Patient Involvement

Patients and public involvement (PPI) has been crucial in the prioritisation of this research topic, design of the TRACE-COPD trial and preparation of the project's plain English summary.

We conducted a focus group discussion with seven patients with varying severity of COPD and twenty face-to-face interviews with inpatients admitted with an AECOPD. After providing relevant training on the mechanisms, burden, diagnosis and management of COPD and exacerbations and the basic principles of clinical trials, we presented unanswered research questions identified by our team and by a recent ERS/ATS task force[90]. Finally, using open-ended questions and encouraging open dialogue, we elicited patients' views:

- Participants highlighted AECOPD as the largest source of burden to their lives. After we provided information on the heterogeneity of AECOPD and current diagnostic and therapeutic limitations, all participants considered characterisation and targeted treatment of AECOPD an urgent research priority, due to AECOPD burden and the significant risks of unnecessary use of antibiotics and systemic steroids.

- Next, participants contributed to: Prioritisation of the trial outcomes; Optimisation of the patients' experience during the trial; and Preparation of the plain English summary included in this application.

- Participants understood the need to enrol patients before receiving steroids or antibiotics but raised concerns regarding the feasibility of recruitment during an emergency presentation

with AECOPD. In response to these concerns, we developed a strict protocol to minimise time from presentation to treatment and improve patients' experience during recruitment. In addition, we decided to evaluate recruitment rate and participants' feedback during the first month of recruitment and to consider accepting the administration of a single dose of systemic steroids and/or antibiotics, prior to recruitment. Many previous AECOPD trials followed this approach.

- A COPD patient, after participating in our focus group, expressed an interest in further engaging with the trial and was invited to sit in the Trial's Management Group and co-ordinate PPI in the duration of this project.

We will continue seeking input from patients and the public throughout the TRACE-COPD trial and associated mechanistic studies.

Firstly, two COPD patients will sit in the trials' management group. Kenneth Leach, who has already agreed to sit in the TSC, was previously enrolled in a COPD trial and as a result of his participation, he has developed a deep understanding of his disease and of clinical research principles. The second patient will be identified by our PPI team. Both patients will attend two courses: The first will focus on how members of the public can be involved in clinical research, on the responsibilities of a lay member in a TSC, on the principles of clinical research and bioethics (to be organised by our PPI team). The second will be organised by our research team and will aim to provide an excellent understanding of the relevant background knowledge, rationale, objectives and methodology of the TRACE-COPD trial. Both patients will:

- Participate in all TSC meetings and provide feedback on the study progress. Importantly, they will review any concerns that study participants may raise and contribute to the optimisation of patients' experience throughout the trial.

- Participate in regular focus group meetings with COPD patients organised by our PPI team, to present the progress of the TRACE-COPD trial and elicit other patients' and stakeholders' views on the process.

- Contribute to the preparation of an informative leaflet for potential study participants and a plain English report of our results, to be disseminated to media and patients' organisations.

Upon completion of our study, we will conduct another focus group, with COPD patients and relevant stakeholders, to present our results, to further assess the acceptability of biomarker-guided treatments for AECOPD and to plan future research. The plain English report of our results will be circulated to patients by our PPI group, the British and European Lung Foundations, specifically aiming to raise awareness regarding the efficacy and safety of targeted treatments for AECOPD, the risks of unneeded administration of antibiotics and systemic steroids and to inspire patients and the public to support a future, confirmatory trial.

8.1.17. Ethics & Regulatory Approvals

The TRACE-COPD trial will be conducted in compliance with the principles of the Declaration of Helsinki (2013 amendment), the principles of Good Clinical Practice and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This study protocol and related documents will be submitted to the Integrated Research Application System (IRAS) and for ethical approval. Any subsequent protocol amendments will also be submitted for ethical approval to the IRAS. We will comply with relevant regulations, including Pharmacovigilance reporting. The Chief Investigator will submit a final report at conclusion of the trial to the Sponsor, the Funder, the allocated Research Ethics Committee (REC) and the MHRA, within the timelines defined in the Regulations.

8.1.17.1. Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC (via IRAS) for the trial protocol, informed consent forms, patient information sheets and other relevant documents.

Substantial amendments of the protocol that require review by REC will not be implemented until the REC and the participating NHS trust R&D departments grant a favourable opinion for the study.

All correspondence with the REC will be retained in the Trial Master File and Investigator Site Files.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is

the Chief Investigator's responsibility to produce the annual reports as required. We fully expect that the TRACE-COPD trial will be completed within one year.

The Chief Investigator will notify the REC of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

8.1.17.2. Regulatory Compliance

The protocol and trial conduct of the TRACE-COPD study will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee will apply for NHS permission from the site's Research & Development (R&D) department.

For any amendments that will potentially affect a site's NHS permission, the Chief Investigator/Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (both substantial amendments, and amendments considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D).

8.1.18. Quality Control

We will follow MFT SOP for Monitoring Procedures.

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained by Professor Dave Singh, as per the study monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standards operating procedures, the monitors will verify that the clinical trial is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Each member of the research team must have an up-to-date GCP training certificate (less than 3 years old) and to attend the trial induction training, organised by the chief and principal investigators.

Compliance to the study protocol will be closely monitored. We will follow MFT SOP for Recording and Reporting of Protocol Deviations and Violations, Serious Breaches of Protocol or GCP (see next paragraph).

8.1.19. Protocol Compliance

We will follow MFT SOP for Recording and Reporting of Protocol Deviations and Violations, Serious Breaches of Protocol or GCP.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and will not be used (e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol).

Extensive training of all members of the research team will aim to minimise accidental protocol deviations. However, if they happen, they will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as serious breach. The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor of a clinical trial will notify the licensing authority (MHRA) in writing of any serious breach of (a) The conditions and principles of GCP in connection with that trial; or (b) The protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

8.1.20. Amendments

If amendments are deemed necessary by the TSC, we will follow the procedure described in MFT SOP for Amendment approval. Substantial amendments of the protocol that require review by REC will not be implemented until the REC and the participating NHS trust R&D departments grant a favourable opinion for the study.

8.1.21. Post trial care

We will not routinely continue providing any intervention. After the 2 weeks of the intervention, patients will receive routine care.

8.1.22. Data protection and patient confidentiality

Patients' data protection and confidentiality will be a priority.

All investigators and trial staff must comply with the requirements of the General Data Protection Regulation 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Raw data from case record forms will be transcribed onto anonymized excel spreadsheets, where the participant's identifying information will be replaced by an unrelated sequence of characters.

As described, case record forms will be destroyed 6-12 months after the completion of the trial (after completion of the transcription of all data). In the meantime, they will be safely locked and only the chief and principal investigators will have access. More details on data management and maintenance are available in the chapter "Data Handling".

8.1.23. Publication Policy

8.1.23.1. Publication information

All data arising from the TRACE-COPD trial will be owned by the Sponsor and the Chief Investigator. Upon completion of the trial, the data will be anonymised, analysed and tabulated and a Final Study Report will be prepared and distributed to the Sponsor and the funder.

Results of the TRACE-COPD trial will be presented to national and international congress and will be published in high-impact, peer reviewed journals. The Chief Investigator will have full publishing rights and he will lead manuscript preparation and publication. All publications generated by the TRACE-COPD trial will follow the Consort Guidelines and checklist.

In addition, a plain English summary will be prepared and distributed to study participants, the Manchester BRC Patient and Public Involvement team and the British Lung Foundation.

Funding by Boehringer Ingelheim will be acknowledged in all publications generated by the TRACE-COPD trial.

8.1.23.2. Authorship eligibility guidelines and any intended use of professional writers

The final trial report (main trial publication) will be authored by the Chief and Principal Investigators and other researchers with substantial contribution to the project, who fulfil the International Committee of Medical Journal Editors (ICMJE) criteria for authorship.

Any additional manuscripts generated by the TRACE-COPD study will be authored by the Chief Investigator and other researchers with substantial contribution to the individual subprojects, who fulfil the ICMJE criteria for authorship. The final decision regarding manuscript authorship will lie with the Chief Investigator.

Manuscripts generated by the TRACE-COPD trial will be reported by the study investigators and we do not intend to use professional medical writers.

8.1.24. Insurance / Indemnity

The TRACE-COPD trial will be sponsored by Manchester University NHS Foundation Trust and therefore NHS indemnity scheme will apply for the design, management and conduct of the research.

8.1.25. Financial Aspects and disclosures

8.1.25.1. Financial aspects

Funding to conduct the TRACE-COPD trial is provided by Boehringer Ingelheim. Trial costs were estimated by the investigators and approved by the Manchester Foundation Trust Research and Innovation Division and Salford Royal Hospital Research and Development Department.

8.1.25.2. 26.2 Disclosures

The TRACE-COPD trial will be funded by Boehringer Ingelheim as an investigator initiated trial. Boehringer Ingelheim was not involved in the design of this study. None of the authors have any conflicts of interest relevant to this work.

The Chief Investigator (Prof Jørgen Vestbo has received personal fees from Chiesi Pharmaceuticals, Boehringer Ingelheim, Novartis and AstraZeneca, outside this work.

Alexander Mathioudakis (PI – Wythenshawe Hospital) has received personal fees from GlaxoSmithKline and Boehringer Ingelheim, outside this work.

8.2. Chapter 4: Methodological Systematic Review

8.2.1. List of Included Studies

8.2.1.1. Systematic Reviews

1. Ma Z, Zhang W. Short-term versus longer duration of glucocorticoid therapy for exacerbations of chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2016 Aug 6.

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8.3. Chapter 5: The Core Outcome Set

8.3.1. The DECODE-NET investigators

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8.3.2. List of professional and patient organizations that facilitated the Delphi survey dissemination

We are very thankful to the following organizations for distributing the Delphi Survey to their memberships and/or through their social media: Allergy and Asthma Network, Alpha-1 Netherlands, Alpha-1 Spain, Alpha-1Plus (Belgium), Asian Pacific Society of Respirology (APSR), Association of Pulmonologists of Greece, Australian Lung Foundation, Brazilian Respiratory Society, British Lung Foundation (BLF), COPD Canada, COPD Foundation (USA), COPD Ireland, Danish Lung Association, Dutch Lung Foundation, Georgian Respiratory Association, Global Allergy & Airways Patient Platform, Greek Association of General Practitioners, Hellenic Thoracic Society, Hungarian Respiratory Society, Indonesian Respiratory Society, Irish Thoracic Society, Jedra Organisation to Help Those Suffering of Lung Cancer and Other Lung Diseases (Croatia), Kazakhstan Respiratory Society, Lovexair (Spain), National Institute for Health Research (NIHR) BEAT Respiratory Disease, NTM Info & Research (USA), Pan African Thoracic Society (PATS), Philippine College of Chest Physicians, Respiriamo Insieme (Italy), Russian Respiratory Society, Swiss Society of Pulmonology, Sociedad Española de Neumología y Cirugía Torácica (SEPAR), Swedish Heart and Lung Association, Task Force for Lung Health, Thoracic Society of Australia and New Zealand (TSANZ), US COPD Coalition, Turkish Respiratory Society.

8.3.3. Systematic review of Qualitative Data: Search strategy and PRISMA Flowchart

Chronic Obstructive Pulmonary Disease

#1 Chronic Obstructive Pulmonary Disease [MH]

#2 Lung Diseases, Obstructive [MH:NOEXP]

#3 Emphysema [MH]

#4 Chronic Bronchitis [MH]

#5 COPD [tiab]

#6 COAD [tiab]

#7 "Chronic Bronchitis" [tiab]

#8 Emphysema [tiab]

#9 Obstructive[ti]

#10 (Pulmonary OR Respiratory OR Airway OR Airflow OR Lung)[ti]

#11 #9 AND #10

#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #11

Exacerbation

#13 Disease Exacerbation [MH]

#14 Exacerbation [tiab]

#15 Exacerbation* [tiab]

#16 flare* [tiab]

#17 #13 OR #14 OR #15 OR #16

Qualitative

#18 qualitative [tiab]

#19 themes [tiab]

#20 #18 or #19

Disease outcomes

#21 symptom* [tiab]

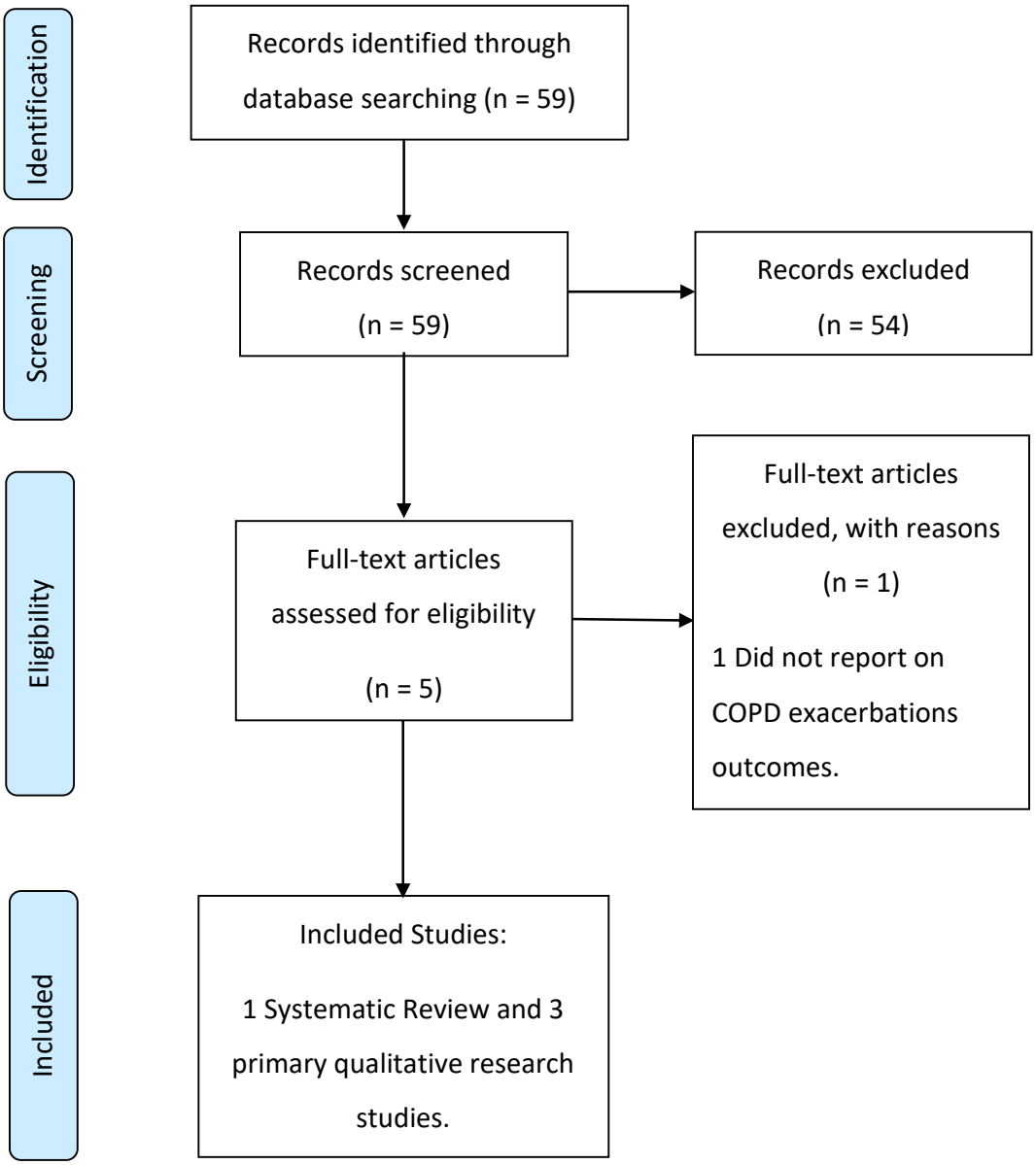
#22 treatment* [tiab]

#23 living with [tiab]

#24 patient* [tiab]

#25 #21 OR #22 OR #23 OR #24

#26 #12 AND #17 AND #20 AND #25


Identification
Records identified through database searching (n = 59)
Screening
Records screened (n = 59)
Records excluded (n = 54)
Eligibility
Full-text articles assessed for eligibility (n = 5)
Full-text articles excluded, with reasons (n = 1)
1 Did not report on COPD exacerbations outcomes.
Included
Included Studies:
1 Systematic Review and 3 primary qualitative research studies.

8.3.4. Summary of the Delphi Survey Results

COPD exacerbations outcomes considered	Round 1			Round 2			Final set
Sources of outcomes Methodological SR Qualitative interviews Delphi survey (Round 1)	**Outcomes' selection results (for each round)** Prioritized by all groups Prioritized by 1-2 groups Not prioritized by any group	Patients & Patient representatives	Health professionals	Researchers	Patients & Patient representatives	Health professionals	Researchers	
Death outcomes								
Death from COPD Exacerbation		93.0%	82.3%	93.1%	81.8%	94.5%	96.9%	
Death from any cause		63.6%	64.6%	68.9%	68.5%	74.8%	84.0%	
Clinical and Physiological Outcomes								
Anxiety		29.8%	33.6%	34.7%	35.5%	27.0%	28.3%	
Breathlessness		91.2%	75.0%	84.3%	79.3%	93.3%	94.9%	
Chest discomfort		49.7%	49.8%	40.6%	15.8%	5.8%	8.2%	
Fatigue		47.6%	53.8%	45.9%	54.2%	46.3%	44.7%	
Cough		52.3%	49.4%	53.1%	49.3%	54.3%	53.6%	

Coughing up blood (haemoptysis)	56.7%	62.0%	43.3%	62.1%	58.3%	46.8%	
Production of dark-coloured sputum	60.2%	52.5%	50.2%	56.7%	58.5%	53.6%	
Sputum amount	52.3%	38.3%	40.8%	38.4%	42.0%	35.5%	
Sputum thickness (ease of expectoration)	46.7%	39.3%	36.1%	40.4%	41.8%	29.0%	
Wheeze	52.3%	40.3%	42.0%	39.4%	46.8%	35.2%	
Appetite	21.6%	25.7%	20.5%	24.6%	17.5%	14.0%	
Change in weight	29.8%	29.8%	30.2%	33.5%	25.8%	23.9%	
Respiratory muscle strength				65.5%	58.8%	47.8%	
Low mood/ depression	32.4%	39.2%	39.3%	41.9%	35.5%	40.6%	
Sleep quality	37.1%	51.2%	38.6%	51.7%	38.3%	35.5%	
Early morning symptoms	39.1%	33.9%	34.0%	36.5%	32.0%	25.6%	
Night time symptoms	50.7%	41.5%	42.3%	45.8%	50.3%	41.3%	
Treatment success (or failure)	77.2%	67.5%	74.7%	80.3%	87.8%	89.1%	
Worsening of symptoms after the initial treatment	69.6%	64.0%	66.6%	71.9%	78.5%	77.1%	
Disease progression	80.1%	78.1%	72.5%	83.7%	88.8%	86.7%	
Future exacerbations	80.7%	78.1%	72.5%	75.9%	89.3%	90.4%	
Lung function during and immediately after the exacerbation	56.2%	70.3%	46.5%	71.4%	54.3%	43.0%	

Permanent deterioration in lung function	80.5%	82.6%	67.8%	87.7%	88.5%	82.3%	
Levels of oxygen and carbon dioxide in the blood (arterial blood gases)	71.8%	70.6%	64.6%	76.4%	80.3%	75.4%	
Development of pneumonia	78.0%	73.3%	70.4%	76.4%	86.8%	83.6%	
Development of resistant bacteria	73.1%	71.4%	61.5%	73.4%	80.8%	70.6%	
Damage of lung cells and lung tissue	64.7%	78.2%	51.9%	81.3%	71.5%	57.3%	
Infection by bacteria (bugs) or viruses	64.2%	69.8%	57.1%	72.4%	68.0%	64.8%	
Inflammation in the lungs/airways	59.9%	70.2%	47.0%	73.4%	61.5%	49.1%	
Adverse event outcomes							
Adverse events of treatments	56.9%	58.4%	61.4%	60.6%	58.3%	65.9%	
Serious adverse events from treatments	84.1%	75.0%	89.0%	76.8%	89.5%	93.5%	
Development and/or progression of other diseases (e.g. heart attack)				67.5%	69.5%	69.6%	
Resources use outcomes							
Need for hospital admission for the presenting exacerbation	76.4%	56.0%	85.2%	69.0%	84.6%	90.8%	
Length of hospital stay for the exacerbation	57.7%	47.0%	64.3%	45.3%	62.3%	68.3%	
Future hospital admissions	63.4%	47.8%	69.6%	52.2%	70.5%	76.5%	

Need for non-invasive ventilation (NIV) use for the exacerbation	74.9%	62.6%	67.9%	64.0%	83.5%	81.9%	
Length of non-invasive ventilation (NIV) use for the exacerbation	58.6%	60.0%	52.8%	58.1%	60.25%	57.0%	
Need for admission to the intensive care unit for the exacerbation	78.4%	71.1%	72.7%	71.9%	86.8%	88.7%	
Length of stay in the intensive care unit for the exacerbation	64.9%	65.2%	59.8%	63.1%	72.8%	71.0%	
Need for additional medications to achieve symptoms control	59.2%	61.2%	53.8%	64.5%	59.5%	57.3%	
Need for long-term administration of supplemental oxygen after the exacerbation				58.6%	62.8%	66.9%	
Need for long-term use of non-invasive ventilation (NIV) after the exacerbation				55.7%	69.5%	65.5%	
Life impact outcomes							
Ability to exercise	53.0%	53.4%	57.2%	57.6%	51.0%	60.4%	
Physical strength	42.8%	47.6%	39.8%	48.8%	38.3%	35.5%	
Walking distance	64.9%	56.4%	64.0%	57.6%	67.3%	68.3%	
Activities of daily living	72.6%	61.8%	73.7%	70.4%	82.5%	84.6%	
Health related quality of life	75.0%	69.6%	79.3%	75.4%	82.5%	87.7%	
Social engagement/ isolation	50.9%	49.4%	47.7%	54.2%	50.5%	50.5%	
Treatment adherence	76.3%	64.2%	73.9%	72.4%	83.8%	84.6%	

Impact of family members and caregivers		56.7%	50.3%	47.4%	
Impact on sexual function		36.0%	36.3%	37.5%	

Table 28. Summary of the Delphi survey results. The proportion of participants that considered a particular outcome critical (both rounds).

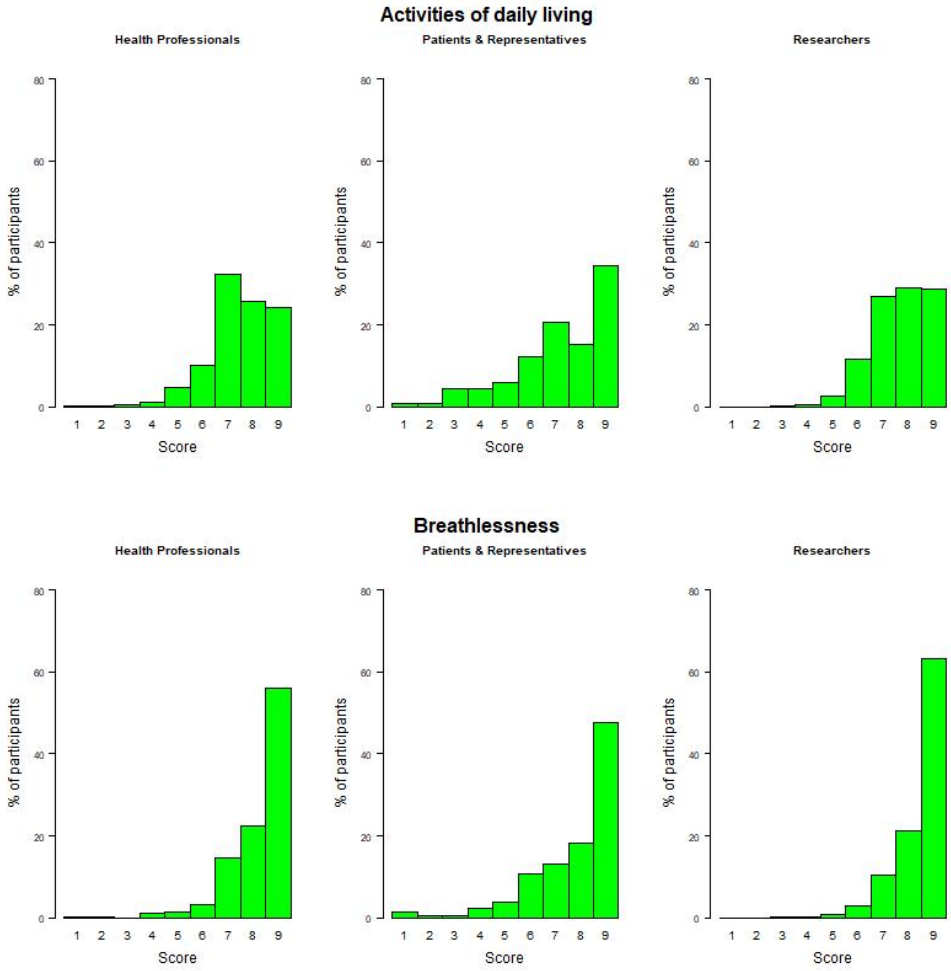
8.3.5. Detailed results of the second round of the Delphi survey

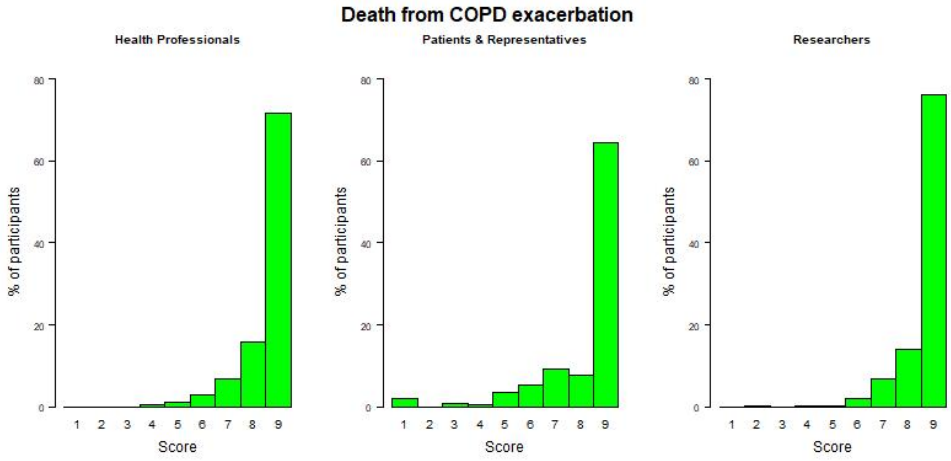
Colour coding:

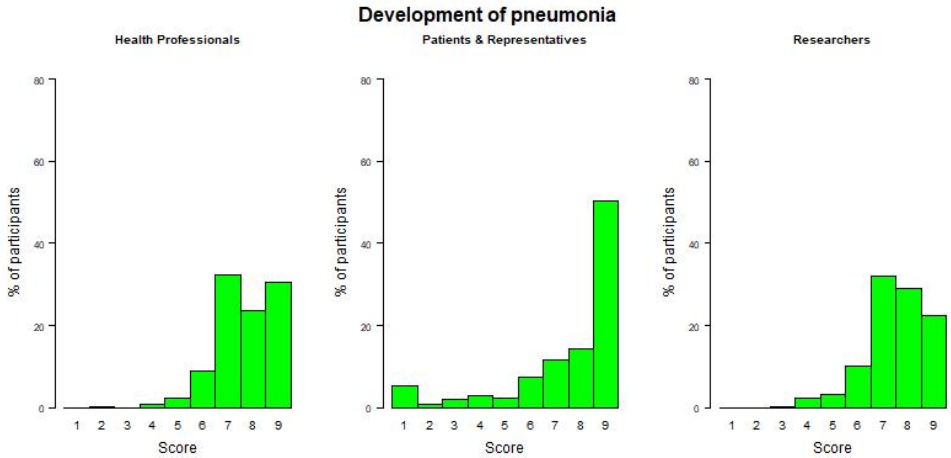
Green: The outcome was considered a priority by the respondents group. More specifically, it was rated between 7-9 (critical) by ≥70% and between 1-3 (of limited importance) by ≤15% of all participants from that stakeholder group.

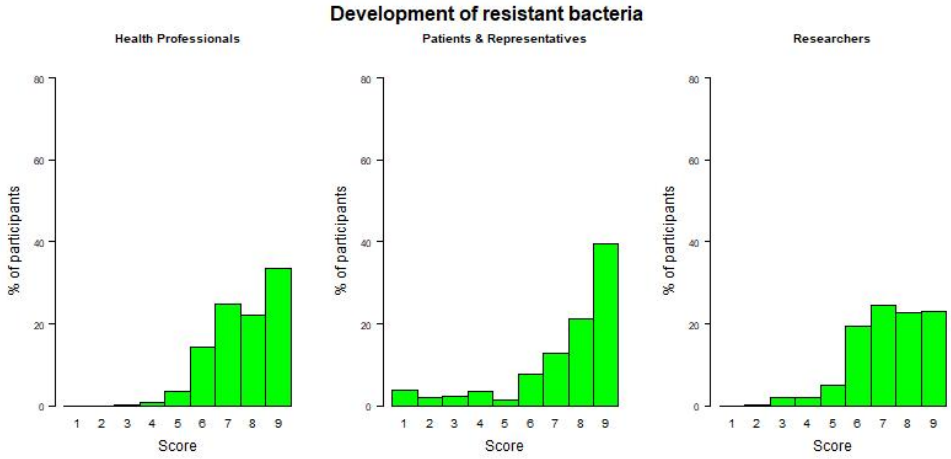
Red: The outcome was considered of limited importance by the respondents group. It was rated between 7-9 (critical) by ≤50% of all participants from that stakeholder group.

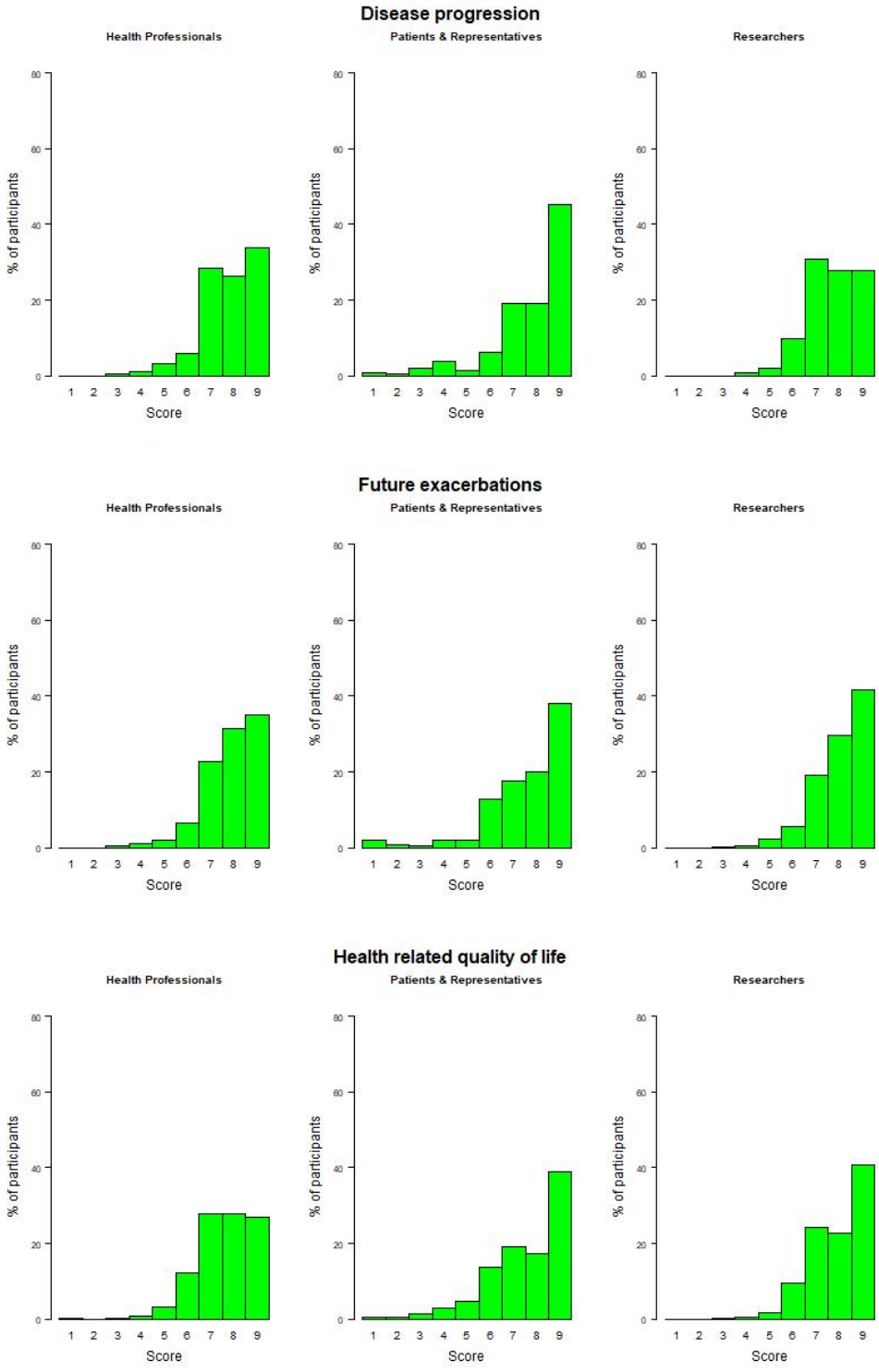
OR: The ratings were intermediate and did not fulfil either of the previously described thresholds.

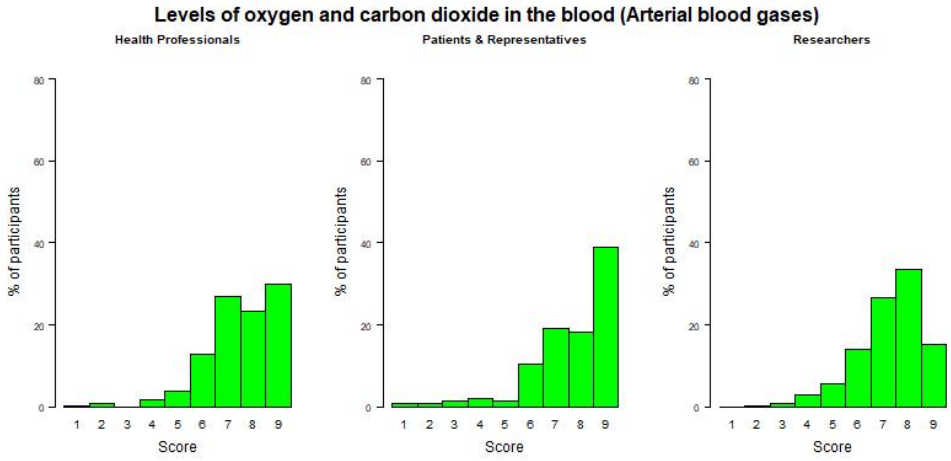


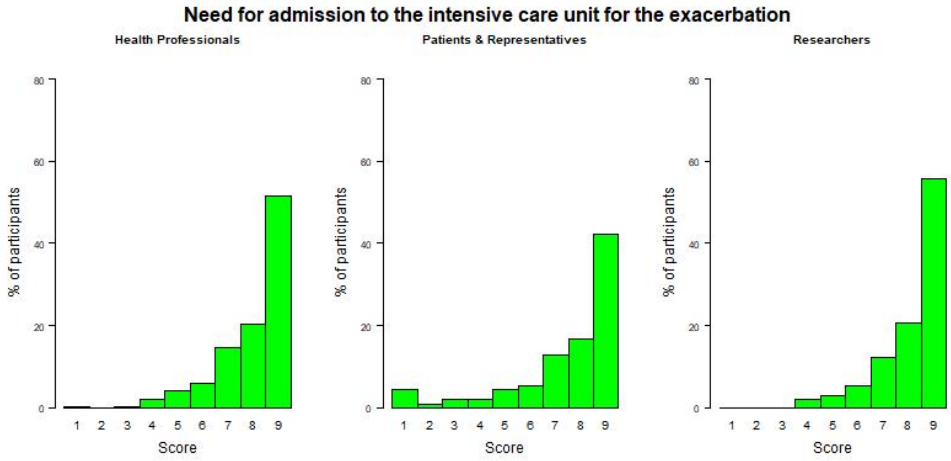

Death from COPD exacerbation
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

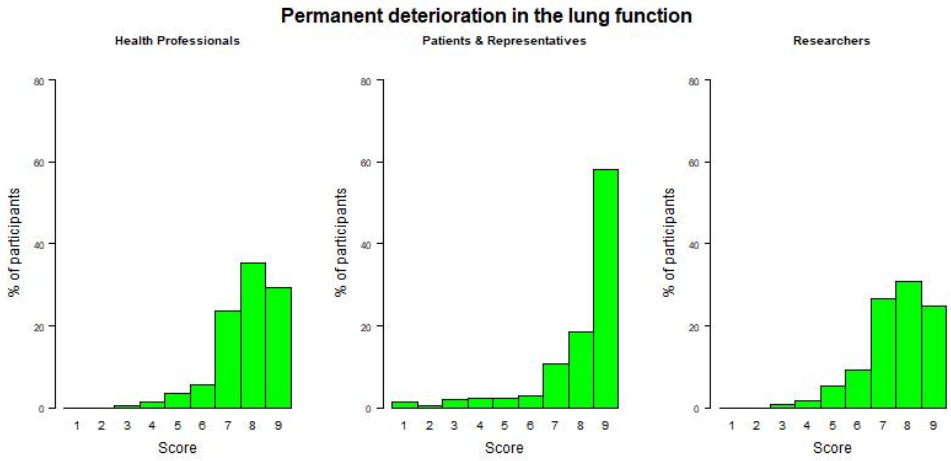

Development of pneumonia
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

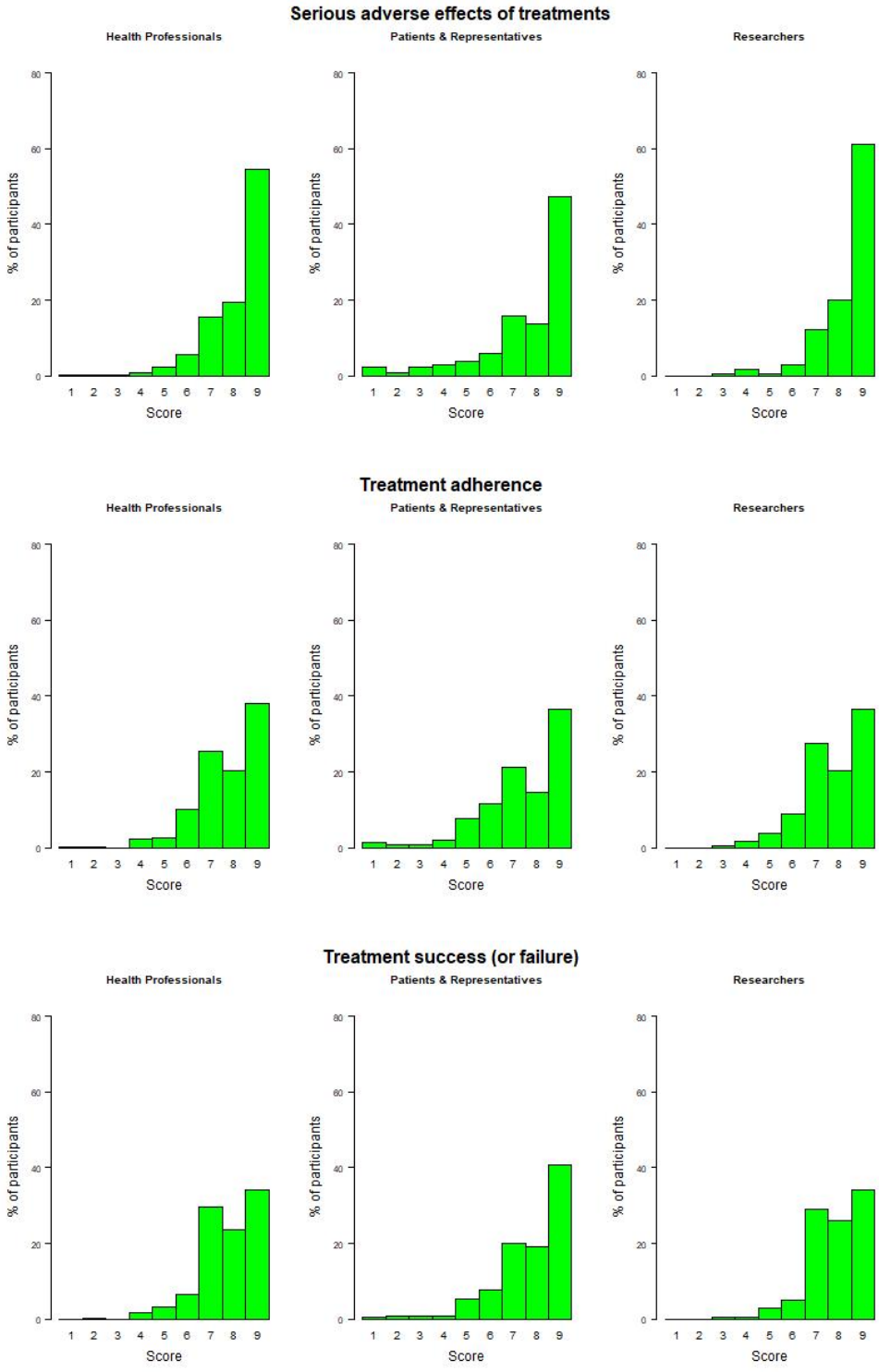

Development of resistant bacteria
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

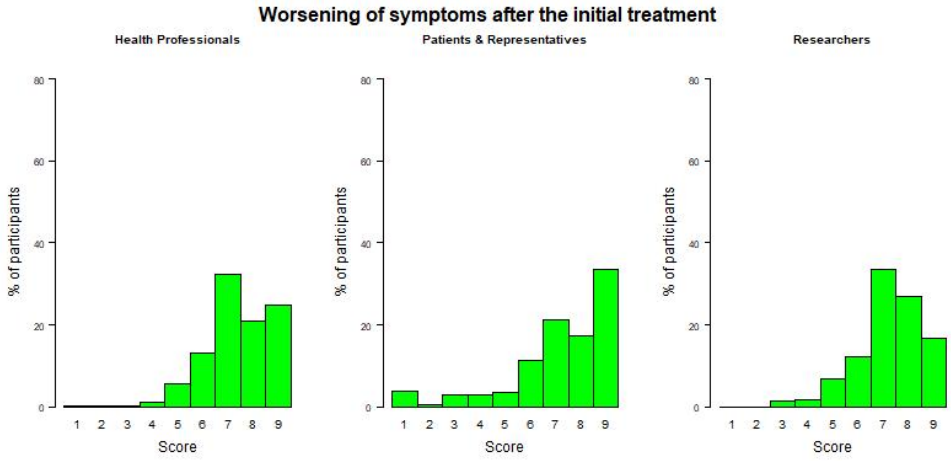

Disease progression
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Future exacerbations
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Health related quality of life
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

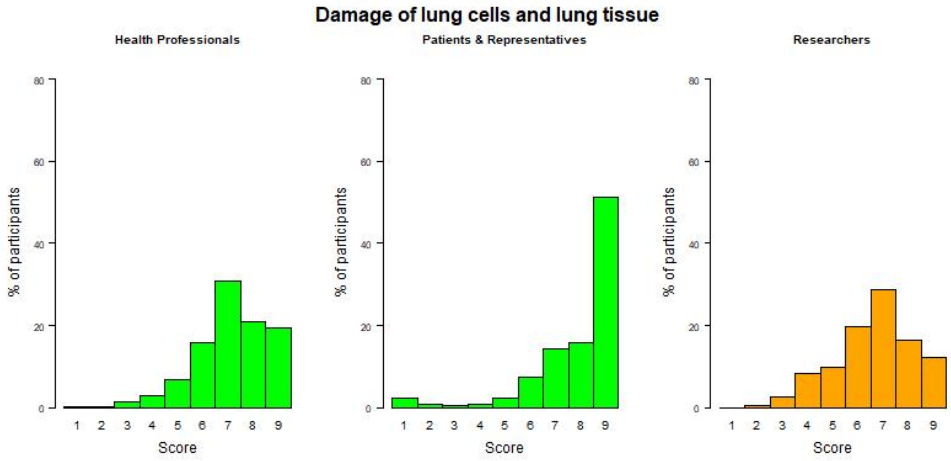

Levels of oxygen and carbon dioxide in the blood (Arterial blood gases)
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

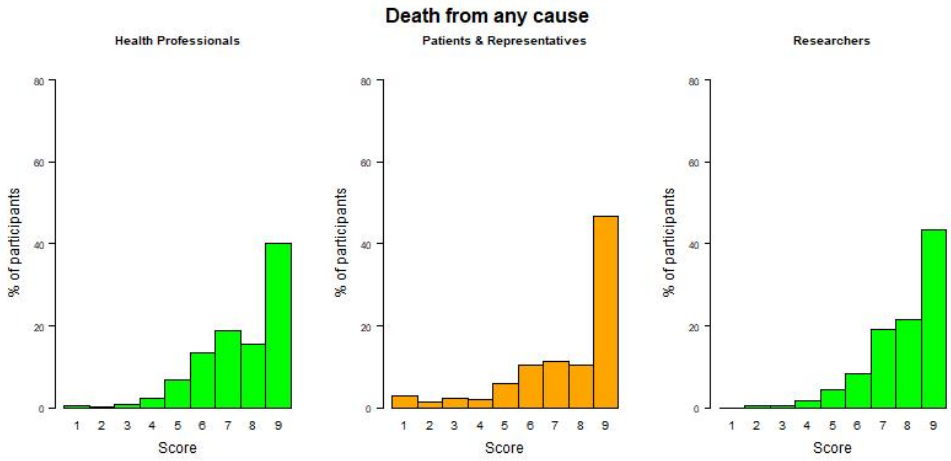

Need for admission to the intensive care unit for the exacerbation
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

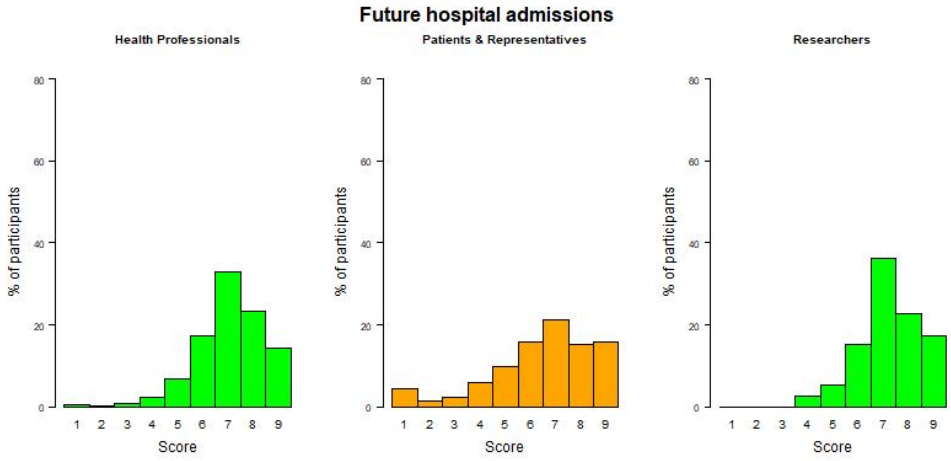

Permanent deterioration in the lung function
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

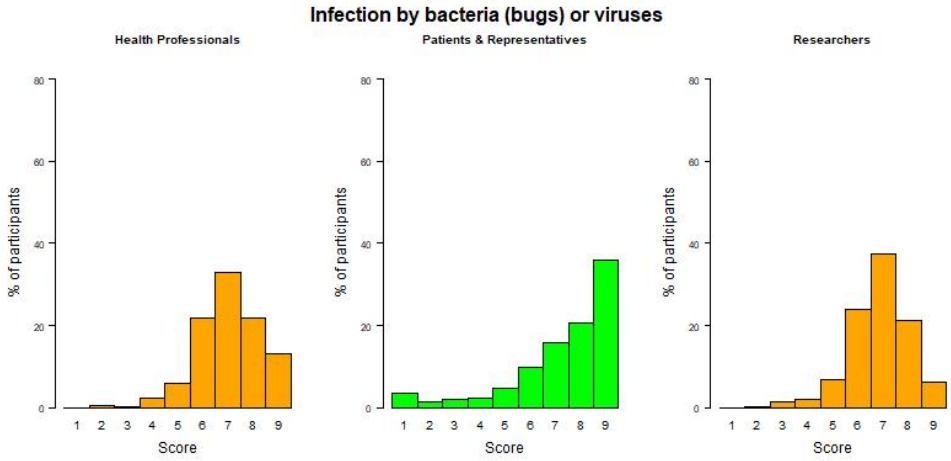

Serious adverse effects of treatments
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Treatment adherence
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Treatment success (or failure)
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

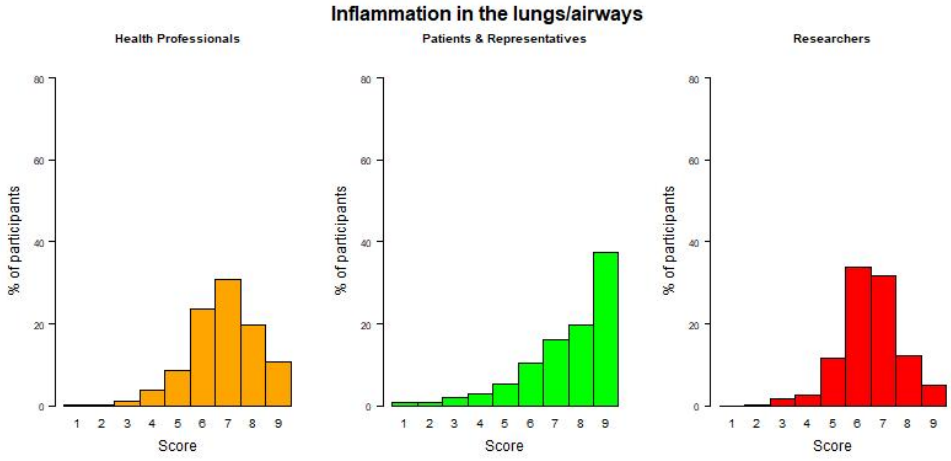

Worsening of symptoms after the initial treatment
Health Professionals
Patients & Representatives
Researchers
% of participants
Score


Damage of lung cells and lung tissue
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

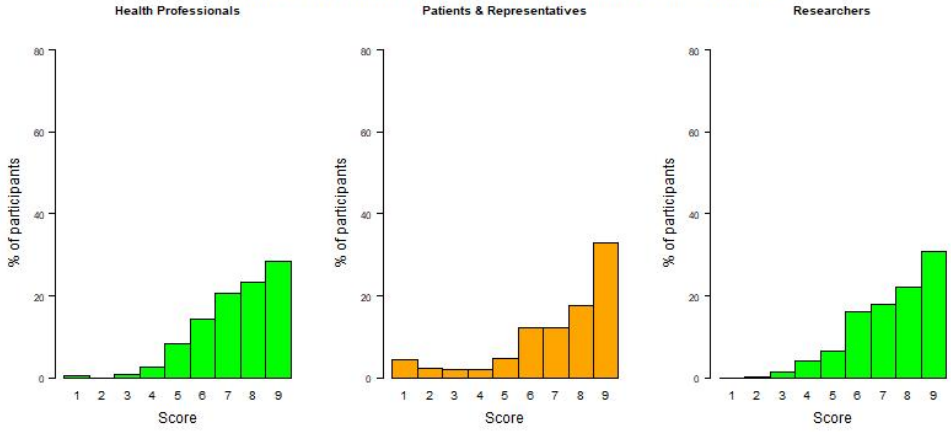

Death from any cause
Health Professionals
Patients & Representatives
Researchers
% of participants
Score


Future hospital admissions
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

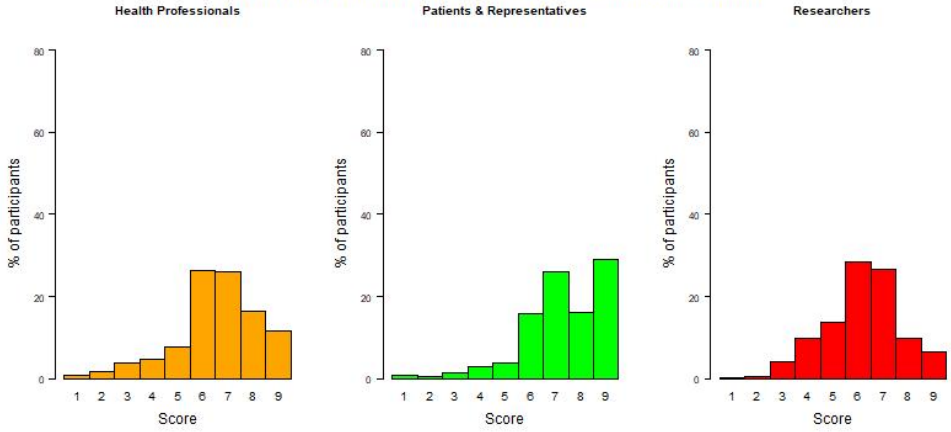

Infection by bacteria (bugs) or viruses
Health Professionals
Patients & Representatives
Researchers
% of participants
Score


Inflammation in the lungs/airways
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

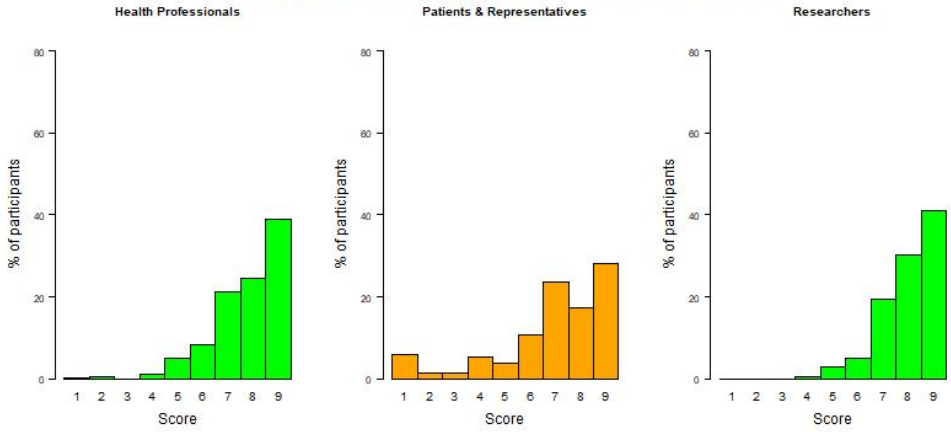
Length of stay in the intensive care unit for the exacerbation

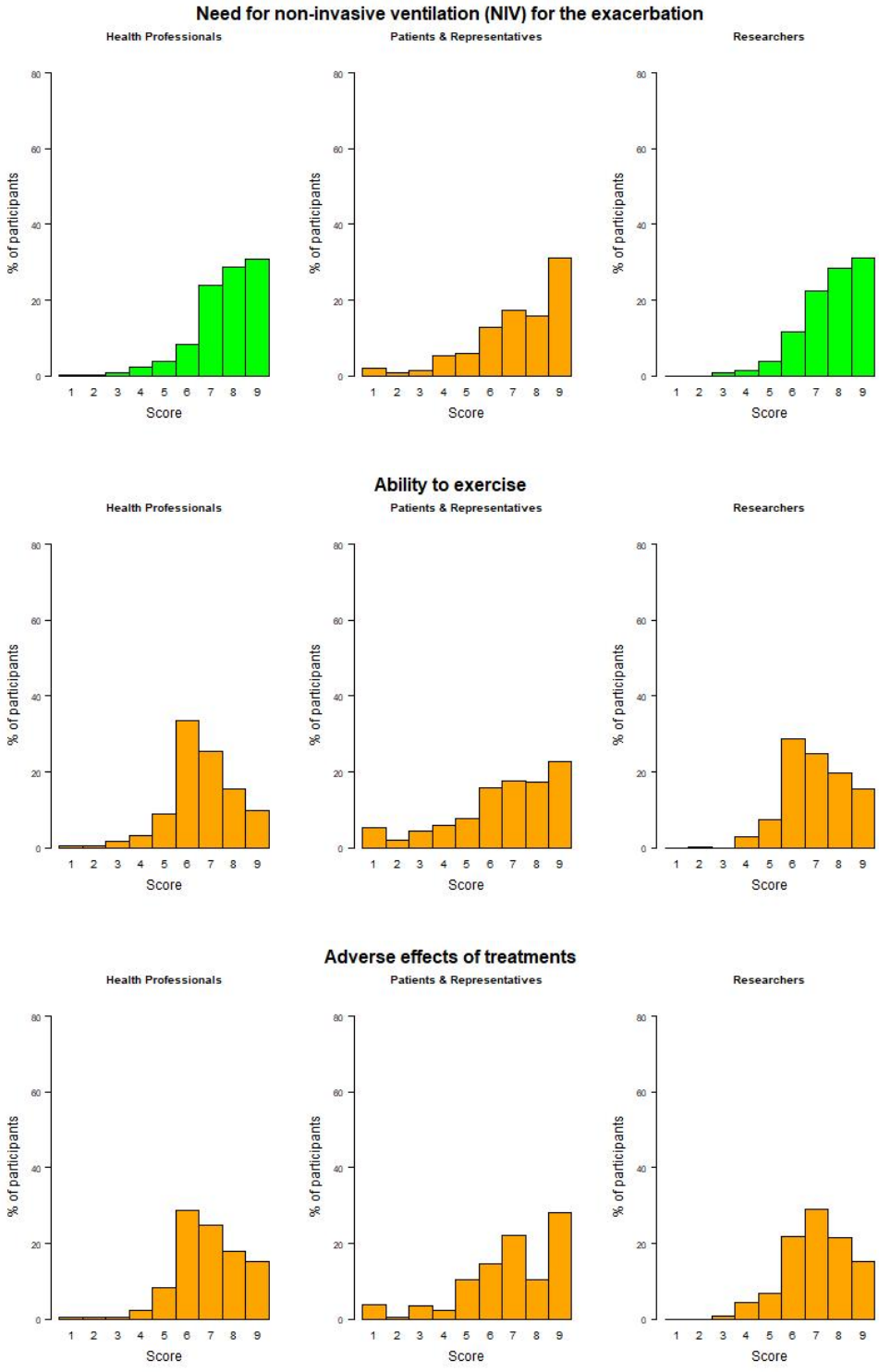


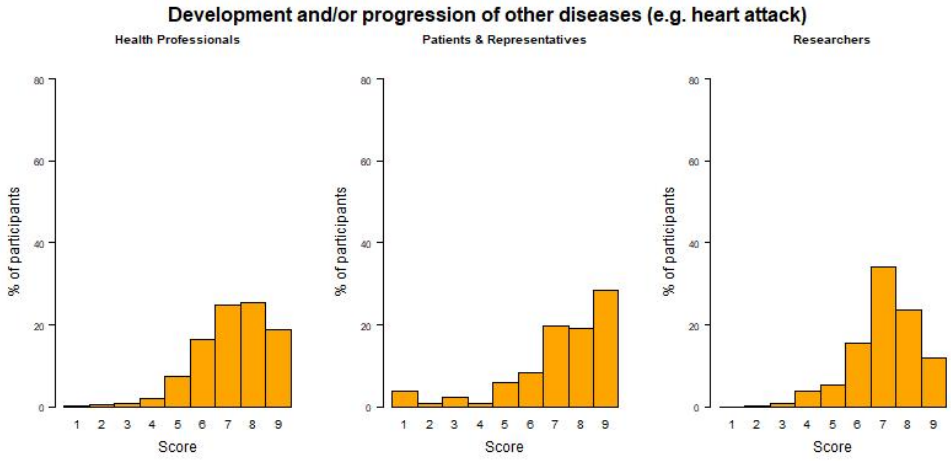
Lung function during and immediately after the exacerbation

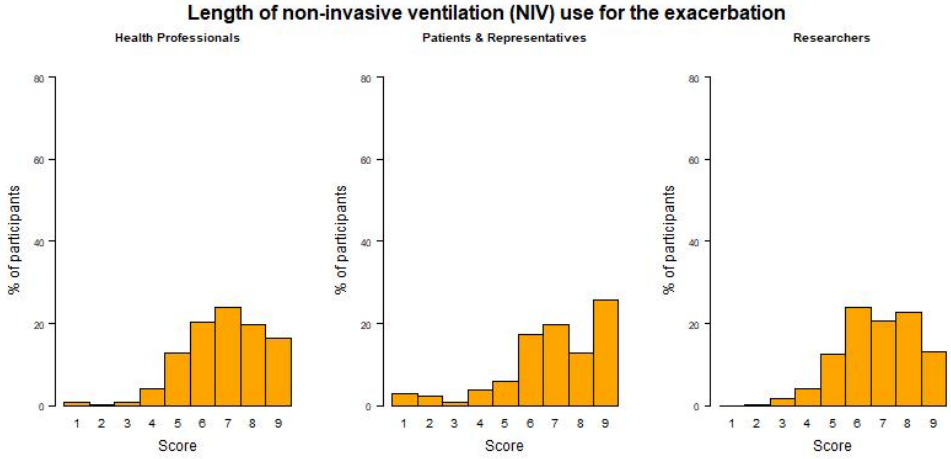


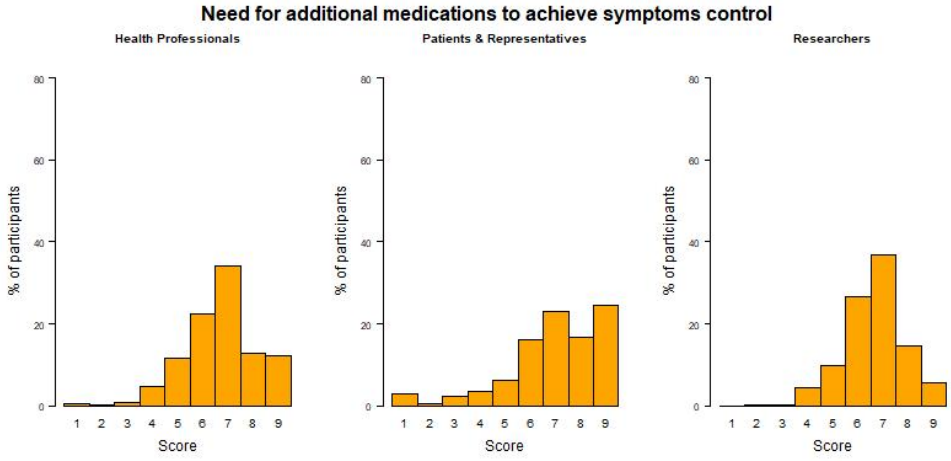
Need for hospital admission for the presenting exacerbation



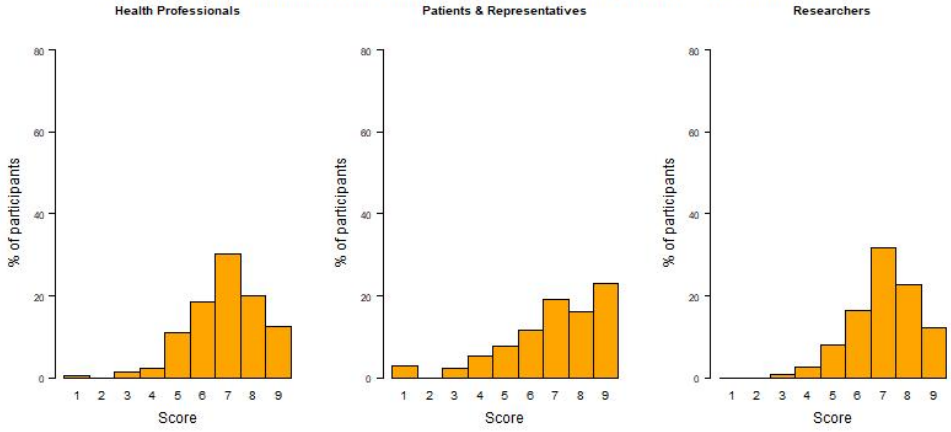

Need for non-invasive ventilation (NIV) for the exacerbation
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Ability to exercise
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Adverse effects of treatments
Health Professionals
Patients & Representatives
Researchers
% of participants
Score


Development and/or progression of other diseases (e.g. heart attack)
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

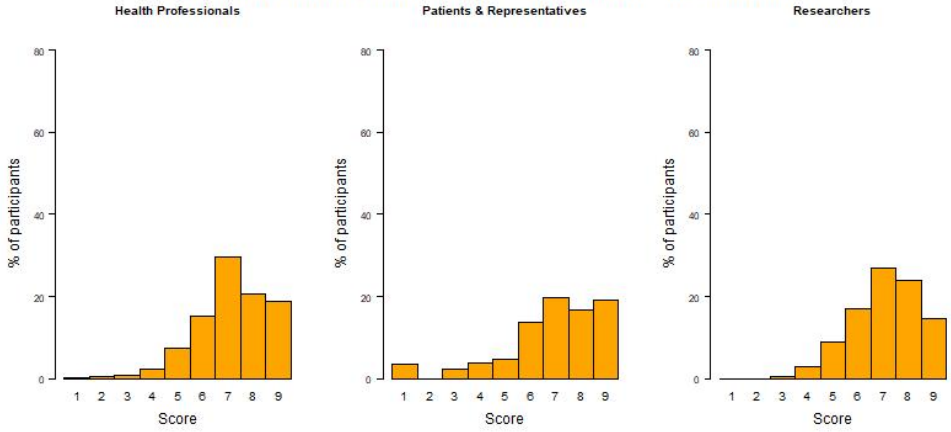

Length of non-invasive ventilation (NIV) use for the exacerbation
Health Professionals
Patients & Representatives
Researchers
% of participants
Score


Need for additional medications to achieve symptoms control
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

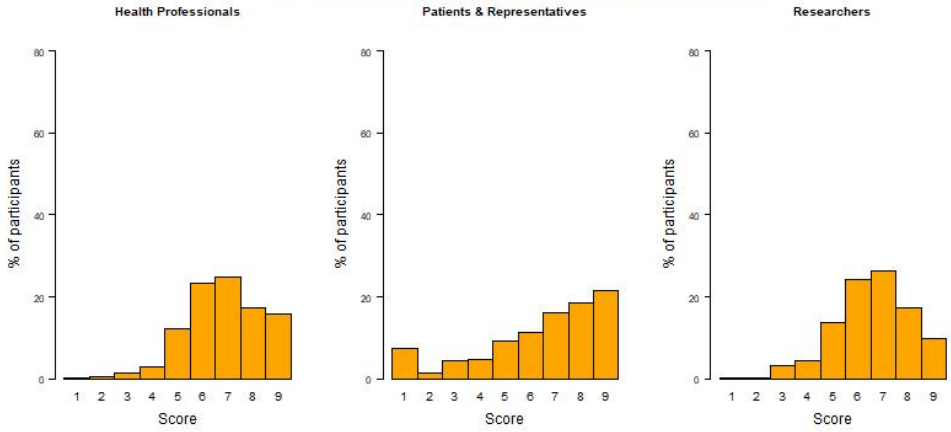
Need for long-term administration of supplemental oxygen after the exacerbation.

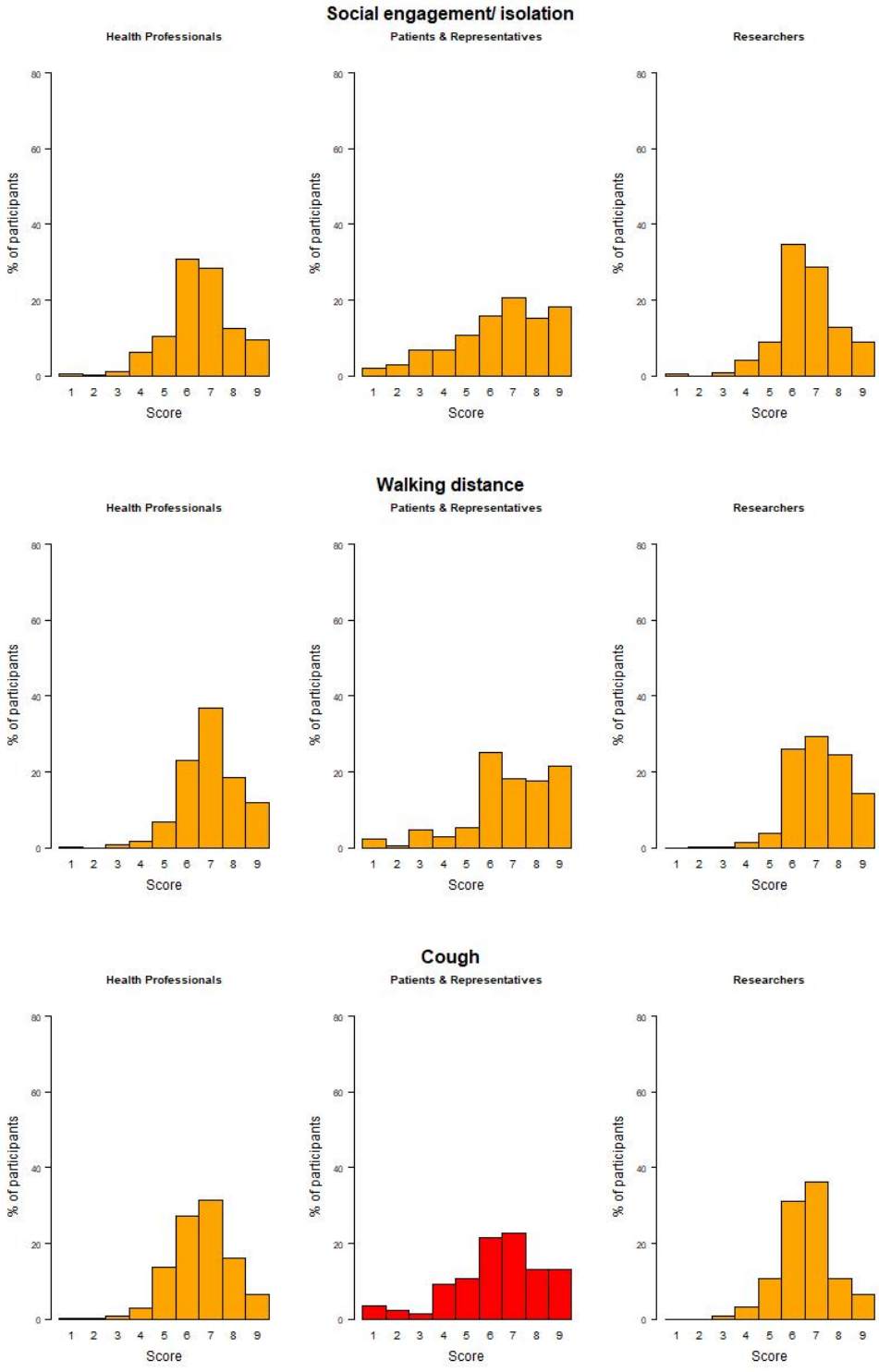


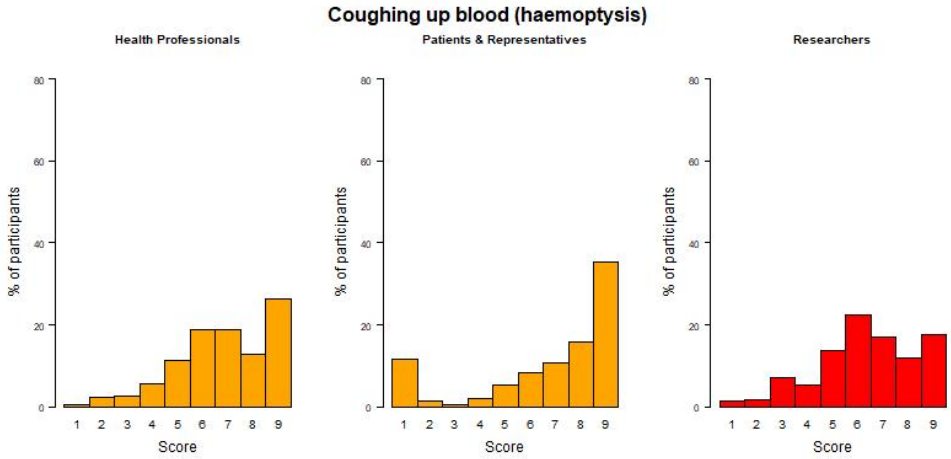
Need for long-term use of non-invasive ventilation after the exacerbation.

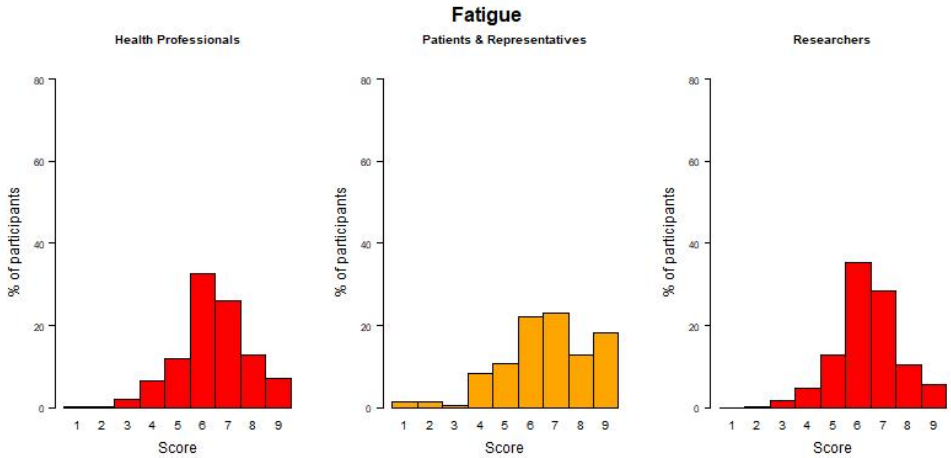


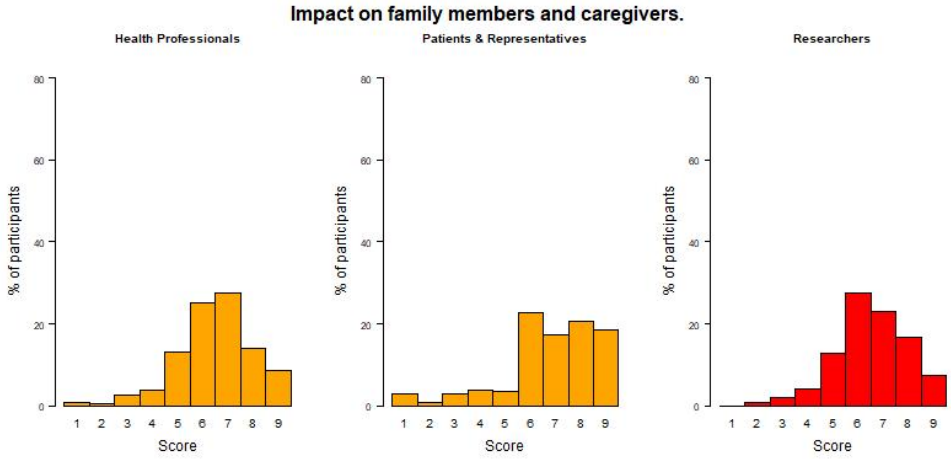
Production of dark-coloured sputum (sputum purulence)

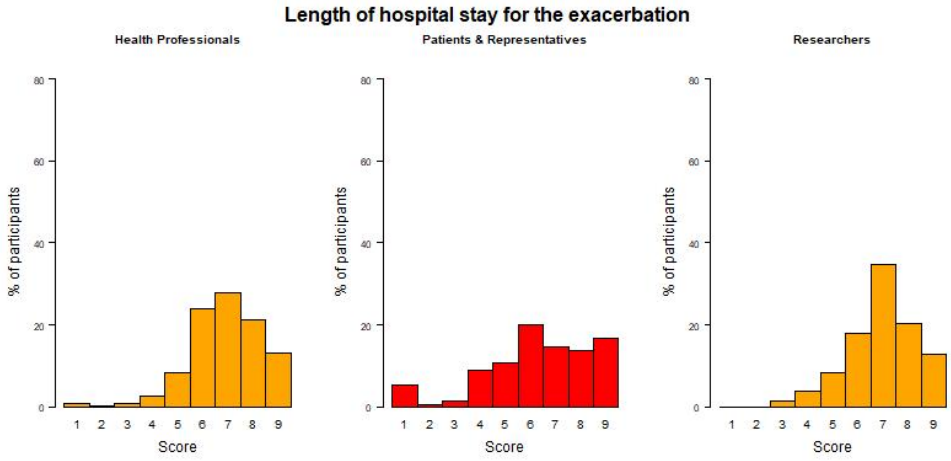


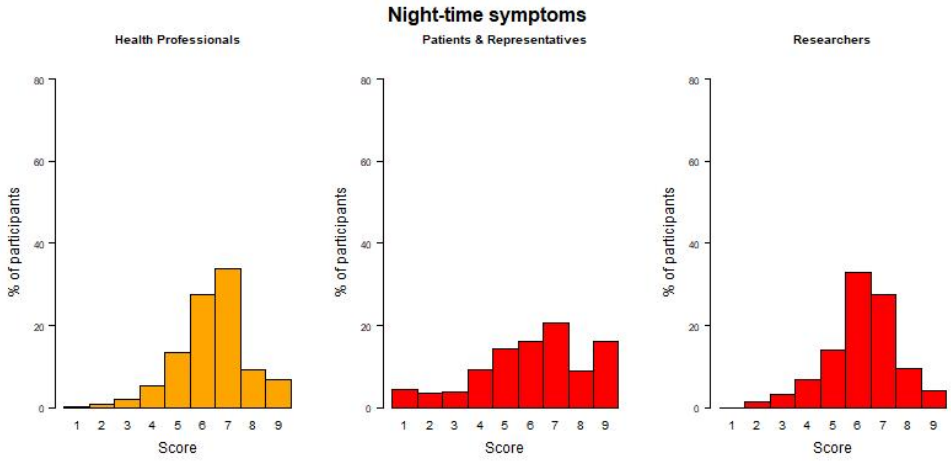

Social engagement/ isolation
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Walking distance
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Cough
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

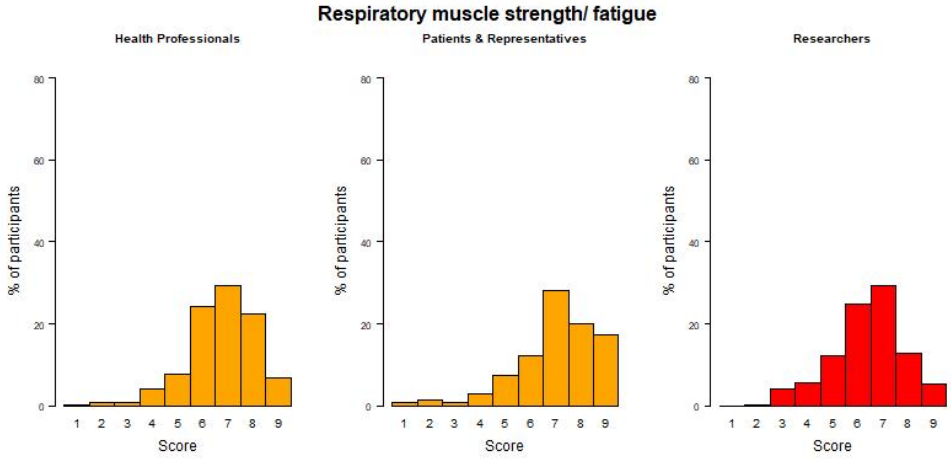

Coughing up blood (haemoptysis)
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

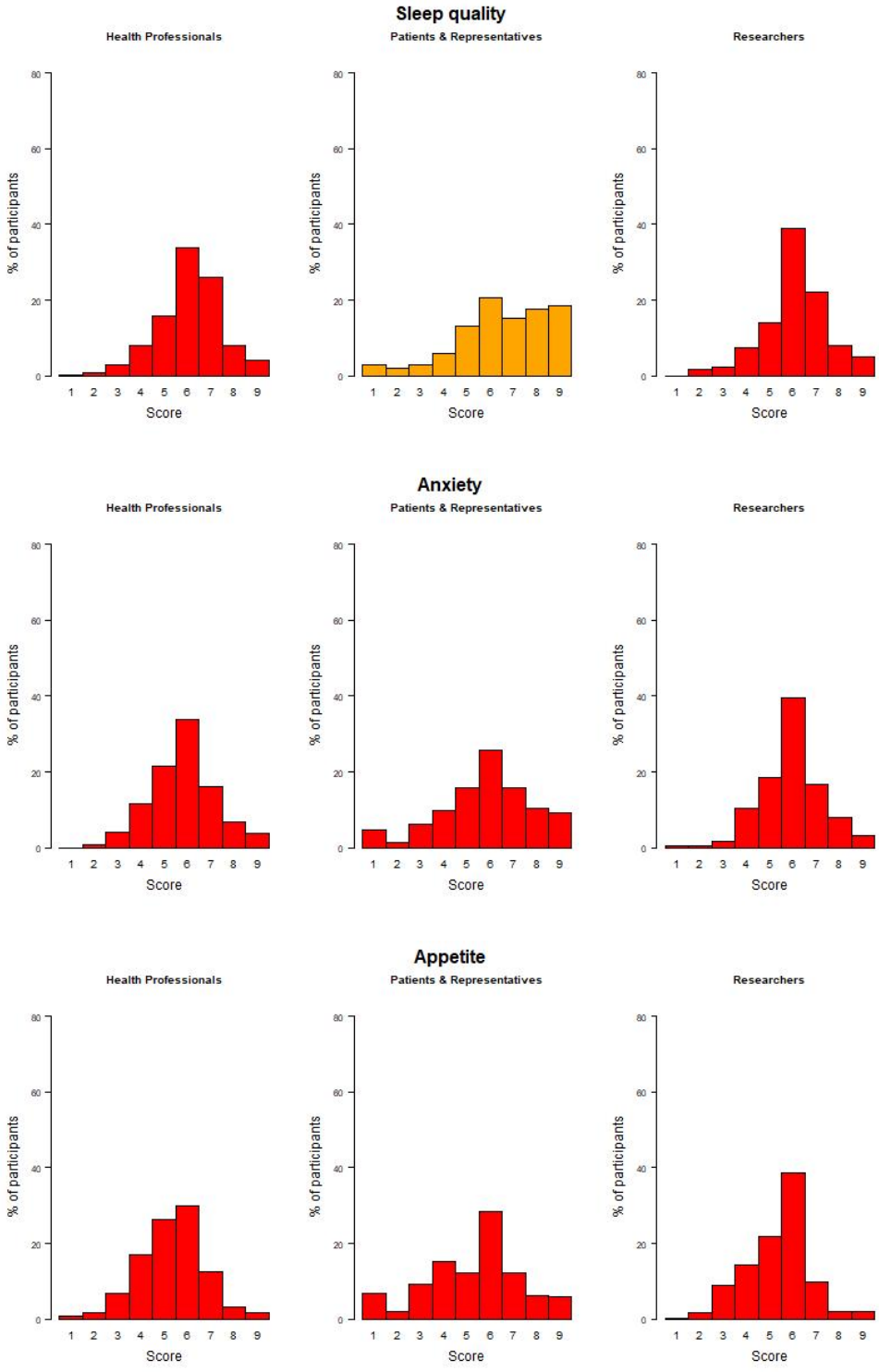

Fatigue
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

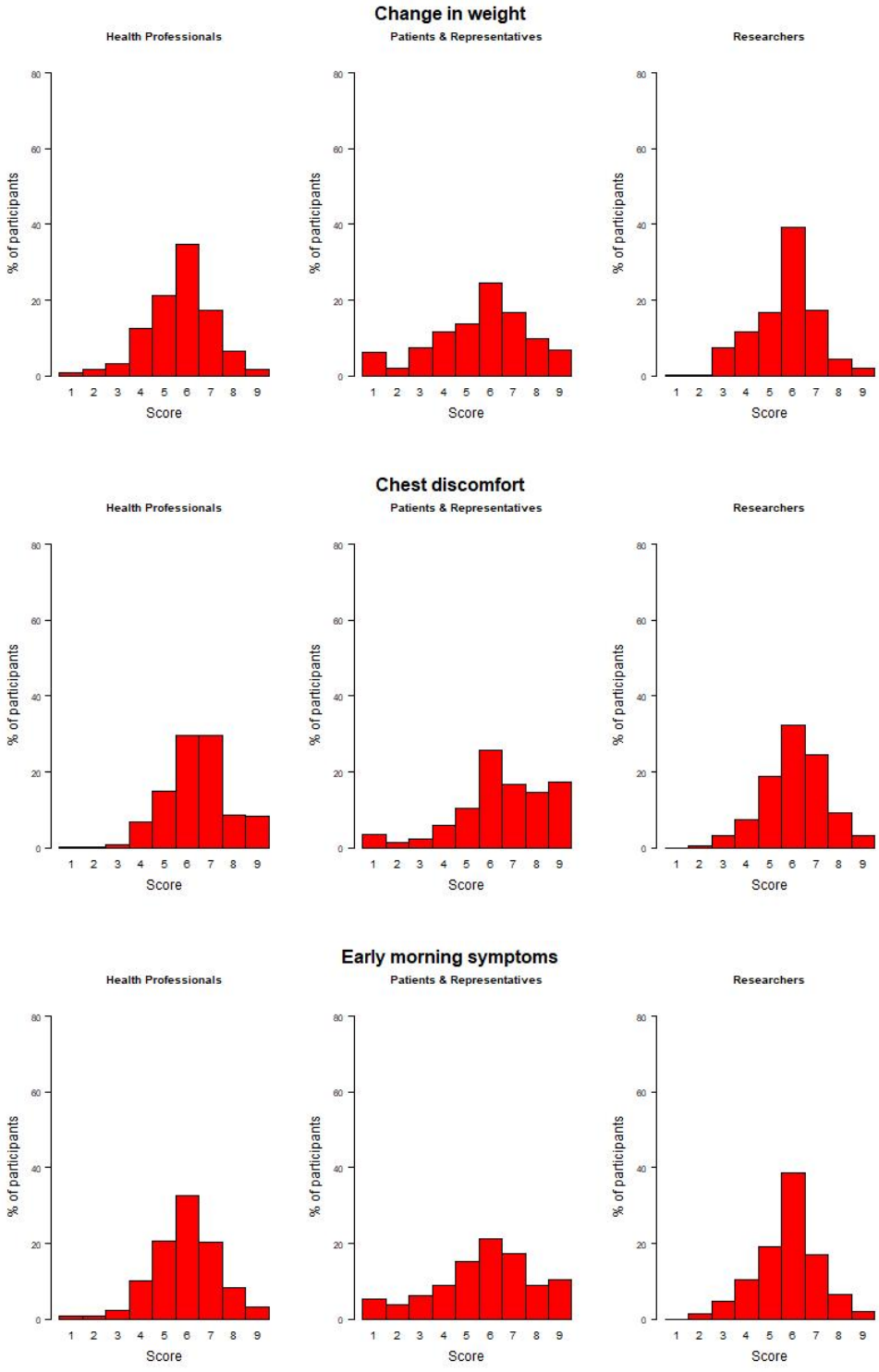

Impact on family members and caregivers.
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

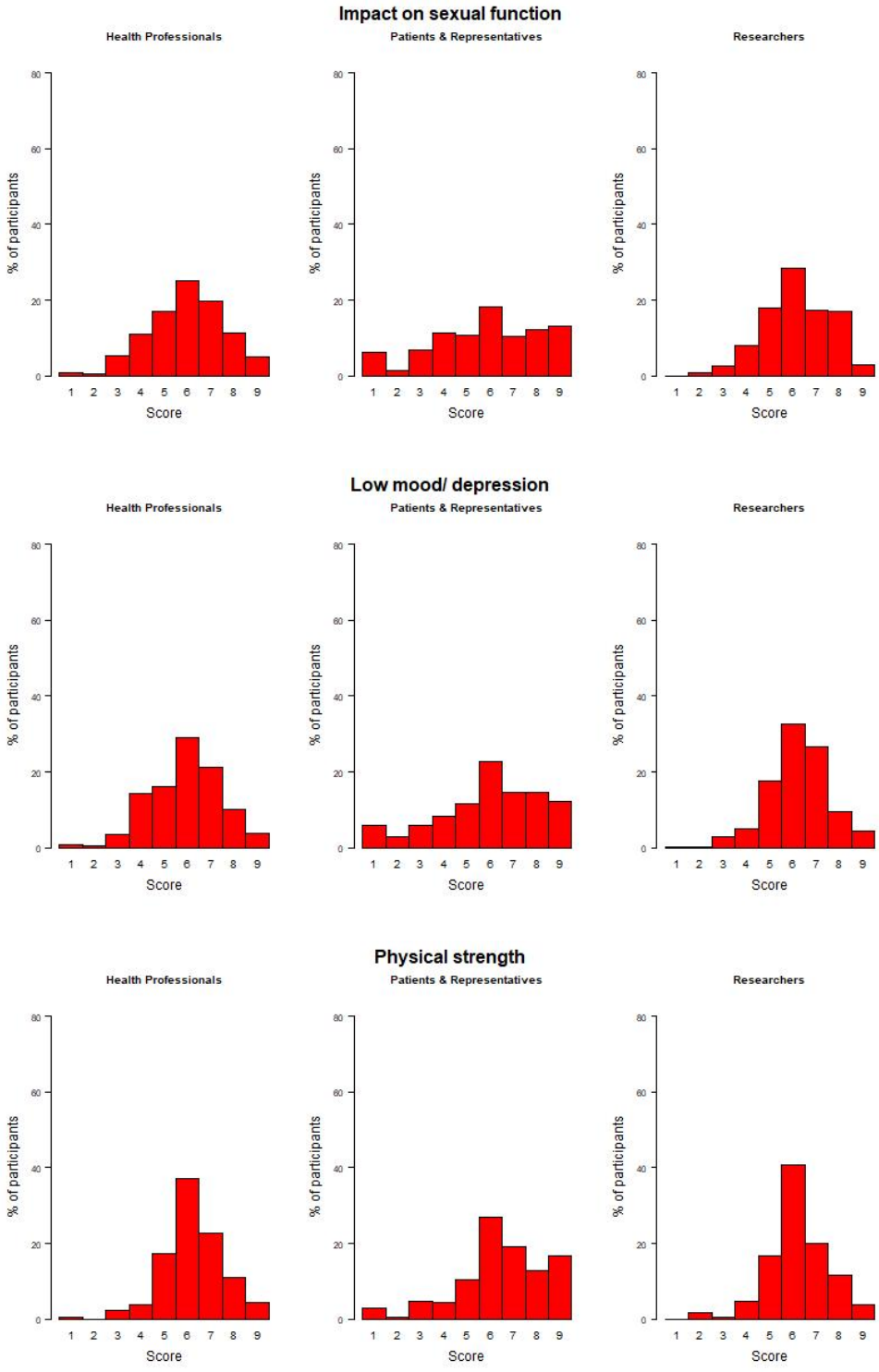

Length of hospital stay for the exacerbation
Health Professionals
Patients & Representatives
Researchers
% of participants
Score


Night-time symptoms
Health Professionals
Patients & Representatives
Researchers
% of participants
Score


Respiratory muscle strength/ fatigue
Health Professionals
Patients & Representatives
Researchers
% of participants
Score


Sleep quality
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Anxiety
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Appetite
Health Professionals
Patients & Representatives
Researchers
% of participants
Score


Change in weight
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Chest discomfort
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Early morning symptoms
Health Professionals
Patients & Representatives
Researchers
% of participants
Score


Impact on sexual function
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Low mood/ depression
Health Professionals
Patients & Representatives
Researchers
% of participants
Score
Physical strength
Health Professionals
Patients & Representatives
Researchers
% of participants
Score

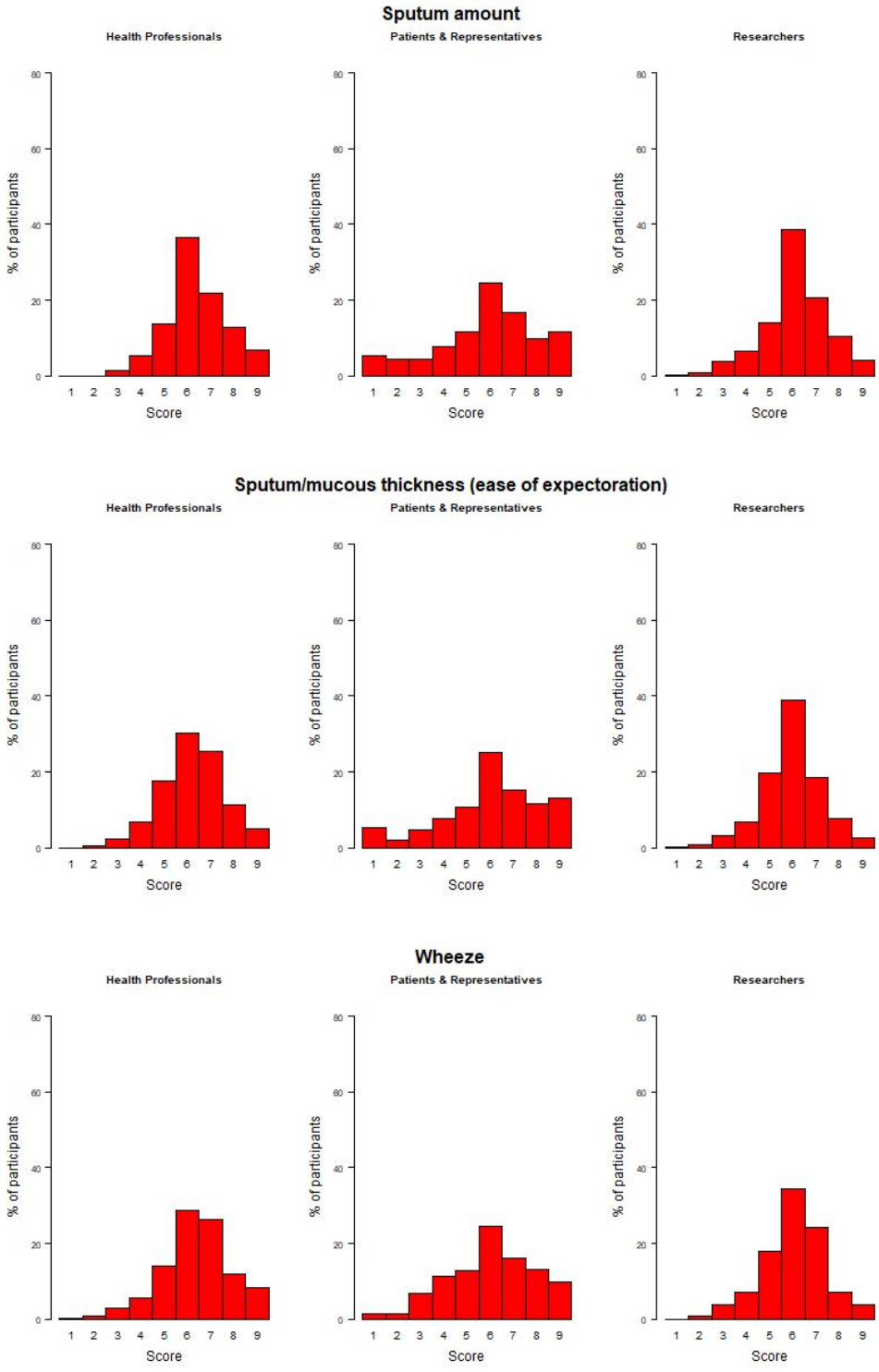


Figure 17. *Detailed results of the second round of the Delphi survey. (53 panels)*

8.3.6. Outcome Measurement Instruments Literature Review: Search strategies

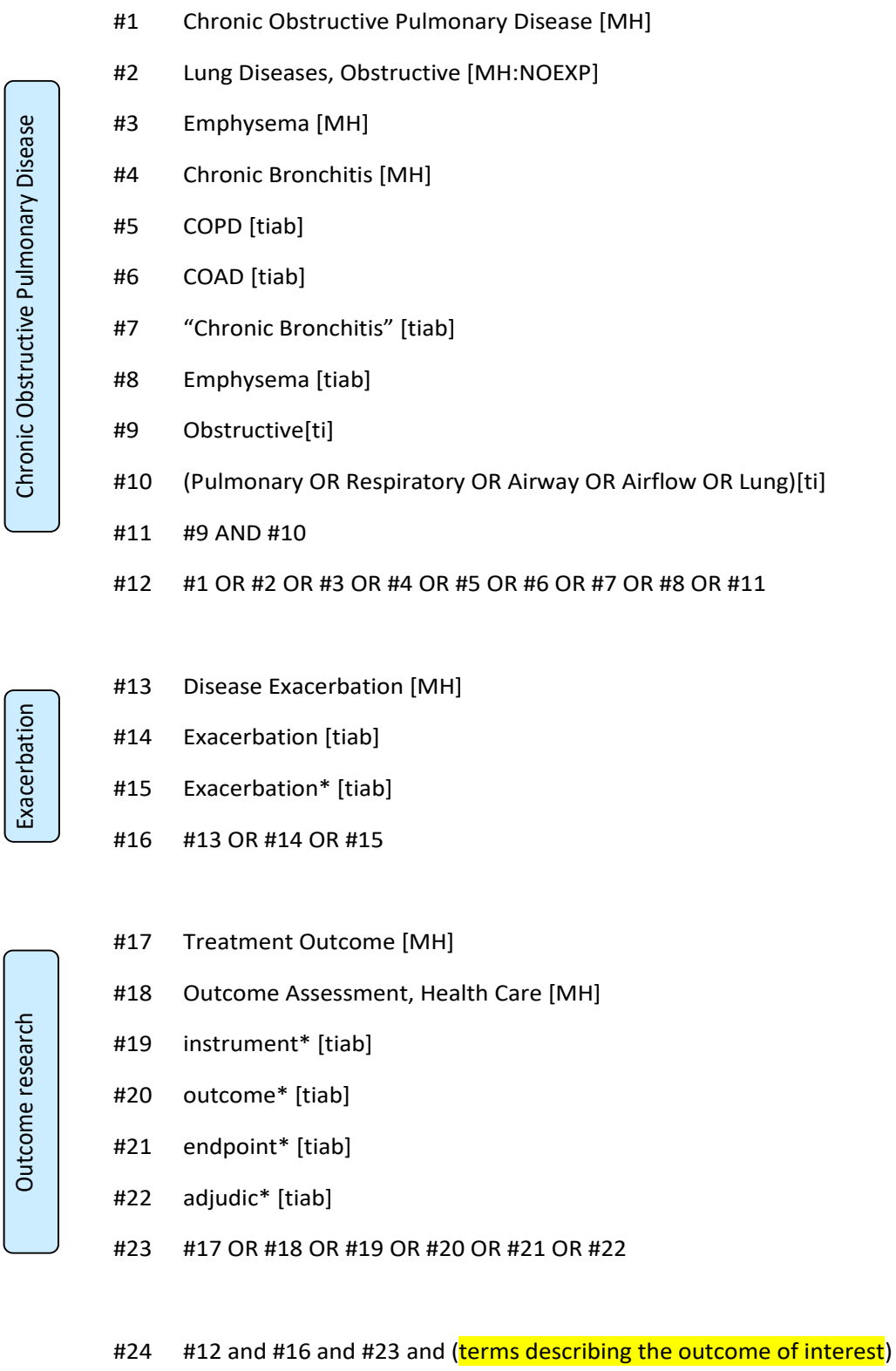


Figure 18. *Outcome measurement instrument literature reviews: Search strategy.*

Outcome	Search strategy	Titles screened	Relevant studies
Death from COPD exacerbation	((Cause of death [MH]) or (death [ti]) or (mortality [ti]))	232	Methodological SRs: 0 Other references: 3
Treatment success	((Treatment failure [MH]) or (cure [tiab]) or (treatment success [tiab]) or (treatment failure [tiab]))	269	Methodological SRs: 0 Other references: 0
Breathlessness	((Dyspnea [MH]) or (dyspnea [ti]) or (dyspnoea [ti]) or (breathlessness [ti]))	269	Methodological SRs: 3 Other references: Not considered - Adequate SR data.
Quality of life	((Quality of life [MH]) or (quality of life [ti]) or (health status[ti]))	1,018	Methodological SRs: 4 Other references: Not considered - Adequate SR data.
Activities of daily living	((Activities of daily living [MH]) or (Functional Status [MH]) or ((activities [ti]) and ((life[ti]) or (living[ti]))) or ((function* [ti]) and (status [ti])))	221	Methodological SRs: 3 Other references: Not considered - Adequate SR data.
Disease progression	((Disease Progression [MH]) or (progression [ti]))	1,530	Methodological SRs: 0 Other references: 19

Table 29. Search strategies for the focused literature reviews: Terms used to search for outcomes and search results.

8.3.7. Treatment Success: Detailed description of the meta-epidemiological study

8.3.7.1. Methods

This meta-epidemiological study was based on a prospectively registered protocol (PROSPERO ID: CRD42020222287) [374]. For conducting and reporting this systematic review, we followed standard methodology recommended by the Cochrane Collaboration [276] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [375], respectively.

We systematically searched Medline/PubMed, the Cochrane Airways Trials Register [376] and the COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) database on 12th November 2020, to identify trials testing pharmacological and non-pharmacological interventions for the management of COPD exacerbations. We also looked for methodological studies assessing the performance characteristics of different instruments for assessing treatment success or failure in clinical trials on COPD exacerbations. We used the search strategies that were developed for Chapter 3. Ongoing and completed trials and relevant methodological studies reported in the English language during the last 15 years (from 2006 onwards) were considered eligible. The titles and abstracts of all studies identified through the searches and the full texts of all potentially eligible studies were independently evaluated for eligibility by two review authors. We selected studies reporting on any of the following outcomes: cure, resolution, treatment success, treatment failure, time-to-cure, time-to-resolution, time-to-treatment success, or time-to-treatment failure. Relevant data on the design, interventions, baseline characteristics and imbalances, as well as data on the outcomes of interest, including the definitions used, measurement timepoints and outcome data (findings) were extracted in a structured Excel form by one author and cross-checked by a second review author. The risk of methodological bias was assessed using the Cochrane Risk of Bias 1 tool by one author and cross-checked by a second author [377]. Disagreement in each stage of the process was resolved by consensus, involving a third author.

For the purposes of this review, we defined treatment success/ failure, or cure of the exacerbation, as a dichotomous measure of the overall outcome of the exacerbation (*table 28*). We excluded continuous measures evaluating change in variables without prespecified

thresholds of success or failure (e.g., change in symptom scores from baseline) and outcomes that did not focus on an overall assessment of the treatment outcome but on specific aspects of the exacerbation (e.g., death; admission to the intensive care unit; hospital admission; bacteriological eradication).

The definitions and timepoints of evaluation of the relevant outcomes were described narratively and in a tabulated format. Instruments used to measure the outcome of interest were grouped based on their characteristics into (i) composite instruments and (ii) descriptive instruments (definitions in *table 28*). Grouping was based on consensus among the authors.

Treatment success or failure is a time-dependent outcome. Therefore, it is crucial to select the optimal timepoint for evaluating this outcome. For this reason, we explored the proportion of participants receiving usual care that fulfilled the criteria of treatment success or failure at different timepoints. Studies were stratified according to (i) the instrument used for assessing treatment success and (ii) the treatment setting, that was considered to reflect the severity of the exacerbations. In this analysis, we included all treatment arms of the included trials in which participants received treatments that are consistent with international guideline recommendations (i.e., we excluded study arms that received novel experimental treatments).

Finally, to assess which instrument group and timepoints are more effective in identifying treatment effects, we explored between group differences in treatment success or failure in trials assessing an intervention hypothesised by the trial investigators to be superior to the control group treatment (i.e., trials evaluating additional treatment compared to standard care; we excluded non-inferiority trials or trials comparing treatments without a prospective hypothesis around superiority). Outcome data from studies that were eligible for this analysis are presented in forest plots and described narratively.

Term	**Definition**
Treatment success/ failure, or cure	A dichotomous measure of the overall outcome of the exacerbation. We excluded continuous measures evaluating change in variables without prespecified thresholds of success or failure (e.g., change in symptom scores from baseline) and outcomes that did not focus on an overall

	assessment of the treatment outcome but on specific aspects of the exacerbation (e.g., death; hospital admission; bacteriological eradication).
Composite instruments	Instruments consisting of several undesirable outcomes of an exacerbation (e.g., death; need for treatment intensification; admission to the intensive care; or hospital admission), together defining an overall unfavourable outcome
Descriptive instruments	Instruments defining treatment success or failure based on qualitative or semi-quantitative descriptions of the patients' clinical status with regards to the exacerbation at a specific time point. The following states are often defined: cure, marked improvement, improvement, or treatment failure

Table 30. Definitions of treatment success/ failure and of the measurement instruments classification.

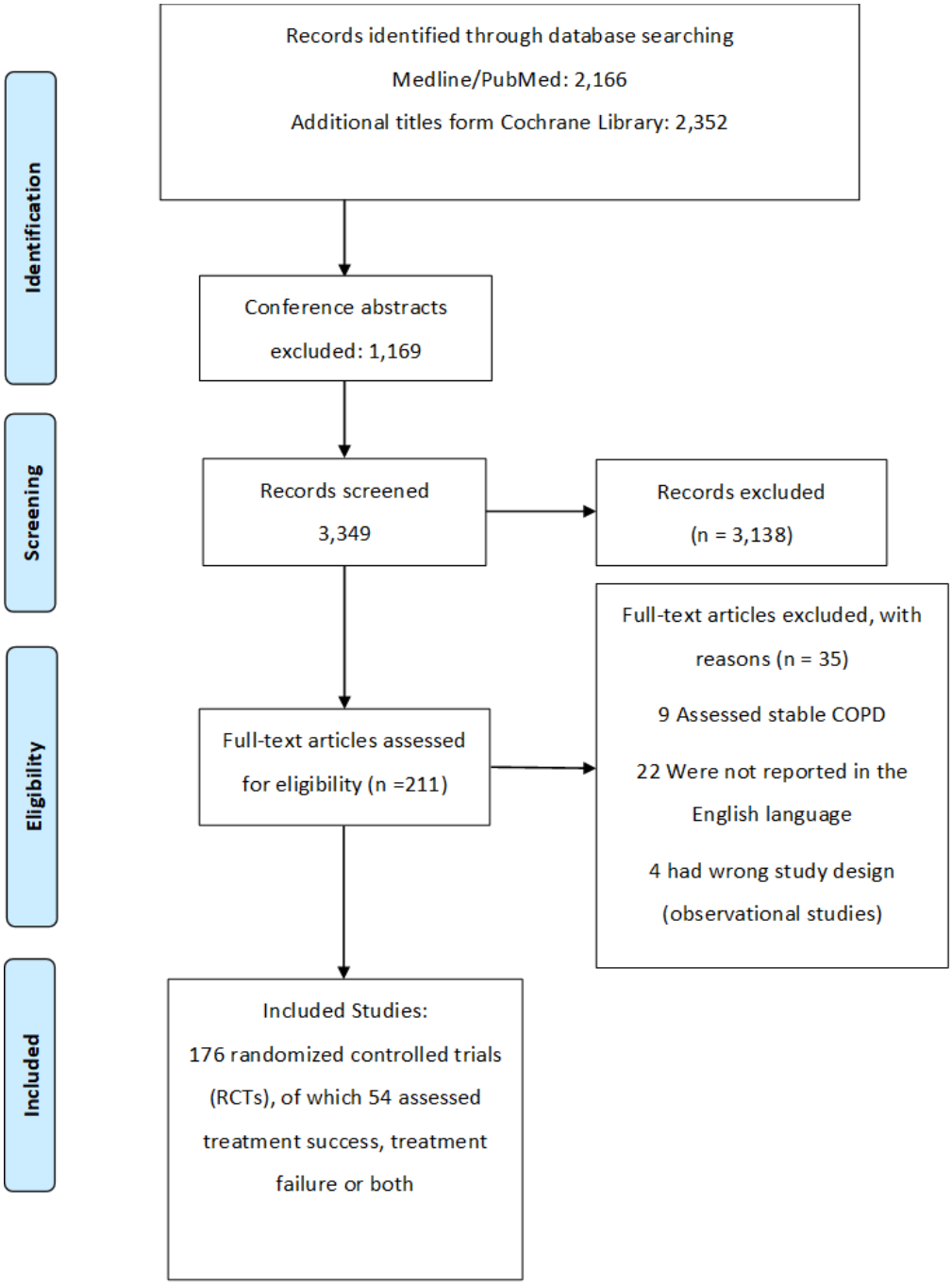


Figure 19. *Treatment success methodological SR: PRISMA flowchart*

8.3.7.2. Additional Findings

After removing duplicate records and conference abstracts, our searches yielded 3,349 records. Selection process is described in a PRISMA diagram (*figure 19*). We did not identify any eligible methodological studies evaluating the performance characteristics of instruments used to assess treatment success or failure in COPD exacerbations trials.

We identified 176 ongoing or completed RCTs evaluating pharmacological or non-pharmacological interventions for the management of COPD exacerbations, of which 54 (30.7%) assessed the overall outcome of the index exacerbation. The interventions evaluated in the 54 included RCTs were antibiotics (n=28), anti-inflammatories (11), oxygenation or non-invasive ventilation techniques (8), Chinese traditional medicine (3) or other interventions (4).

Measurement timepoints and treatment effects.

Finally, we explored treatment effects observed on the overall outcome of the exacerbations in superiority trials comparing an intervention hypothesised to be superior to the control group treatment by the trial investigators. Our aim was to explore whether specific instruments or measurement timepoints are more likely to yield a positive result. Forest plots summarizing the findings from eligible outcomes are presented in *figures 20 and 21*.

Composite treatment failure outcomes appear to infrequently yield significant results (3/11, 27% of the evaluated outcomes; it should be noted that two of the three outcomes revealing a positive effect among hospitalised patients represent different timepoints from the same trial). We did not observe an association between specific measurement instruments or timepoints and positive treatment effects.

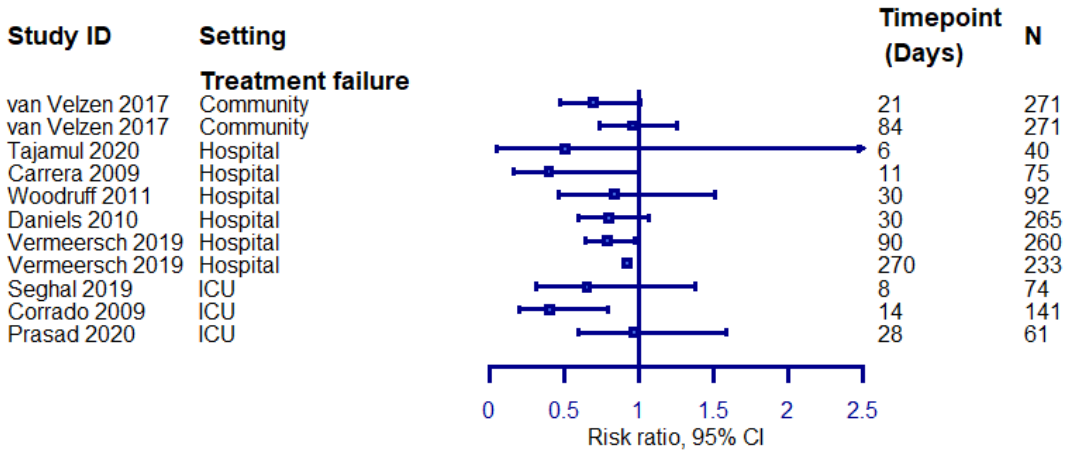


Figure 20. *Treatment effects on treatment failure rates in superiority trials assessing treatment failure as a composite outcome. Left-hand side favours the intervention. N: Study population.*

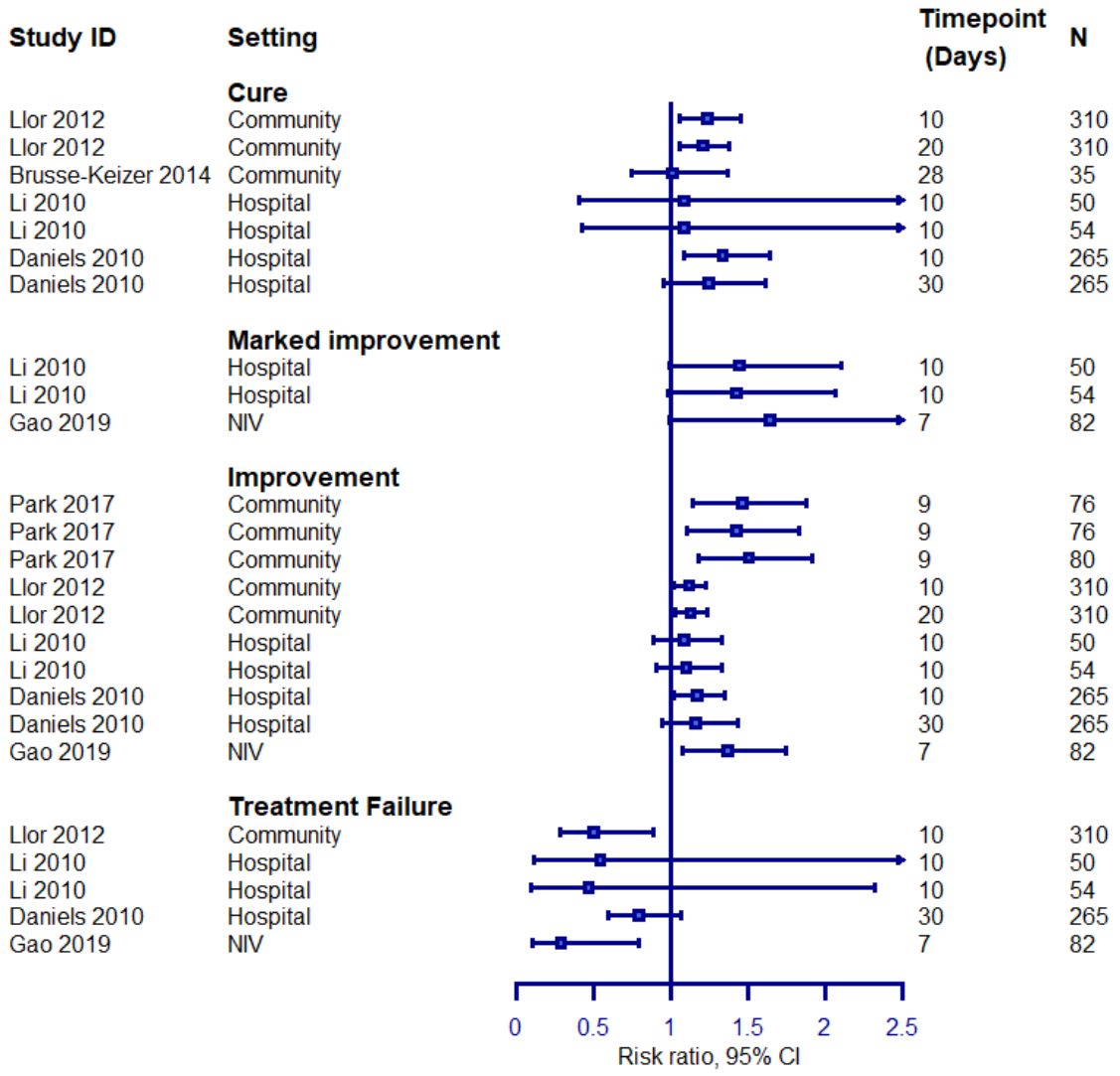


Figure 21. *Treatment effects on treatment failure rates in superiority trials assessing cure, marked improvement, improvement or treatment failure defined using descriptive instruments. Left-hand side favours the intervention. N: Study population.*

Over half of the outcomes evaluating cure or improvement yielded significant results, while 40% of those assessing treatment failure using descriptive instruments also yielded significant results. Nonetheless, the main difference between outcomes yielding positive or negative results was the study population of the included studies, rather than the measurement instruments or timepoints. Only two studies included in this analysis evaluated marked improvement, and the lack of any positive treatment effects most likely reflects the limited study population included in the respective analyses.

8.3.7.3. Strengths and limitations

This meta-epidemiological study was limited by the inadequate number of included RCTs and was therefore not able to identify an optimal instrument and timepoints for assessing treatment success in clinical trials in COPD exacerbations. We only included trials published from 2006 onwards. However, we considered that the inclusion of older trials might have introduced heterogeneity in our findings, as the diagnosis, severity stratification and management of exacerbations may have differed in studies conducted previously. Similarly, clinical trial methodology has changed over the last decades and so has our approach towards trial outcomes. Moreover, we did not include data from observational studies, as our work focuses on clinical trials and the instruments used in observational studies are often different.

The thorough systematic search, which included the Cochrane Airways Trials Register, sourcing clinical trials from five electronic databases and the abstract proceedings of all major international respiratory conferences, is one of the strengths of this study. Another major strength is the thorough analysis of the instruments used to assess treatment failure, the timepoints they were evaluated and the results they yielded.

8.3.8. Consensus meeting participants

8.3.8.1. First consensus meeting: Finalization of the Core Outcome Set

Patients with COPD and patient representatives

Name (if consented)	**Country**
Arrowsmith, Christine	UK
Branch, Kay	UK
Bruce, Elaine	Ireland
Coleman, Courtney	UK (ELF representative)
Jessica Denning	UK (ELF representative)
Jensen, Bo Hammer	Denmark
Hood, David	UK
Janssen, Elly	Netherlands
Jelen, Tessa	UK
Linnell, John	USA
Jonsdottir, Aldis	Iceland
Meggitt, Richard	Australia
Preston, Allan	UK
Ratcliffe, John	Australia
Ruttle, John	Australia
Winders, Tonya	USA
Vinuela, Alfonso	Spain

Health professionals and clinical researchers

Name	Country
Agusti, Alvar	Spain
Bartziokas, Konstantinos	Greece
Bradbury, Thomas	Australia
Corlateanu, Alexandru	Moldova
Csoma, Balazs	Hungary
Emelyanov, Alexander	Russia
Fernandez Romero, Gustavo	USA
Jenkins, Christine	Australia
Jensen, Jens-Ulrik	Denmark
Kharevich, Olga	Belarus
Kostikas, Konstantinos	Greece
Lazar, Zsofia	Hungary
Lopez-Giraldo, Alejandra	Spain
Mathioudakis, Alexander	UK
McDonald, Vanessa	Australia
Papi, Alberto	Italy
Sergeeva, Galina	Russia
Sivapalan, Pradeesh	Denmark
Stovold, Elizabeth	UK
Vestbo, Jørgen	UK/ Denmark
Wang, Hao	China

Wen, Fuqiang	China

COMET representatives / methodologists

Name	**Role**
Brookes, Sara	Meeting facilitator
Williamson, Paula	Methodological input

8.3.8.2. Second consensus meeting: Selection of outcome measurement instruments

Patients with COPD and patient representatives

Name	**Country**
Coleman, Courtney	UK (ELF representative)
Linnell, John	USA
Saraiva, Isabel	Portugal

Health professionals and clinical researchers

Name	**Country**
Ananth, Sachin	UK
Bartziokas, Konstantinos	Greece
Beghe, Bianca	Italy
Bradbury, Thomas	Australia
Corlateanu, Alexandru	Moldova
Emelyanov, Alexander	Russia
Fernandez Romero, Gustavo	USA

Jenkins, Christine	Australia
Jensen, Jens-Ulrik	Denmark
Kostikas, Konstantinos	Greece
Lazar, Zsofia	Hungary
Mathioudakis, Alexander	UK
McDonald, Vanessa	Australia
Papi, Alberto	Italy
Sergeeva, Galina	Russia
Sioutkou, Agni	Greece
Sivapalan, Pradeesh	Denmark
Stovold, Elizabeth	UK
Vestbo, Jørgen	UK/ Denmark
Wang, Hao	China
Wen, Fuqiang	China

COMET representative / methodologist

Name	**Role**
Williamson, Paula	Methodological input & Meeting facilitator

8.4. Chapter 6: Prevalence of respiratory viruses in COPD

8.4.1. Search Strategies

8.4.1.1. Search Strategy - Medline, PubMed & Cochrane Library

#1 Chronic Obstructive Pulmonary Disease [MH]

#2 Lung Diseases, Obstructive [MH:NOEXP]

#3 Emphysema [MH]

#4 Chronic Bronchitis [MH]

#5 COPD [tiab]

#6 COAD [tiab]

#7 “Chronic Bronchitis” [tiab]

#8 Emphysema [tiab]

#9 Obstructive[ti]

#10 (Pulmonary OR Respiratory OR Airway OR Airflow OR Lung)[ti]

#11 #9 AND #10

#12 AECOPD[tiab]

#13 IECOPD[tiab]

#14 /OR 1-8, 11-13

#15 Viruses[MH]

#16 Influenza, Human[MH]

#17 Rhinovirus[MH]

#18 Respiratory Syncytial Viruses[MH]

#19 Coronavirus[MH]

#20 Paramyxoviridae Infections[MH]

#21 Orthomyxoviridae[MH]

#22 Adenoviridae [MH]

#23 Picornaviridae[MH]

#24 Metapneumovirus[MH]

#25 Enterovirus[MH]

#26 Cytomegalovirus[MH]

#27 Herpesvirus 3, Human[MH]

#28 Virus*[tiab]

#29 Viral*[tiab]

#30 Influenza*[tiab]

#31 Rhinovir*[tiab]

#32 Respiratory Syncytial Vir*[tiab]

#33 Coronavir*[tiab]

#34 Paramyxovir*[tiab]

#35 Orthomyxovir*[tiab]

#36 Adenovir*[tiab]

#37 Picornavir*[tiab]

#38 Metapneumov*[tiab]

#39 vzv[tiab]

#40 varicella[tiab]

#41 Enterovir*[tiab]

#42 Parainfluenza[tiab]

#43 Echovir*[tiab]

#44 /OR 15-44

#45 Animals[mh] not (humans[mh])

#46 (child[mh]or (adolescent[mh])) not (adult[mh])

#47 editorial[pulication type]

#48 review[publication type] not (systematic review [publication type])

#49 #14 and #44

#50 #49 NOT (#45 or #46 or #47 or #48)

8.4.1.2. Search Strategy: EMBASE

#1 exp Chronic Obstructive Pulmonary Disease/

#2 exp Lung diseases, obstructive/

#3 exp Chronic bronchitis/

#4 exp emphysema/

#5 COPD.tw.

#6 COAD.tw.

#7 (chronic adj2 bronchit$).tw.

#8 (obstructive adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw.

#9 AECOPD.tw

#10 IECOPD.tw

#11 ECOPD.tw

#12 /OR 1-11

#13 exp virus/

#14 exp influenza/

#15 exp rhinovirus/

#16 exp Respiratory Syncytial Virus/

#17 exp Coronavirus/

#18 exp Paramyxoviridae Infections/

#19 exp Orthomyxoviridae/

#20 exp Adenoviridae/

#21 exp Picornaviridae/

#22 exp Metapneumovirus/

#23 exp Enterovirus/

#24 exp Cytomegalovirus/

#25 exp bocavirus/

#26 virus$.tw.

#27 viral$.tw.

#28 Influenza$.tw.

#29 (("haemophilus influenzae" or "h. influenza") not influenza).tw.

#30 28 not 29

#31 Rhinovir$.tw.

#32 Respiratory Syncytial Vir$.tw.

#33 Coronavir$.tw.

#34 Paramyxovir$.tw.

#35 Orthomyxovir$.tw.

#36 Adenovir$.tw.

#37 Picornavir$.tw.

#38 Metapneumov$.tw.

#38 Enterovir$.tw.

#40 Parainfluenza.tw.

#41 Echovir$.tw.

#42 Bocavir$.tw.

#43 vzv.tw.

#44 varicella.tw.

#45 /OR 13-27, 30-44

#46 exp animals/ not exp humans/

#47 (exp child/ or exp adolescent/) not exp adult/

#48 exp editorial/ or (exp review/ not (exp systematic review/))

#49 12 and 45

#50 49 not (46 or 47 or 48)

8.4.2. Forest and funnel plots

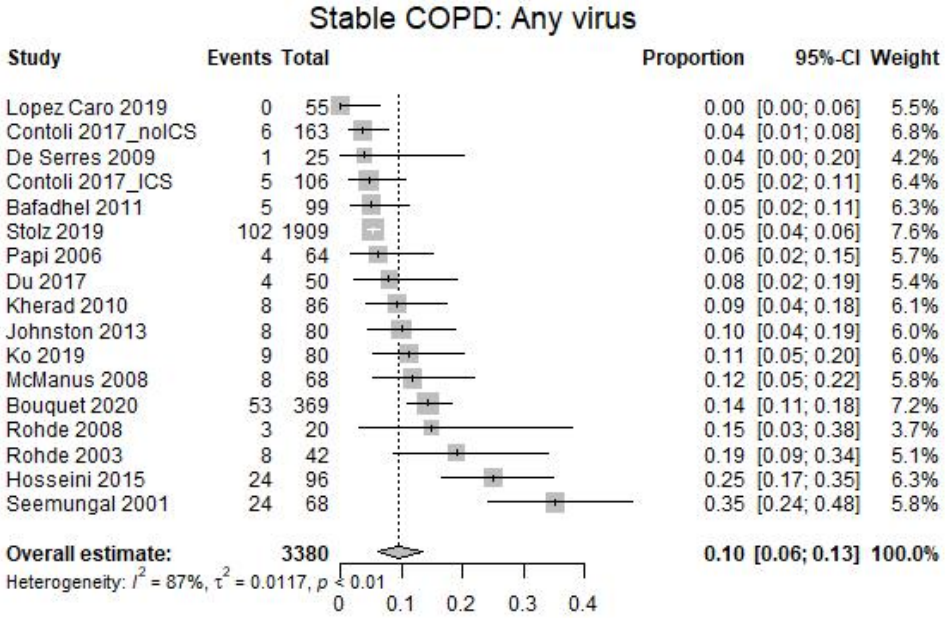


Figure 22. *Meta-analysis of the prevalence of any virus in stable COPD*

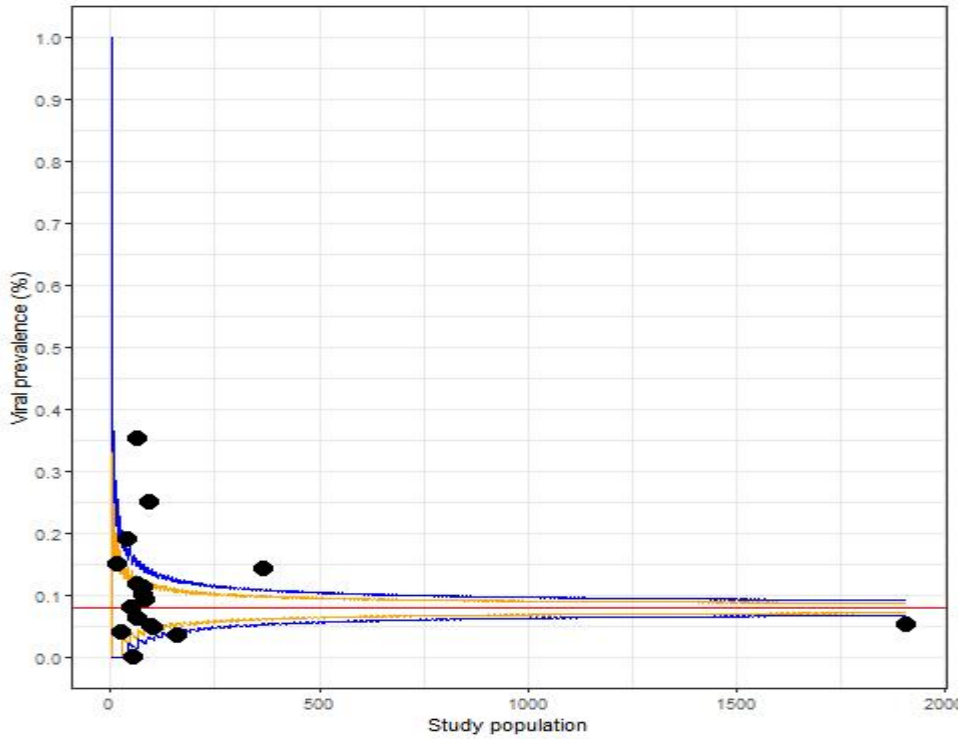


Figure 23. *Funnel plot of the meta-analysis assessing prevalence of any virus in stable COPD*

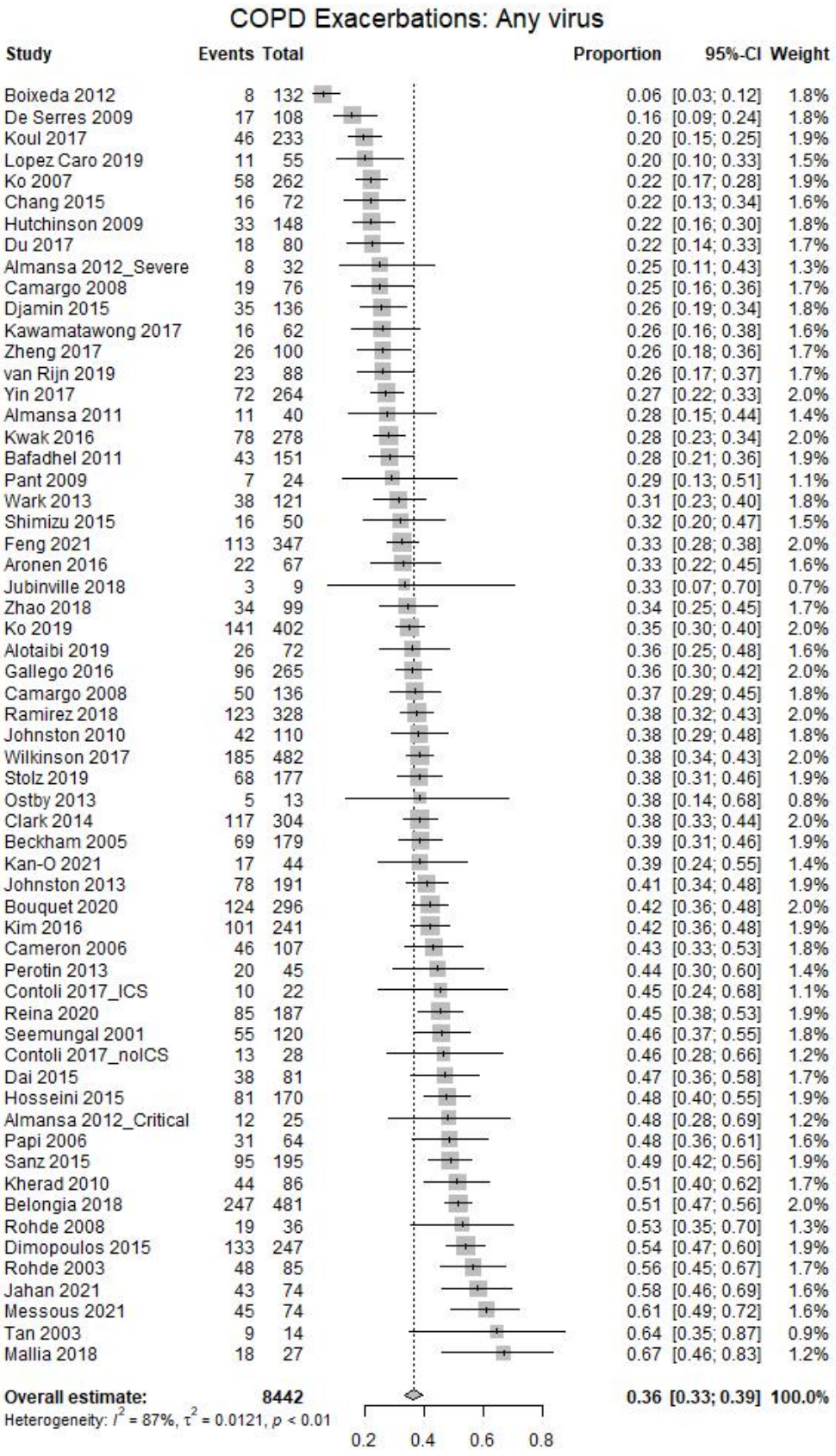


Figure 24. *Meta-analysis of the prevalence of any virus in COPD Exacerbations*

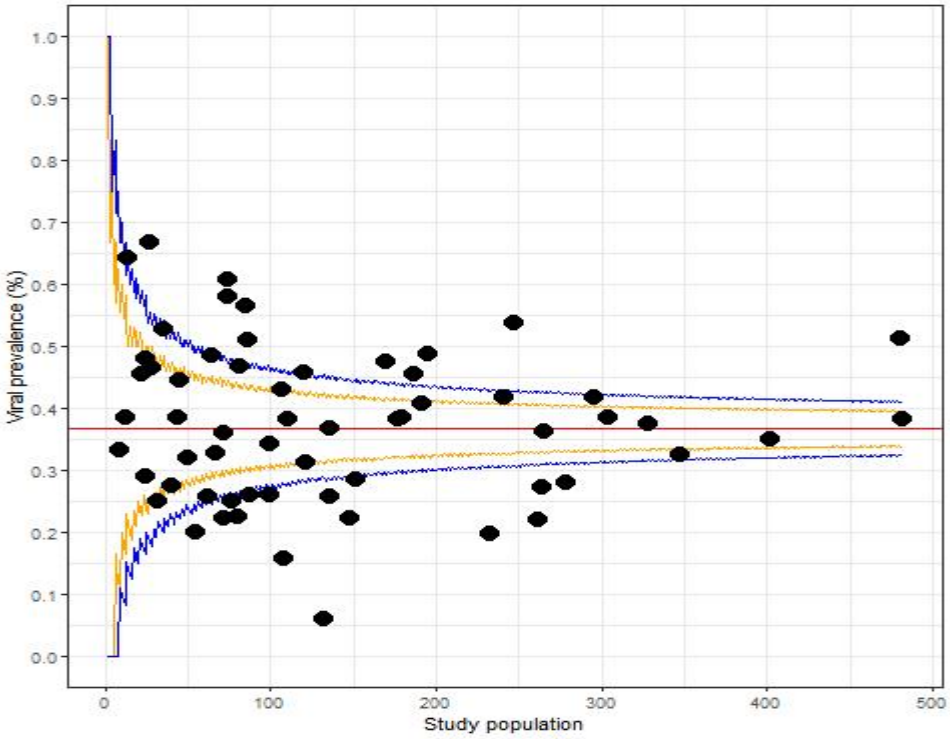


Figure 25. *Funnel plot of the meta-analysis assessing prevalence of any virus in COPD exacerbations.*

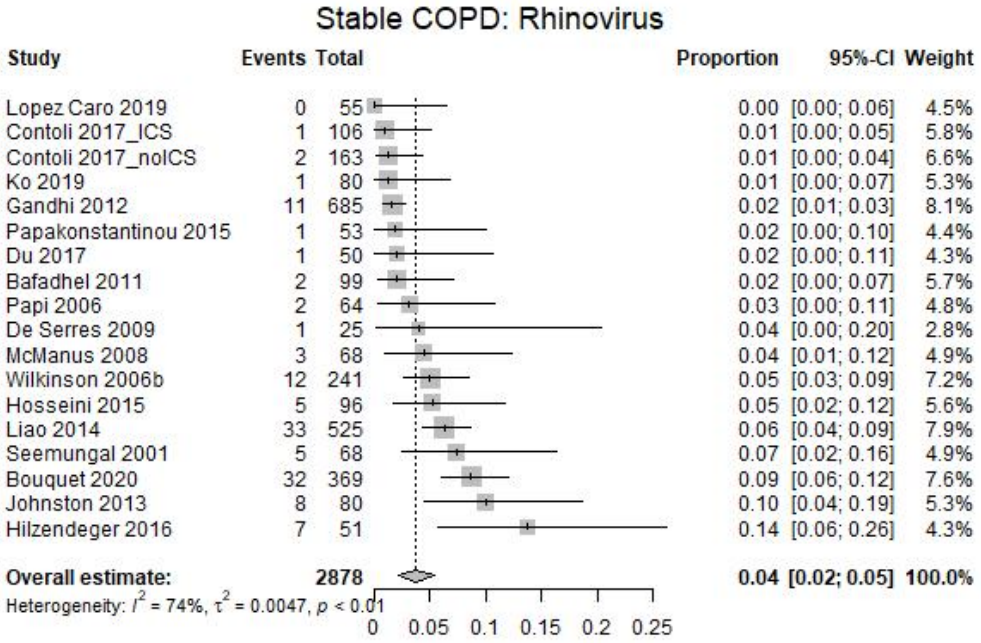


Figure 26. *Meta-analysis of the prevalence of rhinovirus in stable COPD*

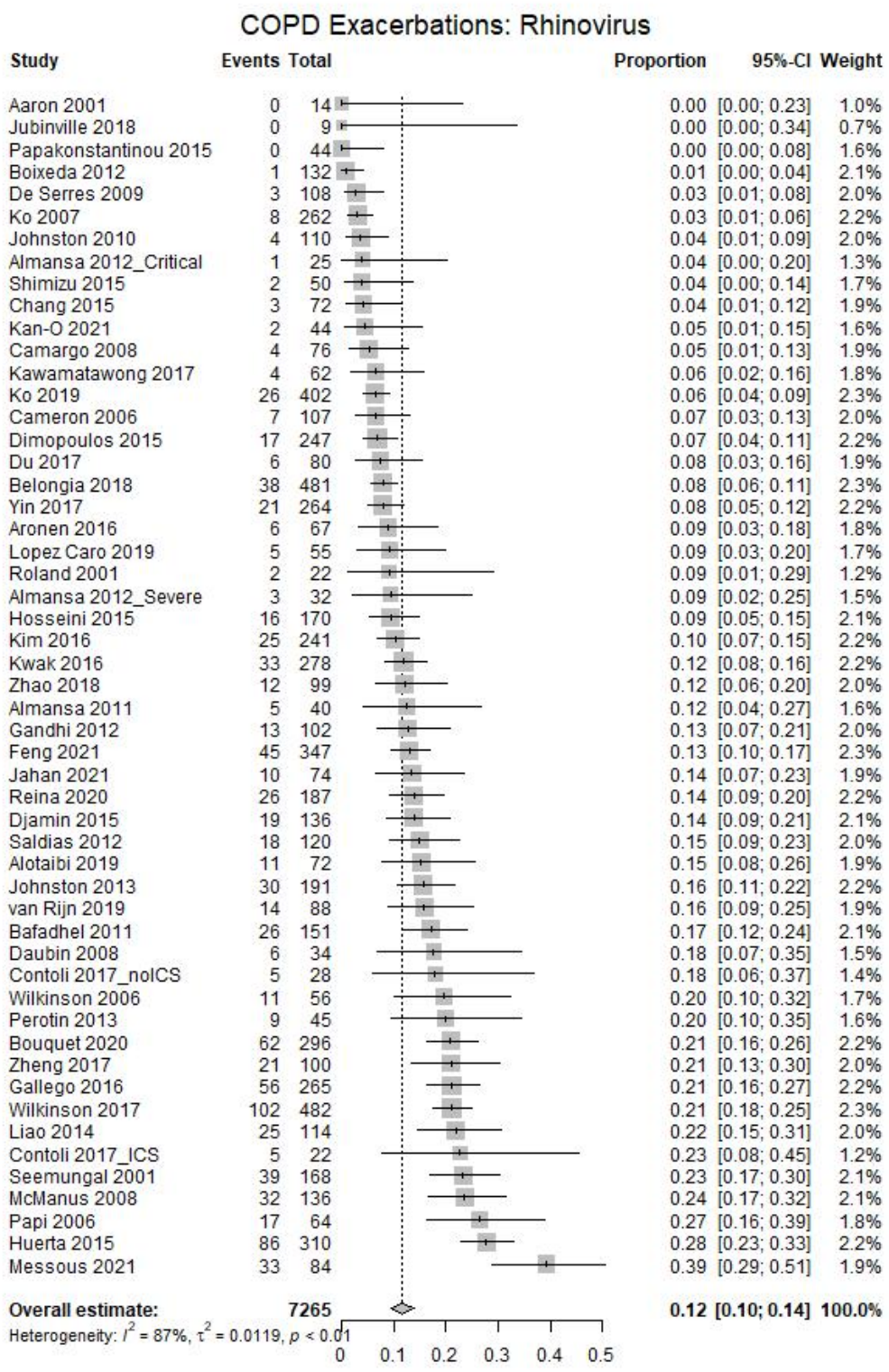


Figure 27. *Meta-analysis of the prevalence of rhinovirus in COPD Exacerbations*

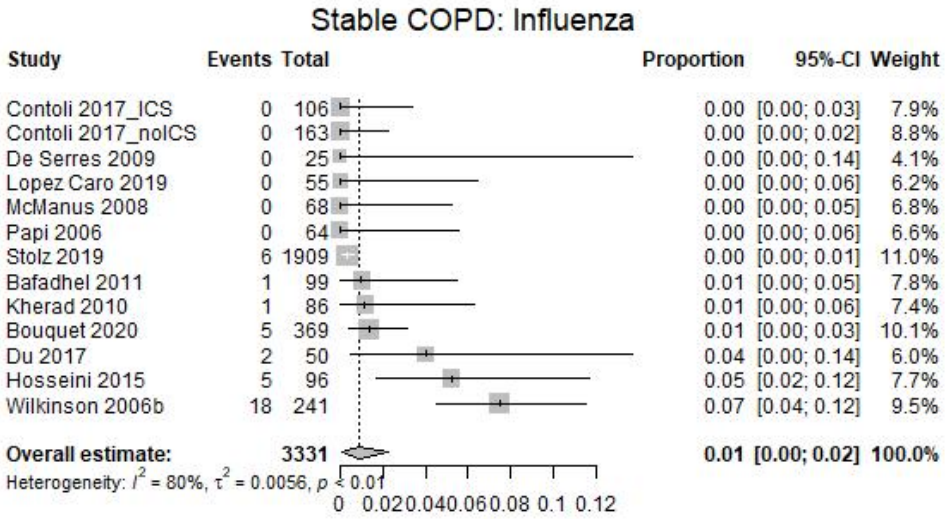


Figure 28. *Meta-analysis of the prevalence of influenza in stable COPD*

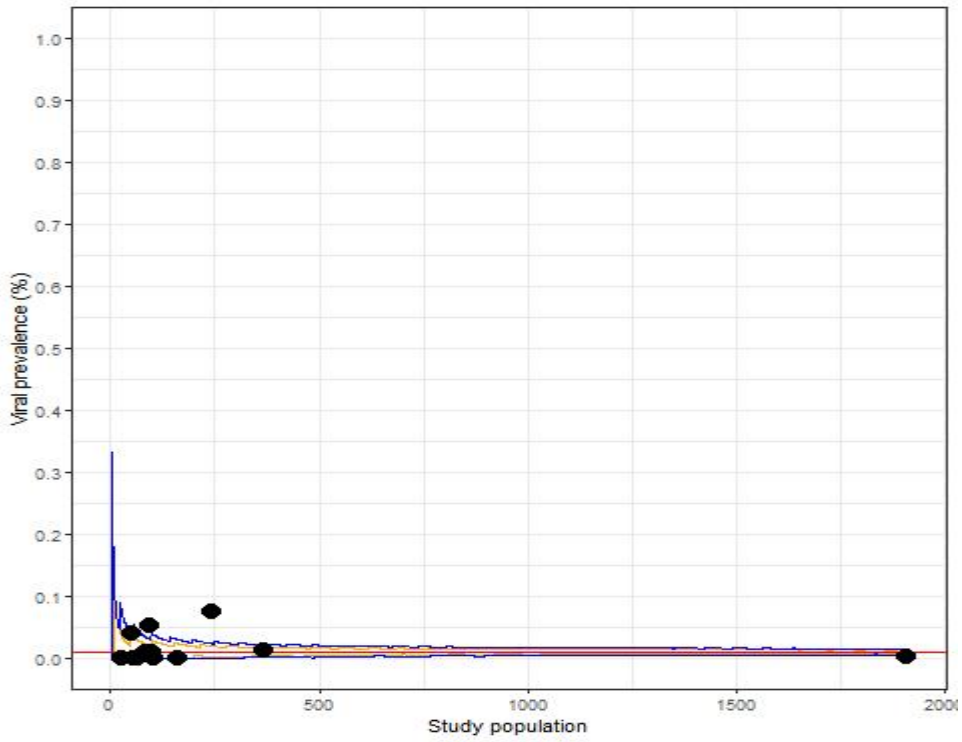


Figure 29. *Funnel plot of the meta-analysis assessing prevalence of influenza in stable COPD*

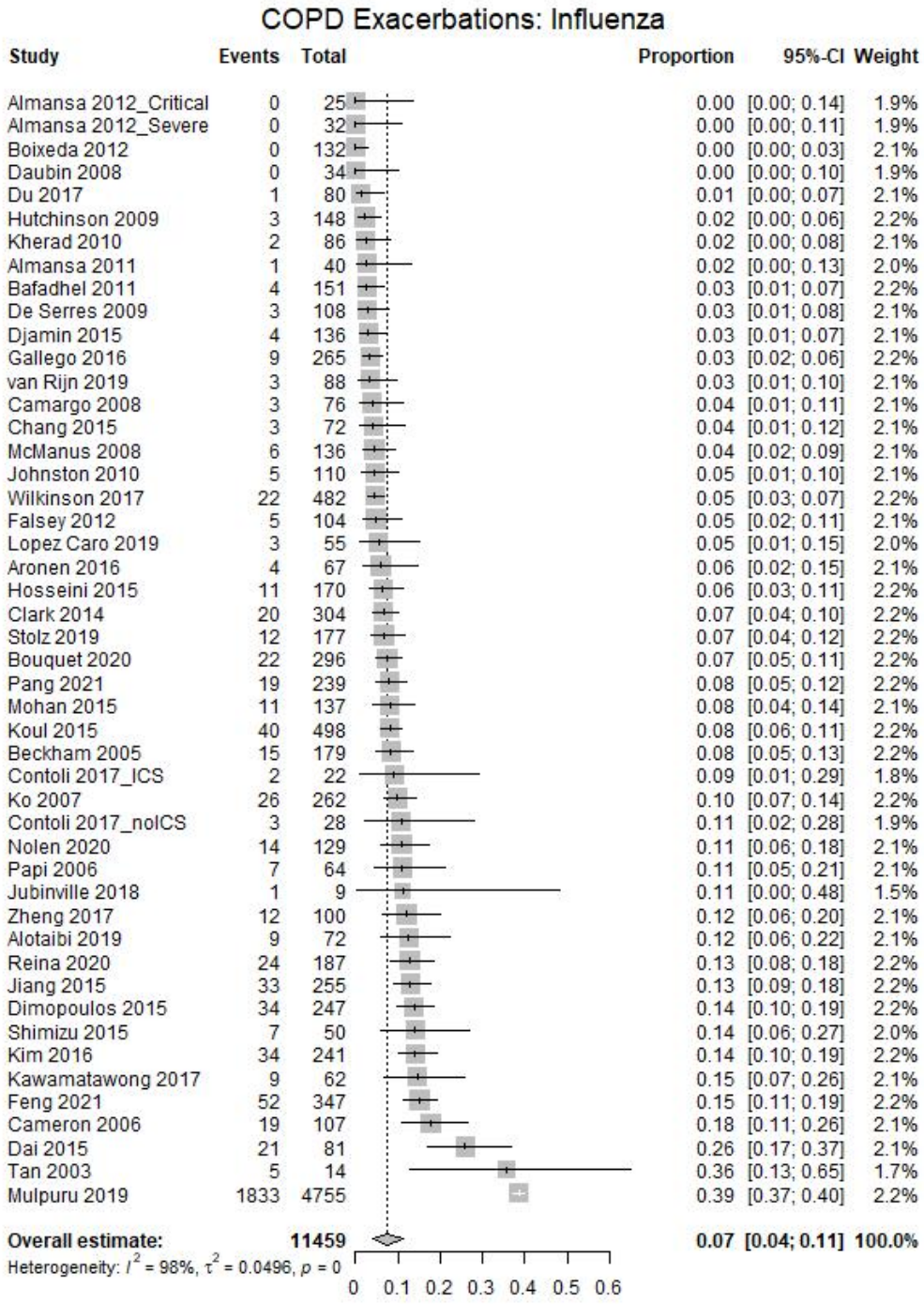


Figure 30. *Meta-analysis of the prevalence of influenza in COPD Exacerbations*

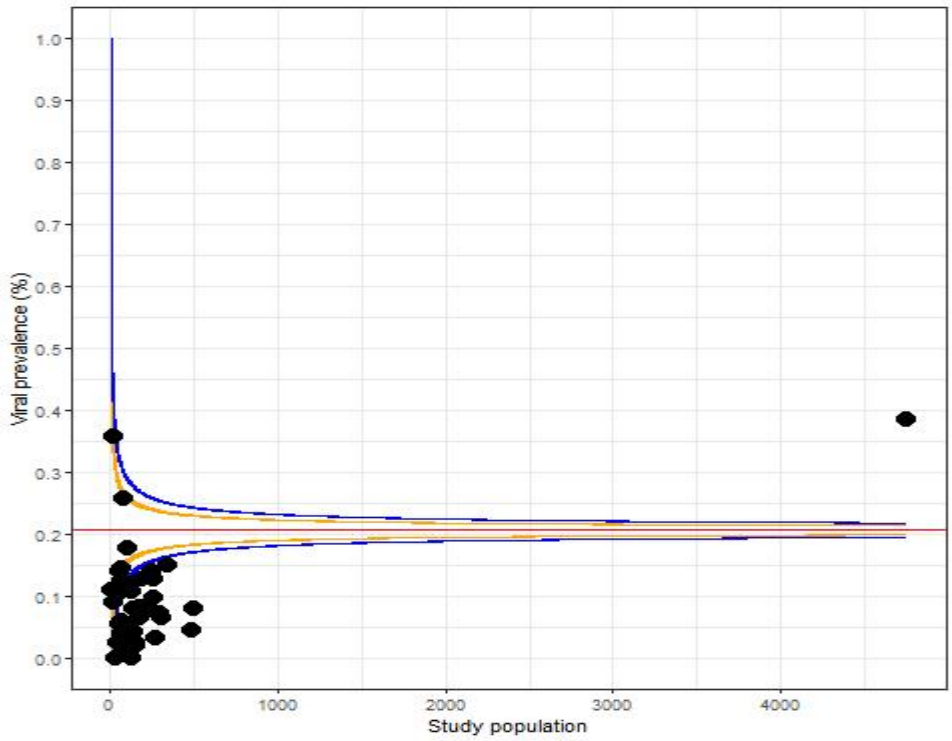


Figure 31. *Funnel plot of the meta-analysis assessing prevalence of influenza in COPD Exacerbations*

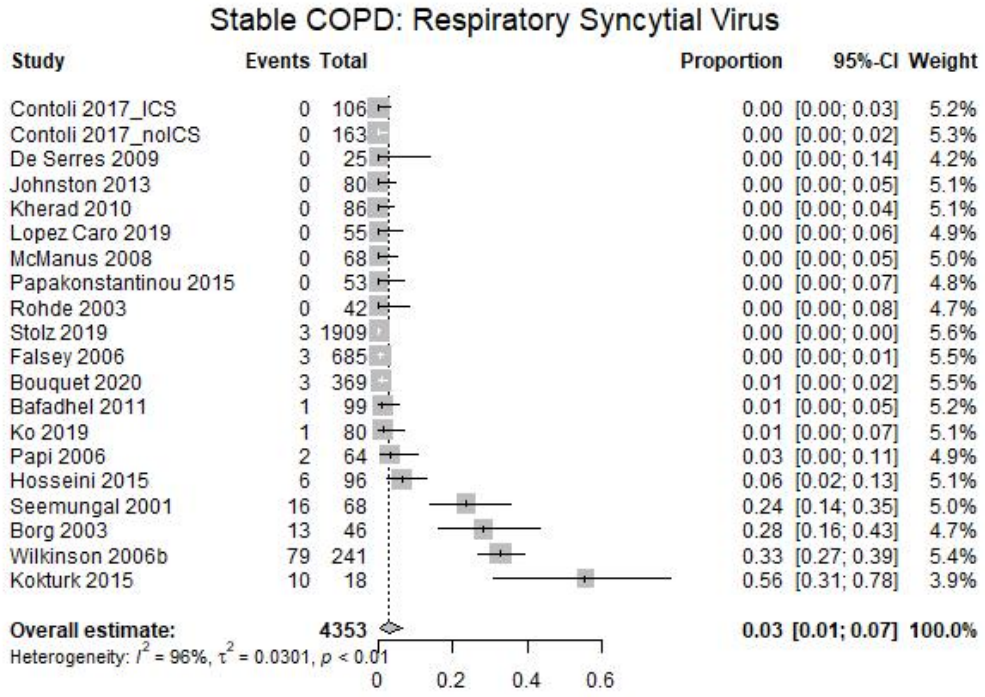


Figure 32. *Meta-analysis of the prevalence of RSV in stable COPD*

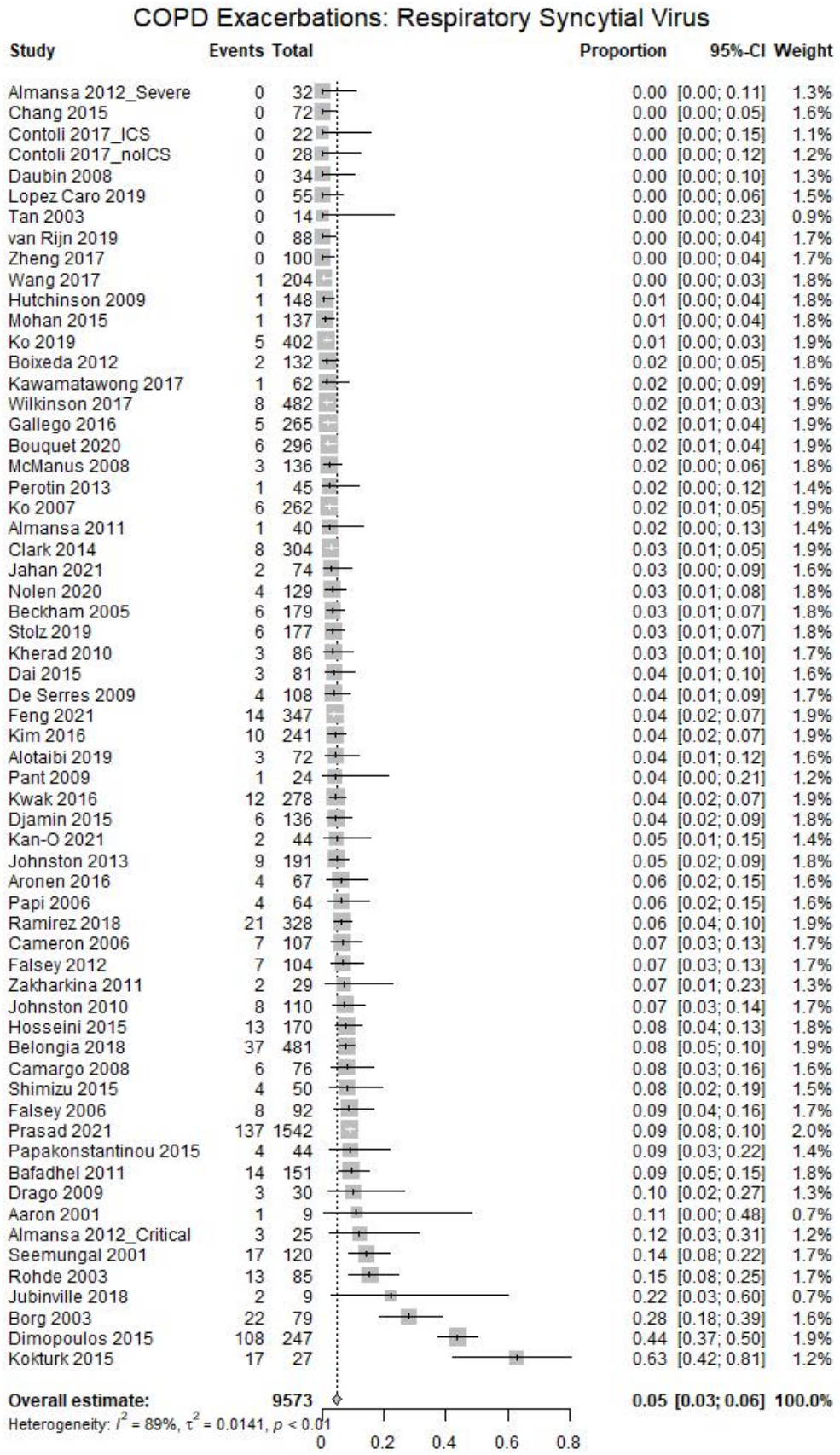


Figure 33. *Meta-analysis of the prevalence of RSV in COPD Exacerbations*

8.4.3. Subgroup analysis by exacerbations severity

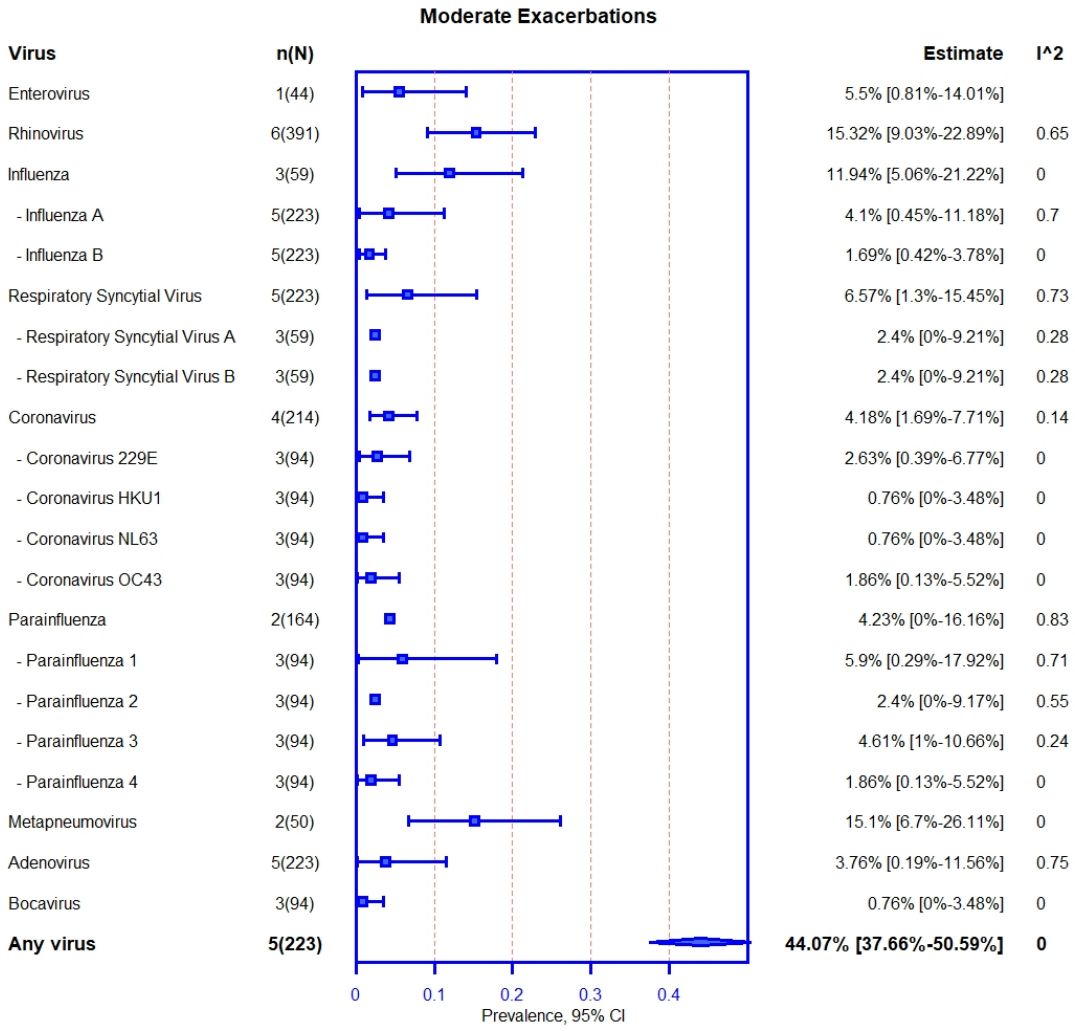


Figure 34. *Prevalence of respiratory viruses in moderate COPD Exacerbations*

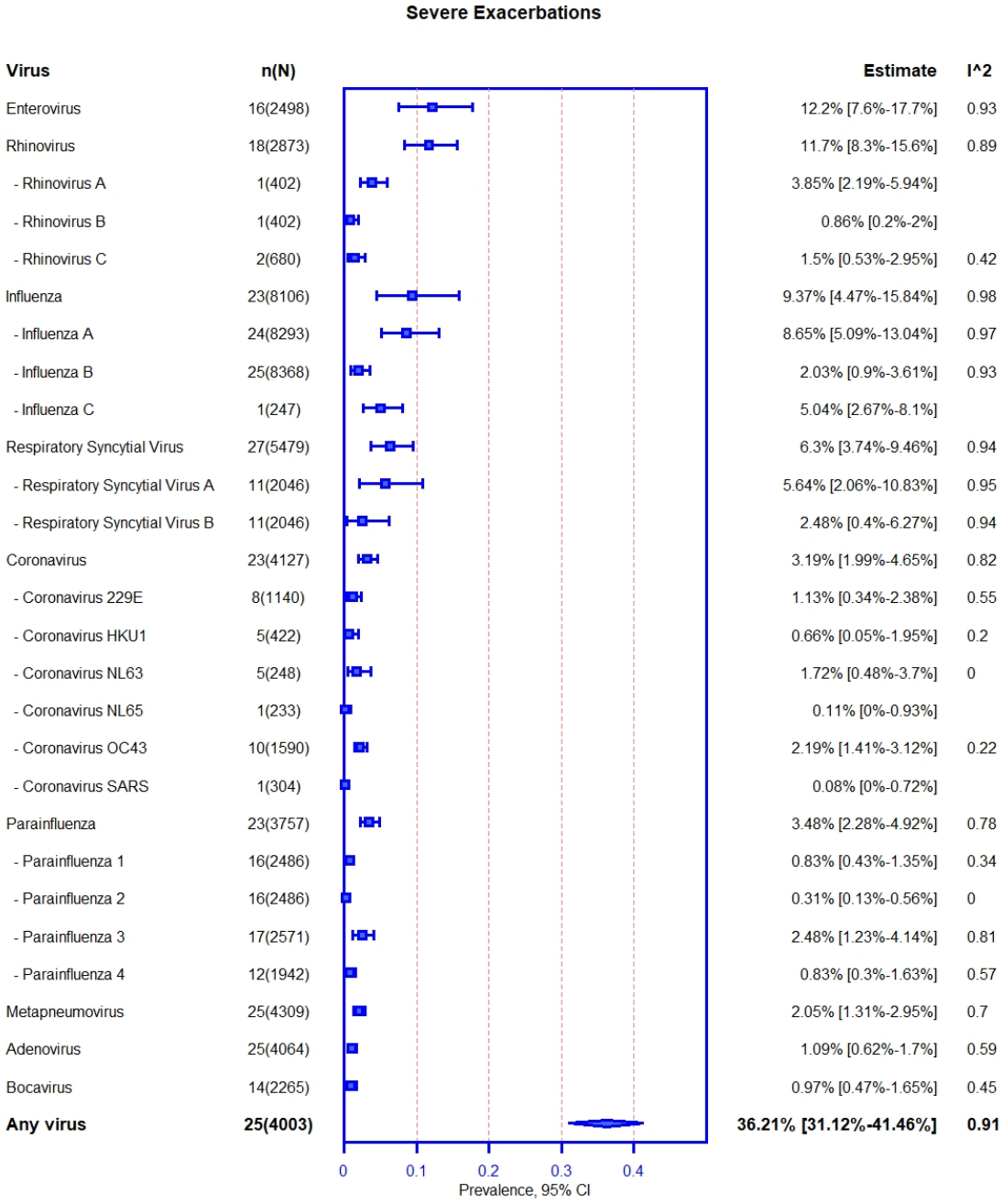


Figure 35. *Prevalence of respiratory viruses in severe COPD Exacerbations*

8.4.4. Sensitivity analysis by source of the respiratory viral sample.

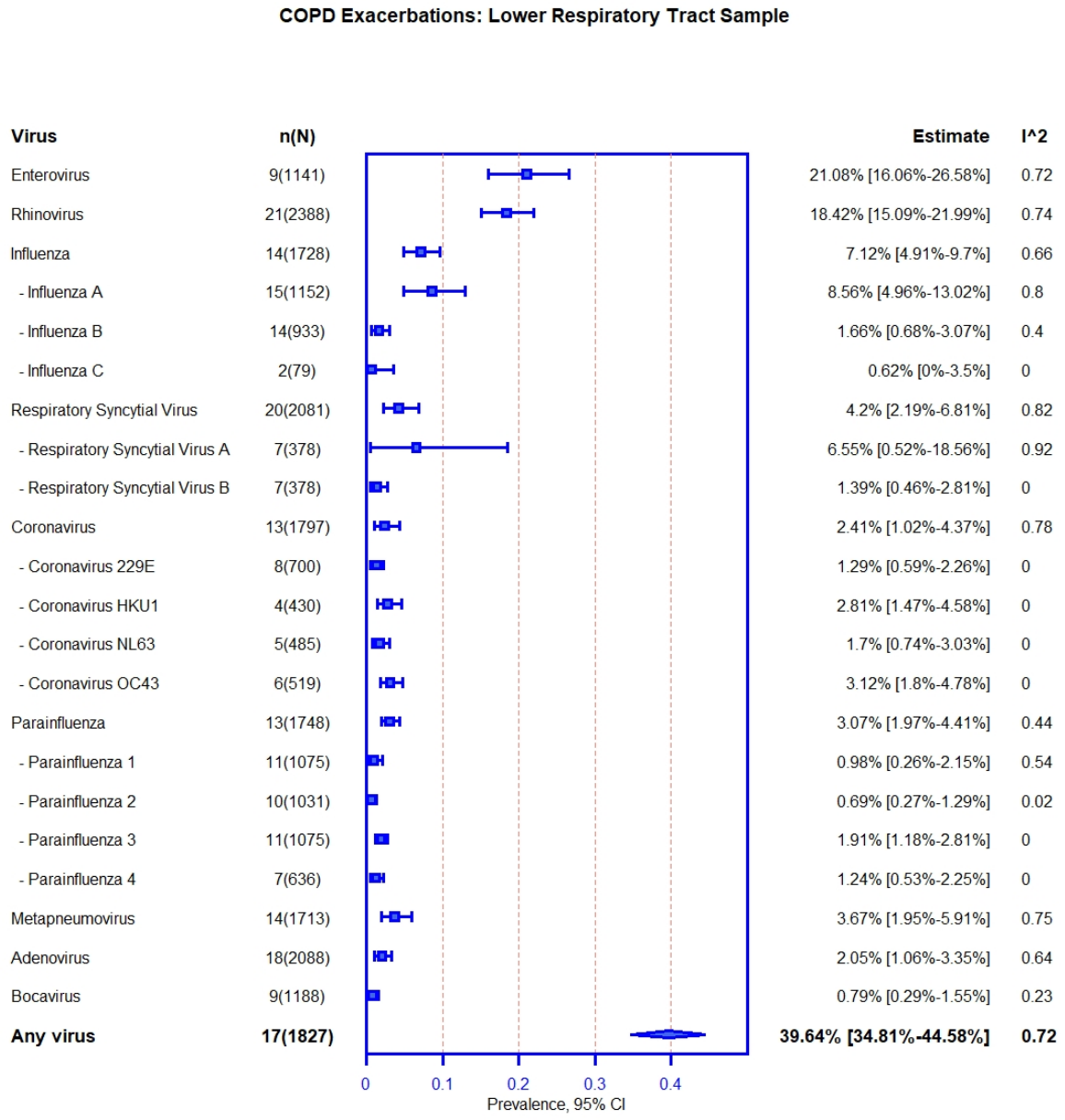


Figure 36. *COPD Exacerbations: Prevalence of respiratory viruses in lower respiratory tract samples.*

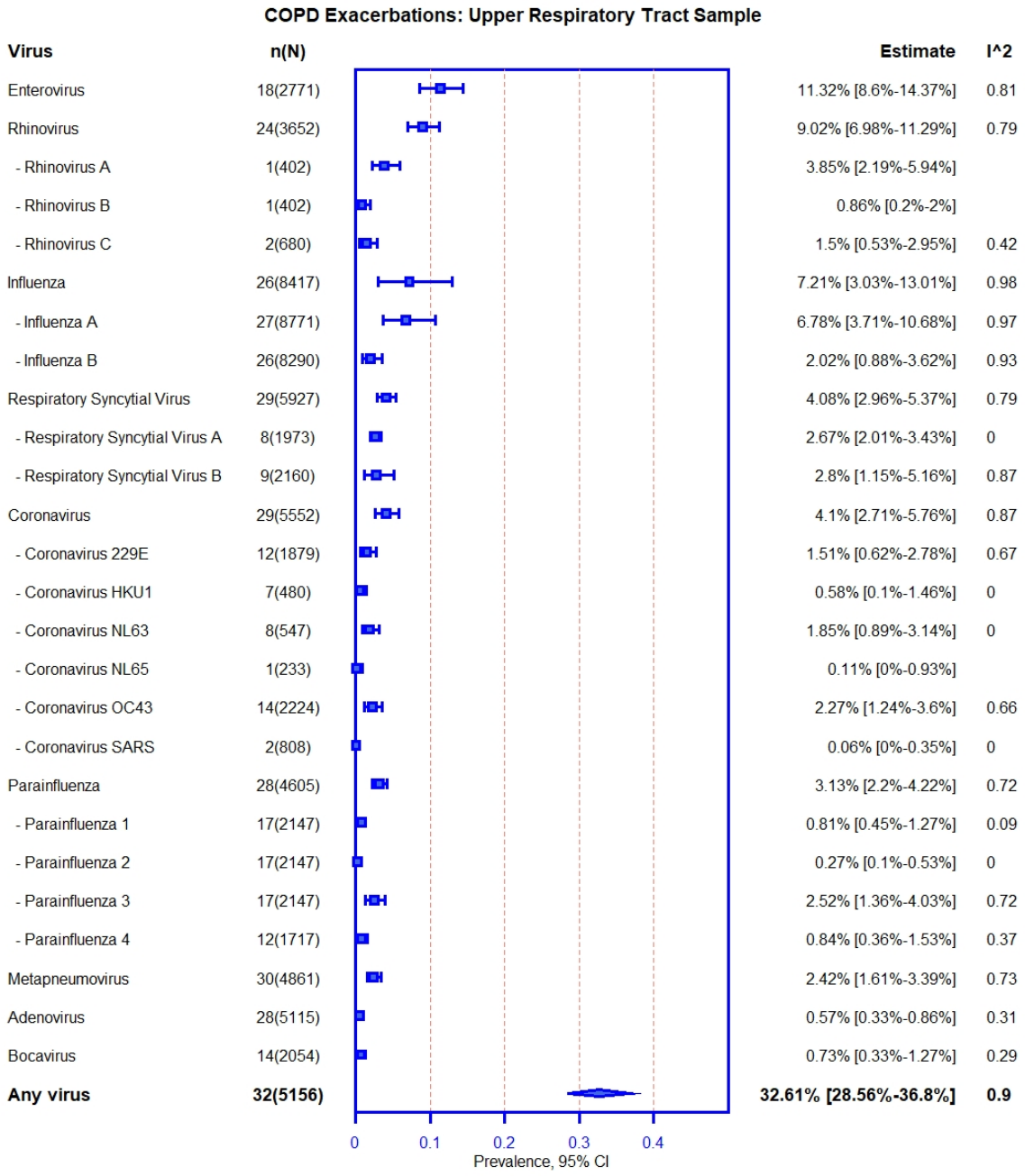


Figure 37. *COPD Exacerbations: Prevalence of respiratory viruses in upper respiratory tract samples.*

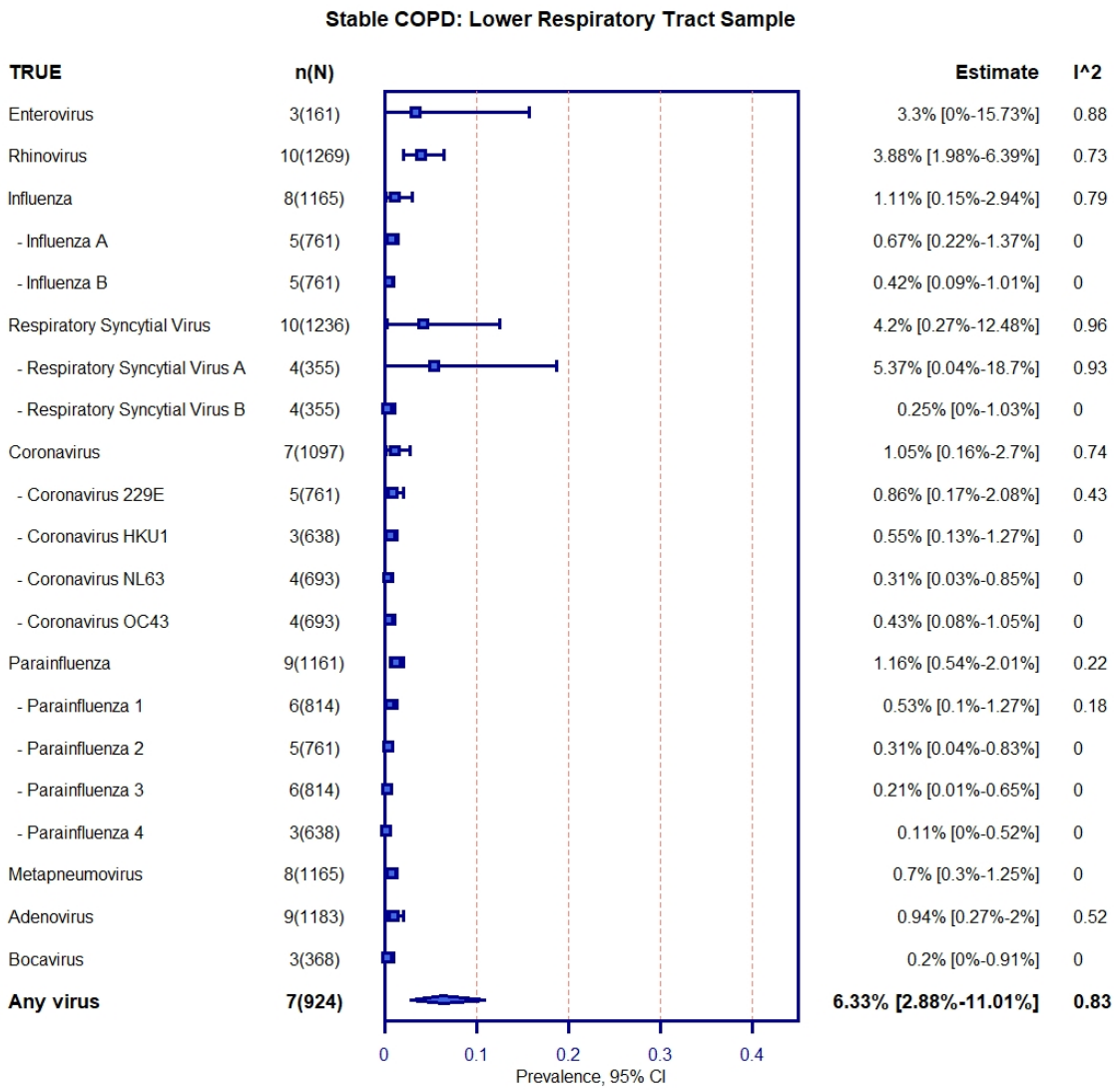


Figure 38. *Stable COPD: Prevalence of respiratory viruses in lower respiratory tract samples.*

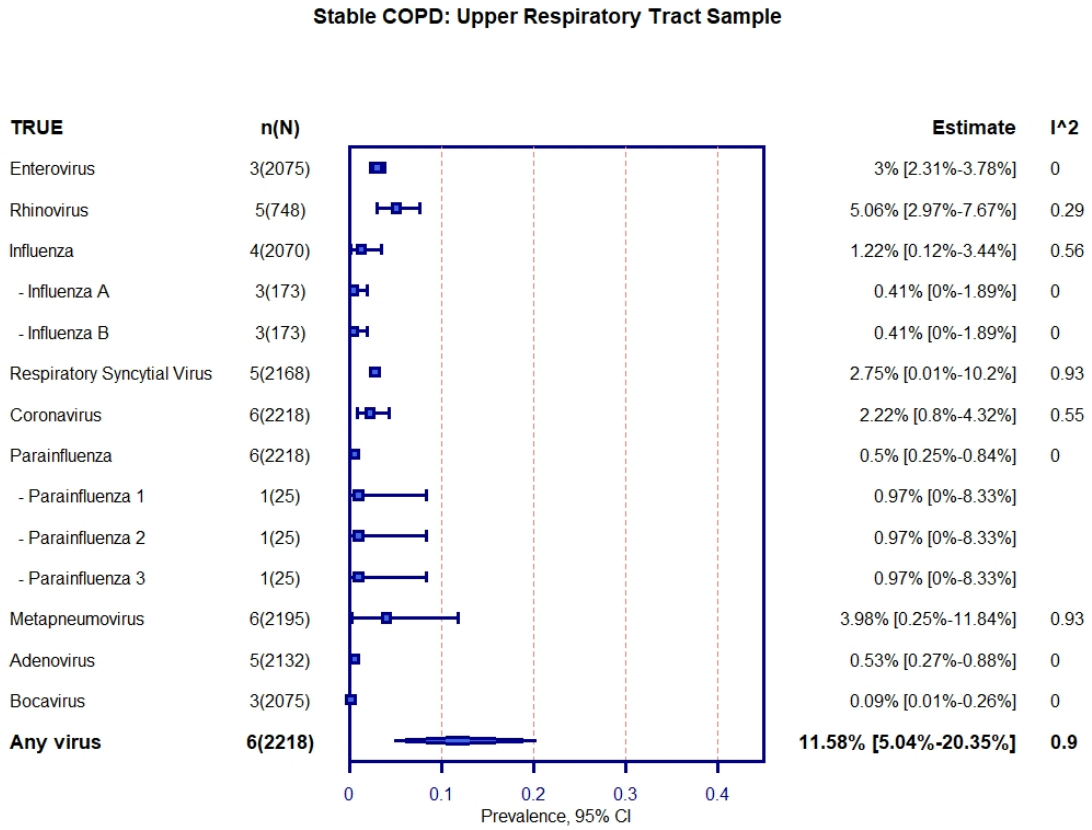


Figure 39. *Stable COPD: Prevalence of respiratory viruses in upper respiratory tract samples.*

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