Research Priorities for Exacerbations of COPD

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Chronic obstructive pulmonary disease (COPD) affects more than 250 million people around the world. In addition to daily symptoms and functional limitation, people living with COPD are susceptible to acute deteriorations in respiratory health. People living with COPD say that these exacerbations are the most disruptive aspect of their disease [1] and frequent exacerbations are associated with more rapid disease progression, impaired quality of life and excess mortality ~~[2]~~. Exacerbations therefore cause most of the costs associated with COPD: personal cost to those affected and financial costs to health services and society more broadly.

Exacerbation prevention is a major goal of COPD guidelines [3]. Even when used optimally, however, interventions to prevent exacerbations are incompletely effective and there have been no new therapies to treat exacerbations in decades [3]. Progress can only occur through research ~~[4]~~. Respiratory research has been neglected in relation to disease burden [5] and there is a strong argument for prioritising research that addresses the questions most important to those living with the condition given that research agendas set by academics or the pharmaceutical industry do not necessarily reflect the priorities of patients and health-services [6].

The James Lind Alliance (JLA), part of the UK National Institute for Health Research has pioneered robust and transparent methodology to bring together patients, carers, and clinicians as equal partners in 'Priority Setting Partnership' (PSP) to systematically collect 'uncertainties' and prioritise resulting research questions. The final output is a list of top-ten questions that patients and clinicians want the research community to address.

A JLA PSP for Exacerbations of COPD was undertaken from February 2019 to April 2021 (detailed Methodology can be found in the JLA Guidebook, ~~publications relating to other PSPs [7]~~ and in the Supplementary Appendix). In brief, there are five stages: 1) establishing the PSP and agreeing project scope, 2) gathering and identifying 'uncertainties' using a survey, 3) summarising and processing uncertainties to develop over-arching research questions, 4) interim prioritisation of these questions using a Web survey, 5) a final priority setting workshop to reach consensus on the top-ten questions.

A total of 571 respondents submitted 1912 individual responses, of which 791 were in-scope and reduced to 59 overarching research questions. 418 (73.2%) of initial respondents were COPD patients, 39 (6.8%) were carers and 110 (19.3%) were clinicians. 51 of the 59 overarching research questions were judged to be unanswered on checking for robust evidence and these were taken through to interim ranking. A total of 191 respondents (43.5% patients and carers) ranked the questions to produce a shortlist of 16 research priorities to go forward to the final top-ten raking workshop. The top ten research questions were identified through consensus at a final one-day online priority setting workshop.

The final top-ten list of research questions is listed in Table 1, which includes the joint ranking of the questions at the interim priority stage, and separate ranking for patients/carers and clinicians. Further detail on the Results (including the ranking of all 51 research questions at the interim priority stage) can be found in the Supplementary Appendix.

The highest rated question was to identify better ways to prevent exacerbations. Despite the availability of many pharmacological and non-pharmacological interventions to reduce exacerbations [3], these remain incompletely effective even when implemented well and our results highlight the importance of developing novel approaches to exacerbation prevention. Specific questions relating to prevention focused on understanding links between co-morbidity and exacerbation risk including optimal ways to manage anxiety and depression in COPD, and optimal use of antibiotic prophylaxis which whilst known to be effective [8] is associated with adverse effects including the development of bacterial resistance. One question sought to better understand exacerbation recurrence (with the ultimate aim to intervene and prevent recurrent exacerbations).

Regarding diagnosis, two questions related to the important concept that COPD exacerbation is a clinical diagnosis of exclusion without a diagnostic test. One sought to find ways to assist patients and clinicians to differentiate the start of an exacerbation from day-to-day symptom variation in COPD, whilst a second aimed to assist differentiation of exacerbations from other causes of symptom deteriorations that may mimic (or complicate) COPD exacerbations – for example cardiac dysfunction, pneumonia, and pulmonary embolus.

Questions relating to treatment focused on the benefits and risks of 'rescue packs', which treatments to use to treat exacerbation in which people (personalised medicine) and – notably – a question on the optimal use of palliative care approaches in COPD.

This is the first research prioritisation devoted to exacerbations of COPD. The key strength of this work is the use of robust and transparent JLA methodology. The methodology transcends the different perspectives of patients in clinicians to create a rank of shared priorities. Whilst we had a large sample size, we had few people from black and minority ethnic backgrounds. People mostly responded online which risks digital exclusion. The study was conducted in the UK and whilst the research questions are likely to be of relevance in other high-income settings, our work does not address priorities for COPD exacerbation research in low- and middle-income countries.

Prioritising research questions using rigorous methodology positions the COPD community to submit commissioned and investigator-led research calls in the knowledge that these have been transparently co-developed via a multi-professional team, in partnership with patients and carers, such that questions can be considered relevant to people living with

COPD and practice changing. Research proposals developed in this way are much more likely to be funded [9]. We will now lobby for research commissioned on these top-ten priorities, to secure funding to address these prioritised topics and reduce the burden of exacerbations for patients and their carers.

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Author Contributions

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The British Lung Foundation funded this work as a project grant. They assisted with dissemination of the surveys but had no other role in conduct of the work. All authors had full access to the full data in the study and accept responsibility to submit for publication.

Table 1: The final top ten research priorities for COPD exacerbations. Ranking at the interim priority setting stage is also included: both joint ranking and separately for patients/carers and clinicians.

FINAL RANK	Research Question	Patient/Carer rank at Interim prioritisation
1	**What can prevent exacerbations of COPD?**	1
2	**What is the best way to tell the start of an exacerbation from day-to day variation in symptoms?**	=7
3	**What is the best way to tell the difference between an exacerbation and a different cause of changing symptoms in a person with COPD?**	6
4	**What is the optimal combination of treatments at COPD exacerbations and what is the best way to decide this for individual patients?**	=13
5	**What are the associations between co-morbidity and risk of COPD exacerbations?**	24
6	**Which palliative care regimes should be used to treat an exacerbation, in which circumstances, and what are the potential benefits?**	=14
7	**Why do some exacerbations recur following treatment?**	11
8	**What are the risks and benefits of 'rescue packs' used to prevent COPD exacerbations, and how should they be best used?**	=11
9	**How does the presence of anxiety and depression affect the prevention, diagnosis, and treatment of COPD exacerbations?**	=20
10	**What are the risks and benefits of long-term antibiotics to prevent COPD exacerbations, and how should they be best used?**	9