Priorities for pulmonary hypertension research: a James Lind Alliance priority setting partnership

Running Head: Research priorities for pulmonary hypertension

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JW, LM, JH, ND, JS, SP obtained funding and designed the study.

JW, HI, LM, LL, TR, JS, and SP acquired the data.

JW, HI, ARS, and TR analyzed the data.

JW, HI, LM, ARS, LL, JH, ND, TR, JS, and SP interpreted the data.

JW wrote the first draft of the manuscript and all authors provided critical input to the manuscript.

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Abbreviations

JLA – James Lind Alliance

PAH – Pulmonary arterial hypertension

PH – Pulmonary hypertension

PSP – Priority setting partnership

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Abstract

Pulmonary hypertension (PH) is a rare condition associated with significant morbidity and mortality. The priorities for future research in PH according to patients, caregivers, and clinicians have not been established. We performed a James Lind Alliance priority setting partnership in Canada. An initial survey of 249 respondents (76% patients/caregivers, 12.5% clinicians) generated 1588 questions, which were combined into 187 summary questions. An evidence check identified 352 systematic reviews and guidelines which were mapped to the summary questions, which determined that 157 summary questions were unanswered by existing research. An interim prioritisation survey (240 respondents, 66% patients/caregivers, 18% clinicians) asked respondents to choose which of the 157 summary questions were among the 30-40 most important. In a final workshop patients, caregivers, and clinicians discussed and ranked the top 25 questions from the interim survey to identify the Top 10 PH research priorities. These results will inform researchers and funding bodies about patient, caregiver, and clinician priorities for future research on PH.

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Pulmonary hypertension (PH) is defined by elevated pressure in the pulmonary artery, that is classified into five clinical groups [1]. Pulmonary arterial hypertension (PAH, Group 1 PH) is a rare form of PH that leads to significant morbidity, reduced quality of life, and increased mortality [2]. Major advances in PAH research over the past few decades has led to several effective treatments and improved outcomes [2]. There has been increasing emphasis on patient-oriented research, which engages and involves patients, family members, and caregivers as partners in all stages of research [3]. Understanding the questions and problems that patients with PH most want answered by future research can inform funders and researchers where to prioritize resources. The objective of this study was to determine research priorities for PH according to clinicians, caregivers, and patients with lived experience.

We used the validated James Lind Alliance methodology for research priority setting partnerships (PSP) [4]. The output of a PSP is a top 10 list of researchable questions, which can be used by researchers, health systems, and funders to consider strategically which future research areas to pursue. We conducted a Canadian PH PSP between May 2019 and February 2022. The detailed methods and study protocol are available on the JLA website: https://www.jla.nihr.ac.uk/priority-setting-partnerships/pulmonary-hypertension-canada/ and the study was approved by the University of Calgary ethics board (REB20-0212). Briefly, there were 5 steps in this PSP (**Figure**): 1) identification of partners, 2) identification of potential questions through a national survey of patients, caregivers and PH clinicians, 3) refining questions and confirming uncertainties with a systematic literature search, 4) an interim prioritization survey, and 5) a final priority setting workshop to determine the top 10 priorities for future research. The initial survey asked respondents what questions they have that they would like answered by

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future research on the diagnosis, causes, risk factors, aggravating factors, prognosis, treatment, and management, living well with PH, and management of co-existing conditions. These categories and questions were formulated by the Steering Group, which consisted of PH clinicians, an advisor from the James Lind Alliance, and two patient representatives (**Supplemental Table 1**). Surveys were disseminated through PH clinics and two patient advocacy organizations (Pulmonary Hypertension Association of Canada and Hypertension Artérielle Pulmonaire Québec) in English and French. Surveys were open to patients with all types of PH, their family members and clinicians including physicians and non-physicians. The interim prioritization survey was conducted in January 2022. In the interim survey, respondents were asked to select which summary questions should be included among the top 30-40 most important questions for future research but were not asked to prioritize these in order of importance. The 25 most frequently selected questions were brought forward for final prioritization in a workshop held virtually on February 3rd and 5th, 2022. Workshop participants consisted of 13 PH patients, 3 caregivers, and 6 clinicians. These participants were divided into 3 groups with balanced representation of patients, caregivers, and clinicians. Three facilitators trained in James Lind Alliance methodology moderated group discussions and ensured the principles of inclusivity of patients and clinicians, equal involvement of those groups, and transparency of process. In the small groups, each participant contributed their views on the questions they felt are most and least important for research. These were noted by the JLA facilitator. To ensure equal speaking time, each person shared their top 3 and bottom 3 choices. Facilitators guided then guided discussion to further explore areas of agreement or divergence and to clarify any aspects of the uncertainties. The groups made an initial ranked list of the Top 25. The sum of the rankings from each group was then calculated and sorted from lowest to

highest. New groups were formed in the second half of the workshop, to allow the participants to hear a wider range of views, and a second round of prioritization of the 25 questions took place. Finally, the sum of the rankings from each group was again calculated and sorted from lowest to highest to arrive at the final Top 10.

There were 249 individuals who completed the initial survey, of which 61% were female. 170 (68%) were patients with PH, 20 (8%) were caregivers, friends or family members, and 31 (12.5%) were clinicians, with 11.5% preferring not to specify. There were 1847 individual responses submitted of which 1588 were in-scope. Submitted responses were grouped into similar concepts and summarized as 187 unique summary questions by two authors (J.W. and H.I.), with review by the Steering Group and patient partners to ensure summary questions reflected the intended meaning of survey submissions (**Supplemental Table 2**). Two questions (48 and 72) were combined due to perceived overlap in meaning and rephrased to "*How can PH be reversed or put into remission and how can we measure disease modification or reversal, clinically*?". We next performed an evidence check to verify which summary questions were unanswered by existing research. For JLA PSPs, questions are considered uncertain if there are no systematic reviews or guidelines on the topic, or if these exist but specifically note that uncertainty exists. To verify which summary questions were true uncertainties, we performed a literature search of Ovid MEDLINE, Cochrane Database of Systematic Reviews and Embase on September 2, 2021. We identified 1611 unique citations of which 352 were systematic reviews or guidelines on PH published between 2011-2021 (**Supplemental Figure 1**). After these systematic reviews and guidelines were mapped to the summary questions, 157 of the 187 summary questions were considered uncertain and were included in the interim prioritization

survey. A total of 240 respondents (66% patients and caregivers, 18% clinicians, 16% other or preferred not to say) selected their top 30-40 most important questions in the interim survey. The 25 most frequently selected uncertainties from the interim survey were discussed and ranked in the final virtual prioritization workshop (**Table**). The Top 10 list of uncertainties on PH and their rank from the final workshop are highlighted in the **Table**.

This is the first PH research prioritization project founded on patient and other stakeholder engagement to identify their most important questions and areas for future research. Importantly, PSPs deliver researchable questions, not research questions. It is left to the scientific community to develop these uncertainties into focussed research questions for future inquiry, ideally with patient consultation and partnership. Some of the top 10 questions are currently areas of active research, globally, which is common in PSPs and should encourage researchers and funding agencies of the importance to patients of continuing these avenues of inquiry. Other questions in the top 25 have been largely overlooked, such as research on management of PH medication side effects and complications in long-term PH survivors.

There was unanimous agreement between groups in the final workshop on the top 3 questions. The highest ranked question emphasized that the mechanisms that lead to PAH, a rare cause of PH characterized by proliferative remodelling in the pulmonary arteries, are incompletely understood [5]. Improved understanding of pathophysiologic mechanisms across heterogenous clinical subtypes of PAH (e.g. connective tissue disease vs. congenital heart disease) is an essential prerequisite to develop novel therapies. The second most important priority was development of therapies that can reverse PAH. This question also highlights the uncertainty in

how to best measure disease modification or disease reversal as an endpoint in future clinical trials. The third highest ranked priority related to precision medicine and personalization of therapies. This emphasizes the importance of biomarker-based or other enrichment strategies in future research to identify patients most likely to respond to new therapies [6]. Research on mechanisms of right ventricular adaptation and failure was also ranked fourth among the top 10 priorities, which reinforces several of the knowledge gaps and research areas identified in a 2018 American Thoracic Society Research Statement [7].

Some questions that were frequently chosen by patients in the interim survey ultimately did not end up in the Top 10 (e.g. questions 15 and 16 in the **Table**). Importantly, respondents to the interim survey were not asked to prioritize questions in order of importance but only to identify which questions stood out as being more important. The relative priority ranking was determined during the final workshop using the James Lind Alliance methodology and this consensus was influenced by patients and caregivers sharing their unique perspectives and by clinicians providing additional context or clarity to questions. In a post-workshop feedback survey after the workshop, no patients or caregivers reported feeling unduly influenced by clinicians, and several commented that the process helped them to reconsider questions from other perspectives. One quote from a patient participating in the workshop illustrated this well, "*The process was better than expected - allowed to consider other influences and ideas, and open my mind to what other patients feel are important. For example, biomarkers was not ranked by me at all, but our discussion opened my mind to how they might be important*".

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This study has some limitations. The surveys were distributed through the Canadian PH advocacy organizations, which could limit generalizability to other settings. Priorities could differ for PH patients in low- and middle-income countries, for example. Certain areas of PH research were not captured in this PSP (e.g. pediatric PH), and ongoing engagement and research prioritization among other PH groups (e.g. PH due to left heart disease or PH due to chronic lung disease) is still needed. In conclusion, this PSP provided a patient-centred approach to research prioritization, which may guide PH researchers and funding bodies to which problems are most important to patients and clinicians.

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Competing Interest Statement

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Table – The Top 10 and Top 25 priorities for future pulmonary hypertension research.

Rank from Final Workshop	Question	Number of patients contributing at Initial Survey[1]	Number of clinicians contributing at Initial Survey[1]	Patient rank at Interim Prioritization Survey[2]	Clinician rank at Interim Prioritization Survey[2]	Final Workshop Combined Rank-Group 1	Final Workshop Combined Rank-Group 2	Final Workshop Combined Rank-Group 3
1	What are the specific mechanisms that lead to development of Pulmonary Arterial Hypertension?	46	6	15	14	1	1	1
2	How can PH be reversed or put into remission and how can we measure disease modification or reversal, clinically?	6	2	1	4	2	2	2
3	How can we predict which treatment or combination will work best for an individual PH patient (e.g. personalized medicine)?	5	7	24	11	3	3	3
4	What are the mechanisms of	0	1	25	3	7	4	7

	right heart adaptation to PH and right heart failure?							
5	Which interventions or treatment strategies result in the best outcomes for patients with PH?	1	0	23	17	6	8	5
6	What is the role of the immune system and auto-immunity in the development of pulmonary arterial hypertension (PAH) and can treatments directed at the immune system help with PAH?	0	0	13	7	5	5	10
7	What are the best tools to predict progression of pulmonary hypertension and how fast the disease will progress?	14	0	2	2	8	9	6
8	What is the most effective and safe amount of exercise	6	0	11	9	10	6	9

	training for PH patients?							
9	Are there biomarkers that allow early detection of PH?	12	3	4	1	12	10	4
10	Are stem cell therapies effective and safe for treating PH?	2	0	17	18	11	7	8
11	What is the underlying cause of idiopathic pulmonary arterial hypertension?	14	1	9	5	4	15	14
12	What are the mechanisms by which cardiac function continues to deteriorate despite an improvement in symptoms?	1	0	20	16	13	12	13
13	When a PH patient needs surgery what are the best anesthetic approaches and if general anesthesia is required, which anesthetics are safest?	0	0	6	10	16	13	11

14	How can we detect when the disease process (pulmonary hypertension) starts and how long does it take for symptoms to develop after it starts?	1	0	12	13	14	14	12
15	What are the long-term consequences and complications in PH patients who are long term survivors?	0	0	5	20	15	11	15
16	How can the delay to diagnosis of PH be reduced?	5	2	3	12	9	19	16
17	For how long is PH treatment effective and will the effect wear off with time?	5	0	18	21	17	16	17
18	Is there a relationship between iron deficiency and the development or progression of pulmonary arterial hypertension and if so, does treatment	2	0	19	15	18	17	18

	of iron deficiency improve outcomes?							
19	Can exercise testing be used to identify early PH and predict the risk of developing PH in the future?	1	1	22	6	19	18	19
20	How can the side effects of pulmonary hypertension therapies be managed or reduced?	21	2	21	19	20	20	20
21	What is the most accurate method to classify the severity or risk of a patient with PH?	1	0	10	8	21	22	21
22	Are there any harmful longterm effects of medications used for PH?	11	0	8	25	22	21	22
23	How can universal coverage for all PH medications be ensured in Canada?	8	0	7	22	23	23	23
24	Can educational interventions targeted at clinicians in-	25	2	14	24	24	24	24

	training, primary care and second line (e.g. specialist) clinicians improve awareness of PH and lead to earlier diagnosis of PH?							
25	How do COVID-19 and COVID-19 vaccinations affect people with PH?	2	0	16	23	25	25	25

[1]Some initial submissions came from respondents belonging to other categories (e.g. caregivers, friends or family members) or were submitted by respondents who did not indicate a category.
[2]Interim survey respondents were asked to select which questions should be included among the top 30-40 most important questions for future research but were not asked to prioritize these in order of importance. Interim survey ranking was determined according to the relative frequency that participants in each group selected the question as a top 30-40 priority.

Figure Legend

Figure – Overview of James Lind Alliance Pulmonary Hypertension Priority Setting Partnership

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