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Developing a Neonatal Pulmonary Hypertension Core Outcome Set (NeoPH COS)—A Study Protocol

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ABSTRACT

Pulmonary hypertension (PH) in newborn babies is a relatively rare, heterogeneous condition that has high associated mortality in the neonatal period and beyond. There are limited evidence-based strategies to treat or prevent this condition. Over the last two decades, there has been an increase in the number of studies assessing new therapies and treatment strategies in babies with PH. However, comparison of different treatments between studies is limited by inconsistency in outcome reporting. To address this issue, we aim to develop a core outcome set (COS) for neonates and infants less than 3 months of age, corrected for prematurity, diagnosed with PH, through international consensus with key stakeholders including parents and/or guardians, healthcare professionals and researchers. The development of the COS will be divided into two stages: (1) identification of potential outcomes through a mixed methods systematic literature review and qualitative interviews with parents and/or guardians of babies with pulmonary hypertension; (2) determining core outcomes through an online Delphi survey and consensus meeting. An advisory group with global membership including parents and/or guardians, healthcare professionals, and researchers recruited internationally was formed to guide the COS. The methodology utilized to develop a neonatal PH COS aims to ensure applicability and adoption in international settings and relevance across disciplines. The COS will help to improve trial design and homogeneity of outcomes reported in neonatal trials of PH. This will translate into higher-quality evidence for therapeutic strategies for PH in neonates.

1 | Introduction

1.1 | Background

Neonatal pulmonary hypertension (PH) is a rare, heterogeneous condition with few effective therapeutic strategies. Approximately 0.2% of term babies develop PH [1, 2], with increased incidence of 8% in preterm babies, ranging from 4.4% at 27 weeks' gestation to 18.5% at 22 weeks' gestation [3]. Despite advances in the management of PH in the neonate over the last three decades, hospital mortality remains high: 11% overall and 18% in preterm infants [1, 3]. Neonatal PH encompasses all forms of PH that result in the elevation of pulmonary artery pressure in the newborn infant. Broadly speaking, there are two main neonatal PH phenotypes, early/transient and late/sustained [4]. Whereas, in pediatric and adult-onset PH there is an

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established classification system by World Symposium on Pulmonary Hypertension (WSPH), which defines five clinical groups based on the cause of the disease: (1) pulmonary arterial hypertension; (2) PH caused by left heart disease; (3) PH caused by lung disease and/or hypoxia; (4) PH caused by pulmonary artery obstruction; (5) PH with unclear and/or multifactorial mechanisms [5]. Early/transient PH presents early in the newborn period, typically in the first 24–48 h after birth, and gradually resolves over a period of hours to days. This includes persistent pulmonary hypertension of the newborn (PPHN), which is a physiological syndrome resulting from failure of the normal postnatal decline in pulmonary vascular resistance, which is classified as Group 1 by the WSPH. By contrast, late/sustained PH characteristically evolves in the first few weeks after birth and subsequently may persist over months and years. Late/sustained neonatal PH is often a result of developmental lung disease or congenital diaphragmatic hernia which is classified as Group 3 by the WSPH. There is some overlap between phenotypes and in some cases, babies may have PH classified as both Group 1 and Group 3 within the first few months of age and beyond. More rare forms of neonatal PH span the WSPH classification, such as pulmonary vein stenosis (Group 2, typically late/sustained) and congenital anemia (Group 5, typically early/transient). In both early/transient and late/sustained PH there is an increased risk of developing right heart failure, which is associated with a higher risk of morbidity and mortality in both the newborn period and beyond [6, 7]. In babies with ongoing PH discharged from neonatal care, there is a 48% risk of mortality in the first 2 years of life [8–10]. Survivors may have resolution, or persistence of PH with serious cardio-respiratory co-morbidities requiring ongoing therapy and poor growth and/or impaired neurodevelopment [11–13]. Children with chronic PH frequently require life-long follow-up and have an increased risk of mortality [4, 14]. Therefore, there is an urgent need for improved treatments in babies with PH. Currently, only one treatment, inhaled nitric oxide, is licensed by the United States Food and Drug Administration and European Medicines Agency for use in infants under 1 year and only for use in the term or near-term newborn with PH. In the last two decades there has been an emergence of studies on the management of neonatal PH [15, 16]. However, the comparison of these studies is limited by the heterogeneity of reported outcomes. This is due to a lack of international consensus on what outcomes to include in trials or to assess in clinical practice in neonates or infants with PH. Hence, meta-analyses of existing studies have thus far been unable to develop evidence-based recommendations for alternative therapies in neonatal PH [17]. Furthermore, outcomes may not directly reflect a change in patients' and families' wellbeing and functioning. In adult PH, the use of patient-reported outcome measure (PROMS) tools have been established in clinical trials [18], but none have been developed for use in neonates and children. Hence, research in neonatal PH may be limited by outcomes not being meaningful to patients and their families. One approach to address these issues is to develop a neonatal PH-specific core outcome set (COS). The development of disease-specific COS is an increasingly recognized approach to improve trial design and to allow for more meaningful comparison between trials [19–21]. A COS is a clearly defined, and systematically derived set of outcomes that can be assessed by a standardized measure for a given disease or condition [22]. This protocol aims to address the unmet need for a Neonatal Pulmonary Hypertension COS (NeoPH COS), developed via consensus methodology through the engagement of relevant stakeholders including parents and/or guardians of babies with neonatal PH, ex-patients, medical practitioners, and academics.

1.2 | Key Objectives

The aim of the study is to determine a core outcome set for neonatal PH as follows:

1. Determine which outcomes have been reported in published clinical trials, observational studies, and qualitative studies of PH in neonates and infants less than 3 months of age, corrected for prematurity.
2. Identify outcomes that are relevant to parents or guardians of infants diagnosed with PH less than 3 months of age, corrected for prematurity.
3. Use consensus methodology involving a range of stakeholders to define a core outcome set for neonatal PH.

2 | Methods

2.1 | Overview

We will use methodology described in the Core Outcome Measures in Effectiveness Trials (COMET) Handbook [23] and utilized in previously published protocols for the development of COS in perinatal care [19–21, 24]. The study will be conducted in two sequential stages shown in Figure 1 and include: (1) identification of potential list of outcomes through a scoping review of the literature and interviews with parents and/or guardians of current or former patients; (2) determining the core outcome set through an online Delphi survey and stakeholder consensus meeting. The protocol outlined below was developed in accordance with the recommendations set out in the Core Outcome Set STAndards for Development (COS-STAD) [25].

2.2 | Scope of the NeoPH COS

The core outcome set will apply to babies who are diagnosed with PH, less than 3 months of age, corrected for prematurity, while receiving inpatient neonatal care. There will be no limit to gestational age at birth or illness severity. Currently, the World Symposium of Pulmonary Hypertension only defines PH in children above the age of 3 months [4] and there is no fixed definition for PH in the newborn [26, 27]. Neonatal research studies have historically used a pragmatic approach to identifying babies with PH using clinical and/or echocardiography parameters, which we shall also adopt in this study [1, 4, 27–32]. Babies with PH associated with major congenital heart disease (CHD) will be excluded, justification for this exclusion is provided in the Supporting Information S1.

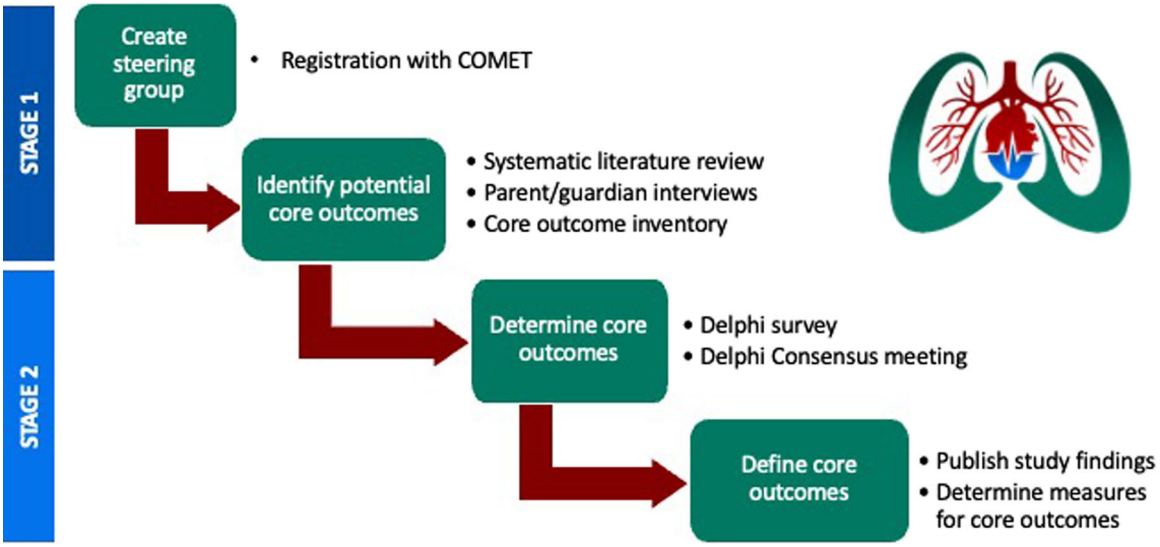

FIGURE 1 | Flow-diagram of the stages of development of the core outcome set for neonatal pulmonary hypertension. COMET = core outcome measures effectiveness trials.

2.3 | Registration

This COS has been prospectively registered through the COMET Initiative website (3026) [33]. The systematic review is prospectively registered with Prospective Register of Systematic Reviews (PROSPERO) (CRD42024504020) [34].

2.4 | Research Ethics Review

This study has been approved by the University of Liverpool Ethics Committee, reference number 13458 on April 3, 2024.

2.5 | Patient, Parent/Guardian and Public Involvement and Engagement (PPIE)

Parent and/or guardian perspectives are integral at every stage of development of this project including advisory group membership. Through local networks we engaged parents of newborn babies who received neonatal care in the development of this protocol to ensure sensitivity and appropriateness of study literature for bereaved parents and/or guardians. Parent and/or guardians will also be involved in the dissemination of results.

2.6 | Advisory Group

An international advisory group has been formed to guide the development of the core outcome set. The advisory group was selected to cover a range of expertize in neonatal nursing and medical care, neonatal hemodynamics, pediatric cardiology, pediatric pulmonary hypertension, and pediatric respiratory medicine. The advisory group includes a parent of a child with previous neonatal PH. The advisory group has representation from Asia, Australia, Europe, and North America. The advisory group terms of reference are in the online Supporting Information S1. Members are listed at the end of this manuscript.

2.7 | Participant Eligibility

Participants will be deemed eligible if they meet the criteria of one or more of the stakeholder groups defined below. Due to funding limitations, translation costs, and time constraints of the study, non-English speakers will be excluded.

2.8 | Stakeholders

1. *Parents or guardians* of children who were diagnosed with PH when they were less than 3 months of age, corrected for prematurity.
2. *Current or ex-patients* who were diagnosed with PH when they were less than 3 months of age, corrected for prematurity, and now over the age of 18 years.
3. *Nurses* (neonatal, pediatric, clinical nurse specialists, advanced nurse practitioners) with expertize in treating and caring for babies and children with PH diagnosed before 3 months of age, corrected for prematurity.
4. *Allied health professionals* (physiotherapist, occupational therapist, health care assistant, psychologist) with expertize in treating and caring for babies and children with PH diagnosed before 3 months of age, corrected for prematurity.
5. *Medical practitioners* (neonatologists, pediatricians, pediatric and adult physicians with specialism in cardiology, respiratory, intensive care and anesthesia) with expertize in treating and caring for babies and children with PH.
6. *Academics and researchers* in the field of neonatal and pediatric PH.

2.9 | Patient and Parent/Guardian Participation

Parents and/or guardians, adult patients, and ex-patients who were diagnosed with PH as a baby will also be integral in the

development of the COS. We will engage their participation in the Delphi Survey and consensus meeting. In addition, parents and/or guardians will be invited to participate in qualitative interviews.

2.10 | Data Collection and Confidentiality

Anonymised data will be stored on a University of Liverpool secure online server and will be managed according to UK the General Data Protection Regulation (GDPR) and Data Protection Act 2018 [35].

2.11 | Access to Data

The study research group chair (NS) will have access to the final data produced from the development of the COS. Any pertinent data will be made available from the chief investigator upon reasonable request.

2.12 | Stage 1: Identifying Potential Outcomes

2.12.1 | Systematic Review: What Outcomes in Neonatal PH Have Been Reported in the Literature?

Searches of the Cochrane Library and PROSPERO databases identified no systematic reviews of outcomes in neonatal pulmonary hypertension (searched on February 15, 2024). A systematic review will be conducted to identify outcomes recorded in clinical trials, observational studies, and qualitative studies of neonates and infants with all forms of pulmonary hypertension. Medline, Cochrane, and CINHAL databases will be searched (search strategy is included in the online supplement). Studies of neonates and infants with CHD will be excluded. All studies with more than 15 participants published in the last 10 years will be included. Screening for inclusion will be performed by two independent reviewers (C.M. and S.C.); where there is a discrepancy, an additional third independent reviewer (N.S.) will assess inclusion.

Data will be extracted using a pilot-tested form (online Supporting Information S2) to include definition of pulmonary hypertension, number of recruited infants, primary and secondary outcomes, whether the study was prospectively registered and whether there was evidence of parent, patient, or public involvement in the outcome selection. Timepoints of outcomes will be reported including the neonatal period and beyond. Results will be summarized in a narrative synthesis with outcomes grouped into categories where appropriate and the frequency of outcomes reported.

2.12.2 | Qualitative Interviews: What Outcomes Are Important to Parents/Guardians of Babies With Neonatal PH?

The aim of the qualitative parent and/or guardian interviews is to answer the following questions:

1. Do parents and/or guardians have knowledge of existing outcomes used to assess PH in babies?
2. What outcomes are important to parents and/or guardians of babies with PH?
3. Of these outcomes, what are the most important to parents and/or guardians of babies with PH?
4. What are the potential barriers to assessing outcomes in babies with PH?
5. Do outcomes considered important to parents and/or guardians differ by early/transient or late/sustained PH phenotype?

2.12.2.1 | Recruitment and Sampling. Parents and/or guardians with a lived experience of a child with neonatal PH, as defined above, will be recruited through gatekeepers (e.g., charity leads, Chief Executive Officers) of international patient support groups for babies who require neonatal care or infants with PH. We shall utilize online recruitment adverts on support groups websites and/or social media pages. A participant information sheet will be provided to interested participants. Eligibility will be screened by the study team (C.M., K.W.) before seeking informed consent for interview participation via an online consent form. Participants will be recruited consecutively while sampling for variance in geographical location and role of care giver, and the total number recruited will depend upon when information power is reached. This is when the sample size has sufficient information based on the aims of the study, sample specificity, use of framework, and quality of dialogue [36–38]. Based on previous, similar studies interviewing patients and/or parents, this is anticipated to be approximately 15–25 [39–41].

2.12.3 | Interview Conduct

Interviews will be conducted online either via teleconference software or by telephone depending on participant preference. Where more than one parent and/or guardian wishes to participate, they will be offered individual or joint interviews. Interviews will be digitally recorded and transcribed verbatim using a third-party company. A researcher trained in qualitative interview methods will conduct the interviews (C.M.) supported by an experienced qualitative researcher (K.W.). Interviews will be conducted in a semi-structured manner using an interview topic guide (see online Supporting Information S3). A list of potential outcomes (see online Supporting Information S4) derived from a subset of outcomes from the systematic review for use in the interviews has been developed in consultation with existing parent contacts at the Liverpool Women's NHS Trust. Before the interview, participants will be emailed the potential list of outcomes. Additional unanticipated topics or outcomes will be added to the topic guide and/or potential list of outcomes via respondent validation as interviewing and analysis progress [42].

2.12.3.1 | Qualitative Interview Analysis. An iterative approach will be used to guide data collection and analysis to allow for analysis of early interviews to enrich information collated in later interviews. Organization and indexing of

qualitative data will be managed using NVivo software. While reflective thematic analysis [38, 43] will be informed by the constant comparison approach, the focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and practice. Findings from the qualitative interviews will be reported using the consolidated criteria for reporting qualitative research (COREQ) checklist and fed into the outcome list used for the Delphi survey [37].

2.12.3.2 | Creation of Long-List of Outcomes. A comprehensive list of outcomes and descriptors obtained from data extraction and analysis of the systematic review and qualitative interviews will be generated. Outcomes will be categorized and grouped by two researchers (C.M. and N.A.) through consensus. Where disagreement occurs, the opinion of a third researcher (N.S.) will be sought. Initially, outcomes will be grouped into either short-term, defined as neonatal stay, or medium to long-term defined as outcomes following discharge and categorized by systems according to Taxonomy for Outcomes in Medical Research [44]. Secondly, outcomes will be further categorized by common physiological systems. Finally, outcomes will be grouped to reflect their relevance to early/transient or late/sustained PH phenotype. Where appropriate duplicated or closely related outcomes will be grouped and mapped to a domain. The final list of categorized outcomes will be formatted into appropriately phrased questions for round one of the Delphi survey and reviewed by the advisory group. We will create an advisory group with representation from parents and/or guardian support groups to screen the outcome questions to ensure appropriate phrasing.

2.13 | Stage 2: Determining Core Outcome Set

A core outcome set in neonatal PH will be determined through a two-round online Delp hi survey and online consensus meeting involving key stakeholders with expert knowledge, as defined above.

2.13.1 | Delphi Participants and Recruitment and Sample Size

We will recruit participants for the Delphi survey and consensus meeting from the stakeholder groups as follows. Parents and/or guardians will be recruited in two ways: *first*, those who participated in qualitative interviews will be invited to participate; and *second* via online recruitment adverts on the parents and/or guardian support group's website and/or social media pages. Healthcare professionals, academics, and researchers will be identified through existing networks accessed through the advisory group and will be invited to participate via email. In addition, researchers will also be identified through Scival Trend Analysis [19]. We will utilize Scival, a bibliometric tool, to identify the most prolific authors in neonatal PH over the last 10 years, based on number of publications and field-weighted citation impact.

There is no accepted minimum number of participants for a Delphi survey. Decision on sample size is pragmatic, dependent on ensuring participant diversity, including sex, age, ethnicity, and location, and not based on statistical power [23]. The sample size for our study will be based on previous surveys of practitioners and parents/guardians conducted by collaborators with our group through previous work on the development of the neonatal core outcome set [45]. In view of the rarity of this condition we anticipate a lower number of participants will be required than used for the neonatal core outcome set and, considering an expected 35% drop-out rate we anticipate recruiting approximately 200 participants to the first Delphi round. Each stakeholder group, as defined above, will have a minimum of 20 participants. Our recruitment process will aim to have a spread of diversity across geographic location of participants, including a minimum of five different countries of practice/origin. The consensus meeting will be limited to a maximum of 20 participants to facilitate discussion [46]. Participants for the consensus meeting will be recruited from both advisory group members and Delphi survey participants, with minimum of 2 representatives from each stakeholders group and representation from at least 5 separate countries.

2.14 | Attrition Bias

Attrition bias will be assessed across each Delphi round and separately for each stakeholder group [20, 23, 45]. For each outcome assessed, the median score will be compared between those who only complete one round of the Delphi survey and those who completed two rounds. We will compare median scores for outcomes using Wilcoxon rank-sum test.

2.15 | Consensus Definition

A two-stage Delphi consensus process will be used to identify outcomes for discussion at the final consensus meeting; consensus will be defined as follows:

1. *Consensus in (classify as a core outcome): over 70% of participants score the outcome as critical for decision making (a score of seven or more) and less than 15% of participants score the outcome of limited importance for decision making (a score of three or less).*
2. *Consensus out (do not classify as a core outcome): over 70% of participants score the outcome as limited importance for decision making (a score of three or less) and less than 15% of participants score the outcome critical for decision making (a score of seven or more).*
3. *Consensus not determined (do not classify as a core outcome): if either of the above criteria are not met.*

2.16 | Delphi Survey

The process will consist of a two-round e-Delphi survey. The Delphi survey will be conducted electronically via the Research Electronic Data Capture application (REDCap) [47, 48] hosted at the University of Liverpool. In the first-round stakeholders will be invited to score the importance of each outcome of the

long-list of outcomes using the 9-point Likert scale devised by the Grading of Recommendations Assessment Development and Evaluations working group [49]. To maximize response rates, the survey will be kept as short as possible. For each outcome from round 1, the study team will anonymously summarize the responses from all participants in a frequency table that will be presented to participants in the second round of the Delphi survey with their individual scores. Participants will be asked to reflect on the summary and their own scores and asked whether they want to re-score their responses. The responses from round 2 will be analysed as in round 1.

Each round of the Delphi survey will remain open for 4 weeks. To mitigate against potential attrition for each round a weekly reminder email will be sent to those who have not completed the survey. Participants who have not completed the survey by the end of the allocated 4 weeks will be assumed to have not participated and will be excluded from future rounds. If the projected minimum sample size has not been reached the study group will consider extending the deadline for completion and those failing to complete the survey will be approached individually.

2.17 | Subgroup Analysis

We will perform sub-group analysis to compare whether views on outcomes' importance from the Delphi survey vary between the four stakeholder groups. Pairwise comparison of mean scores for each outcome between groups will be made. Pearson's correlation coefficient will be calculated for each comparison and differences between coefficients will be tested using Fisher's r-to-z transformation.

2.18 | Consensus Meeting

A consensus meeting will be held to review the results of the Delphi survey and determine a final core outcome set. No new outcomes will be considered at this stage. The meeting will include members from each stakeholder group and be conducted online using video-conference software to allow for recording and transcribing. The meeting will be run sensitively by researchers experienced in running research meetings with parents of infants requiring neonatal care. To prioritize outcomes classified as core a modified nominal group technique will be applied to ensure that all participants can provide their perspectives and hear the views of others [50]. A meeting facilitator will present the results of each round of the Delphi survey across each stakeholder group. Meeting attendees will also be sent a reminder of their own personal Delphi score, which will also be made available at the meeting. All potential core outcomes reaching the definition for “consensus in” will be discussed, followed by a round of voting with the aim to achieve consensus, using definition above, and ratify the final COS. The final core outcomes will also be categorized by relevance to the WSPH classification [4].

2.19 | Dissemination

The final COS will be reported in line with reporting guidelines [25] and will be published including justification for inclusion and exclusion of outcomes on the COMET Initiative website (www.comet-initiative.org). A participant version of the findings will be written and sent to participants who consented to receiving a copy and will be made available externally on the Registry for Pulmonary Hypertension in Neonates (RePHyNe) website (www.rephyneregistry.com). Findings from NeoPH COS study will also be disseminated to an international audience via publication in an open access, peer-reviewed journal, and presentation at relevant medical conferences. Involvement of parents and/or guardians in the study will be described using the Guidance for Reporting on Involvement of Patients and Public (GRIPP2) check list [51].

3 | Discussion

This is the first study protocol to identify core outcomes to study in babies with PH. Although a generic neonatal COS exists [45] it does not address the complexity and specificity of outcomes, particularly cardio-respiratory outcomes, in babies with PH. Additional COSs are being developed for other conditions specific to perinatal and neonatal care to address disease-specific outcomes [19–21]. Furthermore, commonly used trial outcomes in both pediatric and adult PH, such as 6-min walk-test or invasive haemodynamic assessment [52], cannot be applied to babies and justifies the necessary creation of a neonatal PH-specific COS.

The major strength of this COS protocol is the involvement of grown-up ex-patients and parents and/or guardians of affected babies with PH from across the world. While we acknowledge that much of their lived experience is beyond the first few months of an infant's life, their experience is vital to develop core outcomes that matter and that are not necessarily limited to the first 3 months of age. In addition, ex-patients and parents and/or guardians experiences may highlight the differences in views on outcomes internationally. We intend to involve parents and/or guardians in writing up the COS findings for dissemination more widely. In addition, we have created an advisory group to oversee the development of the COS, consisting of stakeholders recruited internationally. The composition of the advisory group ensures a range and diversity of expertize spanning across different geographical, clinical, research, and public settings.

We acknowledge a limitation of our protocol is the involvement of only English-speaking stakeholders due to time and financial constraints. As a result, excluding potential stakeholders introduces a bias of participant views towards mainly English-speaking countries. Another limitation of this protocol is that we will not determine a consensus on time points and outcome measurement instruments in the final NeoPH COS. Currently, there is no consensus guidance on how to determine optimal outcome measures for outcomes included in core outcome sets. The Delphi consensus meeting, in part, will be utilized to ensure the feasibility and measurability of the outcomes included in the final COS. Development of guidance for measuring outcomes will form part of our future research work. This will include identification and assessment of measurement instruments from the systematic review using the Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) methodology framework [53]. We acknowledge the

importance of such a systematic approach to determining outcome measures that are feasible in clinical practice so that the COS can be consistently applied in future research across different clinical settings.

The methodology utilized to develop a neonatal pulmonary hypertension COS aims to ensure applicability and adoption in international settings and relevance across disciplines. The COS will help to improve trial design and homogeneity of outcomes reported in neonatal trials of pulmonary hypertension. The final COS will be adopted by and included in the data collected by the prospective international multicentre Registry of Pulmonary Hypertension in Neonates (RePHyNe). This will translate into much needed higher-quality evidence for therapeutic strategies for pulmonary hypertension in neonates.

3.1 | Study Status

At the time of manuscript submission, we are analysing the results of the systematic review, conducting parent and/or guardian interviews and constructing the Delphi survey.

3.2 | Study Research Group Members

Study research group chair: Dr. Nimish Subhedar (N.S.). Members: Dr. Natasha Aikman (N.A.), Professor Chris Gale (C.G.), Dr Cara Morgan (C.M.), and Professor Kerry Woolfall (K.W.).

3.3 | Advisory Group Members and Affiliations

Advisory group chair: Dr. Nimish Subhedar (Liverpool Women's NHS Foundation Trust, Liverpool, UK). Members: Dr. Steven Abman (Children's Hospital Colorado, Colarado, USA), Dr. Shazia Bhombal (Stanford University, San Francisco, USA), Dr. Rolf Berger (Beatrix Children's Hospital, Groningen, Netherlands), Dr. Willem de Boode (Radboud University Medical Centre, Nijmegen, Netherlands), Dr. Eugene Dempsey (Cork University Maternity Hospital, Cork, Ireland), Dr. Jeffrey Fineman (University of California San Francisco Benioff Children's Hospital, San Francisco, USA), Dr. Chris Gale (Chelsea and Westminster NHS Foundation Trust, London, UK), Dr. Kara Goss (University of Texas Southwestern, Dallas, USA), Lorna Gravenstede (UK), Dr. Samir Gupta (Sidra Medicine, Doha, Qatar), Dr. Audrey Hebert (CHU de Québec, Université Laval, Quebec, Canada), Dr. Amish Jain (Mount Sinai Hospital, Toronto, Canada), Dr. Martin Kluckow (North Sydney Local Health District, Sydney, Australia), Dr. Satyan Lakshminrusimha (UC Davis Children's Hospital, Sacramento, USA), Dr. Philip Levy (Boston Children's Hospital, Boston, USA), Dr. Patrick J. McNamara (University of Iowa Stead Family Children's Hospital, Iowa, USA), Dr. Souvik Mitra (British Columbia Children's Hospital, Halifax, Canada), Dr. Shahin Moledina (Great Ormond Street Hospital for Children, London, UK), Dr. Eirik Nestaas (Akershus University Hospital, Oslo, Norway), Dr. Neil Patel (Royal Hospital for Children, Glasgow, UK), Dr. Arvind Sehgal (Monash Children's Hospital, Melbourne, Australia), Dr. Robin Steinhorn (Children's National Hospital, San Diego, USA), Dr. Mark Turner (Liverpool Women's NHS Foundation Trust, Liverpool, UK).

Author Contributions

N.S. and C.G. conceptualized the project. C.M. and N.S. led on development of protocol. N.A. assisted with the systematic review. K.W. supervised the qualitative interview phase development. C.M. drafted the manuscript. N.S. and C.G. edited and critically appraised the manuscript. All authors read and approved the final manuscript.

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Ethics Statement

This study has been approved by the University of Liverpool Ethics Committee, reference number 13458 on April 3, 2024.

Conflicts of Interest

C.G. reports grants from the Medical Research Council of the United Kingdom, National Institute for Health Research (NIHR), Chiesi Pharmaceuticals, and the Canadian Institute for Health Research and support to attend educational meetings from Chiesi Pharmaceuticals outside the submitted work. C.G. chairs the London Regional Panel of the NIHR Research for Patient Benefit Programme. N.S. as Chair of the RePHyNe registry is funded in part by commercial partnership with Beyond Air and Mallinckrodt Pharmaceuticals. C.M., K.W., and N.A., The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. M. C. Walsh-Sukys, J. E. Tyson, L. L. Wright, et al., "Persistent Pulmonary Hypertension of the Newborn in the Era Before Nitric Oxide: Practice Variation and Outcomes," *Pediatrics* 105 (2000): 14–20.

2. M. A. Steurer, L. L. Jelliffe-Pawlowski, R. J. Baer, J. C. Partridge, E. E. Rogers, and R. L. Keller, "Persistent Pulmonary Hypertension of the Newborn in Late Preterm and Term Infants in California," *Pediatrics* 139 (2017): e20161165, https://doi.org/10.1542/peds.2016-1165.

3. H. Nakanishi, H. Suenaga, A. Uchiyama, and S. Kusuda, "Persistent Pulmonary Hypertension of the Newborn in Extremely Preterm Infants: A Japanese Cohort Study," *Archives of Disease in Childhood—Fetal and Neonatal Edition* 103 (2018): F554–F561.

4. D. Ivy, E. B. Rosenzweig, S. H. Abman, et al., "Embracing the Challenges of Neonatal and Paediatric Pulmonary Hypertension," *European Respiratory Journal* 64 (2024): 2401345.

5. G. Simonneau, D. Montani, D. S. Celermajer, et al., "Haemodynamic Definitions and Updated Clinical Classification of Pulmonary Hypertension," *European Respiratory Journal* 53. (2019): 1801913, https://doi.org/10.1183/13993003.01913-2018.

6. P. D. Evers, B. Scottoline, and L. B. Armsby, "Acute Right Ventricular Failure Associated With Pulmonary Hypertension in Pediatrics: Understanding the Hemodynamic Profiles," *Journal of Perinatology* 42 (2022): 139–142.

7. D. Ivy, "Right Heart Failure in Pediatric Pulmonary Hypertension." in *Heart Failure in the Child and Young Adult* (Elsevier, 2018), 399–412.

8. S. Arjaans, E. A. H. Zwart, M. J. Ploegstra, et al., "Identification of Gaps in the Current Knowledge on Pulmonary Hypertension in Extremely Preterm Infants: A Systematic Review and Meta-Analysis," *Paediatric and Perinatal Epidemiology* 32 (2018): 258–267.

9. M. J. del Cerro, A. Sabaté Rotés, A. Cartón, et al., "Pulmonary Hypertension in Bronchopulmonary Dysplasia: Clinical Findings, Cardiovascular Anomalies and Outcomes," *Pediatric Pulmonology* 49 (2014): 49–59.

10. S. Arjaans, M. G. Haarman, M. T. R. Roofthooft, et al., "Fate of Pulmonary Hypertension Associated With Bronchopulmonary Dysplasia Beyond 36 Weeks Postmenstrual Age," *Archives of Disease in Childhood—Fetal and Neonatal Edition* 106 (2021): 45–50.

11. G. G. Konduri, B. Vohr, C. Robertson, et al., "Early Inhaled Nitric Oxide Therapy for Term and Near-Term Newborn Infants With Hypoxic Respiratory Failure: Neurodevelopmental Follow-Up," *Journal of Pediatrics* 150 (2007): 235–240.e1.

12. Inhaled Nitric Oxide in Term and Near-Term Infants: Neurodevelopmental Follow-Up of The Neonatal Inhaled Nitric Oxide Study Group (NINOS)," *Journal of Pediatrics* 136 (2000): 611–617.

13. R. H. Clark, J. L. Huckaby, T. J. Kueser, et al., "Low-Dose Nitric Oxide Therapy for Persistent Pulmonary Hypertension: 1-Year Follow-Up," *Journal of Perinatology* 23 (2003): 300–303.

14. A. Constantine, K. Dimopoulos, S. G. Haworth, V. Muthurangu, and S. Moledina, "Twenty-Year Experience and Outcomes in a National Pediatric Pulmonary Hypertension Service," *American Journal of Respiratory and Critical Care Medicine* 206 (2022): 758–766, https://doi.org/10.1164/rccm.202110-2428OC.

15. U. Kumaran and A. Shenoi, "Management of Pulmonary Hypertension in Term Infants—A Review," *Journal of Neonatology* 35 (2021): 29–37.

16. U. Kumaran and A. Shenoi, "Management of Pulmonary Hypertension in Preterm Infants—A Review," *Journal of Neonatology* 36 (2022): 143–152.

17. K. J. Barrington, N. Finer, T. Pennaforte, and G. Altit, "Nitric Oxide for Respiratory Failure in Infants Born at or Near Term," *Cochrane Database of Systematic Reviews* 1, no. 1 (2017): CD000399, https://doi.org/10.1002/14651858.CD000399.pub3.

18. A. Yarlas, S. C. Mathai, S. D. Nathan, et al., "Considerations When Selecting Patient-Reported Outcome Measures for Assessment of Health-Related Quality of Life in Patients With Pulmonary Hypertension," *Chest* 162 (2022): 1163–1175.

19. D. H. Klerk, O. C. van Varsseveld, M. Offringa, et al., "Development of an International Core Outcome Set for Treatment Trials in Necrotizing Enterocolitis—A Study Protocol," *Trials* 24 (2023): 367.

20. S. Hermelijn, C. Kersten, D. Mullassery, et al., "Development of a Core Outcome Set for Congenital Pulmonary Airway Malformations: Study Protocol of an International Delphi Survey," *BMJ Open* 11 (2021): e044544.

21. S. Vergote, F. De Bie, J. Bosteels, et al., "Study Protocol: A Core Outcome Set for Perinatal Interventions for Congenital Diaphragmatic Hernia," *Trials* 22 (2021): 158.

22. P. R. Williamson, D. G. Altman, J. M. Blazeby, et al., "Developing Core Outcome Sets for Clinical Trials: Issues to Consider," *Trials* 13 (2012): 132.

23. P. R. Williamson, D. G. Altman, H. Bagley, et al., "The COMETHandbook: Version 1.0," *Trials* 18 (2017): 280.

24. J. Webbe, G. Brunton, S. Ali, J. M. Duffy, N. Modi, and C. Gale, "Developing, Implementing and Disseminating a Core Outcome Set for Neonatal Medicine," *BMJ Paediatrics Open* 1 (2017): e000048.

25. J. J. Kirkham, K. Davis, D. G. Altman, et al., "Core Outcome Set-STAndards for Development: The COS-STAD Recommendations," *PLoS Medicine* 14 (2017): e1002447.

26. E. B. Rosenzweig, S. H. Abman, and R. M. F. Berger, "Response: Still Puzzling About a Clear Definition of Pulmonary Arterial Hypertension in Newborns," *European Respiratory Journal* 53 (2019): 1900135.

27. E. S. Hoyle, S. L. Slee, and N. V. Subhedar, "Variation in the Definition of Pulmonary Hypertension and Clinical Indications for the Use of Nitric Oxide in Neonatal Clinical Trials," *Acta Paediatrica* 109 (2020): 930–934.

28. Y. Singh, "Echocardiographic Evaluation of Hemodynamics in Neonates and Children," *Frontiers in Pediatrics* 5 (2017): 201, https://doi.org/10.3389/fped.2017.00201.

29. B. Mathew and S. Lakshminrusimha, "Persistent Pulmonary Hypertension in the Newborn," *Children* 4 (2017): 63.

30. C. Kang, E. Zhao, Y. Zhou, et al., "Dynamic Changes of Pulmonary Arterial Pressure and Ductus Arteriosus in Human Newborns From Birth to 72 Hours of Age," *Medicine* 95 (2016): e2599.

31. A. Jain and P. J. McNamara, "Persistent Pulmonary Hypertension of the Newborn: Advances in Diagnosis and," *Seminars in Fetal and Neonatal Medicine* 20 (2015): 262–271.

32. R. E. Giesinger, K. More, J. Odame, A. Jain, R. P. Jankov, and P. J. McNamara, "Controversies in the Identification and Management of Acute Pulmonary Hypertension in Preterm Neonates," *Pediatric Research* 82 (2017): 901–914.

33. N. Subhedar, K. Woolfall, C. Morgan, C. Gale, and K. Reilly, COMET database, 2024, accessed June 10, 2024, https://www.comet-initiative.org/Studies/Details/3026.

34. NIH, "PROSPERO: International Prospective Register of Systematic Reviews," accessed June 10, 2024, https://www.crd.york.ac.uk/prospero/.

35. "Data Protection Act, c 12 United Kingdom," published 2018, https://wwwlegislation.gov.uk/ukpga//12/contents/enacted.

36. K. Malterud, V. D. Siersma, and A. D. Guassora, "Sample Size in Qualitative Interview Studies," *Qualitative Health Research* 26 (2016): 1753–1760.

37. A. Tong, P. Sainsbury, and J. Craig, "Consolidated Criteria for Reporting Qualitative Research (COREQ): A 32-Item Checklist for Interviews and Focus Groups," *International Journal for Quality in Health Care* 19 (2007): 349–357.

38. V. Braun and V. Clarke, "Reflecting on Reflexive Thematic Analysis," *Qualitative Research in Sport, Exercise and Health* 11 (2019): 589–597.

39. M. J. Peters, K. Woolfall, I. Khan, et al., "Permissive Versus Restrictive Temperature Thresholds in Critically Ill Children With Fever and Infection: A Multicentre Randomized Clinical Pilot Trial," *Critical Care* 23 (2019): 69.

40. B. Prodinger and P. Taylor, "Improving Quality of Care Through Patient-Reported Outcome Measures (PROMs): Expert Interviews Using the NHS PROMs Programme and the Swedish Quality Registers for Knee and Hip Arthroplasty as Examples," *BMC Health Services Research* 18 (2018): 87.

41. C. B. O'Hara, R. R. Canter, P. R. Mouncey, et al., "A Qualitative Feasibility Study to Inform a Randomised Controlled Trial of Fluid Bolus Therapy in Septic Shock," *Archives of Disease in Childhood* 103, no. 1 (2018): 28–32.

42. N. Mays, "Qualitative Research in Health Care: Assessing Quality in Qualitative Research," *British Medical Journal* 320 (2000): 50–52.

43. V. Braun, V. Clarke, N. Hayfield, et al., "Thematic Analysis," in *Handbook of Research Methods in Health Social Sciences* (Springer Singapore, 2019), 843–860.

44. S. Dodd, M. Clarke, L. Becker, C. Mavergames, R. Fish, and P. R. Williamson, "A Taxonomy Has Been Developed for Outcomes in Medical Research to Help Improve Knowledge Discovery," *Journal of Clinical Epidemiology* 96 (2018): 84–92.

45. J. W. H. Webbe, J. M. N. Duffy, E. Afonso, et al., "Core Outcomes in Neonatology: Development of a Core Outcome Set for Neonatal Research," *Archives of Disease in Childhood—Fetal and Neonatal Edition* 105 (2020): 425–431.

46. Harvard Business Review Press ib, *Running Meetings* (Harvard Business Review Press, 2014).

47. P. A. Harris, R. Taylor, B. L. Minor, et al., "The REDCap Consortium: Building an International Community of Software Platform Partners," *Journal of Biomedical Informatics* 95 (2019): 103208.

48. P. A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, and J. G. Conde, "Research Electronic Data Capture (REDCap)—A Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support," *Journal of Biomedical Informatics* 42 (2009): 377–381.

49. G. H. Guyatt, A. D. Oxman, R. Kunz, et al., "GRADE Guidelines: 2. Framing the Question and Deciding on Important Outcomes," *Journal of Clinical Epidemiology* 64 (2011): 395–400.

50. N. Harvey and C. A. Holmes, "Nominal Group Technique: An Effective Method for Obtaining Group Consensus," *International Journal of Nursing Practice* 18 (2012): 188–194.

51. S. Staniszewska, J. Brett, I. Simera, et al., "GRIPP2 Reporting Checklists: Tools to Improve Reporting of Patient and Public Involvement in Research," *British Medical Journal* 358 (2017): j3453.

52. M. M. Hoeper, R. J. Oudiz, A. Peacock, et al., "End Points and Clinical Trial Designs in Pulmonary Arterial Hypertension," *Journal of the American College of Cardiology* 43 (2004): S48–S55.

53. C. A. C. Prinsen, S. Vohra, M. R. Rose, et al., "How to Select Outcome Measurement Instruments for Outcomes Included in a "Core Outcome Set"—A Practical Guideline," *Trials* 17 (2016): 449.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.