

Protocol: A national priority setting partnership to develop neonatal research questions suitable for practice-changing randomised trials in the United Kingdom.

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Abstract:

Introduction. Methodologically robust clinical trials are required to improve neonatal care and reduce unwanted variations in practice. Previous neonatal research prioritisation processes have identified important research themes rather than specific research questions amenable to clinical trials. Practice-changing trials require well defined research questions, commonly organised using the Population, Intervention, Comparison, Outcome (PICO) structure. By narrowing the scope of research priorities to those which can be answered in clinical trials and by involving a wide range of different stakeholders, we aim to provide a robust and transparent process to identify and prioritise research questions answerable within the NHS to inform future practice-changing clinical trials.

Methods and Analysis. A steering group comprising parents, doctors, nurses, allied health professionals, researchers, and representatives from key organisations (Neonatal Society (NS), British Association of Perinatal Medicine (BAPM), Neonatal Nurses Association (NNA) and Royal College of Paediatrics and Child Health (RCPCH)) was identified to oversee this project. We will invite submissions of research questions formatted using the PICO structure from the following stakeholder groups using an online questionnaire: parents, patients, healthcare professionals and academic researchers. Unanswered, non-duplicate research questions will be entered into a two round eDelphi survey of all stakeholder groups. Research questions will be ranked by mean aggregate scores.

Ethics and Dissemination. The final list of prioritised research questions will be disseminated through traditional academic channels, directly to key stakeholder groups through representative organisations and on social media. The outcome of the project will be shared with key research organisations such as the National Institute for Health Research (NIHR). Research ethics committee approval is not required.

Registration Details. Not registered.

Strengths and Limitations of this study:

- By involving parents and former patients alongside a wide range of healthcare professionals we will ensure that research questions are important to all key stakeholder groups.
- We will use established strategies (two round eDelphi process) to rank research questions based upon mean scores.
- The study will rank research questions based upon subjective input from a large number of key stakeholders, however questions may need further work prior to being addressed in a clinical trial.
- The final list of prioritised questions will be disseminated widely to inform neonatal clinical research.

Introduction:

The importance of involving different stakeholders including parents, patients, healthcare professionals and researchers to identify and prioritise research is well recognised¹. In neonatal and perinatal medicine these stakeholder groups have prioritised research uncertainties in the fields of preterm birth^{2,3}, stillbirth⁴, diabetes in pregnancy⁵ and pregnancy hypertension⁶. Although these processes have been invaluable for prioritising research themes, the broad topics commonly identified have not been readily amenable to testing in randomised trials. Methodologically robust randomised controlled trials are the gold standard for assessing effectiveness of a healthcare intervention, drug or technology⁷ and are critical to improving quality and reducing variation in neonatal care. Randomised clinical trials require clearly structured and focused research questions, which can be organised using the PICO model which guides the questioner to clearly identify the Participant (P), Intervention (I), Comparator (C) and Outcome (O)^{8,9} (figure 1)¹⁰.

There is wide variation in neonatal care^{11,12} and an incomplete evidence base for many neonatal treatments,¹³ consequently, there is a need to identify and prioritise research questions that can be tested in randomised trials. Involving all relevant stakeholders in such a process will ensure that research addresses questions that are important to healthcare professionals, former neonatal patients and parents, as well as relevant to current neonatal care.

The aim of this project is to identify and prioritise neonatal research questions in PICO format, suitable for practice-changing randomised trials, using a robust, transparent, and inclusive methodology. The results of this identification and prioritisation process will inform the development and design of neonatal randomised controlled trials in high income settings, including the National Healthcare System (NHS) in the United Kingdom.

Methods and Analysis

Steering Group

A steering group has been formed to agree the scope and facilitate the process of identifying and prioritising research questions. The following key stakeholders are represented on the steering group: the Neonatal Society (NS), British Association of Perinatal Medicine (BAPM), Neonatal Nurses Association (NA), Royal College of Paediatrics and Child Health, neonatal Allied Health Professionals (AHPs), neonatal clinical trial methodologists, neonatal trainees

and parents with experience of neonatal care. The steering group is co-chaired by representatives of the NS and BAPM. Details of the steering group members can be found in figure 2.

The roles of the steering group are as follows:

- Agreeing the scope of the process.
- Disseminating details of the process.
- Engaging with clinical stakeholders to take part in identifying and prioritising research questions.
- Review of submitted research questions to identify duplicate questions, questions that have already been answered and questions outside the scope.
- Disseminating the final ranked list of research questions.

Identification of stakeholders

The utility and validity of this project will depend on ensuring that representative questions are generated and prioritised by a wide group of neonatal stakeholders including:

- Clinicians involved in neonatal care: Neonatologists, paediatricians, neonatal nurses, advanced neonatal nurse practitioners (ANNPs) working in paediatrics or neonatal medicine. Recruitment will be through advertisements on the RCPCH website and through other relevant professional organisations including BAPM, the NNA and the NS. Trainee doctors and nurses will be additionally contacted through local training schools and use of communication methods such as regional teaching and social media channels.
- Allied Health Professionals: Occupational therapists, physiotherapists, dieticians, speech and language therapists and clinical psychologists working in neonatal care: Advertisements will be placed through professional websites and organisations and co-ordinated by the AHP steering group representative.
- Academics and researchers working within neonatology: Recruitment will be targeted through academic organisations, existing research networks, national meetings and through Clinical Trials Units with a neonatal interest.
- Parents and former neonatal patients: These groups will be contacted through the National Care Coordinator Group, Maternity Voices partnerships, charity websites and through social media platforms.

To ensure maximal engagement across all stakeholder groups, various communications strategies will be employing including email contact, professional websites and social media routes.

Patient and Public Involvement

Parents and patients have been involved in this work from its inception. A parent representative sits on the steering group to plan the project and optimise parent and patient involvement. Communication to parents and former neonatal patients will be through parent and patient networks charities, regional support networks and social media groups. Parents and former neonatal patients will be involved in identifying neonatal research questions through the online identification process. To further facilitate the identification of research questions from parents and former neonatal patients we will develop targeted online support resources and run an online workshop focused on developing questions using a PICO format. Parents and former neonatal patients will then be involved in the prioritisation of research questions through the eDelphi process.

Scope

The scope of the prioritisation process has been agreed by the steering group as follows:

- Limited to research questions relevant to high income neonatal care settings.
- Limited to research questions related to care provided by neonatal teams:
 - On neonatal units, transitional care units, or as part of neonatal transport.
 - On postnatal wards (excluding care exclusively provided by midwifery teams without neonatal input).
 - In the community after receiving neonatal care as an inpatient (care may be provided by community neonatal teams or associated community allied health professionals with neonatal interest).

Overview

This study will be divided into four stages:

1. Identification of neonatal research questions suitable for analysis in randomised controlled trials.
2. Review of submitted neonatal research questions to remove duplicate questions and previously answered questions.

3. Prioritisation of neonatal research questions by all relevant stakeholders using a two-round eDelphi process.
4. Dissemination of ranked list of PICO questions.

Stage 1: Identification of testable neonatal research questions

We will identify neonatal research questions suitable for evaluation in practice changing randomised controlled trials through an open process. Individual stakeholders (neonatal clinicians, neonatal nurses, ANNPs, neonatal AHPs, neonatal researchers and former neonatal patients and patients) will be contacted via professional organisations, social media platforms, networks and organisational mailing lists. The process for identifying research questions will also be openly publicised on organisational websites seeking submission of research questions from stakeholders. Publicity will precede and continue throughout a four-week submission period¹⁴ to optimise engagement and inclusion of all key groups.

Stakeholders will be invited to submit as many questions as they would like using an online system that facilitates submission using the PICO structure:

- Populations will be able to be selected from a pre-defined selection of gestations and clinical cohorts, or specified by the submitter
- Intervention and Comparisons will take the form of free text to allow full descriptions
- Outcomes will be able to be selected from Core Outcomes in Neonatology (COIN)¹⁵, or specified by the submitter

Support in structuring research questions using PICO will be facilitated by the steering group members and organisations using techniques such as short videos. Contact details and basic demographic data will be requested from individuals who submit questions to monitor the representativeness of stakeholder involvement, and to invite participation in the subsequent prioritisation process.

Submission of relevant PICOs from previous priority setting work¹⁶ will be welcomed.

Stage 2: Review and Refinement of the long-list of neonatal research questions

Submitted research questions will be reviewed by the steering group to remove duplicate, already answered and out of scope questions, and to refine those not consistent with the PICO

structure. Prior to exclusion, questions will be independently reviewed by two members of the steering group. A final long-list of research questions will be taken forward for prioritisation.

Stage 3: Prioritisation of Neonatal Research Questions

All research questions included in the long-list will be included in a two-round eDelphi prioritisation process. Involvement of stakeholders in the prioritisation process will be facilitated as follows:

- All stakeholders who submitted questions will be contacted by email and asked to take part.
- Invitations to take part will be circulated by professional organisations and open links will be made available on professional organisational websites and social media accounts.
- Parents and previous neonatal patients will be contacted through professional organisations and networks and through social media.

All research questions will be ranked using a 9-point Likert scale. After the first round there will be the opportunity to submit new PICO questions. At the second stage, stakeholders will be provided with information on how individual research questions were prioritised at the first stage.

After completion of the second round of ranking all research questions will be collated into a ranking list of research priorities for the UK neonatal community. Ranking will be ordered based upon mean score. Results will also be presented by mean score within each stakeholder group. All questions not excluded in the initial review process will be included in the final list.

Ethics and Dissemination:

Research Ethics Committee approval is not required for this work.

The ranked list of defined neonatal research questions will be disseminated as follows:

- We will share results directly with the NIHR prioritisation panel and other funders of neonatal trials.
- We will circulate the list to stakeholder organisations and their members.

- Individuals who participated in question setting or the prioritisation process will be emailed directly with the finalised rankings and named as group authors in any published work.
- Results will be disseminated amongst the scientific community through a publication and presented at relevant neonatal meetings.

Discussion:

More than 1 in 10 babies in many high-income settings will receive neonatal care. Neonatal conditions are important, contributing to almost half of all child deaths in the UK and to many long-term health conditions. Despite this importance, much neonatal care is not based upon high-quality research evidence. Historically, the perinatal research environment has proudly fostered collaborative working, demonstrated by studies such as EPICure¹⁷. The SARS-CoV-2 pandemic has further highlighted the benefits of joined up working across multiple geographical regions, scientific institutions and research groups in achieving practice changing outcomes within much shorter timeframes¹⁸. This has resulted in increased focus on prioritisation projects within healthcare using initiatives such as the James Lind Alliance to support unified decision making across specific specialities. Neonatology within the UK is ideally placed for such prioritisation work and future collaborative research due to centrally funded healthcare, the neonatal network structure facilitating close relationships between units and the accessibility of large national databases. Ultimately this process seeks to involve a wide range of key neonatal stakeholders, to identify and prioritise research questions addressing the many clinical uncertainties, suitable for evaluating in well-structured clinical trials.

Author Contributions:

CG and CB conceived this project. KE, JPB, HM, CG and CB planned and coordinated the initial steering group and protocol. The first draft of the manuscript was written by KE and revised by CB/ JPB/ WC/ JD/ KG/ PH/ EJ/ HM/ JW and CG. CG edited and reviewed the manuscript. It was approved by all members of the steering group.

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Competing Interests Statement:

CG is vice chair of the NIHR Research for Patient Benefit London Regional Advisory Panel and a member of the Glasgow Children's Hospital Charity External Panel; he holds a Medical Research Council Transition Support Award.

JPB is a member of the Wellcome Trust's Career Development Award Panel and the Great Ormond Street Hospital Charity Research Assessment Panel.

CB is the NIHR deputy chair of HTA prioritisation committee for hospitals.

JD is a member of the NIHR HTA CET Funding Committee.

CM is funded by HEE-NIHR Integrated Clinical Academic Programme and holds a NIHR ICA CSRF Fellowship.

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Figure 1:

**Example PICO from PlaNeT-2 Trial
(Platelet transfusion thresholds in
premature neonates)¹⁸**

Participants: Preterm Infants < 34 weeks gestation at birth

Intervention: Low transfusion threshold (transfusing patient if platelet count < $25 \times 10^9/L$)

Control: High transfusion threshold (transfusing patient if platelet count < $50 \times 10^9/L$)

Outcome: Primary Outcomes were mortality or major bleeding within 28 days. (Secondary Outcomes were bronchopulmonary dysplasia, sepsis, retinopathy of prematurity and necrotising enterocolitis.)

Figure 2:

<u>Steering Group Member</u>	<u>Role and affiliation</u>
Cheryl Battersby (CB)	Academic Neonatologist, BAPM Data/Informatics lead and member of NIHR prioritisation committee.
James Boardman (JB)	Professor of Neonatal Medicine and immediate past president of the Neonatal Society.
William Carroll (WC)	Consultant Paediatrician and RCPCH officer for Research.
Jon Dorling (JD)	Professor of Paediatrics, Neonatal Consultant and BAPM research lead.
Kate Dinwiddy (KD)	Chief Executive of BAPM.
Katie Evans (KE)	Project Co-ordinator and Honorary Clinical Research Fellow in Neonatal Medicine.
Chris Gale (CG)	Academic Neonatologist and Neonatal Society Meeting Secretary.
Katie Gallagher (KG)	Academic Neonatal Nurse and Neonatal Nursing Association representative.
Pollyanna Hardy (PH)	Clinical Trials Statistician and Director of National Perinatal Epidemiology Unit.
Emma Johnston (EJ)	Parent representative and Parents and family engagement lead with the Thames valley and Wessex ODN.
Helen Mactier (HM)	Consultant Neonatologist, Honorary Clinical Associate Professor and President of BAPM.
Claire Marcroft (CM)	Neonatal Physiotherapist and Allied Health Professionals Representative.
James Webbe (JW)	Trainee Representative and Neonatal GRID Trainee.