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# Incorporating parent, former patient, and clinician perspectives in the design of a national UK double-cluster, randomised controlled trial addressing uncertainties in preterm nutrition



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**Incorporating parent, former patient, and clinician perspectives in the design of a national UK double-cluster, randomised controlled trial addressing uncertainties in preterm nutrition**

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Patient and public involvement, PPI, parent involvement, neonatal medicine, qualitative methodology, patient information leaflet, patient information sheet, opt-out consent

## ABSTRACT

### Background

Comparative effectiveness randomised controlled trials are powerful tools to resolve uncertainties in existing treatments and care processes. We sought parent and patient perspectives on the design of a planned national, double-cluster randomised controlled trial (COLLABORATE) to resolve two longstanding uncertainties in preterm nutrition.

### Methods

We used qualitative focus groups and interviews with parents, former patients and clinicians. We followed the COREQ checklist (Consolidated Criteria for Reporting Qualitative Research) and conducted inductive and deductive thematic analysis.

### Results

We identified support for the trial's methodology and vision, and elicited themes illustrating parents' emotional needs in relation to clinical research. These were: relieving the pressure on mothers to breastfeed; opt-out consent as reducing parent stress; the desire for research to be a partnership between clinicians, parents, and researchers; the value of presenting trial information in a collaborative tone; and in a format that allows assimilation by parents at their own pace. We identified anxiety and cognitive dissonance among some clinicians in which they recognised the uncertainties that justify the trial but felt unable to participate because of their strongly held views.

### Conclusions

The early involvement of parents and former patients identified the centrality of parents' emotional needs in the design of comparative effectiveness research. These insights have been incorporated into trial enrolment processes and information provided to participants. Specific outputs were a two-sided leaflet providing very brief as well as more detailed information, and use of language that parents perceive as inclusive and participatory. Further work is warranted to support clinicians to address personal biases that inhibit trial participation.

**KEY MESSAGES**

**What is known about the subject?**

- Comparative effectiveness randomised controlled trials are powerful means of resolving uncertainties in existing treatments and care processes.
- Many areas of neonatal practice lack an adequate evidence base, hence treatments often vary, within and between centres.
- The uncertainty around optimal practice creates risks for patients, anxiety for parents, and confusion among staff.

**What this study adds?**

- In addition to resolving practice uncertainties, comparative effectiveness research can help alleviate parent anxieties through metered study information, and partnership to improve newborn care.
- Early involvement of parents and former patients in trial development also enables researchers to support parents emotional needs through appropriate recruitment materials and methods.
- Incorporating clinicians as stakeholders has potential to understand and address their personal biases that inhibit trial participation.

## INTRODUCTION

Many areas of neonatal practice lack an adequate evidence base, hence treatments often vary, within and between centres. Comparative effectiveness research refers to approaches to try and resolve uncertainties in established treatments.

COLLABORATE is a planned national, UK, double-cluster randomised controlled trial aiming to recruit at least 4700 babies to resolve two longstanding global uncertainties in preterm nutrition, the benefits of i) pasteurised human donor milk in comparison with preterm formula to supplement a baby's own mother's milk when more milk is needed and ii) routine versus no routine protein-carbohydrate fortification of human milk.[1, 2] The co-primary outcomes are survival to 36 weeks postmenstrual age without surgery for necrotising enterocolitis (NEC) and survival to age two-years without moderate-severe neurodevelopment impairment.

Currently in the UK less than twenty percent of very preterm babies receive any pasteurised donor milk and less than forty percent receive any fortifier.[3] The uncertainty around optimal practice creates risks for patients, anxiety for parents, and confusion among staff. COLLABORATE offers a pragmatic response to these uncertainties. COLLABORATE will use data from the National Neonatal Research Database to minimise clinical burden,[4-6] and evaluate two-year language and cognitive outcomes with a parent-completed questionnaire, the Parent Report of Children's Abilities-Revised (PARCA-R).[7] Our aim at this preliminary stage was to involve parents, former patients, and clinicians in trial development.

## METHODS

We recruited former neonatal intensive care patients and parents of patients from across the UK through a network of individuals with experience of preterm birth who had consented to be invited to participate in neonatal research activities.[8] We invited the participation of healthcare professionals through a national webinar. We held six virtual focus groups and semi-structured interviews with patients and parents in October 2020, and clinician-centred focus groups with eleven participants in November 2020, with group attendance for all capped at four.[9, 10] Sessions with single participants utilised the same topic guide. No clinicians attended the parent-patient groups to avoid inhibiting or influencing the discussions.[9, 10] Participants gave verbal consent for participation and recording at the start of every discussion session.

We followed the COREQ checklist (Consolidated Criteria for Reporting Qualitative Research) for qualitative studies and created a topic guide to probe parent-patient and clinician experiences and understanding of the trial, based upon a hybrid blend of deductive and inductive approaches to facilitate discussion and allow themes to emerge.[11, 12] We provided a draft Parent Information Leaflet (Supplementary Materials). Each session lasted approximately 90 minutes, and all were recorded with participant consent. WL and BM, non-clinical qualitative researchers led the discussions and conducted interviews. They transcribed recordings using Descript software, coded the data,[13] and organised the transcripts thematically using NVivo

software, Version 1.3.[14] Participants were provided contact information for psychological support services in the event that discussions elicited strong emotions.

**Patient and Public Involvement**

At this preliminary stage of the development of COLLABORATE, we have utilised patient-public involvement to assist in developing the consent process and trial information leaflet. We have also involved clinicians to understand and address concerns related to their perspectives on opt-out consent, cluster randomisation, and clinical uncertainties. This paper embodies the first phase of the study's public involvement strategy which includes parents, adults born preterm, and clinicians as research collaborators throughout the research cycle.[15]

**RESULTS**

Nine volunteers, all women (seven parents, one former patient, and one parent who is also a former patient) participated in parent-patient focus groups (Table 1). Eleven volunteers for clinician focus groups included eight neonatologists, a dietician and an infant feeding specialist midwife. One non-clinician adult born preterm also chose to attend a clinician focus group. Seven of the eleven participants were men. No participant required the psychological support services that were offered.

**Table 1 Parent and Patient Participant Characteristics i**

| Participant | Gestational Age of Child or Patient | Position Attributing Knowledge | Feeding Method | Single/Multiple Birth | Incidence of necrotising enterocolitis [NEC]? | Survival of Baby(ies) | Support for Trial |
|---|---|---|---|---|---|---|---|
| Parent 1 | 33+3 weeks | Pharmacist w/RCT experience | Mum's milk | Single | N | Y | Y |
| Parent 2 | n/a | NEC/preterm charity volunteer | Mum's milk & Formula | Single | Y | Y | N |
| Parent 3 | n/a | Breastfeeding peer supporter | Mum's milk & Formula | Single | N | Y | Y |
| Parent 4 | 22 weeks | NEC/preterm charity volunteer | Mum's milk & Donor milk | Twins | N/N | Y/N | Y |
| Parent 5 | 33 weeks | n/a | Mum's milk & Fortifier | Single | Y | N | Unsure |
| Parent 6 | 29+5 weeks | n/a | Mum's milk & Formula | Twins | Suspected NEC/N | Y/Y | Y |
| Parent 7 | 28 weeks | n/a | Mum's milk & Formula | Single | Y | Y | Y |

i Please note that we have excluded details on clinician participants to protect clinician identities and anonymity.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Patient/Parent 1ii | 29 weeks | NEC/preterm charity volunteer | Formula & Donor Milk/Formula & Donor Milk | Single/Single | Y/Y | Y/Y | Y |
| Patient 1 | 28+4weeks | Paediatric nurse | Mum's milk & Formula | Twin | N/suspected NEC | Y/Niii | Y |

We identified four parent-patient themes, two of which also emerged in the clinician discussions, and an additional clinician theme. We provide extended quotations in Table 2.

**Table 2 Extended Versions of Quotes**

| Participant | Quotation |
|---|---|
| **Theme 1: Pressure to breastfeed** | |
| Patient 1 | …my mum will share with me that she cried with her breasts bleeding, trying to express because she was told it was the best... And she had a woman sitting next to her in the expressing room who had, you know, 500 mils of milk sitting there…and this woman was saying, 'Oh, it's not enough.' My mom was like, 'you're kidding me. I've got five ml from the last four hours. And I'm bleeding into it.' |
| Patient/Parent 1 | I remember when they talked about putting him onto formula, I said to the consultant, 'I'm really, really worried about him getting NEC [necrotising enterocolitis]. I'm really worried.' Cause I had it and…I know how bad it is…they assured me that the risk with formula was just as high as it was with donor milk. So I was like…if they need to gain weight and it's such a balancing act, isn't it?...I suppose it's the same for the doctors. They're just trying to balance the best options. |
| Parent 7 | … And at the end of the day, it has to be what's best…for your circumstances and what's best for your baby because your mom's milk is best, but if mom's milk is not available… you shouldn't make mums feel as if they're kind of a failure. |
| **Theme 2: Consent process** | |
| Parent 2 | …I appreciate the opt-out allows a much larger number of people, and often families don't go there. Not because they don't necessarily want to do it, but for whatever reason they have…they're not thinking about it or they read…and forget to fill out... |
| **Theme 3: Collaboration and inclusivity** | |
| Parent 6 | They need to be able to sometimes slightly dumb it down so we can understand it really well… I'm focusing on 'add extra protein and carbohydrate' [in the parent information leaflet.] I've never heard of that before…if I was in NICU [Neonatal Intensive Care Unit] and…I was still in the theatre and coming out of all of that and I had that to read, I'd be like, What? |
| Clinician 1 | 'On a ward round, one negative sentence, a loose comment about something … just spoils everything. We try to police that to some extent [and] share all our anxieties and disagreement beforehand ….we have our own personal agendas or personal biases but keep them to ourselves when we are … in front of other people.' |
| **Theme 4: Trauma, powerlessness, and parental learning in the neonatal unit** | |
| Parent 7 | …I had this baby ripped from me…I didn't see her after birth. It was horrific…her first nappy was changed by somebody else... All her cares were done by somebody else. The first person she saw was somebody else… |

ii Participant had NEC as a preterm baby and mothered a preterm baby who had NEC.
iii Patient 1 was one of 2 preterm twins. Her twin had suspected NEC and passed away thereafter.

| | |
|---|---|
| Parent 1 | …when you're in hospital and you've just had a new baby, especially if the baby's premature and you just have so little time… between trying to express and then trying to clean equipment |
| Parent 2 | At the same time often you do have a lot of time to kill in the neonatal unit…you will read every leaflet front to back, back to front, out of sheer boredom, more than anything else. |
| Parent 7 | I'm the sort of person that likes to know everything, so I would want to read every tiny little detail of everything…but I know from speaking to other parents in the neonatal unit that a lot of parents…don't want to be involved as much and they don't want to know things. |
| **Theme 5: Equipoise and personal beliefs** | |
| Clinician 1 | We [clinicians] have our own personal agendas or…biases…that's where I see the issue about [a] unit that's sort of consenting to participate, but not then sticking to the protocol…and then bringing some of their own ideas into the consenting … [and] recruitment process" |
| Clinician 6 | 'We've been asking these questions for so long and we still haven't got the answer' |

**Theme 1 Pressure to breastfeed**

Participants almost universally cited the refrain, "breast is best," but mothers' experiences of expressing milk and breastfeeding provoked stress and feelings of inadequacy. One former patient articulated the challenges of breastfeeding with an anecdote from her own mother:

> '… my mum will share with me that she cried with her breasts bleeding, trying to express because she was told it was the best ...'

Parents showed understanding of the trial's aim of resolving feeding uncertainties. The discussion identified confusion around feeding options that were brought to the fore by the challenges of expressing sufficient milk.

> 'I'm really, really worried about him getting NEC [necrotising enterocolitis] ...' they assured me that the risk with formula was just as high as it was with donor milk. So I was like … it's such a balancing act, isn't it?'

Participants emphasised sensitivity was needed to support mothers when discussing feeding.

> '… if mum's milk is not available … you shouldn't make mums feel as if they're kind of a failure …

**Theme 2 Consent process**

Parent-patient participants and most clinicians supported opt-out as minimising the added stress of trial consent in an already stressful environment. One parent stated

> '… often families don't go there … for whatever reason they have … they're not thinking about it or they read … and forget to fill out ...'.

Other participants echoed this sentiment noting that usual trial consent and information processes are often cumbersome and confusing. Some clinicians went further, suggesting that cluster randomisation meant that opt-out consent was required only from a neonatal unit rather than from parents themselves.

However, worries around transparency led some clinicians to feel uncomfortable with opt-out consent. For example, one told us they felt opt-out was only appropriate when a rapid decision was needed for a time-critical intervention.

**Theme 3 Collaboration and inclusivity**

Parent-patient participants emphasised the confusion and anxiety that results from lack of clarity or consistency in medical information communicated to them. They felt researchers can help alleviate these anxieties through the tone they adopt as well as the clarity of their communications.

> 'I'm focusing on 'add extra protein and carbohydrate' [in the parent information leaflet.] I've never heard of that before…'

They recommended we remove phrases in the draft parent information leaflet such as "if a mother has insufficient milk" (Supplementary Materials). They encouraged general use of words and phrases that expressed empathy for mothers' difficulties as opposed to ones that provoked feelings of guilt or inadequacy, supportive of an "inclusive" tone.

> 'The document, as it reads, is looking to me like dumbed down 'science-y' stuff. Whereas I think it needs to come from a person to person, like where you have concerns and fears, and this is what we are trying to do together as a community of NICU [neonatal intensive care unit] survivors and clinicians …'

This parent's reference to a "community of survivors" illustrates their need for empathy.

Clinician participants recognized the importance of fostering a collaborative relationship with parents:

> 'I think this whole thing about us having to approach parents in a really collaborative way around the importance of … feeding [is key] ...'

They perceived a tension between ensuring information was shared transparently and managing parental anxiety. Offering clear and consistent explanations was seen as paramount, but this was sometimes difficult because of clinical uncertainties and professional differences of opinion.

**Theme 4 Trauma, powerlessness, and parental learning in the neonatal unit**

Mothers experience trauma and feelings of powerlessness, when their babies were "taken away" for intensive care almost immediately following birth.

> … I had this baby ripped from me … I didn't see her after birth. It was horrific …

A lack of knowledge of neonatal care typically amplified these emotional experiences and participants described feelings of urgency to obtain more information.

> … when you're in hospital and you've just had a new baby, especially if the baby's premature and you just have so little time …
>
> At the same time, often, you do have a lot of time to kill in the neonatal unit … you will read every leaflet front to back …

Pursuing knowledge helped remedy feelings of powerlessness for some mothers, though a broader awareness of dangers facing babies often increased anxiety for others.

> I would want to read every tiny little detail of everything … but … other parents in the neonatal unit … don't want to be involved as much and they don't want to know things.

In summary, parents reported varying degrees of desire for knowledge, from those who wanted to know "everything" and those who wanted a more general understanding.

**Theme 5: Equipoise and personal beliefs**

Clinicians described the difficulty of managing their own anxieties about treatments in discussions with parents to minimise parent feelings of emotional distress and ensure equipoise across the unit.

> 'On a ward round, one negative sentence, a loose comment about something … just spoils everything. We try to police that to some extent [and] share all our anxieties and disagreement beforehand …

Clinicians identified that the anxieties, disagreements, and biases that are common to care could amount to complications in trial procedures for some units. Despite broad acceptance of the need for a trial, many clinicians predicted neonatal units with a standardised feeding regimen would not agree to change them and would therefore decline to participate.

> We [clinicians] have our own personal agendas or … biases … that's where I see the issue about [a] unit that's sort of consenting to participate, but not then sticking to the protocol … and then bringing some of their own ideas into the consenting … [and] recruitment process …

Clinical focus group participants accepted the existence of clinical uncertainties and understood the need for a definitive trial. For example, one said:

> 'We've been asking these questions for so long and we still haven't got the answer'.

**DISCUSSION**

Our study of parent, former patient and clinician views about a planned national double-cluster randomised controlled trial involved participants with intimate knowledge of neonatal care, and the corresponding relevance and depth of their contributions provide novel insights. We identified support for the rationale and proposed methodology, and themes within and across groups. Particularly powerful themes related to the emotional needs of parents and the

personal beliefs of clinicians. Parents experience stress and anxiety because of their baby's admission to intensive care. A novel insight provided by our study is that comparative effectiveness research might help alleviate parent anxieties in several ways. Clinician participants identified anxieties arising from the tension between their personal views and their acknowledgement of the need for evidence to guide practice.

Participants voiced support for the use of opt-out consent, noting it reduced the anxiety of decision making. Some authors have criticised opt-out consent as not supporting informed consent.[16] However, the stress of neonatal intensive care complicates parent understanding of studies.[17] Our group has previously shown opt-out taps "into parents' desire for normality in an abnormal situation."[18] We have also have shown that opt-out can be viewed as an ongoing consent process, leaving parents able to withdraw participation at any time, and that this approach is acceptable to the UK National Research Ethics Service.[19] Opt-out also allows parents to understand the trial and decline to participate without imposing a burden of additional information processing.[18]

The insights provided by study participants indicated the Parent Information Leaflet could be structured to provide emotional assistance by minimising the anxiety provoked by varying desires for information. This could be achieved by presenting information in a collaborative tone that situates the research as a partnership between clinicians, parents, and researchers, and employing a format that allows parents to assimilate information at their own pace. The language used can also help avoid making mothers feel inadequate by recognising the challenges of providing milk for their babies and alleviating the pressure to breastfeed. Our participants advised metering trial information to accommodate the needs of parents who want only a small amount of information as well as those who want to know more. The rationale for comparative effectiveness research is the relevance to patient safety of resolving uncertainties in care. However, "uncertain" does not necessarily describe how parents experience the moment of selecting a nutritional option. What is "uncertain" in terms of clinical practice is experienced as "worry", guilt, and even trauma by parents. This stems from a mixture of a shortfall in knowledge and the requirement to process substantial new information. The information provided through research participation enables parents to understand the issues facing their babies, providing direct benefit and a safe space to learn about neonatal treatments. As a consequence of these insights we undertook a redesign of the information leaflet to allow parents to adjust how much information they would receive by converting it into a two-sided format with a very brief explanation of the study on the front and a more detailed explanation on the back (Supplementary Materials).

We identified anxiety among clinicians that manifest as a strong tendency to focus on the detail of the trial rather than the bigger picture even though the trial compares standard clinical practices. The main driver of anxiety was difficulty in managing uncertainty, both in terms of explaining this to parents and in accommodating it in their own practice. We found a cognitive dissonance at play, whereby the rationale for the trial is acceptable, yet involvement and being

forced to confront their own personal views and biases led many to reject participation. In contrast, parents and patients felt that the proposed trial helped allay the anxieties invoked by the very uncertainties that justified the trial.

Our research has identified important areas for incorporation into the design of COLLABORATE and other comparative-effectiveness studies. Participating in research provides parents with a forum in which to learn about neonatal treatments, participate in knowledge production, and shape future care. Furthermore, in addition to the baby's medical care needs, our study, along with others, has identified that the provision of information to participants and enrolment to trials should consider the emotional needs of the parents as affected by study decision making, information processing, and language in study materials.[20, 21] Our study illustrates the need for further work to address the anxieties described and experienced by healthcare professionals. We hope this will help spearhead a truly collaborative research culture between parents, clinicians, and researchers.

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**Competing Interests Statement**

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**Contributors**

All authors contributed to the research design of the parent, patient, and public involvement, qualitative methods, the revision of this manuscript, approval of the final draft for publication, and responsibility for the intellectual content within. Specific specialisations are described below.

WL – Writing, draft editing, thematic analysis, qualitative design, public involvement design, and data collection

BM – Writing, draft editing, thematic analysis, qualitative design, public involvement design, and data collection

CB – Writing, draft editing, qualitative participant recruitment

VC – Writing, Draft editing, randomised controlled trial (RCT) design

DB – Writing, Draft editing, RCT design

NM – Writing, draft editing, qualitative design, public involvement design, RCT Design

**Patient Consent for Publication**

This manuscript was shared with all participants to receive feedback and improve the paper's integrity. Participant names have been included only if participants have given explicit permission for their names to be published under our acknowledgements section.

**Research Ethics Approval**

Participation was voluntary. Parents and former patients were approached through the neoWONDER collaboration (REC reference: 20/YH/0330).

**Data Availability Statement**

Anonymised data are available upon request from the corresponding author.

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## SUPPLEMENTARY MATERIALS

### Draft Parent Information Leaflet

**This information sheet provides details of a landmark approach to improve the care of very preterm babies. Please read it carefully and ask us if anything is unclear.**

**Background:** This neonatal unit is taking part in a large, national study to find out the best way to feed very preterm babies. This will involve using data that doctors and nurses record routinely for all babies admitted to neonatal units. This leaflet is to provide you with information. You do not need to do anything unless you do not wish us to use your baby's data.

You can "opt-out" at any time by telling [NAME OF STAFF MEMBER]. If you opt-out, your baby will continue to receive the same treatment and his or her care will not be affected. However, your baby's data will not be included in the analysis of the results.

**What we are trying to find out:** We ask all mothers who have a very preterm baby to express milk. However, if a mother has insufficient milk we do not know whether it is beneficial for a baby to receive pasteurised donated milk or formula specially made for preterm babies. We also do not know whether it is beneficial to very preterm babies to add extra protein and carbohydrate routinely to human milk. These are important questions affecting the care of all very preterm babies.

**Why there is uncertainty:** Preterm formula is made from cow's milk in a factory to strict regulatory standards. It has a consistent amount of nutrition and is used very widely. However, some clinicians believe cow's milk may increase the risks in very preterm babies of a gut inflammation called necrotising enterocolitis that can be very serious. About 3 in 100 very preterm babies in the UK develop severe necrotising enterocolitis.

Human milk provides more than just nutrition, for example, it has factors that strengthen immunity. However, human milk from a donor must be pasteurised to reduce the risk of transmitting infection. Pasteurisation reduces or destroys some beneficial properties of human milk; therefore, donor milk is not the same as milk from a baby's own mother. Pasteurised human donor milk is expensive and has very variable nutrition. This means that doctors may need to add extra protein and carbohydrate from cow's milk which some feel may also be a risk for necrotising enterocolitis.

**What happens at present:** Because we do not know which options are better for babies, some neonatal units use preterm formula and some use pasteurised human donor milk; some routinely add extra protein and carbohydrate to human milk feeds for very preterm babies and some do not. Overall, in the UK, the majority of babies receive their own mother's milk with some formula; less than 20% receive any donor milk, and about 40% receive some extra protein and carbohydrate.

**How to resolve these uncertainties:** The most reliable way to resolve uncertainties is by fairly allocating neonatal units to a feeding strategy, using a computer programme that makes the choice without influence so that half will use one approach and half will use the other, for each of the two uncertainties. This is ethical because it gives patients an equal, fair chance of receiving any of the alternative treatments. We will need to compare information from about 4700 babies to find out which options are more beneficial. In this neonatal unit we will be using [X] and [Y].

**Other information:** There are no risks to your baby from participation in this study because all feeding options are already widely used. Standard NHS indemnity operates in relation to the clinical treatment your baby receives. The UK Health Research Authority has approved the study. Imperial College London is coordinating the study and [x] is funding it. We will keep all details about your baby private. The only people allowed to look at your baby's data are the team running the study and the regulatory authorities responsible for checking it is carried out correctly.

**Thank you for reading this.**

**SUPPLEMENTARY MATERIALS (CONTINUED)**

**Revised Parent Information Leaflet**

**SIDE ONE**

This information sheet provides details of a landmark approach to improve the care of very preterm babies.

This neonatal unit is taking part in a large, national study to find out the best way to feed very preterm babies (born at less than 29 weeks gestation).

This will involve using data that doctors and nurses record routinely for all babies admitted to neonatal units.

This sheet is to provide you with information. You do not need to do anything unless you do not wish us to use your baby's data.

You can "opt-out" at any time by telling [NAME OF STAFF MEMBER].

If you opt-out, your baby will continue to receive the same treatment and his or her care will not be affected. However, your baby's data will not be included in the analysis of the results.

**If you are interested in learning more about why the study is taking place, please turn overleaf.**

**SIDE TWO**

**What we are trying to find out:** We ask all mothers who have a very preterm baby to express milk, as we know this is the optimum way to feed neonates. However, breast-feeding a premature baby can often present challenges, despite their mother's effort and commitment. This means that sometimes a baby will need an additional source of nutrition. At present, we do not know whether it is beneficial for a baby to receive pasteurised donated milk or formula specially made for preterm babies. We also do not know whether it is beneficial to very preterm babies to add extra protein and carbohydrate routinely to human milk. These are important questions affecting the care of all very preterm babies.

**Why there is uncertainty:** Preterm formula is made from cow's milk in a factory to strict regulatory standards. It has a consistent amount of nutrition and is used very widely. However, some clinicians believe cow's milk may increase the risks in very preterm babies of a gut inflammation called necrotising enterocolitis that can be very serious. About 3 in 100 very preterm babies in the UK develop severe necrotising enterocolitis.

Human milk provides more than just nutrition, for example, it has factors that strengthen immunity. However, human milk from a donor must be pasteurised to reduce the risk of transmitting infection. Pasteurisation reduces or destroys some beneficial properties of human milk and for these and other reasons, donor milk is not the same as milk from a baby's own mother. Pasteurised human donor milk is expensive and has very variable nutrition. This means that doctors may need to add extra protein and carbohydrate from cow's milk which some feel may also be a risk for necrotising enterocolitis.

**What happens at present:** Because we do not know which options are better for babies, some neonatal units use preterm formula and some use pasteurised human donor milk; some routinely add extra protein and carbohydrate to human milk feeds for very preterm babies and some do not. Overall, in the UK, the majority of babies receive their own mother's milk with some formula; less than 20% receive any donor milk, and about 40% receive some extra protein and carbohydrate.

**How to resolve these uncertainties:** The most reliable way to resolve uncertainties is by fairly allocating neonatal units to a feeding strategy, using a computer programme that makes the choice without influence so that half will use one approach and half will use the other, for each of the two uncertainties. This is ethical because it gives patients an equal, fair chance of receiving any of the alternative treatments. We will need to compare information from about 4700 babies to find out which options are more beneficial. In this neonatal unit we will be using [X] and [Y].

**Other information:** There are no risks to your baby from participation in this study because all feeding options are already widely used. Standard NHS indemnity operates in relation to the clinical treatment your baby receives. The UK Health Research Authority has approved the study. Imperial College London is coordinating the study and [x] is funding it. We will keep all details about your baby private. The only people allowed to look at your baby's data are the team running the study and the regulatory authorities responsible for checking it is carried out correctly.

Once again, if you opt-out of the research study, your baby will continue to receive the same treatment and his or her care will not be affected.

**Thank you for reading this. Please ask us if anything is unclear.**

## SUPPLEMENTARY MATERIALS (CONTINUED)

**Completed Consolidated criteria for reporting qualitative research (COREQ)**

**Domain 1: Research team and reflexivity**

**Personal Characteristics**

1. Interviewer/facilitator – Lammons and Moss

2. Credentials – Lammons, MA; Moss, PhD

3. Occupation: Lammons, PPI Research Lead; Moss, PPI Research Lead

4. Gender – Lammons, male; Moss, female

5. Experience and training – Lammons, Imperial College London PPI Training; Moss, original PPI research on improving outcomes for aphasia patients

**Relationship with participants**

6. Relationship established – No relationship was established between Lammons, Moss and participants prior to this research. Parent and public were recruited through the neoWONDER network of interested participants who had given consent to contact, which is managed by Battersby. Clinician participants were recruited through a national webinar on the COLLABORATE trial.

7. Participant knowledge of the researchers – Lammons and Moss clearly stated the research goals, vision, and purposes at the start of every focus group and interview. They asserted that their goals were to understand parent, former patient, and clinician experiences, then use these to improve the trial's success in terms of recruitment, retention, relevance, and efficacy.

8. Interviewer characteristics – interviewers clearly stated their motivations and interests in the research topic throughout each focus group and interview. Interviewers shared personal experiences, such as parenthood or lack thereof which impacted their vision and understanding of these phenomena. Most importantly, researchers situated themselves as intermediaries who could receive critiques of the research design, then transmit these to improve the research's inclusivity and engagement with participants and stakeholders.

**Domain 2: study design**

**Theoretical framework**

9. Methodological orientation – Qualitative research, qualitative analysis, and patient and public involvement

**Participant selection**

10. Sampling – Parent and former patient participants were notified of the COLLABORATE qualitative pre-trial from the neoWONDER research participant network, managed by Battersby, which is a network of parents of premature babies and adults born premature who have consented to contact for neonatal medicine related research studies. Given time constraints the research team faced, we opted for this as the most efficient, effective, convenient, and purposeful means for getting feedback on the

COLLABORATE trial prior in tandem with its protocol development. This occurred in tandem with a national webinar presenting the COLLABORATE trial to clinicians. Through the webinar, clinicians were invited to voluntarily participate in the pre-trial focus groups.

11. Method of approach – email invitation for voluntary participation through neoWONDER research participant network, led by Battersby. A separate email invitation for voluntary participation following the webinar was emailed to clinicians. Interested individuals who responded were offered participation times and dates.

12. Sample size – 19

13. Non-participation – 9 showed interest in participating but did not attend due to various reasons, including illness or lack of clear confirmation; follow-up contact and rescheduling was attempted with all four of these individuals twice via email, but no responses were received to schedule additional meeting dates. Two clinicians confirmed attendance but were absent.

**Setting**

14. Setting of data collection – virtual focus groups and interviews held via Zoom and Microsoft Teams. Participants joined the sessions from their personal computers/devices at their homes or offices.

15. Presence of non-participants – only research participants and researchers (Moss and Lammons) were present during sessions

16. Description of sample – Parent and patient participants were all female between the ages of 22 and 55; 7 were mothers of neonatal patients, 1 was a former neonatal patient, and 1 was a mother and former neonatal patient. Eleven volunteers for clinician focus groups included eight neonatologists, a dietician and an infant feeding specialist midwife. One non-clinician adult born preterm also chose to attend a clinician focus group. Seven of the eleven participants were men.

**Data collection**

17. Interview guide – Two separate but similar topic guides were created by Lammons and Moss, one for patients and parents, one for clinicians. Both were shared with the broader research team. Guides were not pilot tested, nor did participants request a copy of the guide, though it was available upon request.

18. Repeat interviews – none were conducted

19. Audio/visual recording – sessions were video recorded using in-app recording functions of Zoom and/or Teams. Audio recordings were extracted from the videos and used to create transcriptions with Descript software. These transcriptions were edited for correctness and understanding, then video recordings were deleted. Audio recordings were saved. One session encountered extensive technical difficulties and was correspondingly conducted by Moss via phone. As a result of technical issues, this session was not recorded.

20. Field notes – Lammons and Moss took field notes during and after interview/focus group sessions. These were included in the NVivo workflow and theming process along with raw data.

21. Duration – Each session lasted roughly 90 minutes.

22. Data saturation – Moss and Lammons reached thematic saturation at the conclusion of all focus groups and review of data.

23. Transcripts returned – transcripts were not returned to participants for comment and/or correction, though quotations used throughout the manuscript have been reviewed and verified by participants.

**Domain 3: analysis and findings**

**Data analysis**

24. Number of data coders – 2, Moss and Lammons

25. Description of the coding tree – The coding tree has not been included in the manuscript but is available on request.

26. Derivation of themes – Moss and Lammons used a "hybrid approach" of deductive themes identified prior to the data collection and inductive themes derived from the data itself.

27. Software – NVivo 1.3 (QSR Technologies)

28. Participant checking – Participants have been included in the writing process as reviewers of findings. When they have given permission to do so, their names have been specifically included in the acknowledgements section.

**Reporting**

29. Quotations presented –Quotations are presented in the results section in brief, with their corresponding long-form versions and identifying participant numbers in Table 2.

30. Data and findings consistent – Data has been used to guide findings, discussion, and analysis. Copies of transcripts and coding are available upon request.

31. Clarity of major themes – Quotes were clearly paired with theme headings and discussions for optimum clarification.

32. Clarity of minor themes – Quotes were clearly paired with theme headings and discussions for optimum clarification.

BMJ Paediatrics Open

# Incorporating parent, former patient, and clinician perspectives in the design of a national UK double-cluster, randomised controlled trial addressing uncertainties in preterm nutrition



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| | |

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**Incorporating parent, former patient, and clinician perspectives in the design of a national UK double-cluster, randomised controlled trial addressing uncertainties in preterm nutrition**

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**Keywords**

Patient and public involvement, PPI, parent involvement, neonatal medicine, qualitative methodology, patient information leaflet, patient information sheet, opt-out consent

## ABSTRACT

### Background

Comparative effectiveness randomised controlled trials are powerful tools to resolve uncertainties in existing treatments and care processes. We sought parent and patient perspectives on the design of a planned national, double-cluster randomised controlled trial (COLLABORATE) to resolve two longstanding uncertainties in preterm nutrition.

### Methods

We used qualitative focus groups and interviews with parents, former patients and clinicians. We followed the COREQ checklist (Consolidated Criteria for Reporting Qualitative Research) and conducted inductive and deductive thematic analysis.

### Results

We identified support for the trial's methodology and vision, and elicited themes illustrating parents' emotional needs in relation to clinical research. These were: relieving the pressure on mothers to breastfeed; opt-out consent as reducing parent stress; the desire for research to be a partnership between clinicians, parents, and researchers; the value of presenting trial information in a collaborative tone; and in a format that allows assimilation by parents at their own pace. We identified anxiety and cognitive dissonance among some clinicians in which they recognised the uncertainties that justify the trial but felt unable to participate because of their strongly held views.

### Conclusions

The early involvement of parents and former patients identified the centrality of parents' emotional needs in the design of comparative effectiveness research. These insights have been incorporated into trial enrolment processes and information provided to participants. Specific outputs were a two-sided leaflet providing very brief as well as more detailed information, and use of language that parents perceive as inclusive and participatory. Further work is warranted to support clinicians to address personal biases that inhibit trial participation.

**KEY MESSAGES**

**What is known about the subject?**

- Comparative effectiveness randomised controlled trials are powerful means of resolving uncertainties in existing treatments and care processes.
- Many areas of neonatal practice lack an adequate evidence base, hence treatments often vary, within and between centres.
- The uncertainty around optimal practice creates risks for patients, anxiety for parents, and confusion among staff.

**What this study adds?**

- In addition to resolving practice uncertainties, comparative effectiveness research can help alleviate parent anxieties through metered study information, and partnership to improve newborn care.
- Early involvement of parents and former patients in trial development also enables researchers to support parents emotional needs through appropriate recruitment materials and methods.
- Incorporating clinicians as stakeholders has potential to understand and address their personal biases that inhibit trial participation.

## INTRODUCTION

Many areas of neonatal practice lack an adequate evidence base, hence treatments often vary, within and between centres. Comparative effectiveness research refers to approaches to try and resolve uncertainties in established treatments.

COLLABORATE is a planned national, UK, double-cluster randomised controlled trial aiming to recruit at least 4700 babies to resolve two longstanding global uncertainties in preterm nutrition, the benefits of i) pasteurised human donor milk in comparison with preterm formula to supplement a baby's own mother's milk when more milk is needed and ii) routine versus no routine protein-carbohydrate fortification of human milk.[1, 2] The co-primary outcomes are survival to 36 weeks postmenstrual age without surgery for necrotising enterocolitis (NEC) and survival to age two-years without moderate-severe neurodevelopment impairment.

Currently in the UK less than twenty percent of very preterm babies receive any pasteurised donor milk and less than forty percent receive any fortifier.[3] The uncertainty around optimal practice creates risks for patients, anxiety for parents, and confusion among staff. COLLABORATE offers a pragmatic response to these uncertainties. COLLABORATE will use data from the National Neonatal Research Database to minimise clinical burden,[4-6] and evaluate two-year language and cognitive outcomes with a parent-completed questionnaire, the Parent Report of Children's Abilities-Revised (PARCA-R).[7] Our aim at this preliminary stage was to involve parents, former patients, and clinicians in trial development.

These clinical uncertainties, which affect the care provided to babies as well as the information provided to families, present an opportunity to understand how parents of very preterm babies can improve the recruitment materials for the COLLABORATE trial and clarify the acceptability of consent methods, as well as compare their views and reactions with those of clinicians. PPI consultations are enriching mechanisms to improve design, making studies more successful and relevant to their stakeholders [8-12]. In paediatric research they have identified important guiding themes for future research, largely through centring the narratives and experiences of survivors and families [13, 14].

## METHODS

We recruited former neonatal intensive care patients and parents of patients from across the UK through a network of individuals with experience of preterm birth who had consented to be invited to participate in neonatal research activities.[15] We invited the participation of healthcare professionals through a national webinar. In total, twenty volunteers; ten clinicians, seven parents, two former patients, and one parent/former patient; participated in virtual focus groups or semi-structured interviews [16, 17]. Sessions with single participants utilised the same topic guide. No clinicians attended the parent-patient groups to avoid inhibiting or influencing the discussions.[16, 17] Participants gave verbal consent for participation and recording at the start of every discussion session.

We followed the COREQ checklist (Consolidated Criteria for Reporting Qualitative Research) for qualitative studies and created a topic guide to probe parent-patient and clinician experiences and understanding of the trial, based upon a hybrid blend of deductive and inductive approaches to facilitate discussion and allow themes to emerge.[18, 19] We provided a draft Parent Information Leaflet (Supplementary Materials). Each session lasted approximately 90 minutes, and all were recorded with participant consent. WL and BM, non-clinical qualitative researchers led the discussions and conducted interviews. They transcribed recordings and conducted interviews.

WL and BM analysed all qualitative data using Framework Analysis. [20] Initial themes and concepts were identified through reviewing the data, then used to construct a thematic index and assign an index label to each phrase or passage of the transcripts. [20] The labelled raw data was then summarised and synthesised into the thematic charts to facilitate systematic exploration of the range of views, both between cases and within cases, to produce both descriptive and explanatory accounts of the data. [20] Data were organised and analysed using NVivo, version 1.0 (QSR International) [21]. Participants were provided contact information for psychological support services in the event that discussions elicited strong emotions.

**Patient and Public Involvement**

At this preliminary stage of the development of COLLABORATE, we have utilised patient-public involvement to assist in developing the consent process and trial information leaflet. We have also involved clinicians to understand and address concerns related to their perspectives on opt-out consent, cluster randomisation, and clinical uncertainties. This paper embodies the first phase of the study's public involvement strategy which includes parents, adults born preterm, and clinicians as research collaborators throughout the research cycle.[22]

**RESULTS**

Nine volunteers, all women (seven parents, one former patient, and one parent who is also a former patient) participated in parent-patient focus groups (Table 1). Eleven volunteers for clinician focus groups included eight neonatologists, a dietician and an infant feeding specialist midwife. One non-clinician adult born preterm also chose to attend a clinician focus group. Seven of the eleven participants were men. No participant required the psychological support services that were offered.

**Table 1 Parent and Patient Participant Characteristics i**

| Participant | Gestational Age of Child or Patient | Reason for Interest in Participating | Feeding Method | Single/Multiple Birth | Incidence of necrotising enterocolitis [NEC]? | Survival of Baby(ies) | Support for Trial |
|---|---|---|---|---|---|---|---|
| Parent 1 | 33+3 weeks | Pharmacist w/RCT experience | Mum's milk | Single | N | Y | Y |
| Parent 2 | n/a | NEC/preterm charity volunteer | Mum's milk & Formula | Single | Y | Y | N |
| Parent 3 | n/a | Breastfeeding peer supporter | Mum's milk & Formula | Single | N | Y | Y |
| Parent 4 | 22 weeks | NEC/preterm charity volunteer | Mum's milk & Donor milk | Twins | N/N | Y/N | Y |
| Parent 5 | 33 weeks | n/a | Mum's milk & Fortifier | Single | Y | N | Unsure |
| Parent 6 | 29+5 weeks | n/a | Mum's milk & Formula | Twins | Suspected NEC/N | Y/Y | Y |
| Parent 7 | 28 weeks | n/a | Mum's milk & Formula | Single | Y | Y | Y |
| Patient/Parent 1ii | 29 weeks | NEC/preterm charity volunteer | Formula & Donor Milk/Formula & Donor Milk | Single/Single | Y/Y | Y/Y | Y |
| Patient 1 | 28+4weeks | Paediatric nurse | Mum's milk & Formula | Twin | N/suspected NEC | Y/Niii | Y |

We identified three parent-patient themes; "pressure to breastfeed", "consent process", and "emotional trauma"; one clinician theme, "equipoise and personal beliefs"; and one theme combining parent-patient and clinician discussions, "collaboration and inclusivity."

### Theme 1 Pressure to breastfeed

Participants almost universally cited the refrain, "breast is best," but mothers' experiences of expressing milk and breastfeeding provoked stress and feelings of inadequacy. One former patient articulated the challenges of breastfeeding with an anecdote from her own mother:

> *"…my mum will share with me that she cried with her breasts bleeding, trying to express because she was told it was the best... And she had a woman sitting next to her in the expressing room who had, you know, 500 mils of milk sitting there…and this woman was*

i Please note that we have excluded details on clinician participants to protect clinician identities and anonymity.
ii Participant had NEC as a preterm baby and mothered a preterm baby who had NEC.
iii Patient 1 was one of 2 preterm twins. Her twin had suspected NEC and passed away thereafter.

*saying, 'Oh, it's not enough.' My mum was like, 'you're kidding me. I've got five ml from the last four hours. And I'm bleeding into it." (NICU patient born at 28+4 weeks, now a paediatric nurse)*

Parents showed understanding of the trial's aim of resolving feeding uncertainties. The discussion identified confusion around feeding options that were brought to the fore by the challenges of expressing sufficient milk.

*"I remember when they talked about putting him onto formula, I said to the consultant, 'I'm really, really worried about him getting NEC [necrotising enterocolitis]. I'm really worried.' Cause I had it and…I know how bad it is…they assured me that the risk with formula was just as high as it was with donor milk. So I was like…if they need to gain weight and it's such a balancing act, isn't it?...I suppose it's the same for the doctors. They're just trying to balance the best options." (Mother who had NEC as a preterm baby, whose baby was born at 29 weeks)*

Participants emphasised sensitivity was needed to support mothers when discussing feeding.

*"… And at the end of the day, it has to be what's best…for your circumstances and what's best for your baby because your mum's milk is best, but if mum's milk is not available… you shouldn't make mums feel as if they're kind of a failure." (Mother of twins born at 29+5 weeks)*

**Theme 2 Consent process**

Parent-patient participants and most clinicians supported opt-out as minimising the added stress of trial consent in an already stressful environment. One parent stated

*"…I appreciate the opt-out allows a much larger number of people, and often families don't go there. Not because they don't necessarily want to do it, but for whatever reason they have…they're not thinking about it or they read [the consent form]…and forget to fill out..." (Mother of a preterm baby who had NEC)*

Other participants echoed this sentiment noting that usual trial consent and information processes are often cumbersome and confusing. Some clinicians went further, suggesting that cluster randomisation meant that opt-out consent was required only from a neonatal unit rather than from parents themselves.

However, worries around transparency led some clinicians to feel uncomfortable with opt-out consent. For example, one told us they felt opt-out was only appropriate when a rapid decision was needed for a time-critical intervention.

**Theme 3 Collaboration and inclusivity**

Parent-patient participants emphasised the confusion and anxiety that results from lack of clarity or consistency in medical information communicated to them. They felt researchers can

help alleviate these anxieties through the tone they adopt as well as the clarity of their communications.

> *"They need to be able to sometimes slightly dumb it down so we can understand it really well… I'm focusing on 'add extra protein and carbohydrate' [in the parent information leaflet.] I've never heard of that before…" (Mother of twin boys born at 22 weeks, one of whom did not survive)*

They recommended we remove phrases in the draft parent information leaflet such as "if a mother has insufficient milk" (Supplementary Materials). They encouraged general use of words and phrases that expressed empathy for mothers' difficulties as opposed to ones that provoked feelings of guilt or inadequacy, supportive of an "inclusive" tone.

> *"The document, as it reads, is looking to me like dumbed down 'science-y' stuff. Whereas I think it needs to come from a person to person, like where you have concerns and fears, and this is what we are trying to do together as a community of NICU [neonatal intensive care unit] survivors and clinicians…" (Mother of twin boys born at 22 weeks, one of whom did not survive)*

This parent's reference to a "community of survivors" illustrates their need for empathy.

Clinician participants recognized the importance of fostering a collaborative relationship with parents:

> *"I think this whole thing about us having to approach parents in a really collaborative way around the importance of…feeding…managing their expectations and their understanding of what is happening with that baby's gut, and that we're trying to help promote a healthy gut, not just for the time when they're in their unit, but beyond that time as a healthy gut for life – here is the one of the fundamental things that's going to influence their feeding for not just weeks, but months and years to come." (Neonatal clinician)*

They perceived a tension between ensuring information was shared transparently and managing parental anxiety. Offering clear and consistent explanations was seen as paramount, but this was sometimes difficult because of clinical uncertainties and professional differences of opinion.

**Theme 4 Trauma, powerlessness, and parental learning in the neonatal unit**

Mothers experience trauma and feelings of powerlessness, when their babies were "taken away" for intensive care almost immediately following birth.

> *"…I had this baby ripped from me…I didn't see her after birth. It was horrific…her first nappy was changed by somebody else... All her cares were done by somebody else. The first person she saw was somebody else" (Mother of a preterm baby with NEC)*

A lack of knowledge of neonatal care typically amplified these emotional experiences and participants described feelings of urgency to obtain more information.

> *… when you're in hospital and you've just had a new baby, especially if the baby's premature and you just have…so little time…" (Mother of a baby born at 33+3 weeks, pharmacist)*

> *At the same time, often, you do have a lot of time to kill in the neonatal unit … you will read every leaflet front to back" (Mother of a preterm baby)*

Pursuing knowledge helped remedy feelings of powerlessness for some mothers, though a broader awareness of dangers facing babies often increased anxiety for others.

> *"I'm the sort of person that likes to know everything, so I would want to read every tiny little detail of everything…but I know from speaking to other parents in the neonatal unit that a lot of parents…don't want to be involved as much and they don't want to know things. (Mother of a preterm baby who had NEC)"*

In summary, parents reported varying degrees of desire for knowledge, from those who wanted to know "everything" and those who wanted a more general understanding.

**Theme 5: Equipoise and personal beliefs**

Clinicians described the difficulty of managing their own anxieties about treatments in discussions with parents to minimise parent feelings of emotional distress and ensure equipoise across the unit.

> *"On a ward round, one negative sentence, a loose comment about something … just spoils everything. We try to police that to some extent [and] share all our anxieties and disagreement beforehand ….we have our own personal agendas or personal biases but keep them to ourselves when we are … in front of other people. that's where I see the issue about [a] unit that's sort of consenting to participate, but not then sticking to the protocol…and then bringing some of their own ideas into the consenting … [and] recruitment process." (Neonatal clinician)*

Clinicians identified that the anxieties, disagreements, and biases that are common to care could amount to complications in trial procedures for some units. Despite broad acceptance of the need for a trial, many clinicians predicted neonatal units with a standardised feeding regimen would not agree to change them and would therefore decline to participate. Clinical focus group participants accepted the existence of clinical uncertainties and understood the need for a definitive trial. For example, one said:

> *'We've been asking these questions for so long and we still haven't got the answer" (Neonatal clinician)*

**DISCUSSION**

This PPI consultation with parent, former patient and clinician views about a planned national double-cluster randomised controlled trial involved participants with intimate knowledge of neonatal care, and the corresponding relevance and depth of their contributions provide novel insights. We identified support for the rationale and proposed methodology, and themes within and across groups. Particularly powerful themes related to the emotional needs of parents and the personal beliefs of clinicians. Parents experience stress and anxiety because of their baby's admission to intensive care. A novel insight provided by this consultation is that comparative effectiveness research might help alleviate parent anxieties in several ways. Clinician participants identified anxieties arising from the tension between their personal views and their acknowledgement of the need for evidence to guide practice. The methodology around PPI consultations continues to evolve [23]. Utilising PPI consultations in a study's early stages can assure relevance for patients and parents in the study's recruitment methods, ethics application, research protocol, and outcomes.[8] Our group illustrated an example of PPI consultations to identify a core outcome set for neonatology through consensus meetings around stakeholder viewpoints.[4] Others have called for "integration" of parents in research by frequently inviting their feedback.[14]

Participants voiced support for the use of opt-out consent, noting it reduced the anxiety of decision making. Some authors have criticised opt-out consent as not supporting informed consent.[24] However, the stress of neonatal intensive care complicates parent understanding of studies.[25] Our group has previously shown opt-out taps "into parents' desire for normality in an abnormal situation."[26] We have also shown that opt-out, as with opt-in consent, can be viewed as an ongoing consent process, leaving parents able to withdraw participation at any time, and that this approach is acceptable to the UK National Research Ethics Service.[27] Opt-out also allows parents to understand the trial and decline to participate without imposing a burden of additional information processing.[26]

The insights provided by consultation participants indicated the Parent Information Leaflet could be structured to provide emotional assistance by minimising the anxiety provoked by varying desires for information. This could be achieved by presenting information in a collaborative tone that situates the research as a partnership between clinicians, parents, and researchers, and employing a format that allows parents to assimilate information at their own pace. The language used can also help avoid making mothers feel inadequate by recognising the challenges of providing milk for their babies and alleviating the pressure to breastfeed. Our participants advised metering trial information to accommodate the needs of parents who want only a small amount of information as well as those who want to know more. The rationale for comparative effectiveness research is the relevance to patient safety of resolving uncertainties in care. However, "uncertain" does not necessarily describe how parents experience the moment of selecting a nutritional option. What is "uncertain" in terms of clinical practice is experienced as "worry", guilt, and even trauma by parents. This stems from a mixture of a shortfall in knowledge and the requirement to process substantial new information. The information provided through research participation enables parents to understand the issues facing their babies, providing direct benefit and a safe space to learn

about neonatal treatments. As a consequence of these insights we undertook a redesign of the information leaflet to allow parents to adjust how much information they would receive by converting it into a two-sided format with a very brief explanation of the study on the front and a more detailed explanation on the back (Supplementary Materials).

We identified anxiety among clinicians that manifest as a strong tendency to focus on the detail of the trial rather than the bigger picture even though the trial compares standard clinical practices. The main driver of anxiety was difficulty in managing uncertainty, both in terms of explaining this to parents and in accommodating it in their own practice. We found a cognitive dissonance at play, whereby the rationale for the trial is acceptable, yet involvement and being forced to confront their own personal views and biases led many to reject participation. In contrast, parents and patients felt that the proposed trial helped allay the anxieties invoked by the very uncertainties that justified the trial.

Our research has identified important areas for incorporation into the design of COLLABORATE and other comparative-effectiveness studies. Participating in research provides parents with a forum in which to learn about neonatal treatments, participate in knowledge production, and shape future care. Furthermore, in addition to the baby's medical care needs, this consultation, along with others, has identified that the provision of information to participants and enrolment to trials should consider the emotional needs of the parents as affected by study decision making, information processing, and language in study materials.[28, 29] This consultation illustrates the need for further work to address the anxieties described and experienced by healthcare professionals. We hope this will help spearhead a truly collaborative research culture between parents, clinicians, and researchers.

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deputy chair of the NIHR Health Technology Assessment Prioritisation Committee for Hospital based care, NM is a member of the Nestle International Scientific Advisory Board (accepts no personal remuneration for this role).

**Contributors**

All authors contributed to the research design of the parent, patient, and public involvement, qualitative methods, the revision of this manuscript, approval of the final draft for publication, and responsibility for the intellectual content within. Specific specialisations are described below.

WL – Writing, draft editing, thematic analysis, qualitative design, public involvement design, and data collection

BM – Writing, draft editing, thematic analysis, qualitative design, public involvement design, and data collection

CB – Writing, draft editing, qualitative participant recruitment

VC – Writing, Draft editing, randomised controlled trial (RCT) design

DB – Writing, Draft editing, RCT design

NM – Writing, draft editing, qualitative design, public involvement design, RCT Design

**Patient Consent for Publication**

This manuscript was shared with all participants to receive feedback and improve the paper's integrity. Participant names have been included only if participants have given explicit permission for their names to be published under our acknowledgements section.

**Research Ethics Approval**

Research ethics approval for PPI consultations is not required [9]. However, we approached parents and former patients through the neoWONDER group that has agreed to be invited to participate in consultations (REC reference: 20/yh/0330).

**Data Availability Statement**

Anonymised data are available upon request from the corresponding author.

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**Supplementary Materials**

**Draft Parent Information Leaflet**

**This information sheet provides details of a landmark approach to improve the care of very preterm babies. Please read it carefully and ask us if anything is unclear.**

**Background:** This neonatal unit is taking part in a large, national study to find out the best way to feed very preterm babies. This will involve using data that doctors and nurses record routinely for all babies admitted to neonatal units. This leaflet is to provide you with information. You do not need to do anything unless you do not wish us to use your baby's data.

You can "opt-out" at any time by telling [NAME OF STAFF MEMBER]. If you opt-out, your baby will continue to receive the same treatment and his or her care will not be affected. However, your baby's data will not be included in the analysis of the results.

**What we are trying to find out:** We ask all mothers who have a very preterm baby to express milk. However, if a mother has insufficient milk we do not know whether it is beneficial for a baby to receive pasteurised donated milk or formula specially made for preterm babies. We also do not know whether it is beneficial to very preterm babies to add extra protein and carbohydrate routinely to human milk. These are important questions affecting the care of all very preterm babies.

**Why there is uncertainty:** Preterm formula is made from cow's milk in a factory to strict regulatory standards. It has a consistent amount of nutrition and is used very widely. However, some clinicians believe cow's milk may increase the risks in very preterm babies of a gut inflammation called necrotising enterocolitis that can be very serious. About 3 in 100 very preterm babies in the UK develop severe necrotising enterocolitis.

Human milk provides more than just nutrition, for example, it has factors that strengthen immunity. However, human milk from a donor must be pasteurised to reduce the risk of transmitting infection. Pasteurisation reduces or destroys some beneficial properties of human milk; therefore, donor milk is not the same as milk from a baby's own mother. Pasteurised human donor milk is expensive and has very variable nutrition. This means that doctors may need to add extra protein and carbohydrate from cow's milk which some feel may also be a risk for necrotising enterocolitis.

**What happens at present:** Because we do not know which options are better for babies, some neonatal units use preterm formula and some use pasteurised human donor milk; some routinely add extra protein and carbohydrate to human milk feeds for very preterm babies and some do not. Overall, in the UK, the majority of babies receive their own mother's milk with some formula; less than 20% receive any donor milk, and about 40% receive some extra protein and carbohydrate.

**How to resolve these uncertainties:** The most reliable way to resolve uncertainties is by fairly allocating neonatal units to a feeding strategy, using a computer programme that makes the choice without influence so that half will use one approach and half will use the other, for each of the two uncertainties. This is ethical because it gives patients an equal, fair chance of receiving any of the alternative treatments. We will need to compare information from about 4700 babies to find out which options are more beneficial. In this neonatal unit we will be using [X] and [Y].

**Other information:** There are no risks to your baby from participation in this study because all feeding options are already widely used. Standard NHS indemnity operates in relation to the clinical treatment your baby receives. The UK Health Research Authority has approved the study. Imperial College London is coordinating the study and [x] is funding it. We will keep all details about your baby private. The only

people allowed to look at your baby's data are the team running the study and the regulatory authorities responsible for checking it is carried out correctly.

**Thank you for reading this.**

**Supplementary Materials (Continued)**

**Revised Parent Information Leaflet**

**SIDE ONE**

This information sheet provides details of a landmark approach to improve the care of very preterm babies.

This neonatal unit is taking part in a large, national study to find out the best way to feed very preterm babies (born at less than 29 weeks gestation).

This will involve using data that doctors and nurses record routinely for all babies admitted to neonatal units.

This sheet is to provide you with information. You do not need to do anything unless you do not wish us to use your baby's data.

You can "opt-out" at any time by telling [NAME OF STAFF MEMBER].

If you opt-out, your baby will continue to receive the same treatment and his or her care will not be affected. However, your baby's data will not be included in the analysis of the results.

**If you are interested in learning more about why the study is taking place, please turn overleaf.**

**SIDE TWO**

**What we are trying to find out:** We ask all mothers who have a very preterm baby to express milk, as we know this is the optimum way to feed neonates. However, breast-feeding a premature baby can often present challenges, despite their mother's effort and commitment. This means that sometimes a baby will need an additional source of nutrition. At present, we do not know whether it is beneficial for a baby to receive pasteurised donated milk or formula specially made for preterm babies. We also do not know whether it is beneficial to very preterm babies to add extra protein and carbohydrate routinely to human milk. These are important questions affecting the care of all very preterm babies.

**Why there is uncertainty:** Preterm formula is made from cow's milk in a factory to strict regulatory standards. It has a consistent amount of nutrition and is used very widely. However, some clinicians believe cow's milk may increase the risks in very preterm babies of a gut inflammation called necrotising enterocolitis that can be very serious. About 3 in 100 very preterm babies in the UK develop severe necrotising enterocolitis.

Human milk provides more than just nutrition, for example, it has factors that strengthen immunity. However, human milk from a donor must be pasteurised to reduce the risk of transmitting infection. Pasteurisation reduces or destroys some beneficial properties of human milk and for these and other reasons, donor milk is not the same as milk from a baby's own mother. Pasteurised human donor milk is expensive and has very variable nutrition. This means that doctors may need to add extra protein and carbohydrate from cow's milk which some feel may also be a risk for necrotising enterocolitis.

**What happens at present:** Because we do not know which options are better for babies, some neonatal units use preterm formula and some use pasteurised human donor milk; some routinely add extra protein and carbohydrate to human milk feeds for very preterm babies and some do not. Overall, in the UK, the majority of babies receive their own mother's milk with some formula; less than 20% receive any donor milk, and about 40% receive some extra protein and carbohydrate.

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Once again, if you opt-out of the research study, your baby will continue to receive the same treatment and his or her care will not be affected.

**Thank you for reading this. Please ask us if anything is unclear.**

**Supplementary Materials (Continued)**

**Completed Consolidated criteria for reporting qualitative research (COREQ)**

**Domain 1: Research team and reflexivity**

**Personal Characteristics**

1. Interviewer/facilitator – Lammons and Moss

2. Credentials – Lammons, MA; Moss, PhD

3. Occupation: Lammons, PPI Research Lead; Moss, PPI Research Lead

4. Gender – Lammons, male; Moss, female

5. Experience and training – Lammons, Imperial College London PPI Training; Moss, original PPI research on improving outcomes for aphasia patients

**Relationship with participants**

6. Relationship established – No relationship was established between Lammons, Moss and participants prior to this research. Participants were recruited through the neoWONDER network of interested participants who had given consent to contact, which is managed by Battersby.

7. Participant knowledge of the researchers – Lammons and Moss clearly stated the research goals, vision, and purposes at the start of every focus group and interview. They asserted that their goals were to understand parent and former patient experiences, then use these to improve the trial's success in terms of recruitment, retention, relevance, and efficacy.

8. Interviewer characteristics – interviewers clearly stated their motivations and interests in the research topic throughout each focus group and interview. Interviewers shared personal experiences, such as parenthood or lack thereof which impacted their vision and understanding of these phenomena. Most importantly, researchers situated themselves as intermediaries who could receive critiques of the research design, then transmit these to improve the research's inclusivity and engagement with participants.

**Domain 2: study design**

**Theoretical framework**

9. Methodological orientation – Qualitative research, qualitative analysis, and patient and public involvement

**Participant selection**

10. Sampling – Participants were selected from the neoWONDER research participant network, managed by Battersby, which is a network of parents of premature babies and adults born

premature who have consented to contact for neonatal medicine related research studies. Given time constraints the research team faced, we opted for this as the most efficient, effective, convenient, and purposeful means for getting feedback on the COLLABORATE trial prior in tandem with its protocol development.

11. Method of approach – email invitation through neoWONDER research participant network, led by Battersby. Interested individuals who responded were offered participation times and dates.

12. Sample size – 9

13. Non-participation 4 showed interest in participating but did not attend due to various reasons, including illness or lack of clear confirmation; follow-up contact and rescheduling was attempted with all four of these individuals twice via email, but no responses were received to schedule additional meeting dates.

**Setting**

14. Setting of data collection – virtual focus groups and interviews held via Zoom and Microsoft Teams. Participants joined the sessions from their personal computers/devices at their homes.

15. Presence of non-participants – only research participants and researchers (Moss and Lammons) were present during sessions

16. Description of sample – participants were all female between the ages of 22 and 55; 7 were mothers of neonatal patients, 1 was a former neonatal patient, and 1 was a mother and former neonatal patient.

**Data collection**

17. Interview guide – a topic guide was created by Lammons and Moss which was shared with the broader research team. The guide was not pilot tested, nor did participants request a copy of the guide, though it was available upon request.

18. Repeat interviews – none were conducted

19. Audio/visual recording – sessions were video recorded using in-app recording functions of Zoom and/or Teams. Audio recordings were extracted from the videos and used to create transcriptions with Descript software. These transcriptions were edited for correctness and understanding, then video recordings were deleted. Audio recordings were saved. One session encountered extensive technical difficulties and was correspondingly conducted by Moss via phone. As a result of technical issues, this session was not recorded.

20. Field notes – Lammons and Moss took field notes during and after interview/focus group sessions. These were included in the NVivo workflow and theming process along with raw data.

21. Duration – Each session lasted roughly 90 minutes.

22. Data saturation – Moss and Lammons used Malterud et al.'s concept of "information power", or the theory that validity resides in data's strength and quality 23 to emphasize the depth and relevance of the data collected and presented.

23. Transcripts returned – transcripts were not returned to participants for comment and/or correction, though quotations used throughout the manuscript have been reviewed and verified by participants.

**Domain 3: analysis and findings**

**Data analysis**

24. Number of data coders – 2, Moss and Lammons

25. Description of the coding tree – The coding tree has not been included in the manuscript but is available on request.

26. Derivation of themes – Moss and Lammons used a "hybrid approach" of deductive themes identified prior to the data collection and inductive themes derived from the data itself.

27. Software – NVivo 1.3 (QSR Technologies)

28. Participant checking – Participants have been included in the writing process as co-authors and reviewers of findings. Their feedback has contributed to the extant draft.

**Reporting**

29. Quotations presented – Eleven quotations are presented in the results section in brief, with their corresponding long-form versions and identifying participant numbers in Table 2.

30. Data and findings consistent – Data has been used to guide findings, discussion, and analysis. Copies of transcripts and coding are available upon request.

31. Clarity of major themes – Quotes were clearly paired with theme headings and discussions for optimum clarification.

32. Clarity of minor themes – Quotes were clearly paired with theme headings and discussions for optimum clarification.

BMJ Paediatrics Open

# Incorporating parent, former patient, and clinician perspectives in the design of a national UK double-cluster, randomised controlled trial addressing uncertainties in preterm nutrition



| | |
|---|---|
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**Incorporating parent, former patient, and clinician perspectives in the design of a national UK double-cluster, randomised controlled trial addressing uncertainties in preterm nutrition**

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**Authors**

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**Keywords**

Patient and public involvement, PPI, parent involvement, neonatal medicine, qualitative methodology, patient information leaflet, patient information sheet, opt-out consent

## ABSTRACT

### Background

Comparative effectiveness randomised controlled trials are powerful tools to resolve uncertainties in existing treatments and care processes. We sought parent and patient perspectives on the design of a planned national, double-cluster randomised controlled trial (COLLABORATE) to resolve two longstanding uncertainties in preterm nutrition.

### Methods

We used qualitative focus groups and interviews with parents, former patients and clinicians. We followed the COREQ checklist (Consolidated Criteria for Reporting Qualitative Research) and conducted Framework Analysis, a specific methodology within Thematic Analysis.

### Results

We identified support for the trial's methodology and vision, and elicited themes illustrating parents' emotional needs in relation to clinical research. These were: relieving the pressure on mothers to breastfeed; opt-out consent as reducing parent stress; the desire for research to be a partnership between clinicians, parents, and researchers; the value of presenting trial information in a collaborative tone; and in a format that allows assimilation by parents at their own pace. We identified anxiety and cognitive dissonance among some clinicians in which they recognised the uncertainties that justify the trial but felt unable to participate because of their strongly held views.

### Conclusions

The early involvement of parents and former patients identified the centrality of parents' emotional needs in the design of comparative effectiveness research. These insights have been incorporated into trial enrolment processes and information provided to participants. Specific outputs were a two-sided leaflet providing very brief as well as more detailed information, and use of language that parents perceive as inclusive and participatory. Further work is warranted to support clinicians to address personal biases that inhibit trial participation.

**KEY MESSAGES**

**What is known about the subject?**

- Comparative effectiveness randomised controlled trials are powerful means of resolving uncertainties in existing treatments and care processes.
- Many areas of neonatal practice lack an adequate evidence base, hence treatments often vary, within and between centres.
- The uncertainty around optimal practice creates risks for patients, anxiety for parents, and confusion among staff.

**What this study adds?**

- In addition to resolving practice uncertainties, comparative effectiveness research can help alleviate parent anxieties through metered study information, and partnership to improve newborn care.
- Early involvement of parents and former patients in trial development also enables researchers to support parents emotional needs through appropriate recruitment materials and methods.
- Incorporating clinicians as stakeholders has potential to understand and address their personal biases that inhibit trial participation.

## INTRODUCTION

Many areas of neonatal practice lack an adequate evidence base, hence treatments often vary, within and between centres. Comparative effectiveness research refers to approaches to try and resolve uncertainties in established treatments.

COLLABORATE is a planned national, UK, double-cluster randomised controlled trial aiming to recruit at least 4700 babies to resolve two longstanding global uncertainties in preterm nutrition, the benefits of i) pasteurised human donor milk in comparison with preterm formula to supplement a baby's own mother's milk when more milk is needed and ii) routine versus no routine protein-carbohydrate fortification of human milk.[1, 2] The co-primary outcomes are survival to 36 weeks postmenstrual age without surgery for necrotising enterocolitis (NEC) and survival to age two-years without moderate-severe neurodevelopment impairment.

Currently in the UK less than twenty percent of very preterm babies receive any pasteurised donor milk and less than forty percent receive any fortifier.[3] The uncertainty around optimal practice creates risks for patients, anxiety for parents, and confusion among staff. COLLABORATE offers a pragmatic response to these uncertainties. COLLABORATE will use data from the National Neonatal Research Database to minimise clinical burden,[4-6] and evaluate two-year language and cognitive outcomes with a parent-completed questionnaire, the Parent Report of Children's Abilities-Revised (PARCA-R).[7]

These clinical uncertainties, which affect the care provided to babies as well as the information provided to families, present an opportunity to understand how parents of very preterm babies can improve the recruitment materials for the COLLABORATE trial and clarify the acceptability of consent methods, as well as compare their views and reactions with those of clinicians. PPI consultations are enriching mechanisms to improve design, making studies more successful and relevant to their stakeholders [8-12]. In paediatric research they have identified important guiding themes for future research, largely through centring the narratives and experiences of survivors and families [13, 14]. Our aim at this preliminary stage was to involve parents, former patients, and clinicians in trial development.

## METHODS

We recruited former neonatal intensive care patients and parents of patients from across the UK through a network of individuals with experience of preterm birth who had consented to be invited to participate in neonatal research activities.[15] We invited the participation of healthcare professionals through a national webinar. In total, twenty volunteers; ten clinicians, seven parents, two former patients, and one parent/former patient; participated in virtual focus groups or semi-structured interviews [16, 17]. Sessions with single participants utilised the same topic guide. No clinicians attended the parent-patient groups to avoid inhibiting or influencing the discussions.[16, 17] Participants gave verbal consent for participation and recording at the start of every discussion session.

We followed the COREQ checklist (Consolidated Criteria for Reporting Qualitative Research) for qualitative studies and created a topic guide to probe parent-patient and clinician experiences and understanding of the trial, based upon a hybrid blend of deductive and inductive approaches to facilitate discussion and allow themes to emerge.[18, 19] We provided a draft Parent Information Leaflet (Supplementary Materials). Each session lasted approximately 90 minutes, and all were recorded with participant consent. WL and BM, non-clinical qualitative researchers led the discussions and conducted interviews. They transcribed recordings and conducted interviews.

WL and BM analysed all qualitative data using Framework Analysis, a specific methodology within Thematic Analysis.[20] Initial themes and concepts were identified through iterative review of the data, then used to construct a thematic index, or "framework", and assign an index label to each phrase or passage of the transcripts.[20] The indexed and labeled raw data was then summarised and synthesised into thematic charts to preserve the data's context while facilitating systematic exploration. These thematic charts produced salient themes, which serve as descriptive and explanatory accounts of the data.[20] Data were organised and analysed using NVivo, version 1.0(QSR International)[21]. Participants were provided contact information for psychological support services in the event that discussions elicited strong emotions.

**Patient and Public Involvement**

At this preliminary stage of the development of COLLABORATE, we have utilised patient-public involvement to assist in developing the consent process and trial information leaflet. We have also involved clinicians to understand and address concerns related to their perspectives on opt-out consent, cluster randomisation, and clinical uncertainties. This paper embodies the first phase of the study's public involvement strategy which includes parents, adults born preterm, and clinicians as research collaborators throughout the research cycle.[22]

**RESULTS**

Nine volunteers, all women (seven parents, one former patient, and one parent who is also a former patient) participated in parent-patient focus groups (Table 1). Eleven volunteers for clinician focus groups included eight neonatologists, a dietician and an infant feeding specialist midwife. One non-clinician adult born preterm also chose to attend a clinician focus group. Seven of the eleven participants were men. No participant required the psychological support services that were offered.

**Table 1 Parent and Patient Participant Characteristics 1**

| Participant | Gestational Age of Child or Patient | Reason for Interest in Participating | Feeding Method | Single/Multiple Birth | Incidence of necrotising enterocolitis [NEC]? | Survival of Baby(ies) | Support for Trial |
|---|---|---|---|---|---|---|---|
| Parent 1 | 33+3 weeks | Pharmacist w/RCT experience | Mum's milk | Single | N | Y | Y |
| Parent 2 | n/a | NEC/preterm charity volunteer | Mum's milk & Formula | Single | Y | Y | N |
| Parent 3 | n/a | Breastfeeding peer supporter | Mum's milk & Formula | Single | N | Y | Y |
| Parent 4 | 22 weeks | NEC/preterm charity volunteer | Mum's milk & Donor milk | Twins | N/N | Y/N | Y |
| Parent 5 | 33 weeks | n/a | Mum's milk & Fortifier | Single | Y | N | Unsure |
| Parent 6 | 29+5 weeks | n/a | Mum's milk & Formula | Twins | Suspected NEC/N | Y/Y | Y |
| Parent 7 | 28 weeks | n/a | Mum's milk & Formula | Single | Y | Y | Y |
| Patient/Parent 12 | 29 weeks | NEC/preterm charity volunteer | Formula & Donor Milk/Formula & Donor Milk | Single/Single | Y/Y | Y/Y | Y |
| Patient 1 | 28+4weeks | Paediatric nurse | Mum's milk & Formula | Twin | N/suspected NEC | Y/N3 | Y |

We identified three parent-patient themes; "pressure to breastfeed", "consent process", and "emotional trauma"; one clinician theme, "equipoise and personal beliefs"; and one theme combining parent-patient and clinician discussions, "collaboration and inclusivity."

## Theme 1 Pressure to breastfeed

Participants almost universally cited the refrain, "breast is best," but mothers' experiences of expressing milk and breastfeeding provoked stress and feelings of inadequacy. One former patient articulated the challenges of breastfeeding with an anecdote from her own mother:

> *"…my mum will share with me that she cried with her breasts bleeding, trying to express because she was told it was the best... And she had a woman sitting next to her in the expressing room who had, you know, 500 mils of milk sitting there…and this woman was saying, 'Oh, it's not enough.' My mum was like, 'you're kidding me. I've got five ml from the last four hours. And I'm bleeding into it." (NICU patient born at 28+4 weeks, now a paediatric nurse)*

Parents showed understanding of the trial's aim of resolving feeding uncertainties. The discussion identified confusion around feeding options that were brought to the fore by the challenges of expressing sufficient milk.

> *"I remember when they talked about putting him onto formula, I said to the consultant, 'I'm really, really worried about him getting NEC [necrotising enterocolitis]. I'm really worried.' Cause I had it and…I know how bad it is…they assured me that the risk with formula was just as high as it was with donor milk. So I was like…if they need to gain weight and it's such a balancing act, isn't it?...I suppose it's the same for the doctors. They're just trying to balance the best options." (Mother who had NEC as a preterm baby, whose baby was born at 29 weeks)*

Participants emphasised sensitivity was needed to support mothers when discussing feeding.

> *"… And at the end of the day, it has to be what's best…for your circumstances and what's best for your baby because your mum's milk is best, but if mum's milk is not available… you shouldn't make mums feel as if they're kind of a failure." (Mother of twins born at 29+5 weeks)*

**Theme 2 Consent process**

Parent-patient participants and most clinicians supported opt-out as minimising the added stress of trial consent in an already stressful environment. One parent stated

> *"…I appreciate the opt-out allows a much larger number of people, and often families don't go there. Not because they don't necessarily want to do it, but for whatever reason they have…they're not thinking about it or they read [the consent form]…and forget to fill out..." (Mother of a preterm baby who had NEC)*

Other participants echoed this sentiment noting that usual trial consent and information processes are often cumbersome and confusing. Some clinicians went further, suggesting that cluster randomisation meant that opt-out consent was required only from a neonatal unit rather than from parents themselves.

However, worries around transparency led some clinicians to feel uncomfortable with opt-out consent. For example, one told us they felt opt-out was only appropriate when a rapid decision was needed for a time-critical intervention.

**Theme 3 Collaboration and inclusivity**

Parent-patient participants emphasised the confusion and anxiety that results from lack of clarity or consistency in medical information communicated to them. They felt researchers can help alleviate these anxieties through the tone they adopt as well as the clarity of their communications.

> *"They need to be able to sometimes slightly dumb it down so we can understand it really well… I'm focusing on 'add extra protein and carbohydrate' [in the parent information leaflet.] I've never heard of that before…" (Mother of twin boys born at 22 weeks, one of whom did not survive)*

They recommended we remove phrases in the draft parent information leaflet such as "if a mother has insufficient milk" (Supplementary Materials). They encouraged general use of words and phrases that expressed empathy for mothers' difficulties as opposed to ones that provoked feelings of guilt or inadequacy, supportive of an "inclusive" tone.

> *"The document, as it reads, is looking to me like dumbed down 'science-y' stuff. Whereas I think it needs to come from a person to person, like where you have concerns and fears, and this is what we are trying to do together as a community of NICU [neonatal intensive care unit] survivors and clinicians…" (Mother of twin boys born at 22 weeks, one of whom did not survive)*

This parent's reference to a "community of survivors" illustrates their need for empathy.

Clinician participants recognized the importance of fostering a collaborative relationship with parents:

> *"I think this whole thing about us having to approach parents in a really collaborative way around the importance of…feeding…managing their expectations and their understanding of what is happening with that baby's gut, and that we're trying to help promote a healthy gut, not just for the time when they're in their unit, but beyond that time as a healthy gut for life – here is the one of the fundamental things that's going to influence their feeding for not just weeks, but months and years to come." (Neonatal clinician)*

They perceived a tension between ensuring information was shared transparently and managing parental anxiety. Offering clear and consistent explanations was seen as paramount, but this was sometimes difficult because of clinical uncertainties and professional differences of opinion.

**Theme 4 Trauma, powerlessness, and parental learning in the neonatal unit**

Mothers experience trauma and feelings of powerlessness, when their babies were "taken away" for intensive care almost immediately following birth.

> *"…I had this baby ripped from me…I didn't see her after birth. It was horrific…her first nappy was changed by somebody else... All her cares were done by somebody else. The first person she saw was somebody else" (Mother of a preterm baby with NEC)*

A lack of knowledge of neonatal care typically amplified these emotional experiences and participants described feelings of urgency to obtain more information.

> *… when you're in hospital and you've just had a new baby, especially if the baby's premature and you just have…so little time…" (Mother of a baby born at 33+3 weeks, pharmacist)*

> *At the same time, often, you do have a lot of time to kill in the neonatal unit … you will read every leaflet front to back" (Mother of a preterm baby)*

Pursuing knowledge helped remedy feelings of powerlessness for some mothers, though a broader awareness of dangers facing babies often increased anxiety for others.

> *"I'm the sort of person that likes to know everything, so I would want to read every tiny little detail of everything…but I know from speaking to other parents in the neonatal unit that a lot of parents…don't want to be involved as much and they don't want to know things. (Mother of a preterm baby who had NEC)"*

In summary, parents reported varying degrees of desire for knowledge, from those who wanted to know "everything" and those who wanted a more general understanding.

**Theme 5: Equipoise and personal beliefs**

Clinicians described the difficulty of managing their own anxieties about treatments in discussions with parents to minimise parent feelings of emotional distress and ensure equipoise across the unit.

> *"On a ward round, one negative sentence, a loose comment about something … just spoils everything. We try to police that to some extent [and] share all our anxieties and disagreement beforehand ….we have our own personal agendas or personal biases but keep them to ourselves when we are … in front of other people. that's where I see the issue about [a] unit that's sort of consenting to participate, but not then sticking to the protocol…and then bringing some of their own ideas into the consenting … [and] recruitment process." (Neonatal clinician)*

Clinicians identified that the anxieties, disagreements, and biases that are common to care could amount to complications in trial procedures for some units. Despite broad acceptance of the need for a trial, many clinicians predicted neonatal units with a standardised feeding regimen would not agree to change them and would therefore decline to participate. Clinical focus group participants accepted the existence of clinical uncertainties and understood the need for a definitive trial. For example, one said:

*'We've been asking these questions for so long and we still haven't got the answer" (Neonatal clinician)*

**DISCUSSION**

This PPI consultation with parent, former patient and clinician views about a planned national double-cluster randomised controlled trial involved participants with intimate knowledge of neonatal care, and the corresponding relevance and depth of their contributions provide novel insights. We identified support for the rationale and proposed methodology, and themes within and across groups. Particularly powerful themes related to the emotional needs of parents and the personal beliefs of clinicians. Parents experience stress and anxiety because of their baby's admission to intensive care. A novel insight provided by this consultation is that comparative effectiveness research might help alleviate parent anxieties in several ways. Clinician participants identified anxieties arising from the tension between their personal views and their acknowledgement of the need for evidence to guide practice. The methodology around PPI consultations continues to evolve [23]. Utilising PPI consultations in a study's early stages can assure relevance for patients and parents in the study's recruitment methods, ethics application, research protocol, and outcomes.[8] Our group illustrated an example of PPI consultations to identify a core outcome set for neonatology through consensus meetings around stakeholder viewpoints.[4] Others have called for "integration" of parents in research by frequently inviting their feedback.[14]

Participants voiced support for the use of opt-out consent, noting it reduced the anxiety of decision making. Some authors have criticised opt-out consent as not supporting informed consent.[24] However, the stress of neonatal intensive care complicates parent understanding of studies.[25] Our group has previously shown opt-out taps "into parents' desire for normality in an abnormal situation."[26] We have also shown that opt-out, as with opt-in consent, can be viewed as an ongoing consent process, leaving parents able to withdraw participation at any time, and that this approach is acceptable to the UK National Research Ethics Service.[27] Opt-out also allows parents to understand the trial and decline to participate without imposing a burden of additional information processing.[26]

The insights provided by consultation participants indicated the Parent Information Leaflet could be structured to provide emotional assistance by minimising the anxiety provoked by varying desires for information. This could be achieved by presenting information in a collaborative tone that situates the research as a partnership between clinicians, parents, and researchers, and employing a format that allows parents to assimilate information at their own pace. The language used can also help avoid making mothers feel inadequate by recognising the challenges of providing milk for their babies and alleviating the pressure to breastfeed. Our participants advised metering trial information to accommodate the needs of parents who want only a small amount of information as well as those who want to know more. The rationale for comparative effectiveness research is the relevance to patient safety of resolving uncertainties in care. However, "uncertain" does not necessarily describe how parents experience the moment of selecting a nutritional option. What is "uncertain" in terms of

clinical practice is experienced as “worry”, guilt, and even trauma by parents. This stems from a mixture of a shortfall in knowledge and the requirement to process substantial new information. The information provided through research participation enables parents to understand the issues facing their babies, providing direct benefit and a safe space to learn about neonatal treatments. As a consequence of these insights we undertook a redesign of the information leaflet to allow parents to adjust how much information they would receive by converting it into a two-sided format with a very brief explanation of the study on the front and a more detailed explanation on the back (Supplementary Materials).

We identified anxiety among clinicians that manifest as a strong tendency to focus on the detail of the trial rather than the bigger picture even though the trial compares standard clinical practices. The main driver of anxiety was difficulty in managing uncertainty, both in terms of explaining this to parents and in accommodating it in their own practice. We found a cognitive dissonance at play, whereby the rationale for the trial is acceptable, yet involvement and being forced to confront their own personal views and biases led many to reject participation. In contrast, parents and patients felt that the proposed trial helped allay the anxieties invoked by the very uncertainties that justified the trial.

Our research has identified important areas for incorporation into the design of COLLABORATE and other comparative-effectiveness studies. Participating in research provides parents with a forum in which to learn about neonatal treatments, participate in knowledge production, and shape future care. Furthermore, in addition to the baby’s medical care needs, this consultation, along with others, has identified that the provision of information to participants and enrolment to trials should consider the emotional needs of the parents as affected by study decision making, information processing, and language in study materials.[28, 29] This consultation illustrates the need for further work to address the anxieties described and experienced by healthcare professionals. We hope this will help spearhead a truly collaborative research culture between parents, clinicians, and researchers.

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**Contributors**

All authors contributed to the research design of the parent, patient, and public involvement, qualitative methods, the revision of this manuscript, approval of the final draft for publication, and responsibility for the intellectual content within. Specific specialisations are described below.

WL – Writing, draft editing, thematic analysis, qualitative design, public involvement design, and data collection

BM – Writing, draft editing, thematic analysis, qualitative design, public involvement design, and data collection

CB – Writing, draft editing, qualitative participant recruitment

VC – Writing, Draft editing, randomised controlled trial (RCT) design

DB – Writing, Draft editing, RCT design

NM – Writing, draft editing, qualitative design, public involvement design, RCT Design

**Patient Consent for Publication**

This manuscript was shared with all participants to receive feedback and improve the paper's integrity. Participant names have been included only if participants have given explicit permission for their names to be published under our acknowledgements section.

**Research Ethics Approval**

Research ethics approval for PPI consultations is not required [9]. However, we approached parents and former patients through the neoWONDER group that has agreed to be invited to participate in consultations (REC reference: 20/yh/0330).

**Data Availability Statement**

Anonymised data are available upon request from the corresponding author.

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**Supplementary Materials**

**Draft Parent Information Leaflet**

**This information sheet provides details of a landmark approach to improve the care of very preterm babies. Please read it carefully and ask us if anything is unclear.**

**Background:** This neonatal unit is taking part in a large, national study to find out the best way to feed very preterm babies. This will involve using data that doctors and nurses record routinely for all babies admitted to neonatal units. This leaflet is to provide you with information. You do not need to do anything unless you do not wish us to use your baby's data.

You can "opt-out" at any time by telling [NAME OF STAFF MEMBER]. If you opt-out, your baby will continue to receive the same treatment and his or her care will not be affected. However, your baby's data will not be included in the analysis of the results.

**What we are trying to find out:** We ask all mothers who have a very preterm baby to express milk. However, if a mother has insufficient milk we do not know whether it is beneficial for a baby to receive pasteurised donated milk or formula specially made for preterm babies. We also do not know whether it is beneficial to very preterm babies to add extra protein and carbohydrate routinely to human milk. These are important questions affecting the care of all very preterm babies.

**Why there is uncertainty:** Preterm formula is made from cow's milk in a factory to strict regulatory standards. It has a consistent amount of nutrition and is used very widely. However, some clinicians believe cow's milk may increase the risks in very preterm babies of a gut inflammation called necrotising enterocolitis that can be very serious. About 3 in 100 very preterm babies in the UK develop severe necrotising enterocolitis.

Human milk provides more than just nutrition, for example, it has factors that strengthen immunity. However, human milk from a donor must be pasteurised to reduce the risk of transmitting infection. Pasteurisation reduces or destroys some beneficial properties of human milk; therefore, donor milk is not the same as milk from a baby's own mother. Pasteurised human donor milk is expensive and has very variable nutrition. This means that doctors may need to add extra protein and carbohydrate from cow's milk which some feel may also be a risk for necrotising enterocolitis.

**What happens at present:** Because we do not know which options are better for babies, some neonatal units use preterm formula and some use pasteurised human donor milk; some routinely add extra protein and carbohydrate to human milk feeds for very preterm babies and some do not. Overall, in the UK, the majority of babies receive their own mother's milk with some formula; less than 20% receive any donor milk, and about 40% receive some extra protein and carbohydrate.

**How to resolve these uncertainties:** The most reliable way to resolve uncertainties is by fairly allocating neonatal units to a feeding strategy, using a computer programme that makes the choice without influence so that half will use one approach and half will use the other, for each of the two uncertainties. This is ethical because it gives patients an equal, fair chance of receiving any of the alternative treatments. We will need to compare information from about 4700 babies to find out which options are more beneficial. In this neonatal unit we will be using [X] and [Y].

**Other information:** There are no risks to your baby from participation in this study because all feeding options are already widely used. Standard NHS indemnity operates in relation to the clinical treatment your baby receives. The UK Health Research Authority has approved the study. Imperial College London is coordinating the study and [x] is funding it. We will keep all details about your baby private. The only

people allowed to look at your baby's data are the team running the study and the regulatory authorities responsible for checking it is carried out correctly.

**Thank you for reading this.**

**Supplementary Materials (Continued)**

**Revised Parent Information Leaflet**

**SIDE ONE**

This information sheet provides details of a landmark approach to improve the care of very preterm babies.

This neonatal unit is taking part in a large, national study to find out the best way to feed very preterm babies (born at less than 29 weeks gestation).

This will involve using data that doctors and nurses record routinely for all babies admitted to neonatal units.

This sheet is to provide you with information. You do not need to do anything unless you do not wish us to use your baby's data.

You can "opt-out" at any time by telling [NAME OF STAFF MEMBER].

If you opt-out, your baby will continue to receive the same treatment and his or her care will not be affected. However, your baby's data will not be included in the analysis of the results.

**If you are interested in learning more about why the study is taking place, please turn overleaf.**

**SIDE TWO**

**What we are trying to find out:** We ask all mothers who have a very preterm baby to express milk, as we know this is the optimum way to feed neonates. However, breast-feeding a premature baby can often present challenges, despite their mother's effort and commitment. This means that sometimes a baby will need an additional source of nutrition. At present, we do not know whether it is beneficial for a baby to receive pasteurised donated milk or formula specially made for preterm babies. We also do not know whether it is beneficial to very preterm babies to add extra protein and carbohydrate routinely to human milk. These are important questions affecting the care of all very preterm babies.

**Why there is uncertainty:** Preterm formula is made from cow's milk in a factory to strict regulatory standards. It has a consistent amount of nutrition and is used very widely. However, some clinicians believe cow's milk may increase the risks in very preterm babies of a gut inflammation called necrotising enterocolitis that can be very serious. About 3 in 100 very preterm babies in the UK develop severe necrotising enterocolitis.

Human milk provides more than just nutrition, for example, it has factors that strengthen immunity. However, human milk from a donor must be pasteurised to reduce the risk of transmitting infection. Pasteurisation reduces or destroys some beneficial properties of human milk and for these and other reasons, donor milk is not the same as milk from a baby's own mother. Pasteurised human donor milk is expensive and has very variable nutrition. This means that doctors may need to add extra protein and carbohydrate from cow's milk which some feel may also be a risk for necrotising enterocolitis.

**What happens at present:** Because we do not know which options are better for babies, some neonatal units use preterm formula and some use pasteurised human donor milk; some routinely add extra protein and carbohydrate to human milk feeds for very preterm babies and some do not. Overall, in the UK, the majority of babies receive their own mother's milk with some formula; less than 20% receive any donor milk, and about 40% receive some extra protein and carbohydrate.

**How to resolve these uncertainties:** The most reliable way to resolve uncertainties is by fairly allocating neonatal units to a feeding strategy, using a computer programme that makes the choice without influence so that half will use one approach and half will use the other, for each of the two uncertainties. This is ethical because it gives patients an equal, fair chance of receiving any of the alternative treatments. We will need to compare information from about 4700 babies to find out which options are more beneficial. In this neonatal unit we will be using [X] and [Y].

**Other information:** There are no risks to your baby from participation in this study because all feeding options are already widely used. Standard NHS indemnity operates in relation to the clinical treatment your baby receives. The UK Health Research Authority has approved the study. Imperial College London is coordinating the study and [x] is funding it. We will keep all details about your baby private. The only people allowed to look at your baby's data are the team running the study and the regulatory authorities responsible for checking it is carried out correctly.

Once again, if you opt-out of the research study, your baby will continue to receive the same treatment and his or her care will not be affected.

**Thank you for reading this. Please ask us if anything is unclear.**

**Supplementary Materials (Continued)**

**Completed Consolidated criteria for reporting qualitative research (COREQ)**

**Domain 1: Research team and reflexivity**

**Personal Characteristics**

1. Interviewer/facilitator – Lammons and Moss

2. Credentials – Lammons, MA; Moss, PhD

3. Occupation: Lammons, PPI Research Lead; Moss, PPI Research Lead

4. Gender – Lammons, male; Moss, female

5. Experience and training – Lammons, Imperial College London PPI Training; Moss, original PPI research on improving outcomes for aphasia patients

**Relationship with participants**

6. Relationship established – No relationship was established between Lammons, Moss and participants prior to this research. Participants were recruited through the neoWONDER network of interested participants who had given consent to contact, which is managed by Battersby.

7. Participant knowledge of the researchers – Lammons and Moss clearly stated the research goals, vision, and purposes at the start of every focus group and interview. They asserted that their goals were to understand parent and former patient experiences, then use these to improve the trial's success in terms of recruitment, retention, relevance, and efficacy.

8. Interviewer characteristics – interviewers clearly stated their motivations and interests in the research topic throughout each focus group and interview. Interviewers shared personal experiences, such as parenthood or lack thereof which impacted their vision and understanding of these phenomena. Most importantly, researchers situated themselves as intermediaries who could receive critiques of the research design, then transmit these to improve the research's inclusivity and engagement with participants.

**Domain 2: study design**

**Theoretical framework**

9. Methodological orientation – Qualitative research, qualitative analysis, and patient and public involvement

**Participant selection**

10. Sampling – Participants were selected from the neoWONDER research participant network, managed by Battersby, which is a network of parents of premature babies and adults born

premature who have consented to contact for neonatal medicine related research studies. Given time constraints the research team faced, we opted for this as the most efficient, effective, convenient, and purposeful means for getting feedback on the COLLABORATE trial prior in tandem with its protocol development.

11. Method of approach – email invitation through neoWONDER research participant network, led by Battersby. Interested individuals who responded were offered participation times and dates.

12. Sample size – 9

13. Non-participation 4 showed interest in participating but did not attend due to various reasons, including illness or lack of clear confirmation; follow-up contact and rescheduling was attempted with all four of these individuals twice via email, but no responses were received to schedule additional meeting dates.

**Setting**

14. Setting of data collection – virtual focus groups and interviews held via Zoom and Microsoft Teams. Participants joined the sessions from their personal computers/devices at their homes.

15. Presence of non-participants – only research participants and researchers (Moss and Lammons) were present during sessions

16. Description of sample – participants were all female between the ages of 22 and 55; 7 were mothers of neonatal patients, 1 was a former neonatal patient, and 1 was a mother and former neonatal patient.

**Data collection**

17. Interview guide – a topic guide was created by Lammons and Moss which was shared with the broader research team. The guide was not pilot tested, nor did participants request a copy of the guide, though it was available upon request.

18. Repeat interviews – none were conducted

19. Audio/visual recording – sessions were video recorded using in-app recording functions of Zoom and/or Teams. Audio recordings were extracted from the videos and used to create transcriptions with Descript software. These transcriptions were edited for correctness and understanding, then video recordings were deleted. Audio recordings were saved. One session encountered extensive technical difficulties and was correspondingly conducted by Moss via phone. As a result of technical issues, this session was not recorded.

20. Field notes – Lammons and Moss took field notes during and after interview/focus group sessions. These were included in the NVivo workflow and theming process along with raw data.

21. Duration – Each session lasted roughly 90 minutes.

22. Data saturation – Moss and Lammons used Malterud et al.'s concept of "information power", or the theory that validity resides in data's strength and quality 23 to emphasize the depth and relevance of the data collected and presented.

23. Transcripts returned – transcripts were not returned to participants for comment and/or correction, though quotations used throughout the manuscript have been reviewed and verified by participants.

**Domain 3: analysis and findings**

**Data analysis**

24. Number of data coders – 2, Moss and Lammons

25. Description of the coding tree – The coding tree has not been included in the manuscript but is available on request.

26. Derivation of themes – Moss and Lammons used a "hybrid approach" of deductive themes identified prior to the data collection and inductive themes derived from the data itself.

27. Software – NVivo 1.3 (QSR Technologies)

28. Participant checking – Participants have been included in the writing process as co-authors and reviewers of findings. Their feedback has contributed to the extant draft.

**Reporting**

29. Quotations presented – Eleven quotations are presented in the results section in brief, with their corresponding long-form versions and identifying participant numbers in Table 2.

30. Data and findings consistent – Data has been used to guide findings, discussion, and analysis. Copies of transcripts and coding are available upon request.

31. Clarity of major themes – Quotes were clearly paired with theme headings and discussions for optimum clarification.

32. Clarity of minor themes – Quotes were clearly paired with theme headings and discussions for optimum clarification.