Joint Research Management Office (JRMO) Research Protocol for Research Studies

Full Title: BiliNEST: Bilirubin assessment in Neonates of Every Skin Tone, a prospective observational study

Short Title: The BiliNEST observational study: Jaundice assessment in babies of every skin tone

Short Title BiliNEST

Sponsor Queen Mary University of London (Queen Mary)

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020 7476 4000

Royal London Hospital
Barts Health NHS Trust
Whitechapel Rd, London E1 1FR
020 7377 7000

Whipps Cross Hospital
Barts Health NHS Trust
Whipps Cross Rd, London E11 1NR
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Homerton University Hospital
Homerton University Hospitals NHS Foundation Trust
Homerton Row, London E9 6SR
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North Middlesex University Hospital
North Middlesex University Hospital NHS Trust
Sterling way, London N18 1QX
0208 887 2966

Royal Free Hospital
Royal Free London NHS Foundation Trust
Pond St, London NW3 2QG
020 7794 0500

Barnet General Hospital
Royal Free London NHS Foundation Trust
Wellhouse Ln, Barnet EN5 3DJ
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University College London Hospital
University College London Hospitals NHS Foundation Trust
235 Euston Rd., London NW1 2BU
020 3456 7890

Whittington Hospital
Whittington Hospital NHS Trust
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020 7272 3070

West London:

Chelsea & Westminster Hospital
Chelsea & Westminster Hospital NHS Foundation Trust
369 Fulham Rd., London SW10 9NH
020 3315 8000

West Middlesex University Hospital
Chelsea & Westminster Hospital NHS Foundation Trust
Twickenham Rd, Isleworth TW7 6AF
020 8560 2121

St Mary's Hospital
Imperial College Healthcare NHS Trust
Praed St, London W2 1NY
020 3312 6666

Queen Charlotte's and Chelsea Hospital
Imperial College Healthcare NHS Trust
Du Cane Rd, London W12 0HS
020 3313 1111

Northwick Park Hospital
London North West Healthcare NHS Trust
Watford Rd, Harrow HA1 3UJ
020 8864 3232

Hillingdon Hospital
The Hillingdon Hospitals NHS Foundation Trust
Pield Heath Rd, Uxbridge UB8 3NN
01895 238282

South London:

Guy's & St Thomas' Hospital (Evelina Children's Hospital)
Guy's and St Thomas' NHS Foundation Trust
St Thomas' Hospital, Westminster Bridge Rd, London SE1 7EH
020 7188 7188

St George's Hospital
St George's University Hospitals NHS Trust
Blackshaw Rd, London SW17 0QT
020 8672 1255

Kings College Hospital
King's College Hospital NHS Foundation Trust

Denmark Hill, London SE5 9RS
020 3299 9000

Princess Royal Hospital
King's College Hospital NHS Foundation Trust
Farnborough Common, Orpington BR6 8ND
01689 863000

Kingston Hospital
Kingston Hospital NHS Foundation Trust
Galsworthy Rd, Kingston upon Thames KT2 7QB
020 8546 7711

Lewisham University Hospital
Lewisham & Greenwich NHS Trust
Lewisham High St, London SE13 6LH
020 8333 3000

Queen Elizabeth Hospital Woolwich
Lewisham & Greenwich NHS Trust
Stadium Rd, London SE18 4QH
020 8836 6000

Croydon University Hospital
Croydon Health Services NHS Trust
530 London Rd, Thornton Heath CR7 7YE
020 8401 3000

St Helier's Hospital
Epsom & St Helier University Hospitals NHS Trust
Wrythe Ln, Sutton, Carshalton SM5 1AA
020 8296 2000

Epsom General Hospital
Epsom & St Helier University Hospitals NHS Trust
Dorking Rd, Epsom KT18 7EG
01372 735735

List of laboratories NHS laboratories will be used at each site listed above

List of technical departments N/A

List of central facilities N/A

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2. Glossary

CRF	**Case Report Form**
G6PD	**Glucose-6-phosphate Dehydrogenase**
DAT	**Direct Antibody Test**
HCP	**Healthcare Professional**
HDN	**Haemolytic disease of the newborn**
IVIG	**Intravenous immunoglobulin**
NICE	**National Institute for Health and Care Excellence**
NICU	**Neonatal intensive care unit**
PTx	**Phototherapy**
Postnatal area	**Inpatient ward providing primarily midwife-led postnatal care, including eg postnatal wards, labour wards, maternity wards, birth centres, and transitional care units (but excluding neonatal units or paediatric wards)**
REACH	**Research Evaluation and Audit for Child Health**
SBR	**Serum Bilirubin**
SCBU	**Special Care Baby Unit**
TcB	**Transcutaneous Bilirubinometer**
PPI	**Patient and public involvement**
PIS	**Participant information sheet**

3. Signature page

CI Agreement

The study, as detailed within this Research Protocol, will be conducted in accordance with the principles of Good Clinical Practice (GCP), the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I agree to take responsibility for the statistical analysis and oversight of this study.

CI Name:	**Dr Sasha Howard**
Signature:	
Date:	**18.07.2025**

4. Summary and synopsis

Short title	BiliNEST
Methodology	Prospective multicentre observational study utilising the London REACH (Research Evaluation and Audit for Child Health) Network
Objectives / aims	We aim to investigate whether there are disparities in the jaundice assessments for neonates of different skin tones in London through the following objectives: Primary Objectives: 1. To assess the level of first bilirubin measurement in neonates of different skin tones and determine whether neonates with darker skin tones are being assessed for jaundice once they have reached a higher bilirubin level, as compared to lighter skinned neonates. 2. To evaluate the agreement between TcB and SBR measurements in neonates of different skin tones. Secondary Objectives: 1. To investigate immediate management of neonates of different skin tones undergoing assessment for jaundice: length of admission, investigations and receipt of interventions including phototherapy and exchange transfusion. 2. To review the range of existing local guidelines on management of neonatal jaundice, examining inter-guideline variation and variation from national clinical practice guidelines and the extent of guideline adherence. 3. To collate opinions and experiences from a diverse population of parents and carers regarding their understanding of neonatal jaundice and its management, the impact of skin tone and/or ethnicity on jaundice assessment in neonates and the acceptability of the neonatal skin tone tool.
Number of participants	<u>Number of participants</u> A minimum of 560 participants (an estimated 28 participants from each site) will be recruited in order to reach an appropriate total sample size for the quantitative data sections as detailed in Section 10. Much fewer participants will be required for the qualitative data objective, a small group will be included from those in the quantitative section.
Inclusion and exclusion criteria	<u>Study population</u> Participants will be recruited for the primary objectives (quantitative) data collection if they fulfil the following criteria: Inclusion criteria:

	1. Neonates born at ≥ 34 weeks gestation, now between 0-14 days postnatal age 2. Inpatients on any ward providing postnatal care excluding the neonatal unit or paediatric ward 3. Undergoing first objective assessment of bilirubin level for any reason (i.e. targeted screening, suspected jaundice by healthcare professional, suspected jaundice by parent / carer, poor feeding, any other clinical indication) 4. Age of parent/ carer ≥18 years Exclusion criteria: 1. Readmission from the community 2. Parent/carer opted out of the study 3. Any medical condition known to affect skin colour e.g. cyanotic heart disease or widespread skin condition Participants will be recruited for Secondary Objective 3 (qualitative) data collection (survey and / or focus groups or semi-structured interviews) if they fulfil the following criteria: Inclusion criteria: 1. Parent/carer of neonate eligible for inclusion into quantitative data collection section of study (even if they have opted out of quantitative data collection). 2. ≥18 years of age Exclusion criteria: 1. Has not provided consent for participation in the survey and / or focus groups or semi-structured interviews.
Statistical methodology and analysis	A linear mixed model, with skin tone and confounders as fixed effects and hospital as a random effect will be used for Primary Objective 1. 6 will be used for Primary Objective 2. Sample size calculations and a detailed statistical analysis plan, including Secondary Objective 1 can be found in Section 10. Data collected for Secondary Objective 2 consists of web-based survey responses regarding local practice from each site, as well as any available guidelines and relevant information leaflets. A narrative synthesis will be conducted of their content. A thematic content approach will be used to analyse qualitative data collected for Secondary Objective 3. Qualitative manuscripts will utilise the Consolidated criteria for reporting qualitative research (COREQ) checklist.
Study duration	The total anticipated time for the study is 18 months, of which approximately the first 9 months will include local site approval processes

	and data collection, followed by a 9 month period of analysis and preparation for dissemination (see Gantt chart attached for further detail). The expected project milestones are detailed as follows: Milestone 1: Study protocol and documentation finalised and approvals in place. *Outputs*: Parent/carer pre-study survey, parent/carer representatives, IRAS form, REC approval, sponsorship approval, local R&D approvals at participating sites. Milestone 2: Trained study leads in place at each participating site. *Outputs*: Live and recorded training webinars on study methodology including data collection tool with log of training record. Milestone 3: Data collection for clinical data. *Outputs*: Local held study logs, completed pseudonymised data entry into REDCap data collection tool. Milestone 4: Qualitative data collection. *Outputs*: Survey responses and semi-structured interviews or focus groups. Milestone 5: Data analysis. *Outputs*: Statistically valid quantitative results. Descriptive summary and thematic analysis of qualitative findings. Milestone 6: Study write-up and dissemination of findings. *Outputs*: Publication of results in peer reviewed journals, presentation of results in regional and national conferences/meetings, dissemination of results to relevant patient groups and wider public.

5. Introduction

5.1. Background

Jaundice is one of the most common conditions affecting newborns in the first weeks of life[1]. The consequences of delayed recognition and treatment of jaundice can be devastating; kernicterus is an avoidable condition that causes lifelong neurodisability if hyperbilirubinaemia is not promptly treated[2]. A 2020 UK-based study found that infants from Black, South Asian or other ethnic groups were at a disproportionate risk of developing this complication, making up 50% of all cases of kernicterus despite representing only 25% of live births[3]. Another study based in the UK and Ireland in 2007 found an association between ethnic minority origin and severe hyperbilirubinaemia.

The recent NHS Race and Health Observatory review of neonatal assessment and practice in Black, Asian and minority ethnic newborns highlights the potential for bias in the assessment of jaundice in neonates with darker skin tones [4]. It recommends several areas for further research, including a better understanding on the level at which jaundice is visible, particularly in darker skinned neonates, and further investigation into the level at which a transcutaneous bilirubinometer (TcB) reading should be followed up by a serum bilirubin (SBR). The report also highlights that ethnicity does not correlate well with neonatal skin tone [4].

The updated 2023 NICE guidance on neonatal jaundice assessment and management undertook a literature search for papers relating to use of TcB in babies of different skin tones [5]. Only two studies were identified that compared the relationship of TcB and SBR measurements in neonates of multiple skin tones and/or ethnicities. Maya-Enero et al used the Neomar skin colour scale to compare TcB-SBR correlation in neonates of four different skin tone groups [6,7]. The study found increased variance with darker skin tones. However, of a sample size of 1359, only 23 babies were in the darkest skin tone group. Furthermore, this was a single site study and multiple comparison points from the same participants were included in the analysis, limiting internal and external validity. A second study conducted by Starowicz et al included 201 mostly premature neonates[8]. They found that TcB overestimated bilirubin and was less precise in non-caucasian babies. This study is limited by sample size and the lack of defined skin tone groups - the study instead relies on the broad ethnicity categories of caucasian vs non-caucasian.

5.2. Rationale

The recent NHS Race and Health Observatory review of neonatal assessment and practice in Black, Asian and minority ethnic newborns highlights the potential for bias in the assessment of jaundice in neonates with darker skin tones[4]. While multiple factors are likely to contribute to this, the failure to effectively detect jaundice in darker skinned neonates may play a role. In clinical practice, visual assessment remains a common indication for further jaundice investigations (e.g. TcB or SBR). The relationship between neonatal skin tone and jaundice assessment and diagnosis needs to be further explored.

Our first primary objective is to assess the level of first bilirubin measurement in neonates of different skin tones. This will enable us to determine if neonates with darker skin tones are only being assessed for jaundice once they have reached a higher bilirubin level, compared to lighter skinned neonates.

The second primary objective is to evaluate the agreement between TcB and SBR measurements in neonates of different skin tones.

During protocol development, parents and carers of infants in a range of London boroughs were invited to complete a survey to explore the need for the study including an exploration of parental experiences and concerns related to jaundice assessment in the context of different ethnic and racial backgrounds. Survey results represented a wide range of self-identified ethnic backgrounds and a significant proportion felt that their baby's ethnicity impacted their jaundice assessment, with a variety of reason why this might have been. We have used the results to inform protocol development in a number of ways. For example, to formulate focus group and semi-structured interview themes. Parent representatives also agree that the rationale for our study is well founded and the answers to the questions we have posed, will be valuable in the improvement of care for babies and families of all backgrounds.

5.3. Risks / benefits

This is an observational study whereby the majority of data collected is part of routine care, and is anticipated to be very low risk.
The aim of the study is to improve healthcare professional assessment of jaundice in babies of all skin tones, reducing race-related health inequalities. Our study may also provide preliminary data for larger national studies used to inform wider practice in the UK. This study will improve the knowledge gap around why darker skinned babies are at higher risk of severe jaundice and its consequences. In addition, the study will contribute to the evidence base around the utility of non-invasive diagnostic methods (transcutaneous bilirubinometry) for neonatal jaundice. These conclusions will indirectly be helpful to a wide community of families.

Anticipated risks centre around acceptability of the skin tone tool use and concerns raised by parents or carers. We have therefore incorporated patient and public involvement (PPI) from the study's inception, allowing these psychological and sociological aspects to be built-into the study design, and ensure maximal acceptability.

There is a risk of insensitive language use and subsequent parental distress when discussing babies' natural skin tones or colour and the use of the tool. To mitigate this we have conducted a pre-study parental survey where parents gave opinions on acceptable language use and the challenges they have faced when talking about their baby's skin colour with healthcare professionals. Our findings have been incorporated into the phrasing of our parent information sheet and will inform the training we give to those involved in data collection and the language used in the survey and focus groups/ semi-structured interviews.

In addition, a feedback form link will be included in the participant information sheet (PIS), provided when enrolling a baby in the study, which will allow parents and

carers to raise any negative experiences of their interaction with research staff. While responses are anonymous, these will be monitored in real-time, enabling us to respond rapidly by updating the training of the data collection staff.

Our preliminary survey has also helped ensure that language used in the PIS is clear and easily understandable, for all levels of literacy. It will be professionally translated into the languages most relevant to the study population and local site translation services will be used to aid discussions around the opt-out consent process for quantitative data collection as well as consenting for the parent survey and focus groups/ semi-structured interviews.

The risk of data breach will be minimised by entering pseudonymised data into an encrypted data collection tool (REDCap) with data held within QMUL with our data Safehaven. Data entered here will not be linked to any participant-identifiable information. Parent survey responses will also be held in the encrypted NHS Microsoft 365 Forms platform and no patient identifiable data will be collected. Parent focus group/ semi-structured interview transcripts will be securely stored and only accessible to study teams for thematic analysis.

If the study enrolment happens as planned, there should be no delay in receipt of standard of care. However, should there be a misunderstanding between the midwifery and medical staff, there is a very small risk routine care would be delayed. This will therefore be highlighted very clearly in study team training to minimise this risk and ensure any clinical need is prioritised over study enrolment.

There is a risk that given the unblinded nature of the study, health care professional (HCP) perception of need for jaundice testing would be affected. We do not anticipate the number of jaundice tests at each site to increase due to participation in the study. However, we appreciate that the presence of an ongoing study may change healthcare worker behaviour, to minimise this the full details of the study will only be discussed with local study leads, who will not be the healthcare workers identifying patients for investigation for jaundice on data collection days.

6. Study objectives

6.1. Primary objectives

1. To assess the level of the first bilirubin measurement in neonates of different skin tones.
2. To assess the relationship between transcutaneous bilirubin (TcB) and serum bilirubin measurements (SBR) in neonates of different skin tones.

6.2. Secondary objectives

1. To investigate immediate management of neonates of different skin tones undergoing assessment for jaundice; primarily length of admission and need for interventions including phototherapy and exchange transfusion.
2. To review the range of existing local guidelines relating to the management of neonates with jaundice, how these guidelines vary from each other and from

national clinical practice guidelines (such as NICE Jaundice in newborn babies under 28 days Clinical guideline [CG98]) and the extent to which they are being adhered to.
3. To collate opinions and experiences from a diverse population of parents and carers regarding their understanding of jaundice in neonates and its management, the impact of skin tone and/or ethnicity on jaundice assessment in neonates and the acceptability of the neonatal skin tone tool.

6.3. Primary endpoints

1. Absolute value of first bilirubin measurement in neonates of different skin tones
2. Value of first bilirubin measurement relative to NICE phototherapy / exchange transfusion treatment lines in neonates of different skin tones
3. Age of neonates of different skin tones at first bilirubin measurement
4. Indication for bilirubin assessment in neonates of different skin tones

[Assessed through data collected by local teams during prospective data collection]

6.4. Secondary endpoints

1. Diagnostic methods used to assess jaundice in neonates of different skin tones
2. Immediate management of neonates following jaundice assessment

[Assessed through data collected by local teams during prospective data collection]

3. Number of clinical practice guidelines used and variance between guidelines

[Assessed through data collected in pre-study survey of local leads at each site]

4. Acceptability of a validated neonatal skin tone tool in a diverse population of parents and carers
5. Parent and carer understanding of neonatal jaundice
6. Parent and carer opinions and experiences of the impact of skin tone and/or ethnicity on jaundice assessment in neonates

[Assessed through data collected in parents/carer completed surveys and through focus groups and semi-structured interviews]

7. Study population

The annual number of deliveries per NHS Trust in England ranged from 3,000 to 13,000 in the year 2022 to 2023[9]. NICE guidance recommends that all newborn babies are examined for jaundice at every opportunity, especially in the first 72 hours[5]. If jaundice is suspected, a bilirubin level should be measured. This is primarily done by midwives either in the community or in a secondary care setting. While exact guidelines vary within secondary care settings, TcB is commonly used in neonates over 24 hours of age who visibly appear jaundiced or meet a risk factor for jaundice[1]. TcB measurements within a certain threshold of the phototherapy treatment line should then undergo SBR testing[5]. As jaundice affects approximately

60% of term newborn babies, sufficient numbers of patients are expected to meet study inclusion criteria during a short timeframe[5].

7.1. Inclusion criteria

Participants will be recruited for the Primary Objectives (quantitative) data collection if they fulfil the following criteria:

1. Neonates born at ≥ 34 weeks gestation, now between 0-14 days postnatal age
2. Inpatients on any ward providing postnatal care excluding the neonatal unit or paediatric ward
3. Undergoing first objective assessment of bilirubin level for any reason (i.e. targeted screening, suspected jaundice by healthcare professional, suspected jaundice by parent / carer, poor feeding, any other clinical indication)
4. Age of parent/ carer ≥18 years

Participants will be recruited for Secondary Objective 3 (qualitative) data collection (survey and / or focus groups / semi-structured interviews) if they fulfil the following criteria:

1. Parent or carer of neonate eligible for inclusion into the quantitative data collection section of study (even if they have opted out of quantitative data collection).
2. ≥18 years of age.

7.2. Exclusion criteria

Exclusion criteria for the Primary Objectives (quantitative) data collection:

1. Readmission from the community
2. Parent/carer opted out of consent for the study
3. Any medical condition known to affect skin colour e.g. cyanotic heart disease or widespread skin condition
4. Enrollment in a competing and/or overlapping study or trial anticipated to alter in any way data collected in this study

Exclusion criteria for Secondary Objective 3 (qualitative) data collection (survey and / or focus groups / semi-structured interviews):

1. Has not provided consent for participation in the respective section (survey or group).

7.3. Vulnerable participant considerations

The PI is responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence. This study is low risk with minimal deviation from standard care. Participation is based on an opt-out consent model with no change to standard clinical care for patients who do not participate. If a GCP-trained individual providing the explanation of the study

has concerns about the capacity of the parent or carer to understand the study, the participant will not be enrolled.

8. Study design

This is a prospective multicentre observational study utilising the London REACH (Research Evaluation and Audit for Child Health) Network. It will investigate detection of jaundice in neonates of different skin tones, in a clinically relevant population.

The REACH Network has a successful track record in running high quality, multi-site studies with significant outputs with trainee and consultant leads in 26 London Hospitals where routine postnatal care is provided. This study will aim to recruit patients in the majority of these, which may include:

- Whipps Cross Hospital (Barts Health NHS Trust)
- Newham Hospital (Barts Health NHS Trust)
- Royal London Hospital (Barts Health NHS Trust)
- Queen's Hospital (Barking, Havering and Redbridge University Hospitals NHS Trust)
- North Middlesex University Hospital (North Middlesex University Hospital NHS Trust)
- Homerton University Hospital (Homerton University Hospital NHS Foundation Trust)
- Royal Free Hospital (Royal Free London NHS Foundation Trust)
- Barnet General Hospital (Royal Free London NHS Foundation Trust)
- University College London Hospital (University College London Hospitals NHS Foundation Trust)
- Whittington Hospital (Whittington Health NHS Trust)
- Chelsea and Westminster Hospital (Chelsea and Westminster Hospital NHS Foundation Trust)
- West Middlesex Hospital (Chelsea and Westminster Hospital NHS Foundation Trust)
- St Mary's Hospital (Imperial College Healthcare NHS Trust)
- Norwick Park Hospital (London North West University Healthcare NHS Trust)
- Queen Charlotte's and Chelsea Hospital (Imperial College Healthcare NHS Trust)
- Hillingdon Hospital (The Hillingdon Hospitals NHS Foundation Trust)
- Evelina Children's Hospital (Guy's and St Thomas' NHS Foundation Trust)
- St George's Hospital (St George's University Hospitals NHS Foundation Trust)
- Kings College Hospital (King's College Hospital NHS Foundation Trust)
- Princess Royal University Hospital (King's College Hospital NHS Foundation Trust)
- Kingston Hospital (Kingston Hospital NHS Foundation Trust)
- Lewisham University Hospital (Lewisham and Greenwich NHS Trust)
- Queen Elizabeth Hospital Woolwich (Lewisham and Greenwich NHS Trust)
- Croydon University Hospital (Croydon Health Services NHS Trust)
- Queen Mary's Hospital for Children, St Helier Hospital (Epsom and St Helier University Hospitals NHS Trust)
- Epsom General Hospital (Epsom and St Helier University Hospitals NHS Trust)

Following initial sample size calculations (detailed in Section 10) it has been estimated that a total of 560 participants will need to be recruited, to adequately power the study's Primary Objectives 1 and 2. Therefore, we will aim to recruit a

minimum of 28 participants at each site. An initial recruitment window will aim to recruit 10 participants per site. If there is insufficient recruitment to particular skin tone groups, recruitment windows can be reopened in centres where recruitment of participants of that group is most likely.

Data collection periods may need to be staggered according to the timings of individual Trust R&D approval processes. The total anticipated time for the study is currently 18 months, of which approximately the first 9 months will include local site approval processes and data collection, followed by a 9 month period of analysis and preparation for dissemination (see Gantt chart attached for further detail).

Study processes during prospective data collection phase

Potentially eligible neonates will be identified by postnatal area healthcare professionals and REACH/BiliNEST local study team members will determine their eligibility. The research team at each site will consist of the local lead study team member and a number of additional data collectors who have undergone training, all of whom are paediatric resident doctors as part of the direct care team. These individuals will review whether or not these neonates meet the eligibility criteria, and approach the birthing parent to ask if they are happy to discuss a research study. The number of participants deemed ineligible and the reason for exclusion will be documented. The study process and opt-out consent model will be explained verbally, and patient information leaflets will be provided in English or in the most relevant language available.

Local data collectors will receive an SOP detailing the introductory conversation aims with parents / carers, in particular, to be clear that there will be no detrimental consequences to them or their child if they opt out. A filmed, scripted example of an introduction will be included, that uses sensitive, non-coercive language; the script of which has been vetted by our PPI group. In addition, all data collectors will have completed Good Clinical Practice training, which includes the principles of appropriately obtaining informed consent and will have attended a training session on study processes.

The data collected from the parent/carer is listed in Table 1. The only data collected from participant examination is skin tone / colour group. Neonates will undergo a visual inspection by local study team members within twelve hours of their first bilirubin measurement and then categorisation into one of the four skin colour groups. We recognise that babies may be naturally lighter or darker than those depicted in the skin tone tool groups. When this is the case, babies will be assigned to the group closest to their natural skin colour e.g. for a baby who has a skin colour darker than group 4, they will be included within group 4. All study team members will be trained in the use of the tool to ensure the use of acceptable language and to minimise inter-user variability.

During quantitative data collection periods, all eligible neonates undergoing assessment for jaundice will be considered for inclusion, as identified by postnatal area staff. Parents will be approached and given verbal and written (PIS) information about the study. If, after further consideration, the participant meets all inclusion

criteria and no exclusion criteria, and parents do not object, they will be enrolled to participate.

Within the PIS there will be links for the parents and carers to additionally consent for inclusion in the qualitative sections of the study. These will also be verbally explained at the time of enrollment above, and an opportunity given for questions. If participants meet inclusion criteria and no exclusion criteria, they will be enrolled into these sections respectively.

Data Collection Methods

1. **Quantitative data collection**

Data will be collected on predetermined days on the postnatal areas of each participating site. Suitable days will be identified by the local lead at each site to fit with availability of study team members. Data will be collected by trained members of our research team from parents of participants, clinical records and healthcare professionals including nursery nurses and midwives.

The following data will be collected:

Table 1: All datapoints collected for Primary Objectives 1 and 2

Datapoint	**Source**	**Collection timepoint**
Demographic details and baseline data		
Eligibility confirmation	Medical record and/or direct questioning of parent/carer	Enrollment
Date of birth (dd/mm/yyyy)	Medical record	Enrollment
Time of birth (hh:mm)	Medical record	Enrollment
Gestational age (weeks + days)	Medical record	Enrollment
Birthweight (g)	Medical record	Enrollment
Ethnicity of birthing parent (recorded)	Medical record	Enrollment
Ethnicity of birthing parent (reported)	Direct questioning of parent/carer	Enrollment
Ethnicity of 2nd biological parent (if known)	Direct questioning of parent/carer	Enrollment
Index of Multiple Deprivation (as calculated by postcode of birthing	Medical record	Enrollment

parent)		
Need for translator	Direct questioning of parent/carer	Enrollment
Jaundice and skin tone assessment		
Feeding method[a]	Direct questioning of parent/carer	Enrollment
Skin tone as per skin tone tool[b]	Skintone assessment by study team member	Enrollment
Indication for jaundice assessment[c]	Medical record and/or HCP that identified eligible participant	Enrollment
TcB measurement[d]	Medical record and/or HCP that identified eligible participant	Enrollment
Serum bilirubin[e]	Medical record and/or HCP that identified eligible participant	Enrollment
Immediate management plan[f]	Medical record	Enrollment
Retrospective		
Duration of admission	Medical record	14 days
Location of admission	Medical record	14 days
Treatment administered[g]	Medical record	14 days
Feeding at discharge[a]	Medical record	14 days
Investigation results[h]	Medical record	14 days
Has the participant been diagnosed with G6PD deficiency and/or haemolytic disease of the newborn (HDN)	Medical record	14 days

[a] Exclusively breastfeeding, Mixed feeding, Exclusively formula feeding
[b] 1, 2, 3 or 4 as per Maya-Enero et al[6].
[c] Visibly jaundiced (parent/carer noted), visibly jaundiced (HCP noted), risk factors, routine, unwell, incidental
[d] Role of staff member performing measurement, Value and units, Location on body, Brand and model of machine, Time of measurement, Date of measurement
[e] Role of staff member performing measurement, Value and units, Value relative to treatment line (micromol/L above/below line), Type of SBR (blood gas, lab, spun bili),

Time of measurement, Date of measurement
[f]No intervention, feeding plan implemented (e.g. not specified, breastfeeding support, top ups), repeat bilirubin assessment indicated at a later time point (with time point specified), commence single phototherapy, commence double phototherapy, admit to NICU
[g]Received IVIG, received exchange transfusion
[h]Which of the following investigations were performed and what were their results: DAT, G6PD, blood cultures, participant blood group, birthing parent's blood group.

2. Qualitative data collection: parent survey and focus groups / semi-structured interviews

Qualitative data collection tools will include a parent / carer survey and focus groups and/or semi-structured interviews to collate opinions and experiences around the assessment and management of neonatal jaundice. Themes around the impact of neonates' natural skin tone and / or ethnicity on jaundice assessment and the acceptability of different methods of assessment will be explored and compiled.

These tools will be optional extra sections of the study which will be signposted to, both verbally and written within the parent information sheet, at the point of enrollment into the qualitative data section. Links within the PIS will take parents to a secure web-based survey platform containing an electronic consent form for this survey. Separate links will provide the additional option to sign up to parent focus groups or semi-structured interviews, with a separate electronic consent form for recording of sessions.

The survey will include multiple choice and free text questions (See Table 2).

Focus groups will include 4-6 consenting participants and will run on approximately 2 occasions. Senior study leads will guide appropriate content for discussion and parent representative leads will help to facilitate groups.

Semi-structured interviews will run for 30-45 minutes and be recorded after consent. Senior study leads will guide appropriate content for discussion and parent representative leads will help in the inclusion of particular themes.

Themes addressed will include: Understanding of jaundice and experiences of assessment; Interactions between natural skin colour / race / ethnicity and the assessment of jaundice; Opinions on current jaundice guidelines (from local to international); Empowering parents: Parental education on jaundice, its detection and the deteriorating infant (in view of the RHO report recommendation); Opinions on changing practice.

One recommendation from the Race and Health Observatory report was the need for an urgent review and update of written materials given to parents, around detecting jaundice and a deteriorating infant. Therefore this has been included as one of our themes. In addition, a recent paper highlighted the current differences between national and international guidance on the assessment and management of neonatal jaundice[10]. These broad principles will be introduced to parents with short relevant excerpts to generate a discussion on their opinions of different approaches (see Appendix 3 for Focus Group and Semi-Structured Interview Framework).

Table 2: Datapoints collected for Secondary Objective 3

Datapoint	Source	Collection timepoint
Parent and carer survey		
Eligibility confirmation	Microsoft Forms consent	Time of survey completion
Participant identifier	Microsoft Forms	Time of survey completion
Section 1: Experience of Jaundice detection and the Impact of Skin Tone		
What do you understand by the term “newborn jaundice”?[a]	Survey	Time of survey completion
How would you rate your experience of having your baby assessed for jaundice?[c]	Survey	Time of survey completion
What led you to give that rating?[a]	Survey	Time of survey completion
Was there anything that concerned you about how your baby was tested, treated or how you were kept informed, or not?[b]	Survey	Time of survey completion
(If yes) Please tell us more about your answer.[a]	Survey	Time of survey completion
Have you had any other experiences of newborn jaundice?[a]	Survey	Time of survey completion
(If yes) Tell us briefly about this.[a]	Survey	Time of survey completion
Was there anything that concerned you about how the baby was tested, treated or how you were kept informed, or not?[b]	Survey	Time of survey completion
(If yes) Tell us briefly about this.[a]	Survey	Time of survey completion
Section 2: Perception of care and communication		
Were you given any information or guidance by healthcare professionals on how to look for signs of jaundice in your baby?[b]	Survey	Time of survey completion
(If yes) What type of information or guidance did you receive?[b]	Survey	Time of survey completion
(If yes) Did this include an explanation of how your baby’s natural skin tone might affect signs of jaundice?[b]	Survey	Time of survey completion
(If yes) Did this include pictures of jaundice in a baby that matched your baby’s natural skin tone?[b]	Survey	Time of survey completion

(If yes) Do you feel confident in looking for signs of jaundice in your baby after receiving this information?[c]	Survey	Time of survey completion
Whom would you first approach for advice if you were concerned your baby might have jaundice?[b]	Survey	Time of survey completion
How and when would you approach a healthcare provider to check your newborn baby for jaundice?[a]	Survey	Time of survey completion
Section 3: Recommendations		
What are your views on how health professionals currently identify jaundice? Are there any aspects you think could be improved?[a]		
What is one thing you would like healthcare professionals to understand better about identifying jaundice in babies with different skin tones?[a]		
Section 4: Demographic information		
Self-identified ethnicity of participant [b]	Survey	Time of survey completion
How many children (including this baby) have you had?[b]	Survey	Time of survey completion
[a]Freetext answer. [b]Multiple choice answer. [C] Likert scale.		

3. Guideline and local practice information (Secondary Objective 2)

Local leads at each participating site were invited to complete a web-based survey regarding local practices with regards to jaundice assessments in neonates. Local guidelines and information leaflets, where available, were submitted to the REACH network for further narrative analysis. Information extracted from these guidelines will focus on mentions of skin tone, use of routine jaundice screening, thresholds to perform SBRs based on TcB readings, deviation from national guidelines, and availability of community jaundice assessments and/or treatment.

Data Entry Methods

Skin tone and clinical data collected from each participant will be recorded via a Case Report Form (CRF) and stored in a secure database (REDCap). Responses from the parent survey will be collected anonymously onto the secure NHS Microsoft 365 Forms web-based platform, which has routinely been used in other studies. Parent focus group and interview data will be recorded and transcriptions will be securely stored for data extraction to create a narrative summary.

9. Study procedures

Opt-out Consent (Primary Objectives and Secondary Objective 1):

- An opt-out consent model will be used for the primary objectives. This means that all eligible participants will be enrolled unless either of the parents / carers actively opt out. However, agreement from one parent is sufficient if the second parent is not present.
- A verbal and written explanation of the study will be provided, explaining the study objectives, procedures, risks, and benefits alongside the opt-out consent model.
- The written information will be available in a range of languages appropriate to the local population for each site[11].
- If required, a professional translator will be used to translate all relevant information, either in person or telephonically.
- Parents will be given a minimum of 15 minutes to consider the information and to ask questions as required, before study data is collected. The PIS will contain details on how to contact the study team to opt-out at any later stage.
- If parents opt-out of inclusion in the study, there will be no impact on the routine care provided

Informed consent for qualitative data (Secondary Objective 3):

- At the time of enrollment into quantitative data collection, the research team member will verbally explain the optional additional parent survey and parent focus group and/or semi-structured interview enrollment, giving parents the opportunity for further questions.
- The participant information sheet will include a link to the parent survey and an electronic consent form, as well as a separate link to further information on focus groups and / or semi-structured interviews and how parents can sign up to these.
- Electronic consent for the recording of focus group or semi-structured interview transcripts will be obtained at the start of the groups or interviews.
- Parents and carers can withdraw their consent to participate and for their data to be stored and used at any time. It will be made clear that their medical care will not be affected either way.

Screening and recruitment:

- On data collection days, staff members carrying out jaundice assessments in relevant inpatient areas will be notified and asked to alert the research team when any neonates are undergoing their first TCB or SBR
- Standard clinical care will not be delayed for enrollment
- Identification of potential eligible babies will occur via a written identification table in postnatal areas. Outcomes, i.e. included or excluded, and reasons for exclusion will be noted in the infant's clinical record.
- The research team at each site will consist of the local lead and a number of additional data collectors who have undergone training. These individuals will review whether or not these neonates meet the eligibility criteria, and approach the birthing parent to discuss the study if eligible
- Study data will be collected in participants where all eligibility criteria are met

Study procedure:

- The neonate's skin colour will be assessed as per the Neomar neonatal skin colour scale[6] and categorised into one of four groups. We recognise that babies may be naturally lighter or darker than those depicted in the skin tone tool groups. When this is the case, babies will be assigned to the group closest to their natural skin colour e.g. for a baby who has a skin colour darker than group 4, they will be included within group 4.
- Additional data will be collected at two timepoints: enrollment and 14-days
- A full list of data collected including the data source and timepoints can be found in Table 1.
- Parents will be given the option to complete a web-based survey about their understanding of jaundice in neonates and its management and the impact of skin tone and/or ethnicity on jaundice assessment in neonates.

Procedure for collecting data:

Skin colour assessment:
- The skin colour assessment will be performed in a well-lit room as per skin tone tool recommendations
- The neonate will be undressed - ideally fully, or at a minimum down to the nappy depending on parental preference.

Other clinical data:
- The remaining data (Table 1) will be collected from paper or electronic patient records, or on direct questioning of parent/carer and entered into our CRF
- The only data point collected pertaining to the second parent will be their ethnicity, which will not be identifiable. This is routinely collected as part of the infant's medical history. If the birthing parent or second parent agrees to share this on questioning, it will be included.

Survey data:
- Within the participant information sheet, a QR code and written link will be provided for parents to access and fill in the web-based survey.

Focus groups and semi-structured interviews:
- The option to attend a parent and carer focus group or semi-structured interview to further explore parental perceptions and experiences of jaundice assessment will be signposted within the information sheet and at the end of the above survey.
- Parents / carers who are interested will be contacted via email. Travel, childcare and time costs will be reimbursed as per QMUL guidelines.

Laboratory assessments:

No additional laboratory assessments will be carried out on participating neonates by the research team. SBR measurements will only be done by the normal clinical team as part of routine clinical care.

Participant withdrawal:

Participants may withdraw from any section of the study without reason up to 1 month after data collection. Local data collectors will be able to remove the corresponding data from the study database. A replacement participant will be sought at that site if prospective data collection is still ongoing at that site at the time of withdrawal.
At the end of the survey participants will be prompted to retain the initials they used and the date they submitted their responses, if they would like to remove their data at a later date, in order for us to identify their response and remove it from the database,

End of Study Definition:

The end of the study will be the date of the last visit of the last participant in the study.

10. Statistical considerations

10.1. Sample size

We provide two sample size calculations for the two different methods used to address the Primary Objectives: linear mixed effects models (Objective 1) and Bland-Altman (Objective 2).

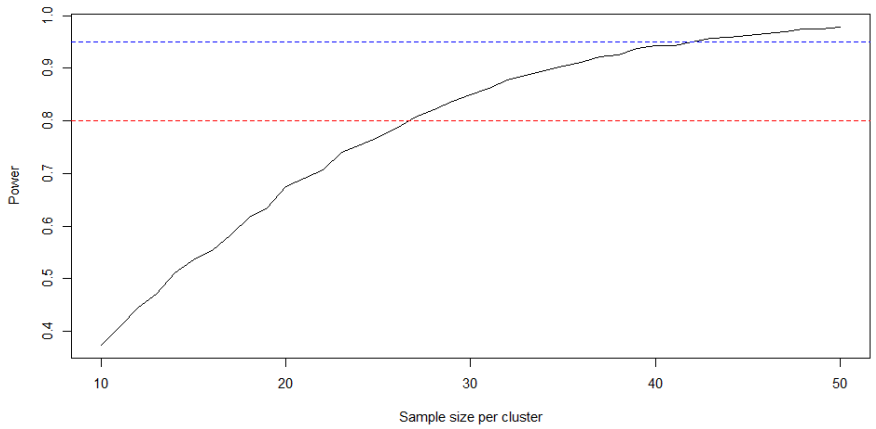
Primary Objective 1

We will be using a linear mixed effects model, where the confounders will be adjusted for as fixed effects, and hospitals will be fitted as a random effect. Due to the complexity of the model we will be using, the optimal method of calculating the sample size requirement *a priori* is with simulation, using *simr* in R[12]. We use the following simulated dataset:

- Exposure - Our exposure, skin tone, will be on 4 levels, with 1 being the lightest and 4 the darkest[6]. No recent research on skin tone within London has been found, therefore we refer to the latest UK census results for ethnicity[13]. For a conservative estimate, we will simulate the data for ethnicity that we would expect in London to act as a proxy for skin tone, as with the 6 categories of ethnicity (White (53.8%), Black (13.5%), Asian (20.7%), Mixed (5.7%) and Other (6.3%)). Therefore we simulate data with probability 50%, 20%, 20% and 10% for tones 1,2,3 and 4, respectively.
- We assume that we will have 20 hospitals collecting data, therefore we have 20 clusters to be a random effect
- The outcome will be simulated depending on skin tone and age. Age will be uniformly distributed between ages 0 and 96 hours. Bilirubin mean will be simulated according to the following formula:
    - Bilirubin (μmol/L)=2.6*age (hours)+60+20*skin tone+60 with standard deviation 10. The coefficient and intercept, 2.6 and 60 respectively, is to fit the line where babies begin to need phototherapy according to the NICE jaundice treatment threshold graphs[5].

We wish to achieve an effect size of 10 μmol/L for skintone 2 compared to skin tone 1, 20 μmol/L for skin tone 3 compared to skin tone 1, and 30 μmol/L for skintone 4

compared to 1. We perform 100 simulations for each simulated cluster size (between cluster sizes of 10 and 50 neonates), and estimate the average power achieved. Assuming a 95% confidence interval (CI), we can plot the number in each cluster against the estimated power.



If we were to assume a power of 80% at minimum, we would require each hospital to contribute at least 28 participants (power is 78% at 27 participants and power is 80% at 28 participants). However, estimating *a priori* is making strong assumptions on the data and we have not accounted for missing data. We recommend that once the study has recruited a minimum of 10 participants in each cluster (hospital), monthly updated target study sample sizes are to be calculated based on the data accumulated so far.

Primary Objective 2

We approximate a sample size needed for Bland-Altman plots[14]. We calculate the minimum sample size needed to detect a difference. A prior study found the following measurements[6]:

	Mean [SD] (mcmol/L)
Colour 1	106 [43]
Colour 2	108 [38]
Colour 3	113 [38]
Colour 4	145 [34]

From this, we take a mean difference of 10 to be our estimated effect size. From above, we take the two largest standard deviations for a cautious estimate of the standard dedication of difference (SD=$\sqrt{43^2 + 38^2} = 57.4$). We set our targeted clinical agreement limit at 145 mcmol/L. Under these assumptions, a sample size of 80% requires 140 study participants , which from above we should easily exceed.

Secondary Objectives

The sample size for Secondary Objective 1 will be guided by that of the Primary Objectives as detailed above.

The sample size for Secondary Objective 2 will be limited to a maximum of 27 neonatal units within the London Neonatal Operational Delivery Network, as listed above.

Secondary Objective 3 will include 2 qualitative data groups. The parent survey, focus groups and semi-structured interview sample sizes will be limited to the number of parent / carer participants eligible for inclusion into the quantitative data section as detailed above. Therefore an approximate minimum of 560 parents will be given the option to register interest for inclusion. A small representative sample of these will be included in focus groups and semi-structured, in depth-interviews.

10.2. Method of analysis

Due to the *a priori* nature of the sample size calculations, these will be redone based on interim data. This is suggested once each hospital has at least 10 participants. Then a readjustment shall be done every two-three months until sample size has been reached for both primary objectives. This will include the use of bilirubin measures, skin tone and age at TcB measurement, but no other data. The statistician will provide the study leads with the updated targets with no other interim analysis. This may reduce or extend study length depending on the targets of both primary objectives.

Data will be analysed on exposure in accordance with the allocation on skin colour scale. We expect limited missing data. If missing data is <5% for any covariate then analysis will be restricted to complete case analysis. Multiple imputation will only be used if missing data is >5% for any category.

All data collated will be presented in summary tables, stratified by skin colour. Continuous data will be summarised in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, when the data are approximately normally distributed.. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic. Categorical data will be summarised in terms of the number of participants providing data at the relevant time point (n), frequency counts and percentages. The number of participants with missing information for a specific variable will be displayed if applicable. Any planned collapsing of categories will be detailed in the SAP text and the data displays. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using non-missing data as the denominator. Confidence intervals (CI) will be presented to one more decimal place than the raw data.

Primary objective 1 will be using a linear mixed model, with skin tone and confounders as fixed effects and hospital as a random effect. The outcomes will be the coefficient difference between baseline skin tone and the other 3, with 95% CI.

Primary objective 2 will use the Bland-Altman to detect differences of measurement between skin tones, stratified by method of how the measurement for how serum bilirubin was taken. The mean of the differences will be provided with 95% CI, along with the IQR of difference with accompanying p-value. The rate of over/under-estimation will also be estimated between different skin tones. Bland-Altman plots will be reported as well as Specificity and sensitivity analyses using Receiver operating characteristic (ROC) curves.

Secondary Objective 1: Primary length of admission differences between skin tone will be compared using survival analysis of time to event data (Kaplan-Meier plot, Cox Proportional Hazards Model). The need for interventions including phototherapy and exchange transfusion will be done using generalised linear mixed models, with outcomes reported as Odds Ratios with 95% CI.

Age of infant at measurement is an important metric and shall be included as a fixed covariate in all models other than Bland-Altman (baseline model). Additionally, IMD and gestational age may be included as additional covariates (adjusted model). However, due to the complex relationship between skin colour and medical intervention, we run the risk of over-adjusting on covariates and inducing collider bias and/or mediators. For example, skin tone may affect what the indication for jaundice assessment was, and this in turn may affect the outcome of bilirubin and if there was a delay for treatment, making it a mediator. With sufficient time, this relationship may be explored to see if different skin tones are affected by how their jaundice is first indicated, which influences clinical guidelines if an association is found between skin tone and indication which in turn affects bilirubin levels.

Secondary Objective 2:
Data collected for Secondary Objective 2 consists of web-based survey responses regarding local practice from local leads at each site, as well as any available guidelines and relevant information leaflets. Information extracted from these guidelines will focus on mentions of skin tone, use of routine jaundice screening, thresholds to perform SBRs based on TcB readings, deviation from national guidelines, and availability of community jaundice assessments and/or treatment. A narrative synthesis will be conducted.

Secondary Objective 3:
Free text answers from the parent survey and transcripts from focus groups and semi-structured interviews will be analysed using a thematic content approach consisting of six steps: familiarisation, coding, generating themes, reviewing themes, defining and naming themes, and writing up[16]. This method will reduce confirmation bias when reviewing data. An inductive approach will be employed during familiarisation, to allow the data to determine themes and a latent approach will be used when analysing the data in order for the coding to consider the subtext and assumptions that may underlie the explicit content of the data. Qualitative manuscripts will utilise the Consolidated criteria for reporting qualitative research (COREQ) checklist[15].

11. Ethics

We will seek ethical approval from the NHS / HSC Research Ethics Committees via the IRAS system. The project IRAS application is currently in progress (identifying number 339043). Local approvals will be sought from each participating hospital site. These applications will be led by the local leads for each trust. Data collection will be started in sites where the project is approved even if we are waiting on approvals for other sites.

Anticipated risks are low but may centre around acceptability of the skin tone tool use and language around race or ethnicity.
Considering results from our pre-study patient and public involvement (PPI) survey, we have clarified the language used to explain the study and skin tone assessment process. As successfully done for this initial survey, we plan to translate all study materials into languages most relevant to the study population (as per the Office for National Statistics data). We further aim to minimise risks of parental distress around these topics including sensitive training for data collectors and maintaining a parent representative as a key part of the team throughout the study. Parents will be offered the opportunity to feedback anonymously when enrolling into the study, allowing them to raise any negative experiences with research staff. Feedback will be monitored and acted on in real time.
Risks of data breach will be minimised by the use of a pseudonymised, encrypted data collection tools including (REDCap) within our data Safehaven and the NHS Microsoft 365 Forms platform.
There is a risk that the consenting process could delay initiation of treatment for a jaundiced baby. It will be clearly stipulated within research team training, that any urgent clinical management is prioritised and carried out simultaneously.
Given the unblinded nature of the study, healthcare professional perception of need for tests could be affected. Study training will emphasise that the overall number of tests carried out should not increase due to a site's participation in this study.
All those working on the study will be GCP trained to minimise risks of harm.

12. Public involvement

As this project focuses on identifying how current neonatal practices contribute to health inequalities, we recognize that families' insights and experiences will be key in understanding current challenges and in planning how to deliver better health outcomes in the future.

We have prioritised patient and public engagement from the project conception, which has allowed study co-production with parent and carer perspectives and priorities at the forefront. As the project is centred around newborn babies, we gathered views from new parents and carers through a web-based scoping survey that included:

- Their understanding of jaundice in the neonatal period, and any previous experience of this
- The impact of their ethnicity on jaundice assessments by healthcare professionals
- How to best explain our project to future participants

- How they would feel about the use of a skin tone tool on their baby, and the language we use around this

The survey was available in 10 languages, to maximise accessibility and reach a diverse audience. Survey links were disseminated via posters and parent whatsapp groups, both through community parent groups and the resident doctor-led REACH network. The network includes local leads at a number of London sites which allowed us to gather insights from parents across Barts Health as well as other London trusts. Please see Appendix 1 for a summary of survey findings.

There are currently three parent representatives within the study team, who are reviewing the initial versions of the study protocol and participant information sheet. They will continue to play a key role in our team throughout the study. A PPI focus group has been held with 5 parents, centred around the Participant Information Sheet and a roleplay of a study team member approaching a parent regarding the study. Feedback was positive and no parent would have opted out of the study. Please see Appendix 2 for a summary of the focus group feedback.

The parent / carer survey, focus groups and semi-structured interviews will be collecting qualitative data on what may be challenging topics and as such, our parent representatives play an important role in ensuring the content of these is as accessible, clear and sensitive as possible. Parents enrolled in the study who would like to feedback or contribute ideas to the study methodology, will have the ability to do so via the feedback link in the participant information sheet.

Parental engagement is crucial in the ongoing study co-production, analysis and dissemination of findings. Representatives will continue to be invited to regular research team meetings and to review amended project protocols to ensure we continue to meet the needs of our study participants. They will be involved in discussions around the analysis of our results in particular when analysing qualitative datasets and considering key themes that have been extracted. Parents will be particularly crucial in guiding the effective publication and dissemination of study findings across both academic and public forums, with the aim to effect improvements in the way we assess jaundice in babies of all backgrounds and skin tones.

13. Data handling and record keeping

13.1. Data management

Study methodology is described in more detail in section 9. On study recruitment days, local leads will inform all postnatal ward staff responsible for jaundice detection to flag potentially eligible patients. During the data collection period, all neonates undergoing their first jaundice investigations will be approached for recruitment. Enrollment processes will not delay routine clinical care. Data on the value of the first bilirubin reading including the diagnostic method(s) used, alongside a number of covariates, will be collected.

Site teams will impute study data into a standardised data collection form using REDCap electronic data capture tools hosted at QMUL on a secure server and accessed via a password protected link on NHS Trust password-secured computers.

Only pseudonymised data will be entered. Age will be entered in hours of life using an online calculator at the point of data entry with no date of birth data being recorded. Deprivation status will be used by entering the postcode locally into a deprivation code calculator and on the collection form only the deprivation code but not the postcode will be entered. Data completeness and validity will be enhanced by making essential data mandatory for submission to REDCap, data validation rules being inbuilt in the database as well as regular incompleteness and discrepancies with any such issues to be resolved through discussion with local teams and on consensus discussion between REACH project leads. Study recruitment logs will be completed contemporaneously with most clinical data collected at recruitment; final diagnosis, management required and relevant test results may be added subsequently.

Qualitative data on carer experience of newborn jaundice will be collected through the parent / carer survey on the NHS Trust Microsoft 365 Forms web-based application. This will be accessed via a link or QR code on the participant information leaflet. No patient identifiable data will be collected here and data will be encrypted. Parent in-person focus groups and semi-structured interviews will be audio-recorded and transcribed for data extraction and thematic analysis. Recordings will not include patient identifiable data and will be stored securely within Microsoft Sharepoint. These sessions will not include specific parent details e.g. name, date of birth, or address. However, data generated may include thematic analysis and quotes which could possibly be identifiable by either study participants themselves or those close to them. While we do not anticipate that this would be identifiable to others, we will warn participants that direct quotes may be used, to ensure transparency.

13.2. Source Data

Site teams will keep a record linking study identifiers to local hospital numbers only for the duration of the study and stored on a local NHS database accessible to the clinical team only.

13.3. Confidentiality

Potential participants will be identified by healthcare staff caring for neonates in postnatal areas. Neonates who meet inclusion criteria and do not meet exclusion criteria will be informed of the study and asked to participate. It will be made clear that their data will be pseudonymised whilst being used for study purposes.

Data will be pseudonymised at the point of collection by the local teams and analysed centrally by the core BiliNEST team. Participant healthcare records will be accessed by local staff to collect only the minimal data required as per the CRF tool. Whilst the QMUL REDCap database will hold the pseudonymised data from all sites, each individual unit will only be able to access their own data. Unique patient identifiers will be used for each patient, with three letters identifying the trust (e.g. RLH=Royal London Hospital, WHI=Whittington Hospital), followed by three numbers from 001. Local project leads will keep a record between pseudonymised study numbers and identifiable data (e.g. the participant's local hospital number), in case there is a need to re-examine the data. No patient identifiable information will leave the local Trust. Data will only be stored on secured password protected Trust

computers. Only pseudonymised data will be shared with the central research team via the encrypted database, RedCAP.

13.4. Record retention and archiving

No physical archiving will be required in light of the opt-out consent process for the quantitative data collection. Consent for qualitative data collection will be obtained electronically and stored on a QMUL-based secure server. Clinical data will be stored on a secure REDCap database, for no longer than 5 years.

14. Safety reporting

Due to the design of this study, no adverse events are anticipated and safety reporting will not occur. We do not anticipate any delay or change to routine clinical care for study participants. Should any clinical concerns be incidentally detected during study assessments, these will be escalated to the relevant clinical team via the normal pathways. For example, should a concern regarding the parental health e.g. a disclosure of low mood, this will be relayed to the midwife caring for the parent. If, for example, the baby is noted to have increased respiratory effort, this will be urgently relayed to the on call team to instigate investigation and management. Should any unexpected safety concern be raised by any member of the study team, this will be escalated to the core study team and CI, and the site clinical management team if appropriate and the site-specific adverse event protocol will be followed.

15. Monitoring and auditing

The Sponsor or delegate retains the right to audit any study, study site or central facility. In addition, any part of the study may be audited by the funders where applicable.

Local site leads will be responsible for on-site monitoring and ensuring that local data collectors are GCP trained and have study-specific training prior to patient recruitment. The study monitoring plan will include periodic source data verification and is to ensure participant safety, data integrity and compliance to the protocol and GCP as well as the UK policy framework for Health and Social Care Research.

16. Study committees

The BiliNEST study management group will consist of the CIs, PIs, statistician, study coordination team and parent representatives. This group will convene for 3-monthly progress meetings. The core study coordination team consisting of the project leads and REACH will meet twice a month during the data collection period.

17. Finance and funding

We have been awarded a Barts Charity Research Seed Grant, which will cover all study-related costs. A summary of projected costings is as follows:

Category	Total

Staff	£0
Materials and Consumables	£12,700
Equipment	£1899
Public and Patient Involvement and Engagement + travel	£14,040
Publications/Dissemination	£4000
Animals	£0
Other	
GRAND TOTAL	**£32,639**

Contact details for our Funding Manager (Natasha Luckhurst) are:
natasha.luckhurst@bartscharity.org.uk

18. Insurance and indemnity

The insurance that Queen Mary has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

19. Dissemination of research findings

We have a number of plans for both academic and non-academic dissemination of research findings.

We anticipate at least three independent publications for submission to peer reviewed journals; a quantitative analysis main results from the primary objectives, the guideline review and a qualitative paper with analysis of the survey data. To further disseminate these we aim to present each of these arms at an appropriate conference e.g. the annual RCPCH conference or international neonatal conferences.

We will offer all study participants the study website details which will be updated with the study progress and results. We will also disseminate our findings on social media. These posts will focus on reaching the wider patient population in an accessible way, and will include summaries of the results from the qualitative branch of our study.

We anticipate that our findings will highlight disparities in care across the region and pave the way to discuss optimal clinical assessment and management of neonates with jaundice that is appropriate for babies of all skin tones. Our regional data may also guide future national studies.

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Appendix 1: Summary of PPI scoping survey

We received 32 responses from parents or carers with experience of postnatal care based within the London region. Many parents / carers understood newborn jaundice to be about “yellowing of the skin” and “elevated bilirubin”. Parents mentioned yellowing of the eyes and problems with the liver as well as a need for it to be treated. Most parents (88%, n= 28/32) had experienced an infant they were caring for, being checked for or diagnosed with jaundice. There was a wide variation of self-identified ethnicity within this group, with 10 distinct ethnic groups as per the standardised NHS categories, and some choosing “any other”. When asked whether they felt the baby’s natural skin tone or ethnic background had any impact on this assessment, roughly a third said yes, a third said no and the remaining third wasn’t sure (36%, 36% and 28% respectively). Themes they raised around this included:

- Feeling healthcare professionals had repeated misplaced concerns about their baby being jaundiced because of mixed race ethnicity;
- Jaundice investigations and treatments not being consented for or explained adequately.
- Baby’s changing natural skin tone in the first days of life, affecting the ease in identifying jaundice.
- Paler babies appeared more jaundiced than they were, so investigated more.
- Difficulties identifying jaundice in some ethnicities over others.

When asked about how parents and healthcare professionals assess babies for jaundice, themes included:

- Many parents are aware that yellowing of the skin and eyes is a sign checked by both parents and HCPs.
- Others did not know how to identify jaundice and there were calls for better explanations and advice for parents on discharge and better trained community staff.
- There were some calls for universal jaundice screening.
- Concerns that the race of the parents or the baby may influence HCP management.
- Concerns over racial microaggressions from HCPs when describing jaundice in mixed race skin tones.

Most parents / carers said they would feel either neutral, comfortable or very comfortable with a healthcare professional using our skin tone / colour tool (94%). 2 parents were uncomfortable with it as they were concerned that the darkest skin tone group would not account for babies with the darkest natural skin tones, therefore missing an important group.

We have recognised this as a limitation of this tool, and noted that the number of darker skin babies in their original cohort was smaller than the lighter groups due to the limited skin colour variation in their original population. However, this is currently the only published validated neonatal skin colour tool, which is valuable seeing that neonatal skin has a notably different appearance from adult skin. There is an appreciable difference between the 4 skin colour groups, and we will be including all babies according to the group closest to their skin tone, as opposed to excluding those who do not perfectly match the pictures in a group. For example, any babies

with a natural skin tone darker than skin colour group 4, will be included within group 4, and any babies lighter than skin colour group 1, will be included within group 1.

Appendix 2: Summary of PPI Focus Group Findings

Collated demographics	
Number of attendees	5
Current age of your youngest baby (in weeks or months)	13 weeks, 3 months, 11 years, 12 weeks
Where was baby born? e.g. Home / Labour ward / Birth centre / Operating theatre	All LW
Estimated days you spent in Hospital (if born in Hospital)	2.5, 8, 2, 209, 3
Was your baby ever checked for jaundice?	All yes
Please choose the best description of your ethnicity: A White - British B White - Irish C White - Any other White background D Mixed - White and Black Caribbean E Mixed - White and Black African F Mixed - White and Asian G Mixed - Any other mixed background H Asian or Asian British - Indian J Asian or Asian British - Pakistani K Asian or Asian British - Bangladeshi L Asian or Asian British - Any other Asian background M Black or Black British - Caribbean N Black or Black British - African P Black or Black British - Any other Black background R Other Ethnic Groups - Chinese S Other Ethnic Groups - Any other ethnic group (please state) Z Not stated 99 Not known	White british, Mixed- any other mixed background, White other, Other ethnic groups- chinese, White british
Please state the ethnicity of baby's other parent? (use list above)	White british, White- any other white background, White other, White british, White british
Willing to be contacted in future about further Patient and Public Involvement and Engagement (PPIE) for this study?	All yes

Study Explanation Roleplay - Initial Reactions

- Parents found the study explanation clear and the communication approach considerate.
- Some parents were unaware that not all babies are checked for jaundice.
- It was suggested that the study team should clarify parents' understanding of their baby's jaundice check at the start of the conversation
- Parents felt flexibility in timing for discussions was important, given the nature of postnatal care.
- All parents felt they understood the explanation

Information Delivery & Materials

- Parents noted overwhelming amount of paperwork at discharge makes it difficult to distinguish key information - make it clear this is for a research study and not part of health records
- Preference for verbal explanations first, followed by written materials.
- Suggestion to minimise reading content and clarify that the provided leaflet is for reference

Skin Tone Tool & Language Use

- Discussion around skin tone tool not covering *all* possible skin tones, worth highlighting we are categorising by closest match and conveying this clearly in PIS and conversation
- Some parents were uncertain about their baby's "natural" skin tone due to jaundice, suggested perhaps "expected skin tone". "Healthy skin tone" not a good alternative due to the connotation of baby being unhealthy.
- Parents agreed that the study team should assign skin tone categories for consistency, but consider how to address situation if parents disagree
- All parents found the language used acceptable and appropriately sensitive

Study Process & Practical Considerations

- Some parents wanted clearer expectations on timing—when assessments happen, how long they take, and who conducts them.
- Suggestion to move the discussion about jaundice to the beginning of the conversation.
- Preferred approach: Inform parents how long they have to read materials and specify how much time further steps will take.
- Need for clearer explanation about what data is collected from medical records, with brief examples to avoid it feeling vague or intrusive.

Participant Information Sheet (PIS)

- Generally well-received: clear, concise, and easy to understand.

- Suggested improvements:
    - Clarify published data will be anonymous
    - Consider translations for non-English speakers.
    - Clearly caveat that skin tone tool does not cover all skin tones
    - Acknowledge that the skin tone tool is not fully representative of all skin tones.
    - Potentially provide a one-page summary with visuals.

Overall Acceptance of the Study

- All participants reported they would not opt out if they were approached for enrollment into this study

Next Steps

- Adjust study materials to address feedback (e.g., clearer explanations, refined language, improved structuring of information).
- Develop a response plan for cases where parents disagree with skin tone categorisation
- Ensure clarity on data collection and timing expectations
- Participants were happy to be contacted for further input during data collection and results dissemination

Appendix 3: focus group and semi-structured interview frameworks

Instruction for facilitators:
The themes and questions below are guides for the discussion. Participants may wish to take the conversation in a different direction, but please ensure that you cover all of the themes listed.

Focus group framework

Introduction for the group:
Thank you for coming today and agreeing to speak with us. Everything we discuss will be confidential. You have kindly agreed for us to make an audio recording and take notes of our discussion so in order to protect your privacy, we ask you not to mention your name (we shall assign you a pseudonym of your choice). We would like to learn a bit more about your experiences with newborn jaundice and how race or ethnicity can affect these.

Theme	Questions	Notes
Understanding of jaundice and experiences of assessment	1. What was / is your understanding of newborn baby jaundice? a. Where did this information come from (e.g. your previous experiences, other family members, friends, own reading, healthcare professional guidance) 2. Tell us about your experiences with jaundice assessment. a. Either personal or when you have been made aware of neonatal jaundice otherwise.	
Interactions between natural skin colour / race / ethnicity and the assessment of jaundice	1. Was there anything that concerned you about how your baby was tested, or not? (e.g. delay in assessment / repeated unnecessary checks / uncertainty about diagnosis etc.) 2. Was there anything that concerned you about how your baby was treated or how you were kept informed, or not? 3. Did anything else contribute to this? (E.g. your healthcare professional's perceived ethnicity, their level of	

	training, culture within the department, institutional racism, racial microaggressions etc.)	
Opinions on current jaundice guidelines e.g. NICE, BAPM, WHO.	Parents will be given excerpts from relevant guidelines regarding the consideration of race and ethnicity when assessing babies for jaundice. 1. What do you think about these recommendations? a. Given variations in guidance- what do you think about these different approaches (e.g. World Health Organisation (WHO) guidance for screening vs National Institute for Clinical Excellence (NICE) guidance not to screen). 2. Do you think any of the content needs to be modified or added to? 3. Do you think the wording is appropriate or should any of it be adjusted? a. Discuss the Race and Health Observatory (RHO) recommendation that all guidelines should explicitly highlight limitations in visual assessment, especially in those from ethnic backgrounds.	

Empowering parents: Parental education on jaundice, its detection and the deteriorating infant (RHO recommendation)	1. Were you given any information/ guidance on jaundice by healthcare professionals before or after your baby was born? a. At which point were you given this? b. When do you think it would have been most helpful? c. Was it helpful / empowering in your parental role? 2. If given written materials, which were you given? a. Were these easily accessible? b. Were they representative of babies from a variety of ethnic backgrounds? 3. Which methods of education / advice did you find most helpful? 4. If you were to co-design written materials for parents, what content would you include and how would they be presented? (e.g. webpages, Apps, online picture banks, videos on assessment etc)	

Opinions on changing practice	Introduce ideas on reducing incidence and late detection of jaundice, particularly in ethnic minorities, from recent papers. Discuss which suggested measures would be most acceptable, from: 1. Earlier home reviews by healthcare professionals e.g. day 3 rather than day 5 (Battersby et al), or standardising the frequency of postnatal reviews (RHO report). 2. Targeted screening for higher risk babies (including ethnic minorities) 3. National jaundice screening 4. Standardising TcB thresholds 5. Better, specific parental education 6. Mobile application development for more accurate detection in all ethnicities (RHO recommendation)	

Semi-structured interview framework

Interview Introduction:

Thank you for coming today and agreeing to speak with us. Everything we discuss will be confidential. You have kindly agreed for us to make an audio recording and take notes of our discussion so in order to protect your privacy, we ask you not to mention your name (we shall assign you a pseudonym of your choice). We would like to learn a bit more about your experiences with newborn jaundice and how race or ethnicity can affect these.

Theme	Questions	Notes

Understanding of jaundice and experiences of assessment	1. What was / is your understanding of newborn baby jaundice? a. Where did this information come from (e.g. your previous experiences, other family members, friends, own reading, healthcare professional guidance) 2. Tell us about your experiences with jaundice assessment. a. Either personal or when you have been made aware of neonatal jaundice otherwise.	
Interactions between natural skin colour / race / ethnicity and the assessment of jaundice	1. Was there anything that concerned you about how your baby was tested, or not? (e.g. delay in assessment / repeated unnecessary checks / uncertainty about diagnosis etc.) 2. Was there anything that concerned you about how your baby was treated or how you were kept informed, or not? 3. Did anything else contribute to this? (E.g. your healthcare professional's perceived ethnicity, their level of training, culture within the department, institutional racism, racial microaggressions etc.)	

Opinions on current jaundice guidelines e.g. NICE, BAPM, WHO.	Parents will be given excerpts from relevant guidelines regarding the consideration of race and ethnicity when assessing babies for jaundice. 1. What do you think about these recommendations? a. Given variations in guidance- what do you think about these different approaches (e.g. World Health Organisation (WHO) guidance for screening vs National Institute for Clinical Excellence (NICE) guidance not to screen). 2. Do you think any of the content needs to be modified or added to? 3. Do you think the wording is appropriate or should any of it be adjusted? a. Discuss the Race and Health Observatory (RHO) recommendation that all guidelines should explicitly highlight limitations in visual assessment, especially in those from ethnic backgrounds.	

Empowering parents: Parental education on jaundice, its detection and the deteriorating infant (RHO recommendation)	1. Were you given any information/ guidance on jaundice by healthcare professionals before or after your baby was born? a. At which point were you given this? b. When do you think it would have been most helpful? c. Was it helpful / empowering in your parental role? 2. If given written materials, which were you given? a. Were these easily accessible? b. Were they representative of babies from a variety of ethnic backgrounds? 3. Which methods of education / advice did you find most helpful? 4. If you were to co-design written materials for parents, what content would you include and how would they be presented? (e.g. webpages, Apps, online picture banks, videos on assessment etc)	

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