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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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ABSTRACT

Introduction

Newborn infants routinely undergo minor painful procedures as part of postnatal care, with infants born sick or premature requiring a greater number of procedures. As pain in early life can have long-term neurodevelopmental consequences and lead to parental anxiety and future avoidance of interventions, effective pain management is essential. Non-pharmacological comfort measures such as breastfeeding, swaddling, and sweet solutions are inconsistently implemented and are not always practical or effective in reducing the transmission of noxious input to the brain. Stroking of the skin can activate C-tactile fibres and reduce pain, and therefore could provide a simple and safe parent-led intervention for the management of pain. The trial aim is to determine whether parental touch prior to a painful clinical procedure provides effective pain relief in neonates.

Methods and analysis

This is a multicentre blinded randomised controlled trial. A total of 112 neonates born at 35 weeks' gestation or more requiring a blood test in the first week of life will be recruited and randomised to receive parental stroking either pre- or post-procedure. We will monitor brain activity (EEG), cardiac and respiratory dynamics, oxygen saturation and facial expression to provide proxy pain outcome measures. The primary outcome will be the reduction of noxious-evoked brain activity in response to a heel lance. Secondary outcomes will be a reduction in clinical pain scores (Premature Infant Pain Profile-Revised), post-procedural tachycardia and parental anxiety.

Ethics and dissemination

The study has been approved by the London – South East Research Ethics Committee (ref:21/LO/0523). The results will be widely disseminated through peer-reviewed publications, international conferences and via our partner neonatal charities Bliss and SSNAP. If the parental tactile intervention is effective, recommendations will be submitted via the NHS clinical guideline adoption process.

Study Status: Commenced September 2021.

Trial Registration: ClinicalTrials.gov NCT04901611; **ISRCTN:** 14135962.

Strengths and limitations of this study

- Petal will be the first randomised controlled trial to investigate whether noxious-evoked brain activity is reduced by pre-procedural parental stroking.
- The trial is based upon published evidence from two mechanistic studies which show a reduction in noxious-evoked brain activity during a heel lance or experimental stimuli in neonates whose skin was brushed by the experimenter prior to the procedure.
- This trial investigates a simple, free, low-risk, non-pharmacological pain-relieving intervention, which could be delivered by parents in partnership with healthcare professionals globally.
- The trial employs multiple proxy measures of pain to determine the impact of the stroking intervention. In addition, it investigates the impact of the intervention on parental anxiety and distress.
- The nature of the intervention prevents the clinical investigators from being blinded at the time of study, which is a limitation of the trial. To mitigate this concern all investigators involved in all other aspects of the trial, including data analysis, are blinded.

INTRODUCTION

Background

Newborn infants undergo painful procedures as part of routine neonatal care. Sick or premature infants experience an average of ten painful procedures per day as part of life-sustaining treatment.[1] It is recognised that repetitive exposure to pain in early life can cause short-term physiological instability as well as long-term neurodevelopmental consequences such as reduced growth, altered structural and functional brain development, and reduced school-age academic performance.[2] Furthermore, repeatedly witnessing their infant in pain can have a significant negative impact on the emotional and psychological wellbeing of parents.[3–5] Effective pain management is therefore essential in neonatal care. However, measuring pain in this non-verbal patient population is challenging, and few safe and effective analgesics have been tested and approved for use in infants. Non-pharmacological strategies have been introduced and promoted over the last few decades for the management of acute procedural pain. Sweet-taste solutions such as sucrose are effective in relieving behavioural responses following minor painful procedures [6] but do not reduce noxious input to the brain.[7] This has caused concern that this intervention may not mitigate the long-term consequences of early life pain, and furthermore, it may have long-term neurodevelopmental effects with repeated use.[8–10] Breastfeeding also reduces behavioural and physiological responses to pain in full-term infants undergoing heel lancing, intramuscular injection, and venepuncture.[11] However, this strategy can be challenging for new mothers, is not always practical to implement in premature and critically ill infants or in mothers with transmissible infections, or due to maternal concerns of developing a negative association with breastfeeding.[12] Other comfort measures include swaddling and facilitated tucking of infants, which, although useful, are less effective in reducing pain.[13] While many studies have reported the potential pain-relieving effects of tactile interventions such as skin-to-skin care [14] and massage [15–21] in the context of minor painful procedures, these non-pharmacological interventions are scarcely used in maternity and neonatal units [22,23] and the mechanisms underpinning their effectiveness are still being established. Despite guidelines recommending the use of non-pharmacological interventions for pain relief, uptake of these practices remains poor and inconsistent.[24,25]

Measuring pain in infants

The assessment of pain and analgesia in infants primarily relies upon measuring changes in infant behaviour. One of the most common validated clinical pain tools is the Premature Infant Pain Profile (original PIPP, revised PIPP-R).[26,27] While subjective evaluations of behavioural responses are a gold standard for the clinical assessment of neonatal pain, electrophysiology based methods have more recently been developed to identify a pattern of noxious-evoked brain activity.[28–30] This objective and quantifiable neurophysiological measure has been previously used in pilot studies [31,32] and as the primary outcome measure in randomised clinical trials published in *The Lancet*, assessing the analgesic efficacy of sucrose [7] and morphine [33]. Noxious-evoked brain activity has specifically been well-characterised in response to heel lancing,[28–30,34] a clinical procedure which is frequently performed in neonates for blood collection, and will be used as the primary outcome of the Petal trial to investigate the efficacy of pre-procedural parental stroking.

Rationale

Maternal touch behaviours are instinctive, evolutionarily conserved amongst mammals [35] and enhance infant growth [36] and development [37]. Stroking, by repeatedly applying gentle pressure to the skin, can activate C-tactile (CT) fibres, a subclass of slow-conducting unmyelinated sensory neurons, mostly found in hairy skin [38–40]. These fibres project to brain regions associated with affective processing such as the insular cortex, prefrontal cortex, superior temporal sulcus, and cingulate cortex [41–45] and are thought to have evolved to promote affiliative behaviours and social touch [46–49]. CT fibres are optimally activated by stroking at a velocity of 3cm/s (optimal range 1–10cm/s) [50–52], and studies in adults of gentle brushing or stroking paradigms at this optimal velocity have demonstrated a reduction in pain ratings [53,54] and noxious-evoked brain activity [54]. CT-optimal stimulation therefore could provide a natural and safe pain-relieving intervention.

We previously conducted a small prospective cohort study of pre-procedural stroking for pain relief in neonates, in which we demonstrated that CT-optimal stroking (at 3cm/s) prior to an experimental noxious stimulus or clinical

1
2 heel lance significantly reduced noxious-evoked brain activity in term neonates compared to no touch
3 intervention.[31] We replicated this study in an independent sample of term neonates and showed consistent results
4 and a similar effect size in the group receiving the stroking intervention.[32] However, in both of these studies
5 stroking was delivered by the researcher using a soft experimental brush with a known force. Although the studies
6 did not identify a significant effect of the intervention on a clinical pain score, it was notably not powered to
7 investigate this. Considering CT-optimal stroking is a natural maternal behaviour [55,56] and evidence suggesting
8 that CT fibres respond optimally to touch at human skin temperature,[57] hands-on parental stroking has the
9 potential to provide even greater benefit than CT-optimal brushstrokes. Pilot work further suggests that stroking a
10 neonate has similar efficacy to researcher-led experimental brushing (unpublished).
11

12 **Aim and Objectives**

13 In the Petal trial, we aim to determine whether parental stroking prior to a common painful clinical procedure (heel
14 lancing) provides effective analgesia in neonates. The primary outcome will be the reduction of noxious-evoked brain
15 activity during a heel lance. Secondary outcomes will be a reduction in clinical pain scores, post-procedural
16 tachycardia and parental anxiety (Table 1). Exploratory outcomes will investigate changes in brain activity during the
17 intervention, as well as effects on physiological recovery post-procedure (using heart rate and respiratory dynamics)
18 and further explore parental anxiety, distress, and attitudes to research.
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Objectives	Outcome Measures
<p>Primary Objective</p> <p>(i) To test whether parental touch prior to the clinical procedure reduces noxious-evoked brain activity following a heel lance.</p> <p>Secondary Objectives</p> <p>(i) To test whether parental touch prior to the clinical procedure reduces clinical pain scores (PIPP-R) during the 30-second period after the heel lance.</p> <p>(ii) To test whether parental touch prior to the clinical procedure reduces incidence of post-procedural tachycardia activity following a heel lance.</p> <p>(iii) To test whether parental touch prior to the clinical procedure reduces parental anxiety, compared with post-procedural touch.</p> <p>Exploratory Objectives</p> <p>(i) To explore how parental touch impacts background brain activity.</p> <p>(ii) To explore whether parental touch prior to the clinical procedure reduces the duration of time for heart rate to return to baseline after a heel lance.</p> <p>(iii) To explore how parental touch prior to the clinical procedure affects respiratory stability.</p> <p>(iv) To explore parental anxiety and distress, and their experience of the trial and infant research.</p>	<p>Primary Outcome Measure</p> <p>(i) Magnitude of noxious-evoked brain activity following a heel lance (EEG data recorded in the 1000ms period following each heel lance).</p> <p>Secondary Outcome Measure</p> <p>(i) PIPP-R score during the 30-second period after the heel lance.</p> <p>(ii) Percentage of neonates who develop tachycardia in the 30-second post-heel lance.</p> <p>(iii) Difference in STAI-S scores pre- and post-procedure.</p> <p>Exploratory Outcome Measures</p> <p>(i) Changes in brain activity during touch intervention.</p> <p>(ii) Time taken for heart rate to return to baseline post-heel lance.</p> <p>(iii) Post-procedural respiratory dynamics and incidence of apnoea.</p> <p>(iv) Scores for individual parameters from the STAI-T and STAI-S; 4-point distress questionnaire score; responses to survey about participation in Petal and infant research.</p>

Table 1. Objectives and Outcome Measures. STAI-T: State-Trait Anxiety Inventory-Trait, STAI-S: State-Trait Anxiety Inventory-State, PIPP-R: Premature Infant Pain Profile – Revised.

METHODS AND ANALYSIS

Trial Description

This is a multicentre randomised-controlled interventional trial, with two research sites (John Radcliffe Hospital, Oxford, and Royal Devon and Exeter Hospital, Devon, UK). The parents of eligible neonates satisfying inclusion criteria (Figure 1) will be approached by a member of the research team. Parental written informed consent will be taken and neonates will be electronically randomised to receive parental stroking either prior to or after a clinically-required heel lance. A unique study ID will be assigned to each individual participant. The randomisation program will use a minimisation algorithm to ensure approximate balance between the groups with respect to gestational age at birth, postnatal age at time of randomisation, sex, the indication for blood sampling, and research site. The users of the system will be blind to the next allocation.

Each neonate will be studied on a single test occasion lasting approximately one hour (Figure 2) and will not require further follow-up. A parent will first complete the State-Trait Anxiety Inventory-Trait (STAI-T) and State-Trait Anxiety Inventory-State (STAI-S) questionnaires, which will be administered verbally by a researcher. This will allow assessment of both trait anxiety and state anxiety prior to the commencement of the stroking intervention or blood test. At least 30 minutes prior to the heel lance, the research team will set up physiological monitoring including electrocardiography (ECG) and pulse oximetry for continuous recording of baseline cardiorespiratory stability. Electroencephalography (EEG) electrodes will then be sited to allow continuous monitoring of baseline brain activity for at least 10 minutes prior to the clinical procedure. A control heel lance will then be performed followed by the clinical heel lance.

The control heel lance is a non-noxious sham procedure whereby the lancet is placed against the participant's foot rotated at 90 degrees, preventing release of the blade into the foot. This procedure simulates the tactile and auditory aspects of the blood sampling experience without the noxious input. Brain activity, physiology and facial expression (video) will be recorded for both the control heel lance and clinical heel lance to allow assessment of outcome measures including noxious-evoked brain activity, PIPP-R scores, tachycardia, and respiratory dynamics (Table 1). The heel lance and control stimulus will be linked electronically to the recording equipment as described in previous studies,[7,28,29] providing precise timing of when the heel lance occurs. In the event of the neonate requiring multiple heel lances, data will only be included from the first heel lance (conditional on data quality). Video monitoring of the face will commence approximately 30 seconds prior to the control lance and end at least 30 seconds after the clinical heel lance to allow PIPP-R scoring. For neonates randomised to receive pre-procedural stroking, the parent will be instructed to begin stroking down the infant's leg immediately prior to the clinical heel lance, with the aid of an animated visual cue to help maintain a velocity of 3cm/s and a duration of 10 seconds. After the heel lance, blood collection will be delayed for 30 seconds to allow PIPP-R scoring. For neonates randomised to receive post-procedural stroking, the parent will be instructed to begin stroking down the infant's leg immediately after blood collection following the animated visual cue. A researcher will then verbally administer the STAI-S and 4-point distress questionnaire after the procedure is completed. Physiological monitoring will continue for 30 minutes and EEG monitoring for at least 10 minutes to allow investigation of post-procedural cardiorespiratory dynamics and brain activity as exploratory outcomes of the trial. Finally, the parents will be invited to complete an anonymous survey of their experience and views on research after completion of the study.

Intervention

The parental touch intervention will involve one parent stroking the infant's leg for 10 seconds. The duration of the intervention is consistent with previous studies.[31,32,53,58] A member of the research team will inform parents of their randomised allocation (either stroking pre-heel lance or post-heel lance) at the start of the test occasion. They will explain and demonstrate how to administer the intervention using their whole hand, stroking in one direction down towards the foot. The infant will lay in a cot during the intervention and procedure. During the demonstration and test occasion, PsychoPy software [59] will be used to provide a visual cue on a computer screen to guide a consistent stroking speed of 3cm/s for 10 seconds.

Recording Techniques

Electroencephalography (EEG)

Electrophysiological activity will be acquired with the SynAmps RT 64-channel headbox and amplifiers (Compumedics Neuroscan) or with the Compumedics Grael V2 EEG system, with a bandwidth from DC - 400 Hz and a sampling rate of 2000 or 2048Hz. Data recorded at 2048Hz will be downsampled to 2000Hz prior to further processing. CURRYscan7 or CURRYscan8 neuroimaging suite (Compumedics Neuroscan) will be used to record the activity. All equipment will conform to the electrical safety standard for medical devices, IEC 60601-1. Eight EEG recording electrodes will be positioned on the scalp at Cz, CPz, C3, C4, FCz, T3, T4 and Oz according to the modified international 10-20 System. Reference and ground electrodes will be placed at Fz and the forehead respectively. EEG conductive paste will be used to optimise contact with the scalp. All impedances will be reduced to approximately 5k Ω by rubbing the skin with EEG preparation gel prior to electrode placement. An ECG electrode will be placed on the left clavicle to record heart rate.

Physiological Monitoring (ECG and Pulse Oximetry)

Heart rate, respiratory rate and oxygen saturation will be recorded continuously throughout the study period (approximately one hour) using ECG and pulse oximetry. Heart rate and oxygen saturation data will be used to calculate the clinical pain scores following the heel lance and control stimulus and to assess clinical stability across the test occasion.

Video Recording

Video recording will be used to measure behavioural responses i.e. changes in facial expression during the control stimulus and clinically-required heel lance. A synchronised LED flash will be activated by the researcher simultaneously with each stimulation as a marker for the time of stimulation.

Parental Questionnaire

The parent administering the intervention will be asked to complete a short series of validated electronic questionnaires assessing anxiety and distress at the start and end of the test occasion (Table 2). The researcher will record the responses to the STAI-T, STAI-S and distress questionnaire in an electronic Case Report Form. The electronic device will then be presented to the parent to independently complete a short survey about trial participation and their research experience. The survey will be completed anonymously, and responses will be stored by trial arm with no link to study IDs.

Questionnaire section	Topic	Timing of administration	Questionnaire administrator
20-point State-Trait Anxiety Inventory (STAI)-T	Trait anxiety	Start of test occasion	Administered verbally by researcher
20-point State-Trait Anxiety Inventory (STAI)-S	State anxiety pre-heel lance	Start of test occasion	Administered verbally by researcher
	State anxiety post-heel lance	After the procedure and intervention are completed	Administered verbally by researcher
4-point distress questionnaire	Emotional constructs experienced at time of the clinical heel lance	After the procedure and intervention are completed	Administered verbally by researcher
Anonymous survey	Views on the trial and infant research	End of test occasion	Completed by parent

Table 2. Trial parental questionnaires.

State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory (STAI) is the gold standard assessment for state anxiety.[60] It is well validated, publicly available and has a trait (STAI-T) version consisting of 20 statements exploring general feelings of anxiety, and a state version (STAI-S) consisting of 20 statements exploring anxiety levels at a particular point in time. Each question is rated on a 4-point scale. The range of possible scores for the STAI varies from a minimum score of 20 to a maximum score of 80 on both the STAI-T and STAI-S subscales. Scores are classified as “no or low anxiety” (20-37), “moderate anxiety” (38-44), and “high anxiety” (45-80).

4-point distress questionnaire

Parents will be asked four questions related to their emotions during the clinical heel lance procedure.[61,62] Each of the four emotional constructs (worried, upset, anxious and sad) will be rated on an 11-point scale ranging from “not at all” (0) to “extremely” (10). A total score between 0 and 40 will be calculated, where higher scores are indicative of greater parental distress. This score is frequently used in research to evaluate parent/child interactions during painful procedures.[61–63]

Outcome Measures

Noxious-evoked Brain Activity

An EEG template that reflects the noxious-evoked brain activity in neonates has previously been defined using principal component analysis, validated in independent data sets [30] and used in clinical studies and a clinical trial.[33] This template will be projected onto the EEG data recorded in the 1000ms period following each heel lance and control heel lance stimulus and the relative weight of the component calculated for each neonate. A greater weight indicates a stronger noxious-evoked response. While the brain activity characterised is directly related to noxious input, it does not reflect all noxious-evoked activity across the brain or all aspects of the pain experience. The response to the non-noxious control heel lance stimulus is being recorded to confirm that it significantly differs from the brain activity evoked by a noxious heel lance. This forms an important data quality control check.[28]

PIPP-R Score

Clinical pain scores will be evaluated using the validated Premature Infant Pain Profile - Revised,[27] which is a composite multimodal measure encompassing behavioural, physiological and contextual indicators of the pain response. It allows for different aspects of the infant pain experience to be captured and has been widely used as the primary outcome measure for infant pain in many clinical trials.[64–66] The PIPP-R score will be calculated for the control heel lance and the clinical heel lance procedure. Heart rate, oxygen saturation and facial expression will be recorded in the 15-second period before and 30-second period after each of the procedures.[26,27] The 15-second period before the heel lance will be recorded immediately prior to the stroking intervention. Videos of the infant’s facial expressions will be scored offline using the PIPP-R facial coding system. Changes in heart rate and oxygen saturation will be recorded with ECG and pulse oximeter and used to calculate the PIPP-R score. A second investigator (blinded to the trial arm) will re-calculate 20% of the PIPP-R scores to measure inter-rater reliability.

Clinical Stability

Clinical stability will be assessed in the 30-minute periods before and after the heel lance. The percentage of neonates who develop post-procedural tachycardia in the 30 seconds post-heel lance will be a secondary outcome measure of the trial. Tachycardia will be defined as a heart rate >160 beats per minute as per Advanced Paediatric Life Support guidelines, reflecting heart rate values >90th centile for newborn infants in the first week of life.[67,68] Exploratory outcome measures will also include the time taken for the heart rate to return to baseline values post-heel lance and respiratory rate variability in the 30 minutes prior and post heel lance (including incidence of apnoea). An episode of apnoea will be defined as the cessation of breathing for at least 20 seconds.[69]

Parental Experience

Parental anxiety will be quantified using the outcomes of the STAI-T and STAI-S questionnaires. Parental distress will be quantified using the 4-point distress score. The anonymous parent survey will assess the parental experience of the trial and parental views on taking part in the trial.

Statistics and Analysis

Analysis of outcome measures

Data pre-processing and statistical analysis will be performed blind to treatment allocation. The analysis and presentation of results will follow the most up-to-date recommendations of the CONSORT group. All comparative analyses will be performed using MatlabR2020a or an updated version, adjusting for important prognostic factors where possible: these are likely to be a subset of the minimisation factors at randomisation. A full statistical analysis plan will be finalised before any comparative analysis of outcome measures is performed.

Significance Levels

For the analysis of the primary outcome measure, a p-value of 0.05 (two-sided 5% significance level) will be used to indicate statistical significance. Significance levels for secondary outcomes will be corrected for multiple comparisons and the method will be specified in the analysis plan. Two-sided statistical tests and corresponding p-values will be presented throughout; however, for the purposes of interpretation of results, confidence intervals will dominate, rather than p-values.

Primary

Noxious-evoked brain activity

The projected weight of the template will be compared between the two groups using linear regression, dependent on the mean and variance of the data. If appropriate, we will present the mean and standard deviation for each group and estimate the adjusted mean difference with a 95% confidence interval. If the outcome data are skewed, we will present the median and interquartile range (or entire range, whichever is appropriate) for each group, and estimate the median difference between groups with a corresponding 95% confidence interval.

Secondary

PIPP-R score

PIPP-R scores (during the 30-second period after heel lance) in the two groups will be compared using linear regression to estimate the adjusted mean difference. If the PIPP-R scores are skewed, we will present the median and interquartile range (or entire range, whichever is appropriate) for each group, and estimate the median difference between groups.

Clinical stability (tachycardia)

The percentage of infants experiencing tachycardia will be compared between the two groups. Depending on the distribution of these counts, either Poisson or linear regression will be used to calculate the adjusted effect estimates. If appropriate, adjustments for the 30-minute baseline period will also be made. Alternatively, we will present the medians and interquartile ranges (or entire range, whichever is appropriate) for each group and estimate the median differences between groups. In the event of occurrences being very infrequent, logistic regression may be used as an alternative.

Parental anxiety

STAI scores in the two groups will be compared to estimate the adjusted mean difference in pre-procedural and post-procedural STAI-S scores. If the scores are skewed, we will present the median and interquartile range (or entire range, whichever is appropriate) for each group, and estimate the median difference between groups.

Exploratory

Exploratory analyses will be conducted to investigate i) the effects of parental touch on background brain activity, ii) whether pre-procedural parental touch reduces the duration of time for heart rate to return to baseline, iii) the effect of pre-procedural parental touch on respiratory rate variability, respiratory dynamics and the incidence of apnoea and iv) the parental experience of the procedure and involvement in research.

Sample Size Determination

Power Calculation

The assumptions for these calculations are based on data from mechanistic studies investigating the effect of (experimenter-led) soft brushing of the skin at CT-optimal rate on the response to an experimental noxious stimulus or clinical heel lance in term neonates.[31,32] The mean (SD) brain activity evoked by heel lancing in the control group is estimated to be 1.07 (0.66). A 40% reduction in the intervention group is considered to be clinically significant and realistic from other studies.[31,54] With 90% power and a two-sided 5% significance level, to observe a 40% reduction in brain activity, a sample size of 102 would be required. Allowing for 10% loss, due to technical difficulties or other clinical issues, this increases to 112.

Missing Data

Missing data may occur in our trial due to equipment failure, EEG artefacts, or clinical issues resulting in withdrawal post-randomisation. If missing data exists, we expect it will occur at random, and collected data will be representative of the population. To account for potential missing data, we have inflated our sample size by 10%. The analysis will be conducted using the available data.

Ethics and dissemination

The trial has been approved by the London South East Research Ethics Committee (ref:21/LO/0523) and will be conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. EEG is a safe tool used routinely in clinical practice and research to measure brain activity. Surface electrodes are used and temporarily fixed without glue. All heel lances performed during the trial will have been requested by the clinical team responsible for the infant's medical care. No extra blood tests or noxious procedures will be performed for the purpose of the study. Every effort will be made to minimise inconvenience and prevent disruption of clinical care. There are no expected serious adverse events (SAE) for this trial. Any SAEs identified will be reported to the CI within 24 hours and they will report any unexpected SAEs deemed related to the trial to the REC and Sponsor in accordance with REC/HRA guidance.

Parent(s) may withdraw their neonate from the trial at any time and they are not obliged to give a reason. If parents choose to withdraw their child after the study has begun, they will be asked whether data already collected may be retained and used for the purposes of the trial. Parents will be made aware that this decision has no impact on any aspects of their infant's continuing care. The attending clinician may also withdraw the neonate from the trial if they consider this to be in their best interest. If any of the exclusion criteria manifest prior to data collection, the participant will be withdrawn.

The results of the study will be disseminated to the scientific and wider community through peer-reviewed publications and national and international meetings and conferences, via the charities SSNAP and Bliss, and through the NHS clinical guideline adoption process.

Patient and Public Involvement (PPI)

A PPI representative will be included in the extended PMG group and invited to join specific PMG meetings to discuss trial progress and developments. Bliss: for babies born premature or sick is a national UK neonatal charity, which is partly funding the trial. They will receive regular trial progress reports and promote the trial across their various channels, and disseminate the results. The research team will also work closely with the on-site local Oxford charity Supporting the Sick Newborn And their Parents (SSNAP) during the design, conduct and dissemination of the trial. SSNAP have reviewed all parent-facing materials, will review manuscripts reporting results, and will be involved in disseminating results to the public.

DISCUSSION

All newborn infants are exposed to clinically-necessary painful procedures. Even healthy neonates on postnatal wards can require repeated painful procedures beyond routine Newborn Screening, such as blood tests for glucose

1
2 monitoring or jaundice, which can be distressing for both neonates and their parents. In the UK, more than 100,000
3 newborn infants receive neonatal care every year as a result of prematurity or illness,[70] which, for some, can entail
4 weeks to months of hospitalisation and procedures. As such, improving the management of pain is recognised as a
5 top neonatal UK research priority [71] and a major concern amongst parents and neonatal nurses.[72]
6

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8 Poor management of neonatal pain can have a significant negative impact on parents. Mothers of hospitalised
9 infants report feeling emotionally and psychologically traumatised due to having to allow their infants to undergo
10 clinically-necessary painful procedures, and due to feelings of helplessness from being unable to protect or comfort
11 their child.[3–5] Actively involving parents in care relieves parental distress[73] and increases the likelihood that
12 infants receive treatment for pain.[1,5,74] Infant massage, a tactile comfort measure which involves patterns of
13 stroking, has been shown to improve mother-infant bonding and improve postnatal depression,[75] a condition
14 afflicting at least one in ten UK mothers in the first-year post-partum[76]. Furthermore, maternal stroking of infants
15 in general has been shown to moderate the behavioural and physiological effects of maternal depression on
16 infants.[77] Promoting the natural tactile behaviour of stroking to provide evidence-based pain-relief would
17 therefore be beneficial to both mothers and infants.

18
19 Anxiety about pain is increasingly recognised as a key factor in parental refusal for procedures such as vitamin-K
20 intramuscular injections at birth[78] and immunisations[79–81]. Avoidance of key interventions in early life could
21 have drastic consequences for child health and this issue must be addressed. Indeed, parental anxiety and attitudes
22 during painful procedures can also impact neonatal distress and subsequent pain experience during clinical
23 procedures in later life[82]. Parental anxiety regarding pain could be alleviated by empowering parents to provide
24 safe and effective pain relief for their child. Unlike other non-pharmacological interventions, this strategy could be
25 broadly implemented regardless of feeding status of the infant or availability of a product like sucrose, in hospital as
26 well as the community, and across high and low resource clinical settings.
27

28
29 CT-fibres likely provide the neurobiological mechanism underlying the benefits of tactile stimulation in early life.
30 Studies have revealed that mothers instinctively stroke their infants at a CT-optimal rate[55,56] and that this tactile
31 stimulation is beneficial. CT-optimal touch significantly decreases resting heart rates in infants aged 1-4 months[58]
32 and 9-months,[83] as well as in premature infants (28–36 weeks' gestation)[84]. Recent studies have also
33 investigated the neurological correlates of CT-optimal touch in early life. In 2-month-old infants, CT-optimal touch
34 produces greater activation of the insular cortex compared to CT non-optimal touch.[84] Similarly, in term infants
35 CT-optimal stroking with a soft brush produces activation of the primary somatosensory and posterior insular
36 cortices,[85] suggesting that the neonatal brain is sensitive to the somatosensory and socio-affective effects of CT-
37 optimal stroking.

38
39 The Petal trial is based upon clear mechanistic evidence from preliminary cohort studies and is, as such, adequately
40 powered to address the clinical question. It employs a range of multimodal outcomes, including electrophysiological,
41 behavioural, and cardiorespiratory measures, to cover the many aspects of pain experience, and seeks to investigate
42 the benefits of the intervention to both neonates and their parents. Blinding of outcome assessment is being
43 performed to ensure the integrity of the trial as it is not possible to blind the researchers at the time of study due to
44 the nature of the intervention. Although parents instinctively stroke at the optimal velocity to stimulate CT-
45 fibres,[55,56] consistency of the intervention is standardised across the trial by providing an animated visual aid for
46 parents to follow. In the event of a positive trial outcome, the intervention could next be translated to more
47 premature infants and other minor painful skin-breaking procedures performed frequently in infants such as
48 immunisation and cannulation and could be performed by parents or healthcare workers in the absence of parents.
49 The Petal trial investigates a simple, free, low-risk, non-pharmacological pain-relieving intervention, which could be
50 rapidly incorporated into routine clinical practice, benefiting infants, their parents, and the wider community.
51

52 **Trial status**

53 Participant recruitment is currently ongoing. Protocol version no. 3.0 (date of submission: 3 February 2022).
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FOOTNOTES

Author contributions

MC: Conceptualization, Methodology, Software, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project Administration. **FM:** Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing, Funding Acquisition. **AH:** Methodology, Investigation, Data Curation, Writing - Review & Editing, Project Administration. **DC:** Methodology, Software, Investigation, Data Curation, Writing - Review & Editing. **VM:** Conceptualization, Methodology, Writing - Original Draft, Project Administration, Funding Acquisition. **CH:** Software, Methodology, Data Curation, Funding Acquisition. **REF:** Conceptualization, Methodology, Investigation, Writing - Original Draft. **SR:** Investigation. **MvdV:** Software, Validation, Data Curation, Writing - Review & Editing. **LB:** Methodology, Data Curation, Writing - Review & Editing. **EA:** Conceptualization, Methodology, Writing - Review & Editing, Supervision. **RP:** Conceptualization, Methodology, Investigation, Data Curation, Supervision, Project Administration. **AB:** Conceptualization, Methodology, Supervision, Writing - Original Draft, Project administration, Funding Acquisition. **RS:** Conceptualization, Methodology, Resources, Writing - Original Draft, Writing - Review & Editing, Supervision, Project Administration, Funding Acquisition.

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Competing interests

None declared.

Ethics approval

London South East Research Ethics Committee (ref:21/LO/0523).

Figure legend

Figure 1. Trial flowchart. IVH: Intraventricular haemorrhage.

Figure 2. Trial procedures

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For peer review only

Inclusion Criteria

- Born at the John Radcliffe Hospital, Oxford or the Royal Devon and Exeter Hospital, Devon
- Born at or after 35+0 weeks' gestation with a postnatal age ≤ 7 days
- Require a clinical heel lance as part of clinical care
- Parents/guardians have given written informed consent for inclusion in the trial.

Exclusion Criteria

- Hypoxic Ischaemic Encephalopathy
- IVH > grade II
- Received any analgesics/sedatives in the last 24 hours
- Born with a congenital malformation or genetic condition known to affect neurological development
- Born to a mother with a history of substance abuse.



Randomisation (1:1 allocation ratio)

Web-based randomisation

30 min baseline data collection

(EEG, heart rate, oxygen saturation)

Group A (n=56)

Parental touch pre-heel lance

Group B (n=56)

Parental touch post-heel lance

Primary Outcome measures

- Magnitude of noxious-evoked brain activity evoked by heel lance.

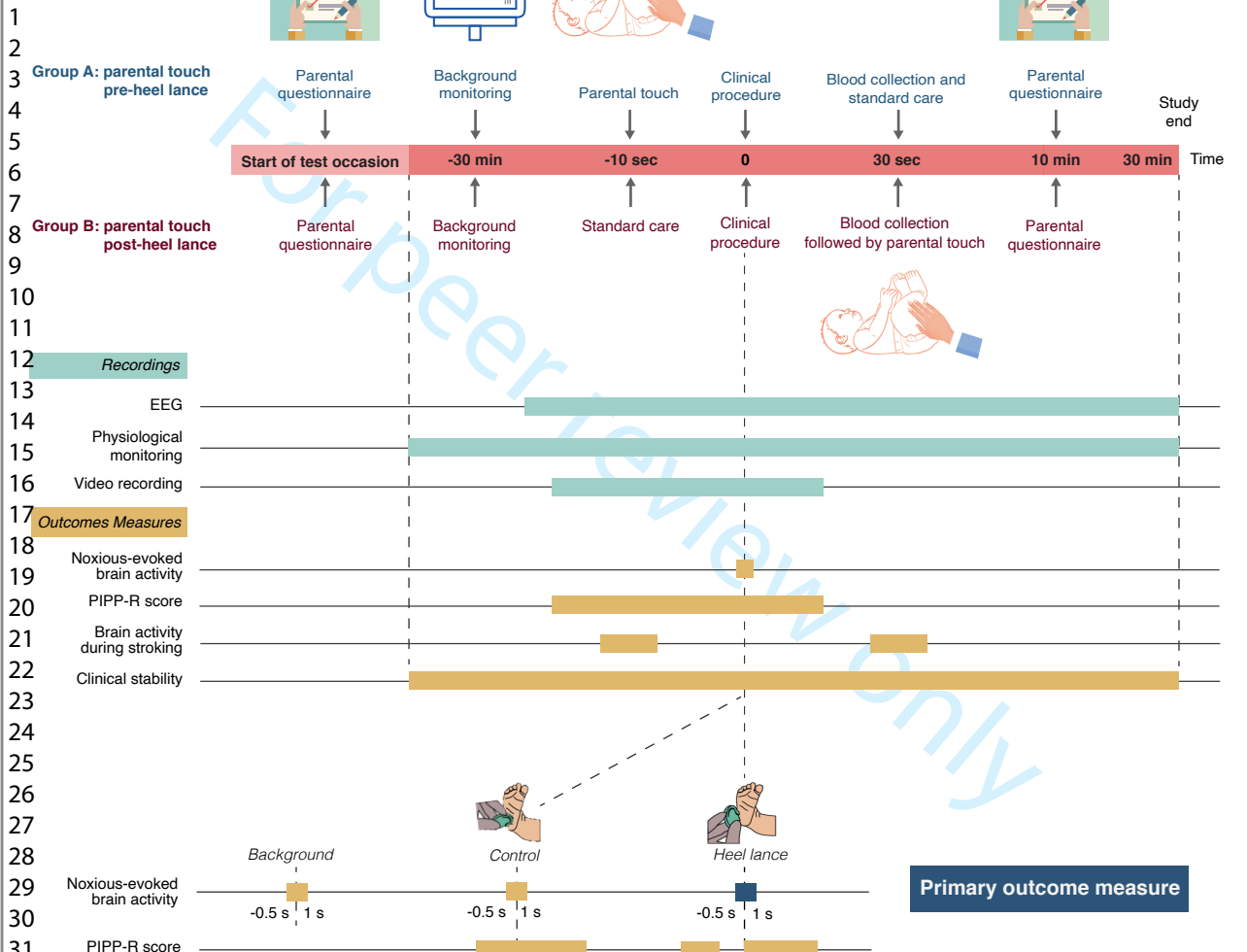
Secondary Outcome measures

- Premature Infant Pain Profile – Revised (PIPP-R) score during the 30-second period after the heel lance.
- Percentage of neonates who develop tachycardia in the 30 seconds post-heel lance.
- Parent questionnaire assessing anxiety.

Exploratory Outcome measures

- Changes in background brain activity during touch intervention.
- Time taken for heart rate to return to baseline post-heel lance.
- Post procedural respiratory dynamics and incidence of apnoea.
- Parental questionnaire assessing parental anxiety, distress, and experience of research.

BMJ Open



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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Included in manuscript	Section/item	ItemNo	Description	Comment
	Administrative information			
X	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	
X	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	
		2b	All items from the World Health Organization Trial Registration Data Set	
X	Protocol version	3	Date and version identifier	
X	Funding	4	Sources and types of financial, material, and other support	
X	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	
		5b	Name and contact information for the trial sponsor	
		5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	

Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
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12	X	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
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16			6b	Explanation for choice of comparators
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18	X	Objectives	7	Specific objectives or hypotheses
19				
20	X	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
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28	X	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
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32	X	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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37	X	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4			11b	Criteria for discontinuing or modifying allocated interventions for a
5				given trial participant (eg, drug dose change in response to harms,
6				participant request, or improving/worsening disease)
7				
8			11c	Strategies to improve adherence to intervention protocols, and any
9				procedures for monitoring adherence (eg, drug tablet return,
10				laboratory tests)
11				
12			11d	Relevant concomitant care and interventions that are permitted or
13				prohibited during the trial
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15				
16	X	Outcomes	12	Primary, secondary, and other outcomes, including the specific
17				measurement variable (eg, systolic blood pressure), analysis metric
18				(eg, change from baseline, final value, time to event), method of
19				aggregation (eg, median, proportion), and time point for each
20				outcome. Explanation of the clinical relevance of chosen efficacy and
21				harm outcomes is strongly recommended
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24	X	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and
25				washouts), assessments, and visits for participants. A schematic
26				diagram is highly recommended (see Figure)
27				
28	X	Sample size	14	Estimated number of participants needed to achieve study objectives
29				and how it was determined, including clinical and statistical
30				assumptions supporting any sample size calculations
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33	X	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
34				target sample size
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Methods: Assignment of interventions (for controlled trials)

Allocation:

Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4	X	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
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12		Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
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17		Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
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21	X	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
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25			17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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Methods: Data collection, management, and analysis

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32	X	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4			18b	Plans to promote participant retention and complete follow-up,
5				including list of any outcome data to be collected for participants who
6				discontinue or deviate from intervention protocols
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8	X	Data management	19	Plans for data entry, coding, security, and storage, including any
9				related processes to promote data quality (eg, double data entry;
10				range checks for data values). Reference to where details of data
11				management procedures can be found, if not in the protocol
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14	X	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes.
15				Reference to where other details of the statistical analysis plan can be
16				found, if not in the protocol
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18			20b	Methods for any additional analyses (eg, subgroup and adjusted
19				analyses)
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21			20c	Definition of analysis population relating to protocol non-adherence
22				(eg, as randomised analysis), and any statistical methods to handle
23				missing data (eg, multiple imputation)
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26		Methods: Monitoring		
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28	X	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
29				and reporting structure; statement of whether it is independent from
30				the sponsor and competing interests; and reference to where further
31				details about its charter can be found, if not in the protocol.
32				Alternatively, an explanation of why a DMC is not needed
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35			21b	Description of any interim analyses and stopping guidelines, including
36				who will have access to these interim results and make the final
37				decision to terminate the trial
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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4	X	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
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8		Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	The project management group (RS, RP, AB, AH, DC, MC, FM) meets monthly throughout the trial to oversee trial conduct and recruitment.
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15		Ethics and dissemination			
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17	X	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	
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20		Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	The Investigator will submit and, where necessary, obtain approval from the relevant parties for all substantial amendments to the original approved documents.
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30	X	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	
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33			26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
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36	X	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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X Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Only the project team will have access to the final trial dataset. After the publication of results, anonymised data can be made available to other researchers upon reasonable request.

Ancillary and post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

X Dissemination policy 31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4 31b Authorship eligibility guidelines and any intended use of professional
5 writers
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7 31c Plans, if any, for granting public access to the full protocol, participant-
8 level dataset, and statistical code
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Appendices

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12 X Informed consent 32 Model consent form and other related documentation given to
13 materials participants and authorised surrogates
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15 Biological 33 Plans for collection, laboratory evaluation, and storage of biological No biological specimens are
16 specimens collected.
17 future use in ancillary studies, if applicable
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20 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on
21 the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative
22 Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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BMJ Open

Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology, Paediatrics, Radiology and imaging
Keywords:	NEONATOLOGY, NEUROPHYSIOLOGY, PAIN MANAGEMENT

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1 **Study protocol: a multicentre, randomised controlled trial to investigate the effects of**
2 **parental touch on relieving acute procedural pain in neonates (Petal)**

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18 ABSTRACT

20 Introduction

21 Newborn infants routinely undergo minor painful procedures as part of postnatal care, with infants born sick or
 22 premature requiring a greater number of procedures. As pain in early life can have long-term neurodevelopmental
 23 consequences and lead to parental anxiety and future avoidance of interventions, effective pain management is
 24 essential. Non-pharmacological comfort measures such as breastfeeding, swaddling, and sweet solutions are
 25 inconsistently implemented and are not always practical or effective in reducing the transmission of noxious input
 26 to the brain. Stroking of the skin can activate C-tactile fibres and reduce pain, and therefore could provide a simple
 27 and safe parent-led intervention for the management of pain. The trial aim is to determine whether parental touch
 28 prior to a painful clinical procedure provides effective pain relief in neonates.

29 Methods and analysis

30 This is a multicentre blinded randomised controlled trial. A total of 112 neonates born at 35 weeks' gestation or
 31 more requiring a blood test in the first week of life will be recruited and randomised to receive parental stroking
 32 either pre- or post-procedure. We will monitor brain activity (EEG), cardiac and respiratory dynamics, oxygen
 33 saturation and facial expression to provide proxy pain outcome measures. The primary outcome will be the
 34 reduction of noxious-evoked brain activity in response to a heel lance. Secondary outcomes will be a reduction in
 35 clinical pain scores (Premature Infant Pain Profile-Revised), post-procedural tachycardia and parental anxiety.

36 Ethics and dissemination

37 The study has been approved by the London – South East Research Ethics Committee (ref:21/LO/0523). The results
 38 will be widely disseminated through peer-reviewed publications, international conferences and via our partner
 39 neonatal charities Bliss and SSNAP. If the parental tactile intervention is effective, recommendations will be
 40 submitted via the NHS clinical guideline adoption process.

41 **Study Status:** Commenced September 2021.

42 **Trial Registration:** ClinicalTrials.gov NCT04901611; **ISRCTN:** 14135962.

Strengths and limitations of this study

- Petal is a randomised controlled trial investigating whether noxious-evoked brain activity is reduced by pre-procedural parental stroking.
- The trial is based upon published evidence from two mechanistic studies which show a reduction in noxious-evoked brain activity during a heel lance or experimental stimuli in neonates whose skin was brushed by the experimenter prior to the procedure.
- This trial investigates stroking as a simple, free, low-risk, non-pharmacological pain-relieving intervention delivered by parents to their newborn infants in the first week of life.
- The trial employs multiple proxy measures to determine the impact of the stroking intervention on neonatal pain and investigates the impact of the intervention on parental anxiety and distress.
- While investigators cannot be blinded to the group allocation at the time of the study, this limitation is mitigated by ensuring that participants and investigators involved in all other aspects of the trial, including data analysis, are blinded.

43 INTRODUCTION

45 **Background**

46 Newborn infants undergo painful procedures as part of routine neonatal care. Sick or premature infants experience
47 an average of ten painful procedures per day as part of life-sustaining treatment.[1] It is recognised that repetitive
48 exposure to pain in early life can cause short-term physiological instability as well as long-term neurodevelopmental
49 consequences such as reduced growth, altered structural and functional brain development, and reduced school-
50 age academic performance.[2] Furthermore, repeatedly witnessing their infant in pain can have a significant
51 negative impact on the emotional and psychological wellbeing of parents.[3–5] Effective pain management is
52 therefore essential in neonatal care. However, measuring pain in this non-verbal patient population is challenging,
53 and few safe and effective analgesics have been tested and approved for use in infants. Non-pharmacological
54 strategies have been introduced and promoted over the last few decades for the management of acute procedural
55 pain. Sweet-taste solutions such as sucrose are effective in relieving behavioural responses following minor painful
56 procedures[6] but do not reduce noxious input to the brain.[7] This has caused concern that this intervention may
57 not mitigate the long-term consequences of early life pain, and furthermore, it may have long-term
58 neurodevelopmental effects with repeated use.[8–10] Breastfeeding also reduces behavioural and physiological
59 responses to pain in full-term infants undergoing heel lancing, intramuscular injection, and venepuncture.[11]
60 However, this strategy can be challenging for new mothers, is not always practical to implement in premature and
61 critically ill infants or in mothers with transmissible infections, or due to maternal concerns of developing a negative
62 association with breastfeeding.[12] Other comfort measures include swaddling and facilitated tucking of infants,
63 which, although useful, are less effective in reducing pain.[13] While many studies have reported the potential pain-
64 relieving effects of tactile interventions such as skin-to-skin care[14] and massage[15–21] in the context of minor
65 painful procedures, these non-pharmacological interventions are scarcely used in maternity and neonatal
66 units[22,23] and the mechanisms underpinning their effectiveness are still being established. Despite guidelines
67 recommending the use of non-pharmacological interventions for pain relief, uptake of these practices remains poor
68 and inconsistent.[24,25]

70 **Measuring pain in infants**

71 The assessment of pain and analgesia in infants primarily relies upon measuring changes in infant behaviour. One of
72 the most common validated clinical pain tools is the Premature Infant Pain Profile (original PIPP, revised PIPP-
73 R).[26,27] While subjective evaluations of behavioural responses are a gold standard for the clinical assessment of
74 neonatal pain, electrophysiology based methods have more recently been developed to identify a pattern of
75 noxious-evoked brain activity.[28–30] This objective and quantifiable neurophysiological measure has been
76 previously used in pilot studies[31,32] and as the primary outcome measure in randomised clinical trials published
77 in *The Lancet*, assessing the analgesic efficacy of sucrose[7] and morphine.[33] Noxious-evoked brain activity has
78 specifically been well-characterised in response to heel lancing,[28–30,34] a clinical procedure which is frequently
79 performed in neonates for blood collection, and will be used as the primary outcome of the Petal trial to investigate
80 the efficacy of pre-procedural parental stroking.

82 **Rationale**

83 Maternal touch behaviours are instinctive, evolutionarily conserved amongst mammals.[35] Previous studies
84 suggest there may also be a potential relationship between enhanced maternal touch and infant growth and
85 development.[36,37] Stroking, by repeatedly applying gentle pressure to the skin, can activate C-tactile (CT) fibres,
86 a subclass of slow-conducting unmyelinated sensory neurons, mostly found in hairy skin.[38–40] These fibres project
87 to brain regions associated with affective processing such as the insular cortex, prefrontal cortex, superior temporal
88 sulcus, and cingulate cortex[41–45] and are thought to have evolved to promote affiliative behaviours and social
89 touch.[46–49] CT fibres are optimally activated by stroking at a velocity of 3cm/s (optimal range 1–10cm/s)[50–52],
90 and studies in adults of gentle brushing or stroking paradigms at this optimal velocity have demonstrated a reduction
91 in pain ratings[53,54] and noxious-evoked brain activity.[54] CT-optimal stimulation therefore could provide a
92 natural and safe pain-relieving intervention.

1
2 94 We previously conducted a small prospective cohort study of pre-procedural stroking for pain relief in neonates, in
3 95 which we demonstrated that CT-optimal stroking (at 3cm/s) prior to an experimental noxious stimulus or clinical
4 96 heel lance significantly reduced noxious-evoked brain activity in term neonates compared to no touch
5 97 intervention.[31] We replicated this study in an independent sample of term neonates and showed consistent results
6 98 and a similar effect size in the group receiving the stroking intervention.[32] However, in both of these studies
7 99 stroking was delivered by the researcher using a soft experimental brush with a known force. Although the studies
8 100 did not identify a significant effect of the intervention on a clinical pain score, it was notably not powered to
9 101 investigate this. Considering CT-optimal stroking is a natural maternal behaviour[55,56] and evidence suggesting
10 102 that CT fibres respond optimally to touch at human skin temperature,[57] hands-on parental stroking has the
11 103 potential to provide even greater benefit than CT-optimal brushstrokes. Pilot work further suggests that stroking a
12 104 neonate has similar efficacy to researcher-led experimental brushing (unpublished).

13 105
14 106 **Aim and Objectives**

15 107 In the Petal trial, we aim to determine whether parental stroking prior to a common painful clinical procedure (heel
16 108 lancing) provides effective analgesia in neonates. The primary outcome will be the reduction of noxious-evoked brain
17 109 activity during a heel lance. Secondary outcomes will be a reduction in clinical pain scores, post-procedural
18 110 tachycardia and parental anxiety (Table 1). Exploratory outcomes will investigate changes in brain activity during the
19 111 intervention, as well as effects on physiological recovery post-procedure (using heart rate and respiratory dynamics)
20 112 and further explore parental anxiety, distress, and attitudes to research.
21 113

Objectives	Outcome Measures
<p>Primary Objective</p> <p>(i) To test whether parental touch prior to the clinical procedure reduces noxious-evoked brain activity following a heel lance.</p> <p>Secondary Objectives</p> <p>(i) To test whether parental touch prior to the clinical procedure reduces clinical pain scores (PIPP-R) during the 30-second period after the heel lance.</p> <p>(ii) To test whether parental touch prior to the clinical procedure reduces incidence of post-procedural tachycardia activity following a heel lance.</p> <p>(iii) To test whether parental touch prior to the clinical procedure reduces parental anxiety, compared with post-procedural touch.</p> <p>Exploratory Objectives</p> <p>(i) To explore how parental touch impacts background brain activity.</p> <p>(ii) To explore whether parental touch prior to the clinical procedure reduces the duration of time for heart rate to return to baseline after a heel lance.</p> <p>(iii) To explore how parental touch prior to the clinical procedure affects respiratory stability.</p> <p>(iv) To explore parental anxiety and distress, and their experience of the trial and infant research.</p>	<p>Primary Outcome Measure</p> <p>(i) Magnitude of noxious-evoked brain activity following a heel lance (EEG data recorded in the 1000ms period following each heel lance).</p> <p>Secondary Outcome Measure</p> <p>(i) PIPP-R score during the 30-second period after the heel lance.</p> <p>(ii) Percentage of neonates who develop tachycardia in the 30-second post-heel lance.</p> <p>(iii) Difference in STAI-S scores pre- and post-procedure.</p> <p>Exploratory Outcome Measures</p> <p>(i) Changes in brain activity during touch intervention.</p> <p>(ii) Time taken for heart rate to return to baseline post-heel lance.</p> <p>(iii) Post-procedural respiratory dynamics and incidence of apnoea.</p> <p>(iv) Scores for individual parameters from the STAI-T and STAI-S; 4-point distress questionnaire score; responses to survey about participation in Petal and infant research.</p>

114
115 **Table 1.** Objectives and Outcome Measures. STAI-T: State-Trait Anxiety Inventory-Trait, STAI-S: State-Trait Anxiety
116 Inventory-State, PIPP-R: Premature Infant Pain Profile – Revised.
117

118 METHODS AND ANALYSIS

119

120 Trial Description

121 This is a multicentre randomised-controlled interventional trial, with two research sites (John Radcliffe Hospital,
122 Oxford, and Royal Devon and Exeter Hospital, Devon, UK). The parents of eligible neonates satisfying inclusion
123 criteria (Figure 1) will be approached by a member of the research team. Parental written informed consent will be
124 taken and neonates will be electronically randomised to receive parental stroking either prior to or after a clinically-
125 required heel lance. Patient information leaflets and consent forms are available as supplementary file 1. A unique
126 study ID will be assigned to each individual participant. The randomisation program will use a minimisation algorithm
127 to ensure approximate balance between the groups with respect to gestational age at birth, postnatal age at time
128 of randomisation, sex, the indication for blood sampling, and research site. The users of the system will be blind to
129 the next allocation.

130

131 Each neonate will be studied on a single test occasion lasting approximately one hour (Figure 2) and will not require
132 further follow-up. A parent will first complete the State-Trait Anxiety Inventory-Trait (STAI-T) and State-Trait Anxiety
133 Inventory-State (STAI-S) questionnaires, which will be administered verbally by a researcher. This will allow
134 assessment of both trait anxiety and state anxiety prior to the commencement of the stroking intervention or blood
135 test. At least 30 minutes prior to the heel lance, the research team will set up physiological monitoring including
136 electrocardiography (ECG) and pulse oximetry for continuous recording of baseline cardiorespiratory stability.
137 Electroencephalography (EEG) electrodes will then be sited to allow continuous monitoring of baseline brain activity
138 for at least 10 minutes prior to the clinical procedure. A control heel lance will then be performed followed by the
139 clinical heel lance.

140

141 The control heel lance is a non-noxious sham procedure whereby the lancet is placed against the participant's foot
142 rotated at 90 degrees, preventing release of the blade into the foot. This procedure simulates the tactile and auditory
143 aspects of the blood sampling experience without the noxious input. Brain activity, physiology and facial expression
144 (video) will be recorded for both the control heel lance and clinical heel lance to allow assessment of outcome
145 measures including noxious-evoked brain activity, PIPP-R scores, tachycardia, and respiratory dynamics (Table 1).
146 The heel lance and control stimulus will be linked electronically to the recording equipment as described in previous
147 studies,[7,28,29] providing precise timing of when the heel lance occurs. In the event of the neonate requiring
148 multiple heel lances, data will only be included from the first heel lance (conditional on data quality). Video
149 monitoring of the face will commence approximately 30 seconds prior to the control lance and end at least 30
150 seconds after the clinical heel lance to allow PIPP-R scoring. For neonates randomised to receive pre-procedural
151 stroking, the parent will be instructed to begin stroking down the infant's leg immediately prior to the clinical heel
152 lance, with the aid of an animated visual cue to help maintain a velocity of 3cm/s and a duration of 10 seconds. After
153 the heel lance, blood collection will be delayed for 30 seconds to allow PIPP-R scoring. For neonates randomised to
154 receive post-procedural stroking, the parent will be instructed to begin stroking down the infant's leg after the start
155 of blood collection, when deemed appropriate by the clinician performing the heel lance in order to ensure that
156 blood collection is not disrupted. Parents will be guided by an animated visual cue. A researcher will then verbally
157 administer the STAI-S and 4-point distress questionnaire after the procedure is completed. Physiological monitoring
158 will continue for 30 minutes and EEG monitoring for at least 10 minutes to allow investigation of post-procedural
159 cardiorespiratory dynamics and brain activity as exploratory outcomes of the trial. Finally, the parents will be invited
160 to complete an anonymous survey of their experience and views on research after completion of the study. This
161 study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines
162 (supplementary file 2).[58]

163

164 Intervention

165 The parental touch intervention will involve one parent stroking the infant's leg for 10 seconds. The duration of the
166 intervention is consistent with previous studies.[31,32,53,59] A member of the research team will inform parents of
167 their randomised allocation (either stroking pre-heel lance or post-heel lance) at the start of the test occasion. They
168 will explain and demonstrate how to administer the intervention using their whole hand, stroking in one direction
169 down towards the foot. The infant will lay in a cot during the intervention and procedure. During the demonstration

170 and test occasion, PsychoPy software[60] will be used to provide a visual cue on a computer screen to guide a
 171 consistent stroking speed of 3cm/s for 10 seconds. During the study all neonates received comfort care in accordance
 172 with the local practice guidelines. These measures included swaddling the infants and providing non-nutritive
 173 sucking.

174

175 Recording Techniques

176

177 Electroencephalography (EEG)

178 Electrophysiological activity will be acquired with the SynAmps RT 64-channel headbox and amplifiers
 179 (Compumedics Neuroscan) or with the Compumedics Graef V2 EEG system, with a bandwidth from DC - 400 Hz and
 180 a sampling rate of 2000 or 2048Hz. Data recorded at 2048Hz will be downsampled to 2000Hz prior to further
 181 processing. CURRYscan7 or CURRYscan8 neuroimaging suite (Compumedics Neuroscan) will be used to record the
 182 activity. All equipment will conform to the electrical safety standard for medical devices, IEC 60601-1. Eight EEG
 183 recording electrodes will be positioned on the scalp at Cz, CPz, C3, C4, FCz, T3, T4 and Oz according to the modified
 184 international 10-20 System. Reference and ground electrodes will be placed at Fz and the forehead respectively. EEG
 185 conductive paste will be used to optimise contact with the scalp. All impedances will be reduced to approximately
 186 5kΩ by rubbing the skin with EEG preparation gel prior to electrode placement. An ECG electrode will be placed on
 187 the left clavicle to record heart rate.

188

189 Physiological Monitoring (ECG and Pulse Oximetry)

190 Heart rate, respiratory rate and oxygen saturation will be recorded continuously throughout the study period
 191 (approximately one hour) using ECG and pulse oximetry. Heart rate and oxygen saturation data will be used to
 192 calculate the clinical pain scores following the heel lance and control stimulus and to assess clinical stability across
 193 the test occasion.

194

195 Video Recording

196 Video recording will be used to measure behavioural responses i.e. changes in facial expression during the control
 197 stimulus and clinically-required heel lance. A synchronised LED flash will be activated by the researcher
 198 simultaneously with each stimulation as a marker for the time of stimulation.

199

200 Parental Questionnaire

201 The parent administering the intervention will be asked to complete a short series of validated electronic
 202 questionnaires assessing anxiety and distress at the start and end of the test occasion (Table 2). The researcher will
 203 record the responses to the STAI-T, STAI-S and distress questionnaire in an electronic Case Report Form. The
 204 electronic device will then be presented to the parent to independently complete a short survey about trial
 205 participation and their research experience. The survey will be completed anonymously, and responses will be stored
 206 by trial arm with no link to study IDs.

207

Questionnaire section	Topic	Timing of administration	Questionnaire administrator
20-point State-Trait Anxiety Inventory (STAI)-T	Trait anxiety	Start of test occasion	Administered verbally by researcher
20-point State-Trait Anxiety Inventory (STAI)-S	State anxiety pre-heel lance	Start of test occasion	Administered verbally by researcher
	State anxiety post-heel lance	After the procedure and intervention are completed	Administered verbally by researcher
4-point distress questionnaire	Emotional constructs experienced at time of the clinical heel lance	After the procedure and intervention are completed	Administered verbally by researcher

Anonymous survey	Views on the trial and infant research	End of test occasion	Completed by parent
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Table 2. Trial parental questionnaires.

State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory (STAI) is the gold standard assessment for state anxiety.[61] It is well validated, publicly available and has a trait (STAI-T) version consisting of 20 statements exploring general feelings of anxiety, and a state version (STAI-S) consisting of 20 statements exploring anxiety levels at a particular point in time. Each question is rated on a 4-point scale. The range of possible scores for the STAI varies from a minimum score of 20 to a maximum score of 80 on both the STAI-T and STAI-S subscales. Scores are classified as “no or low anxiety” (20-37), “moderate anxiety” (38-44), and “high anxiety” (45-80).

4-point distress questionnaire

Parents will be asked four questions related to their emotions during the clinical heel lance procedure.[62,63] Each of the four emotional constructs (worried, upset, anxious and sad) will be rated on an 11-point scale ranging from “not at all” (0) to “extremely” (10). A total score between 0 and 40 will be calculated, where higher scores are indicative of greater parental distress. This score is frequently used in research to evaluate parent/child interactions during painful procedures.[62–64]

Outcome Measures

Noxious-evoked Brain Activity

An EEG template that reflects the noxious-evoked brain activity in neonates has previously been defined using principal component analysis, validated in independent data sets[30] and used in clinical studies and a clinical trial.[33] This template will be projected onto the EEG data recorded in the 1000ms period following each heel lance and control heel lance stimulus and the relative weight of the component calculated for each neonate. A greater weight indicates a stronger noxious-evoked response. While the brain activity characterised is directly related to noxious input, it does not reflect all noxious-evoked activity across the brain or all aspects of the pain experience. The response to the non-noxious control heel lance stimulus is being recorded to confirm that it significantly differs from the brain activity evoked by a noxious heel lance. This forms an important data quality control check.[28]

PIPP-R Score

Clinical pain scores will be evaluated using the validated Premature Infant Pain Profile - Revised,[27] which is a composite multimodal measure encompassing behavioural, physiological and contextual indicators of the pain response. It allows for different aspects of the infant pain experience to be captured and has been widely used as the primary outcome measure for infant pain in many clinical trials.[65–67] The PIPP-R score will be calculated for the control heel lance and the clinical heel lance procedure. Heart rate, oxygen saturation and facial expression will be recorded in the 15-second period before and 30-second period after each of the procedures.[26,27] The 15-second period before the heel lance will be recorded immediately prior to the stroking intervention. Videos of the infant’s facial expressions will be scored offline using the PIPP-R facial coding system. Changes in heart rate and oxygen saturation will be recorded with ECG and pulse oximeter and used to calculate the PIPP-R score. For each participant, PIPP-R scores will be assessed by investigators blinded to the study arm. A second investigator (blinded to the trial arm) will re-calculate 20% of the PIPP-R scores to measure inter-rater reliability.

Clinical Stability

Clinical stability will be assessed in the 30-minute periods before and after the heel lance. The percentage of neonates who develop post-procedural tachycardia in the 30 seconds post-heel lance will be a secondary outcome measure of the trial. Tachycardia will be defined as a heart rate >160 beats per minute as per Advanced Paediatric Life Support guidelines, reflecting heart rate values >90th centile for newborn infants in the first week of life.[68,69] Exploratory outcome measures will also include the time taken for the heart rate to return to baseline values post-heel lance and respiratory rate variability in the 30 minutes prior and post heel lance (including incidence of apnoea). An episode of apnoea will be defined as the cessation of breathing for at least 20 seconds.[70]

Parental Experience

259 Parental anxiety will be quantified using the outcomes of the STAI-T and STAI-S questionnaires. Parental distress will
260 be quantified using the 4-point distress score. The anonymous parent survey will assess the parental experience of
261 the trial and parental views on taking part in the trial.

262

263 **Statistics and Analysis**

264 Analysis of outcome measures

265 Data pre-processing and statistical analysis will be performed blind to treatment allocation. The analysis and
266 presentation of results will follow the most up-to-date recommendations of the CONSORT group. All comparative
267 analyses will be performed using MatlabR2020a or an updated version, adjusting for important prognostic factors
268 where possible: these are likely to be a subset of the minimisation factors at randomisation. A full statistical analysis
269 plan will be finalised before any comparative analysis of outcome measures is performed.

270

271 Significance Levels

272 For the analysis of the primary outcome measure, a p-value of 0.05 (two-sided 5% significance level) will be used to
273 indicate statistical significance. Significance levels for secondary outcomes will be corrected for multiple
274 comparisons and the method will be specified in the analysis plan. Two-sided statistical tests and corresponding p-
275 values will be presented throughout; however, for the purposes of interpretation of results, confidence intervals will
276 dominate, rather than p-values.

277

278 Primary

279 *Noxious-evoked brain activity*

280 The projected weight of the template will be compared between the two groups using linear regression, dependent
281 on the mean and variance of the data. If appropriate, we will present the mean and standard deviation for each
282 group and estimate the adjusted mean difference with a 95% confidence interval. If the outcome data are skewed,
283 we will present the median and interquartile range (or entire range, whichever is appropriate) for each group, and
284 estimate the median difference between groups with a corresponding 95% confidence interval.

285

286 Secondary

287 *PIPP-R score*

288 PIPP-R scores (during the 30-second period after heel lance) in the two groups will be compared using linear
289 regression to estimate the adjusted mean difference. If the PIPP-R scores are skewed, we will present the median
290 and interquartile range (or entire range, whichever is appropriate) for each group, and estimate the median
291 difference between groups.

292

293 *Clinical stability (tachycardia)*

294 The percentage of infants experiencing tachycardia will be compared between the two groups. Depending on the
295 distribution of these counts, either Poisson or linear regression will be used to calculate the adjusted effect
296 estimates. If appropriate, adjustments for the 30-minute baseline period will also be made. Alternatively, we will
297 present the medians and interquartile ranges (or entire range, whichever is appropriate) for each group and estimate
298 the median differences between groups. In the event of occurrences being very infrequent, logistic regression may
299 be used as an alternative.

300

301 *Parental anxiety*

302 STAI scores in the two groups will be compared to estimate the adjusted mean difference in pre-procedural and
303 post-procedural STAI-S scores. If the scores are skewed, we will present the median and interquartile range (or entire
304 range, whichever is appropriate) for each group, and estimate the median difference between groups.

305

306 Exploratory

307 Exploratory analyses will be conducted to investigate i) the effects of parental touch on background brain activity,
308 ii) whether pre-procedural parental touch reduces the duration of time for heart rate to return to baseline, iii) the
309 effect of pre-procedural parental touch on respiratory rate variability, respiratory dynamics and the incidence of
310 apnoea and iv) the parental experience of the procedure and involvement in research.

1
2 311
3 312 Sample Size Determination
4 313

5 314 *Power Calculation*

6 315 The assumptions for these calculations are based on data from mechanistic studies investigating the effect of
7 316 (experimenter-led) soft brushing of the skin at CT-optimal rate on the response to an experimental noxious stimulus
8 317 or clinical heel lance in term neonates.[31,32] The mean (SD) brain activity evoked by heel lancing in the control
9 318 group is estimated to be 1.07 (0.66). A 40% reduction in the intervention group is considered to be clinically
10 319 significant and realistic from other studies.[31,54] With 90% power and a two-sided 5% significance level, to observe
11 320 a 40% reduction in brain activity, a sample size of 102 would be required. Allowing for 10% loss, due to technical
12 321 difficulties or other clinical issues, this increases to 112.
13 322

14 323 *Missing Data*

15 324 Missing data may occur in our trial due to equipment failure, EEG artefacts, or clinical issues resulting in withdrawal
16 325 post-randomisation. If missing data exists, we expect it will occur at random, and collected data will be
17 326 representative of the population. To account for potential missing data, we have inflated our sample size by 10%.
18 327 The analysis will be conducted using the available data.
19 328

20 329 **Ethics and dissemination**

21 330 The trial has been approved by the London South East Research Ethics Committee (ref:21/LO/0523) and will be
22 331 conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. EEG is a safe tool used routinely
23 332 in clinical practice and research to measure brain activity. Surface electrodes are used and temporarily fixed without
24 333 glue. All heel lances performed during the trial will have been requested by the clinical team responsible for the
25 334 infant's medical care. No extra blood tests or noxious procedures will be performed for the purpose of the study.
26 335 Every effort will be made to minimise inconvenience and prevent disruption of clinical care. There are no expected
27 336 serious adverse events (SAE) for this trial. Any SAEs identified will be reported to the CI within 24 hours and they will
28 337 report any unexpected SAEs deemed related to the trial to the REC and Sponsor in accordance with REC/HRA
29 338 guidance.
30 339

31 340 Parent(s) may withdraw their neonate from the trial at any time and they are not obliged to give a reason. If parents
32 341 choose to withdraw their child after the study has begun, they will be asked whether data already collected may be
33 342 retained and used for the purposes of the trial. Parents will be made aware that this decision has no impact on any
34 343 aspects of their infant's continuing care. The attending clinician may also withdraw the neonate from the trial if they
35 344 consider this to be in their best interest. If any of the exclusion criteria manifest prior to data collection, the
36 345 participant will be withdrawn.
37 346

38 347 The results of the study will be disseminated to the scientific and wider community through peer-reviewed
39 348 publications and national and international meetings and conferences, via the charities SSNAP and Bliss, and through
40 349 the NHS clinical guideline adoption process.
41 350

42 351 **Patient and Public Involvement (PPI)**

43 352 A PPI representative will be included in the extended PMG group and invited to join specific PMG meetings to discuss
44 353 trial progress and developments. Bliss: for babies born premature or sick is a national UK neonatal charity, which is
45 354 partly funding the trial. They will receive regular trial progress reports and promote the trial across their various
46 355 channels, and disseminate the results. The research team will also work closely with the on-site local Oxford charity
47 356 Supporting the Sick Newborn And their Parents (SSNAP) during the design, conduct and dissemination of the trial.
48 357 SSNAP have reviewed all parent-facing materials, will review manuscripts reporting results, and will be involved in
49 358 disseminating results to the public.
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DISCUSSION

All newborn infants are exposed to clinically-necessary painful procedures. Even healthy neonates on postnatal wards can require repeated painful procedures beyond routine Newborn Screening, such as blood tests for glucose monitoring or jaundice, which can be distressing for both neonates and their parents. In the UK, more than 100,000 newborn infants receive neonatal care every year as a result of prematurity or illness,[71] which, for some, can entail weeks to months of hospitalisation and procedures. As such, improving the management of pain is recognised as a top neonatal UK research priority[72] and a major concern amongst parents and neonatal nurses.[73]

Poor management of neonatal pain can have a significant negative impact on parents. Mothers of hospitalised infants report feeling emotionally and psychologically traumatised due to having to allow their infants to undergo clinically-necessary painful procedures, and due to feelings of helplessness from being unable to protect or comfort their child.[3–5] Actively involving parents in care relieves parental distress[74] and increases the likelihood that infants receive treatment for pain.[1,5,75] Infant massage, a tactile comfort measure which involves patterns of stroking, has been shown to improve mother-infant bonding and improve postnatal depression,[76] a condition afflicting at least one in ten UK mothers in the first-year post-partum[77]. Furthermore, maternal stroking of infants in general has been shown to moderate the behavioural and physiological effects of maternal depression on infants.[78] Promoting the natural tactile behaviour of stroking to provide evidence-based pain-relief would therefore be beneficial to both mothers and infants.

Anxiety about pain is increasingly recognised as a key factor in parental refusal for procedures such as vitamin-K intramuscular injections at birth[79] and immunisations.[80–82] Avoidance of key interventions in early life could have drastic consequences for child health and this issue must be addressed. Indeed, parental anxiety and attitudes during painful procedures can also impact neonatal distress and subsequent pain experience during clinical procedures in later life.[83] Parental anxiety regarding pain could be alleviated by empowering parents to provide safe and effective pain relief for their child. Unlike other non-pharmacological interventions, this strategy could be broadly implemented regardless of feeding status of the infant or availability of a product like sucrose, in hospital as well as the community, and across high and low resource clinical settings.

CT-fibres likely provide the neurobiological mechanism underlying the benefits of tactile stimulation in early life. Studies have revealed that mothers instinctively stroke their infants at a CT-optimal rate[55,56] and that this tactile stimulation is beneficial. CT-optimal touch significantly decreases resting heart rates in infants aged 1-4 months[59] and 9-months,[84] as well as in premature infants (28–36 weeks' gestation).[85] Recent studies have also investigated the neurological correlates of CT-optimal touch in early life. In 2-month-old infants, CT-optimal touch produces greater activation of the insular cortex compared to CT non-optimal touch.[85] Similarly, in term infants CT-optimal stroking with a soft brush produces activation of the primary somatosensory and posterior insular cortices,[86] suggesting that the neonatal brain is sensitive to the somatosensory and socio-affective effects of CT-optimal stroking.

The Petal trial is based upon clear mechanistic evidence from preliminary cohort studies and is, as such, adequately powered to address the clinical question. It employs a range of multimodal outcomes, including electrophysiological, behavioural, and cardiorespiratory measures, to cover the many aspects of pain experience, and seeks to investigate the benefits of the intervention to both neonates and their parents. Blinding of outcome assessment is being performed to ensure the integrity of the trial as it is not possible to blind the researchers at the time of study due to the nature of the intervention. Although parents instinctively stroke at the optimal velocity to stimulate CT-fibres,[55,56] consistency of the intervention is standardised across the trial by providing an animated visual aid for parents to follow. In the event of a positive trial outcome, the intervention could next be translated to more premature infants and other minor painful skin-breaking procedures performed frequently in infants such as immunisation and cannulation and could be performed by parents or healthcare workers in the absence of parents. The Petal trial investigates a simple, free, low-risk, non-pharmacological pain-relieving intervention, which could be rapidly incorporated into routine clinical practice, benefiting infants, their parents, and the wider community.

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2 4133 414 **Trial status**

4 415 Participant recruitment is currently ongoing. Protocol version no. 3.0 (date of submission: 3 February 2022).

5 416

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9 420

10 421 **FOOTNOTES**

11 422

12 423 **Author contributions**

13 424 **MC:** Conceptualization, Methodology, Software, Investigation, Data Curation, Writing - Original Draft, Writing -
14 425 Review & Editing, Visualization, Project Administration. **FM:** Conceptualization, Methodology, Investigation,
15 426 Writing - Original Draft, Writing - Review & Editing, Funding Acquisition. **AH:** Methodology, Investigation, Data
16 427 Curation, Writing - Review & Editing, Project Administration. **DC:** Methodology, Software, Investigation, Data
17 428 Curation, Writing - Review & Editing. **VM:** Conceptualization, Methodology, Writing - Original Draft, Project
18 429 Administration, Funding Acquisition. **CH:** Software, Methodology, Data Curation, Funding Acquisition. **REF:**
19 430 Conceptualization, Methodology, Investigation, Writing - Original Draft. **SR:** Investigation. **MvdV:** Software,
20 431 Validation, Data Curation, Writing - Review & Editing. **LB:** Methodology, Data Curation, Writing - Review & Editing.
21 432 **EA:** Conceptualization, Methodology, Writing - Review & Editing, Supervision. **RP:** Conceptualization, Methodology,
22 433 Investigation, Data Curation, Supervision, Project Administration. **AB:** Conceptualization, Methodology,
23 434 Supervision, Writing - Original Draft, Project administration, Funding Acquisition. **RS:** Conceptualization,
24 435 Methodology, Resources, Writing - Original Draft, Writing - Review & Editing, Supervision, Project Administration,
25 436 Funding Acquisition.

26 437

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30 441

31 442 **Competing interests**

32 443 None declared.

33 444

34 445 **Ethics approval**

35 446 London South East Research Ethics Committee (ref:21/LO/0523).

36 447

37 448 **Figure legend**

38 449 Figure 1. Trial flowchart. IVH: Intraventricular haemorrhage.

39 450 Figure 2. Trial procedures

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For peer review only

Inclusion Criteria

- Born at the John Radcliffe Hospital, Oxford or the Royal Devon and Exeter Hospital, Devon
- Born at or after 35+0 weeks' gestation with a postnatal age ≤ 7 days
- Require a clinical heel lance as part of clinical care
- Parents/guardians have given written informed consent for inclusion in the trial.

Exclusion Criteria

- Hypoxic Ischaemic Encephalopathy
- IVH > grade II
- Received any analgesics/sedatives in the last 24 hours
- Born with a congenital malformation or genetic condition known to affect neurological development
- Born to a mother with a history of substance abuse.



Randomisation (1:1 allocation ratio)

Web-based randomisation

30 min baseline data collection

(EEG, heart rate, oxygen saturation)

Group A (n=56)

Parental touch pre-heel lance

Group B (n=56)

Parental touch post-heel lance

Primary Outcome measures

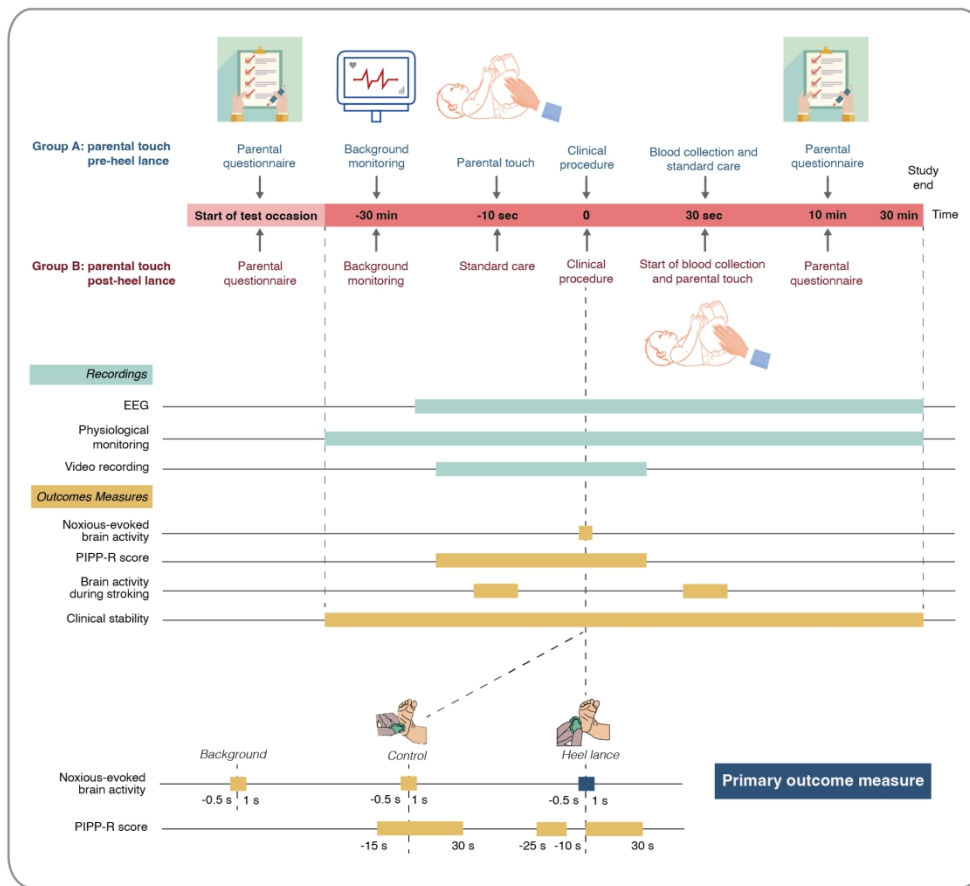
- Magnitude of noxious-evoked brain activity evoked by heel lance.

Secondary Outcome measures

- Premature Infant Pain Profile – Revised (PIPP-R) score during the 30-second period after the heel lance.
- Percentage of neonates who develop tachycardia in the 30 seconds post-heel lance.
- Parent questionnaire assessing anxiety.

Exploratory Outcome measures

- Changes in background brain activity during touch intervention.
- Time taken for heart rate to return to baseline post-heel lance.
- Post procedural respiratory dynamics and incidence of apnoea.
- Parental questionnaire assessing parental anxiety, distress, and experience of research.



Trial procedures.

445x406mm (118 x 118 DPI)

Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Included in manuscript	Section/item	ItemNo	Description	Comment
	Administrative information			
X	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	
X	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	
		2b	All items from the World Health Organization Trial Registration Data Set	
X	Protocol version	3	Date and version identifier	
X	Funding	4	Sources and types of financial, material, and other support	
X	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	
		5b	Name and contact information for the trial sponsor	
		5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	

Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
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12	X	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
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16		6b	Explanation for choice of comparators
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18	X	7	Specific objectives or hypotheses
19			
20	X	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
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28	X	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
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32	X	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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37	X	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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Introduction

Background and rationale

Objectives

Trial design

Methods: Participants, interventions, and outcomes

Study setting

Eligibility criteria

Interventions

Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4			11b	Criteria for discontinuing or modifying allocated interventions for a
5				given trial participant (eg, drug dose change in response to harms,
6				participant request, or improving/worsening disease)
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8			11c	Strategies to improve adherence to intervention protocols, and any
9				procedures for monitoring adherence (eg, drug tablet return,
10				laboratory tests)
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12			11d	Relevant concomitant care and interventions that are permitted or
13				prohibited during the trial
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16	X	Outcomes	12	Primary, secondary, and other outcomes, including the specific
17				measurement variable (eg, systolic blood pressure), analysis metric
18				(eg, change from baseline, final value, time to event), method of
19				aggregation (eg, median, proportion), and time point for each
20				outcome. Explanation of the clinical relevance of chosen efficacy and
21				harm outcomes is strongly recommended
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24	X	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and
25				washouts), assessments, and visits for participants. A schematic
26				diagram is highly recommended (see Figure)
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28	X	Sample size	14	Estimated number of participants needed to achieve study objectives
29				and how it was determined, including clinical and statistical
30				assumptions supporting any sample size calculations
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33	X	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
34				target sample size
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Methods: Assignment of interventions (for controlled trials)

Allocation:

Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4	X	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
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12		Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
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17		Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
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21	X	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
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25			17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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30		Methods: Data collection, management, and analysis		
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32	X	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4			18b	Plans to promote participant retention and complete follow-up,
5				including list of any outcome data to be collected for participants who
6				discontinue or deviate from intervention protocols
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8	X	Data management	19	Plans for data entry, coding, security, and storage, including any
9				related processes to promote data quality (eg, double data entry;
10				range checks for data values). Reference to where details of data
11				management procedures can be found, if not in the protocol
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14	X	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes.
15				Reference to where other details of the statistical analysis plan can be
16				found, if not in the protocol
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18			20b	Methods for any additional analyses (eg, subgroup and adjusted
19				analyses)
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21			20c	Definition of analysis population relating to protocol non-adherence
22				(eg, as randomised analysis), and any statistical methods to handle
23				missing data (eg, multiple imputation)
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26		Methods: Monitoring		
27				
28	X	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
29				and reporting structure; statement of whether it is independent from
30				the sponsor and competing interests; and reference to where further
31				details about its charter can be found, if not in the protocol.
32				Alternatively, an explanation of why a DMC is not needed
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35			21b	Description of any interim analyses and stopping guidelines, including
36				who will have access to these interim results and make the final
37				decision to terminate the trial
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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4	X	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
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8		Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	The project management group (RS, RP, AB, AH, DC, MC, FM) meets monthly throughout the trial to oversee trial conduct and recruitment.
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15		Ethics and dissemination			
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17	X	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	
18					
19		Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	The Investigator will submit and, where necessary, obtain approval from the relevant parties for all substantial amendments to the original approved documents.
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30	X	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	
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33			26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
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36	X	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4	X	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
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7		Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
8				Only the project team will have access to the final trial dataset. After the publication of results, anonymised data can be made available to other researchers upon reasonable request.
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17		Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
18				The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.
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33	X	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
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Study protocol: a multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal)

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4 31b Authorship eligibility guidelines and any intended use of professional
5 writers
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7 31c Plans, if any, for granting public access to the full protocol, participant-
8 level dataset, and statistical code
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Appendices

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12 Informed consent 32 Model consent form and other related documentation given to
13 materials participants and authorised surrogates
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15 Biological specimens 33 Plans for collection, laboratory evaluation, and storage of biological No biological specimens are
16 specimens for genetic or molecular analysis in the current trial and for collected.
17 future use in ancillary studies, if applicable
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20 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on
21 the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative
22 Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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Parental touch trial

Parent Information Leaflet

John Radcliffe Hospital



DEPARTMENT OF PAEDIATRICS
Medical Sciences Division

Oxford University Hospitals **NHS**
NHS Foundation Trust

1 You and your child are eligible to take part in a research study. Before you decide, it is important that
2 you understand why the research is being done and what it involves. Please read the following
3 information and ask us if anything is unclear or if you would like more information.
4
5

6 **Study title:** Parental touch trial (*Petal*)

7 *A randomised controlled trial to investigate the effects of parental touch on relieving*
8 *acute procedural pain in neonates*
9

10
11 **1. What is the purpose of the study?**

12 Babies in hospital often require clinical procedures as part of their routine medical treatment. As babies
13 cannot tell us how much these procedures hurt, it is difficult to make sure that they are receiving the
14 right pain-relief treatments. We know babies can experience discomfort and pain, and we have
15 developed a method to measure changes in brain activity that occur when a baby undergoes a clinical
16 procedure. We also know that babies display specific facial expressions when they are in pain and that
17 their heart rate and breathing rate can increase.
18
19

20 Touch is important for parent and child bonding, and research in adults has shown that stroking the
21 skin at the right speed can reduce pain experienced during some procedures. Stroking and parental
22 touch activates special fibres in the skin that we think can make procedures feel less painful. Some
23 studies have shown that close skin-to-skin contact between babies and their parents can reduce pain
24 during procedures (such as blood tests).
25
26

27 The aim of this research is to understand if parental touch can reduce how much pain their babies
28 experience during a blood test. We also want to know how parents feel when they stroke their baby's
29 leg during a blood test. We would like to see if there are any differences in how a baby responds if a
30 parent strokes their child's leg before or after a blood test.
31
32

33 **2. Why have I been invited?**

34 You and your child have been invited to take part in this study because your child requires a blood test
35 for clinical purposes. We are recruiting parents and their children who were born at least 35 weeks
36 gestation, who need to have a clinical blood test. We hope to recruit in total 112 babies.
37
38

39 **3. Do we have to take part?**

40 No, it is your decision whether or not you and your child take part. If you decide to take part, you will
41 be asked to sign a consent form. If you decide you do not want to take part, this will not affect your
42 child's care.
43
44

45 If you decide you would like to take part, you can change your mind at any time and withdraw you and
46 your child from the study by telling the research team. You do not have to give a reason. You will be
47 asked if we can use the data/images that have already been collected for analysis and if we can publish
48 the anonymised results.
49
50

51 **4. What is involved in the study?**

52 We would like to understand how parental touch (in the form of stroking) may affect how babies
53 respond to a clinically-required blood test. **No blood tests will be carried out solely for research**
54 **purposes.** We will only study your child during a blood test that is needed for clinical purposes. Blood
55 tests will be scheduled according to clinical need and thus you may have less than 24 hours to consider
56 your participation in this trial. Blood tests will be completed in the routine way. On some occasions
57 more than one heel lance is required to collect a sufficient blood sample. If this is the case, the research
58 monitoring equipment will not be removed from your baby between heel lances in order to ensure
59 that we do not interfere with the clinical procedures. As part of the study, we will also administer a
60 'sham' heel lance: this is not a real blood test and will not pierce your baby's skin or cause any pain.

1 This is a control stimulus to simulate the blood test without the 'painful' part. The heel lance is placed
2 against your baby's foot but angled away so that the sharp fires into the air rather than the foot. The
3 study will not interfere with your child's clinical care, nor will there be any delay if an emergency
4 procedure is required.
5
6

7 As part of the study, we will ask you to stroke your child's leg for 10 seconds before, or 10 seconds
8 after, their blood test. Half of the babies in the study will be stroked by a parent before the blood test,
9 and half will be stroked afterwards. Before the study, your baby's details will be entered into a
10 computer programme that will randomly select whether you should stroke your baby before or after
11 the blood test. Where required, we will demonstrate on a doll the speed, location and duration of the
12 stroking. Before we start the study we will make sure you know how to complete the stroking in the
13 correct way. As part of the study, we will also ask you to complete a short questionnaire; the first part
14 will be before the study, the second part at the end. The questionnaire overall should take
15 approximately 15 minutes.
16
17

18 We will assess your child's responses to the blood test by measuring their brain activity. We will also
19 video your child's face, and measure other responses such heart rate, breathing rate and oxygen
20 saturations. We will monitor your child before, during and after the blood test for approximately one
21 hour.
22
23

24 We will use the following recording measures for your child:
25

26 **Measuring brain activity**

27 Electroencephalography (EEG): EEG is a portable imaging system to measure brain activity. It
28 involves gently placing electrodes (small discs) on the head using a paste that can be washed off
29 with soap and water. EEG is routinely used on the neonatal unit, children's wards and clinics.
30
31

32 **Measuring other responses**

33 Vital sign monitoring: Small adhesive discs will be placed on your child's chest to measure changes
34 in breathing rate and heart rate (this is called an ECG).
35
36

37 Videoing your child: We will also video your child during the study. This is so that we can assess
38 changes in facial expression and body movements, and record the exact timing of the blood test.
39

40 We may ask if you are happy for us to use these images for teaching, publicity and/or in scientific
41 journals. If you agree, we will take separate consent for this as your child's face would be present
42 in the video footage. This is an optional part of the study and is not essential. If we do not use the
43 images, this will not affect your child's care or stop your child participating in this research.
44
45

46 **5. Are there any additional risks or benefits for my child?**

47 Recording a video of your child is non-invasive and does not present any risk. EEG and ECG have been
48 used clinically for over 20 years without any adverse effects. All studies have a dedicated team of
49 healthcare professionals and researchers that will ensure the safety of your child at all times. We are
50 not aware of any risks for your child taking part in this study.
51
52

53 The research data collected will not be routinely reviewed by a doctor. If any clinically significant
54 findings are identified at the time of the study then the research team will report these to the clinical
55 care team for further review.
56
57

58 There are no direct benefits of taking part in the study. This study is designed to gather information, to
59 help improve the care we provide for babies in the future. If your child becomes distressed, the
60 research study will be paused or stopped. Any clinically required procedures will still go ahead if the
clinician looking after your child feels that this is appropriate.

6. What information will be collected about me and my child?

We will collect relevant medical (e.g. age), environmental (e.g. medical ward where study was conducted), demographic (e.g. post code) and social (e.g. ethnicity) information about your child from their medical notes. This information helps us to determine which factors may influence the way a baby copes with pain. We will also collect vital sign data (such as heart rate and breathing rate), recordings of their facial expressions and body movements and changes in brain activity caused by the blood test. We will ask you to complete a questionnaire.

All information and videos that are collected during this research study will be stored confidentially. Each baby will be allocated a study number which will be used to label the data. This study forms part of an educational programme.

7. What will happen to the results?

Results will be analysed and published in a journal. All publications will be made available on our website <https://neuroimaging.paediatrics.ox.ac.uk>. The findings may also be used for teaching or academic research presentations. No identifying information will be presented about you or your child, unless you have provided specific consent for us to use videos or images of your child in this way.

8. What will happen to my data and my child's data?

We will use the information about you and your child in order to conduct this study. Research is a task that we perform in the public interest. The University of Oxford, as Sponsor, is the data controller. This means that we, as University of Oxford researchers and collaborators, are responsible for looking after the information collected and using it properly. We will use the minimum personally-identifiable information possible. We will keep identifiable information about you and your child for up to 12 months after the study has finished. This excludes any research documents with personal information, such as consent forms and facial expression recordings, which will be held securely at the University of Oxford for 21 years after the end of the study.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at <http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/>. You can find out more about how we use your information from the contacts in section 12.

Research data may be shared with other researchers, both here and abroad. Responsible members of the University of Oxford and Oxford University Hospitals NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations.

9. Who is organising and funding this research?

This study is sponsored by the University of Oxford and has been funded by the Wellcome Trust and the charity BLISS. Your doctor will not be paid for including you in this study.

10. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by the London - South East Research Ethics Committee.

11. Comments or concerns during the study

The University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment with which your child is provided. If you wish to complain about any aspect of the way in

1 which you have been approached or treated during the course of this study, you should contact Prof
 2 Rebeccah Slater (details below) or the University of Oxford Clinical Trials and Research Governance
 3 (CTRG) office (tel: 01865 616480, email: ctrg@admin.ox.ac.uk).
 4
 5

6 The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with
 7 support for any complaints or queries you may have regarding the care you receive as an NHS
 8 patient. PALS is unable to provide information about this research study. The John Radcliffe Hospital
 9 PALS team can be contacted on: Tel: 01865 221473, Email: PALS@ouh.nhs.uk,
 10 <http://www.ouh.nhs.uk/patient-guide/pals.aspx>.
 11
 12

13 **12. Participation in future research**

14 As we are interested in how your child's response to pain changes as they grow, we may ask if we can
 15 contact you in the future, to ask if you would be happy for your child to take part in other similar
 16 research studies run by our research team. If you agree that we can contact you about other research
 17 studies we will ask you to complete an optional additional consent item on the Consent Form used
 18 when you agree for your child to participate in the study. We will record your contact details, and these
 19 will be kept in a separate electronic database from the rest of the research data. This database is
 20 password-protected and can only be accessed by members of the research team.
 21
 22

23 Your contact details will not be passed onto anyone outside of the research team. All contact will come
 24 from the research team in the first instance. You can opt-out of this at any point by contacting Prof
 25 Rebeccah Slater (details below). Your agreement for us to contact you does not form any obligation to
 26 participate in future research.
 27
 28

29 **What will happen to my data?**

30 If you have provided optional additional consent to be contacted about future studies, we will store
 31 your contact details indefinitely unless you choose to opt-out at any point.
 32
 33

34 **13. Contact for further information**

35 Chief Investigator: Dr Eleri Adams eleri.adams@ouh.nhs.uk 01865 221356
 36
 37

38 Principal Investigator: Prof Rebeccah Slater rebeccah.slater@paediatrics.ox.ac.uk 01865 234229
 39

40 You can also access further information about research or parent support from the following groups:
 41

- 42 • BLISS: UK based charity <https://www.bliss.org.uk/>
- 43 • SSNAP (Support for the Sick Newborn And their Parents): Oxford based
 44 charity <https://www.ssnap.org.uk>
 45



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Representative image
removed for publication

Picture shows example of an EEG study.

Thank you for reading this leaflet.



Parental touch trial

Peer review only

Parent Information Leaflet

Royal Devon and Exeter Hospital



 DEPARTMENT OF PAEDIATRICS
Medical Sciences Division


Royal Devon
University Healthcare
NHS Foundation Trust

1 You and your child are eligible to take part in a research study. Before you decide, it is important
2 that you understand why the research is being done and what it involves. Please read the following
3 information and ask us if anything is unclear or if you would like more information.
4
5

6 **Study title: Parental touch trial (*Petal*)**

7 *A randomised controlled trial to investigate the effects of parental touch on*
8 *relieving acute procedural pain in neonates*
9

10
11 **1. What is the purpose of the study?**

12 Babies in hospital often require clinical procedures as part of their routine medical treatment. As
13 babies cannot tell us how much these procedures hurt, it is difficult to make sure that they are
14 receiving the right pain-relief treatments. We know babies can experience discomfort and pain, and
15 we have developed a method to measure changes in brain activity that occur when a baby
16 undergoes a clinical procedure. We also know that babies display specific facial expressions when
17 they are in pain and that their heart rate and breathing rate can increase.
18
19

20 Touch is important for parent and child bonding, and research in adults has shown that stroking the
21 skin at the right speed can reduce pain experienced during some procedures. Stroking and parental
22 touch activates special fibres in the skin that we think can make procedures feel less painful. Some
23 studies have shown that close skin-to-skin contact between babies and their parents can reduce
24 pain during procedures (such as blood tests).
25
26

27 The aim of this research is to understand if parental touch can reduce how much pain their babies
28 experience during a blood test. We also want to know how parents feel when they stroke their
29 baby's leg during a blood test. We would like to see if there are any differences in how a baby
30 responds if a parent strokes their child's leg before or after a blood test.
31
32

33 **2. Why have I been invited?**

34 You and your child have been invited to take part in this study because your child requires a blood
35 test for clinical purposes. We are recruiting parents and their children who were born at least 35
36 weeks gestation, who need to have a clinical blood test. We hope to recruit in total 112 babies.
37
38

39 **3. Do we have to take part?**

40 No, it is your decision whether or not you and your child take part. If you decide to take part, you
41 will be asked to sign a consent form. If you decide you do not want to take part, this will not affect
42 your child's care.
43
44

45 If you decide you would like to take part, you can change your mind at any time and withdraw you
46 and your child from the study by telling the research team. You do not have to give a reason. You
47 will be asked if we can use the data/images that have already been collected for analysis and if we
48 can publish the anonymised results.
49
50

51 **4. What is involved in the study?**

52 We would like to understand how parental touch (in the form of stroking) may affect how babies
53 respond to a clinically-required blood test. **No blood tests will be carried out solely for research**
54 **purposes.** We will only study your child during a blood test that is needed for clinical purposes.
55 Blood tests will be scheduled according to clinical need and thus you may have less than 24 hours
56 to consider your participation in this trial. Blood tests will be completed in the routine way. On some
57 occasions more than one heel lance is required to collect a sufficient blood sample. If this is the case,
58 the research monitoring equipment will not be removed from your baby between heel lances in
59 order to ensure that we do not interfere with the clinical procedures. As part of the study, we will
60 also administer a 'sham' heel lance: this is not a real blood test and will not pierce your baby's skin

1 or cause any pain. This is a control stimulus to simulate the blood test without the 'painful' part. The
2 heel lance is placed against your baby's foot but angled away so that the sharp fires into the air
3 rather than the foot. The study will not interfere with your child's clinical care, nor will there be any
4 delay if an emergency procedure is required.
5

6
7 As part of the study, we will ask you to stroke your child's leg for 10 seconds before, or 10 seconds
8 after, their blood test. Half of the babies in the study will be stroked by a parent before the blood
9 test, and half will be stroked afterwards. Before the study, your baby's details will be entered into a
10 computer programme that will randomly select whether you should stroke your baby before or after
11 the blood test. Where required we will demonstrate on a doll the speed, location and duration of
12 the stroking. Before we start the study we will make sure you know how to complete the stroking
13 in the correct way. As part of the study, we will also ask you to complete a short questionnaire; the
14 first part will be before the study, the second part at the end. The questionnaire overall should take
15 approximately 15 minutes.
16

17
18 We will assess your child's responses to the blood test by measuring their brain activity. We will also
19 video your child's face, and measure other responses such heart rate, breathing rate and oxygen
20 saturations. We will monitor your child before, during and after the blood test for approximately
21 one hour.
22

23
24 We will use the following recording measures for your child:
25

26 **Measuring brain activity**

27 Electroencephalography (EEG): EEG is a portable imaging system to measure brain activity. It
28 involves gently placing electrodes (small discs) on the head using a paste that can be washed off
29 with soap and water. EEG is routinely used on the neonatal unit, children's wards and clinics.
30

31 **Measuring other responses**

32 Vital sign monitoring: Small adhesive discs will be placed on your child's chest to measure
33 changes in breathing rate and heart rate (this is called an ECG).
34

35 Videoing your child: We will also video your child during the study. This is so that we can assess
36 changes in facial expression and body movements, and record the exact timing of the blood test.
37

38 We may ask if you are happy for us to use these images for teaching, publicity and/or in scientific
39 journals. If you agree, we will take separate consent for this as your child's face would be present
40 in the video footage. This is an optional part of the study and is not essential. If we do not use
41 the images, this will not affect your child's care or stop your child participating in this research.
42
43
44

45 **5. Are there any additional risks or benefits for my child?**

46 Recording a video of your child is non-invasive and does not present any risk. EEG and ECG have
47 been used clinically for over 20 years without any adverse effects. All studies have a dedicated team
48 of healthcare professionals and researchers that will ensure the safety of your child at all times. We
49 are not aware of any risks for your child taking part in this study.
50

51 The research data collected will not be routinely reviewed by a doctor. If any clinically significant
52 findings are identified at the time of the study then the research team will report these to the clinical
53 care team for further review.
54

55 There are no direct benefits of taking part in the study. This study is designed to gather information,
56 to help improve the care we provide for babies in the future. If your child becomes distressed, the
57 research study will be paused or stopped. Any clinically required procedures will still go ahead if the
58 clinician looking after your child feels that this is appropriate.
59
60

6. What information will be collected about me and my child?

We will collect relevant medical (e.g. age), environmental (e.g. medical ward where study was conducted), demographic (e.g. post code) and social (e.g. ethnicity) information about your child from their medical notes. This information helps us to determine which factors may influence the way a baby copes with pain. We will also collect vital sign data (such as heart rate and breathing rate), recordings of their facial expressions and body movements and changes in brain activity caused by the blood test. We will ask you to complete a questionnaire.

All information and videos that are collected during this research study will be stored confidentially. Each baby will be allocated a study number which will be used to label the data. This study forms part of an educational programme.

7. What will happen to the results?

Results will be analysed and published in a journal. All publications will be made available on our website <https://neuroimaging.paediatrics.ox.ac.uk>. The findings may also be used for teaching or academic research presentations. No identifying information will be presented about you or your child, unless you have provided specific consent for us to use videos or images of your child in this way.

8. What will happen to my data and my child's data?

We will use the information about you and your child in order to conduct this study. Research is a task that we perform in the public interest. The University of Oxford, as Sponsor, is the data controller. This means that we, as University of Oxford researchers and collaborators, are responsible for looking after the information collected and using it properly. We will use the minimum personally-identifiable information possible. We will keep identifiable information about you and your child for up to 12 months after the study has finished. This excludes any research documents with personal information, such as consent forms and facial expression recordings, which will be held securely at the University of Oxford for 21 years after the end of the study.

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treatment with which your child is provided. If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr Ravi Poorun (details below) or the University of Oxford Clinical Trials and Research Governance (CTRG) office (tel: 01865 616480, email: ctrg@admin.ox.ac.uk).

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. The Royal Devon and Exeter Hospital PALS team can be contacted on: Tel: 01392 402093, Email: rde-tr.PALS@nhs.net, <https://www.rdehospital.nhs.uk/patients-visitors/patient-advice-liaison-service-pals/#>

12. Participation in future research

As we are interested in how your child's response to pain changes as they grow, we may ask if we can contact you in the future, to ask if you would be happy for your child to take part in other similar research studies run by our research team. If you agree that we can contact you about other research studies we will ask you to complete an optional additional consent item on the Consent Form used when you agree for your child to participate in the study. We will record your contact details, and these will be kept in a separate electronic database from the rest of the research data. This database is password-protected and can only be accessed by members of the research team.

Your contact details will not be passed onto anyone outside of the research team. All contact will come from the research team in the first instance. You can opt-out of this at any point by contacting Prof Rebecca Slater (details below). Your agreement for us to contact you does not form any obligation to participate in future research.

What will happen to my data?

If you have provided optional additional consent to be contacted about future studies, we will store your contact indefinitely unless you choose to opt-out at any point.

13. Contact for further information

Chief Investigator: Dr Eleri Adams eleri.adams@ouh.nhs.uk 01865 221356

Principal Investigator: Dr Ravi Poorun r.poorun@exeter.ac.uk 01392 406980

You can also access further information about research or parent support from the following groups:

- BLISS: UK based charity <https://www.bliss.org.uk/>
- SSNAP (Support for the Sick Newborn And their Parents): Oxford based charity <https://www.ssnap.org.uk>



Representative image
removed for publication

Picture shows example of an EEG study.

Thank you for reading this leaflet.

Consent Form (Oxford)



Study ID:

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Infant's name:

Study Title: Parental touch trial (Petal)

Chief Investigator: Dr Eleri Adams

Principal Investigator: Prof Rebeccah Slater

Please initial each box

Please complete in black ballpoint pen.

1 I confirm that I have read and understood the information sheet (v. , dated / /), for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily.

2 I understand that my participation and my child's participation is voluntary and that me and my child are free to withdraw at any time, without giving any reason, without our medical care or legal rights being affected.

3 I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals from the University of Oxford or Oxford University Hospitals NHS Trust, where it is relevant to my child's taking part in this research. I give permission for these individuals to access to my child's records.

4 I agree to my child being videoed during the study. I understand that recorded images will not be used for public use, only analysis. No identifiable information, including video recordings or imaging, will be used in any publications/presentations. Only anonymised data will be published or presented at meetings.

5 I agree for the collected data to be used for teaching or academic research presentations.

6 I agree to me and my child taking part in the above study.

7 I agree to complete a parental questionnaire related to my child's study.

OPTIONAL

8 I consent to being approached in the future about other similar research studies, by the research team, that my child may be eligible for. I understand that agreeing to be contacted does not oblige me or my child to participate in any further studies.

9 I agree to the images/videos of my child recorded during this study being used for publications and presentations.

Name of parent:

Name of investigator taking consent:

Relationship to baby:

Signature:

Signature:

Date:

Date:

1 to be kept as part of the study documentation (original)

1 copy for parent

1 copy with hospital notes

Consent Form (Exeter)



Study ID:

Infant's name:

Study Title: Parental touch trial (Petal)

Chief Investigator: Dr Eleri Adams **Principal Investigator:** Dr Ravi Poorun

Please initial each box

Please complete in black ballpoint pen.

1 I confirm that I have read and understood the information sheet (v. , dated / /),
 15 for the above study. I have had the opportunity to ask questions and have had these
 16 answered satisfactorily.

2 I understand that my participation and my child's participation is voluntary and that me
 19 and my child are free to withdraw at any time, without giving any reason, without our
 20 medical care or legal rights being affected.

3 I understand that relevant sections of my child's medical notes and data collected
 23 during the study may be looked at by individuals from the University of Oxford, Oxford
 24 University Hospitals NHS Trust or Royal Devon University Healthcare NHS Foundation
 25 Trust, where it is relevant to my child's taking part in this research. I give permission for
 26 these individuals to access to my child's records.

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 30 will not be used for public use, only analysis. No identifiable information, including
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 46 contacted does not oblige me or my child to participate in any further studies.

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Name of parent:

Name of investigator taking consent:

Relationship to baby:

Signature:

Signature:

Date:

Date:

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- 1 copy for parent
- 1 copy with hospital notes
- 1 copy with PI