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Randomised clinical trial comparing the effectiveness of side-lying sleep positioning to back-lying at reducing oxygen desaturation resulting from Obstructive Sleep Apnoea in infants with cleft palate (SLUMBRS2)

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Complete List of Authors:	Metryka, Aleksandra; Manchester University NHS Foundation Trust, Research and Innovation Cuniffe, Claire; Cleft Lip And Palate Association (CLAPA) Evans, Hazel J; Southampton Children's Hospital, Department of Respiratory Paediatrics Gavlak, Johanna G; Southampton Children's Hospital, Department of Respiratory Paediatrics Hudson, Nichola; Salisbury NHS Foundation Trust Kirby, Nigel; Cardiff University Lakhanpaul, Monica; UCL Great Ormond Street Institute of Child Health Population Policy and Practice, Policy & Practice Department; Whittington Health NHS Trust, Policy & Practice Department Lin, Yin-Ling; The University of Manchester Murray, Clare ; Manchester Academic Health Science Centre, Immunity and Respiratory Medicine; The University of Manchester Faculty of Biology Medicine and Health, Division of Infection, Immunity and Respiratory Medicine Rajai, Azita; Manchester University NHS Foundation Trust, Research and Innovation Robson, Helen; Manchester Academic Health Science Centre Schilder, Anne; UCL Ear Institute; NIHR University College London Hospitals Biomedical Research Centre Walsh, Tanya; The University of Manchester Bruce, Iain; Manchester Academic Health Science Centre, Immunity and Respiratory Medicine; The University of Manchester Faculty of Biology Medicine and Health, Division of Infection, Immunity and Respiratory Medicine
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Title: Randomised clinical trial comparing the effectiveness of side-lying sleep positioning to back-lying at reducing oxygen desaturation resulting from Obstructive Sleep Apnoea in infants with cleft palate (SLUMBRS2)

Aleksandra Metryka[1] Aleksandra.Metryka@mft.nhs.uk
Claire Cuniffe[2] Claire.Cunniffe@clapa.com
Hazel J Evans[3] Hazel.Evans@uhs.nhs.uk
Johanna G Gavlak[3] Johanna.Gavlak@uhs.nhs.uk
Nichola Hudson[4] Nichola.Hudson@nhs.net
Nigel Kirby[5] KirbyN@cardiff.ac.uk
Monica Lakhanpaul[6,7] M.Lakhanpaul@ucl.ac.uk
Yin-Ling Lin[8] Yin-Ling.Lin@manchester.ac.uk
Clare S Murray[9,10] Clare.Murray@manchester.ac.uk
Azita Rajai[1] Azita.Rajai@mft.nhs.uk
Helen Robson[9] Helen.Robson@mft.nhs.uk
Anne GM Schilder[11,12] A.Schilder@ucl.ac.uk
Tanya Walsh[8] Tanya.Walsh@manchester.ac.uk
Iain Alexander Bruce[9,10] Iain.Bruce@manchester.ac.uk

1 Research and Innovation, Manchester University Hospitals NHS Foundation Trust, Manchester, UK
2 Cleft Lip And Palate Association (CLAPA)
3 Department of Respiratory Paediatrics, Southampton Children's Hospital, Southampton, UK
4 Salisbury Foundation Trust
5 Centre for Trials Research, Cardiff University
6 Policy & Practice Department, UCL GOS Institute of Child Health
7 Community Paediatrics, Whittington Health NHS Trust
8 School of Dentistry, The University of Manchester
9 Royal Manchester Children's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
10 Division of Infection, Immunity and Respiratory Medicine, Faculty of Biology, Medicine and Health University of Manchester, Manchester, UK
11 evidENT, UCL Ear Institute
12 NIHR University College London Hospitals Biomedical Research Centre

Corresponding Author

Prof Iain Alexander Bruce

Consultant Paediatric Otolaryngologist

Manchester University Hospitals NHS Foundation Trust

Royal Manchester Children's Hospital

Oxford Road

M13 9WL

E-mail: Iain.Bruce@manchester.ac.uk

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Reprints

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Running Title

Which sleep position is better for infants with a cleft palate – RCT protocol.

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ABSTRACT

Introduction:

The craniofacial abnormalities found in infants with cleft palate (CP) decrease their airway patency and increase their risk of obstructive sleep apnoea (OSA). We hypothesise that optimising sleep position in infants with CP may improve airway patency and offer a 'low-cost, high-impact' intervention to prevent the negative impacts of OSA. Because cleft centres give inconsistent advice about sleep position: some recommend back-lying and others side-lying, we will compare these in a randomised controlled trial.

Methods and analysis:

The aim is to determine the clinical effectiveness of side-lying as compared to back-lying sleep positioning in terms of reducing oxygen desaturation resulting from OSA in 244 infants aged 3 to 5 weeks of age, diagnosed with an isolated CP in/by UK cleft centres.

Primary outcome is the 4% oxygen desaturation index (ODI-4) measured using pulse oximetry during sleep.

Research plan:

1. Multicentre randomised controlled trial of side-lying compared with back-lying sleep positioning in reducing oxygen desaturation resulting from OSA in infants with CP at one month of age.
2. Internal pilot questionnaire-based study to support parents and clinicians regarding study participation, seeking to identify and address any barriers to recruitment. Monitoring data from the internal pilot will be used in the final analysis.
3. Co-development of new UK recommendations with CLAPA regarding sleep position for infants with CP.

Ethics and dissemination: The study protocol has received the favourable opinion of the West Midlands - South Birmingham Research Ethics Committee. Study results will be published on affiliated webpages and in peer-reviewed publications and conference contributions.

Trial registration number: ClinicalTrials.Gov (NCT04478201)

Key words:

- Cleft Palate
- Sleep Position
- Sleep Disordered Breathing
- Sleep Oximetry

Article Summary

Strengths and limitations of this study:

- This study addresses an important evidence gap regarding the optimal sleeping position of infants with a cleft palate
- All Cleft Centres in the UK will be invited to participate in the study
- This study will produce sleep-position recommendations for future practice at UK Cleft Centres
- Non-adherence due to randomised allocation being different to advice given by the Cleft Centre

1 Introduction

The craniofacial abnormalities found in children with cleft palate (CP) [1] lead to reduction in airway size, and risk of airway obstruction ranging from intermittent airway collapse during sleep (obstructive sleep apnoea, OSA) [2] to potentially life-threatening airway compromise [3] necessitating intubation or a tracheostomy. Children with CP are at increased risk of OSA when compared to otherwise 'healthy' children. There is evidence that severe OSA may be found in infants before cleft repair [2-4]. In children and adults, sleep position is known to influence the patency of the airway during sleep. When investigating the effect of sleep position on OSA in infants with CP, the best sleep position would be expected to cause less airway collapse and a reduced frequency of oxygen desaturations resulting from OSA. Altering sleep position in infants with CP may offer a 'low-cost, high impact' intervention to limit the negative impacts of OSA.

Oxygen desaturations are known to have negative effects on the wellbeing of children and adults. Children with CP are at increased background risk of impairment in learning, memory and cognition [3] with OSA recognised as having a potentially deleterious effect on cognitive development [3-5]. In addition, infants with CP are at risk of poor weight gain and 'failure to thrive' [4, 6-8] which can be further exacerbated by co-existing OSA. The increased work of breathing associated with OSA, leads to increased energy expenditure, in infants already at risk of reduced calorific intake due to cleft-related feeding difficulties. Poor nutritional status is a significant, and potentially reversible, barrier to the desired surgical repair of a CP in infancy or early childhood.

OSA can have significant and permanent negative effects on health and development in infants with CP. An observational study in a group of children with cleft lip and/or palate, reported that severe OSA in infancy had a significant negative impact on neurocognition, quality of life and weight gain measurable at 3 years [8].

Infant sleeping position is an emotionally charged topic: In 2009, the Department of Health published a leaflet entitled "Reduce the risk of cot death" (www.nhs.uk) which advises parents to "place your baby on the back to sleep, in a cot in a room with you." We have found that there is a lack of evidence and clinical consensus regarding sleep position for infants with CP (7/12 UK centres advised side-lying and 5/12 back-lying) [9]. This is confusing for parents and health professionals who have repeatedly expressed the need for clear and consistent information about the best sleeping position.

1.1 Rationale

Pierre Robin Sequence (PRS) is considered to be an extreme type of CP, associated with a markedly underdeveloped mandible and significantly increased risk of OSA. The standard sleep position advice given for PRS is a side-lying position. Studies in infants with PRS have reported an improvement in feeding difficulty and subsequent weight gain, following early intervention to improve the airway [10]. Side-lying positioning has been postulated as a simple, low-cost therapeutic intervention to improve airway patency in children with OSA [11] and those undergoing general anaesthesia [11-13] or sedation [14].

Cleft lip and/or palate are amongst the most common birth defects, occurring in approximately 1 per 500-700 births [15], of which approximately 45% have an isolated CP [16]. The provision of care for these children is organised into Regional Cleft Networks, comprising of one or two surgical centres. The Cleft Networks have a proven track-record of clinical and research collaboration, enhanced by a highly functional Lead Clinical Nurse Specialists (CNS) Group that serves to facilitate dissemination of knowledge and sharing of best-practice initiatives.

1.2 Aim and objectives

The aim of this project is to determine the clinical effectiveness in infants with CP of side-lying as compared to back-lying sleep positioning in reducing oxygen desaturation resulting from OSA. This is to develop evidence-based recommendations for cleft centres regarding the optimum sleep position for infants with CP. This will be achieved by:

- comparing oxygen saturation during sleep in the side- and back-lying positions at 1 month of age (4 weeks +/- one week).
- comparing self-reported sleep quality between the side-lying and back-lying groups evaluated in a parental questionnaire.
- Providing information in consultation with parents that could be used to inform the development of guidelines and recommendations for sleeping position of infants with a cleft palate.

2 Methods and analysis

This study protocol (v1.1, 2020) describes the design of a multi-centre RCT of sleep position in infants with CP in the UK. The study protocol conforms with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [17] while the RCT will conform to the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting RCTs [18].
An unblended, randomised controlled trial (RCT) of side-lying compared with back-lying sleep positioning in reducing oxygen desaturation resulting from OSA in infants with CP. Infants meeting the eligibility criteria will be randomised to side-lying or back-lying in a ratio 1:1 using a minimisation routine incorporating a random element to reduce predictability. Minimisation factors will be clinical site and syndrome suspected or indicated (yes / no). Allocations will be delivered via a password-protected web-based system. The allocated position will only be used on the night(s) when the infant is monitored for the study purposes. If the first attempt at oxygen monitoring is unsuccessful parents will have the chance to keep the equipment for another night. Thereafter, parents will be free to revert back to the standard sleep position as advised by their cleft centre, should it be different than that used for the monitoring period. All centres represented at our preparatory meeting with the UK Lead Clinical Nurse Specialist group, confirmed that the side-lying position was recommended in some infants at their centre, irrespective of whether it was the standard advice used. As such, all centres had experience of the side-lying position. It was decided not to change the specific advice that centres give to parents regarding how to position the infant in a side-lying position, but any standard written or verbal information would be collected by the study documents.

2.1 Study design

Patient and public involvement

Research described by this protocol follows a feasibility study, entitled: “Does sleep position influence sleep disordered breathing in infants with cleft palate: A feasibility study.” There is an agreement among parents and clinicians that there is an unmet need in this area which requires investigation. SLUMBRS2 development was directed by the results from SLUMBRS feasibility study in which we have investigated the possibility of this trial and spoke with parents about their willingness to take part and the importance of breathing during sleep [19]. Preparation of SLUMBRS and SLUMBRS2 has

been done in collaboration and with full support of the Cleft Lip and Palate Association (CLAPA, working to improve the lives of people born with a cleft and their families in the UK) who have been supportive of the study from the very beginning.

Recruitment setting

The *SLUMBRS2* study is a multi-centred randomised controlled trial. All cleft centres in the UK will be eligible to participate in the study provided that they are prepared to allow sleep-position to be randomised. Participating centres will be required to allow for randomisation of the sleep position for their patients participating in the study. Parents will be randomly assigned advice regarding sleep position for their child, either side-lying or back-lying. It is possible that for some parents this advice will be different to that they received from their local Cleft Centre. Parents will only be asked to follow study related advice during their participation in the study, i.e. up to three days (two nights).
Participants recruited in the initial six months from opening the first study site will be asked to complete an additional questionnaire collecting information about their experience of participating in the study (appendix 1). After 6 months this information will be analysed and used as a basis for potential changes to the recruitment process and technical information on using the monitor, with the aim of supporting parents to consent to join the study.

Parents will be asked to record in a sleep log the starting sleep position and the sleep position when the baby wakes for feeds and/or at the end of sleep. Parents will record the time awake and asleep to aid the respiratory paediatrician and physiologist with reporting the oximetry traces. The mode of feeding (e.g. breast milk, formula or combination feeding) and details of any nutritional supplementation used will be recorded in the sleep questionnaire, completed by parents. Parents will be asked to complete a bespoke sleep questionnaire (appendix 2) to capture information regarding parental perception of sleep quality during the study period.

The study will run for 36 months, with a 30 month recruitment window. We aim to recruit 244 children to the study (122 side-lying and 122 back-lying).

2.2 Target population

2.2.1 Inclusion criteria

- Infants diagnosed with an isolated CP under the care of a collaborating centre
- Parents willing to give consent and able to complete study procedures

2.2.2 Exclusion criteria

- Infants with associated cleft lip
- Infants born prematurely (before 37 week gestation)
- Infants with cardiorespiratory disease
- Infants requiring an intervention to assist with breathing (nasopharyngeal airway)
- Infants requiring an intervention to assist with feeding (nasogastric tube)

2.3 Primary outcome

Oxygen saturation during sleep at 1 month of age (expressed 4% oxygen desaturation index, ODI-4). Oximetry is considered the mainstay of assessment of oxygenation in infants and will be the primary outcome measurement instrument. The ODI-4 represents the average number of times that oxygen saturation falls by at least 4% from baseline every hour.

2.4 Secondary outcomes

i. Other commonly used oximetry parameters including mean SpO2, nadir SpO2, ODI-3, the proportion of total sleep time (TST) with oxygen saturation below 97% [5] 95% [20] 90% [5] and 80% at age 1 month.
ii. Weight at age 1 month (4 weeks +/- one week).
iii. Length and head circumference at age 1 month (4 weeks +/- one week).
iv. Adverse events.

2.5 Sample size

Data from the feasibility study [21] and published studies [22] have reported estimates of the standard deviation (SD) of the primary outcome ODI-4 in the side-lying infants at four weeks to range from 8 to 11 units, with a higher SD observed in the back-lying group. The observed difference in mean ODI-4 between the side-lying and back-lying infant cohorts was 15 units (a standardised effect size of 0.91) [21]. It was considered a smaller but more realistic difference in means of five units to be a clinically important difference (SD 10), a standardised effect size of 0.5. The sample size calculation comparing two means with unequal variances for the primary outcome was, therefore, based on a standardised effect size of 0.5. To account for potential unequal variances in each group a variance ratio of 2 was used in the calculations. To detect a difference of 0.5 SDS with 80% power and alpha equal to 0.05 would require 96 infants to be monitored in each arm of the trial (a total of 192 participants). Informed by the multicentre feasibility and oximetry studies the sample size will be inflated to 244 participants in the RCT, to allow for potential attrition of 21%.

2.6 Statistical analysis

This will follow a pre-specified and approved statistical analysis plan. The primary analysis of the RCT data will use intention-to-treat. Baseline data will be analysed to assess the comparability of the demographic and clinical characteristics of the participants. Data from the trial arms will be compared using generalised linear models and adjusted for minimisation covariates where appropriate under the intention to treat principle. Estimates of treatment effect size will be reported as differences in means for continuous outcomes, and risk ratios / odds ratios for dichotomous outcomes and reported along with 95% confidence intervals. Subgroup analyses will explore the effects of sleep position on infants with, and without, associated syndromes being suspected by the responsible clinical team, through subgroup treatment interactions, at a stricter alpha level 0.01. Reasons for exclusions from analysis will be clearly detailed in the statistical analysis plan.

2.7 Data collection

Sleep oximetry for one night will be recorded in the home at age 3 to 5 weeks. Domiciliary sleep oximetry monitoring (amount of oxygen in the blood) reflects usual UK practice, producing data which is readily applicable to routine clinical practice.
Motion resistant pulse oximetry with a 2 second averaging time (Masimo Rad oximeter) will be recorded during sleep from a securely attached toe sensor. The technical specifications and interpretation guidelines of the Australasian Sleep Association (2019) will guide study protocol development [23]. If the first night's diagnostic study is inadequate or incomplete (less than 5 hours of sleep), then a second night will be offered.
Data from oximeters at relevant participating centres will be downloaded onto their local NHS drives and sent to the University Hospital Southampton NHS Foundation Trust (UHS) for analysis by a respiratory physiologist (Gavlak) or respiratory paediatrician (Evans). Transfer of the oximetry file will be done between encrypted nhs.net emails. In addition to oximetry data participating centres will send a sleep log to UHS to aid with interpreting the data. Data from respective centres sent to UHS will be distinguished with a pseudonym which could only be linked to participant's identifiable information by their recruiting centre. Following analysis at UHS, ODI-3 and -4 values and mean SpO2, nadir SpO2,

the proportion of total sleep time (TST) with oxygen saturation below 97%, 95%, 90% and 80% will be recorded in the study database by CTR staff in Cardiff.

Background and demographic information will be collected including the nature of the cleft palate, smoking habits of family members and first part of the home postcode. Participant's General Practitioner's (GP) and Health Visitor (HV) details will also be collected and their GP will be informed about participation in the SLUMBRS2 study. Participant's GP and HV details will be collected in the Case Report Form (CRF).

During the monitoring period, the parents of participants will be asked to complete the, SLUMBRS2 Sleep questionnaire (appendix 2) and sleep log. Additionally, immediately following the monitoring period the study experience questionnaire (appendix 1) will be completed by parents of those participants who were recruited in the first 6 months of the study opening. Six months will be counted from the time the first study site was open to recruitment to allow for simultaneous data collation and analysis from all sites.

2.8 Study Procedures

Data will be collected at 2 time points;

- Screening / Baseline
- Home monitoring (when the child is aged between 3 to 5 weeks) – At least one overnight sleep period over 1-2 nights

Schedule for study procedures

	Screening	Recruitment and Baseline	Home monitoring at 1 month of age	End of study
Assessment of eligibility criteria	x			
Informed consent		x	x	
Review relevant medical history	x	x		
Demographics		x		
Weight, Length, Head Circumference		x	x	
Sleep log			x	
SpO_2 monitoring			x	
Assess adverse events		x	x	x
Concomitant medication check		x	x	
Study experience questionnaire*				x

*only for study participants recruited within the initial six months of the study opening

2.8.1 Screening

All babies with isolated cleft palate will be screened by the CNS for their inclusion into the SLUMBRS2 RCT (i.e. it will be checked if they fulfil the inclusion criteria). Parents with babies that fulfil the inclusion criteria, will be approached initially by the specialist nurses from the cleft team at that site. The nurse specialist will talk to the parents in more detail about the study and will give parents the Parent/Guardian Information Sheet. All sites will be asked to keep a screening log

throughout the study. Information regarding eligibility, reasons for ineligibility, and the eventual recruitment outcome (consented/not consented) will be collected. This will help to monitor recruitment levels, participation rates, and the number of patients seen within the site.

The screening log should be maintained by the research team at the site and should be emailed (to secure nhs.net email address only) to the SLUMBRS2 trial manager at the MFT every 2 months.

2.8.2 Baseline

After consent is obtained, baseline demographics (including nude birth weight (measured at 0-7 days) – from the *personal child health record (The Red Book*), related medical history, parental smoking status will be collected and recorded in the CRF. This information will either be obtained at a routine visit or at the Home Visit, whichever one occurs first. It is possible that due to the Covid-19 pandemic routine visit with the cleft nurse will take place over the telephone or via a video call.

2.8.3 Home monitoring 1, Day 1

The cleft nurse will arrange home monitoring to help with the setup of the oximeter (sleep monitoring).

The Home monitoring will be scheduled to occur when the infant is 4 weeks old (+/- one week) and free of signs of respiratory tract infection. The sleep study should be done overnight. We are aiming to record sleep oximetry during one period of sleep lasting at least 5h. The infants' weight, length and head circumference measured within the last one week of the oximetry monitoring will be recorded (if available) – from *personal child health record (The Red Book*).

2.8.3.1 Sleep questionnaire

Parents will be given a questionnaire to complete (appendix 2). The questionnaire aims to capture information regarding parental perception of sleep quality during the sleep study. The questionnaire will enable the comparison with reported symptoms of OSA in infants with CP and sleep position.

2.8.3.2 Sleep oximetry monitoring

The cleft nurse will set up the oximeter with the participant study number. The information will enable the study team to identify which baby the recording belongs to once it is downloaded. The nurse will then explain to the parent/s how to switch the monitor on/off and how to attach the SpO_2 sensor to their infant. This will be done either in person if a home visit is possible or via the telephone/ video call if a visit is to be a virtual one as part of the local measures for Covid-19. Parents will also be given a written instructions showing how to use the oximeter and web-link to an instruction video which they could view at any time to refresh their knowledge. The parents will be instructed to record in the sleep log if they remove the monitor or the baby wakes for a feed. The SpO_2 probe can be left on while the baby is feeding.
It is standard practice to silence the oximeter alarm for NHS home oximetry services. However, for the purposes of this study we will set the alarm at SpO_2 70% and heart rate 80, a value that we would not expect to normally record during infant sleep.

The monitor will record the following parameters:
Mean SpO_2
Nadir SpO_2
Oxygen desaturation index 3 and 4 (ODI-3 and 4)
Total sleep time with oxygen saturation below 97%, 95%, 90% and 80%

After the monitoring period has finished, parents will remove the SpO_2 probe and switch off the machine (switching off the machine will not lose the data, it will be stored). For safety purposes, all of

the sleep oximetry sessions will be reviewed by the study Respiratory Physiologist or Paediatrician within 2 weeks of the date of monitoring.

The Respiratory Physiologist and Paediatrician (assessors) who will analyse oximetry readings will be blinded to the sleep position allocation. On the night of oximetry monitoring parents will complete the sleep log, where they will record if the sleep position is as randomised, as well as wake times. The sleep log will be provided to the oximetry assessors to aid with the analysis by helping to identify the sleep and wake times. Sleep log will also measure compliance with randomisation. As such assessors will not know the sleep position and will be blinded.

Procedures for Assessing Safety

All of the sleep oximetry studies will be reviewed by the study Respiratory Physiologist (Gavlak) or Paediatrician (Evans) within 2 weeks of the date of monitoring. Sleep monitoring is usually done at home in babies with CP who present with airway problems. Babies recruited to this study will not have airway concerns sufficient to mandate an airway intervention and therefore we would not expect clinically significant desaturation events. At initial site recruitment the 'emergency' contact details for each cleft team will be collated, along with a written description of the local pathway for onward referral of any infant with suspicion of significant OSA.

2.8.3.3 Abnormal result suspicious of OSA

In the event that a sleep oximetry study is considered abnormal, as indicated by the review from the study Respiratory Physiologist (Gavlak) or Respiratory Paediatrician (Evans) within 2 weeks of the date of monitoring, the local cleft team will contacted by UHS (Gavlak and/or Evans). All abnormal readings considered of clinical concern will prompt an urgent written report of the oximetry findings to the responsible cleft team within 2 weeks, and an additional telephone contact may be made with the cleft team dependent upon the level of concern. An example of an oximetry finding that would be considered of clinical concern would be an ODI-4% >25. The Chief Investigator will be informed of an abnormal sleep study at the same as the local cleft team.

2.8.3.4 Result not suspicious of OSA

The parents and responsible cleft team will receive written confirmation from the UHS (Gavlak and/or Evans) of studies considered to be normal, not later than 4 weeks after the date of monitoring.

2.9 End of study

The day after the oximetry monitor is delivered to the participant, study staff will telephone families to check if successful monitoring has occurred. In an instance when more time with the machine is needed the participant will keep the oximetry machine for another night. Following the completion of sleep oximetry recording, oximetry machines will be either collected by the study staff or by a courier who will return them to the site which recruited the participant. Collection will be arranged by the recruiting site. In order for a courier to be arranged the recruiting site will share the participant's address with the courier. Participants' permission to share their address with the courier will be recorded in the ICF.

2.10 Adverse events

No medicinal product is being given in this study. Reactions to the monitoring are highly unlikely but the study staff will record any adverse events in the CRF during the phone call following the delivery of the oximetry machine or when the equipment is returned. We will record what the illness is (e.g. upper respiratory tract infection), whether any medication was given. Adverse events will be followed up for up to 28 days or until resolution, which ever date is sooner.

2.11 Potential Risks and Benefits

2.11.1 Potential Risks

SLUMBRS2 is an RCT which means that infants will be randomly allocated to one of the two sleeping positions, side- or back-lying. This means that there is a chance that for the 1-2 nights during the study some participants will be asked to follow advice that is contrary to the standard advice given by their cleft centre. This may cause distress to some participants. Current UK practice is that some Cleft Networks recommend side- and others back-lying sleep position as standard, and all recommend side-lying in some infants if they are concerned about airway obstruction. As such, both of the sleep positions being compared would represent 'standard' practice in some UK centres. The probe from the oximeter will be attached to a toe, to limit the chance of entanglement in the cable.

2.11.2 Known Potential Benefits

There are no known direct potential benefits to participating. However, the infant will have an oximetry reading which will be reviewed by a respiratory physiologist, which they would not obtain as part of routine care. This may offer additional reassurance for parents or identification of potential health care issues as indicated by parents in the SLUMBRS feasibility study.

2.12 Study Closure

The end of the study is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the study database. However, the study may be closed prematurely by the Data Monitoring Committee. The SMG have the right at any time to terminate the study for clinical or administrative reasons.
Review of study continuation will be initiated by the SMG within 2 weeks of the following instances taking place:

- Recorded cot death of one of the study participants, past and active.
- Recall of study equipment
- Harm to the participant caused by study equipment.
- New evidence unequivocally showing one of the study positions was safer than other.

The end of the study is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the study database. An end of study notification will be submitted to the REC within 90 days of this date. An end of the study notification will be submitted to the REC within 15 days if the study is terminated prematurely. Investigators will inform the parents of participants of any premature termination of the study and ensure that the appropriate follow up is arranged for all involved. A summary report of the study will be provided to the REC within 12 months of the end of study notification.

All data will be stored for at least 10 years, in accordance with the sponsor's Standard Operating Procedure (SOP). Any queries or concerns about the data, conduct or conclusions of the study can also be resolved in this time. Limited data on the participants and records of any adverse events may be kept for longer if recommended by an independent advisory board.

3 Study Monitoring

Study monitoring will be carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust (MFT), the study sponsor, in line with applicable MFT SOP and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the local research team.

4 Ethics and Dissemination

The study protocol has received the favourable opinion of the West Midlands - South Birmingham Research Ethics Committee. All participating sites must be granted NHS permission by their local Research Office prior to commencing recruitment. Upon completion of our study, the findings will be incorporated into clinical practice for the benefit of patients via the Lead CNS group (Hudson, chair). CNSs provide 'hands-on' care for infants with cleft palate in the home and hospital settings and are ideally placed to highlight research priorities. They have been instrumental in defining and contextualising the research question. In addition, we will disseminate study results through Cleft Network study days and will create a short video which will summarise our study findings and recommendations which will be hosted on the websites https://www.clapa.com/news-item/slumbers-sleep-study/, https://Healthtalk.org , https://Mft.nhs.uk, http://craniofacialsociety.co.uk/, https://www.lullabytrust.org.uk/. It will be co-developed with parents and CLAPA to inform parents and healthcare practitioners about the best sleep practice for infants with CP.

5 Steps to mitigate against the impact of the COVID-19 Pandemic

The study team acknowledge that the COVID-19 pandemic has impacted upon the delivery of clinical research. Wherever possible and safe, the RCT will be delivered as intended. Steps are being taken to ensure that study information (e.g. PIS) can be distributed electronically or by mail. Similarly any data that we collect (e.g. sleep questionnaires and the sleep log) and informed consent can be collected electronically or by mail, to limit contact between researchers and families. Details of the impact of local and national restrictions at individual sites will be recorded on a monthly basis, using a bespoke *Impact Document* that would be available to the SMG, Sponsor and Funder.

Author Contributions

AM contributed to the study design and drafted the manuscript.

CC, HJE, JGG, NH, NK, ML, YLL, CSM, HR, AS, TW, IAB contributed to the study design and revised the manuscript.

All authors read and approved the final manuscript.

Declarations

Ethics Approval and Consent to Participate

West Midlands - South Birmingham Research Ethics Committee

Consent for Publication

Not applicable.

Data Sharing Statement

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' Information

Not applicable.

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Study ID: |__|__|__|__|__|__|

SLUMBRS2 parental experiences questionnaire

The purpose of this questionnaire is to make sure that the study is the best it can be to maximise participation and parental satisfaction. Please can you complete as best you can and return with other study documents.

Date of completion |__|__| / |__|__| / 20|__|__|

1. Which health professional asked you whether you would like to take part in the study? free text

2. Consider your answer in Question1, do you think it was appropriate for them to ask you to take part in the study? Yes/No/Not sure

    a. Can you tell us why? Free text

3. Were you given a Patient Information Sheet (PIS)? Yes/No/Not sure

    a. Were you given enough time to read the PIS and decide whether you wanted to take part in the study? Yes/No/Not sure/I did not read the PIS

4. Did you find the information on the PIS:
    a. Easy to understand: strongly agree/agree/don't know/disagree/strongly disagree
    b. Easy to read: strongly agree/agree/don't know/disagree/strongly disagree
    c. Easy to find answers if unclear: strongly agree/agree/don't know/disagree/strongly disagree

5. What would you change on the PIS to make it better: free text

6. What were the main reasons that made you decide to take part in the study? free text

7. Do you think that this study is important to families of children with cleft? Yes/No/Not sure

8. What is your experience of being part of the study: excellent/good/ok/bad/terrible

9. Can you explain your response in Q8? free text

10. What are the challenges of being part of the study? free text

11. If we were to do this study again, what would you change to make it easier for other parents to take part? free text

SLUMBRS2 Sleep Questionnaire

Study ID: |__|__|__|__|__|

Date of completion |__|__| / |__|__| / 20|__|__|

Below are some questions we would like to ask you about your baby's sleeping habits. This questionnaire is divided into two parts, general questions and more specific questions. Please tick the response that best describes your baby. It should take about 10 minutes to fill in.

General questions

1. Have you been given information about what position to place your baby in whilst asleep?

☐ Yes ☐ No

2. If yes to question 1, what advice were you given about the best position to put your baby to sleep? ☐ Not applicable

☐ On their back ☐ On their side ☐ On their front

☐ Other, please describe:

_____

_____

3. Who gave you this information?

☐ Nurse ☐ Doctor ☐ Someone who is not a health care professional, e.g., family friend

☐ Other (specify):

4. How was that information given to you (you can choose more than one answer)?

☐ Verbally ☐ Pamphlet / leaflet ☐ Email

☐ Facebook ☐ Online forum

5. If written information was given, was this about? ☐ Not applicable

☐ Sleeping position for babies in general ☐ Sleeping position in babies with cleft palate

6. If verbal information was given, was this about? ☐ Not applicable

☐ Sleeping position for babies in general ☐ Sleeping position in babies with cleft palate

SLUMBRS2 Sleep Questionnaire **Study ID:** |__|__|__|__|__|

7. In general, do you think your baby has good quality sleep?

☐ Yes ☐ No

8. Is your baby fed

☐ Breast milk ☐ Formula milk ☐ Combined breast milk / formula feeding

9. Does your baby have medicine for gastric / stomach / acid reflux? (e.g. Gaviscon, Ranitidine, Omeprazole, Domperidone)

☐ Yes ☐ No

If yes, please specify: _____

10. Has your baby had any difficulty in gaining weight?

☐ Yes ☐ No

a) If yes, what advice was given to you about your baby's weight and who gave you the advice?

_____

_____

b) What action (if any) did you take?

_____

_____

11. Is your baby receiving any nutritional supplements?

☐ Yes ☐ No

If yes, please specify: _____

SLUMBRS2 Sleep Questionnaire

Study ID: |__|__|__|__|__|

Specific Questions

For each of the following questions please tick the most appropriate answer to describe your baby's sleep (either during the daytime or at night).

12. Does your baby have difficulty breathing when they are asleep?

Every day	Frequently (more than 3 days per week)	Sometimes (3 days or less per week)	Occasionally (every 1 – 2 weeks)	Only when they have a cold	Never
☐	☐	☐	☐	☐	☐

13. Does your baby stop breathing for periods or have pauses in their breathing during sleep?

Every day	Frequently (more than 3 days per week)	Sometimes (3 days or less per week)	Occasionally (every 1 – 2 weeks)	Only when they have a cold	Never
☐	☐	☐	☐	☐	☐

14. Does your baby snore / make a noise when they are asleep?

Every day	Frequently (more than 3 days per week)	Sometimes (3 days or less per week)	Occasionally (every 1 – 2 weeks)	Only when they have a cold	Never
☐	☐	☐	☐	☐	☐

15. Does your baby make snoring noises while they are awake?

Every day	Frequently (more than 3 days per week)	Sometimes (3 days or less per week)	Occasionally (every 1 – 2 weeks)	Only when they have a cold	Never
☐	☐	☐	☐	☐	☐

16. How would you describe your baby's sleep?

Poor / restless	Sometimes restless	Mostly peaceful	Peaceful
☐	☐	☐	☐

17. If you described your baby's sleep as being poor / restless or sometimes restless, how often is this? ☐ Not applicable

Every day	Frequently (more than 3 days per week)	Sometimes (3 days or less per week)	Occasionally (every 1 – 2 weeks)	Only when they have a cold	Never
☐	☐	☐	☐	☐	☐

SLUMBRS2 Sleep Questionnaire

Study ID: |__|__|__|__|__|

18. Do you regularly have to change your baby's sleeping position to help them sleep easier?

☐ Yes ☐ No

19. If yes, what position helps your baby sleep easier?

☐ On their back ☐ On their side ☐ On their front

☐ Other (specify):

20. Does your baby sleep with a dummy?

☐ Yes ☐ No

21. Is there anything else you would like to tell us about your baby's sleep?

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet	2

		registered, name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	10
Roles and responsibilities: sponsor and funder	#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	n/a this information is not includedi n the paper, but is present in the protocol.
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the	n/a this information is not includedi n the paper, but is

		trial, if applicable (see Item 21a for data monitoring committee)	present in the protocol.
Introduction			
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	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4
Objectives	#7	Specific objectives or hypotheses	4
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, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data	4

		will be collected. Reference to where list of study sites can be obtained	
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)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a for this trial
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a for this trial
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical	5

		relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: 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	4

		unavailable to those who enrol participants or assign interventions	
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	4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a for this trial
Methods: Data collection, management, and analysis			
Data collection plan	#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	6

		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	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a for this trial
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle	6

		missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a for this trial
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	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a for this trial
Ethics and dissemination			
Research ethics	#24	Plans for seeking research ethics committee /	10

approval		institutional review board (REC / IRB) approval	
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)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a for this trial
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	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	n/a for this trial

trial care		and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#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	10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a for this trial
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a for this trial
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a for this trial

Notes:

- 5c: n/a this information is not includedi n the paper, but is present in the protocol.
- 5d: n/a this information is not includedi n the paper, but is present in the protocol.
- 11b: n/a for this trial
- 11d: n/a for this trial
- 17b: n/a for this trial
- 20b: n/a for this trial
- 21b: n/a for this trial
- 23: n/a for this trial
- 26b: n/a for this trial
- 30: n/a for this trial
- 31b: n/a for this trial
- 31c: n/a for this trial
- 33: n/a for this trial This checklist was completed on 20. January 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Study protocol for randomised clinical trial comparing the effectiveness of side-lying sleep positioning to back-lying at reducing oxygen desaturation resulting from Obstructive Sleep Apnoea in infants with cleft palate (SLUMBRS2).

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Ear, nose and throat/otolaryngology, Respiratory medicine
Keywords:	Paediatric otolaryngology < OTOLARYNGOLOGY, Community child health < PAEDIATRICS, Cot death < PAEDIATRICS, SLEEP MEDICINE

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Title: Study protocol for randomised clinical trial comparing the effectiveness of side-lying sleep positioning to back-lying at reducing oxygen desaturation resulting from Obstructive Sleep Apnoea in infants with cleft palate (SLUMBRS2).

Aleksandra Metryka[1] Aleksandra.Metryka@mft.nhs.uk
Claire Cuniffe[2] Claire.Cunniffe@clapa.com
Hazel J Evans[3] Hazel.Evans@uhs.nhs.uk
Johanna G Gavlak[3] Johanna.Gavlak@uhs.nhs.uk
Nichola Hudson[4] Nichola.Hudson@nhs.net
Nigel Kirby[5] KirbyN@cardiff.ac.uk
Monica Lakhanpaul[6,7] M.Lakhanpaul@ucl.ac.uk
Yin-Ling Lin[8] Yin-Ling.Lin@manchester.ac.uk
Clare S Murray[9,10] Clare.Murray@manchester.ac.uk
Azita Rajai[1] Azita.Rajai@mft.nhs.uk
Helen Robson[9] Helen.Robson@mft.nhs.uk
Anne GM Schilder[11,12] A.Schilder@ucl.ac.uk
Tanya Walsh[8] Tanya.Walsh@manchester.ac.uk
Iain Alexander Bruce[9,10] Iain.Bruce@manchester.ac.uk

1 Research and Innovation, Manchester University Hospitals NHS Foundation Trust, Manchester, UK
2 Cleft Lip And Palate Association (CLAPA)
3 Department of Respiratory Paediatrics, Southampton Children's Hospital, Southampton, UK
4 Salisbury Foundation Trust
5 Centre for Trials Research, Cardiff University
6 Policy & Practice Department, UCL GOS Institute of Child Health
7 Community Paediatrics, Whittington Health NHS Trust
8 School of Dentistry, The University of Manchester
9 Royal Manchester Children's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
10 Division of Infection, Immunity and Respiratory Medicine, Faculty of Biology, Medicine and Health University of Manchester, Manchester, UK
11 evidENT, UCL Ear Institute
12 NIHR University College London Hospitals Biomedical Research Centre

Corresponding Author

Prof Iain Alexander Bruce

Consultant Paediatric Otolaryngologist

Manchester University Hospitals NHS Foundation Trust

Royal Manchester Children's Hospital

Oxford Road

M13 9WL

E-mail: Iain.Bruce@manchester.ac.uk

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Running Title

Which sleep position is better for infants with a cleft palate – RCT protocol.

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ABSTRACT

Introduction:

The craniofacial abnormalities found in infants with cleft palate (CP) decrease their airway patency and increase their risk of obstructive sleep apnoea (OSA). We hypothesise that optimising sleep position in infants with CP may improve airway patency and offer a 'low-cost, high-impact' intervention to prevent the negative impacts of OSA. Because cleft centres give inconsistent advice about sleep position: some recommend back-lying and others side-lying, we will compare these in a randomised controlled trial.

Methods and analysis:

The aim is to determine the clinical effectiveness of side-lying as compared to back-lying sleep positioning in terms of reducing oxygen desaturation resulting from OSA in 244 infants aged 3 to 5 weeks of age, diagnosed with an isolated CP in/by UK cleft centres.

Primary outcome is the 4% oxygen desaturation index (ODI-4) measured using pulse oximetry during sleep.

Research plan:

1. Multicentre randomised controlled trial of side-lying compared with back-lying sleep positioning in reducing oxygen desaturation resulting from OSA in infants with CP at one month of age.
2. Internal pilot questionnaire-based study to support parents and clinicians regarding study participation, seeking to identify and address any barriers to recruitment. Monitoring data from the internal pilot will be used in the final analysis.
3. Co-development of new UK recommendations with CLAPA regarding sleep position for infants with CP.

Ethics and dissemination: The study protocol has received the favourable opinion of the West Midlands - South Birmingham Research Ethics Committee. Study results will be published on affiliated webpages and in peer-reviewed publications and conference contributions.

Trial registration number: ClinicalTrials.Gov (NCT04478201)

Key words:

- Cleft Palate
- Sleep Position
- Sleep Disordered Breathing
- Sleep Oximetry

Article Summary

Strengths and limitations of this study:

- This study addresses an important evidence gap regarding the optimal sleeping position of infants with a cleft palate
- All Cleft Centres in the UK will be invited to participate in the study
- This study will produce sleep-position recommendations for future practice at UK Cleft Centres
- Non-adherence due to randomised allocation being different to advice given by the Cleft Centre

1 Introduction

The craniofacial abnormalities found in children with cleft palate (CP) [1] lead to reduction in airway size, and risk of airway obstruction ranging from intermittent airway collapse during sleep (obstructive sleep apnoea, OSA) [2] to potentially life-threatening airway compromise [3] necessitating intubation or a tracheostomy. Children with CP are at increased risk of OSA when compared to otherwise 'healthy' children. There is evidence that severe OSA may be found in infants before cleft repair [2-4]. In children and adults, sleep position is known to influence the patency of the airway during sleep. When investigating the effect of sleep position on OSA in infants with CP, the best sleep position would be expected to cause less airway collapse and a reduced frequency of oxygen desaturations resulting from OSA. Altering sleep position in infants with CP may offer a 'low-cost, high impact' intervention to limit the negative impacts of OSA.

Oxygen desaturations are known to have negative effects on the wellbeing of children and adults. Children with CP are at increased background risk of impairment in learning, memory and cognition [3] with OSA recognised as having a potentially deleterious effect on cognitive development [3-5]. In addition, infants with CP are at risk of poor weight gain and 'failure to thrive' [4, 6-8] which can be further exacerbated by co-existing OSA. The increased work of breathing associated with OSA, leads to increased energy expenditure, in infants already at risk of reduced calorific intake due to cleft-related feeding difficulties. Poor nutritional status is a significant, and potentially reversible, barrier to the desired surgical repair of a CP in infancy or early childhood.

OSA can have significant and permanent negative effects on health and development in infants with CP. An observational study in a group of children with cleft lip and/or palate, reported that severe OSA in infancy had a significant negative impact on neurocognition, quality of life and weight gain measurable at 3 years [8].

Infant sleeping position is an emotionally charged topic: In 2009, the Department of Health published a leaflet entitled "Reduce the risk of cot death" (www.nhs.uk) which advises parents to "place your baby on the back to sleep, in a cot in a room with you." We have found that there is a lack of evidence and clinical consensus regarding sleep position for infants with CP (7/12 UK centres advised side-lying and 5/12 back-lying) [9]. This is confusing for parents and health professionals who have repeatedly expressed the need for clear and consistent information about the best sleeping position.

1.1 Rationale

Pierre Robin Sequence (PRS) is considered to be an extreme type of CP, associated with a markedly underdeveloped mandible and significantly increased risk of OSA. The standard sleep position advice given for PRS is a side-lying position. Studies in infants with PRS have reported an improvement in feeding difficulty and subsequent weight gain, following early intervention to improve the airway [10]. Side-lying positioning has been postulated as a simple, low-cost therapeutic intervention to improve airway patency in children with OSA [11] and those undergoing general anaesthesia [11-13] or sedation [14].

Cleft lip and/or palate are amongst the most common birth defects, occurring in approximately 1 per 500-700 births [15], of which approximately 45% have an isolated CP [16]. The provision of care for these children is organised into Regional Cleft Networks, comprising of one or two surgical centres. The Cleft Networks have a proven track-record of clinical and research collaboration, enhanced by a highly functional Lead Clinical Nurse Specialists (CNS) Group that serves to facilitate dissemination of knowledge and sharing of best-practice initiatives.

1.2 Aim and objectives

The aim of this project is to determine the clinical effectiveness in infants with CP of side-lying as compared to back-lying sleep positioning in reducing oxygen desaturation resulting from OSA. This is to develop evidence-based recommendations for cleft centres regarding the optimum sleep position for infants with CP. This will be achieved by:

- comparing oxygen saturation during sleep in the side- and back-lying positions at 1 month of age (4 weeks +/- one week).
- comparing self-reported sleep quality between the side-lying and back-lying groups evaluated in a parental questionnaire.
- Providing information in consultation with parents that could be used to inform the development of guidelines and recommendations for sleeping position of infants with a cleft palate.

2 Methods and analysis

This study protocol (v1.1, 2020) describes the design of a multi-centre RCT of sleep position in infants with CP in the UK. The study protocol conforms with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [17] while the RCT will conform to the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting RCTs [18].
An unblended, randomised controlled trial (RCT) of side-lying compared with back-lying sleep positioning in reducing oxygen desaturation resulting from OSA in infants with CP. Infants meeting the eligibility criteria will be randomised to side-lying or back-lying in a ratio 1:1 using a minimisation routine incorporating a random element to reduce predictability. Minimisation factors will be clinical site and syndrome suspected or indicated (yes / no). Allocations will be delivered via a password-protected web-based system. The allocated position will only be used on the night(s) when the infant is monitored for the study purposes. If the first attempt at oxygen monitoring is unsuccessful parents will have the chance to keep the equipment for another night. Thereafter, parents will be free to revert back to the standard sleep position as advised by their cleft centre, should it be different than that used for the monitoring period. All centres represented at our preparatory meeting with the UK Lead Clinical Nurse Specialist group, confirmed that the side-lying position was recommended in some infants at their centre, irrespective of whether it was the standard advice used. As such, all centres had experience of the side-lying position. It was decided not to change the specific advice that centres give to parents regarding how to position the infant in a side-lying position, but any standard written or verbal information would be collected by the study documents. Study is planned to begin recruitment in June 2021.

2.1 Study design

Patient and public involvement

Research described by this protocol follows a feasibility study, entitled: “Does sleep position influence sleep disordered breathing in infants with cleft palate: A feasibility study.” There is an agreement among parents and clinicians that there is an unmet need in this area which requires investigation. SLUMBRS2 development was directed by the results from SLUMBRS feasibility study in which we have investigated the possibility of this trial and spoke with parents about their willingness to take part

and the importance of breathing during sleep [19]. Preparation of SLUMBRS and SLUMBRS2 has been done in collaboration and with full support of the Cleft Lip and Palate Association (CLAPA, working to improve the lives of people born with a cleft and their families in the UK) who have been supportive of the study from the very beginning.

Recruitment setting

The *SLUMBRS2* study is a multi-centred randomised controlled trial. All cleft centres in the UK will be eligible to participate in the study provided that they are prepared to allow sleep-position to be randomised. Participating centres will be required to allow for randomisation of the sleep position for their patients participating in the study. Parents will be randomly assigned advice regarding sleep position for their child, either side-lying or back-lying. It is possible that for some parents this advice will be different to that they received from their local Cleft Centre. Parents will only be asked to follow study related advice during their participation in the study, i.e. up to three days (two nights).
Participants recruited in the initial six months from opening the first study site will be asked to complete an additional questionnaire collecting information about their experience of participating in the study (appendix 1). After 6 months this information will be analysed and used as a basis for potential changes to the recruitment process and technical information on using the monitor, with the aim of supporting parents to consent to join the study.

Parents will be asked to record in a sleep log the starting sleep position and the sleep position when the baby wakes for feeds and/or at the end of sleep. Parents will record the time awake and asleep to aid the respiratory paediatrician and physiologist with reporting the oximetry traces. The mode of feeding (e.g. breast milk, formula or combination feeding) and details of any nutritional supplementation used will be recorded in the sleep questionnaire, completed by parents. Parents will be asked to complete a bespoke sleep questionnaire (appendix 2) to capture information regarding parental perception of sleep quality during the study period.

The study will run for 36 months, with a 30 month recruitment window. We aim to recruit 244 children to the study (122 side-lying and 122 back-lying).

2.2 Target population

2.2.1 Inclusion criteria

- Infants diagnosed with an isolated CP under the care of a collaborating centre
- Parents willing to give consent and able to complete study procedures

2.2.2 Exclusion criteria

- Infants with associated cleft lip
- Infants born prematurely (before 37 week gestation)
- Infants with cardiorespiratory disease
- Infants requiring an intervention to assist with breathing (nasopharyngeal airway)
- Infants requiring an intervention to assist with feeding (nasogastric tube)

2.3 Primary outcome

Oxygen saturation during sleep at 1 month of age (expressed 4% oxygen desaturation index, ODI-4). Oximetry is considered the mainstay of assessment of oxygenation in infants and will be the primary outcome measurement instrument. The ODI-4 represents the average number of times that oxygen saturation falls by at least 4% from baseline every hour.

2.4 Secondary outcomes

i. Other commonly used oximetry parameters including mean SpO2, nadir SpO2, ODI-3, the proportion of total sleep time (TST) with oxygen saturation below 97% [5] 95% [20] 90% [5] and 80% at age 1 month.
ii. Weight at age 1 month (4 weeks +/- one week).
iii. Length and head circumference at age 1 month (4 weeks +/- one week).
iv. Adverse events.

2.5 Sample size

Data from the feasibility study [21] and published studies [22] have reported estimates of the standard deviation (SD) of the primary outcome ODI-4 in the side-lying infants at four weeks to range from 8 to 11 units, with a higher SD observed in the back-lying group. The observed difference in mean ODI-4 between the side-lying and back-lying infant cohorts was 15 units (a standardised effect size of 0.91) [21]. It was considered a smaller but more realistic difference in means of five units to be a clinically important difference (SD 10), a standardised effect size of 0.5. The sample size calculation comparing two means with unequal variances for the primary outcome was, therefore, based on a standardised effect size of 0.5. To account for potential unequal variances in each group a variance ratio of 2 was used in the calculations. To detect a difference of 0.5 SDS with 80% power and alpha equal to 0.05 would require 96 infants to be monitored in each arm of the trial (a total of 192 participants). Informed by the multicentre feasibility and oximetry studies the sample size will be inflated to 244 participants in the RCT, to allow for potential attrition of 21%.

2.6 Statistical analysis

This will follow a pre-specified and approved statistical analysis plan. The primary analysis of the RCT data will use intention-to-treat. Baseline data will be analysed to assess the comparability of the demographic and clinical characteristics of the participants. Data from the trial arms will be compared using generalised linear models and adjusted for minimisation covariates where appropriate under the intention to treat principle. Estimates of treatment effect size will be reported as differences in means for continuous outcomes, and risk ratios / odds ratios for dichotomous outcomes and reported along with 95% confidence intervals. Subgroup analyses will explore the effects of sleep position on infants with, and without, associated syndromes being suspected by the responsible clinical team, through subgroup treatment interactions, at a stricter alpha level 0.01. Reasons for exclusions from analysis will be clearly detailed in the statistical analysis plan.

2.7 Data collection

Sleep oximetry for one night will be recorded in the home at age 3 to 5 weeks. Domiciliary sleep oximetry monitoring (amount of oxygen in the blood) reflects usual UK practice, producing data which is readily applicable to routine clinical practice.
Motion resistant pulse oximetry with a 2 second averaging time (Masimo Rad oximeter) will be recorded during sleep from a securely attached toe sensor. The technical specifications and interpretation guidelines of the Australasian Sleep Association (2019) will guide study protocol development [23]. If the first night's diagnostic study is inadequate or incomplete (less than 5 hours of sleep), then a second night will be offered.
Data from oximeters at relevant participating centres will be downloaded onto their local NHS drives and sent to the University Hospital Southampton NHS Foundation Trust (UHS) for analysis by a respiratory physiologist (Gavlak) or respiratory paediatrician (Evans). Transfer of the oximetry file will be done between encrypted nhs.net emails. In addition to oximetry data participating centres will send a sleep log to UHS to aid with interpreting the data. Data from respective centres sent to UHS will be distinguished with a pseudonym which could only be linked to participant's identifiable information by their recruiting centre. Following analysis at UHS, ODI-3 and -4 values and mean SpO2, nadir SpO2,

the proportion of total sleep time (TST) with oxygen saturation below 97%, 95%, 90% and 80% will be recorded in the study database by CTR staff in Cardiff.

Background and demographic information will be collected including the nature of the cleft palate, smoking habits of family members and first part of the home postcode. Participant's General Practitioner's (GP) and Health Visitor (HV) details will also be collected and their GP will be informed about participation in the SLUMBRS2 study. Participant's GP and HV details will be collected in the Case Report Form (CRF).

During the monitoring period, the parents of participants will be asked to complete the, SLUMBRS2 Sleep questionnaire (appendix 2) and sleep log. Additionally, immediately following the monitoring period the study experience questionnaire (appendix 1) will be completed by parents of those participants who were recruited in the first 6 months of the study opening. Six months will be counted from the time the first study site was open to recruitment to allow for simultaneous data collation and analysis from all sites.

2.8 Study Procedures

Data will be collected at 2 time points (Table 1);

- Screening / Baseline
- Home monitoring (when the child is aged between 3 to 5 weeks) – At least one overnight sleep period over 1-2 nights

Table 1 Schedule for study procedures

	Screening	Recruitment and Baseline	Home monitoring at 1 month of age	End of study
Assessment of eligibility criteria	x			
Informed consent		x	x	
Review relevant medical history	x	x		
Demographics		x		
Weight, Length, Head Circumference		x	x	
Sleep log			x	
SpO_2 monitoring			x	
Assess adverse events		x	x	x
Concomitant medication check		x	x	
Study experience questionnaire*				x

*only for study participants recruited within the initial six months of the study opening

2.8.1 Screening

All babies with isolated cleft palate will be screened by the CNS for their inclusion into the SLUMBRS2 RCT (i.e. it will be checked if they fulfil the inclusion criteria). Parents with babies that fulfil the inclusion criteria, will be approached initially by the specialist nurses from the cleft team at that site. The nurse specialist will talk to the parents in more detail about the study and will give parents the Parent/Guardian Information Sheet (appendix 3 and Informed Consent Form appendix 4).

All sites will be asked to keep a screening log throughout the study. Information regarding eligibility, reasons for ineligibility, and the eventual recruitment outcome (consented/not consented) will be collected. This will help to monitor recruitment levels, participation rates, and the number of patients seen within the site.

The screening log should be maintained by the research team at the site and should be emailed (to secure nhs.net email address only) to the SLUMBRS2 trial manager at the MFT every 2 months.

2.8.2 Baseline

After consent is obtained, baseline demographics (including nude birth weight (measured at 0-7 days) – from the *personal child health record (The Red Book*), related medical history, parental smoking status will be collected and recorded in the CRF. This information will either be obtained at a routine visit or at the Home Visit, whichever one occurs first. It is possible that due to the Covid-19 pandemic routine visit with the cleft nurse will take place over the telephone or via a video call.

2.8.3 Home monitoring 1, Day 1

The cleft nurse will arrange home monitoring to help with the setup of the oximeter (sleep monitoring).

The Home monitoring will be scheduled to occur when the infant is 4 weeks old (+/- one week) and free of signs of respiratory tract infection. The sleep study should be done overnight. We are aiming to record sleep oximetry during one period of sleep lasting at least 5h. The infants' weight, length and head circumference measured within the last one week of the oximetry monitoring will be recorded (if available) – from *personal child health record (The Red Book*).

2.8.3.1 Sleep questionnaire

Parents will be given a questionnaire to complete (appendix 2). The questionnaire aims to capture information regarding parental perception of sleep quality during the sleep study. The questionnaire will enable the comparison with reported symptoms of OSA in infants with CP and sleep position.

2.8.3.2 Sleep oximetry monitoring

The cleft nurse will set up the oximeter with the participant study number. The information will enable the study team to identify which baby the recording belongs to once it is downloaded. The nurse will then explain to the parent/s how to switch the monitor on/off and how to attach the SpO_2 sensor to their infant. This will be done either in person if a home visit is possible or via the telephone/ video call if a visit is to be a virtual one as part of the local measures for Covid-19. Parents will also be given a written instructions showing how to use the oximeter and web-link to an instruction video which they could view at any time to refresh their knowledge. The parents will be instructed to record in the sleep log if they remove the monitor or the baby wakes for a feed. The SpO_2 probe can be left on while the baby is feeding.
It is standard practice to silence the oximeter alarm for NHS home oximetry services. However, for the purposes of this study we will set the alarm at SpO_2 70% and heart rate 80, a value that we would not expect to normally record during infant sleep.

The monitor will record the following parameters:
Mean SpO_2
Nadir SpO_2
Oxygen desaturation index 3 and 4 (ODI-3 and 4)
Total sleep time with oxygen saturation below 97%, 95%, 90% and 80%

After the monitoring period has finished, parents will remove the SpO_2 probe and switch off the machine (switching off the machine will not lose the data, it will be stored). For safety purposes, all of

the sleep oximetry sessions will be reviewed by the study Respiratory Physiologist or Paediatrician within 2 weeks of the date of monitoring.

The Respiratory Physiologist and Paediatrician (assessors) who will analyse oximetry readings will be blinded to the sleep position allocation. On the night of oximetry monitoring parents will complete the sleep log, where they will record if the sleep position is as randomised, as well as wake times. The sleep log will be provided to the oximetry assessors to aid with the analysis by helping to identify the sleep and wake times. Sleep log will also measure compliance with randomisation. As such assessors will not know the sleep position and will be blinded.

Procedures for Assessing Safety

All of the sleep oximetry studies will be reviewed by the study Respiratory Physiologist (Gavlak) or Paediatrician (Evans) within 2 weeks of the date of monitoring. Sleep monitoring is usually done at home in babies with CP who present with airway problems. Babies recruited to this study will not have airway concerns sufficient to mandate an airway intervention and therefore we would not expect clinically significant desaturation events. At initial site recruitment the 'emergency' contact details for each cleft team will be collated, along with a written description of the local pathway for onward referral of any infant with suspicion of significant OSA.

2.8.3.3 Abnormal result suspicious of OSA

In the event that a sleep oximetry study is considered abnormal, as indicated by the review from the study Respiratory Physiologist (Gavlak) or Respiratory Paediatrician (Evans) within 2 weeks of the date of monitoring, the local cleft team will contacted by UHS (Gavlak and/or Evans). All abnormal readings considered of clinical concern will prompt an urgent written report of the oximetry findings to the responsible cleft team within 2 weeks, and an additional telephone contact may be made with the cleft team dependent upon the level of concern. An example of an oximetry finding that would be considered of clinical concern would be an ODI-4% >25. The Chief Investigator will be informed of an abnormal sleep study at the same as the local cleft team.

2.8.3.4 Result not suspicious of OSA

The parents and responsible cleft team will receive written confirmation from the UHS (Gavlak and/or Evans) of studies considered to be normal, not later than 4 weeks after the date of monitoring.

2.9 End of study

The day after the oximetry monitor is delivered to the participant, study staff will telephone families to check if successful monitoring has occurred. In an instance when more time with the machine is needed the participant will keep the oximetry machine for another night. Following the completion of sleep oximetry recording, oximetry machines will be either collected by the study staff or by a courier who will return them to the site which recruited the participant. Collection will be arranged by the recruiting site. In order for a courier to be arranged the recruiting site will share the participant's address with the courier. Participants' permission to share their address with the courier will be recorded in the ICF.

2.10 Adverse events

No medicinal product is being given in this study. Reactions to the monitoring are highly unlikely but the study staff will record any adverse events in the CRF during the phone call following the delivery of the oximetry machine or when the equipment is returned. We will record what the illness is (e.g. upper respiratory tract infection), whether any medication was given. Adverse events will be followed up for up to 28 days or until resolution, which ever date is sooner.

2.11 Potential Risks and Benefits

2.11.1 Potential Risks

SLUMBRS2 is an RCT which means that infants will be randomly allocated to one of the two sleeping positions, side- or back-lying. This means that there is a chance that for the 1-2 nights during the study some participants will be asked to follow advice that is contrary to the standard advice given by their cleft centre. This may cause distress to some participants. Current UK practice is that some Cleft Networks recommend side- and others back-lying sleep position as standard, and all recommend side-lying in some infants if they are concerned about airway obstruction. As such, both of the sleep positions being compared would represent 'standard' practice in some UK centres. The probe from the oximeter will be attached to a toe, to limit the chance of entanglement in the cable.

2.11.2 Known Potential Benefits

There are no known direct potential benefits to participating. However, the infant will have an oximetry reading which will be reviewed by a respiratory physiologist, which they would not obtain as part of routine care. This may offer additional reassurance for parents or identification of potential health care issues as indicated by parents in the SLUMBRS feasibility study.

2.12 Study Closure

The end of the study is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the study database. However, the study may be closed prematurely by the Data Monitoring Committee. The SMG have the right at any time to terminate the study for clinical or administrative reasons.
Review of study continuation will be initiated by the SMG within 2 weeks of the following instances taking place:

- Recorded cot death of one of the study participants, past and active.
- Recall of study equipment
- Harm to the participant caused by study equipment.
- New evidence unequivocally showing one of the study positions was safer than other.

The end of the study is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the study database. An end of study notification will be submitted to the REC within 90 days of this date. An end of the study notification will be submitted to the REC within 15 days if the study is terminated prematurely. Investigators will inform the parents of participants of any premature termination of the study and ensure that the appropriate follow up is arranged for all involved. A summary report of the study will be provided to the REC within 12 months of the end of study notification.

All data will be stored for at least 10 years, in accordance with the sponsor's Standard Operating Procedure (SOP). Any queries or concerns about the data, conduct or conclusions of the study can also be resolved in this time. Limited data on the participants and records of any adverse events may be kept for longer if recommended by an independent advisory board.

3 Study Monitoring

Study monitoring will be carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust (MFT), the study sponsor, in line with applicable MFT SOP and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the local research team.

4 Ethics and Dissemination

The study protocol has received the favourable opinion of the West Midlands - South Birmingham Research Ethics Committee. All participating sites must be granted NHS permission by their local Research Office prior to commencing recruitment. Upon completion of our study, the findings will be incorporated into clinical practice for the benefit of patients via the Lead CNS group (Hudson, chair). CNSs provide 'hands-on' care for infants with cleft palate in the home and hospital settings and are ideally placed to highlight research priorities. They have been instrumental in defining and contextualising the research question. In addition, we will disseminate study results through Cleft Network study days and will create a short video which will summarise our study findings and recommendations which will be hosted on the websites https://www.clapa.com/news-item/slumbers-sleep-study/, https://Healthtalk.org , https://Mft.nhs.uk, http://craniofacialsociety.co.uk/, https://www.lullabytrust.org.uk/. It will be co-developed with parents and CLAPA to inform parents and healthcare practitioners about the best sleep practice for infants with CP.

5 Steps to mitigate against the impact of the COVID-19 Pandemic

The study team acknowledge that the COVID-19 pandemic has impacted upon the delivery of clinical research. Wherever possible and safe, the RCT will be delivered as intended. Steps are being taken to ensure that study information (e.g. PIS) can be distributed electronically or by mail. Similarly any data that we collect (e.g. sleep questionnaires and the sleep log) and informed consent can be collected electronically or by mail, to limit contact between researchers and families. Details of the impact of local and national restrictions at individual sites will be recorded on a monthly basis, using a bespoke *Impact Document* that would be available to the SMG, Sponsor and Funder.

Author Contributions

AM contributed to the study design and drafted the manuscript.

CC, HJE, JGG, NH, NK, ML, YLL, CSM, AR, HR, AS, TW, IAB contributed to the study design and revised the manuscript.

All authors read and approved the final manuscript.

Declarations

Ethics Approval and Consent to Participate

West Midlands - South Birmingham Research Ethics Committee

Consent for Publication

Not applicable.

Data Sharing Statement

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' Information

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Ethical Approval

West Midlands - South Birmingham Research Ethics Committee, REC reference: 20/WM/0302

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Study ID: |__|__|__|__|__|__|

SLUMBRS2 parental experiences questionnaire

The purpose of this questionnaire is to make sure that the study is the best it can be to maximise participation and parental satisfaction. Please can you complete as best you can and return with other study documents.

Date of completion |__|__| / |__|__| / 20|__|__|

1. Which health professional asked you whether you would like to take part in the study? free text

2. Consider your answer in Question1, do you think it was appropriate for them to ask you to take part in the study? Yes/No/Not sure

    a. Can you tell us why? Free text

3. Were you given a Patient Information Sheet (PIS)? Yes/No/Not sure

    a. Were you given enough time to read the PIS and decide whether you wanted to take part in the study? Yes/No/Not sure/I did not read the PIS

4. Did you find the information on the PIS:
    a. Easy to understand: strongly agree/agree/don't know/disagree/strongly disagree
    b. Easy to read: strongly agree/agree/don't know/disagree/strongly disagree
    c. Easy to find answers if unclear: strongly agree/agree/don't know/disagree/strongly disagree

5. What would you change on the PIS to make it better: free text

6. What were the main reasons that made you decide to take part in the study? free text

7. Do you think that this study is important to families of children with cleft? Yes/No/Not sure

8. What is your experience of being part of the study: excellent/good/ok/bad/terrible

9. Can you explain your response in Q8? free text

10. What are the challenges of being part of the study? free text

11. If we were to do this study again, what would you change to make it easier for other parents to take part? free text

SLUMBRS2 Sleep Questionnaire

Study ID: |__|__|__|__|__|

Date of completion |__|__| / |__|__| / 20|__|__|

Below are some questions we would like to ask you about your baby's sleeping habits. This questionnaire is divided into two parts, general questions and more specific questions. Please tick the response that best describes your baby. It should take about 10 minutes to fill in.

General questions

1. Have you been given information about what position to place your baby in whilst asleep?

☐ Yes ☐ No

2. If yes to question 1, what advice were you given about the best position to put your baby to sleep? ☐ Not applicable

☐ On their back ☐ On their side ☐ On their front

☐ Other, please describe:

_____

_____

3. Who gave you this information?

☐ Nurse ☐ Doctor ☐ Someone who is not a health care professional, e.g., family friend

☐ Other (specify):

4. How was that information given to you (you can choose more than one answer)?

☐ Verbally ☐ Pamphlet / leaflet ☐ Email

☐ Facebook ☐ Online forum

5. If written information was given, was this about? ☐ Not applicable

☐ Sleeping position for babies in general ☐ Sleeping position in babies with cleft palate

6. If verbal information was given, was this about? ☐ Not applicable

☐ Sleeping position for babies in general ☐ Sleeping position in babies with cleft palate

SLUMBRS2 Sleep Questionnaire

Study ID: |__|__|__|__|__|

7. In general, do you think your baby has good quality sleep?

☐ Yes ☐ No

8. Is your baby fed

☐ Breast milk ☐ Formula milk ☐ Combined breast milk / formula feeding

9. Does your baby have medicine for gastric / stomach / acid reflux? (e.g. Gaviscon, Ranitidine, Omeprazole, Domperidone)

☐ Yes ☐ No

If yes, please specify: _____

10. Has your baby had any difficulty in gaining weight?

☐ Yes ☐ No

a) If yes, what advice was given to you about your baby's weight and who gave you the advice?

_____

_____

b) What action (if any) did you take?

_____

_____

11. Is your baby receiving any nutritional supplements?

☐ Yes ☐ No

If yes, please specify: _____

SLUMBRS2 Sleep Questionnaire

Study ID: |__|__|__|__|__|

Specific Questions

For each of the following questions please tick the most appropriate answer to describe your baby's sleep (either during the daytime or at night).

12. Does your baby have difficulty breathing when they are asleep?

Every day	Frequently (more than 3 days per week)	Sometimes (3 days or less per week)	Occasionally (every 1 – 2 weeks)	Only when they have a cold	Never
☐	☐	☐	☐	☐	☐

13. Does your baby stop breathing for periods or have pauses in their breathing during sleep?

Every day	Frequently (more than 3 days per week)	Sometimes (3 days or less per week)	Occasionally (every 1 – 2 weeks)	Only when they have a cold	Never
☐	☐	☐	☐	☐	☐

14. Does your baby snore / make a noise when they are asleep?

Every day	Frequently (more than 3 days per week)	Sometimes (3 days or less per week)	Occasionally (every 1 – 2 weeks)	Only when they have a cold	Never
☐	☐	☐	☐	☐	☐

15. Does your baby make snoring noises while they are awake?

Every day	Frequently (more than 3 days per week)	Sometimes (3 days or less per week)	Occasionally (every 1 – 2 weeks)	Only when they have a cold	Never
☐	☐	☐	☐	☐	☐

16. How would you describe your baby's sleep?

Poor / restless	Sometimes restless	Mostly peaceful	Peaceful
☐	☐	☐	☐

17. If you described your baby's sleep as being poor / restless or sometimes restless, how often is this? ☐ Not applicable

Every day	Frequently (more than 3 days per week)	Sometimes (3 days or less per week)	Occasionally (every 1 – 2 weeks)	Only when they have a cold	Never
☐	☐	☐	☐	☐	☐

SLUMBRS2 Sleep Questionnaire

Study ID: |__|__|__|__|__|

18. Do you regularly have to change your baby's sleeping position to help them sleep easier?

☐ Yes ☐ No

19. If yes, what position helps your baby sleep easier?

☐ On their back ☐ On their side ☐ On their front

☐ Other (specify):

20. Does your baby sleep with a dummy?

☐ Yes ☐ No

21. Is there anything else you would like to tell us about your baby's sleep?

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Comparing the effectiveness of side-lying sleep positioning to back-lying at reducing oxygen desaturation resulting from Obstructive Sleep Apnoea in infants with cleft palate (SLUMBRS2).

Parent/Guardian Information Sheet (Version 1.1, 25 Nov 2020)

We would like to invite you and your baby to take part in our research study. Joining the study is entirely up to you, so before you decide we would like you to understand why the research is being done and what it would involve for your child and you. One of our team will go through the information sheet with you and answer any questions you have. Please take time to read the information and feel free to talk to others about the study if you wish.

Important things you need to know

- We want to find the best way to answer the question, "what is the best sleeping position for a baby with isolated cleft palate?"
- SLUMBRS2 study will answer this question by comparing the levels of oxygen in the bloodstream of babies whilst sleeping on their side or on their back.
- Taking part will involve monitoring your baby sleeping at home, using a sensor attached to their foot that records changes in the amount of oxygen levels in the blood. This will not involve any discomfort for your baby.
- Sleep monitoring will take place at night.
- We will be randomly assigning babies to one of two sleeping positions: side or back lying. We will ask you to follow the assigned sleeping position only during the monitored sleep.

Why are we doing this research?

Currently, doctors and nurses working within your cleft team do not know the best advice to give parents about the safest sleep position for a baby with a cleft palate. Although some UK cleft centres advise that babies should sleep on their backs other centres advise positioning the baby on their side as their experience has been that the child breathes easier during sleep in this position. However, we still do not know which sleeping position is best.

If a baby's airway becomes regularly narrowed during sleep then the levels of oxygen in the blood stream will drop and the levels of the waste gas carbon dioxide will increase, which can affect health in severe cases. Children with cleft palate can be at increased risk of this airway narrowing which has led doctors and nurses to think about what is the best sleeping position for children with a cleft palate.

We want to find out the answer the question, "what is the best sleeping position for a baby with isolated cleft palate?"

We have asked all Cleft Centres in the United Kingdom to be involved in the study. Each of the centres will invite parents and their babies to take part in the study.

Insert your Trust logo

Why have we been asked to take part?
You and your baby have been invited to take part because you are a parent of a baby who has an isolated cleft palate and your cleft network is participating in the study. We would like to recruit 244 babies and their families.

What would taking part involve?
We would like to look at the effect of sleeping position on oxygen level in the blood.

This will involve monitoring your baby sleeping at home, using a sensor attached to their foot that records changes in the amount of oxygen in the blood. This will not involve any discomfort for your baby.

We would like to monitor your baby for a period of 1 night's sleep, hopefully lasting 5 hours or more, when they are about 1 month old. We will also ask you to complete a form about your baby's sleep. Participants recruited in the first 6 months from the start of the study will also be asked to complete a questionnaire about their experiences of participating in the study. Please check with your cleft nurse if this will be applicable to you.

We will randomly assign your child to one of the sleeping positions: side or back lying. You will only need to adhere to that advice during the 1 night of sleep when your child will be monitored. After your participation has finished you will follow the advice given by your cleft centre.

If you agree for your baby to take part, you will be asked to sign a consent form. Once you have consented to take part we will collect some information about you and your baby, this may be done at a routine clinic visit, during the first research home visit or telephone/ video call visit, whichever occurs first.

Day 1

- The research nurse will collect your baby's most recent weight, length and head circumference as recorded in the Red Book and ask you some questions about your baby's medical history.
- We will ask you to complete a short questionnaire about your baby's sleeping habits and a "sleep log" – which will collect information such as your baby's sleeping position and feeding times. This will be provided to you as a paper or electronic version, depending on your preference.
- Your cleft nurse will set up the sleep monitoring machine (oximeter) and show you how to switch the monitor on and off and also how to connect the sensors to your baby. This may be done during the home visit or via a video call.
- You will be given written instructions of how to use the monitor as well as information of where to find an instruction video, in case you need to refresh your knowledge.
- You will be asked to monitor your baby for a period of time (at night) while they are asleep. The nurse will not be there for the sleep monitoring *but you will be able to contact her / him if you have any concerns.*

What to do when the alarm goes off on the machine (oximeter)?

The alarm on the machine that measures oxygen levels in the bloodstream (oximeter) is a safety measure to alert if there is a prolonged fall in blood oxygen levels that could be a risk to your baby. Thankfully, life-threatening events are very rare, and in fact the alarms are usually switched off for home sleep studies in the UK. We have decided to have the alarms switched on for this research study. Both of the sleep positions being compared in our study are used as standard in different parts of the country.

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We know that all babies have brief falls in oxygen levels during sleep which may trigger the alarm. This is entirely normal and is due to normal variations in breathing patterns in babies. The alarm can also go off for other reasons such as the baby moving or the sensor becoming detached from the foot. It is very unlikely if the alarm goes off that your baby is in danger especially if the alarm is brief. We recommend that the baby's cot is placed in your bedroom for the night(s) of monitoring. If the alarm goes off and does not stop within a few seconds you should check that your baby is breathing (like you would do if you bought a home apnoea alarm) and make sure that your baby has not rolled over into a face down position.

We want to find out what is happening to the amount of oxygen in your baby's blood stream whilst they are asleep. To help us recognize when the oxygen recording from the machine is from sleep, we ask you to pull the cable out of the machine while keeping the sensor on your child's foot during feeds/nappy changes and complete the sleep log accordingly.

Do we have to take part?
It is up to you whether you and your baby take part in this study. Not taking part will have no effect on the care your baby receives now or in the future.
If you decide you do want to take part you will be asked to sign a consent form. This is to say that you understand what will happen. Even after signing the consent form, if you decide at any time that you and your baby no longer want to take part that is OK. You can withdraw from the study at any time without having to give a reason why.

What are the possible benefits of taking part?
This study will not help you or your baby directly. Instead it will help to answer the question of which sleep position is better for children with an isolated cleft palate. As part of this study you will find out your child's oxygenation levels during sleep. A Sleep Physiologist and Respiratory Paediatrician will review all collected data and will report all results to parents who are taking part in the study, via their local cleft team.

What are the possible disadvantage and risks of taking part?
You will be randomised to one of the two sleeping positions: side or back lying therefore for the night of the study you child may be asked to sleep in a position that is different to that advised by your centre. The equipment used to monitor the levels of oxygen is standard equipment that is routinely used, has no risk associated with it and is not uncomfortable for your baby.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the research nurse who will do their best to answer your questions [*local contact number*]. If you remain unhappy and wish to complain formally, you can do this by contacting your hospitals Patient Advice and Liaison Service (PALS). Details can be obtained from [*insert local details*]

Will our information be kept confidential?
Yes. All information collected about your child and you will be kept confidential and stored anonymously and securely under the provisions of the 2018 Data Protection Act.

Your name and your baby's name will be removed from all the information we collect and the information will be given a code so that you, and they, cannot be identified. The information with the code will be entered into the main computer (database) via a secure internet connection. The database is kept securely in the Centre for Trials Research at the University of Cardiff. Members of the research team entering the information will have a personal password to access the database.

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With your permission, your baby's GP, their health visitor and any other doctors involved in their clinical care will be told of their participation in the study. Your baby's relevant medical records may be inspected by the study team and regulatory authorities. This is to check that the study is being carried out correctly.

If you agree we would like to share with you relevant future research opportunities led by the Chief Investigator of SLUMBRS2, by the members of the SLUMBRS2 study management group or affiliated organisations: Cleft Lip and Palate Association (CLAPA) and the Cleft Collective.
Data collected for the purpose of this study will be stored for 10 years after the study finishes.

Impact of COVID-19 on the study.
Your local Cleft Centre will follow national and their local guidance with regards to Covid-19. All the equipment that you receive will have been cleaned as per the local policy. Sensors for the oximetry machine that you will receive are single use and will come to you in an unopened packaging. Any information that is gathered from you will be done in accordance with local practice, e.g. this may be via telephone or video call and not in person. If appropriate and agreed by you, study documents will be exchanged with you via email.

What will happen to the results of the study?
The results of the study (using only anonymous data) will be made available to the parents that took part in the study, parents and children affected by cleft via the Cleft Lip and Palate Association (CLAPA) website and through UK Cleft lip and palate centres. We will also publish a study summary on the following websites:
1. Healthtalk.org
2. Mft.nhs.uk
3. Cleft Palate Professional Organisations (http://craniofacialsociety.co.uk/)
4. https://www.lullabytrust.org.uk/

We have commissioned Healthtalk.org to produce an animated video summary of research to be shared on the websites mentioned.
The results will also be published in scientific journals and may be presented at conferences.

Who is organising and funding the study?
The organisation responsible the study is Manchester University Hospital NHS Foundation Trust. The study is funded by a "Research for Patient Benefit" grant from the National Institute of Health Research (NIHR). The NIHR is funded by the Department of Health and is part of the NHS.

How have patients and the public been involved in this study?
The Cleft Lip and Palate Association (CLAPA) were involved in the design of this study. We will have input from parent representatives, who are part of the Study Advisory Group, throughout the study. The Study Advisory Group provides independent advice to the SLUMBRS2 study team.

Who has reviewed this study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your / your baby's interests. This study has been reviewed and given favourable opinion by [*Insert name*] Research Ethics Committee.

If you decide you do not want to take part
We also understand that parents may have many different reasons for choosing not to consent and this is also important information for researchers. We would like to know (if you wish to tell us) your reasons for declining to be involved in the study. Knowing this will help

Insert your Trust logo

us amend the study. Your decision will be respected and nobody will try to change your mind.

How will we use information about you?

Medical records of your baby will be accessed to obtain information for the research purposes. We will also need to use information from [you] for this research project.

This information will include:

- Your child's date of birth
- Your contact details including e-mail address
- Your home address for courier equipment pick up

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to slumbrs@mft.nhs.uk , or
- by ringing us on [insert number]

Thank you for reading this Parent/Guardian information sheet and considering yours and your baby's participation in this study.

If you'd like to find out more about the study please contact:

Name and Surname of the local PI [telephone] and [email]
Or please email the Study Manager slumbrs@mft.nhs.uk

Insert Your Trust's Logo

Comparing the effectiveness of side-lying sleep positioning to back-lying at reducing oxygen desaturation resulting from Obstructive Sleep Apnoea in infants with cleft palate.

Parent / Guardian Informed Consent Form, V 1.0 19 Oct 2020

Site No. / Participant ID: __ __ / __ __ __

Please initial each of the boxes

1. I confirm that I have read the parent information sheet dated 19 Oct 2020 (Version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my and my baby's participation is voluntary and that I am free to withdraw my baby at any time without giving any reason, without my baby's medical care or legal rights being affected. ☐
3. I understand that my baby's sleeping position will be randomly assigned for the duration of the study and may differ from the sleeping position that is advised by our local Cleft Centre. ☐
4. I understand that relevant sections of my baby's medical notes and information collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my baby taking part in this research. I give permission for these individuals to have access to my baby's records. ☐
5. I agree to my baby's General Practitioner and Health Visitor being informed of my participation in the study. ☐
6. I agree to share my address with the courier used by the study sponsor to collect the study equipment. ☐
7. I agree for my e-mail address to be collected and stored for the purpose of this study. ☐
8. I agree for my baby to take part in the above study. ☐
9. **Optional:** I agree to be contacted regarding future research opportunities lead by the study management group or its collaborators. ☐

_____
Child's Name (Print)

_____ _____ _____
Parent / guardian's name (Print) Signature Date

_____ _____ _____
Name of person taking consent (Print) Signature Date

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet	2

		registered, name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	10
Roles and responsibilities: sponsor and funder	#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	n/a this information is not includedi n the paper, but is present in the protocol.
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the	n/a this information is not includedi n the paper, but is

		trial, if applicable (see Item 21a for data monitoring committee)	present in the protocol.
Introduction			
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	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4
Objectives	#7	Specific objectives or hypotheses	4
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, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data	4

		will be collected. Reference to where list of study sites can be obtained	
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)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a for this trial
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a for this trial
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical	5

		relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: 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	4

		unavailable to those who enrol participants or assign interventions	
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	4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a for this trial
Methods: Data collection, management, and analysis			
Data collection plan	#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	6

		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	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a for this trial
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle	6

		missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a for this trial
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	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a for this trial
Ethics and dissemination			
Research ethics	#24	Plans for seeking research ethics committee /	10

approval		institutional review board (REC / IRB) approval	
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)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a for this trial
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	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	n/a for this trial

trial care		and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#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	10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a for this trial
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a for this trial
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Attached as an appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a for this trial

Notes:

- 5c: n/a this information is not includedi n the paper, but is present in the protocol.
- 5d: n/a this information is not includedi n the paper, but is present in the protocol.
- 11b: n/a for this trial
- 11d: n/a for this trial
- 17b: n/a for this trial
- 20b: n/a for this trial
- 21b: n/a for this trial
- 23: n/a for this trial
- 26b: n/a for this trial
- 30: n/a for this trial
- 31b: n/a for this trial
- 31c: n/a for this trial
- 33: n/a for this trial This checklist was completed on 20. January 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai