FULL/LONG TITLE OF THE STUDY

"CoolCuddle" study: Development and evaluation of a standard procedure of a cuddling process allowing parents to cuddle their babies undergoing cooling therapy.

SHORT STUDY TITLE / ACRONYM

CoolCuddle Study: Refining and evaluating a care pathway for parents to cuddle their babies undergoing cooling therapy.

PROTOCOL VERSION NUMBER AND DATE

Version 1.6

11.02.2020

RESEARCH REFERENCE NUMBERS

IRAS Number:	257430
SPONSORS Number:	CH/2018/6611
FUNDERS Number:	PB-PG-1217-20020

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:

.....

Date:

...../...../.....

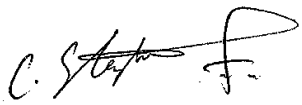
Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: 

Date:

..12/06/2019.....

.....

Name: (please print):

.....Dr Ela Chakkarapani.....

LIST of CONTENTS

KEY STUDY CONTACTS

Insert full details of the key study contacts including the following

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Joint-sponsor(s)/co-sponsor(s)	NA
Funder(s)	NIHR RfPB
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Committees	Study steering group Prof Andrew Whitelaw (Chair of the steering group) Level D, St Michael's Hospital Southwell street Bristol BS2 8EG Email: Andrew.whitelaw@bristol.ac.uk

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
NIHR RfPB	£148,412.00

STUDY SUMMARY

Study Title	**"CoolCuddle" study: Development and evaluation of a standard procedure of a cuddling process allowing parents to cuddle their babies undergoing cooling therapy.**
Internal ref. no. (or short title)	CoolCuddle
Study Design	Cohort Study
Study Participants	Infants undergoing therapeutic hypothermia who are admitted to the NICU at St Michael's Hospital or at Southmead Hospital in Bristol and their parents Neonatal staff involved in the "CoolCuddle" process
Planned Size of Sample (if applicable)	Stage 1: 4-6 cooled parent/s-infant pairs over 3 months Stage 2: 20-24 cooled parent/s-infant pairs over 12 months
Follow up duration (if applicable)	
Planned Study Period	1st Sept 2019 to 1st April 2021
Research Aim	To incorporate a refined "CoolCuddle" protocol into the existing cooling therapy pathway that will allow parents to cuddle their babies during cooling therapy.
Objectives	To develop the existing cuddling technique for non-cooled babies receiving intensive care into a "CoolCuddle" protocol using the physiology stability data during cuddling and qualitative data from nurses, parents and medical staff by adopting "talk aloud " technique. To investigate whether the "CoolCuddle" protocol would maintain stable cooling therapy, respiratory, cardiovascular and neurophysiology.

	To develop a modified cooling therapy pathway with the "CoolCuddle" protocol incorporated into the pathway.
Outcomes	Refined "CoolCuddle" protocol at the end of phase 1. Physiological stability as measured by means and variability of surface and core temperature, ventilation, cardiovascular and neurophysiology parameters between the epochs of pre, during and post "CoolCuddle". Modified cooling therapy pathway with "CoolCuddle" protocol integrated within the pathway. Maternal mood, mother-infant bonding, father-infant attachment, mode of feeding at discharge and length of stay at hospital. Qualitative feedback on the "CoolCuddle" technique from parents and neonatal staff to refine the pathway and facilitate rollout into practice. Incidence and detailed description of any adverse events

ROLE OF STUDY SPONSOR AND FUNDER

University Hospitals Bristol NHS Foundation Trust are the sponsor for this study and overall responsibility for the initiation and management of the research.

National Institute for Health Research under its Research for Patient Benefit programme (RfPB) funds this study. The sponsor or the funder does not influence the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The chief investigator will send a draft copy of any proposed publication, articles, presentations and press releases to the RfPB at the same time as submission for publication or at least 28 days before the date intended for publication whichever is earlier.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Study management group

The study management group will comprise Ms S Okano, Dr J Ingram, Dr E Chakkarapani and Dr A Billetop and will meet every 4-6 weeks to discuss the progress of the study and deal with issues arising from the study to enable achieving the deadlines.

Study steering group

The study steering group is chaired by Prof Andrew Whitelaw, Emeritus Professor of Neonatology. Other members of the steering group include an independent statistician and neonatologist from another Trust. The steering committee is independent of the sponsor and the funder and will meet soon after study initiation to agree on the terms of reference of the group. They will meet four times during the study. The committee will monitor the study progress, advise on its further progression, and review adverse events.

Periodic reports of all adverse events, and other events of interest (detailed in Section 8.6) will be sent to the study steering group for review.

The Committee will make a recommendation to the study management group about continuation of the study. The study may be terminated early on the instruction of the study steering group and with agreement by sponsor. Study steering group meeting minutes will be provided to the sponsor.

Parent advisory group:

We have formed a parent advisory group (PAG) comprising 5 parents which includes four sets of parents and one mother(4 fathers and 5 mothers) The research nurse (SO) and Dr Jenny Ingram will liaise with the parent advisory group. The parent advisory group is currently contactable via email. We will organise a face-to-face (including Skype options) meeting with PAG to discuss the steps involved in the study and their roles. Members of PAG will be appropriately compensated as per the INVOLVE guidance.

We have asked the PAG for their input on the parent-facing materials including the parent information sheet and consent form. We will have another meeting at the end of stage 1 informing them of the progress and any challenges in the study which they can help us with. At the end of stage 2, we will discuss the qualitative findings with them and ask for their views. At the end of stage 3, we will share the “CoolCuddle” protocol and seek their views on it and their support in dissemination. We have also established a partnership with the national neonatal charity Bliss to disseminate the output of the research to parents and NICUs.

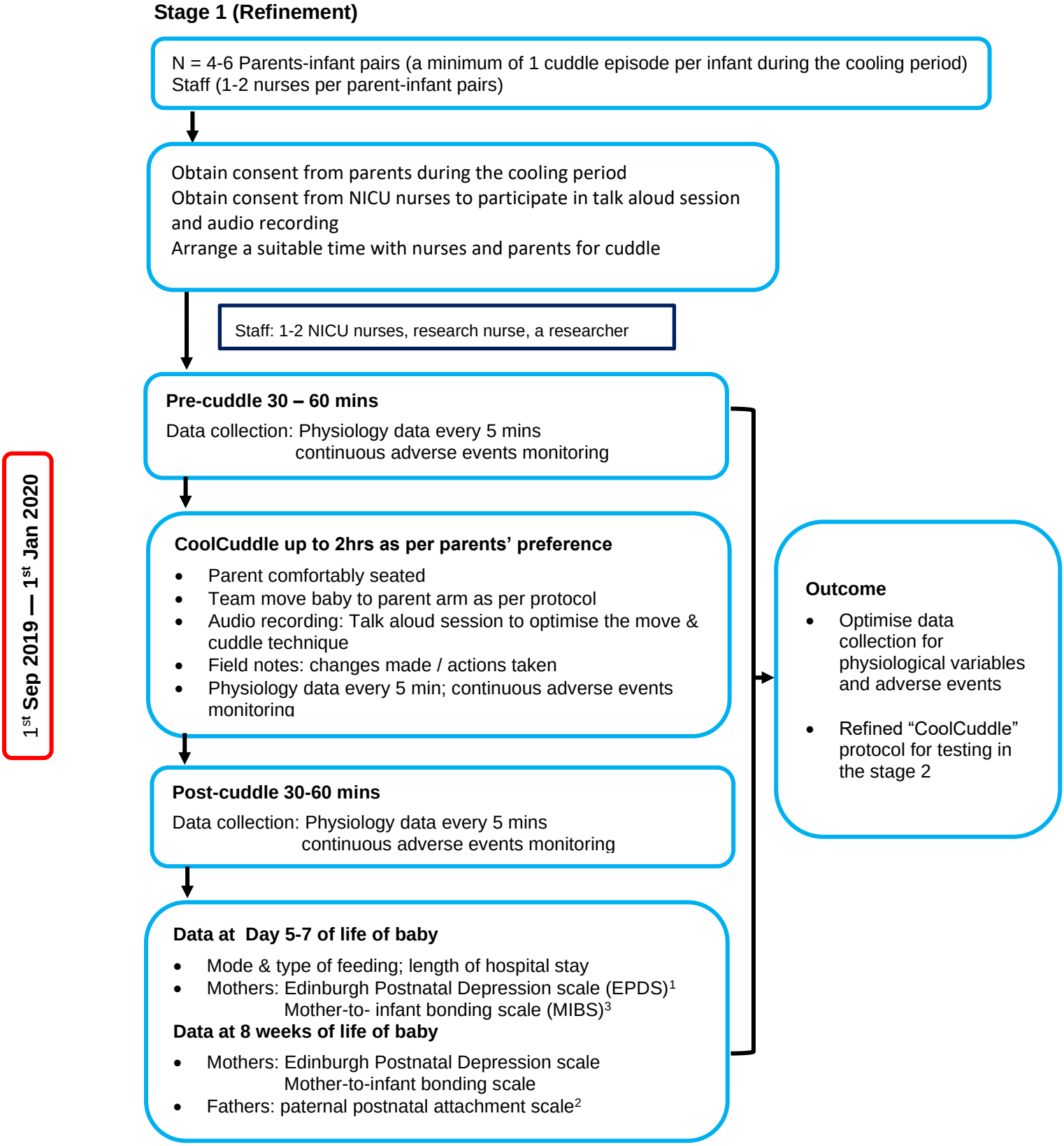
PROTOCOL CONTRIBUTORS

Co-investigators Prof Pete Blair and Dr David Odd reviewed and commented on the protocol. The parent advisory group had already commented on the feasibility of the study design. Their views on the protocol, participant information sheet and consent form are considered before finalising these documents.

KEY WORDS: Therapeutic hypothermia, hypoxic ischaemic encephalopathy, cuddle, temperature, mother-infant bonding, postnatal depression, father-infant attachment

STUDY FLOW CHART

Fig 1. Schematic overview of the study



Stage 2 (Main dataset)

N = 20-24 Parents-infant pairs

(a minimum of one cuddle episode per infant)

Obtain consent from parents during the cooling period

Arrange a suitable time with nurses and parents for cuddle

Refined CoolCuddle protocol

Pre-cuddle 30-60mins → **CoolCuddle Up to 2hrs** → **Post-cuddle 30-60mins**

1st Jan 2020 — 1st Jan 2021

Data

Every cuddle episode:

- *Physiology:* Ventilation, oxygenation, heart rate, blood pressure, aEEG, temperature, NIRS (if available)
- *Adverse events:* dislodgement of tubes/catheters, escalation of intensive care etc..

NICU stay:

- *Qualitative:* opinions of staff (n=6) about "CoolCuddle" in focus group meeting

Before discharge:

- Mode of feeding, length of hospital stay
- Mother: EPDS[1], MIBS[2] at 5-7 day of life of baby

When baby is 8 weeks old:

- Mother: EPDS[1], MIBS[3].Father: paternal postnatal attachment scale[2]
- Qualitative: opinion of parents regarding the CoolCuddle

Entire duration of study

Outcomes

- Difference in the distribution, mean/ median and variability of ventilatory, cardiovascular, temperature and neurophysiology between the pre-cuddle, CoolCuddle and post-cuddle
- Mode of feeding compared to existing audit data
- Parent-infant bonding scores compared to normative data
- Qualitative feedback on the "CoolCuddle" protocol
- Rate and type of adverse events

Stage 3 (Report and dissemination)

1st Jan 2021 – 1st April 2021

Final data analyses

- NIHR report
- Manuscript preparation, submission to journal
- Dissemination: presentation, publication, Bliss and parent advisory group involvement, southwest
- neonatal network
- "CoolCuddle" protocol + data collection tool of adverse events and bonding scores for roll out or further study

STUDY PROTOCOL

"CoolCuddle" study: Development and evaluation of a standard procedure of cuddling process allowing parents cuddle their babies undergoing cooling therapy.

1 BACKGROUND

In the NHS, each year around 2100 infants (3/1000 live births) undergo cooling therapy to reduce brain injury following exposure to lack of oxygen and blood supply to the whole body around the time of birth[4]. This condition is called hypoxic-ischemic encephalopathy (HIE) and cooling therapy is the current standard treatment[5] for infants with HIE. The cooling therapy involves cooling the whole body with a blanket or wrap that contains cold or warm water circulating through it and covering the baby's body. During cooling therapy, body temperature is maintained at 33-34°C for three days followed by 6-8 hours of rewarming to normal temperature of 36.5°C[6]. Most of the cooled infants often need intensive care including support for breathing, heart function and monitoring of brain activity including identifying and treating seizures[6]. As cooling therapy needs to be delivered in tertiary neonatal intensive care units (NICUs)[5], babies with HIE born in peripheral hospitals will be transferred to tertiary NICU soon after birth and mothers who will be recovering from the delivery typically arrive a day later to the tertiary NICU. On arrival, parents often receive the news that their baby may die or suffer brain damage[7]. Furthermore, our national survey of neonatal intensive care units (NICU) offering cooling therapy showed that 95% of units do not allow parents to cuddle their babies during the entire cooling therapy period due to concerns of destabilising the cooling process and intensive care[8]. This practice has been reported to compromise parent-infant bonding by 80% of mothers in a recent cross-sectional survey[9]. The physical separation ensuing from transferring the baby to a distant NICU offering cooling therapy and the lack of emotional support after receiving the news that their baby may die or suffer brain damage further impedes the development of parent-infant bonding[10]. Impaired parent-infant bonding affects the establishment of breastfeeding[11], leads to emotional neglect in the newborn period[12], influences the emotional and cognitive development of children[13], and results in postnatal stress or depression in parents[14,15], which if persistent may lead to behavioural problems in childhood[16,17]. Given that the survivors of cooling therapy are already at a higher risk of neurodevelopmental disability with 22% having disability at 18 months[18], and 18-20% having cerebral palsy[19,20]and 30-40% having intellectual disabilities at school-age[21 22], compromised parent-infant bonding might contribute to or worsen the outcome in these vulnerable infants.

To promote parent-infant bonding for preterm infants in the neonatal intensive care unit (NICU), it is standard practice to encourage family-centred care and cuddling of babies undergoing intensive care[23]. A recent small feasibility study from the United States showed that cuddling stable cooled

babies not needing intensive care did not affect cooling therapy and was favoured by parents and nurses[24]. However, the majority of cooled babies in the UK (approximately 80%) receive intensive care, including breathing support with mechanical ventilation and are cooled using a different servo-control machine compared to the US units (Criticool vs Blanketrol)[25]. It is not yet known whether adopting the standard NICU practice of cuddling babies during intensive care for cooling babies will affect the cooling process and the intensive care. Therefore in this study, we will refine the usual technique of parents cuddling babies receiving intensive care and develop a "CoolCuddle" protocol (stage 1) and adapt it to babies receiving cooling therapy after evaluating the safety to babies and the impact on parents and health care staff (stage 2). This research involves the nursing care of the babies undergoing cooling therapy addressing the ongoing uncertainty about parents cuddling babies during cooling therapy and could potentially improve parent-infant bonding with a long-term effect on the mental wellbeing of parents and cognitive development of children.

2 RATIONALE

The study will initially refine the cuddling technique that is part of the standard care for non-cooled babies receiving intensive care and develop a cuddling protocol ("CoolCuddle") for cooled babies with input from parents and neonatal staff. Subsequently we will test the "CoolCuddle" protocol for 1] its ability to offer physiological stability; 2] potential adverse effects during CoolCuddle; 3] views of parents and neonatal staff about the "CoolCuddle",4] impact of CoolCuddle on mother's mood, bonding with their babies and father's attachment with their babies. Lastly the study will aim to incorporate the "CoolCuddle" protocol in the cooling therapy pathway along with outcomes to be measured including the adverse outcome, maternal mood and parental bonding.

Impaired parent-infant bonding could affect the mental health of parents influencing the emotional and cognitive development of cooled children who are already at higher risk of cerebral palsy and cognitive impairments. The additional lifetime health and social care costs for a child with cerebral palsy are about £750,000; costing the UK economy £650million per year[26]. The direct costs of cognitive disabilities in Europe are estimated at €43.3 billion accruing from health and mental health services utilisation[27] while lifelong welfare support and lost earnings costs additional impacts[28]. Indeed, HIE is the 12th most prominent contributor to the global burden of disease or disability-adjusted life years and ranks second in the group of neonatal disorders[29]. Furthermore, postnatal depression needs input from psychological, social and health services costing £8.1 billion per year[30]. The benefits of improved parental bonding have been widely studied in the preterm infant population, where skin-to-skin and early attempts at supporting parental interaction have been shown to improve breastfeeding rates[31,32]. Other studies suggest that in term infants NICU admission can also disrupt

the bonding process[33]. Due to the high risk of long-term adverse consequences following HIE, even small improvements in outcomes would yield substantial health benefits for individuals and economic benefits for health care services. The anticipated output of this study is a refined "CoolCuddle" protocol that does not affect the cooling therapy or intensive care, and which may enhance parental infant bonding for cooled infants. Better parent-infant bonding may improve the cognitive function of cooled infants and is likely to improve the mental health of parents, reducing the costs to educational, health and social care services.

We have developed this research question through discussions with parents who have had babies with HIE and underwent cooling therapy. They all agreed that evaluating the cuddling of babies during cooling is a very important and relevant question. They all said that they would have loved to do it, had they been offered. Half of fathers interviewed said that they would have liked to cuddle their babies during cooling. All the mothers and the remaining 50% of fathers interviewed wanted to ensure that the cuddling will be safe for the babies, which informed the outcome we wanted to study. Bliss has informed us that this piece of work will provide an important insight into giving babies a better start in life.

3 THEORETICAL FRAMEWORK

There is an urgent need to improve the parent-infant bonding in parents whose babies are cooled for HIE. One of the interventions, which has been shown to promote parent-infant bonding in preterm infants is early parent infant interaction in the form of cuddling. To address the concerns of the impact of cuddling babies during cooling on the effectiveness of cooling therapy, support for breathing and heart function, and brain activity monitoring, we will undertake this study in three stages. In stage 1, we will refine the standard cuddling protocol used in non-cooled babies receiving intensive care using a robust methodology called "talk aloud". In this methodology, nurses involved in moving the baby undergoing cooling from the open incubator to the parents, researchers overseeing the process and the parents will openly and consciously talk about what is happening and how they are feeling during the process. This will involve giving a verbal commentary of their actions during the cuddle process and vocalising the changes they are doing to the standard cuddle. These vocal thoughts will be captured by an audio recorder and a researcher will also make field notes of the process. The research group will meet soon after the cuddle to reflect on the process and use the information collected to refine the cuddling protocol in an iterative process after each cuddle. This stage will involve 4-6 parents-infant pairs in the two sites between September 2019 to January 2020.

In stage 2, we will test the impact of the “CoolCuddle” protocol on the stability of cooling process, intensive care support including support for breathing, heart function and brain activity monitoring, and whether there are any adverse effects. This will be undertaken in 20-24 parents - infant pairs over a period of 12 months. Each infant will have a minimum of one cuddle with their parents. We will compare the physiology data between the pre, during and post cuddle to assess the short-term safety of cuddling babies during cooling. These data will tackle the concerns of the neonatal community regarding the short-term safety of cuddling the babies during cooling by reporting any safety issues including any adverse or serious adverse events. To address the issue of long-term impact of cuddling the babies undergoing cooling therapy, as parent-infant bonding has been shown to be improved with early parent-infant interaction in non-cooled babies, we will measure the maternal mood and parent-infant bonding using validated questionnaires around discharge and when the baby is 8 weeks of age.

Given that the early parent infant interaction including cuddling is the standard care for babies receiving intensive care in the NICU, we will adopt a traffic light system in stage 3 to progress with the findings of stage 2.

Green zone: If there are no adverse effects with the “CoolCuddle” protocol, we will integrate the “CoolCuddle” protocol into the existing cooling therapy pathway at the study centres. The modified “CoolCuddle” protocol including the steps of the “CoolCuddle” process and a data collection tool comprising adverse events and bonding questionnaires will be published on the southwest neonatal network website. We will consider appropriate further methods of investigation to confirm the short and long-term safety in larger sample sizes or rolling out the “CoolCuddle” study to other networks with collection of safety data and bonding scores with further potential funding.

Orange zone: If modifiable adverse events or adverse physiological changes or resolvable issues from parents or healthcare staff persist at the end of the study, we will modify the “CoolCuddle” protocol taking these issues into account. We will explore if there is a specific subgroup of cooled infants where the “CoolCuddle” might not be suitable . We will discuss with the steering committee whether further funding is needed to test the protocol or whether we can proceed as outlined in the green zone.

Red zone: If there are unmodifiable adverse effects at the end of the research, we will abandon the implementation and publish our findings.

During stage 3, we will complete the NIHR report, prepare the manuscript for publication and disseminate the findings.

4 RESEARCH QUESTION/AIM(S)

The overarching aim of the study is to incorporate a robust “CoolCuddle” protocol into the existing cooling therapy pathway.

4.1 Objectives

1 To refine the existing cuddling technique practised in neonatal intensive care and develop a “CoolCuddle” protocol using an iterative process employing ‘talk-aloud’ qualitative methods with parents, neonatal nurses and neonatologists and quantitative temperature and physiology data (Stage 1).

2 To investigate the safety and effect of the “CoolCuddle” protocol on the temperature, respiratory, cardiovascular and amplitude integrated electroencephalogram (aEEG) during the “CoolCuddle” episodes and qualitative interviews to explore parents’ and healthcare staff’s opinions (Stage 2).

3 To produce a modified “Coolcuddle” protocol with a data collection tool that can be incorporated into the existing cooling therapy pathway (Stage 3).

4.2 Outcomes

- Difference in mean/median and variability of surface and core temperature, ventilation, cardiovascular and neurophysiology parameters between the pre-cuddle, “CoolCuddle” and post cuddle epochs.
  - Day of life when oral feeds established
  - Mode and type of feeding at discharge and 8 weeks
  - Maternal mood assessed using Edinburgh postnatal depression scale[1] when the baby is 5-7 days of age and at 8 weeks.
  - Maternal-infant bonding assessed using Mother-infant bonding score[3] when the baby is 5-7 days of age and at 8 weeks.
  - Father-infant attachment assessed using paternal postnatal attachment scale[2] at 8 weeks
  - Qualitative feedback on the “CoolCuddle” protocol
  - Incidence of adverse events including frequency of administering stop rules for “CoolCuddle”, and dislodgement of endotracheal tube, central or peripheral arterial catheter, central venous catheter

5.STUDY DESIGN, METHODS OF DATA COLLECTION AND DATA ANALYSIS

This study will be a cohort study involving a controlled trial without randomisation design recruiting the cooled infants admitted to the NICUs of St Michael's and Southmead Hospital and their parents between September 2019 and January 2021.

5.1 Stage 1: Developing "CoolCuddle" protocol by refining existing cuddling technique using an iterative process (3 months)

Over 3 months, we will use the current family centred cuddling technique that we use for non-cooled babies receiving intensive care for babies receiving cooling treatment on 4-6 parents-infant pairs. We will attempt a minimum of one cuddle session per family up to 2 hours in length. We will refine the protocol by using 'talk-aloud' qualitative methods during each of the "CoolCuddle" sessions. Talk-aloud methods are used to gather data on usability and development of products and tasks[34]. Talk-aloud methods involve participants describing their actions and how they go about completing the task. The audio-recordings made are used to improve the process through insights and modifications that arise during the session. A member of the research team will also observe all the "CoolCuddle" sessions and make field notes of changes made and actions taken.

We will explore the optimum time and duration to compare physiological data from our pre-set 30-60 minutes epochs before and after the parents cuddle their baby. Using an iterative process, we will refine the cuddling technique throughout stage 1 into a "CoolCuddle" protocol. We have modified our current cuddling technique for the study based on advice from NICU nurses who have expertise in transporting sick newborn infants in ambulances and developmental care specialists. We have undertaken three mock "CoolCuddle" processes in a simulation session to further modify the technique (one of them shown in fig 2). One to two nurses will co-ordinate the cuddling technique. A research nurse will oversee the procedure including collecting the data**.** A member of the research team will be overseeing the process making field notes.

5.1.1 Cuddle technique

We will postpone the cuddle if the baby has any exclusion criterion before any cuddling episode. (section 7.12) If the baby has status epilepticus, we will post pone the cuddling episode until the status epilepticus is resolved.

5.1.1.1 Baseline

We will use the following standard operating procedure in the form of a check list (Appendix Fig 3). After obtaining consent, both parents will be invited for the cuddle and an appropriate time will be agreed between the parents and the nurses. If one parent consents to participate in the study and the other parent does not, we will offer the "CoolCuddle" to the parent consenting to the study after

ensuring that the parent with parental responsibility provides consent for the baby to participate in the "CoolCuddle". The research nurse will record the baseline data of temperature, respiratory, cardiovascular, amplitude integrated EEG (aEEG), pain score using the Neonatal-Pain Agitation Sedation Scale [35], cerebral oxygenation monitoring using near infrared spectroscopy and blood gas over a 30-60 minute period prior to the cuddle. Infusion rates and medication doses will also be noted.

5.1.1.2 Cuddle

During a cuddle, the parent will be seated on a comfortable chair on one side of the cot. The chair may have reclining options or a footstool to enable foot elevation and a cushion/pillow for the lap will be available. One to two nurses will coordinate the process of transferring the baby from the cot to the parent along with the research nurse. We will ensure adequate space between the baby's cot and the parent's chair to allow a nurse to walk between the baby and the parent.

5.1.1.3 Preparation of baby (Fig 2) The nursing team will ensure all the tubes and catheters are secured appropriately noting the length at which they are attached to the baby. The tubes and catheters include endotracheal tube, central arterial and venous catheter and urinary catheter. Attachment of rectal probes and the aEEG leads will be checked. The infusion lines and the monitoring cables will be organised into two separate bundles using a Velcro strap ensuring adequate slack is available. Babies undergoing cooling are typically covered by the cooling blanket /wrap with a pillow for their head (to prevent the fluctuating water temperature in the cooling blanket affecting the superficial brain temperature)[36]. The nursing team will clip the infusion lines and monitoring cables onto the edge of the cooling blanket. The aEEG head box will be clipped onto the cooling pillow using a Velcro strap. The urine collection container will be moved to the side where the parent is sitting and hung on to the side of the cot. The tube circulating water to the cooling jacket from the machine will be disconnected after clamping the tubes. Air entry on both sides of the chest will be checked and airway suction will be used if needed.

5.1.1.4 Moving the baby

The endotracheal tube and the ventilator circuits will be checked for any tangles. The nurse will stand at the bottom of the cot and support the baby's head and the cooling pillow with one hand and forearm approaching from the opposite side to the parents. The lower trunk and legs will be supported using the other arm with the infusion lines and the cables resting on the arm. When everyone is ready, the baby will be lifted from the bed maintaining the midline position. After a final check of the pathway of cables and lines ensuring there are no twists, the baby will be placed onto the parent's arms or on the lap or the top of a cushion/pillow (if used). If end-tidal carbon dioxide (CO2) monitoring is used, it will ascertain the patency of the endotracheal tube after transferring the baby onto the parent's arm or lap. Using the waveform morphology or the ventilator waveforms and air entry into the lungs will confirm

the endotracheal tube patency. The tubes from the cooling machine will be connected to the jacket to continue the cooling process. The cooling machine uses a servo control mechanism to maintain the set rectal temperature consistently[25]. All monitoring of circulation and other physiological measures will be continued throughout the process as before the move. Once the baby is stable in the parent's arms, the baby will be turned to the side facing the parent maintaining the midline position. The Velcro straps that hold the infusion lines and the cables have a clip which will be clipped onto the parent's clothes.

The cuddle will continue for up to 2 hours but can be stopped earlier if the parent wishes or if any of the stop rules for cuddle are met. After the cuddle period, two nurses will move the baby back onto the cot following a similar process to that described above.

5.1.1.5 Stop rules for the cuddle

Cuddle will be stopped, and the baby transferred back to the cot, if any of the following occurs continuously for 5 to10 minutes during cooling without responding to any potential resolvable causes:

1. Rectal temperature < 30.0°C or >35.0°C
2. Mean blood pressure < 30mmHg or > 75 mmHg
3. Heart rate < 50 beats per minute
4. Heart rate >180 beats per minute
5. Oxygen saturation < 80%
6. Fraction of inspired oxygen >70%
7. Electroclinical or electrical status epilepticus

If any of the following occurs for greater than 20 minutes after any remediable causes are attended to:

- Rectal temperature between 30.0 and 32.9°C or between 34.1 and 34.9°C
- Mean blood pressure 10 mmHg below or above the pre-cuddle period
- Heart rate <20 beats per minute from the pre-Cuddle period or >20 beats per minute from the pre-Cuddle period
- Oxygen Saturation 80-88%
- Increase in Fraction of inspired oxygen by 20% above the pre-CoolCuddle period

or

- Medical or nursing concern that the infant is not adequately supported

If cuddle is undertaken during the rewarming period, the following stop rules will apply if they occur continuously for 5 to 10 mins despite attending to the potentially remediable actions:

1. Mean blood pressure < 30 mmHg or > 75 mmHg
2. Heart rate < 50 beats per minute
3. Heart rate > 180 beats per minute
4. Oxygen saturation < 80%
5. Fraction of inspired oxygen >70%
6. Electroclinical or electrical status epilepticus

The following stop rules will apply during the rewarming period, if they persist for greater than 20 minutes after any remediable causes are attended to:

- Rectal temperature greater than 4.0°C or less than 4.0°C from the pre-CoolCuddle period
- Heart rate 30 beats per min above or below the pre-CoolCuddle period
- Mean Blood pressure 20mmHg above or below the pre-CoolCuddle period
- Oxygen saturation 80-88% below the pre-CoolCuddle period
- Increase in Fraction of inspired oxygen by 20% above the pre-CoolCuddle period

Or

Medical or nursing concern that the infant is not adequately supported

We will have a 30-60 min pre-cuddle and post-cuddle epochs of data collection. A minimum of one cuddle episode per parents-infant pair during the four days of cooling therapy and rewarming period will be studied. Depending on the availability of nursing staff more frequent cuddle episodes will be encouraged. All cooled babies receive one to one nursing care in both the NICUs. An additional nurse is routinely involved in preparing drug infusions or delivering complicated care for babies receiving one-to-one nursing. Therefore, there will be no additional impact on the nursing workload.

Data collection

We will collect the demographic data of cooled infants and their parents, and maternal medical, social, pregnancy and labour history. The severity of encephalopathy, presence of multi-organ dysfunction, doses of drugs and continuous infusions received by the infant will be collected. During the pre-cuddle, cuddle and post cuddle time periods the following physiology data will be collected on the case report form (CRF). Most of these data are stored digitally on the patient monitor every minute as part of routine care. These data can be used as a backup for the CRF and data at a sampling frequency of 1 minute can be obtained.

Physiology data

Every 5 minutes during pre-cuddle, cuddle and post-cuddle:

- Ventilation parameters: fraction of inspired oxygen, tidal volume, maximum peak inspiratory pressure, peak end expiratory pressure, mean airway pressure, inspiratory time, respiratory rate and oxygen saturation.

- Cardiovascular parameters: heart rate, blood pressure (the blood pressure transducer will be calibrated with the transducer at the level of the right atrium, every time the baby is moved)

- Surface and rectal temperature.

Other data to be collected

- End-tidal CO2 (if used in the NICU). Blood gas (measuring blood pH, pO2, pCO2, lactate, glucose) in the pre and post cuddle epoch. Blood gas is performed to ensure the babies are stable before and after cuddle in terms of oxygenation, ventilation and blood sugar. This is part of the standard care when babies are moved out of the incubator for longer periods.

- aEEG and NIRS (if used on the babies) will be marked at the onset of pre-cuddle, cuddle and post cuddle. aEEG will be analysed offline for continuity and seizures. NIRS data will be entered every 5 mins in the CRF.

- Adverse events

- Any instances of the following during the cuddling procedure:
  - Accidental extubation
  - Dislodgement of vascular catheters
  - Dislodgement of aEEG electrodes
  - Needle-stick injury from aEEG electrodes

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Data at discharge

We will collect data on mode and type of feeding. We will give mothers a mother-infant bonding (MIB) questionnaire and Edinburgh postnatal depression scale (EPDS) to complete around day 5-7 and at 8 weeks. We will collect father-infant attachment scores using a paternal postnatal attachment scale.

Data analysis

We will use the audio recordings of the talk aloud after each CoolCuddle episode to modify the CoolCuddle protocol. After the completion of “CoolCuddle” for each parent-infant pair, key investigators will use the talk aloud audio recordings and field notes made by the researchers to decide on the potential changes to the “CoolCuddle” protocol. We will aim to carry out the talk aloud

process with 4-6 parents-infant pairs. At the end of 3 months, a refined “CoolCuddle” protocol will be produced with involvement from the parent advisory group.

Stage 2: Effect of “CoolCuddle” protocol on the stability of cooling process and intensive care, and parents and healthcare staff opinion. (12 months)

We will use the refined “CoolCuddle” protocol and process on 20-24 cooled infant-parents pairs. The study participants will be recruited as for stage 1. Both parents will be invited for the cuddle. The intervention will be administered by nurses overseen by a research nurse.

All parents will be invited to be interviewed by the qualitative researcher and all who agree will be interviewed at an agreed convenient location or by phone/Skype. These interviews, with up to 20 parents, will explore their views on the refined CoolCuddle protocol and how best to roll it out to other NICUs. Interviews will take place after the 8 weeks questionnaires are collected and will mostly be by telephone so verbal consent will be recorded before each interview takes place. Parents will be sent an interview information sheet and consent form in advance of the interview date.

Staff involved in delivering the CoolCuddle protocol (6 nurses or doctors) at each site (St Michael’s NICU and Southmead NICU) will also be invited to participate in focus groups meeting towards the end of Stage 2.

Data collection

The physiology data collection will be similar to stage 1; frequency and duration of data collection will be informed by the learning from the stage 1. The physiology data will be collected in the CRF and stored in the electronic databases. The questionnaire data including the responses from the EPDS, MIBS and paternal postnatal attachment scale will be stored in a REDCap database.

Data including the reasons parents did not want to consent for the study or cut short the cuddling episodes will be recorded.

The qualitative interviews will be audio-recorded, transcribed and anonymised.

Data Analysis

We will use descriptive statistics to report the parental questionnaire data and the adverse events. We will measure the mean or median (as appropriate) for the main physiological measures (see above). We will undertake three pairwise comparisons of pre-cuddle versus during-cuddle, during-cuddle versus post-cuddle and pre-cuddle versus post-cuddle using parametric t test or non-parametric Wilcoxon tests depending on the data distribution. We will derive the differences between the three

epochs (pre-cuddle, cuddle, and post-cuddle) and identify the magnitude of the differences, or variability which occurs. Using multilevel mixed-effects linear regression models, using data clustered by infant (or cuddle), we will assess if any difference in measures is likely to be due to chance (using a conventional level of statistical significance of $p<0.05$). We will also explore continuous monitoring of the physiological measures to establish variability over longer periods and the potential for adverse events. All data analysis will be conducted using the software SPSS or STATA.

We will compare our findings from the parental questionnaires with normative data. To compare parental bonding, we will collect these scores in our study to ensure they are in the satisfactory range following the "CoolCuddle". There are published normative data for mother-infant bonding scores[3] and cut-offs for the father-infant attachment scores[2]. We will compare our scores against these published data. We will also have detailed audit data on breastfeeding initiation and duration before September 2019 to compare with our study findings. If the cuddling process is stopped this will be treated as an adverse event and fully investigated to realise whether the problem is endemic, or modifiable and preventable.

Analysis of the qualitative interviews will be ongoing and iterative and will follow recognised thematic analysis procedures using NVivo software. Transcripts will be coded, and global themes developed from the codes. Two researchers will be involved in the analysis and will discuss any discrepancies and achieve agreement for a robust analysis. The findings will inform any changes that are needed to the final CoolCuddle protocol. The findings will also be discussed with the Parent Advisory Group to help us understand wider parent perspectives.

Stage 3: Modified "CoolCuddle" protocol along with data collection tool (3 months)

In this stage, we will finalise the "CoolCuddle" protocol producing a manual/standard operating procedure (SOP) of the process, monitoring required, training package for nurses, support for parents and follow up. The SOP will contain a data collection tool including data on adverse events and bonding scales to measure bonding at discharge and at 8 weeks. We will incorporate this with the existing southwest neonatal network cooling therapy pathway publishing it on the network website. During this stage, we will analyse all the data, prepare the NIHR report and manuscript.

6 STUDY SETTING

This is a multicentre study and will take place in two sites including the tertiary NICUs at St Michaels Hospital and the Southmead Hospital. We look after, on average, 65 cooled infants each year between the two NICUs. This will give adequate numbers of cooled infants and parents who could be

potentially recruited for the study. The inborn infants will be identified by the staff in the neonatal unit and will inform the research nurse. Infants with HIE born in the peripheral hospitals will be transferred by the dedicated neonatal transport team to St Michael's and Southmead NICU. The neonatal transport team will inform the research nurse about the baby. A short parent information sheet will be available in the peripheral hospitals and the neonatal transport team for the staff to give to the parents. The research nurse or the principal investigators and GCP compliant colleagues at St Michaels and Southmead Hospitals will approach the parents of infants undergoing cooling therapy to inform them about the study and recruit the families into the CoolCuddle study after getting the informed consent.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

The cooled infants admitted to the NICUs of St Michael's and Southmead Hospital and their parents between Sept 2019 and Jan 2021.

7.1.1 Inclusion criteria

- Newborn infants born at gestation ≥ 36+0 weeks
- undergoing whole-body cooling for hypoxic-ischemic encephalopathy as per the national and south west neonatal network cooling therapy pathway and their parents who consent to participate in the study.
- cooling provided by a cooling device offering servo-controlled cooling using a wrap or blanket covering the whole body.
- receiving intensive care and will have probes monitoring core temperature and scalp EEG electrodes, may have central or peripheral arterial or venous catheter and may have a urinary catheter.

7.1.2 Exclusion criteria

Any of the following in a cooled infant at the time of screening

1. needing fraction of inspired oxygen (FiO2) >70%
2. receiving high-frequency oscillatory ventilation
3. requiring a mean airway pressure > 12cm H2O
4. receiving inhaled nitric oxide for persistent pulmonary hypertension
5. > 1 chest drain inserted for pneumothorax

6. receiving three or more inotrope infusions
7. Congenital anomalies such as hydrops fetalis and congenital diaphragmatic hernia
8. Non-English speaking parents
9. If potential participants are involved in another intervention study, an eligibility check to participate in the “CoolCuddle” study will be needed before recruitment.
10. If a baby excluded during the initial screening because of criteria 1 to 6, becomes eligible later during the cooling period due to resolution of those criteria, the baby can be screened again for participation in the study.

7.2 Sampling

In 2017, 69 cooled infants were admitted between St Michael’s and Southmead NICU. Seven infants would have been excluded leaving 62 potentially eligible infants. With this projected number of potential infants in 2019, we anticipate being able to enrol our target of 24 infants over 12 months (39% recruitment rate).

7.2.1 Size of sample

The sample size chosen is pragmatically based on a conservative estimate of the number of parents we believe will consent to this process in the time available.

Stage 1 (Iterative refinement): 4-6 cooled parents-infant pairs over 3 months (Fig 1).

Stage 2 (main data set): 20-24 cooled parents-infant pairs over 12 months (Fig 1).

7.2.2 Sampling technique

We will use a purposive sampling strategy and approach sequentially all the parents of babies admitted for cooling therapy at the St Michael’s Hospital or Southmead Hospital NICU. Depending on staff availability, we may not be able to recruit families if two or more infants are admitted for cooling therapy simultaneously.

7.3 Recruitment

7.3.1 Sample identification

Potential participants will be identified by medical or nursing team at both St Michael’s and Southmead NICUs. The transport team retrieving babies to both the NICUs will also identify the outlying patients and inform the research team. All parents will receive the participant information sheet from the medical team looking after the baby and/or the research team looking after the baby. For families who are unlikely to visit the baby in the recruiting sites within 24hours of age, the research team will obtain

consent over telephone and reconfirm the consent when the parents visit their baby. When two babies receive cooling therapy at the same time in a recruiting site, we will recruit the families in a staggered manner so that the “CoolCuddle” episodes are offered and undertaken at convenient separate time points and they do not overlap. Regular newsletters and study days will be conducted to remind the clinical team of the study. Details of the study including the research question, inclusion and exclusion criteria of the participants will be placed on the notice board in both NICUs.

7.3.2 Consent

We will invite both parents with an eligible baby to take part. From those who agree we will obtain informed consent during the cooling period (72 hours from the initiation of active cooling) from the parent with parental responsibility (mother for unmarried parents, mother or father for married parents) for the baby and the parent to participate in the “CoolCuddle” and the other parent if they will be willing to participate in the “CoolCuddle”. If one parent is willing and the other parent does not wish to participate in the “CoolCuddle”, we will offer “CoolCuddle” to the parent consenting to participate in the study as long as the parent with parental responsibility provides consent for the baby to participate in the “CoolCuddle”. In same sex marriage, we will seek consent from the birth mother or the other parent if they are married. Stage 1 of the study requires the participants to contribute to improving the cuddling process by vocalising their thoughts.

7.4 Discontinuation / withdrawal of Participants from Study

Parents will have the right to withdraw their infant from the study at any time. Parents who wish to discontinue with the study intervention will be asked for permission for the study team to complete data collection and follow up. They may withdraw consent for any aspect of the study including future procedures and data collection. In addition, the treating clinician may discontinue a participant from the study at any time if they consider it to be in the best interests of the infant’s health and wellbeing. Researchers will withdraw a participant from the study, if the infant after recruitment was unable to undergo at least one cuddling episode due to fulfilling an exclusion criterion or parental reasons. Parents who have consented to both themselves and their infant’s participation will be able to withdraw either or both consent.

8. SAFETY REPORTING

Adverse events will be recorded and reported in accordance with University Hospitals Bristol’s Research Safety Reporting SOP. The trial steering committee will periodically review all serious adverse events. Serious adverse events will be collected until the infant is discharged home. . As parental participation is limited to filling in Edinburgh postnatal depression scale, mother-to-infant

bonding scale and paternal postnatal attachment scale, no adverse event or serious adverse event recording or reporting will be conducted for this group.

8.1 Adverse event (AE)

An adverse event (AE) is any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.

8.2 Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect

*Life threatening in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical judgement should be exercised in deciding whether an AE is serious. SAE that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one or the other outcomes listed in the definition above, should also be considered serious.

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8.3 Suspected unexpected serious adverse reaction (SUSAR)

An SAE that occurs and is

- "Related" – that is, possibly, probably or definitely resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

8.4 Assessment of Adverse events

All adverse events will be assessed as follows:

8.4.1 Intensity assessment

- The assessment of intensity will be based on the investigator's clinical judgement using the following definitions:
- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

8.4.2 Causality

- Not related: Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
- Unlikely: Temporal relationship of the onset of the event, relative to administration of the intervention, is likely to have another cause which can by itself explain the occurrence of the event.
- *Possibly related: Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.
- *Probably related: Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the product than any other cause.
- *Definitely related: Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

*Where an event is assessed as possibly related, probably related, or definitely related the event is an adverse reaction"

8.5 Expected Adverse Events

In neonates with HIE, adverse events are not unexpected and are not infrequent. The following list of events are 'anticipated' as part of the signs and symptoms of HIE and will not be reported to the Sponsor if the event is classified as serious, unless deemed related to intervention . All other SAEs will be reported to Sponsor within 24 hours of the team becoming aware of the event. :

Seizures

Hypotension

Coagulopathy

Renal impairment with decreased urine output

Liver impairment

Difficulty establishing feeding

Abnormalities in neuroimaging

Sepsis / infection

Thrombocytopenia

Hyponatraemia

Hypoglycaemia

Pneumothorax

Necrotizing enterocolitis

8.6 Other Events of Interest

Other events of interest also to be recorded if they occur during the cuddling process:

Accidental extubation
Accidental dislodgement of vascular catheters
Needle stick injury from the aEEG electrodes

The frequency of the above events will be reviewed by the study steering committee.

8.7 Reporting procedures for serious adverse events

Unexpected SAEs and SAEs assessed as causally related to the cuddling intervention must be reported to the sponsor within 24 hours of a member of the research team becoming aware of it in accordance with University Hospitals Bristol's Research Safety Reporting SOP.

All deaths regardless of causality must be reported to Sponsor.

All Serious Adverse Events will be reported to the study steering group in the form of a periodic report and discussed at each study steering group meeting.

9 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Ethical considerations

The ethical issues involved in this research are the safety of the technique and potential adverse events. Given that we have learnt from a NICU in the NHS which is practising cuddle in a selected few stable cooled infants and from the NICU at Maine, US, that has studied this technique in stable infants, the technique is unlikely to induce harm. Furthermore, this cuddling technique is the standard practice for newborn babies who are undergoing intensive care but not the cooling therapy in the NICUs. We will have trained personnel around when the cuddle is happening to mitigate any harms that could occur. The study has carefully considered inclusion and exclusion criteria so that the research could produce important data about the physiological stability of cuddling for the group of babies and parents who might benefit from the cuddle. Other participants in this study include the parents of the babies who are undergoing cooling and the neonatal staff looking after the baby. Our work with previous parents of cooled babies indicate that most parents will be looking forward to cuddling their baby. However, there is a small chance that some parents may find it challenging to cuddle their sick baby, whose skin will feel cold and the wrap covering their body may switch between being cold to warm. This will be explored in the informed consent process. Furthermore, the protocol includes stopping the cuddle if the parents do not feel comfortable with the process. The benefits to the parents may include reduced stress, empowerment and they might feel that they are positively contributing to the care of their babies, better breast milk production and improved chance of establishing breastfeeding and enhanced parent-infant bonding. Previous work shows that after the cuddle, babies appeared more stable with their breathing and heart rate, the parents were emotionally stable, and many nurses felt that they have helped the family and the baby. The data collection involves the standard practice of acquiring the physiology data that are routinely recorded for the babies undergoing cooling therapy and the questionnaires given to parents for completion are validated questionnaires. The Edinburgh Postnatal Depression Scale is the standard questionnaire used to screen maternal mood and depression and several studies have used this in mothers who have their sick babies admitted in the NICU.

The protocol aligns with the current research governance requirements for obtaining approval and conducting the study.

9.2 Assessment and management of risk

Potential risks to the participants include the adverse effects identified in the protocol for the babies. These include dislodgement of endotracheal tube and arterial or venous catheters. Appropriate techniques that will prevent these happening will be developed in stage 1. In our current family centred cuddling practice these adverse incidents are extremely rare. If an adverse incident occurs, babies

can be quickly transferred in to the incubator and airway or the site of arterial access can be secured preventing any potential harm to the babies. The research nurse running the study is an experienced senior advanced neonatal nurse practitioner who is competent in anticipating any of these potential risks and managing them.

Some parents may feel uncomfortable to hold their sick baby being connected to several intensive care monitors. Their baby's skin will feel cold and they will be sedated to counteract the distress induced by cooling. Holding their cold baby may be emotionally challenging to some parents. In our current standard practice, parents are familiarised with all the intensive care monitoring that their babies receive, and parents touch their baby including the cooling wrap covering their body. This will familiarise the parents with their baby before they cuddle their baby.

Mothers will be completing the Edinburgh postnatal depression scale. If the questionnaire identifies that the scores reach the threshold for further evaluation, we will discuss the result with the woman and ask if she is ok to be referred to the perinatal mental health team for support. In both recruiting sites, parents of babies receiving intensive care needing psychology or mental health support are identified during the weekly social care rounds. A referral will be made to the perinatal psychologist/mental health team, who then offers the parents a convenient appointment. Furthermore, a family support worker supports all families who have their babies admitted in the neonatal intensive care unit.

In the standard practice of cuddling, we have not identified any potential risks to the nursing team. However, if any potential adverse event occurs during the cuddling process, appropriate debrief sessions will be used to mitigate any potential emotional distress to the staff involved.

9.3 Review by an NHS Research Ethics Committee and Health Research Authority

The research will be performed subject to a favourable opinion from an NHS REC and Health Research Authority (HRA) and local site capacity and capability confirmation. Ethics review of the protocol for the study and other study related essential documents (e.g. PIL and consent form) will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be authorised by the sponsor and then submitted to the REC and HRA for approval prior to implementation

9.4 Amendments to protocol

Any amendments to the study documents must be approved by the sponsor prior to submission to the HRA and REC.

9.5 Peer review

The study has undergone the NIHR RfPB peer review with four independent expert reviewers before the funding was approved.

9.6 Patient & Public Involvement

We have involved 5 sets of parents of children who received cooling for HIE in the NICU within the last 3-5 years and the neonatal charity Bliss. Four sets of parents and one mother continue to be part of the parent advisory group and will continue to advise us through the study.

Shaping the research question

They were involved in refining the research question. They all agreed that evaluating the cuddling of babies during cooling is a very important and relevant question. They all said that they would have loved to do it, had they been offered. Half of the fathers interviewed said that they would have liked to have cuddled their babies during cooling. All the mothers and the remaining 50% of fathers interviewed wanted to ensure that the cuddling will be safe for the babies, which informed the outcome we wanted to study. Bliss has informed us that this piece of work will provide an important insight into giving babies a better start in life.

Intervention

Parents said that they would consider cuddling their babies only when there is expertise to do it safely. This enabled us to confirm that the research nurse will be an experienced advanced neonatal nurse practitioner coordinating the cuddling process with the nurses to ensure the safety of the cooled babies and reassure parents. Parents informed us some of them would like to have several cuddles depending on their postpartum condition.

Outcomes of interest

Parents felt that the outcomes should include breastfeeding and bonding scores. They reviewed the parental questionnaires and have informed us which parental questionnaires they would have preferred to complete and captured the key outcomes. We have discussed the project with the intensive care nurses. Many nurses felt that this research will be hugely beneficial to the parents and their practice. Several nurses felt that cuddling of cooled babies can be undertaken as long as they are not critically unwell and helped us to design the stop rules for CoolCuddle.

9.7 Protocol compliance

Protocol deviations will be documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Any recurring deviations in the protocol will be carefully assessed for the possible need for an amendment. A recurring protocol violation will be classified as a serious breach.

9.8 Monitoring and Audit

The study will be monitored in accordance with University Hospitals Bristol's Monitoring SOP. All study related documents will be made available on request for monitoring and audit by UH Bristol, the relevant Research Ethics Committee and for any other regulatory authorities.

9.9 Data Management

Where applicable a random sample of at least 10% of CRFs will be checked, by the study Research Team, against entries within the database and with the source data for quality purposes. The percentage checked will be increased if a significant error rate is found. In addition, the first set of recruitment data collected from a new site will be scrutinised.

9.10 Data Handling and Protection

The database system will be designed so as to protect patient information in line with the General Data Protection Regulation. Study staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at the study centres (as relevant) in line with the Ethics approval. All documents will be stored securely and only accessible by study staff and authorised personnel. Data will be collected and retained in accordance with the General Data Protection Regulation.

9.11 Storage of Records

Study documents (paper and electronic) will be retained in a secure location during and after the study has finished. Digital versions of the audio recordings and qualitative interview will be transcribed to paper version. Following transcription, audio recordings of the "talk-aloud" sessions, qualitative interview of parents and the staff focus group will be deleted and destroyed. All essential documents, including patient records and other source documents will be retained until the participant reaches the age of 25. Where study related information is documented in the hard copy medical records – those records will be identified by a 'Do not destroy before dd/mm/yyyy' label where date is 25 years after the last patient last visit. Where electronic records are in use, trust policy will be followed.

9.12 Indemnity

This is an NHS-sponsored research study. If there is negligent harm during the study when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

9.13 Research Governance Statement

This study will be conducted in accordance with:

• The principles of Good Clinical Practice, as set out in the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines

• The UK Policy Framework for Health and Social Care Research.

10 DISSEMINIATION POLICY

10.1 Dissemination policy

Ownership of the data resides with the study investigator team and the rights to publish any study data will be finalised by the study team. On completion of the study, the data will be analysed, tabulated and a final study report will be prepared. The study report will be submitted to the funder NIHR, where the report can be accessed. Publications will acknowledge the funder as “this independent research was funded by the National Institute of Health Research (NIHR) under its Research for Patient Benefit (RfPB) programme (Grant reference number PB-PG-1217-20020).” A draft copy of the proposed publication will be sent to the RfPB at the same time as submission. The funder will not have any publication rights of the data and the views expressed in the publication will be those of the investigators and not necessarily those of the NIHR or the Department of Health and Social Care. The participants will be sent a copy of the publication. Participants may request the specific results after the results are published. The study protocol will be published. The results of the study will include a SOP of the cuddling process along with the safety data and bonding questionnaires. This will be published on the Southwest neonatal network website and will be available for other networks to download and use. The study data will be deposited in the University of Bristol repository.

10.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be based on “The International Committee of Medical Journal Editors” authorship criteria including substantial contributions to the conception or design of the work or the acquisition, analysis or interpretation of data for the work; AND drafting the work or revising it critically for important intellectual content; AND final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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