FULL/LONG TITLE OF THE STUDY

Process evaluation of embedding the CoolCuddle intervention into neonatal intensive care units.

SHORT STUDY TITLE / ACRONYM

CoolCuddle2 Study: Embedding CoolCuddle into NICUs

PROTOCOL VERSION NUMBER AND DATE

Version 1.4 05.07.2023

RESEARCH REFERENCE NUMBERS

IRAS Number:	
SPONSORS Number:	CH/2021/7268
FUNDERS Number:	NIHR203024

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigators agree 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.

We 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

We also confirm that we will make the findings of the study publicly 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:

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Name (please print):

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Position:

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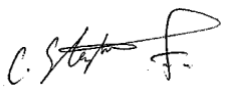
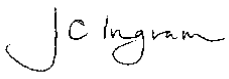
Chief Investigators:

Date: .....

Signatures:  

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Name: (please print):

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Committees	Study advisory group Parent advisory group

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	£147,853.00

STUDY SUMMARY

Study Title	**"CoolCuddle2" study: Process evaluation of embedding the CoolCuddle intervention into neonatal intensive care units.**
Internal ref. no. (or short title)	CoolCuddle2
Study Design	Cohort Study and process evaluation
Study Participants	Infants undergoing therapeutic hypothermia who are admitted to the NICU at 4 tertiary units and their parents Neonatal staff involved in the "CoolCuddle" process
Planned Size of Sample (if applicable)	Up to 40 to 45 families with a cooled infant
Follow up duration (if applicable)	2-3 months
Planned Study Period	1st July 2022 to 1st October 2023
Research Aim	To assess the process of embedding the CoolCuddle intervention into standard care during cooling therapy for neonatal HIE in the NHS.
Objectives	1. Track intervention implementation in 4 diverse tertiary NICUs using continuous monitoring with the NoMAD Implementation measure based on NPT (www.normalizationprocess.org). 2. Examine barriers and facilitators for implementing CoolCuddle using NPT informed qualitative interviews with neonatal staff and parents. 3. Evaluate cooling process and intensive care during cuddles, rates of postnatal depression, parent-infant bonding or attachment and breastfeeding at discharge and 8 weeks. 4. Examine safety issues associated with CoolCuddle and develop corrective actions.

Outcomes	1. NoMAD questionnaire responses for each of the four domains of NPT (coherence, cognitive participation, collective action and reflexive monitoring) at up to 6 time points during implementation to illustrate the implementation of CoolCuddle in 4 NICUs with a refined training package. 2. Views of neonatal nurses and clinicians regarding barriers and facilitators of embedding CoolCuddle into routine practice. 3. Views of parents on the integration of CoolCuddle into infant care practices at the four sites. 4. Stability of infants and deliverability of CoolCuddle in different NICUs.

ROLE OF STUDY SPONSOR AND FUNDER

University Hospitals Bristol and Weston 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.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Study management group

The study management group will comprise Dr J Ingram, Dr E Chakkarapani, Dr D Odd, Dr L Beasant, Dr J Horwood 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 advisory group

The study advisory group includes a statistician, neonatologist, neonatal network nurse and implementation science expert. This group 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 three times during the study. They 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 will be sent to the study advisory group for review.

Study advisory group meeting minutes will be provided to the sponsor.

Parent advisory group:

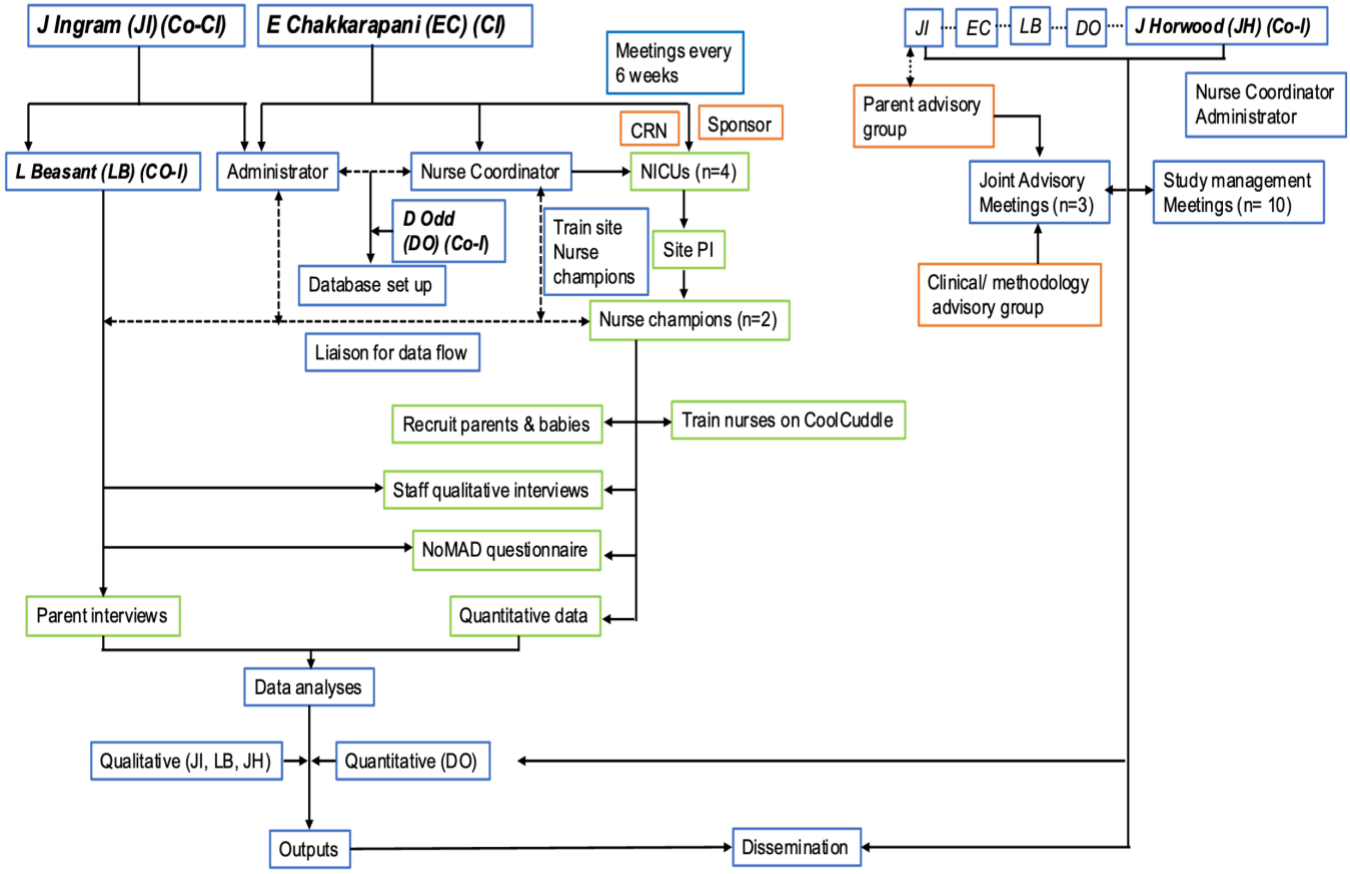
Our parent advisory group (PAG) comprises 8 parents, all of whom were involved the previous feasibility CoolCuddle study and have babies with HIE. The parent advisory group will meet three times during the study to advise on: good ways to encourage families to take part and complete the questionnaires, participant information sheet wording for mothers and fathers, interpretation of findings and dissemination to wider audiences. We will hold the meetings at a time convenient to them (probably in the evenings) when they are able to commit to attending and led by JI. They will be supported by the inclusion of an induction into the role of advisory group member where we will agree 'safety ground rules' for our meetings and time to build rapport with the group. We will use NIHR INVOLVE guidance to provide support with voicing opinions, understanding research terms, signposting for emotional support and ensuring barriers to accessing meetings are broken down and that vouchers/payment for participation are paid promptly.

PROTOCOL CONTRIBUTORS

Co-investigators Dr David Odd, Lucy Beasant and Jeremy Horwood 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



STUDY PROTOCOL

"CoolCuddle2" study: Process evaluation of embedding the CoolCuddle intervention into neonatal intensive care units.

1 BACKGROUND

What is the problem being addressed?

Parents cuddling their babies soon after birth is the first step to developing physical and emotional bonding with their babies,[1, 2] which plays a key role in their later intellectual and emotional development.[3, 4] Consequently, parents cuddling their sick babies receiving intensive care has been standard care in the neonatal intensive care unit to promote parent infant bonding.[5] Recently cuddles are promoted for vulnerable preterm infants soon after birth in the delivery room.[6] However, over 2000 babies each year who undergo cooling therapy over the first four days of life to mitigate the brain injury occurring following birth asphyxia (hypoxic-ischaemic encephalopathy, (HIE))[7] are not given the opportunity to have cuddles with their parents during this critical period. This is due to concerns of disrupting the cooling treatment or dislodging vascular catheters, breathing tube, or monitoring electrodes.[8] This impacts the mental health of parents,[9] the development of parent-infant bonding, breastfeeding [10, 11] and potentially the intellectual development of these babies; who are already at a higher risk of developmental disabilities.[12, 13] HIE is one of the leading causes of intellectual disability and costs the UK economy around £6 billion/year in health care and educational costs.[14]

To enhance parent infant bonding, parents' mental health, breastfeeding, and development of infants cooled for HIE, we have developed the CoolCuddle intervention, with support from RfPB funding. CoolCuddle enables parents to cuddle their babies during cooling therapy and intensive care. This intervention was refined with 27 families cuddling their babies during cooling treatment cumulatively over 115 hours in 70 cuddle episodes. An experienced advanced neonatal nurse practitioner facilitated and monitored all the cuddles along with neonatal nurses looking after the babies. Parents reported that cuddling during cooling helped them to bond with their babies and establish breastfeeding. Mental health of mothers improved at 8 weeks postnatally. We have delivered the CoolCuddle intervention predominantly in one tertiary Neonatal Intensive Care Unit (NICU) with one advanced neonatal practitioner leading the process. We observed no adverse effects and the temperature during cooling, cardiorespiratory parameters and brain activity and oxygenation remained within clinically acceptable limits; but did identify differences in some of these physiological measures during cuddles. We do not know yet whether CoolCuddle can be administered, by nurses in other NICUs, during routine daily practice, without encountering

any adverse effects or safety issues, without the facilitation from a neonatal nurse practitioner used in our previous work. Therefore, we now need to determine how other tertiary NICUs can embed it into usual care, with several different nurses leading the process, after training with an online package.

2 RATIONALE

Implementing interventions in standard practice that would improve the mental health of parents, parent-infant bonding, breastfeeding and consequently the intellectual and emotional development of babies with HIE are the health and care needs addressed by this proposal. Worldwide, perinatal asphyxia is estimated to be the 12th biggest cause of disability life years.[15] Furthermore, postnatal depression and intellectual disabilities cost the NHS over £12 billion every year. [14, 16] The benefits of CoolCuddle in reducing postnatal depression, promoting breastfeeding and enhancing parent-infant bonding for these parents would augment the intellectual development of children with HIE
which is reported to be impaired at school age.[12, 13] To optimise the benefits of the CoolCuddle intervention in standard practice, we need to find out how this intervention can be safely embedded in usual care in busy tertiary NICUs, identifying the factors that would facilitate or hamper its implementation. Evidence generated from this proposal will enable CoolCuddle to be used in routine practice nationally.
From our CoolCuddle study, we showed that compared to historical non-cuddled cooled infants, more CoolCuddle infants received breast milk at discharge (72% vs 50%), and the CoolCuddle group had improved mother-infant bonding scores (mean (SD): 3.38 (3.65) vs. 2.86 (3.05)).[11] The proportion of CoolCuddle mothers screened at risk of postnatal depression decreased from hospital discharge to 8 weeks (57% to 24%). Given the beneficial effects and indication of safety in our study, we propose to introduce CoolCuddle into four NICUs with different working practices to identify mechanisms of efficient implementation, benefits and risks before rolling it out nationally.

To assess implementation of the CoolCuddle intervention, we will use a mixed methods process evaluation informed by Normalization Process Theory (NPT). Process evaluations aim to understand how interventions work, for whom and in what context, including delivery and implementation processes.[18, 19] NPT provides a conceptual framework to highlight important issues relating to implementing complex interventions in health care and how new practices become embedded in everyday work.[20, 21] NPT proposes that implementation of interventions is dependent on the ability of participants to fulfil four criteria:

1. Coherence (making sense of the content and purpose of the intervention and their part within it);
2. Cognitive participation (buy-in with the intervention and their role in implementation);
3.Collective action (actions to push the intervention forward);
4. Reflexive monitoring (appraisal of the intervention).

3. RESEARCH QUESTION/AIM(S)

The overarching aim of the study is to assess the process of embedding the CoolCuddle intervention into standard care during cooling therapy for neonatal HIE in the NHS.

3.1 Objectives

1 Track intervention implementation in 4 to7 diverse tertiary NICUs using continuous monitoring with the NoMAD Implementation measure based on NPT(www.normalizationprocess.org).[22, 23]

2 Examine barriers and facilitators for implementing CoolCuddle using NPT informed qualitative interviews with neonatal staff and parents.

3 Evaluate cooling process and intensive care during cuddles, rates of postnatal depression, parent-infant bonding or attachment and breastfeeding at discharge and 8 weeks.

4. Examine safety issues associated with CoolCuddle and develop corrective actions.

3.2 Outcomes

1. NoMAD questionnaire responses for each of the four domains of NPT (coherence, cognitive participation, collective action and reflexive monitoring) at up to 6 time points during implementation to illustrate the implementation of CoolCuddle in 4 to 7 NICUs with a refined training package.

2. Views of neonatal nurses and clinicians regarding barriers and facilitators of embedding CoolCuddle into routine practice.

3. Views of parents on the integration of CoolCuddle into infant care practices at the four sites.

4. Stability and deliverability of CoolCuddle in different NICUs:

- Number and duration of cuddles;
- Difference in mean core temperature, oxygen requirement, heart rate, blood pressure between pre-cuddle, cuddle and post-cuddle epochs;

- Safety issues and instigation of mitigating factors.
- Frequency of stopping cuddles as per SOP and reasons for this: thermal control, endotracheal tube, vascular or urinary catheter, EEG electrode dislodgement.
- Proportion of women breastfeeding, median EPDS, and proportion at risk of depression (EPDS ≥13), and bonding scores (MIBS) at discharge and 8 weeks

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

This study will be a cohort study with a process evaluation of the intervention recruiting cooled infants admitted to the NICUs of four to seven tertiary units and their parents between July 2022 and October 2023.

4.1 Target population.

All eligible babies will be offered the CoolCuddle according to the SOP. Criteria for the data collection and process evaluation study are:

Inclusion criteria: Infants ≥35 weeks' gestation undergoing therapeutic hypothermia using a servo-controlled cooling machine and intensive care for HIE.

Exclusion criteria. Parents of babies whose are not able to complete the consent form or questionnaires in English. Parents under the age of 16.

Sites: Four to seven tertiary NICUs in England including Leicester, , Birmingham, Manchester, South Tees, Newcastle, Nottingham and Southampton. Each site will have 2 nurse champions and a clinical principal investigator. These centres are carefully chosen to represent diverse NICU environments and population coming from different ethnicities and socio- economic backgrounds.

We have developed an online training package comprising a video of the CoolCuddle intervention, and a Standard Operating Procedure (SOP) including a checklist. Training will start from the beginning of the study as a rolling programme which will continue in parallel to recruitment. Sites will be open to recruitment from the start of the study. The training package will be refined by gathering feedback from the sites and rolled out to sites to be available. The refined package will be available to other nurses who will be looking after babies undergoing cooling therapy in each NICU. The nurse champions at each site will facilitate the training and oversee initial cuddles at each centre until the team feels competent to carry out cuddles. Nurse champions will complete the data entry for each cuddle.

4.2. Recruitment

Screening and consent

CoolCuddle has been developed and refined in our previous clinical study.[30] CoolCuddle did not impact the cooling therapy or intensive care and there were no adverse effects. These data support offering CoolCuddle to parents according to the CoolCuddle SOP, by nurses who were trained in the CoolCuddle process. Parents of infants with HIE are often in a stressful situation which in CoolCuddle 1 study resulted in them not being approached for many hours after cooling had started as the clinical team considered it too burdensome for parents to be approached for written consent at that time. This resulted in the consent process being delayed, sometimes resulting in offering cuddles when the infants were up to 50 hours of age. Therefore, obtaining written informed consent for rolling out an intervention which has been investigated in a previous clinical study delays the opportunity for parents to cuddle their baby.

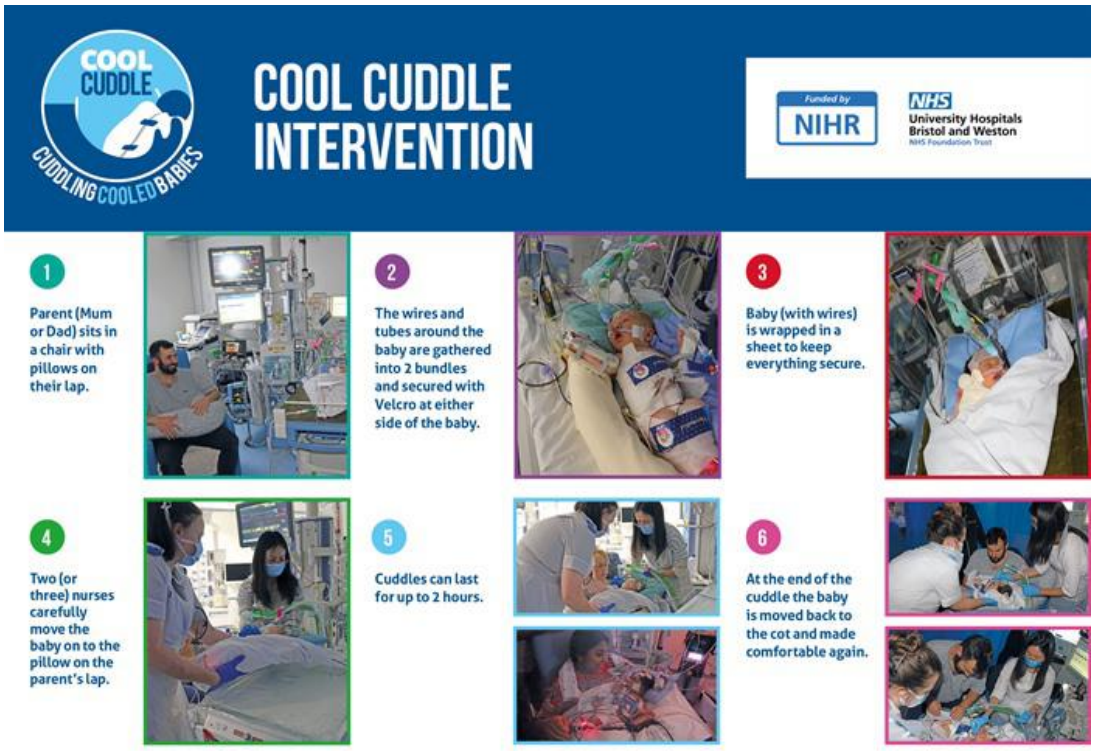
Parents cuddling babies receiving intensive care for other reasons is part of standard intensive care and nurses routinely promote and oversee parents cuddling babies receiving intensive care. CoolCuddle involves parents cuddling their babies undergoing intensive care and cooling therapy, adopting principles similar to that used in the standard care for parents cuddling babies receiving intensive care for other reasons. Offering cuddles to this group of parents will help to facilitate a family-centred ethos for the whole NICU population of babies. CoolCuddle was investigated in 27 parent-infant dyads undergoing 70 CoolCuddles over 115 cumulative hours. There was no clinically significant impact on the intensive care or cooling therapy and cuddling enhanced breastfeeding rates.[30] Therefore, for CoolCuddle2, we will utilise a verbal consent model similar to that used in other neonatal studies such as the Feed1 study(feed1-protocol-final-version-1-4-17-jun-2021-so-tg-signed.pdf) Nurses will inform parents of infants undergoing cooling therapy and intensive care that their unit is implementing the practice of cuddling babies during cooling therapy as part of a research study and invite parents to cuddle their babies during cooling. Parents will be given the short 'parent information flyer' and both parents will be offered to cuddle their babies undergoing cooling therapy. For parents who are willing to cuddle their babies, nurses will obtain verbal consent (which will be documented in the medical notes) and inform the parents that the research team will approach them within three days to discuss the study again and seek written consent to include their own and their baby's data in the study.

The research team will approach those parents who cuddled their babies during cooling to obtain written informed consent within 72 hours of the initial cuddle. Informed consent will be

obtained from parents either using an online version of informed consent form on RedCap or on a paper version. If a paper version of consent form was used, a scanned copy of the signed consent form will be uploaded on to the RedCap. The local research team will give the parents information sheet and explain the study data collection. This includes the use of their infant's physiological data collected during the cuddle, completing parent bonding and postnatal depression questionnaires at discharge and 8 weeks postpartum and about being contacted by the qualitative researcher when their baby will be 8 weeks of age. Written informed consent will be obtained from the parent with parental responsibility.

Intervention: The CoolCuddle intervention uses a checklist for the entire process involving two nurses. Please see the standard operating procedure document for the CoolCuddle process (CoolCuddle-2 Standard Operating Procedure V1.0 210322) uploaded in the checklist section of IRAS under Sample diary card/ patient card. This document will be used when the CoolCuddle is conducted. After ensuring the baby is stable, monitoring cables, infusion lines and respiratory tubing are stabilised. Baby is swaddled in a cot sheet for the move to the seated parent's arms. After 2 hours of cuddling or at the parent's request the baby is moved back to the cot. Routine intensive care monitoring including checking on the comfort level of parent will occur. The site nurse champions will train the site nurses who will be looking after babies receiving cooling therapy using the training video and the CoolCuddle-2 Standard Operating Procedure V1.0 210322. Given that cuddles are offered for babies undergoing intensive care, but not cooling therapy, as standard care in the NICU, nurses may feel competent to offer CoolCuddle after the training. Depending on the competencies of the nurses, the site nurse champions will oversee the first few cuddles as needed and will encourage the nurses to administer CoolCuddle independently when they are able.

Figure 1 illustrates steps involved in the CoolCuddle intervention.



A minimum of one cuddle episode per parents-infant pair during the four days of cooling therapy will be offered and data will be collected from all cuddles. Depending on the availability of nursing staff more frequent cuddle episodes will be encouraged. All cooled babies receive one to one nursing care in all 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.

4.3 Quantitative data collection

We will collect the demographic data of all cooled infants and their parents who take part in a CoolCuddle, including 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. The CoolCuddle SOP will include physiology data collection which will take place at 30-minute intervals starting just before the baby is moved to just after the baby is settled back in the cot after the cuddle. 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. These data will be collected routinely on all babies being cuddled but we will only use them in the study after informed consent has been obtained.

Physiology data

Every 30 minutes from pre-cuddle, cuddle to 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 collected every 30 mins.

- 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

Data at discharge

For participants who have provided written informed consent for their babies data to be included in the CoolCuddle2 study, they will be asked to complete online questionnaires. An email or text will be sent to the parents containing a secure hyperlink to the REDCap database. Parents will complete Edinburgh Postnatal Depression Scale (EPDS), [24,25] and bonding questionnaires (mother-infant bonding questionnaire (MIBS)[26] for mothers at discharge and 8 weeks postpartum, and paternal postnatal attachment scale (PPAS) for fathers[27] at 8 weeks postpartum. There will also be brief questions about breastfeeding at discharge and 8 weeks. Automatic reminders will be sent one week later if the

questionnaires have not been completed. Site research teams will also remind parents regarding completing questionnaires.

The physiology data will be collected in the CRF and stored in the REDCap database. The questionnaire data including the responses from the EPDS, MIBS and paternal postnatal attachment scale will be stored in a REDCap database.

On the screening log we will record the reasons parents did not want to consent for the CoolCuddle2 data collection study.

4.4 *Process evaluation.*

NoMAD questionnaires

To assess implementation of the CoolCuddle intervention, we will use NoMAD questionnaires completed by staff at up to 6 time points (approximately every 6 weeks) to track the translation of the intervention into routine practice. We will identify the barriers and facilitators for implementation through a rolling programme of short staff interviews based on what is being revealed over time by NoMAD scores. We will also identify any safety issues and implement corrective actions.

Staff and parent interviews.

A purposive sample of parents from each site will be invited for an interview to understand how CoolCuddle is being integrated into family-centred care within each NICU. All parents who agree will be interviewed at an agreed convenient location or by phone/online. These interviews, with up to 20 parents, will take place after the 8 weeks questionnaires are completed and will mostly be by telephone or via online platform such as teams or zoom, 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 (neonatal nurses or doctors) at each site will also be invited to participate in focus groups meeting or interviews towards the end of recruitment to explore barriers and facilitators for embedding CoolCuddle. Staff who agree to take part in interviews or focus groups will be sent an information sheet and consent form and will provide written or online informed consent to participate.

Data Analysis

The main outputs of this work will be the qualitative semi-structured interviews and a descriptive analysis of the NOMAD outputs over time. For the NOMAD outputs we expect to present the trajectory of the 4 different domains in order to guide implementation. For

evaluating the process of implementing the CoolCuddle, each NICU will be the unit of measurement. Recruiting a minimum of 4 families per NICU, will allow us to robustly examine the implementation of CoolCuddle using the NoMAD questionnaire. We will aim to recruit a total of 40 to 45 parent-infant dyads. This will also enable us to show an improvement for some quantitative measures and will collect additional data (similar to the initial CoolCuddle project) to ensure safety. For example, we hope to be able to show if the low historic breastfeeding rates we have previously observed in this cohort of infants (50% in infants who require Therapeutic Hypothermia) is improved to the UNICEF Baby Friendly Hospital targets (75%). Using conventional power calculation we will have 70% power, with an alpha of 5%, to identify if the breastfeeding rates in our cohort have increased to this (75%) rate in the 40-45 dyads, compared to the historical known low rate of 50% in this group.

Quantitative.

Descriptive statistics will summarise the demographic and outcome variables and depending on the distribution, confidence intervals will be calculated. Distribution of categorical variables will be presented as frequency and percentage.

Measures of the 'normalisation' of practice (using scores from the NOMAD questionnaire) will be summarised as mean scores and plotted over time using radar or petal plots. Linear regression will be used to describe the nature of the relationship between the NPT scores over time and allow comparison of trajectory and differences between units.

All quantitative data analysis will be conducted using SPSS or STATA.

We will compare our findings from the parental questionnaires with normative data and our previous study. 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 also have detailed audit data on breastfeeding initiation and duration 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.

Qualitative.

Staff: Semi-structured interviews (and focus groups if possible) with neonatologists and nurses at all sites will explore how CoolCuddle was embedded into practice as a rolling programme across the sites. Purposive sampling will facilitate a maximum variation sample of 12-16 staff in terms of role, site and experience with the technique. Interview schedules will be informed by NPT [28] and interviews are expected to take 30-45 minutes.

Parents: We aim to interview a sample of parents with maximum diversity in terms of age, gender and ethnicity. Parents will be invited for interview after completing their 8-week questionnaires, topic guides will be informed by PPI, NPT and research team experience and are expected to take 40-50 minutes.

All interviews will be transcribed and anonymised by a University of Bristol approved, authorised and legally compliant transcription service with all data protection agreements in place. Analysis will be ongoing and iterative, will inform further data collection and follow recognised thematic analysis procedures using Nvivo software[29] and interpreted in the light of NPT.

The findings will also be discussed with the Parent Advisory Group to help us understand wider parent perspectives.

Reporting and dissemination.

The finalised "CoolCuddle" protocol will include a manual/standard operating procedure (SOP) of the process, monitoring required, training package for nurses, support for parents and follow up. The training package will include animation explaining the process of CoolCuddle. We will work with neonatal network nurse who is part of the study advisory group to develop the SOP and liaise with BAPM to incorporate the SOP into the national therapeutic hypothermia framework. During this final stage of the project, we will analyse all the data, prepare the NIHR report and manuscript.

Study endpoint.

The study will end for babies when they complete the CoolCuddles and the cooling therapy by day 4 of life. Parents will complete the study after they complete the questionnaires in the postnatal period and the interviews, which will be 4 months from the date of recruitment.

5 STUDY SETTING

This is a multicentre study and will take place in up to 7 sites including the tertiary NICUs at Southampton, Leicester, Birmingham, Manchester, Newcastle, South Teesand Nottingham hospitals. Nurses will provide the short parent information leaflet about cuddling their baby to parents of cooled infants. This leaflet will contain pictures demonstrating the cuddle process. After gaining verbal consent, nurses will administer CoolCuddle as per the SOP.

6 SAMPLE AND RECRUITMENT

6.1 Sampling

Approximately 2 babies are cooled per month in each tertiary NICU. Previous experience suggests we can recruit around 70% of these families. CoolCuddle was developed and investigated in two tertiary NICUs on 27 parent infant dyads with 70 CoolCuddles over a cumulative duration of 115 hours. There were no adverse events associated with CoolCuddles.[30] Therefore sites will offer CoolCuddle after verbal consent (see section 4.2 for details of verbal consent process). We have observed a reduction in infants who require cooling therapy across the sites. Therefore, to answer the primary objective of the study, we aim to recruit between 40 and 45 families from 7 NICUs over a period of 11 months.

The primary outcome of the study will be involving the staff in neonatal units to understand the best strategy for embedding CoolCuddle in their usual practice. The primary outcome will be measured using the NoMAD instrument, which will be completed by the nurse champions at up to 6 time points who will be paid for their time spent on the study. Qualitative interviews with nurses will be conducted online or over the phone and last around 40 minutes per nurse. This method was well received in the CoolCuddle study.

6.2 Sampling technique

We will use a purposive sampling strategy and approach sequentially all the parents of babies admitted for cooling therapy and who are eligible for the study in up toseven tertiary units. Depending on staff availability, we may not be able to recruit families if two or more infants are admitted for cooling therapy simultaneously. Nurses, research nurses and clinicians in the participating sites will approach all parents of babies who fulfil the inclusion criteria. The exclusion criteria are designed to ensure that sicker infants requiring significant levels of intensive care do not come to harm. We will be inclusive in approaching and recruiting families into the study but some will not wish to complete the questionnaires. While we will aim to obtain complete physiology datasets on 40-45 infants, we are more likely to obtain complete questionnaires from only 35 parents.

To minimise the burden of completing questionnaires for parents, they are kept simple and can be completed online at two time points, before discharge and at 8 weeks postpartum. Nurse champions at each site will encourage the completion of questionnaires. Parents willingly took part in qualitative interviews in our previous study and the qualitative researcher is very experienced in talking to parents in their situation. The topic guides will be based on those used previously and were designed with our Parent Advisory Group (who have experience of CoolCuddle) to ensure that the questions are sensitive to their situations. The outcome of the study will be sent to all participants and participating sites as a plain English summary.

6.3 Recruitment

Sample identification

All parents will be shown the parent booklet illustrating the steps involved in the CoolCuddle and a study flyer. After verbal consent to participate in the study is given, parents will be offered the CoolCuddle intervention. Before the end of the cooling therapy, the participant information sheet detailing the data to be collected from parents and the data that will be collected from their baby will be given to parents from the medical team looking after the baby and/or the research team looking after the baby. After explaining the study, parents will be asked to provide written informed consent (paper or online) to participate in the study.

If 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 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 the NICUs.

Consent

We will invite both parents with an eligible baby to take part. From those who do CoolCuddle after verbal consent, we will obtain written informed consent during the cooling period (72 hours from the initiation of active cooling) from a carer with parental responsibility for the baby and from each parent for their own data, for the bonding and postnatal depression questionnaires, and to allow the research team to contact them for qualitative study.

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 will be asked for permission for the study team to complete data collection and follow up. If the parent changes their mind before giving written consent, then any data collected onto the CRF will need to be destroyed. If consent is withdrawn after written consent has been obtained, we will use the data already collected.

Parents 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.

7. SAFETY REPORTING

Adverse events will be recorded and reported in accordance with UHBWs Research Safety Reporting SOP. The study advisory 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.

7.1 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.

7.2 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.

7.3 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.

7.4 Assessment of Adverse events

All adverse events will be assessed as follows:

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.

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”

7.5 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

7.6 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 advisory committee.

7.7 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 advisory group in the form of a periodic report and discussed at each study group meeting.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Ethical considerations

The ethical issues involved in this research are the safety of the technique and potential adverse events. 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.

8.2 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. In our current family centred cuddling practice these adverse incidents are extremely rare and did not occur in the first CoolCuddle study. If an adverse incident occurs, babies can be

quickly transferred into the incubator and airway or the site of arterial access can be secured preventing any potential harm to the babies.

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, the local research team will discuss the result with the woman and ask if she agrees to a referral to the local perinatal mental health team for support. Depending on the local policies and guidelines, families with babies receiving intensive care will routinely receive some level of enhanced perinatal mental health support.

In the standard practice of cuddling and CoolCuddle1 study, 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.

8.3 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

8.4 Amendments to protocol

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

8.5 Peer review

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

8.6 Advisory groups:

Patient & Public Involvement

Our parent advisory PPI group comprises 8 parents, all of whom were involved the previous feasibility CoolCuddle study and have babies with HIE. The parent advisory group will meet three times during the study to advise on: good ways to encourage families to take part and complete the questionnaires, participant information sheet wording for mothers and fathers, interpretation of findings and dissemination to wider audiences. We will hold the meetings at a time convenient to them (probably in the evenings) when they are able to commit to attending. They will be supported by the inclusion of an induction into the role of advisory group member where we will agree 'safety ground rules' for our meetings and time to build rapport with the group. We will use NIHR INVOLVE guidance to provide support with voicing opinions, understanding research terms, signposting for emotional support and ensuring barriers to accessing meetings are broken down and that vouchers/payment for participation are paid promptly.

Clinical and methodological advisory group.

Our second advisory group has expertise from Prof Carl May (implementation science using NPT), Prof Marianne Thoresen (HIE and therapeutic hypothermia), Prof Peter Fleming (developmental paediatrics), Prof Peter Blair (medical statistics) and Ms Robyn Smart (Lead nurse, southwest neonatal network manager). We will seek their advice at regular meetings throughout the study to aid study management and interpretation of the results. Ms Smart will support the engagement with the national neonatal networks in the national meetings and enable the dissemination of the outputs and the resources developed from the proposed study to implement the CoolCuddle intervention successfully in the NICUs within the networks.

8.7 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.

8.8 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.

8.9 Data Management

Where applicable a random sample of at least 10% of CRFs will be checked, by the local study Research Team, against entries within the database and with the source data for quality purposes.

8.10 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.

8.11 Storage of Records

Study documents (paper and electronic) will be retained in a secure location during and after the study has finished. Following analysis, the digital versions of the qualitative interviews will be deleted and destroyed. All essential research documents, including patient records and other source documents will be retained until the participant reaches the age of 25. All hard copy medical records and electronic records will be stored as per each trust policy.

8.12 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.

8.13 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.

9 DISSEMINIATION POLICY

9.1 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 plain English summary of the results and a link to the publication if they wish. 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.

9.2 Authorship eligibility guidelines

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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