This protocol has regard for the HRA guidance and order of content

FULL/LONG TITLE OF THE STUDY

"CoolBonding": Impact of COVID-19 visiting restrictions on bonding, attachment and mental health of parents of babies cooled for hypoxic-ischaemic encephalopathy: multicentre prospective cohort study.

SHORT STUDY TITLE / ACRONYM

CoolBonding study

PROTOCOL VERSION NUMBER AND DATE

Version 1.4 14.12.20

RESEARCH REFERENCE NUMBERS

IRAS number: 257431

Sponsor number: 2019 - 2165

LIST of CONTENTS

KEY STUDY CONTACTS

Insert full details of the key study contacts including the following

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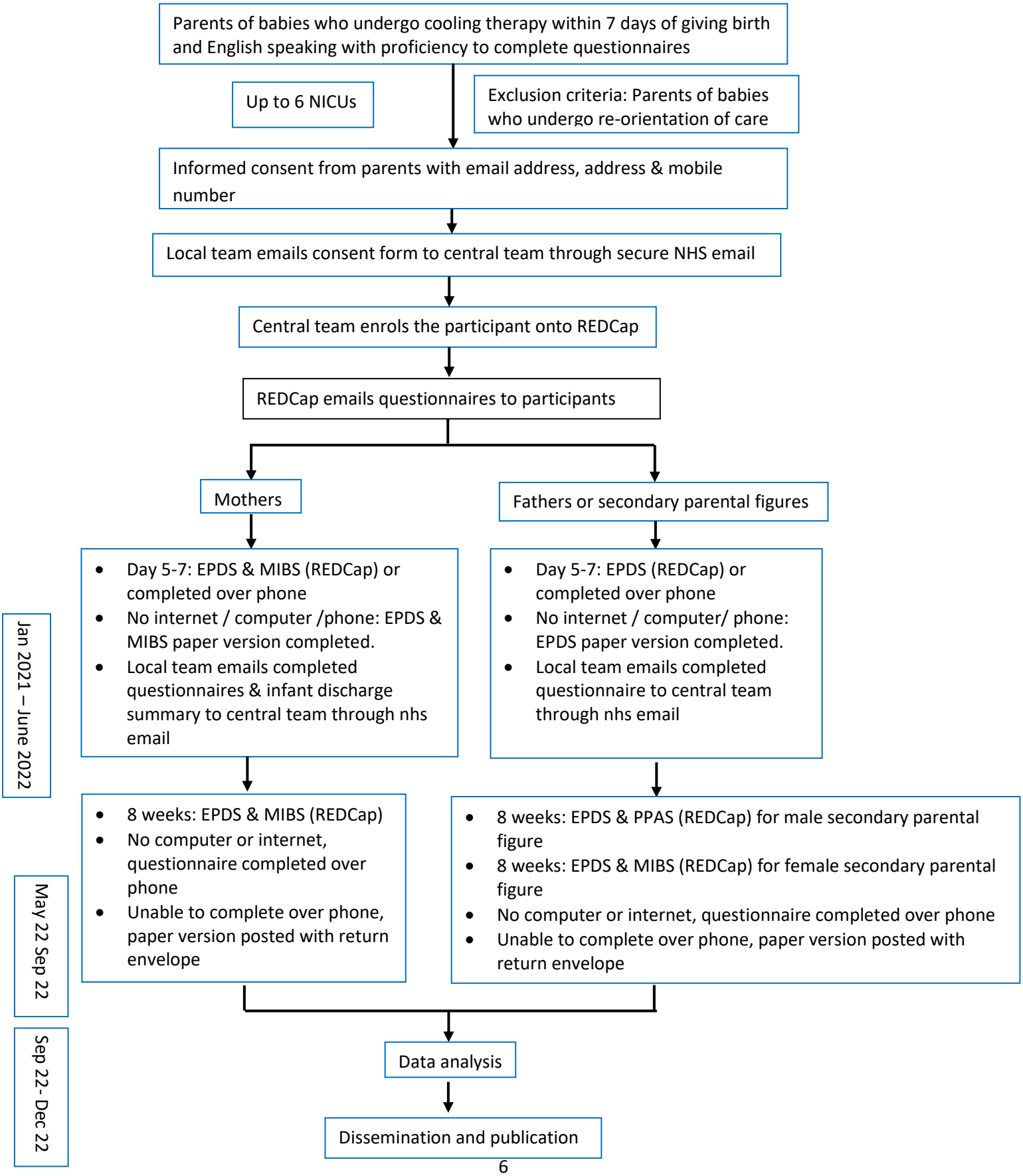
Study Co-ordinator	Ms Satomi Okano Advanced Neonatal Nurse Practitioner Level D St Michael's Hospital Southwell street, Bristol. BS2 8EG Tel : 01173425711 Email: satomi.okano@bristol.ac.uk
Sponsor	University of Bristol Beacon House Queens Road Bristol. BS8 1QU, UK
Key Protocol Contributors	Dr Ela Chakkarapani Ms Satomi Okano Dr David Odd Dr Jenny Ingram

Study Title	"CoolBonding": Impact of COVID-19 visiting restrictions on bonding, attachment and mental health of parents of babies cooled for hypoxic-ischaemic encephalopathy: multicentre prospective cohort study.
Internal ref. no.	2019 - 2165
Study Design	A multicentre prospective cohort study investigating maternal bonding, paternal attachment and postnatal depression scores measured using validated questionnaires in parents of babies who underwent therapeutic hypothermia and intensive care for perinatal hypoxic brain injury during the visiting restrictions imposed on parents due to COVID-19 pandemic. After obtaining informed consent, mothers will complete Maternal-Infant Bonding Scale, Edinburgh Postnatal Depression Scale at 5-7 postnatal days and again at 8 weeks postnatally. Fathers or secondary parental figures will complete Edinburgh postnatal depression scale at 5-7 postnatal days and at 8 weeks after birth as well as Paternal Postnatal Attachment Scale at 8 weeks after birth.
Study Participants	Mothers and fathers or secondary parental figures of babies who require therapeutic hypothermia and intensive care for hypoxic-ischaemic encephalopathy.
Planned Sample Size	50 mothers and fathers or secondary parental figures of cooled infants.
Follow-up duration	Up to 12 postnatal weeks
Planned Study Period	01/12/2020 to 01/12/2022
Primary Objective	To investigate the impact of restrictions imposed on parents visiting their babies admitted to intensive care due to COVID-19 pandemic on postnatal depression scores and mother-infant bonding scores at 5-7 days and 8 weeks postpartum in mothers of babies who received cooling therapy.
Secondary Objectives	1. To examine the distribution of postnatal attachment scores between fathers or secondary parental figures and babies who received cooling therapy. 2. To investigate the evolution of bonding in mothers and postnatal depression in mothers and fathers or secondary parental figures of babies who received cooling therapy. 3. To explore the prevalence of postnatal depression in mothers and fathers or secondary parental figures of cooled babies.
Outcomes	1. Mean and confidence intervals of mother-infant bonding score and Edinburgh postnatal depression score (EPDS) in mothers of cooled neonates at 5-7days and 8 weeks postpartum.
Secondary	1. Mean and confidence intervals of paternal-postnatal attachment scores at 8 weeks postpartum.

	2. Change in mother-infant bonding scores and postnatal depression scores in mothers and fathers or secondary parental figures between 5-7 days and 8 weeks postpartum. 3. Proportion of parents with postnatal depression at 5-7 days and 8 weeks postpartum.

CoolBonding study flowchart



ROLE OF STUDY SPONSOR

Sponsor for this study will be the University of Bristol. Sponsor takes the responsibility for the initiation and management of the study. Sponsor and funder will not have any role in the study design, conduct, data analysis and interpretation and manuscript writing. Sponsor will be involved in the dissemination of the results of the study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The study will have the investigator group involving two primary investigators (Dr Ela Chakkarapani and Ms Satomi Okano) and will liaise with principal investigators at each site, who will oversee the study coordination and conduct at each site. This study was developed with input from the NIHR Southwest Research Design service.

Patient and Public involvement group

Parents of cooled infants form the group. We have discussed about the study design and the outcomes. Parents agree that the outcomes are appropriate to study.

KEY WORDS: Hypoxic-ischaemic encephalopathy, Therapeutic hypothermia, maternal-infant bonding, paternal infant attachment, Edinburgh postnatal depression score, COVID-19

STUDY PROTOCOL

"CoolBonding": Impact of COVID-19 on bonding, attachment and mental health of parents of babies cooled for hypoxic-ischaemic encephalopathy: multicentre prospective cohort study.

1. BACKGROUND AND RATIONALE

In the NHS, each year around 2100 infants (3/1000 live births) undergo cooling therapy to reduce death and disability due to brain injury following hypoxic-ischaemic encephalopathy (HIE) occurring secondary to birth asphyxia[1]. Cooling therapy involves cooling the whole body of the newborn baby with encephalopathy within 6 hours of birth using a cooling blanket covering the baby along with intensive care for three days[2]. Cooling therapy is offered in tertiary neonatal intensive care units (NICUs). Babies born in peripheral local neonatal units requiring cooling therapy are transferred to tertiary neonatal units soon after birth. Mothers of these babies are transferred to the cooling centre once they are stable which is typically around 1-2 days after delivery resulting in early separation from their babies. During cooling therapy there is limited physical contact between the babies and their parents for 4 days due to concerns of affecting the process of cooling therapy or intensive care[3]. Further, restrictions imposed on parents visiting their babies admitted in the NICUs during COVID-19 pandemic might worsen the physical and emotional separation between the parents and their babies undergoing cooling therapy[4].

Parents of babies with HIE experience extreme distress due to the risk of their baby dying (11% of cooled babies die)[5], developing long- term disabilities (22% of cooled babies)[5] or intellectual difficulties (30-40%)[6,7]. Interviews with mothers of cooled infants conducted 4 months to 4 years after giving birth suggested that development of maternal-infant bonding may be affected by the prolonged separation from their baby during cooling therapy, the high-tech NICU environment and the inability to cuddle or hold their baby during cooling therapy[8-10]. Mothers of cooled babies report poorer bonding compared to control mothers when their babies were 18 months old[11]. We already know that poor maternal- infant bonding can affect the intellectual development[12] of infants. This effect may be exacerbated in cooled babies, already at a higher risk of developmental problems. Direct costs of intellectual disabilities in Europe are estimated at £5.97 billion accruing from health and mental health services utilisation[13] while lifelong welfare support and lost earnings leads to a significant burden to the society and economy[14].

In addition, postnatal depression may influence the development of maternal-infant bonding. Nearly 21% of mothers of cooled babies report postpartum depression 1 week after delivery.[15]. This recent study has shown that mothers of HIE babies may be twice likely to be at risk of having postnatal depression during the first postpartum week, however the prevalence of persistent postnatal depression at 8 weeks postpartum and its influence on maternal-infant bonding in cooled infants, is not known. Fathers or secondary parental figures are important attachment figures for infants. Postnatal depression in fathers or secondary parental figures may influence the development of paternal-infant attachment as well as family dynamics but little attention has been given to father-infant attachment and postnatal mental health of fathers or secondary parental figures of babies with HIE.

For these parents of babies with HIE who are already vulnerable to emotional distress, we do not know whether the visiting restrictions imposed on parents due to COVID-19 impacts the mental health of parents and the bonding and attachment with their infants. There is wide variation across NICUs in allowing parents

to visit their infants who are admitted to intensive care. For example, while St. Michael's hospital NICU in Bristol allows unrestricted access to parents whose babies are admitted to intensive care, Southmead NICU in Bristol only allows 2 hours access for both parents at a pre-booked time and unlimited access is allowed for one parent per baby. Other NICUs have allowed access to one parent per baby. These variations in visiting restrictions might impact the parents' mental health and parent-infant bonding, which are reported to be impacted in parents of infants with HIE in other health care settings.

RESEARCH QUESTIONS/AIMS

2.1 Population

Mothers and/or fathers or secondary parental figures of infants who underwent 72 hours of cooling therapy and intensive care for hypoxic-ischaemic encephalopathy.

Inclusion Criteria

1. Parents of babies who have undergone therapeutic hypothermia
2. Up to 7 days postpartum

Exclusion Criteria

1. Parents of babies who underwent re-orientation of care during the first 7 days of life
2. Non English-speaking parents which will preclude them from completing questionnaires.

2.2 Objectives

2.2.1. Primary objective

To investigate the impact of restrictions imposed on parents visiting their babies admitted to intensive care due to COVID-19 pandemic on maternal postnatal depression scores and mother-infant bonding scores at 5-7 days and 8 weeks postpartum in mothers of babies who received cooling therapy.

2.2.2. Secondary objectives

- To examine the distribution of postnatal attachment scores between fathers or secondary parental figures and babies who received cooling therapy.
- To investigate the evolution of bonding in mothers and postnatal depression in mothers and fathers or secondary parental figures of babies who received cooling therapy.
- To explore the prevalence of postnatal depression in mothers and fathers or secondary parental figures of cooled babies.

2.3 Outcomes

2.3.1. Primary outcome

Mean and confidence intervals of mother-infant bonding score and Edinburgh Postnatal Depression Score in mothers at 5-7 days and 8 weeks postpartum.

2.3.2. Secondary outcomes

- Mean and confidence intervals of paternal-postnatal attachment scores at 8 weeks postpartum.
- Change in mother-infant bonding scores in mothers and postnatal depression scores in mothers and fathers or secondary parental figures between 5-7 days and 8 weeks postpartum.
- Proportion of parents with postnatal depression at 5-7 days and 8 weeks postpartum.

3. STUDY DESIGN/METHODS

3.1. Study design

Prospective multicentre cohort study

3.2. Study setting

3.2.1. Main coordinating centre

Regional Neonatal Intensive Care Unit, St Michael's Hospital, University Hospitals Bristol and Weston NHS Foundation Trust, University of Bristol, Bristol, UK.

3.2.2. Participating NICUs

Up to 6 NICUs that offer cooling therapy including
Southmead Hospital, North Bristol Trust, Bristol
Neonatal Intensive Care Unit, University Hospitals Plymouth NHS Trust, Plymouth, Devon. PL6 8DH.
University Hospital of Wales, Heath Park, Cardiff, CF14 4XW.
Royal Gwent Hospital, Cardiff Road, Newport, NP20 2UB.
Princess Anne Hospital, Coxford Road, Southampton, SO16 5YA.

4. SAMPLE SIZE AND RECRUITMENT

4.1 Recruitment

The number of cooled babies cared for in tertiary NICUs in the past years range between 15-20 babies per year. Recruitment will be from up to 6 centres. Doctors or nurses from participating centres will be identified and form a recruitment team under the supervision of the principal investigator. Initial approach to participants regarding the study will always be by a member of their direct care team. Following this, a member of the recruitment team will approach the parents of babies who had received cooling therapy as soon as possible after the clinical team have updated parents of the clinical status of their baby and the treatment plan. They will explain the aims and

content of the study, give the participant information sheet to the parents and give opportunity to ask questions. After sufficient time, parents will have a further opportunity to ask questions. If the parents decide to participate, informed consent will be obtained. Participation will be voluntary. An informed written consent will be obtained from both mother and father or secondary parental figure separately. If only one of the parents consent, they will still be able to participate in the study. In families with same sex parents, we will send the mother-infant bonding questionnaire to the female secondary parent at 8 weeks instead of the paternal postnatal attachment scale.

During COVID-19, most neonatal units are allowing one or both parents to visit their baby at a time to reduce the footfall within the unit and practice adequate physical distancing between people within the unit. The research team will approach whenever parents visit their baby. If the partner is absent when mother is consented, we will obtain mother's permission to approach their partner. We will not approach mothers or fathers who are separated from their babies. They will be approached for the study within 5-7 days of birth when they are with their babies. If either parent has coronavirus infection and not allowed to visit, we will endeavour to approach parents via their telephone number if it is deemed to be appropriate after consulting the clinical team looking after the baby.

If the baby dies after 7 days of age, local team will inform the central research team so that the 8 weeks questionnaires will not be sent.

4.2 Sample size

We estimated there will be a minimum of 90 eligible sets of parents of cooled infants over 12 months. After excluding 10% due to infant mortality and a further 10% that decline participation or are not recruited due to possible lack of clinical team availability to approach the parents, we anticipate we will recruit 80% of the eligible families of cooled infants (72 families). With a conservative estimate, if a further 20% of the families are lost to follow-up at 8 weeks, we will have 58 families over 12 months. We will aim to recruit 50 families over 18 months to estimate the distribution of bonding, attachment, and postnatal depression scores in parents and associations of centres with different visiting restrictions during COVID-19.

5. DATA COLLECTION

We will use REDCap (a secure web application for managing online surveys and databases) to enable parents to complete questionnaires online as well as entering other data collected during the study.

REDCap will be used to send emails and reminders to parents. For parents not able to access the questionnaires online, we will complete the questionnaires over phone. For participants who are unable to complete the questionnaires over phone, we will post the questionnaires with stamped addressed envelopes for return. The recruiting team at each site will email the consent form to the study coordinator with participants' email address, telephone number and home address via secure NHS email after recruitment. The central study coordinator will register the participant in the REDCap database. Emails containing the link to the questionnaires will be sent to participants at 5-7 days and 8 weeks

postpartum. If the questionnaires are not completed by 8 weeks, an automated email reminder from REDCap will be sent at 9 weeks postpartum. Further reminders may include a text or phone call from the local recruiting team, if the questionnaires are not completed despite the reminder from the REDCap.

5.1. Questionnaires

Validated scales of mother infant bonding and paternal postnatal attachment will be used. As postnatal depression can influence parent infant bonding and attachment, postnatal depression will also be measured using a validated questionnaire. Each questionnaire will take up to a maximum of 10 minutes to complete.

Mothers:

5-7 days following delivery: mother-to-infant bonding scale[16] and Edinburgh postnatal depression scale[17]

8 weeks following delivery: mother-to-infant bonding scale, Edinburgh postnatal depression scale[17].

Fathers or secondary parental figures:

5-7 days following delivery: Edinburgh postnatal depression scale[17,18]

8 weeks: paternal postnatal attachment scale[19], Edinburgh postnatal depression scale[17,18] for male secondary parental figure.

8 weeks: mother-to-infant bonding scale, Edinburgh postnatal depression scale[17] for female secondary parental figure.

5.2 Other quantitative data

We will collect the demographic data of cooled infants and their parents, perinatal data, and course of neonatal care using Badger.Net (Neonatal Clinical Information System) and from REDCap questionnaires directly entered by the parents. This also includes the impact of COVID-19 such as visiting restrictions, social isolation (childcare/family support), breastfeeding rate.

Demographic data includes parental age, ethnic background, socio economic status, maternal education, family support.

Perinatal Data includes antenatal history, peripartum history, COVID-19 screening, mode of delivery, resuscitation, maternal medication, maternal medical history and birthing hospital.

Neonatal Data includes gestation, sex, severity of HIE, parental participation in care giving, timing of 1st cuddle, mode of feeding, accommodation, visiting restrictions due to COVID-19, length of hospital stay.

6. DATA ANALYSIS

Variables that influence the maternal infant bonding and paternal infant attachment including parental age, parity, psychiatric illness, intake of antidepressants, parental education, ethnicity,

socio-economic status and severity of encephalopathy and the implications and degree of COVID-19 restrictions will be summarised for the cohort. The central tendency and dispersion of maternal-infant bonding, paternal-infant attachment scores and postnatal depression scores will be presented as means with 95% confidence intervals for different levels of COVID-19 visiting restrictions by centres. Change in maternal infant bonding and depression scores from week 1 to 8 will be presented as mean or median difference using parametric or non-parametric tests depending on the distribution of the data. We will report the proportion of parents with depression (EPDS ≥ 13) at 5-7 days and 8 weeks postpartum.[20] If the visiting restrictions are eased during the study, we will compare the postnatal depression and bonding scores between the restrictions and no-restrictions epochs accounting for the potential confounders.

7. ETHICAL AND REGULATORY CONSIDERATION

The study involves collecting questionnaire data and does not pose any risk to the participants. The study team will be experienced and trained in explaining the study appropriately and sensitively to parents when they are approached for consent. The families of babies who are receiving cooling therapy are usually supported by appropriate health care providers including perinatal mental health psychologists, family support workers and clinicians. If the participation in the study causes distress to the participants, they will be able to contact the study team or contact the community midwifery team or General Practitioner to seek appropriate mental health support. If parents identify themselves as depressed during the study period or the perinatal depression questionnaire highlights depression, we will refer the participants to the General Practitioner or perinatal mental health team, whichever service is available locally.

The study will need the approval by the Health Research Authority and an NHS Research Ethics Committee. Confirmation of capacity and capability from participating Trusts will also be secured. The study will be conducted under the sponsorship of University of Bristol.

7.1. Assessment and management of risk

Data will be held in the previously allocated secure server at the University of Bristol. We will anonymise the data and the master file linking the patient details with anonymised ID will be stored in secure computer file with the respective PIs and the CI.

7.3 Peer review

The protocol was reviewed by an independent reviewer, who has the knowledge in the field and is familiar with the analysis described in the study.

7.4 Patient & Public Involvement

This protocol was developed with input from the NIHR South West Research Design Service. We have discussed the design of the research with parents of cooled infants. The group agreed on the outcomes to be studied and have contributed to the design and content of the parent information

sheet. The participant information sheet was revised based on the suggestions from parents of babies who have undergone cooling therapy in the past.

7.5 Data protection and patient confidentiality

All the investigators will comply with the requirements of the Data Protection Act 1998 with regards to the storage, processing and disclosure of personal information and will uphold the Act's core principles.

The study involves depersonalised data and the data will be maintained in secure servers. Chief investigator will be the data custodian.

7.6 Indemnity

This study will be sponsored by the University of Bristol. The University has Public Liability Insurance to cover the liability of the University to research participants. In the event that something goes wrong and a participant is harmed during the research study there are no special compensation arrangements. If a participant is harmed and this is due to someone's negligence then they may have grounds for a legal action for compensation against Bristol University or the NHS Trust or one of the other parties to the research, but they may have to pay their own legal costs.

7.7 Access to the final study dataset

The chief investigator will have access to the full datasets. Data analysis and appropriate sections of the datasets will be shared with co-investigators.

8. Discontinuation / withdrawal of Participants from Study

Parents will have the right to withdraw themselves 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. 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 parent's health and wellbeing.

9. SAFETY REPORTING

Parents of infants who undergo cooling therapy are the participants of the study and the infants undergo standard care. Given there is no intervention involved in the study for the parents, and 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. However, if the postnatal depression questionnaire scored above 13 and/ or the thought of harming was scored as either "sometimes" or "yes, quite often", we will refer the participant to the general practitioner or perinatal mental health team services, if they are available.

10. DISSEMINATION POLICY

All co-applicants (and where appropriate collaborators) will take an active part in the preparing and reviewing of all manuscripts and reports generated during or as a result of this study. Results will be presented locally, at the national and international conferences followed by publication in a peer reviewed journal.

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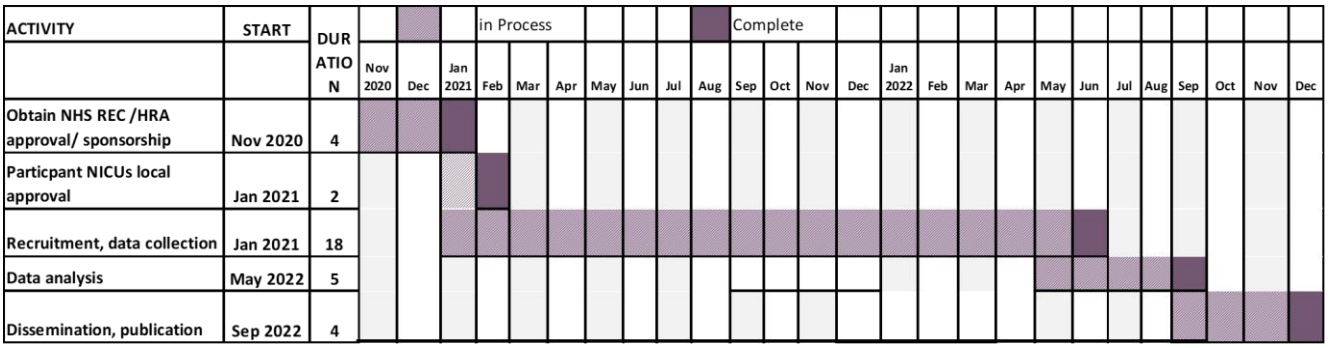
10. APPENDICIES

10.1 Appendix 1- Required documentation

Curriculum vitae of Chief investigator

10.2 Appendix 2 – Schedule of Procedures



10.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
	1.3			