Nottingham Trent University

Cluster Randomised Controlled Trial of a Service to Support the Mental Health and Coping of Parents with Excessively Crying Infants

Surviving Crying

Trial Protocol Version 5.0 30/06/2023

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Declaration of HRA protocol template use

This protocol has regard for the Health Research Authority (HRA) guidance and order of content, in line with Version 1.1 (March 2016) of the HRA Qualitative Protocol Development Tool.

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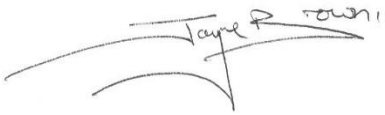
SIGNATURE PAGE

The undersigned confirms that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial 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 also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Chief Investigator: Professor Jayne Brown



Signature: _____

Date: 14/09/2023 _____

Sponsor: Nottingham Trent University

Print Name: _____Suvo Mitra_____

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Date: ___25/09/2023_____

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Contents

1 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BAME	Black, Asian and Minority Ethnic
CBT	Cognitive Behavioural Therapy
CEHR	Centre for Ethnic Health Research
CDMS	Clinical Data Management System
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CPN	Community Psychiatric Nurse
CRF	Case Report Form
CRN	Clinical Research Network
DSMC	Data Safety Monitoring Committee
e-CRF	Electronic case report form
EPDS	Edinburgh Postnatal Depression Scale
EQ5D	Quality of Life Questionnaire
GAD-7	Generalised Anxiety Disorder Assessment
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEE	Generalised Estimating Equations
GLM	Generalised linear Models
HRA	Health Research Authority
HCP	Health Care Professional
HRQoL	Health Related Quality of Life
HV(s)	Health Visitor(s)
ICC	Intraclass Correlation Coefficient
ICF	Informed Consent Form
ICH GCP	International Conference on Harmonisation Good Clinical Practice
ICER	Incremental Cost-Effectiveness Ratio

iHV	Institute of Health Visiting
IM&T	Information Management and Technology
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LCTU	Leicester Clinical Trials Unit
MCID	Minimally Clinically Important Difference
MCQ	Maternal Confidence Scale
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIHR HTA	National Institute for Health Research Health Technology Assessment
NPT	Normalisation Process Theory
NMB	Net Monetary Benefits
PHE	Public Health England
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RDC	Remote Data Capture
REC	Research Ethics Committee
R&I	Research and Innovation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Surviving Crying
SD	Standard Deviation
SF-6D	Short-Form Six Dimension
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group

TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
UoL	University of Leicester

2 SUMMARY OF TERMS

Research Administrator	Will notify and coordinate participant allocation at sites in addition to entering data onto the trial database.
ICON	A programme that provides information about Infant crying and how to cope.
Regular Health Visitor (HV)	Provides usual HV services and request verbal consent to refer to SC trial, if notified of parent/carer with excessively crying infant.
Parents	Term parent refers to parents and carers
Site	NHS or Local Authority Health Visitor services
Surviving Crying (SC) Trained Health Visitor (HV)	Trained in the delivery of the Surviving Crying Cognitive Behaviour Therapy (CBT)

3 TRIAL SUMMARY

Trial Title	Cluster Randomised Controlled Trial of a Service to Support the Mental Health and Coping of Parents with Excessively Crying Infants
Trial Acronym	Surviving Crying
Research Question	Are usual HV services supplemented by the SC package more clinically effective and cost-effective than usual services in improving the mental health and coping of parents/carers with an excessively crying infant up to 20 weeks of age?
Trial Design	Multi-centre (8 sites) cluster (HV teams) randomised controlled trial with an internal pilot and embedded qualitative studies to assess service delivery to minority communities and participants' views of usual and SC-based services.
Randomised controlled trial (RCT) Eligibility	Inclusion Criteria • Parents/Carers aged 18 years or older with an infant up to 20 weeks old (at time of consent), who express concern about their infant's excessive crying • Written informed consent Exclusion Criteria • Any seriously ill infant requiring inpatient hospitalisation at time of consent. • Involved with any other clinical trial at the time of consent or 3 months prior.
Recruitment sample size	**Internal Pilot :** 56 participants from 20 clusters in 2-4 sites **Main phase:** 336 participants from 66 Clusters in 6-8 sites
Primary Outcome Measure	**Primary Outcome:** • Validated measure of parental depression using the Edinburgh Post Natal Depression Scale (EPDS) score at 8 weeks follow-up.
Secondary Outcome Measures	**Secondary Outcomes**: • Edinburgh Postnatal Depression Scale (EPDS) score 16 weeks post baseline; proportion of parents with EPDS score of 10 or more • Generalised Anxiety Disorder Assessment GAD-7 Scale self-rated measure of anxiety measured at 8 and 16 weeks post baseline. • EuroQol-5D-5L, self-rated health utility and quality of life measured at 8 and 16 weeks post baseline. • Maternal Confidence Scale (MCQ) measures the confidence of a parent/carer in their parenting role at 8 and 16 weeks post baseline. • Crying knowledge scale measures knowledge of infant crying, amount of perceived infant crying, and parents' ratings of how frustrating and problematic the crying is for them, at 8 week follow-ups. • Partner Relationship Quality (CSI-4) measures the relationship satisfaction at 8 and 16 weeks post baseline. • Health, breast–feeding maintenance will measure Parental and infant health, breast-feeding persistence at 8 week and 16 week post baseline. • Health economic measures will be assessed at 8 week and 16 weeks post baseline. • Contacts with the NHS; parents' use and parents' and HVs' ratings of services to be collected and measured at 8 weeks post baseline assessment.

4 ROLES AND RESP0NSIBILITIES OF TRIAL MANAGEMENT GROUPS, OVERSIGHT COMMITTEES AND INDIVIDUALS

4.1 Role of Trial Sponsor and funder

The trial has been funded by a grant from the National Institute of Health Research (NIHR131341). Additional support and resources for the trial will be provided by the participating sites and their corresponding Clinical Research Networks (CRN) in the UK. The funder will be responsible for funding the trial but will not be part of the trial conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The Sponsor, Nottingham Trent University, will be responsible for all aspects of the study. The Sponsor may choose to delegate duties to other parties, including the Leicester Clinical Trials Unit, this delegation will be formally documented. However, like the funder, the Sponsor will not be part of the trial conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

4.2 Trial Management Groups (TMGs)

TMGs will oversee the day to day running of the project. The TMG will meet according to the demands of the study, but approximately monthly in the first stages, utilising video calls for ease of attendance. The TMG will highlight any key day-to-day trial issues and monitor progress of all research activity to ensure that project is being delivered to target. The TMG will provide input to the protocol and protocol amendment(s), recommend protocol amendments where applicable, ensure the protocol is adhered to and take action as necessary to remedy any difficulties and consider and act on the recommendations of the Trial Steering Committee and Data Safety Monitoring Committee.

4.3 Trial Steering Committee (TSC)

An independent TSC will be convened, with membership comprising of an independent Chair, at least two independent members, two lay members, the Chief Investigator and a representative of the LCTU. All independent members will need to be approved and then subsequently invited to be a member of the committee by the NIHR. TSC Charter will be put in place and 'Conflict of Interest' declarations obtained for all members and attendees. The TSC will be responsible for the scientific and ethical conduct of the trial and will supervise progress of the study. The TSC members will be required to attend TSC meetings which will be held prior to the commencement of the trial opening to recruitment and six monthly or as required throughout the study. The LCTU will facilitate these meetings, acting as a liaison and co-ordination point as necessary.

4.4 Data Safety Monitoring Committee (DSMC)

An independent DSMC will be convened with its own Independent Chair, Statistician and one other Clinician. The DSMC will convene at least every 12 months after recruitment begins to provide independent advice on trial conduct and safety issues. Meetings will also be held as necessary should any urgent issues occur. The DSMC will develop a Charter which describes the framework within which it will operate. It will meet to review the trial information and accruing data provided by the LCTU and advise on whether the trial should be discontinued early due to safety concerns. The trial statistician will present the trial data un-blinded in a closed session, the blinded progress and demographic data will be reviewed in an open session attended by the chief

investigator, trial manager The DSMC will be responsible for the interests of the participants and its main role will be to make recommendations to the TSC.

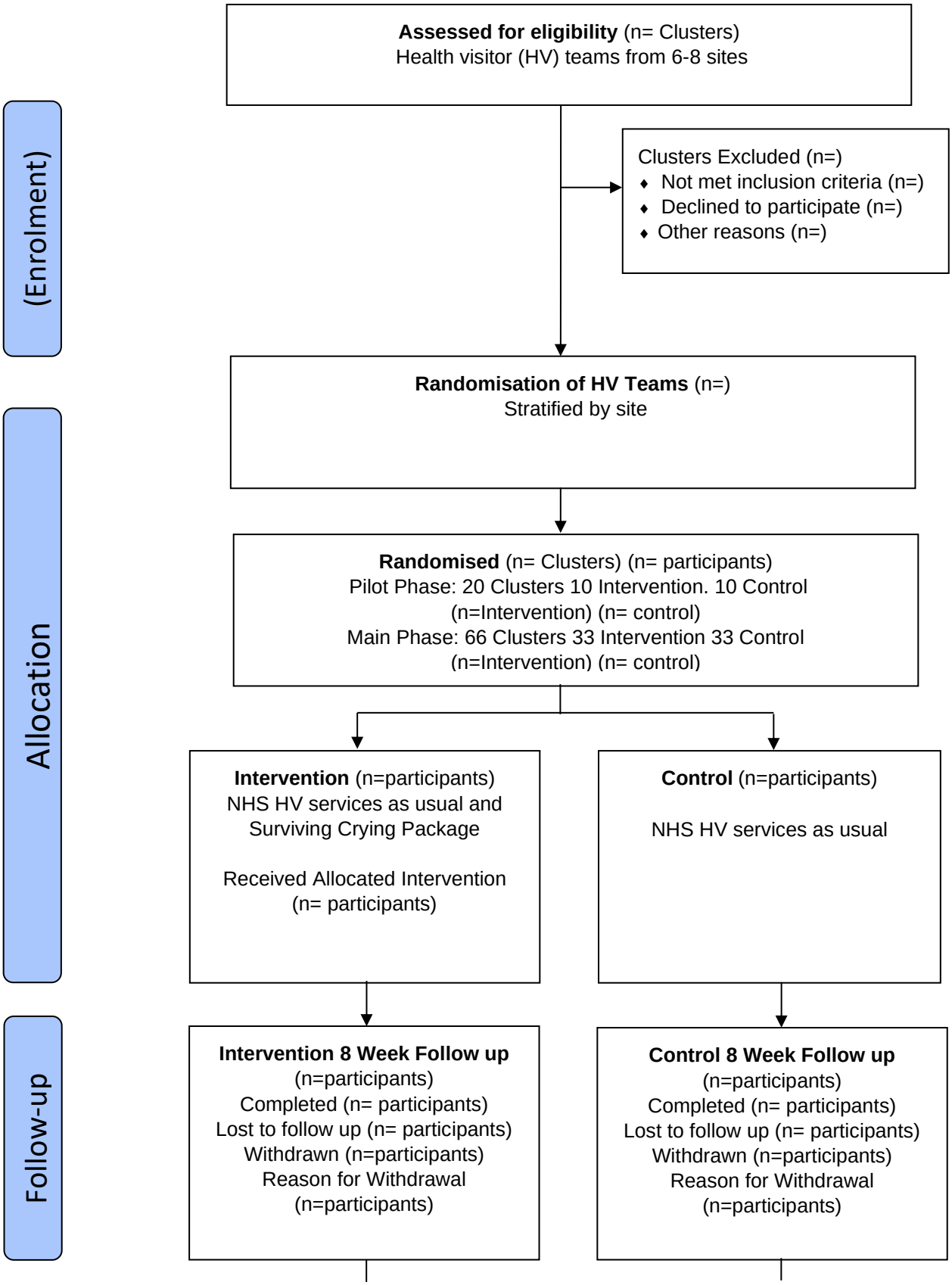
4.5 Patient and Public Involvement

This trial has been developed with extensive input from members of the public and parents. A parent of an excessively crying infant from the feasibility trial has been included as a co-applicant in this trial. He will continue to examine and provide feedback on all trial materials, take part in its Management Committee meetings and participate in disseminating the trial findings.
We intend to increase PPI numbers from each participating community and provide training as the trial progresses. . An annual PPI meeting will be arranged.

4.6 Protocol Contributors

- Prof Jayne Brown, Prof Ian St James-Roberts, Prof Dieter Wolke, Prof Traolach Brugha, Dr Andrew Willis, Prof Elaine Boyle, Matthew Rumbelow, Louise Wolstenholme, Prof Stephen Morris and Dr Cheryll Adams – trial design and protocol write-up.
- Dr Shaun Barber and Cassandra Brookes, Leicester Clinical Trials Unit – power calculations, statistical analysis and randomisation aspects.
- Rachel Hobson and Yvette Walters, Leicester Clinical Trials Unit – trial management, safety reporting, ethical and regulatory considerations, data management.

4.7 Flow Diagram (Clusters)



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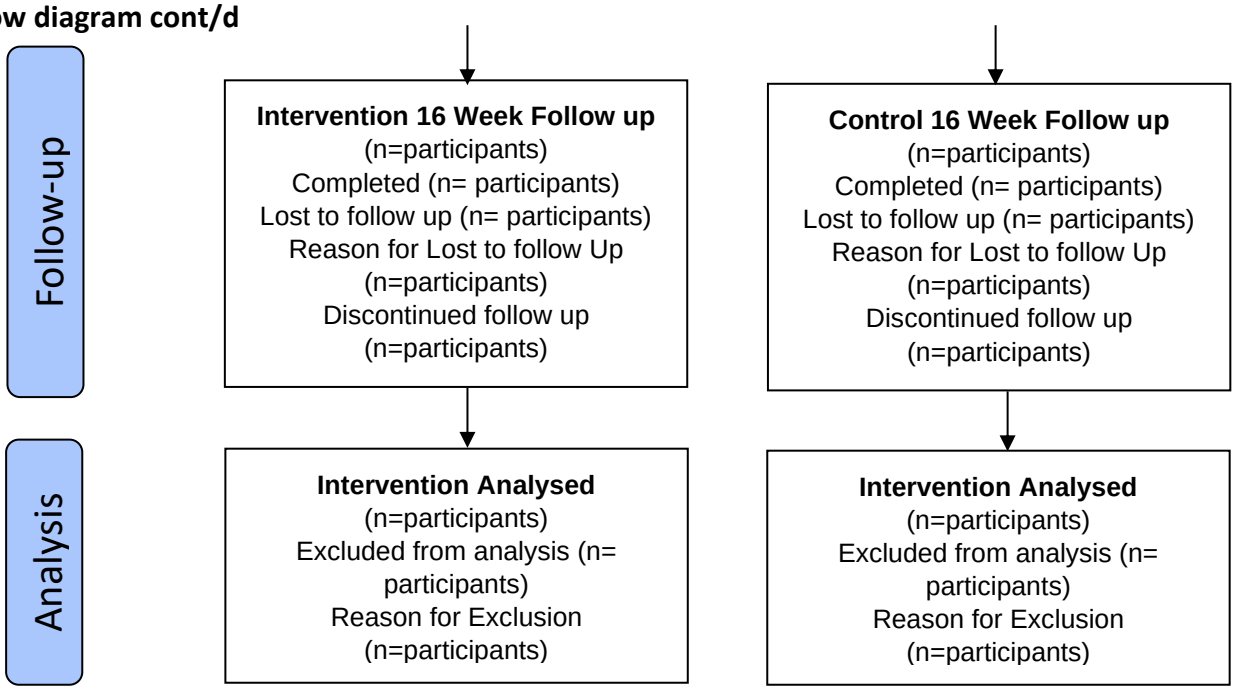


5 SCIENTIFIC ABSTRACT

Around 20% of infants cry for prolonged periods during the first four postnatal months. Where parents cannot cope, this can lead to parental depression, poor parent-child relationships, problems with child development, and infant abuse in rare cases. With National Institute for Health Research Health Technology Assessment (NIHR HTA) support, we have completed a feasibility study to develop the 'Surviving Crying' (SC) package with the aim of supporting parents in this position. 52 parents of excessively crying infants and 50 NHS health visitors (HVs) provided evaluation data. 30 parents met clinical criteria for depression at baseline, halving to 15 after receiving the SC package. Parents' NHS contacts reduced. All 52 parents and 85% of the HVs wanted the package to be included in the NHS. Most (86%) parents were willing to participate in a controlled trial of the package.

Population: Parents/carers over 18 years of all backgrounds with a healthy infant up to 20 weeks old who report concern about their infant's excessive crying to their HV.

Intervention: Access to the SC support package, SC Booklet, Website, and option of CBT session 1- 6 session delivered to parents by SC Trained HVs, in addition to usual NHS HV services. Comparator: Usual NHS HV services.

Primary outcome: Edinburgh Postnatal Depression Scale (EPDS) score measured 8 weeks after baseline.

Secondary outcomes: EPDS score at 16 weeks post baseline; proportion of parents with EPDS score of 10 or more, validated measures of parental anxiety, sleep, social supports, parent knowledge of infant crying, amount of infant crying, parents' ratings of how frustrating and problematic the crying is for them, at both 8 & 16-week follow-ups.

Other measures: Parental and infant health, breast-feeding persistence; NHS contacts; parents' use and parent and HV ratings of services; at 8 weeks post baseline, health economic measures at both 8 and 16 weeks follow ups.

Design & Timelines: Multi-centre (8- 10 sites) cluster (HV teams) randomised controlled trial with an internal pilot. The sample size is designed to detect a 2-point difference in mean EPDS score (10.5 for the control group and 8.5 for the intervention group). With a 5% level of significance (two-sided) 90% power, allowing for attrition and cluster trial methods, this gives a total target sample size of 86 clusters (43 per arm) and 392 participants (196 per arm).

Pilot Phase: (Progression Criteria) 56 participants to be recruited from approximately 20 clusters (10 intervention and 10 control) recruited in 9 months. SC package plus usual NHS HV services or control service usual NHS HV services, delivered to 56 participants with an excessively crying infant. SC Trained HVs will be trained and certified in delivering the SC package and procedures implemented to avoid participant bias in intervention and control groups.

Main Trial: If progression criteria are met, the trial will be extended to the planned number of clusters, HVs and participants.

Dissemination: We will work with NHS and Social Care administrative and commissioning groups and networks (CRN, PHE, iHV) throughout the trial. We will disseminate via conferences, peer-reviewed publications, clinical networks, media and social media.

Outcomes: (1) Evidence-based NHS services for parents distressed by their infant's excessive crying; (2) improved parental coping, reduced parental depression, improved infant outcomes, enhanced health visiting as an evidence-based profession; improvement in how NHS money is spent; (3) The SC website, booklet, made freely available at the end of the trial.

6 BACKGROUND and RATIONALE

Parents report that around 20% of infants cry persistently without an apparent reason during the first four postnatal months.[1] There is objective evidence that they are often correct in reporting prolonged crying.[2] Based on 2018 live birth rates, this affects some 146,000 UK families per year. Traditionally, this phenomenon was known as 'colic', implying that the crying is due to gastro-intestinal disorder and pain. In spite of many studies, however, the crying remains unexplained and there is no reliable way to prevent or resolve it.[3;4] Recently, the need for a focus on the impact of this crying on parent/carers, and subsequent outcomes, has become apparent. Crying in early infancy includes long lasting bouts and is sometimes resistant to normal soothing measures, which parents find particularly challenging.[2;5] They worry that the crying is a sign their infant is unwell.[6] However, the impact on parental emotions and actions depends partly on how parents cope with the crying. Anxiety and emotional arousal influence how parents interpret infant crying [7-9] and this can precipitate parental depression.[10] Other adverse outcomes include premature termination of breastfeeding [11], over-feeding [12], poor parent-child relationships and child development outcomes [13;14], and infant abuse in rare cases.[15]

Against this background, the lack of evidence-based NHS services to support parents in managing infant crying is striking. Instead, parents turn to popular media, which give conflicting advice [16], or take infants to GPs or hospitals [17], adding to NHS costs, which are substantial. [18] In Canada, a support programme for parents reduced hospital admissions for infant abusive head trauma and proved to be cost-effective over the long-term.[19;20] Based on these findings, the 'Surviving Crying' (SC) feasibility study was designed to develop materials which support UK parents who judge their infant to be crying excessively. The resulting package includes a website, information booklet, and short Cognitive Behaviour Therapy (CBT) programme tailored to support parents' coping with excessive infant crying. Following NICE guidelines [21], the website or booklet were intended to be inexpensive and available to all parents; the CBT sessions were intended for families with greater need. To evaluate the package provisionally, 52 parents with excessively crying infants were referred to the study by HVs and completed standardised measures before receiving the support package (baseline) and afterwards. Almost all parents accessed the website or booklet; half accessed the CBT sessions. At baseline, 30 of 52 parents met clinical criteria for depression, halving to 15 after receiving the SC package.[22] In regression analyses, these improvements were not explained by changes in infant crying.[22] Reductions occurred in the number of parents reporting the crying to be a large or severe problem (from 28 to 3 parents) or feeling very or extremely frustrated by the crying (from 31 to 1 parent). Other findings included improvements in parents' confidence, knowledge of infant crying, sleep, and reductions in NHS contacts. [22-24] All 52 parents and 85% of 50 HVs agreed the package should be included in the NHS and 94% of the HVs wanted materials of this kind to be included in HV training.[23] Most (86%) of the parents were willing to take part in a controlled trial to fully evaluate the SC package [24.]

Because HVs and allied professionals provide primary healthcare support for all UK parents and infants, the research so far has been carried out together with HVs and the SC package

was designed to be delivered by HVs and compatible with statutory HV 'universal' and 'universal-plus' services. There is also robust evidence that nurses can deliver tailored CBT sessions similar to those in the SC package. [25-27] Unfortunately, HV services have been subject to recent cuts and re-organisations which query whether HVs can deliver the SC materials in practice. In the feasibility study, researchers delivered the website and booklet; a psychologist the CBT sessions. Potentially, HVs might deliver digital services such as the SC website, other professionals provide CBT. We continue to view health visiting as the best way to deliver these supports as a joined-up primary healthcare service, but accept that has to be demonstrated. It also needs to be demonstrated that the reductions in depression symptoms found in the SC feasibility study are due to the SC intervention, rather than to care as usual. To provide the evidence needed, we have designed a trial to compare SC with usual services for their effectiveness and cost.

6.1 Evidence explaining why this research is needed now

This research is important and timely because parental perinatal mental health has been prioritized by the NHS.[28] Our initial work has produced evidence that services which support coping with infant crying will be particularly effective in reducing parental depression and improving parents' independent coping. [22]

Our HV Co-applicant (LW) tells us that the only intervention open to HV's for parents with an infant who cries excessively is a listening ear, and that giving that time is a costly and unfocused response. She and her colleagues have welcomed participation in the SC trial because it gives HV's help and support to offer, much of which parents can access in their own homes. HV services are able to adapt service delivery on a needs basis, providing the opportunity to enhance health visiting as an evidence-based profession and improve the cost-effectiveness of NHS primary healthcare.

6.2 Health Technologies being assessed

The 'Surviving Crying' (SC) support package developed in our feasibility study includes: (1) a website; (2) a printed booklet; (3) a programme of CBT- based sessions delivered to parents/carers by a specially trained HV. Parents/carers and HVs were closely involved in the package development and evaluation.

The SC website home page informs parents that:

'This website is for parents who are worried about their infant's excessive crying. Here you'll find:

- Reliable information about the crying
- Guidance for parents
- Access to other sources of support
- Stories from parents who've survived their infant's crying'

A prominently highlighted section for parents feeling overwhelmed by their infant's crying (Need Help Now?) is accessible from the home and other pages. Other page headings include: Infant Health Checklist; Settling and Soothing Your Baby; Can Parents Stop the Crying?; Is it Colic?; Coping Tips for Parents; For Dads/male carers; Surviving as a Family; Waking and Crying

at Night; Your Stories (videos and parental accounts of their experiences, coping, and life after the crying stopped); News and Research (the evidence behind the guidance), About Us (introduces the research team background and qualifications). The information is presented in a variety of formats, including a "Baby Myths" box, giving information to help challenge unhelpful assumptions, quotations from parents, and videos of professionals or parents providing information and advice. Hyperlinks enable easy navigation between sections of the site. In the feasibility study, almost all parents who accessed the website rated it as 'clear', 'helpful' and 'relevant'. Parents liked its ease of access; practical suggestions; the expert opinion and advice; that it gave other parents' experiences and ideas; that it was aimed at both parents; and that they could trust the information supplied.[24]

We aim to make the SC Website and booklet accessible to all ethnic communities. Google translate, widely used for language translation in the NHS, will be used for this purpose.

The SC Booklet: - The booklet is based on the website, using printed text and colourful images to convey the same information, as far as possible for parents who prefer this format or for those who are unable to access the internet. This will also ensure fairness of access to all participants. In the feasibility study, parents who read the booklet gave it high ratings similar to those for the website.

The SC CBT-Based Programme:-The CBT Programme was developed together with a CBT qualified psychologist with extensive experience in supporting adult mental health in the NHS. Parents/carers will be offered between 1-4 sessions. Each session will for be conducted for an average of 1 hour (based on the feasibility study). Additional sessions of up to a maximum of 6 can be provided where the SC CBT trained HV considers these to be needed The sessions will be delivered weekly at home, in a clinic location or by remote means either over the telephone or a video call . Based on the feasibility study it is expected that parents will receive between 2-4 sessions.
Three key topics will be included in each practitioner-delivered session:
Assessing infant crying and health, making arrangements to obtain any other information or support needed, and providing parents with information and reassurance.

- Monitoring the soothing and infant-care methods parents were using and exploring alternatives.
- Supporting parents in developing coping strategies which helped them to manage their own emotions and actions and ensure their own and their infant's wellbeing.

Each support session is based on core CBT principles, introduced to parent/carers in Sessions 1 and 2. These materials plus handouts will be included in a Parent Handbook where information could be kept over the course of the sessions. The materials use a large amount of full-colour graphics to illustrate the topics. Materials for other topics will also be provided, to be delivered flexibly in response to parents' needs over subsequent sessions. Each session will include home activities for parents to undertake between sessions and review at the next meeting. A Practitioner Manual enables the materials to be delivered in a reliable and consistent way by CBT practitioners. This manual provides an introduction to and overview of the sessions, together with step-by-step guidance on how to use the resources to facilitate

the sessions, including a plan of activities and session notes. Record sheets for practitioners to log their activities and the outcome of the individual sessions are also included. The CBT and other package elements underwent iterative revisions, have been piloted, adjusted to suit a 12-year-old reading age, and reviewed by parent and health visitor collaborators.

Adapting the SC Package for Use in the Proposed Trial: Following NICE recommendations for tiered services, we will include all three SC components in the trial. The less expensive (website and booklet) elements will be made available to all parents in the intervention group; the CBT-based sessions included as HV statutory 'universal-plus' services will be for intervention group parents with greater need, expressed by the parent/carer. Our finding that 50% of parents with excessively crying infants chose the CBT-based sessions is compatible with this approach.

All three components have been updated to take account of feedback from parents in the feasibility study, advice from our current PPI collaborators, and recent developments in online services, including making them compliant with guidelines for such services.[29] To complete this updating and make the SC materials suitable for delivery by HVs, we obtained a grant from the Burdett Trust for Nursing for a 1-year study based at De Montfort University:

1). To develop the SC materials into a training module delivered mostly online and tailored to the needs of busy NHS professionals;
2). Working with De Montfort University, the Institute of Health Visiting and senior HVs, to develop standard methods for assessing HV competence in delivering CBT to parents.
3). To train 10 volunteer HVs in delivering the CBT-based sessions to parents and examine and certify their competence in level 2 CBT skills.

This award from the Burdett Trust for nursing has provided further evidence of the support for this research which exists among primary healthcare professionals.

In keeping with the NIHR HTA programme's focus on translational research, this randomised controlled trial will be a pragmatic effectiveness trial, to test whether the SC package is effective when delivered in everyday NHS conditions by HVs working in diverse cultural and ethnic contexts.

6.3 Hypothesis to be tested

Usual HV services supplemented by the SC package is more clinically effective and cost-effective than usual services alone in improving the mental health and coping of parents/carers with an excessively crying infant up to 20 weeks of age.

7 TRIAL DESIGN AND SETTING

Cluster Randomised Controlled Trial following CONSORT and Ottawa guidelines[30,31] for such trials.

The proposed trial is in two phases: the pilot and main phase. The trial will run an internal pilot to prove recruitment of the relevant number of participants during 9 months from approximately 20 clusters.

Agreed Stop-go criteria:

- Randomise 20 Clusters (HV Teams) from 2-4 sites.
- Train and certify 10 SC Trained HVs to deliver the Surviving Crying CBT based sessions to parents.
- Achieve participant recruitment (target 56 participants) at an average rate of 0.4/cluster/month.

Progression:
GO: 100% of target achieved
REVISE: At least one target falls below 100% but achieves at least 80%
STOP: At least one target falls below 80%

7.1 Aims of the study

The overall aim of the trial is to test the clinical effectiveness and cost effectiveness of statutory health visiting (HV) services supplemented by SC-based service compared to statutory health visiting (HV) services alone. Objectives;

- To assess ability to recruit HV teams, train HVs in the delivery of the SC intervention, and recruit parents of excessively crying infants in a 9-month internal pilot study.
- To measure the effect of the SC intervention compared to usual care in participating parents as measured with the EPDS at 8 weeks follow-up.
- To measure the effect of the SC intervention compared to usual care in participating parents in terms of secondary outcome measures.
- To evaluate the cost-effectiveness of the SC intervention compared with standard care alone.

Embedded Studies
Process evaluations within randomised controlled trials enable questions about what works, for whom and under what circumstances to be answered, so as to inform impact and implementation. Recent assessment has pointed to the value of qualitative methods in this regard.[48;49] Accordingly, we will embed two studies using qualitative and quantitative methods within the main trial. Both studies will enable the views of parents to be assessed and contribute positively to the PPI aims of the trial.

7.2 Outcome measures

7.2.1 Primary clinical outcome

Edinburgh Postnatal Depression Scale (EPDS) score is a measurement of parental depression measured at 8 weeks post baseline measures.

7.2.2 Secondary outcome measures

- Edinburgh Postnatal Depression Scale (EPDS) score 16 weeks post baseline; proportion of parents/carers with EPDS score of 10 or more
- Generalised Anxiety Disorder Assessment GAD-7 Scale self-rated measure of anxiety measured at 8 and 16 weeks post baseline.
- EuroQol-5D-5L, self-rated health utility and quality of life measured at 8 and 16 weeks post baseline.
- Parental Confidence Scale (MCQ) measures the confidence of a parent/carer in their parenting role at 8 and 16 weeks post baseline.
- Crying Knowledge Scale measures knowledge of infant crying, amount of perceived infant crying, and parents/carers' ratings of how frustrating and problematic the crying is for them, at 8 week post baseline follow-ups.
- Partner Relationship Quality (CSI-4) measures the relationship satisfaction at 8 and 16 weeks post baseline.
- Health, breast–feeding maintenance will measure parental and infant health, breast-feeding persistence at 8 weeks and 16 weeks post baseline.
- Health economic measures will be assessed at 8 weeks and 16 weeks post baseline.
- Contacts with the NHS; parents' use and parents' and HVs' ratings of services to be collected and measured.

7.3 Outcome Measure Table

Outcome measures	**Baseline Measures. (Consent to study)**	8 Week (From Baseline Assessment) **Follow up Measures**	**16 Week** (From Baseline Assessment) **Follow Up Measure**
Visit Window	(Within 3 working days of identification of parent/carer)	(+/- 1 week within follow up due date)	(+/- 1 week within follow up due date)
EPDS	✓	✓	✓
GAD7	✓	✓	✓
EQ-5D-5L	✓	✓	✓
Parenting Confidence Questionnaire	✓	✓	✓

(Maternal Confidence Questionnaire)*			
Couple Satisfaction Index (CSI-4)	✓	✓	✓
Health Economics	✓	✓	✓
Crying Knowledge Scale **	✓	✓	
Parental Sleep Adequacy***	✓	✓	✓
Social Support ****	✓	✓	✓
Health, breast-feeding maintenance	✓	✓	✓
Parent/HV Evaluation of Services received.		✓	

*. (Originally Maternal Confidence Q. replacing 'mothers' with 'parents').

*** 8 items from Barr RG, Barr M, Fujiwara T, et al. CMAJ 2009;180. DOI:10.1503/cmaj.081419.
*** 2 items from Pittsburgh Sleep Quality Index, following Hiscock et al. 2014
**** 2 items from Hiscock et al. 2014

8 ELIGIBILITY CRITERIA

8.1Cluster Identification criteria

Clusters are defined as a 'team' of health visitors who work closely together to cover families in a given geographical area within an NHS or Local Authority Health Visitor services site. All HV teams that offer services to parents that have new babies are eligible to take part in the trial. Commissioners and providers of HV services for a given geographical area will be approached to take part in the trial through Clinical Research Networks, Social Services, Institute of Health Visiting networks and 'snowballing techniques'. Once a site has agreed to take part in the trial it will be asked to identify the HV teams that could potentially take part. Consent to randomise each HV team within a site is assumed to have been given once a site agrees to take part in the trial.

8.2 Participant Inclusion criteria

- Parents/Carers aged 18 years or older with an infant up to 20 weeks old (at time of consent), who express concern about their infant's excessive crying.

- Written informed consent

8.3 Participant Exclusion criteria

- Any seriously ill infant (at time of consent), requiring inpatient hospitalisation.
- Involved with any other clinical trial at the time of consent or 3 months prior.

The hospital admission would only apply at time of consent and we would not withdraw any participants where their infant was subsequently admitted to hospital after consent into the study. This information is collected at baseline and in the follow up data so can be recorded as secondary information.

9 TRIAL PROCEDURES

9.1 Cluster Identification

The sites participating in the trial have been chosen to represent diverse urban and rural settings and socio-economic and cultural groups. HV teams within sites vary in size and the communities they serve. Therefore, with their clinical leaders, we will identify the team(s) that will form a cluster within the trial, comprising of HVs working closely together. Consent to randomise a cluster will be sought. These HV team clusters will be randomised between control (usual HV services) and intervention (usual plus SC services) groups.

Randomisation of a HV team cluster will occur when the first participant is consented from that team cluster. Within each site area, we will ensure that socioeconomically diverse and minority, as well as majority, communities, are represented. As well as using the NIHR BAME Toolkit [33] to involve and recruit minority groups in culturally appropriate ways, we will include a sub-study directly aiming to improve these groups' involvement in the trial. We will also work with our PPI Co-applicant and collaborators to refine our recruitment methods and ensure that they recognise community as well as scientific priorities.

The target recruitment rate (estimated from the feasibility study data) will be on average 0.4 participants per month per cluster, across all clusters. Feasibility data indicated the incidence of excessive crying babies is around 20%; of those asked to participate the consent rate was around 60%. Each site will have varying birth rates, however, and the recruitment rate will be partly determined by the blinded researcher team capacity to contact, consent and assess potential participants in each of the sites and HV team clusters.

9.2 Identification and Recruitment

<u>Participant Identification</u>

Parent/Carers will be introduced to the trial with a leaflet that will either be sent to all Parent/Carers with their new birth letter (wherever possible) and /or provided at the first (HV) visit.

If a parent/carer raises a concern of an excessive crying infant with their Regular HV, that HV will seek verbal consent from the parent/carer for their details to be passed onto a member of the research team. Regular HV will notify the trial site specific researcher by site secure email the details of the parent/carer to be contacted.
GP's located within the recruiting site will also be able to refer parents/carers who raise a concern of an excessive crying infant at their GP review/appointment to a member of the study research staff. They will need to obtain verbal consent from the parent/carer, to provide their contact details to the research team. The GP will be asked to complete a GP referral form which will confirm the Health Visitng team that parent/carer is registered with, this will also provide confirmation that verbal consent has been obtained from the parent/carer. This referral form will be sent by secure email to the local Surviving Crying research team.
Parents/carers can also contact their local site research team directly, to find out more about the study. Researchers will ask parents/carers which Health Visiting Team (Cluster) they are assigned. For any potential participant' that the researcher is not informed of the Health Visitng Team (Cluster), they will check on their local system for this information only.
All participants taking part in the study will continue to receive Usual Health Visiting services as normal.
The study will be promoted with Study Promotional Posters, these will be displayed in several different settings such as GP surgeries in community settings where parent/carers might attend, which will also include maternity, ante-natal units and charities. Additionally promotional material will be used for social media for Charities and websites such as 'mumsnet' and 'crysis'.

Participant Information Sheet

A written/electronic version of the PIS will be emailed/given to the participants by the research team, detailing no less than: the exact nature of the trial; the implications and constraints of the protocol and any risks involved with taking part. At this time a screening number will be allocated to the parent/carer (by the research team) which should be used until they have been randomised into the study and a trial ID allocated. Due to time constraints parent/carer will be contacted by telephone/text or email for any subsequent appointments should they wish to participate in the trial.
It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to current or future care, and with no obligation to give the reason for withdrawal. A potential participant may wish to consider the information, and take the time and opportunity to ask questions of the Investigator, their GP or other independent parties to help inform their decision of whether they would like to participate in the trial. The parent/carer will be given time (at least 24 hours to consider the information before being asked to provide consent); where a parent/carer doesn't require any additional time consent can be obtained without delay.

Informed Consent will be obtained before any trial procedures are performed, by the trial site specific researcher at a face to face meeting at the participant's home where possible. Where this isn't possible it will be obtained by remote means on a video call facilitatedby a consent

form posted to parent/carer prior to appointment. . The research team member will check the parent/carers eligibility to participate, provide a detailed unbiased explanation as to what the trial involves (including benefits, risks and details contained in the PIS) and answer any questions they may have.

Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who explained the trial and obtained the Informed Consent. If this process is completed remotely by video call, a consent form will be posted to the parent/carer with the PIS. The researcher taking the consent will request the parent /carer signs the form, which will be witnessed by the researcher. The researcher will also sign a consent form to confirm they have witnessed this. The researcher will then request that participant shows a copy of the completed consent form and a recording/copy will be taken of the document only. A pre-paid envelope will be provided for the participant to return the original signed consent form to the researcher.

The person who obtained the consent will be authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the trial. For remote informed consent procedure recording /copy of forms will be retained with along with the original signed form which will be retained at each site within the Investigator Site File (ISF). A copy of the signed ICF will be given to participants and a copy sent to their GP informing them of parents/carers participation in the study.

Baseline Assessment will take place at the same time immediately following consent. Data relating to each participant including administration of the questionnaires with the parent/carer will take place. Once the baseline Case Report Forms (CRFs) and questionnaires have been completed the researcher will notify the Leicester Clinical Trials Unit (LCTU) of the new participant. This will be conducted within 3 working days from the researcher receipt of confirmation of verbal consent from the Regular HV of the identification of a parent/carer. At this point a unique personal trial identification number will be assigned.

9.3 Randomisation

Randomisation will be managed and carried out by LCTU. To ensure HV team clusters are evenly distributed, they will be randomly allocated either to the control or intervention group on a 1:1 basis, stratified by site.

Allocation of each HV Team cluster will be carried out when the first parent/carer's informed consent is obtained in each HV team.

The regular HV will be not be notified which group their HV team has been allocated at any point during the trial.

The researcher who has performed the consent with the parent/carer and subsequently completes all assessments, will also be blinded to the allocation of each cluster and will not know which allocation an individual participant belongs to.

Any unintended unblinding by the researcher will be recorded and another assessor will complete all further assessments for that participant. At each assessment, the outcomes assessor will be asked to guess the treatment allocation of the participant.

There will be a Research Administrator team member who will remain unblinded to the allocation and will be informed by LCTU of which of the two trial arms each HV team cluster has been allocated to and which HV team cluster subsequent participants belong to. This Research Administrator team member will be responsible for informing all participants after they have attended their baseline assessment, of their arm allocation within the trial. They will also be informed that they should not disclose the results of this allocation to the researcher who is performing the follow-up visits or their regular HV. SC trained HV will be informed if a new participant is enrolled into an intervention cluster and has requested CBT to enable delivery of the intervention. The SC Trained HV whilst not openly unblinded to cluster allocations, will be aware of those participants that require them to conduct intervention delivery.

9.4 Trial Allocation

Participants will be notified of which arm they have been allocated to Intervention or Control, by the Research Administrator team member. This will be performed within 1 working day of notification of the allocation of randomisation, with a telephone call, followed up by an email. At this point the participant will be reminded that that they should not disclose what arm of the trial, they have been allocated to, to any other member of the research or HV team.

Intervention Arm (SC Package) consists of three elements:

1. SC Booklet
2. SC Website
3. Cognitive Behaviour Therapy (CBT) Session's

Participants will be given the choice as to which of the three possible intervention packages they can access; the SC website, a copy of the SC booklet and CBT sessions. They can chose all of these elements or a combination of any of the three. The research administrator will provide the participant with individualised access to SC website, post or email the SC booklet if requested and notify the SC Trained HV if the participants requests CBT sessions.
The SC Trained HV will organise the CBT sessions with the participants where requested. Participants will also have access to usual NHS HV services delivered by their regular HV.
Where randomised to the intervention arm, participants should receive delivery of the first session within 3 working days of the date the SC Trained HV was notified of their request. Continuity between members of the research team and intervention delivery and responding quickly once a participant is enrolled should be ensured. Participants will be contacted by telephone text or email. This is to help retention in the trial and ensure support is received quickly by the participant who has requested this.

Participants will normally be offered between 1 and 4 sessions of one to one support from a SC Trained Health Visitor which would normally be delivered at home but could be delivered remotely if circumstances (such as Covid-19) demand this. Additional sessions up to a maximum of 6 can be provided where the SC CBT trained HV considers these to be needed. All sessions will be delivered on a weekly basis but must not exceed 6 weeks from date of the first CBT session.

Participants sessions will be recorded (if selected) to allow SC Trained Health Visitors to be monitored and assessed to certify their competence in level 2 CBT skills.
SC Trained HV will audio record the sessions with parents, using an access restricted trial mobile phone/laptop, no identifiable information will be recorded.

All SC trained HV's will upload the recording using trial ID numbers only, to the NIHR Hub secure site where restricted access will only be provided to the SC CBT practitioner trainer. Once accreditation has been received no further recordings will be required and all recordings will be destroyed. We will ask participants and SC Trained HVs to consent to the recordings of these sessions.

Participants will also have access to usual NHS HV services delivered by their regular HV throughout the duration of the study.

Website use will be measured by the objective metrics provided by Google Analytics.

SC Trained HV's will record on a paper CRF the type and amount of intervention each participant in the intervention received. This data will be entered into the SC Database.
This will help to assess cost of their overall package to be compared to routine services.

Control Arm

Participants allocated to the control arm, will continue to receive usual NHS HV services. However they can request on completion of the trial (16 weeks post baseline assessment, the SC booklet and/or access to the SC website.
They will be provided with an individualised access code for the website (identifiable as control participant).

9.5 Follow up

Follow-up assessments will take place at 8 and 16 weeks after baseline assessment, (which should be completed -1/+1week of the due date). The researcher will telephone or text the participant with appointment times. The researcher will go through each of the questionnaires with the participant in order to complete them. This can be undertaken via the telephone/video call or at the participant's home. Parental/Carer Evaluation of how they found the care they received has the potential to unblind the researcher, therefore the researcher will give a questionnaire to the participant to capture their views of the package received, both groups will also be asked about sharing of the SC materials. This will be completed by the participant not in sight of the researcher (blinded to allocation) and returned in a sealed signed envelope to the research administrator (unblinded to allocation). If the follow up appointment is completed over the telephone /video call, this will be emailed to the participant from the research administrator (unblinded) and requested it is emailed directly back to a secure access restricted email address. Data relating to this will be entered by the research administrator into the SC database, managed by the Leicester Clinical Trials Unit.

To support parents/carers and HV involvement and minimise differential recruitment or follow-up, parents/carers in both groups will be advised at the point of consent by the research team, that their GP will be notified of their participation by letter. However, only when the participants has completed their 16 week follow-up assessment and their participation in the trial has concluded, will the GP be informed of which group the participant was allocated to, intervention or control group. Any parents/carers still concerned about their infant's excessive crying at follow-up or those who require further support will be advised to contact their Regular HV or contact their GP. The GP will also be informed of this.

Participants in the **control group** can request a copy of the SC booklet or access to the SC website intervention resources if required on completion of their involvement in the trial.

To recognize their contribution to the research, participants in both the intervention and control groups will be given a £30.00 shopping voucher at their 16 week follow-up and where indicated on the consent form a summary of the trial findings upon completion and publication of the trial.

Contamination between the groups is unlikely, given the precautions taken, as described previously. Accidental prior knowledge of a HV team's trial arm allocation may bias the recruitment selection process whilst participants who are allocated to control may lose interest and withdraw from the trial prematurely. At the 8 and 16 week follow up the researcher will be asked to guess the treatment allocation of the participant. Additionally, HV team's recruitment and retention rates will be monitored and compared across the trial duration.

9.6 Withdrawal of Consent

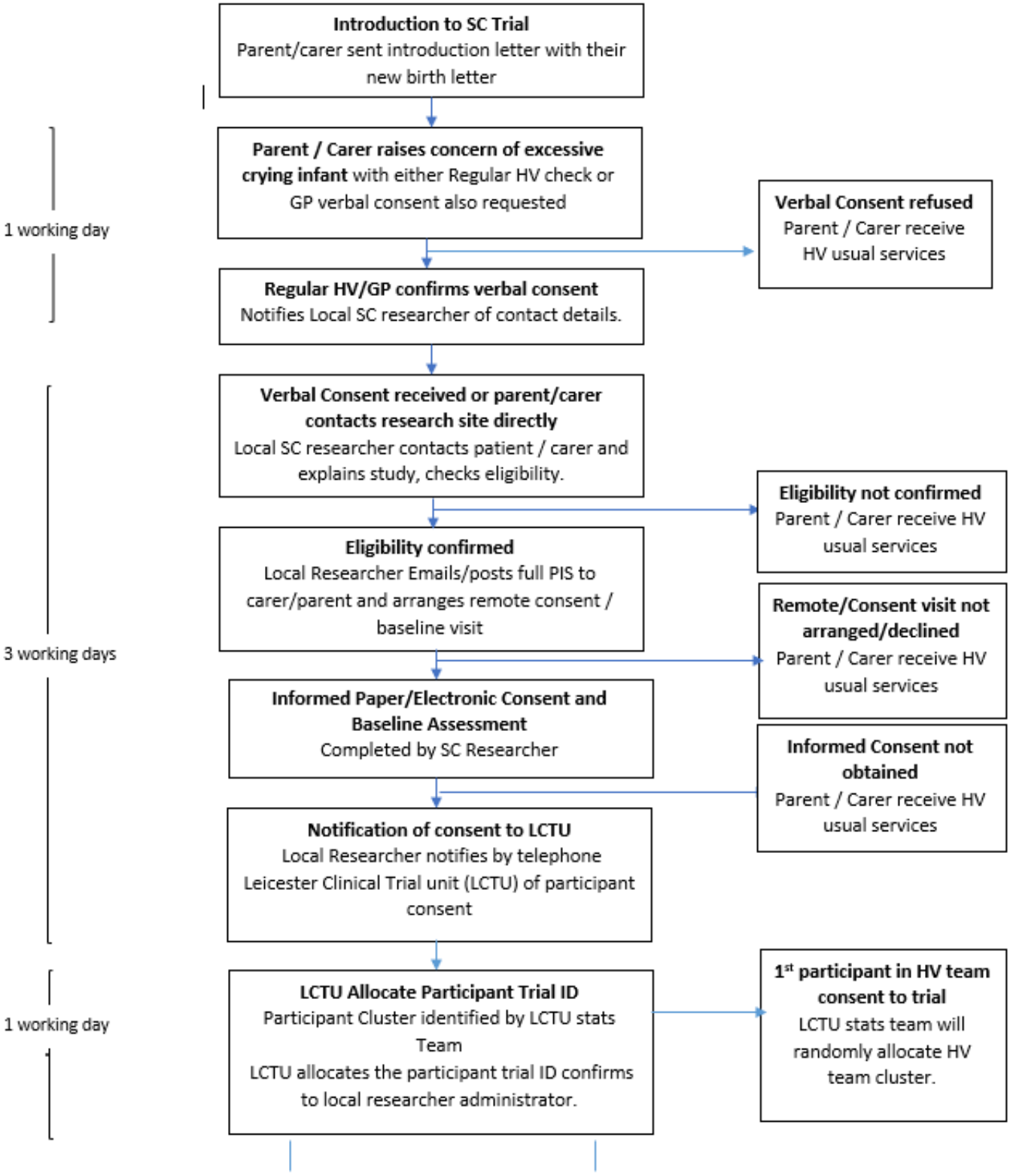
Participants may withdraw their consent to participate in the trial at any time without giving a reason and without compromising the services they would normally receive outside of the trial. Participants do not have to give a reason for withdrawal but if they provide a reason for leaving the trial, this will be documented in the e-CRF. Any data collected until this point will be retained, analysed and used in the final analysis under public task. In addition, the Principal investigator may discontinue a participant from the active trial intervention (CBT) at any time if deemed necessary. Compliance with trial intervention will be recorded. Participants not taking up or discontinuing with the trial intervention will be encouraged to attend follow up assessments. Failure to obtain follow- up data will be classed as lost to follow up.

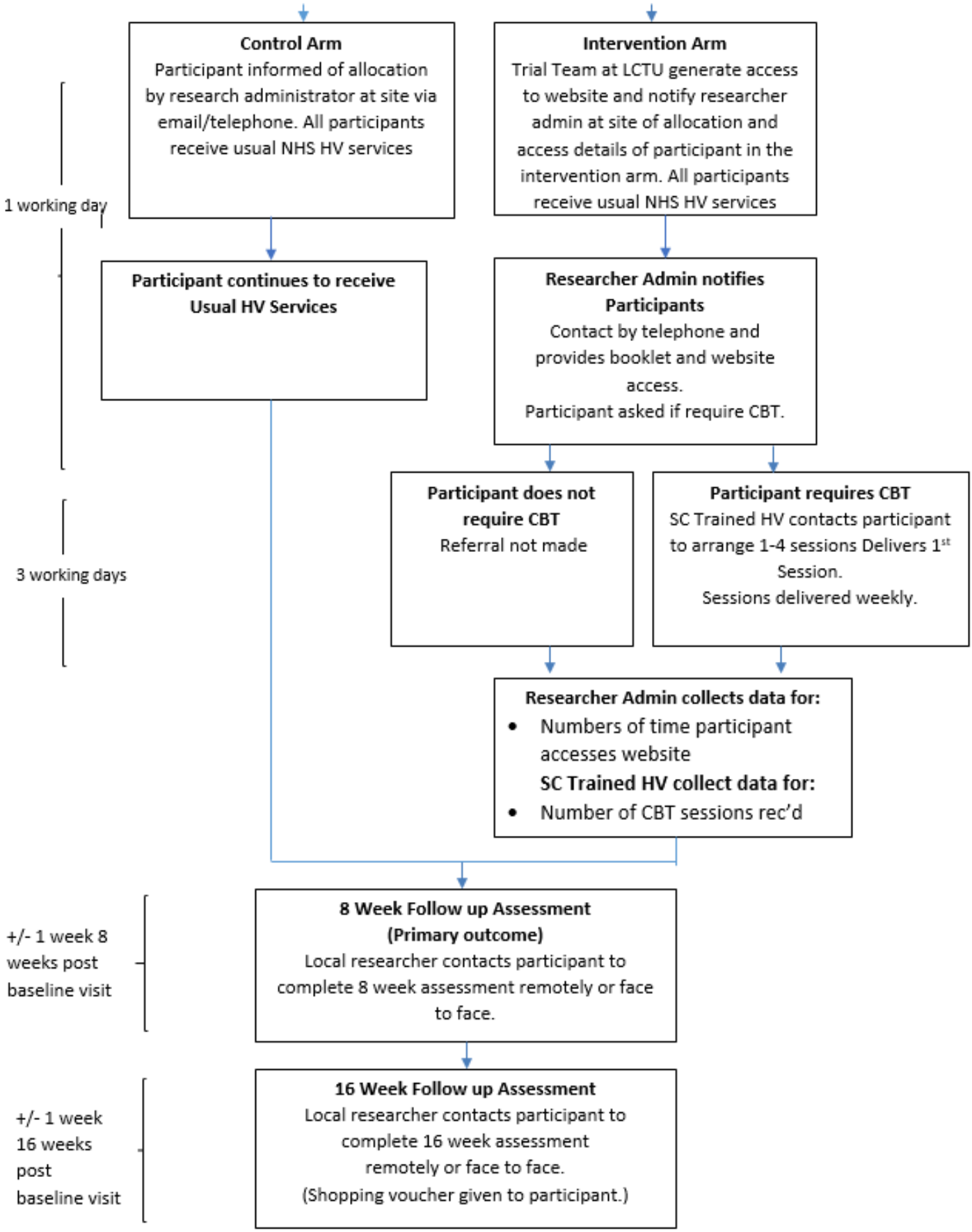
Projected dropout of participants is accounted for in the sample size calculation and therefore participants who withdraw consent and those lost to follow up will not be replaced.

9.7 End of Trial

The end of the trial will be defined as the collection of 16 week outcome data from the last participant recruited. This is also the last follow-up time point.

9.8 Trial Participant Flow Chart




Control Arm
Participant informed of allocation by research administrator at site via email/telephone. All participants receive usual NHS HV services
Intervention Arm
Trial Team at LCTU generate access to website and notify researcher admin at site of allocation and access details of participant in the intervention arm. All participants receive usual NHS HV services
1 working day
Participant continues to receive Usual HV Services
Researcher Admin notifies Participants
Contact by telephone and provides booklet and website access.
Participant asked if require CBT.
Participant does not require CBT
Referral not made
Participant requires CBT
SC Trained HV contacts participant to arrange 1-4 sessions Delivers 1st Session.
Sessions delivered weekly.
3 working days
Researcher Admin collects data for:
• Numbers of time participant accesses website
SC Trained HV collect data for:
• Number of CBT sessions rec'd
+/- 1 week 8 weeks post baseline visit
8 Week Follow up Assessment (Primary outcome)
Local researcher contacts participant to complete 8 week assessment remotely or face to face.
+/- 1 week 16 weeks post baseline visit
16 Week Follow up Assessment
Local researcher contacts participant to complete 16 week assessment remotely or face to face.
(Shopping voucher given to participant.)

10 EMBEDDED STUDIES

10.1 Embedded study 1: Enhancing SC and Usual Service Uptake in Ethnic minority Communities.

Parents from socio-economically deprived and ethnic minority communities could be under represented in studies such as this one. Here, the focus is on the embedded study we have designed to explore uptake further. To explore this issue, we approached the Centre for Ethnic Health research (CEHR) and a member (AW) has become a Co-applicant in designing and delivering the proposed trial and will be completing the work for this embedded study. A second Co-applicant (TB) has demonstrated expertise in reaching British South Asian mothers in one almost completed large scale trial [50] and socio-economically deprived communities in previous trials. [26; 44]South Asian parent/carers are among the largest minority groups in the UK. The decision to focus on accessibility for this group for this embedded study is informed by our feasibility study finding that these parent/carers' cultural barriers often impeded their access to earlier SC research and routine NHS postnatal services. Furthermore, the CEHR has established links with maternity support groups within South Asian and African Caribbean communities in the East Midlands, including the Sharma Women's Centre, Mammas Leicester and the Bangladeshi Youth and Cultural Shomiti. The trial team will also have access to the Centre's Community Partners Panel who will provide feedback on trial design and the refinement of trial documentation and resources. The panel is made up of community members from diverse backgrounds across the East Midlands who have received training in research methods including patient involvement. Participating sites with a high population of ethnic communities will be contacted to establish connections in these areas as well.

In this embedded study, we propose to conduct a Community-Based Awareness Campaign in addition to developing more accessible recruitment and trial documents to increase awareness and involvement in the trial among ethnic minority communities. The resources and any associated translated versions will be developed following input from parents and HVs in the area of interest. Working with HVs, members of the CEHR Community Partners Panel and our PPI collaborators, we will also produce a cultural competency toolkit for use in this Awareness Campaign. This toolkit will be promoted through existing HV and community networks and local media and social media. The CEHR have experience of developing HCP toolkits successfully to support trial implementation and cultural competency. [51]

Although it would be preferable to carry out these activities to address barriers in a wider range of minority communities, cost and other considerations suggest a more limited study should be used to develop and evaluate a model which could be further adapted to suit the needs of other underserved communities in the UK, which will be identified through analysis of recruitment data for the main trial.

It is important to note that the methods of recruitment and assessment involved in the trial will not be changed for this embedded study. Instead, the aim is to explore the factors involved in optimal service delivery, involvement in the trial and uptake of the SC-based and usual services, in these minority communities. The findings will indicate whether strategies which facilitate minority community involvement are associated with increases in rates of postnatal service uptake and in use and approval of the SC-based service.

10.2 Embedded Study 2: Process evaluation of participants' understanding of excessive infant crying and the SC-based service.

To understand the experience and usefulness of the SC programme from the perspective of both parent/carers and HV's a process evaluation will be undertaken. This will be informed by realist evaluation principles [52;53] and built upon the premise that context may mediate the implementation of the SC-based service. The rationale is to give parents/carers and HVs a voice in the health technology of which they will be the recipient and or provider.

Aims

- to examine the views of parents/carers and HVs on SC, distinguish between the components of the intervention and explore how effects vary in subgroups, such as parents/carers with lower socio-economic resources

- to provide data that will assist in interpreting the trial outcomes and contribute to knowledge of HV practice by providing insight into:

    - the training of HVs in CBT approaches;
    - the implementation of the SC-based service;
    - contextual factors which help or hinder the implementation of the SC based service;
    - potential for organisational integration and
    - detail about individual (parent/carer, HV) experience of the process to illustrate what works well, for whom, and in what circumstances.

This will provide evidence to support the implementation and adoption of the SC-based service.

Informed by implementation research [53] this work will assume an ethnographic approach combining observation, documentary analysis and interview/focus groups with a range of stakeholders. We will use the most appropriate methods as guided by the participants and these may include one to one interviews, using phone or online meetings and or focus groups.

Sample:

We will collect data from between 4 and 6 trial sites. At each of these we will recruit:

- 5-8 parents for interview [data collection only to begin once the 16 week follow up data has been collected],
- At least 3 SC trained HVs [to be interviewed once they have completed their work with parents]
- A selection of health visitors, from the site who have referred participants to the trial to take part in a focus group
- At least 3 senior HV managers and/ or service commissioners for individual interview

Data Collection:

Monitoring Training in the CBT-based Programme: The training of specialist HVs in delivery of the CBT element of the SC service will be observed to explore how training and assessment

are undertaken, and to understand application of the principles of CBT in relation to infant crying. This observation illuminates the cascade of SC from a CBT qualified psychologist to the specialist HVs responsible for delivery of CBT in the trial.

Implementation of the SC-based Service Elements: HV's trained in CBT based methods will be sought to consent to an interview, to discuss the training, their experience of undertaking CBT with parents/carers, their perceptions of its usefulness and acceptability, facilitators and barriers to its use. Parents/carers will be invited to take part in the qualitative arm of the study at the same time as they consent to participate in the main trial. If a participant provides consent interviews will explore their experience of having an infant who cries excessively, information and help seeking behaviours, and in the intervention arm; their use and experience of the SC service elements.

SC Service Implementation**:** upon trial completion, staff focus groups will be undertaken in a selection of health visitor clusters taking part in the intervention arm to capture perspectives on the implementation of the SC-based service, local contextual factors that may influence the uptake, use and acceptability of the service.

Data Analysis: all data will be analysed using framework analysis.[54] Framework Analysis Centre for Black and Minority Ethnicity Health is a matrix based method developed for applied qualitative research and is well suited to research where timescales are limited and goals are clearly defined. Normalisation Process Theory (NPT) [55] (used successfully in a previous evaluation of an intervention in a Randomised Controlled Trial [54]) will be used as a sensitising theoretical framework. NPT identifies four mechanisms which indicate how interventions are embedded and 'normalized' within routine care: Coherence (how the SC is understood, rendered meaningful and invested in, in respect of knowledge, skills and behaviours of parent/carers and of HVs); Cognitive Participation (explores commitment and engagement of participants with the SC service); Collective Action (how far existing work practices have to be changed to implement the SC service); Goals: is the service consistent with existing norms and goals of HVs and the organisation?

Outputs: Findings will be presented in the Final Report, papers and briefings. An enhanced logic model will be developed to highlight ways of enhancing roll-out and integration of SC-based services into regular practice. A care pathway for parent/carers of excessively crying babies will be produced and the CBT-based training package will be enriched in light of HV feedback.

11 COMPLIANCE WITH TRIAL PROTOCOL

The trial team will monitor and review protocol compliance and deviations from the protocol will be captured both within the source data and the LCTU Quality Management System. A protocol deviation is defined as any departure from the protocol's procedures. Where deviations frequently reoccur this may meet the criteria for a Serious Breach of GCP and will be reported in line with Sponsor SOPs. A protocol deviation/change may be implemented in response to an immediate hazard to a trial participant without prior approval from the Sponsor/Research & Innovation/HRA. This is defined as an Urgent Safety Measure under UK Regulation 30.

For the purposes of this regulation, a 'serious breach' is a breach which is likely to affect to a significant degree:

- The safety, physical or mental integrity of the subjects of the study; or
- The scientific value of the trial

In each case, any serious breaches or Urgent Safety Measures must be reported to the Sponsor by the Chief Investigator (CI) or any member of the research team (delegated to perform this task) within 24 hours of them becoming aware of the breach. Protocol deviations not resulting in Urgent Safety Measures do not need to be immediately reported to the Sponsor but must be documented in the CRF, Trial Master File (TMF) and ISF using a signed and dated file note. All protocol deviations must also be logged on a tracking log which must be retained in the ISF at site and the TMF at the coordinating centre (LCTU).

11.1 Loss to follow-up

Participants are followed up for a short period of time – 8 and 16 weeks, therefore, as found in the feasibility study we expect loss to follow up to be minimal.

12 RISK MITIGATION DURING THE COVID-19 PANDEMIC OR ANY OTHER EPIDEMIC OR PANDEMIC AFFECTING TRIAL CONDUCT

To mitigate against the risk of the trial being impacted by any future pandemics the following steps will be followed:

All Research assessments will have the ability to be conducted remotely by telephone or video call. This will help to reduce face to face contact with participants. Method of delivery will be recorded in data collection.

Trial intervention with exception of CBT can be accessed remotely with a booklet and access to a website.

All HVs will follow their normal trust procedure for COVID 19 effective at that time. If a participant tests positive and needs to isolate under government guidelines, CBT will not take place face to face. However, participants will be offered CBT sessions delivered by video call, where possible, until such time as deemed fit by those guidelines. At this time sessions can resume face to face.

13 ADVERSE EVENT MONITORING

SC is not a clinical trial of an investigational medicinal product, therefore the usual monitoring of pharmacovigilance and associated terminology is not relevant.

Any Serious adverse events (any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect), must be collected by the research team and reported to the sponsor within 24 hours of the research team being made aware of the event.
Throughout the study, participants will be asked about their infant's health at each follow up visit and be asked to report any change in health. Local safe-guarding procedures will be followed by the researcher if deemed appropriate by the Principal Investigator.

On identification of a potential serious adverse event (SAE), the relevant local Principal Investigator will be informed and will review the SAE to determine the likelihood that this is related to the study intervention or to the infant's excessive crying. It will then be reported through the study reporting system.

Family Vulnerability and Safeguarding:
It is recognised that some families may be more vulnerable than others. However, it is important to note that all families in the trial will receive care as usual and will be able to seek advice and support from health visitors and other services at any time, without this affecting their participation in the trial. Those in the intervention group will receive the SC package in addition to usual services.

HVs and other primary healthcare professionals working in the community encounter these vulnerable families with complex issues on a daily basis and established safeguarding and referral procedures are in place to guide them [46;47]. In addition, HVs in each area are likely to know the community support organisations available in that area and have access to guidelines which adapt their working methods to local needs.

During the feasibility study for this trial, the study paediatrician (EB), worked with healthcare professionals and the local NHS Trust Safeguarding Officer to adapt the existing professional guidelines into a safeguarding protocol which ensured the safety of infants and parent/carers involved in the study. As well as setting clear boundaries between researcher and professional responsibilities, the protocol included stepped progression criteria to ensure safety and guide access to other services and supports where needed. EB remains involved as a Co-applicant in this trial. Working with our HV Co-applicant, community and PPI representatives, the protocol has been revised to meet both current professional and ethical guidelines and the needs of the families involved in all the trial sites.

14 STATISTICAL ASPECTS

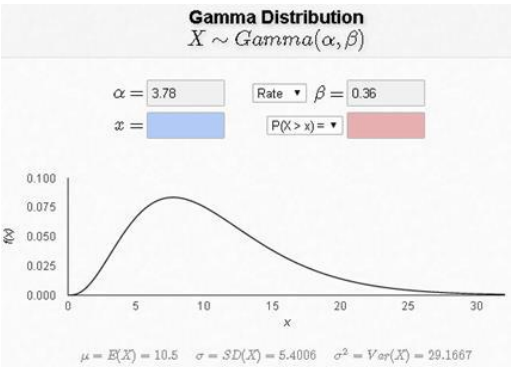
14.1 Power calculations Sample size

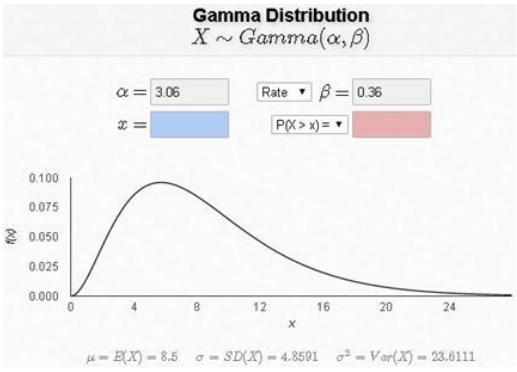
The primary analysis aims to show whether the SC package leads to a clinically important reduction in EPDS scores (0-30 range) as determined by the difference in the mean EPDS score between the control and intervention groups at 8 weeks follow-up. Individual patient data was obtained from the PoNDER trial, an NIHR HTA supported cluster RCT [26], which showed that control and intervention group participants with EPDS of ≥12 at baseline had mean (SD) EPDS of 11.3 (5.8) and 9.2 (5.4) respectively at 6 months follow-up (mean difference=2.1). However, an EPDS score of ≥10 is considered a sensitive cut-off for screening for poor mental health [35, 36] and more appropriate for our proposed trial population. Therefore, a cut-off of ≥10 was derived for EPDS at baseline in the PoNDER data and we found that the control and intervention group participants with EPDS of ≥10 at baseline had mean (SD) EPDS of 10.3 (5.4) and 8.5 (5.1) respectively at 6 months (mean difference=1.8). A reduction of 2 points in the EPDS score is considered clinically important, therefore, this trial is powered to detect a difference of 2 points in EPDS in intervention group participants.

Inspection of the PoNDER data showed that EPDS was a right positively skewed outcome variable characteristic of a Gamma distribution. Therefore, given that sample size calculations should correspond to the intended method of analysis, and as our case involves a comparison of two means, we used generalised linear models (GLM) theory and assumed a Gamma distribution to derive the sample size required [37]. Data from control participants in the PoNDER data informed the choice of parametrisation for a Gamma distribution (k=3.78; θ=2.8 or β=1/θ=0.36).[38]

The sample size has been derived to detect a 2-point difference in the mean EPDS score (10.5 for the control group and 8.5 for the intervention group). With a 5% level of significance (two-sided), 90% power and assuming a Gamma family distribution with a log link function and scale parameters (k) 3.78 and 3.06 for the control and intervention groups respectively (1:1 allocation), equation 14 in 37 estimates that a total of 280 participants are required for an individually randomised trial.

Illustrations below: a 2-point reduction from 10.5 to 8.5 shifts the distribution to the left.





Calculating the sample size required for a cluster randomised trial involves inflating the estimated sample size of 280 assuming individual randomisation by a design effect. [39]

Assuming an average cluster size of 4 with data available for the primary analysis, with a range of 2 to 12 giving coefficient of variation equal to 0.625 and ICC of 0.037 (observed in 40 results in a design effect of 1.17 (using equation 18 in [39]). Inflating 280 by 1.17 gives a target sample size of 328 (164 per arm). Furthermore, a sample size of 328 and 4 participants per cluster would require a total of 82 clusters to be randomised (41 per arm). Standard convention means we add 1 cluster per arm to allow for the use of the t distribution. [41] and 1 extra cluster per arm is also added to account for potential whole cluster drop out. [42] The sample size is further inflated by 12% to allow for individual loss of data and non-compliance with the primary outcome (data loss occurred in 9% of participants in our feasibility study [24], but we chose a more conservative rate). Therefore, each cluster should recruit 4.55 participants on average to allow for drop out (our projections show clusters could recruit an average of 4.8 so this is feasible). This gives a total target sample size of 86 clusters (43 per arm) and 392 participants (196 per arm). The effect on the sample size of assuming alternative model parameters, MCIDs, ICC values (0.01 and 0.05) and wider cluster size ranges was evaluated. These sensitivity analyses showed that the trial is robust to differences in these parameters.

14.2 Minimal Important Clinical Difference

We have included the difference in numbers of intervention and control group parent/carers who meet a clinical criterion for depression as a secondary outcome measure. However, the trial's primary aim, described above, is to shift the EPDS scores of all parent/carers with excessively crying infants, so that intervention group parent/carers as whole score 2 points lower on this measure than control parent/carers. As pointed out in a widely cited analysis. [43-45] far more members of a general population benefit from this approach than when an intervention is delivered only to the small numbers who meet an arbitrary criterion for poor mental health. In particular, this approach is likely to have the maximum benefit for parent/carers as a whole with an excessively crying infant, most of whom are not psychiatrically disturbed so much as distressed by their infant's uncontrollable crying.

14.3 Statistical analysis plan

Statistical analyses will be undertaken according to a pre-trial Statistical Analysis Plan (SAP) written prior to database lock. Descriptive characteristics at baseline will be presented by treatment arm.

The LCTU Trial Statistician will be responsible for planning, monitoring and carrying out data analyses throughout the study, supervised by the LCTU Principal Statistician. The trial will be analysed and reported following the CONSORT statement for cluster RCTs.[30]

The primary analysis will be performed using generalised estimating equations (GEE), which require a minimum of 40 clusters in order to produce reliable estimates.[56, 57] An Analysis of Covariance (ANCOVA) approach will be used with each participant's continuous EPDS score at 8 weeks follow-up as the outcome variable, adjusting for their EPDS at baseline and for the baseline cluster mean, with GEE to allow for differences between clusters.[57] The model will also include a categorical variable for randomisation group and terms for the stratification

factors. The GEE model specification will include a log link function and a Gamma family distribution assumed for the outcome.

The primary analysis will analyse complete cases (i.e. missing data will not be replaced) and participants will be included in the group to which they were randomised irrespective of the intervention received. Secondary analyses will repeat the analysis on both an intention-to treat and per-protocol basis. Missing data will be imputed using multilevel multiple imputation methods in order to account for the clustered nature of the data. [58] Exploratory analyses of the primary outcome will investigate the effect of differing levels of compliance over and above the minimum level. Secondary outcomes will be analysed using a complete case population, in a similar manner to the primary outcome, modelled assuming an appropriate distribution family and link function. A sensitivity analysis of the primary outcome will adjust for ethnicity and social deprivation index at the individual level. Subgroup analyses of the primary outcome will be performed on the following factors: clusters participating in ICON, SC HV practitioner trained in CBT, social deprivation index and ethnicity.

14.4 Health economic analysis

Approach: An economic analysis is warranted given the potential cost and outcome differences between the SC package and usual HV services. Our analysis will conform to accepted economic evaluation methods. [59] We will estimate costs and health outcomes to determine the cost-effectiveness of the SC package during 'within-trial' period only, since there is evidence that most infants in the trial will go on to have normal health. Costs will be assessed from the perspective of the NHS and personal social services (PSS), and also from a wider societal perspective, which includes productivity loss and out of pocket costs incurred by the parents. The economic analysis outcome measures will be: (1) quality-adjusted life years (QALYs) accrued by parent/carers (QALYs are the recommended outcomes for economic evaluations in the UK [59] and were used in the economic evaluation accompanying the PoNDER HV trial); (2) parental depression measured using the EPDS at 8 weeks (primary outcome of the trial); (3) interruption-free nights based on parental sleep amount and quality (which has been used in previous economic evaluations of interventions to address infant crying problems. [18] Measuring intervention costs: We will collect detailed information on the cost of CBT training and of each of the three components of the Surviving Crying package identified during the feasibility study: (1) the costs of maintaining the website and registering new users to it (we will not include the one-off costs of setting the website up as these are sunk costs); (2) the costs of printing the booklet; and, (3) the cost of delivering the CBT programme, including therapist time (for face-to-face CBT sessions, telephone contacts with participating families, text, email or internet contacts with participating families, preparation for the CBT sessions, general administration, and travel to the participants' homes), other costs to travel to participants' homes, and the costs of the CBT manual and booklet. The costs of maintaining the website and registering new users and printing booklets will be based on market prices. The costs of activities related to therapist time will be based on published estimates of the cost per minute of senior health visitor time[60] combined with duration data for each activity collected by trial researchers.

Measuring other NHS, PSS and broader societal costs: The costs we include have been informed by our feasibility study and the economic evaluation accompanying the PoNDER trial.[51] We will collect data on use of NHS services occurred during the 12 months before the birth of the child and after their birth due to excessive crying. The data on resource consumption due to excessive crying will be collected during the follow-up period using retrospective questionnaires that parent/carers will be asked to fill in at baseline (covering the period from birth), 8 weeks (covering the period since baseline) and 16 weeks (covering the period since 8 weeks). This will include contacts and remedies for excessive crying for either the infant or parents/carers. In the feasibility study, resource use data were collected for 52 participants (91%) at all follow-up points and there were non-zero contacts due to excessive crying for the following types of contact:

a) Health visitor (HV) home visit
b) HV clinic visit
c) HV contact by telephone
d) GP surgery visit
e) GP contact by telephone
f) Nurse home visit
g) Midwife home visit
h) A&E department
i) Outpatient visit
j) Walk-in-centre visit
k) Health centre visit

We will also ask participants to record whether or not the contact was for the infant or the parent/carer and how much contact time was devoted to excessive infant crying. As in the feasibility study we will ask about medications/remedies prescribed by the doctor for excessive crying, and over the counter. For each of these items we will include specific data fields in the resource use questionnaires asking about each of these including durations of treatment and dosages and whether or not the remedy was for the infant or the parent/carer. We will also include free text boxes where all other remedies for excessive crying (both prescribed and paid for by families) may be recorded. We will ask parents/carers to record other contacts by ticking an "Other contacts" box on the questionnaire and then recording in a free text box the nature of the contact (e.g., A&E visit, hospital admissions to mother and baby psychiatric units; other mental health contacts, including counsellor, community psychiatric nurse (CPN), community mental health team, mental health nurse, crisis services, psychologist, psychotherapist, psychiatric outpatient and mother and baby psychiatric outpatient contacts admission), plus any other details (e.g., number of contacts, length of stay).

In terms of PSS costs we will ask parents/carers to record contacts with social workers and children's and families' services, selecting the type of contact from a list, and recording details about the number of contacts. Other social care/local authority costs will be captured using free text boxes. In terms of broader societal costs, we will also ask parents/carers to record travel costs or distances for families going to and from NHS visits and additional days taken off work by parent/carers, both due to excessive infant crying. Unit costs will be obtained from

published sources and inflated where appropriate, before being applied to the volume of resource use data to calculate costs.

Assessing health economic outcomes: QALYs per parent/carer will be calculated based on the health related quality of life (HRQoL). HRQoL will be measured using the EQ-5D-5L[62] which we will collect at each time point. Our feasibility study showed it was feasible to measure HRQoL in parents using the EQ-5D-5L so we use this measure over the SF-6D (which was used in the economic evaluation accompanying the PoNDER trial): it was completed by 100% parents at baseline (57/57) and 89% at follow-up (51/57), with no errors or missing data in the completed returns. Parent-specific utility profiles will be constructed assuming a linear trend between each of the patient's EQ-5D-5L scores at each follow-up point, by measuring the area underneath this profile. Deriving QALYs for infants during the first weeks of life is problematic given their physical and cognitive ability at such a young age, their dependence on parents and other family members, and the lack of appropriate and relevant generic quality of life measures. [63] Therefore, cost-utility analyses will focus on measurement of utilities among parents only. We will calculate QALYs for the primary caregiver and for both parents where available and present results as mean QALYs per parent/carer in each trial group. Other outcomes to be included in the economic analysis (parental depression, interruption free nights) will be collected directly in the trial.

Analysis: Multiple imputation by chained equations will be used to deal with missing outcome and resource use values. The multiple imputation equation will include baseline variables showing a significant association with the trial outcomes alongside the pre-specified subgroups: clusters participating in ICON, SC HV practitioner trained in CBT, social deprivation index and ethnicity and their interaction terms.[64] Subsequent analyses of imputed data will use the Rubin's rule to account for additional variability introduced into parameter values as a result of the imputation process. [64] Cost-effectiveness will be calculated as the mean cost difference between groups divided by the mean difference in outcomes (QALYs, parental depression, interruption-free nights) to give the incremental cost-effectiveness ratio (ICER) and (in the case of QALYs) incremental net monetary benefits (incremental NMBs). We will subject the results to extensive deterministic (one-, two- and multi-way) and probabilistic sensitivity analysis. For the latter, non-parametric methods for calculating the uncertainty around the mean cost and outcome differences will be ascertained using a non-parametric bootstrap. [65] The bootstrap replications will be used to construct cost-effectiveness acceptability curves, which will show the probability that each strategy is cost-effective for different values of the NHS' and society's cost-effectiveness for an additional unit of outcome.[17] Likewise, the bootstrap replications will be used to calculate the 95% confidence interval around the mean NMBs and incremental NMB.

We will combine data on incremental costs with epidemiological data on projected numbers and undertake a budget impact analysis to evaluate what the total cost impact of rolling out the use of the SC package strategy would be were it to be scaled up. We will also use the probabilistic sensitivity analyses combined with the epidemiological information on projected numbers to undertake a value of information analysis[66] to evaluate the potential economic value of future research on this topic.

15 DATA MANAGEMENT

15.1 Data collection and source data identification

CRFs and participant reported outcome questionnaires will be the primary data collection instruments and treated as source data. All data requested in the CRFs should be recorded. All missing data will be followed up and resolved where possible. If the item is not applicable to the individual case, N/A will be written. All entries will be printed legibly in black ink, following ICH guidelines for Good Clinical Practice. All CRFs will be stored in a secure area with restricted access. Each enrolled participant will be allocated a unique Trial ID so that the CRFs and electronic database remains pseudonymised.

A copy of the participant consent form and information sheet will be placed in the health visitor notes and in the ISF.

Source Data is defined as the first place data is recorded, this will include:

- CRFs
- Participant completed questionnaires

15.2 Data entry

Data entry will be conducted by the trial delivery team at site. Data collected from the source data as detailed above will be entered onto a validated web-based Remote Data Capture (RDC) system provided and managed by the LCTU. Access to the electronic CRF will be granted to authorized trial personnel only via a secure password-protected web-interface. The investigator and designated personnel must ensure accuracy, completeness and timeliness of data reported in the e-CRF and all required reports. Data reported on the e-CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. No identifiable data will be stored.

On-entry validation checks will be applied where required, and data entered will be checked for completeness, accuracy and timeliness by the trial team/trial manager/data manager, with queries managed using the data clarification functionality within the clinical data management system (CDMS) system. A Data Management Plan will be created with specific details on data handing and record keeping.

If trial data is required to be transferred electronically between the LCTU and the CI for the purposes of data management, this will be done in a secure manner. Information capable of identifying individuals will be held in a separate database with passwords restricted to the trial staff. Identifiable information will not be removed from the clinical centres or made available in any form to those outside the centre or the study.

15.3 Data protection and participant confidentiality

Participants' personal data included in the study-related databases shall be treated in confidence and in compliance with ICH-GCP, the UK Policy Framework for Health and Social Care, the Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR).

When processing or archiving personal data, the Sponsor or its representative shall take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

Each participant will be assigned a unique identification number upon recruitment. The database will be password protected and only researchers collecting data will have access to this database. All personalised information for participants will be kept confidentially at the recruiting site unless there is specific consent and HRA approval for transfer of this to another site for study-related purposes.

Paper documentation will be stored in a locked filing cabinet in the relevant research office. Neither hard copies nor electronic files containing personal information will be removed from the research office or stored in a non-secure manner electronically. The trial research team will comply with the Data Protection Policy of the UoL and local NHS Trusts.

15.4 Data access and storage

All source data, trial documents and participant notes will be made available for monitoring, audits and inspections by the appropriate regulatory authorities, the Sponsor, NHS host organisations and LCTU.

All trial documentation will be retained in a secure location during the conduct of the study. Personal identifiable data will be retained for a maximum of 12 months following the end of the study, after which it will be destroyed, unless participants have expressed an interest in being invited to the results dissemination event and/or receiving a copy of the trial newsletter. In these circumstances, personal identifiable details such as names and contact details will be retained on a password protected database until required, and then destroyed.
All electronic data will be stored on secure network systems, to which only the relevant site and central trial research team staff have access. The secure networks are backed up daily by the University of Leicester IM&T.

For the purposes of this study, Nottingham Trent University, Leicester and University of Leicester will act as the joint Data Controller. University of Leicester will process data for analysis purposes.

15.5 Archiving

Personal identifiable data generated by the trial will be retained for the minimum time determined by the regulatory authorities following the notification of the end of the trial before being destroyed in a confidential manner.

Following completion of the trial data analysis, data and essential trial records, including the final trial report, will be archived in a secure location for at least 15 years after the completion of the study, in accordance with LCTU SOPs. The data will be archived at a Sponsor approved archiving facility which will ensure that it is stored securely and accessed only by authorised

individuals. No study-related records, including hospital medical notes, will be destroyed unless or until the Sponsor gives authorisation to do so.

16 TRIAL ORGANISATION, REGULATION AND OVERSIGHT

16.1 Ethical and regulatory considerations

Once Sponsor authorisation has been confirmed, the protocol, ICF, PIS and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA, and host institution(s) for written approval. The trial will commence once all relevant approvals are in place and Sponsor 'Green Light' has been issued. Once Sponsor authorisation has been confirmed, the CI (or CI delegated team) will submit and, where necessary, obtain approval from all relevant regulatory authorities for all substantial amendments to the original approved documents. The only exception to this is when the change is necessary to eliminate urgent safety measures to the participants or when the change involves only logistical or administrative aspects of the trial when not meeting the requirements of non-substantial amendment submissions.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. If the trial is ended prematurely, the CI will notify the REC, including the reasons for the premature termination. Otherwise, the CI (or delegate) will notify the REC of the end of the study. Within one year after the end of the study, the CI (or delegate) will submit a final report with the results, including any publications/abstracts, to the REC.

This trial will be conducted according in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004) and the UK Policy Framework for Health and Social Care Research (2017). It will also be conducted according to ICH GCP, relevant regulations and the SOPs and quality management procedures of Sponsor, host organisations and LCTU.

16.2 Monitoring, audit and inspection

Nottingham Trent University, is the Sponsor of the study. The LCTU is responsible for the trial management and operates a risk-based Quality Management System, which will apply to this trial with quality checks and quality assurance audits performed as required.

As part of the quality management process, the trial will be subject to a risk assessment and a monitoring plan will be developed by the LCTU in accordance with the level of risk identified to participant safety, integrity of the trial and trial data validity. All trial monitoring will be conducted in accordance with the monitoring plan and will be undertaken by the LCTU. All monitoring will be performed by staff who are ICH/GCP trained and are competent in monitoring to all applicable regulatory guidelines. A documented monitoring log and audit trail will be maintained throughout the lifetime of the study.

16.3 Trial registration

The SC trial will be registered on a recognised clinical trials database ISRCTN prior to recruitment commencing.

16.4 Insurance and indemnity

Nottingham Trent University holds an insurance policy to compensate trial participants for any study-related injury participating in the UK. The University's insurance cover routinely provides for negligent harm. If a patient is harmed due to negligence this would be covered by the Sponsor indemnity arrangements for all participants in clinical studies. If a trial participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them.

16.5 Trial management

Trial management will be provided by the LCTU in collaboration with the CI and the TMG. The LCTU is a fully registered UK Clinical Research Collaboration (UKCRC) Clinical Trials Unit (UKCRC No.43), with expert knowledge in the design, conduct and analysis of randomised clinical trials, and a track record in supporting complex intervention RCTs. The LCTU will ensure that the trial runs according to the pre-agreed timetable, ethical requirements are complied with, and that all aspects of the trial are performed to the highest quality.

16.6 Competing interests

None of the authors declare any competing interests.

17 DISSEMINATION & PUBLICATION POLICY

Regular newsletters will be made available to all investigators and participants taking part in the study, which can be sent by email or post where participants do not have an email address. All participants will be sent a summary of the results of the trial once the analysis has been completed, where they have consented to this.

Input from the study's lay members will inform the dissemination plan for patients and public. Access to the findings of the trial will be made available in a contemporary and user-friendly way and full details of the results provided if the participant requests them.

The CI will be responsible for ensuring that the results of the trial are disseminated through peer review journals, conference presentations and local mechanisms at all participating centres irrespective of the outcome within six months after the final trial report. Authorship on the manuscript will be determined by the CI, according to contribution to the trial after discussion with the TSC, and according to the guidelines of leading medical journals. The TSC will be responsible for approval of all manuscripts arising from the trial prior to submission for publication. All publications will quote the clinical trials registration number and will

acknowledge the participating investigators, TSC and DSMC, LCTU, the Sponsor and the Funder.

Approval of the TSC will be sought prior to publication of any study-related papers.

The trial will be reported in line with the CONSORT statement, which is an evidence-based, minimum set of recommendations for reporting randomised trials. [30]

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19 Appendix 2: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NSA01.	1.1	12/05/2022	Yvette Walters	• Confidential Statement removed as per NIHR request • Added REC and ISCTRN Registry reference added.
SA01	2.0	08/07/2022	Yvette Walters Professor Jayne Brown	• Sponsorship of the study transferred from De Montfort University to Nottingham Trent University. • Minor Changes to Consent Participant Information sheets to incorporate the change above.
NSA02	3.0		Yvette Walters Professor Jayne Brown	• Remote Consent procedure changed • Parent/care Information sheet amended to incorporate the change above. • Amendment to intervention booklet which included change of sponsor.
NS03	3.0		Yvette Walters	• Amendment to add 2 new recruiting sites for the main phase of the study.
NSA04	4.0		Yvette Walters Professor Jayne Brown	• Referral procedure changed ti add in GP referrals and self referrals. • Amendment to parent/carer introduction letter and parent information sheet to incorporate the change above. • Promontial Study matrials included for the above change.
NSA05	5.0		Yvette Walters	• Removal of the wording 'Local site research team will ensure with parent/carer that their baby has received their 6 week review before proceeding any further.' from section 9.2 of the protocol • Changes to Inclusion & Exclusion criteria • Added option to record interviews with laptops.

				• Trial Participant Flow chart updated in line with changes made in NSA04