Community singing interventions for postnatal depression: a hybrid type II effectiveness-implementation trial

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Study Title:	Community singing interventions for postnatal depression: a hybrid type II effectiveness-implementation trial
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Sponsor:	King's College London
Funder:	Wellcome Trust

Chief Investigators Signatures: Daisy Fancourt

Confidentiality Statement
This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. TRIAL IDENTIFIERS

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2. SYNOPSIS

Study Title	Community singing interventions for postnatal depression: a hybrid type II effectiveness-implementation trial
Internal ref. no. / short title	SHAPER-PND
Intervention	Experimental: A 10-week singing programme for mothers and their babies delivered in community Children's Centres or via an online platform Control: 10 weeks during which mothers are encouraged to attend existing non-music classes in the community or online; this will be followed by the option to attend the 10-week singing programme but outside the study
Study Design	Randomised controlled trial Hybrid type II effectiveness – implementation study

Study Participants	Trial participants: New mothers with babies from 0 to 9 months post-birth with postnatal depression (they will be involved in **clinical effectiveness and implementation** research) Wider stakeholders: artists, psychiatrists, GPs, health visitors, commissioners and others involved in the delivery of the intervention (they will be involved **just in implementation** research)	
Planned Sample Size	800 participants: 400 mothers and 400 babies, randomised 2:1 intervention: control, mother and respective baby will be allocated to the same group c. 30-50 wider stakeholders involved in the intervention	
Planned Study Period	December 2020-December 2023	
	Objectives	**Endpoints**
Primary: effectiveness	To reduce symptoms of postnatal depression in mothers	Psychological scale: Edinburgh Postnatal Depression Scale (EPDS)
Primary: implementation	To assess the acceptability of the intervention	Acceptability of Intervention Measure (AIM)

3. REVISION HISTORY

Document ID	Description of changes from previous revision	Effective Date

4. ABBREVIATIONS

AD-SUS	Adult service receipt schedule
AIM	Acceptability of Intervention Measure
BDI	Beck Depression Inventory
CAS	Composite Abuse Scale
CCI	Crittenden Child-Adult Relationship Experimental (CARE)-Index
CECA-Q	Child Experience of Care and Abuse-Q
CFIR	Consolidated Framework for Implementation Research
CI	Chief Investigator
DOB	Date of Birth
eCRF	Electronic Case Report Form
EPDS	Edinburgh Postnatal Depression Scale

EQ5D-5L	EuroQol Five Dimension Scale
FIM	Feasibility of Intervention Measure
GCP	Good Clinical Practice
GP	General Practitioner
GSE-6	Short General Self-Efficacy Scale
HDRS	Hamilton Depression Rating Scale
IAM	Intervention Appropriateness Measure
ICF	Informed Consent Form
KCL	King's College London
M4M	Melodies for Mums
MPAS	Maternal Postpartum Attachment Scale
MRC	Medical Research Council
MSPSS	Multidimensional Scale of Perceived Social Support
NHS	National Health Service
NoMAD	Normalisation MeAsure Development questionnaire
NRES	National Research Ethics Service
ONS	Office for National Statistics Wellbeing Scale
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PND	Post-Natal Depression
PRFQ	Parental Reflective Functioning Questionnaire
PSS	Perceived Stress Scale
R&D	NHS Trust R&D Department
RE-AIM	Reach Effectiveness Adoption Implementation Maintenance
REC	Research Ethics Committee
SCID	Structured Clinical Interview for DSM-IV
SLAM	South London and Maudsley NHS Foundation Trust
STAI	State Trait Anxiety Inventory
UCL	University College London

5. ROLE OF TRIAL SPONSOR AND FUNDER

The funder for this RCT is the Wellcome Trust. The responsibility of Chief Investigators will be taken by Professor Carmine Pariante and Dr Daisy Fancourt. Sponsorship is provided by King's College London (KCL).

KCL is the data controller. University College London (UCL) and Breathe Arts Health Research (Breathe) will be data processors. Breathe, UCL and KCL will have access to personal data collected for trial purposes and this access will be defined by a data sharing agreement.

6. BACKGROUND AND RATIONALE

6.1. Postnatal depression

Postnatal depression (PND) affects at least 12.9% of new mothers, with symptoms including low mood, fatigue, anhedonia, insomnia and irritability[1,2]. However, challenges surround the fact that there is still no complete treatment solution. Although pharmacological treatment has had positive results, these are hampered by low uptake and adherence amongst mothers, while psychotherapy has produced mixed results and also has similar challenges around low uptake or delayed treatment[2–5]. However, many mothers engage in community group activities with their babies, such as attending mother-infant play groups. Such activities have been identified as ways of relaxing mothers, providing good sources of social interaction, decreasing the monotony of each day and also providing a sense of personal fulfilment for mothers[6].

There is also a growing body of evidence demonstrating the effects of community group singing on mental health[7,8]. Singing to new babies is practised in cultures around the world, and research has demonstrated valuable benefits such as improving mother-infant interaction and reducing distress in babies[9–11]. Listening to music during pregnancy is also associated with higher levels of wellbeing and reduced symptoms of PND in the first 3 months post-birth, while daily singing to babies is associated with fewer symptoms of PND and higher levels of wellbeing, self-esteem and perceived mother-infant bond[12]. Consequently, there is a strong theoretical background to why singing could support mothers with PND.

6.2. Melodies for Mums

Melodies for Mums (M4M) is an intervention that was developed and tested as part of a collaboration between the Royal College of Music, Imperial College London and University College London from 2015-2017. The programme involved weekly singing classes for mothers and their babies delivered in groups of 8-12 in Children's Centres for 10 weeks. M4M was tested in a three-arm RCT involving 134 mothers with PND (with an Edinburgh Postnatal Depression Scale (EPDS) score ≥ 10), compared to a comparison group (10 weeks of creative play classes for mothers and their babies) or care as usual (wait-list control). The study found that mothers with moderate-severe symptoms of PND who participated in the programme with their baby had a significantly faster improvement in symptoms than mothers in usual care[13]. Specifically, the mothers in the singing group had an average EPDS score of 15.7 at baseline, indicating moderate depression, and this had dropped to 10.3 by week 6 and 9.4 by week 10. This improvement equated to an average 35% decrease in depressive symptoms across the first 6 weeks, by which point 65% of the singing group no longer had an EPDS ≥ 13, i.e., indicating more than just mild depression. This decrease in depressive symptoms in the singing group extended to a 40% decrease by week 10, by which point 73% of the singing group no longer had an EPDS ≥ 13. When comparing the average changes in EPDS scores in all recruited mothers, the mean change between baseline and end of treatment (10 weeks) was a -5.2 (SD=2.8) in the singing group and -4.25 (SD=3.2) in the care-as-usual group (effect size = 0.32).

In exploring the mechanisms underlying these changes, these improvements were accompanied by an increase in the frequency of mothers singing to their babies outside the classes, their confidence in singing, and the breadth of their singing repertoire[14]. Moreover, group singing led to significant increases in perceived mother-infant closeness and positive affect and decreases in negative affect compared to social play. Singing also led to a greater decrease in the stress hormone, cortisol, than social play[15]. While both singing and play interventions supported hedonic wellbeing, singing appeared to elicit a functional psycho-emotional response rooted in the needs of new motherhood. Group singing provided an authentic and social multicultural creative experience, was able to calm babies, provided mothers with immersive 'me time', facilitated a sense of achievement and identity and enhanced perceived mother-infant closeness[16].

A process evaluation of the study showed that the intervention was delivered with a high level of fidelity, there were no indications of significant adaptations that could have confounded results, and the correct target demographic was reached. Women attended an average of 7.2 of the 10 sessions, with 73.5% of the women attending more than half of the sessions. Moreover, the programme had a satisfaction rating of 8.8/10, with 87.8% of the mothers agreeing that the classes were well tailored, and 100% of mothers saying that they would recommend the programme to another mother. However, the process evaluation also highlighted several challenges perceived by mothers, workshop leaders and the project coordinator (e.g., challenges in timing session attendance with babies' routines). Whilst none of these became an obstacle the running of the intervention, more work is required to explore the implementation of the programme.

Following the initial study, M4M has been taken on as a service by Breathe Arts Health Research across Lambeth and Southwark. However, there has been no further research surrounding the programme, so its efficacy at a larger scale remains to be tested, as do the acceptability, appropriateness and feasibility of its delivery on a larger-scale, and its potential to be adopted and sustained as a cost-effective and beneficial service for mothers. We plan to investigate these issues by drawing on methodologies from the field of implementation science. Implementation science is defined as "the study of methods and strategies to promote the uptake of interventions that have proven effectiveness into routine practice, with the aim of improving population health"[17]. This is a rapidly evolving field, dedicated to helping to understand how evidence-based interventions can be implemented at scale. In the context of this trial, alongside assessing how effective M4M is in improving symptoms of PND in a larger group of mothers, we will also examine how effectively it has been implemented to help us determine the overall success of the programme and how (if efficacious) it could be rolled out on a wider regional or national level. In addition, we will explore biological (for example, hormones) and psychological (for example, mother-infant interaction) mechanisms underpinning the beneficial effects.

7. TRIAL OBJECTIVES AND DESIGN

The objectives of the trial are:

- To explore the **clinical effectiveness** of the intervention in a larger sample size than previous studies. This will allow us to ascertain whether the initial findings can be replicated at a larger scale.
- To explore the **implementation effectiveness** of the intervention, including its uptake, suitability, acceptability, appropriateness and feasibility. This will help us to identify not just 'if' but also 'why' the intervention works and support our understanding of how it can be successfully delivered within clinical pathways. It will also explore the cost effectiveness of the intervention, including the cost of delivering the interventions and the balance of benefit for the health sector, in order to be able to develop strong business plan for the intervention.

7.1. Clinical outcomes

Objectives	Outcome Measures/Endpoints
Primary Objective To assess the effectiveness of group singing interventions on symptoms of postnatal depression (Baseline, 6, 10, 20 and 36)	Symptoms measured before, during and after the intervention using the Edinburgh Postnatal Depression Scale (EPDS). The primary outcome measure is changes in EPDS total score between Baseline and Week 10 (end of treatment)
Secondary Objectives - clinical	**Outcome Measures/Endpoints**
To assess whether singing improves further aspects of mental health	Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Office for National Statistics Wellbeing Scale (ONS), State Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS), Short General Self-Efficacy Scale (GSE-6)
To ascertain whether singing affects mother-infant bond	Crittenden CARE-Index (CCI), Maternal Postpartum Attachment Scale (MPAS), Parent Reflective Functioning Questionnaire (PRFQ)
To ascertain whether singing improves social support and reduces loneliness	UCLA Loneliness Scale, Multidimensional Scale of Perceived Social Support (MSPSS)
To identify whether there are biological mechanisms underpinning the psychological outcomes assessed	Stress hormones, including hair cortisol, diurnal cortisol, salivary cytokines and salivary oxytocin
To identify how the singing sessions affect the lived experience of mothers with PND	Focus groups
To explore the phenomenology of PND and how singing intersects with PND among women with particular risk factors for PND (traumatic birth, adverse childhood experiences, and social isolation/loneliness)	Semi structured interviews

7.2. Implementation outcomes

Objectives	Outcome Measures/Endpoints
Primary objective	
To assess the acceptability of the intervention	Total score of the acceptability of Intervention Measure (AIM)
Secondary objectives	
To assess reasons for perceived acceptability of the intervention	Semi-structured interviews
To assess uptake/reach of the intervention	Number of eligible women that sign up to the intervention
To assess the appropriateness of the intervention	Total score of the Intervention Appropriateness Measure (IAM) Semi-structured interviews

To assess the feasibility of the intervention	Total score of the Feasibility of Intervention Measure (FIM) Semi-structured interviews
To assess intervention adherence and attrition rates	Data on the overall adherence to the intervention, number of drops-outs each week and reasons why
To assess the adoption of the intervention	The number of individuals signing mothers up to the intervention, the number of individuals delivering the intervention and the number of individuals supporting the intervention (and continuing to do so)
To assess the cost effectiveness of the intervention	EQ5D-5L (quality of life measure) and AD-SUS (adult service receipt schedule) and implementation activity logs (to estimate implementation costs).
To assess factors affecting the sustainability and scalability of the intervention	- Total score of the NOMAD Scale - Semi-structured interviews

Data to assess uptake/reach will be collected from mothers. Data to assess adoption will be collected from the wider stakeholder group ('deliverers', 'referrers', 'supporters'). The remaining measures/endpoints will be collected from all stakeholders (i.e., mothers and the wider stakeholder group).

7.3. Trial design

This is a randomised controlled trial within the framework of **Hybrid Type II Effectiveness-Implementation trials**, where we place equal focus on the effectiveness of the intervention and the effectiveness of its implementation. Hybrid effectiveness-implementation evaluations are the gold standard of modern implementation science and blend design components of clinical effectiveness and implementation research[18]. Such blending provides more rapid translational gains, better guidance for intervention adaptation and effective implementation, and more useful information for decision makers, thereby reducing wastage in research[19].

Our design and methods have been informed by a recently completed Hybrid Type II Effectiveness-Implementation trial which evaluated two complex psychoeducational programmes for severe hypoglycaemia in type 1 diabetes (HARPdoc)[20]. We will employ the hybrid methodology described to collect data on both intervention and implementation effectiveness. The overall trial is informed by evaluation and implementation theoretical frameworks. We used the **Medical Research Council (MRC) framework** for evaluating complex interventions to guide and inform the study design and processes[21–23]. The **Consolidated Framework for Implementation Research** (**CFIR**) was used to develop semi-structured interview topic and coding guides to help to delineate specific barriers/drivers of intervention scaling[24,25] and the compendium of **implementation strategies**[26] (defined as: "methods or techniques used to enhance the adoption, implementation, and sustainability of a clinical programme, practice or intervention")[27] will be drawn upon to help overcome potential obstacles associated with implementing M4M at scale. We also used the **Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework** to guide definition and selection of implementation outcomes[28,29] which will help us to assess how well our chosen implementation strategies to implement M4Ms are working[28]. Implementation outcomes are defined as "the effects of deliberate and purposive actions to implement new treatments, practices, and services, and are distinct from service and client (patient) outcomes".

In addition, the design and measure selections have been adopted from HARPdoc[27] where they were refined and informed by stakeholders including, patients' representatives,

providers/managers and commissioners, and guided by the state of the art **'Implementation Science Research Development tool'** specifically developed to guide the design of high-quality implementation research based on best evidence and expert recommendations.[30] The design and measures will be further refined with the key intervention stakeholders for M4M specifically.

Finally, the design of M4M's itself has been underpinned by the **COM-B model**[31], which postulates that in order for an individual to perform a behaviour (in our case mothers' attendance at M4M as well as other individuals support in delivering the intervention), three things are required: 'capability', 'motivation' and 'opportunity'. Guided by the **CFIR framework** described above, we will examine factors that could affect each of these prerequisites of behaviour so that strategies to overcome potential issues relating to accessing and attending M4M as well as it's long term sustainability and scalability can be determined.

7.3.1. Team expertise

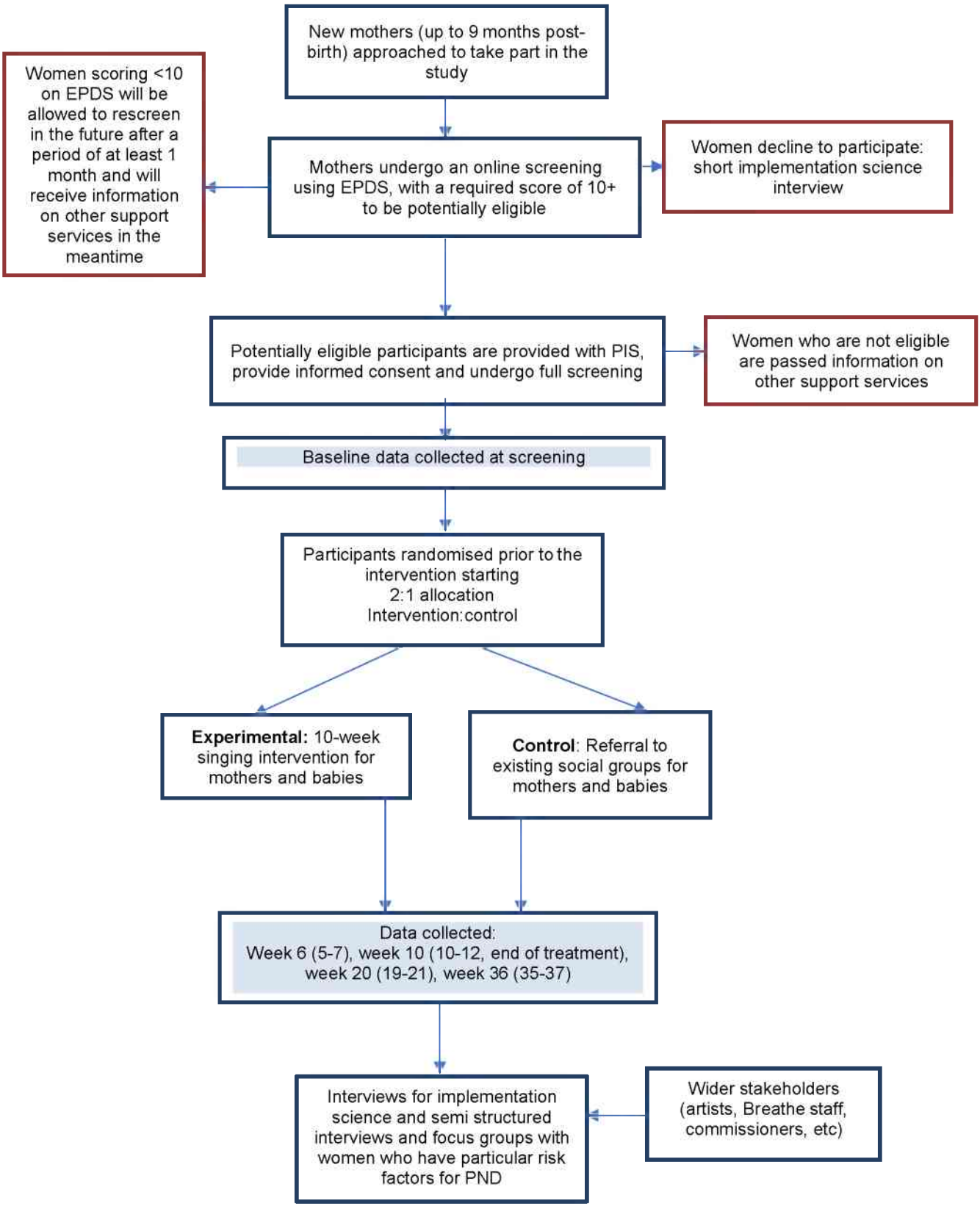
Two members of the team (Fancourt & Perkins) led the RCT on singing and postnatal depression, so have expertise in carrying out a large-scale clinical study with this population, using this intervention and a very similar data collection schedule. Two other members of the team (Pariante & Dazzan) are psychiatrists with expertise in depression and specifically PND. They have previously led large-scale clinical trials using the measures included in this study.

The team at Breathe Arts Health Research have been delivering the intervention for women with PND in the community for over 2 years in the same venues, so have experience leading the sessions, recruiting the mothers, and handling relevant safeguarding issues.

Other members of the team from the King's Centre for Implementation Science (Davis, Bakolis, Soukup, Sevdalis, Healey) are specialists in implementation science and economics with expertise in researching complex health interventions. The methodology that helped inform this study was based on a hybrid trial in the context of diabetes - led by Soukup,[28] with others in the implementation team involved - as well as their involvement in the implementation research develop tool (ImpRes)[30] that has been used to help guide our work.

8. STUDY DESIGN

This will be a randomised control trial using the following procedure:



8.1. Trial Setting

This is a multi-centre trial that will be run in locations across London (primarily in the boroughs of Lewisham, Lambeth and Southwark), specifically in children's or community venues. These venues will be thoroughly safety- and risk-assessed in light of COVID-19 and adherence to any COVID-secure measures will be closely monitored by Breathe.
In order to enrol a sufficiently large sample of women, there will be 12 blocks of the 10-week singing programme in total: 10 intervention blocks will be for the experimental group, and 2 blocks will be for women in the wait-list control group that wish to take part in the singing sessions (this will be offered outside the main study, and we will schedule fewer programmes as we anticipate a lower uptake of the intervention from the wait-list group, following experiences on the first RCT study 2015-2017)[13]. The 2 wait-list blocks will be offered after a woman has completed the first 10 weeks of the study and no data will be collected regarding these singing sessions, apart from the control follow-up data that this group is expected to provide.
In the event that one or several women need to self-isolate due to confirmed or suspected exposure to COVID-19, the sessions will be delivered to her/them online via Zoom. This will allow for the sessions to still be conducted in person with the remaining women.
In the event of the artist or the Breathe officer having to self-isolate, a replacement Breathe-trained artist will be ready to step-in and deliver the sessions. The same will apply to Breathe staff; there will be another staff member available to be present at the sessions.
The most up-to-date government guidelines will always be strictly followed, and the team will remain flexible to adapt to the ever-changing guidelines.

8.2. Study Participants

8.2.1. Trial participants

Study participants will be new mothers with symptoms of postnatal depression defined as diagnosis of major depressive disorder according to the Structured Clinical Interview for DSM-IV (SCID) and scoring 10 or above in the Edinburgh Postnatal Depression Scale (EPDS).

8.2.2. Inclusion Criteria

- Women aged 18 or older
- Satisfactory understanding of English
- Women who have a child between 0 and up to 9 months old
- Women with postnatal depression diagnosed using symptoms of PND at a minimum score of 10 on the Edinburgh Postnatal Depression Scale (EPDS) AND meeting diagnostic criteria for major depressive episode on the Structured Clinical Interview for DSM-IV (SCID)
- Access to an internet-connected device (mobile phone, tablet, computer or laptop) to allow completion of assessments and participation in the singing sessions.

8.2.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:
- Child outside of the age-range specified
- Unable to give informed consent

8.2.4. Wider stakeholder participation

We will engage with wider stakeholders involved in the delivery of the intervention. This will include (i) 'Deliverers' – defined as artists and staff at Breathe Arts Health Research who deliver the intervention, (ii) 'Supporters' – defined as additional staff at community children's centres who support the delivery of the intervention, and (iii) 'Referrers' – defined as psychiatrists, GPs, health visitors, midwives, any other healthcare professionals who refer mothers to the intervention and commissioners.

Any stakeholders will be required to be over 18 years of age and involved in some way with the delivery of the intervention. We will collect data from these stakeholder groups on their perceived acceptability, appropriateness and feasibility of the intervention, together with factors affecting its uptake, sustained use and scalability, and strategies that could be used to overcome potential implementation issues. For further information on these data endpoints and how they link with our objectives, please refer to section 7.

In addition, we will engage with mothers to define the uptake of the intervention. Potential participants that are eligible for the study, following baseline assessments but that decline to participate in the trial will be contacted by the implementation science research team to assess the motivations for declining to participate.

9. STUDY PROCEDURES

9.1. For the clinical trial

9.1.1. Recruitment

Recruitment will be primarily done through:
- Signposting via other health and social care professionals and in the community, including midwives, health visitors, and community publicity
- Social media groups and online forums aimed at new mothers
- Weigh clinics and other community and clinical centres for postnatal mothers and their babies
- Healthcare referrals, including General Practitioner (GPs), clinical psychologists, and psychiatrists
- Self-referral

In order to recruit a sufficient number of women for this study in the current pandemic, most of the signposting will be done through GPs, midwives, health visitors and community mental health teams that remain engaged with the population despite the pandemic. In addition, signposting via social media, especially targeted advertising in local women's groups will be another valuable route for recruitment.

GPs, health visitors and midwives will be made aware of the study through a poster/flyer campaign sent directly to them. Breathe has a database of local contacts in the boroughs where the sessions take place and doctors/midwives/nurses in the database will be made aware via e-mail.

At clinical centres, signposting will take place indirectly through posters and flyers and directly through healthcare professionals that have been made aware of the study. In terms of social media recruitment, the following will be used: various Facebook targeted groups, Instagram & Twitter hashtags to find groups and forums to promote to, plus more traditional routes e.g. to get local authorities to advertise as part of their various tiers of information of available local services.

The project manager for the singing sessions (Melodies for Mums) at Breathe will be present in baby weight clinics and children's centres where he will approach mothers with young babies in waiting areas and offer information on the study. At this stage, no eligibility will be assessed but

any mothers than show interest in the study will provide their name and contact details so that the project manager can contact them to invite them to complete the webform when new singing sessions become available. Names and contact details will be saved in a password-protected laptop that only the project manager has access to and will be retained on the potential participants spreadsheet for up to two months; after that they will be deleted.

The KCL research team will only become involved once the potential participants have completed an online screening form and given consent for the basic information collected onto the online screening (personal information, EPDS score) to be shared with the research team.

The wider stakeholder group will be identified through Breathe's network of artists, staff and others involved in the delivery of the intervention. In addition, others involved in the research, including local commissioners will also be approached for implementation science.

9.1.2. Screening, Eligibility and Informed Consent

All potential participants will initially be directed to a pre-screening online form. This will capture basic information including their name, date of birth (DOB), baby's DOB, address, telephone number, and once this has been submitted, they will be sent EPDS scale to complete. Women will be asked to read an online participant information sheet (PIS) and to electronically confirm consent after reading the informed consent form (ICF) to their personal data being collected. The PIS will explain that their details will be used for further contact related to the study in case their EPDS score is equal or higher than 10.

If a woman's EPDS score is lower than 10, she will receive notification that she is not currently eligible to participate and will be signposted to other support services within the community delivered in-person or online according to current availability determined by the COVID-19 situation (e.g. talking therapies, mother-baby groups, baby activity groups, etc). In the consent form, it will be asked if she would like to be re-contacted at a future date when the next series of workshops is scheduled in the same area, and if she agrees, she will be contacted in the same way as other women who express interest for the first time and screened again. We will wait at least 1 month before inviting re-screening.

If a woman's score is 10 or higher, she will be notified that she is potentially eligible and will proceed straight to the second phase of screening through a home visit, NIHR/Wellcome King's Clinical Research Facility visit, or online assessment via Zoom, according to government guidelines and participant's preference. The PIS for the trial will be sent once the women is booked for the baseline assessment (either at home, at the NIHR/Wellcome King's Clinical Research Facility or on Zoom, depending on government guidelines and participant preference).

When a new round of 10 classes becomes available, recruitment assistants will either visit potential participants at home, arrange a visit to the NIHR/Wellcome King's Clinical Research Facility or assess them via Zoom, to undertake the full screening interview against the inclusion/exclusion criteria outlined in section 8.2. This full screening will take place in the 2 full weeks prior to the classes starting (referred to as 'Baseline'). If the participant is found non-eligible, they will be signposted to other support services within the community, either in person or online (e.g. talking therapies, mother-baby groups, baby activity groups, etc). If the participant is found eligible and has capacity to consent, they will be consented (signing the informed consent form, co-signed by a member of the research team) and the recruitment assistant will carry out the baseline measures. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason, and with no obligation to give the reason for withdrawal. A contact point will be made available for participant in case they wish to ask further questions regarding the trial. If more women are found eligible for each 10-week programme than we have capacity for,

then priority will be given to those with the highest EPDS scores. The others will be invited to rescreen for the next group. Mothers will then be randomised using Sealed Envelope.

A copy of the ICF will be sent electronically to the participant once the baseline assessment has been arranged. The original signed form will be retained at the Maurice Wohl Institute. The ICF will include a section detailing the samples to be collected (saliva and hair) and the other measures to be analysed, as well as the consent to obtain babies' data (in video and other formats) and babies' saliva samples throughout the study (see full table for more information on measures in section 7.8). All participants will be requested to provide biological samples, regardless of their group allocation.

A participant can opt out of the sample collections or babies' data collection and enter the trial for all other measures. There will also be an optional section for participants to consent to being audio-recorded if they choose to take part in a focus group or semi-structured interview after the intervention period. The Informed consent will also include a point stating that the participants might be contacted for further studies. This will allow for the sample of the population enrolled on the trial to be approached for future follow-up research questions. Finally, the ICF will contain a point for participants who are eligible and nevertheless decide not to participate to the study, asking for consent to be contacted by the implementation team to explain the reasons behind the refusal (the PIS will also have a section on this so participants will have been pre-notified).

9.2. For the stakeholders implementation research

Stakeholders described in section 8.2 ('referrers', 'deliverers' and 'supporters') will be approached during the same 2-year period and invited to take part in data collection with the implementation science research team, which will involve completing all the study validated implementation metrics (all of the staff members who belong to the above three categories); and also being invited to attend individual semi-structured interviews. They will receive the PIS for Stakeholders form and the ICF for Stakeholders, which they will be asked to sign and date. In addition, by default, stakeholders' participation in the interviews will also act as their consent to be interviewed. Stakeholders will be selected using purposive selection based on the available stakeholders that consent to stakeholder research.

For stakeholders, an email will be sent out to the individuals involved in the research (deliverers, referrers and supporters) with the Stakeholder PIS asking them if they would be willing to be involved in the study. Those that agree to take part would then be approached by a member of the research team (either over the phone or face-to-face) to go through the study in more detail and provide informed consent (which would be written consent – if face-to-face using the ICFs, electronic signature of ICFs, or if over the phone, we will send sealed pre-paid envelopes for the stakeholders to return the ICFs).

For the mothers, during the initial assessment by KCL researchers, mothers will be asked to sign a Participant ICF. There, they will be given the option to consent to the study – if they decline, there will be an option for them to consent to being contacted for Implementation Science research to explore the reasons why they declined the participation in the study. If they agree to this, they will be contacted by researchers and a short interview will be done.

9.3. Payment

Participants will not receive any payment, but they will be reimbursed for their travel to the locations of the interventions if requested.

9.4. Potential risks and benefits

Risks
Physical harm: No significant physical risks are expected to be associated with the participation in the trial.

Psychological harm: Participation in the trial could result in temporary changes in depressive symptoms for mothers. These changes could either be beneficial or harmful and they can be transitory, recurrent or permanent. The risk of psychological harm is expected to be minimal and published evidence suggests that the intervention would result in beneficial changes in depressive symptoms[13].

It is expected that participation in the study could result in a degree of inconvenience to the trial participants due to the large number of questionnaires and the repeated nature of the assessments and sample collection. It is also expected that participation of mothers will lead to some intrusion of the mother's home life as the trial requires home visits or Zoom assessment that require around one to two hours commitment per visit. However, we are using measures routinely used in similar studies by the PIs of this study or other researchers, and we have always had positive experience in collecting extensive data from women in the perinatal period and their babies. Additionally, if government guidelines do not permit home visits or mothers are not comfortable with it, assessments can be done on Zoom which should be less intrusive to mothers.

Due to the COVID-19 pandemic, there is a risk that mothers and stakeholders might be at risk of COVID-19 exposure. This risk of exposure is comparable to other everyday activities and will be mitigated by the current social distancing measures imposed by current government guidelines at the time of the sessions, for both mothers and their babies. These guidelines will be adopted as soon as they are announced in order to protect all participants, stakeholders and researchers involved in the study.

Benefits
In light of the published data, participants randomised to the intervention arm are expected to improve their depressive symptoms at a faster rate in comparison to the control group. All patients in the trial are expected to improve their symptoms by week 10. Previous research also suggests other benefits such as increased social support networks and signposting to other community activities that could provide benefits to the participants.
The implementation science part of the trial, although not been designed to confer individual participant benefit, is intended to (a) make direct contributions to the subsequent scale-up of the singing programme, so that more people with postnatal depression can benefit from it, and (b) allow participants to contribute to research aimed at understanding these experiences. In the process, the participants may benefit more personally from having an opportunity to discuss in confidence their personal experiences of the singing programme with an impartial researcher who will not be judgmental.

9.5. Monitoring and safety reporting

9.5.1. Monitoring

Monitoring and data quality control will be done centrally (by KCL team) to assess the accuracy of data entry. Regular checks will also be done by the UCL team to assess outliers in the data that could trigger a safety concern to the patients or indicate discrepancies in the database.

9.5.2. Safety reporting

Serious Adverse Events (SAEs) will be reported by KCL team in dedicated SAE forms, using the Non-CTIMP safety report to the Research Ethics Committee (REC) form.

Only related or unexpected SAEs will be reported to the REC in this trial:
- related to the study (i.e., they resulted from any of the research procedures) and
- unexpected (i.e., not listed in the protocol as an expected occurrence)

These specific SAEs will be sent to the REC within 15 days of the CI becoming aware of the event.

9.6. Protocol deviations and Serious Breaches to GCP/protocol

Protocol non-compliances such as changes to the delivery of the intervention due to issues such as illness or strikes will be reported first to the Chief Investigator and then to the Sponsor.

9.7. Randomisation, code-breaking and blinding

9.7.1. Randomisation

Randomisation sequence will be created in the following manner: participants will be stratified by EPDS score, age of the baby and location of preferred delivery centre with a 2:1 intervention:control allocation using random block sizes of 6. Identifiable patient data such as names and contact details will be stored in linked anonymised form. Participants will be randomised using Sealed Envelope.

Participants will be asked to provide details of their GP on registration and a letter will be sent to all GPs explaining that the woman has enrolled to take part in the programme.

9.7.2. Code-breaking and safeguarding procedures

Upon randomisation, participants will be given a unique participant ID in the following format: x-xx (group A-Z and participant number according to order of enrolment into the group 00-99). In order to allow the linkage of the participant ID with the identity of the participants, in addition to the participant ID, the DOB of the mother and the baby will be used in all CRFs. The participant ID will also be used in the implementation science investigation allowing effectiveness and implementation data to be linked and subsequently triangulated. This link will not be destroyed at any point during the trial, allowing an effective and secure code-break strategy if needed.

Code-breaking will be required for safeguarding purposed. For this, we will have three safeguarding checks:

1. The research team will check the EPDS scores of all participants as they come through online (that is, at baseline, 6, 10, 20 and 36) at least once a week, and they will alert the clinical leads of the study if (a) EPDS scores are more than 25 out of 30 or, (b) EPDS includes a score of 2 or more on the question addressing self-harm.
2. Breathe will report to the KCL research team on any concerns during intervention sessions within 24 hours of noting the concern, especially if the behaviour is felt to be indicative that they are at immediate risk of harming themselves or their babies.
3. If the KCL research team thinks that the behaviour (or any responses to the questionnaires collected) of any participant during the home visits or during any other contact (e.g. phone contact, Zoom calls, etc), is felt to be indicative that they are at immediate risk if harming themselves or their babies, the same process will be taken.

The clinical leads (psychiatrists) on the research team will assess each report and decide whether there is a need to contact a participant directly, alert a participant's GP or contact any other healthcare services. This decision will be made within 24 hours of receiving the report. If felt necessary by the psychiatrists in the research team, this participant can also be referred directly to the perinatal mental health service at Maudsley Hospital. Participants will be informed of this process in the PIS. If contact with a health professional is being made on behalf of a participant, the participant will be informed that this is taking place.

In addition to the above-mentioned safeguarding measures, all participants will be asked to report absences on the day or in advance (e.g. in the case of known medical appointments) and these can be noted so that sessions can go ahead unimpeded by trying to anticipate whether a participant will arrive or not. All unaccounted absences are followed up with an email, noting the absence and encouraging the participant to get in touch and to re-attend the following session. Participants have access to a library of music covered in sessions and are encouraged to consider continuing using these during the week.
If any safeguarding concerns arise during a singing session or any contact with the mothers (if they miss a session they will be contacted by Breathe), the clinical team (Dazzan, Pariante, Manoharan) will be made aware and if found necessary, the mother may be contacted and the suggestion to book an appointment to see her GP/attend A&E will be made.
Participants will be asked to inform Breathe if themselves or their baby need to self-isolate due to potential or confirmed exposure to COVID-19 so that appropriate measures can be taken to protect other participants, artists and the extended team. We will also follow government guidelines if other members of the group were around an exposed participant prior to symptom-development.

9.7.3. Blinding

Blinding will apply to outcome assessors (the trial statistician, in the UCL team) to avoid bias in the data processing and analysis. As outlined above, in the event of an emergency where the UCL team has identified a potential safety issue, the KCL team will be notified of any safeguarding concerns for follow-up. Trial participants, care providers and the research team (excluding the trial statistician) will be aware of the intervention allocation.

The CCI scoring will be performed by a blinded collaborator to ensure unbiased analysis.

9.8. Assessments

Participants will be visited either at their homes, at the NIHR/Wellcome King's Clinical Research Facility (King's College Hospital, Denmark Hill), or assessed on Zoom, for baseline, week 10 and week 36 assessments. Week 6 and 20 visits will be completed online without the assistance of a researcher due to the self-reporting nature of the measures to be captured. If a mother cannot access a computer/laptop to complete the online questionnaires, these will be printed and posted to them or provided in printed form at the sessions.

For baseline online measures, participants will be encouraged to complete these a day either side of the first session. For visit 6 measures, participants will be encouraged to complete these in the 3 days of the 6th session. However, in order to allow flexibility in the schedule, it will be accepted a +/-1 week variation in the date of collection of the measures below (apart from week 10, when the window will be weeks 10-12). These measures will be collected from the control and the intervention groups simultaneously.

An optional focus group will take place after session 10 of the intervention and subsequent interviews will be conducted with a sub-group of women who have particular risk factors for PND.

These interviews will take place after the 20-week follow up either by video call or at the woman's home.

FOR THE CLINICAL EFFECTIVENESS PART OF THE TRIAL

S=intervention session, Q=online questionnaire, Wk=week

		Baseline			**Week 6**		**Week 10**			**Week 20**	**Week 36**	
		Visit 1 (up to 2 wks before 1st session)	Q*	1st S	Q*	6th S	Visit 2 (up to 2 wks after 10th session)	Q*	10th S	Q*	Q*	Visit 3 (wks 35-37)
DEMOGRAPHICS												
Baseline demographics[a]	5 min	x										
Repeated demographics[b]	5 min				x			x		x	x	
Brief Life Events Scale	5 min	x										
Child Experience of Care and Abuse (CECA-Q)[c]	30 min	x										
Composite Abuse Scale (CAS) - Pregnancy Version	5 min	x										
Intrusive Life Events Scale	5 min	x										
MENTAL HEALTH												
Structured Clinical Interview for DSM-IV (SCID) - used for screening	10-20 min	x										
Edinburgh Postnatal Depression Scale (EPDS)[d]	3 min		x		x			x		x	x	
Hamilton Depression Rating Scale (HDRS)	10 min	x					x					
Beck Depression Inventory (BDI)	5 min		x		x			x		x	x	
Office for National Statistics Wellbeing Scale (ONS)	2 min		x		x			x		x	x	
State Trait Anxiety Inventory (STAI)	5 min		x		x			x		x	x	
Perceived Stress Scale (PSS)	5 min		x		x			x		x	x	
SOCIAL												

		Baseline			Week 6		Week 10			Week 20	Week 36	
		Visit 1 (up to 2 wks before 1st session)	Q*	1st S	Q*	6th S	Visit 2 (up to 2 wks after 10th session)	Q*	10th S	Q*	Q*	Visit 3 (wks 35-37)
Video for CCI (CARE-Index)	5 min	x					x					x
Maternal Postnatal Attachment Scale (MPAS)	5 min		x		x			x		x	x	
Parent Reflective Functioning Questionnaire (PRFQ)	3 min		x					x			x	
UCLA Loneliness Scale	2 min		x		x			x		x	x	
Short General Self-Efficacy Scale (GSE-6)	2 min		x		x			x		x	x	
Multidimensional Scale of Perceived Social Support (MSPSS)	5 min		x		x			x		x	x	
BIOLOGICAL												
Diurnal saliva samples in mothers and babies[e]	5 min	x					x					
Hair cortisol sample	10 min						x					
Pre-post intervention saliva samples in mothers and babies[f]	5 min	x					x					
QUALITATIVE												
Focus groups	45-60 min								x			
Interviews focusing on subgroups of women[g]	45-60 min									x		

*Questionnaires will be completing online by the mothers, ideally 3 days before or after the respective week sessions (1st, 6th and 10th) or one week either side of the corresponding follow-up date (at 20 and 36 weeks).
[a]Demographics including the mother's age, baby's age, ethnicity, marital status, smoking, drinking, traumatic birth, past history of mental illness, adverse childhood events, number of other children, education, household income, CECA-Q, Brief Life Events Scale, Intrusive Life Events Scale and Composite Abuse Scale will be collected at baseline.
[b] Repeated demographics include medication, psychological therapy, physical health, use of health services, engagement in other baby groups, daily music engagement
[c]Childhood Experience of Care and Abuse Questionnaire (CECA-Q)- interview about maternal childhood experience of trauma
[d]EPDS completed online by all mothers who self-refer to identify who should be sent for full interview screening and completed again at baseline visit.

[e]Salivettes and SalivaBio Children's Swab will be provided to the mothers before the 1st, and 10th sessions; samples to be collected at home by the mothers on the day preceding the in-person or online session or visit, and then collected by the researchers on the day of the visit or session. Alternatively, samples may be posted by participants, using pre-paid UN3373 category-B packaging, provided by researchers, to be compliant with biohazard risk of COVID-19,
[f]Undertaken before session 1 and after session 10 if possible, to measure cortisol, cytokines and oxytocin; collected using both absorbent swabs and the passive drool method, by a researcher attending the session or at the NIHR/Wellcome King's Clinical Research Facility. Samples will be kept on ice and transferred to the laboratory at KCL for long-term storage in freezers. Babies' samples will be collected using SalivaBio Children's Swabs.
[g]There will be two interview points: (1) focus groups will take place immediately following session 10 (if logistically possible) for all mothers focusing on their lived experience of the intervention and their reported mechanisms of effect; (2) further individual or small-group interviews with three sub-groups of women self-reporting particular risk factors for PND: traumatic birth, adverse childhood experiences, and social isolation/loneliness. These interviews will focus in-depth on the phenomenology of PND and how singing intersects with the specific context of PND among the sub-groups. The timings for the interviews will depend on the participants' availabilities and will be conducted between weeks 12 and 20.

FOR THE IMPLEMENTATION EFFECTIVENESS PART OF THE TRIAL

Int=interviews (as part of existing study visits for mothers, and on the telephone for other stakeholders), Q=online questionnaire, Wk=week

	Time to complete	Baseline		Week 1 (1-3)	Week 6 (5-7)	Week 20 (19-21)		Week 36 (35-37)	
		Int	Q	Q	Q	Int	Q	Q	Q
Acceptability of Intervention Measure (AIM)	3 mins				x		x	x	x
Intervention Appropriateness Measure (IAM)	3 mins				x		x	x	x
Feasibility of Intervention Measure (FIM)	3 mins				x		x	x	x
Fidelity	10mins			x	x		x		
Implementation costs & implementation activity log	10 mins					x			
Interviews focusing on a sample of mothers and the wider stakeholder group	30mins					x			
Uptake of the intervention	5 mins	x							
Adherence to the intervention	5 mins		x		x		x		
EQ5D-5L	5 mins		x		x		x	x	x
AD-SUS (self-reported service use)	5 mins				x		x	x	x
NOMAD scale (to assess sustainability)	15 mins						x		x
Adoption of the intervention	30 mins	x						x	

In addition, details on adherence of participants to the programme will be collected through Breathe Arts Health Research, who keep a register of attendance.

The semi-structured interviews will be conducted with a random cross section of M4M participants recruited into the trial. M4M participants will be selected for the interviews using a stratified randomisation process until saturation is reached. Randomisation is necessary to reduce selection

bias, as well as to ensure feasibility of the data collection. For people who declined or dropped out of the trial, a convenience sample will be used.

In terms of recruitment of professional stakeholders involved in the delivery of M4M, i.e., the 'referrers', 'deliverers' and 'supporters' of the intervention, all participating individuals will be recruited. Interviews will be conducted on an individual basis and will focus on perceived acceptability, appropriateness and feasibility of the intervention, whether expectation regarding the intervention were met, together with factors that could affect the sustained use of the intervention, including any perceived and actual costs. Unintended consequences of the intervention will also be explored, together with potential strategies used to deliver and support the intervention, and views from these individuals on how willing they would be to continue to support the delivery of the intervention and their reasons for this.

The Consolidated Framework for Implementation Research will be used to help guide the interview questions on perceived barriers and facilitators (i.e., factors) affecting the intervention's implementation. Consideration will also be paid to the COM- B model - we will specifically examine how 'motivated' and 'capable' stakeholders (including mothers and the wider stakeholder groups) feel they are to sign up and continue participating in the intervention (mothers) and to support the intervention (wider stakeholder group) and the 'opportunities' they feel they have to do this.

See Interview topic guide for further details on the questions asked. Focus groups and interviews will be recorded, and consent will be sought for this specific purpose.

9.9. Biological samples

9.9.1. Collection and transportation

Participants will be given the option to opt out of sample collection at any stage of the study. Samples will be labelled according to participation ID allocated at randomisation so that the samples will not be directly linked to any personal data.
Pre and post intervention saliva samples collected after session or at the NIHR/Wellcome King's Clinical Research Facility from mothers and babies will be collected using both the passive drool method, and absorbent swabs: Salivettes (mothers) or SalivaBio Children's Swab (babies). They will then be transported by one of the researchers in the team to the laboratory for storage, and used for measurement of cortisol, oxytocin, cytokines and other stress hormones.

Hair samples will be collected from mothers at the NIHR/Wellcome King's Clinical Research Facility after the last session. The samples will be transported to the Maurice Wohl Clinical Neuroscience Institute (King's College London, Denmark Hill).

Six saliva samples from mothers (and two samples from their baby, providing consent) will be collected by mothers at home at awakening, +15, +30+ and +60 min after awakening, at 12 noon and 8 pm, and used for diurnal cortisol and other stress hormones. Mothers will be provided with COVID-secure packaging materials in which to store, transport and post their collected samples. Once all samples for a given timepoint have been collected, they will then be posted or transported to the Maurice Wohl Clinical Neuroscience Institute (King's College London, Denmark Hill).

9.9.2. Storage and processing of samples

Hair samples will be kept at room temperature for short-term storage but will be transferred to -20ºC for longer-term storage, until analysis (cortisol and other stress hormones) is conducted.

Saliva samples will be stored at or below -20 degrees C until analysis. For the safety of researchers, all saliva samples will be processed in a COVID-secure way, as risk-assessed by laboratory health and safety teams. All samples collected will be clearly labelled as potentially COVID-positive, and any samples later realised to be COVID-positive will be destroyed according to standard laboratory protocols.

Samples will be processed, analysed and remaining material will be kept for 10 years after completion of the study. Results will be identified according to anonymised codes and stored securely.

Sample logs will be kept in order to maintain a record of collection and storage of samples. These logs will be kept until all the samples are destroyed.

9.10. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening);
- Significant protocol deviation (such as site logistics);
- Withdrawal of Consent.

If a participant withdraws from the study, data already collected with consent will be retained and used in the study, but no further data will be collected, or any other research procedures carried out on or in relation to the participant. The reason for withdrawal will be recorded in the CRF.

Lost to follow-up will be categorised as participants who cannot be contacted after 3 attempts.

9.11. Follow-up data collection

Upon termination of the 10-sessions, participants will be approached to take part in an optional focus group to explore their experiences of receiving the intervention. They will be contacted to complete follow-up questionnaires on weeks 19-21 and weeks 35-37 and a sub-group of women with specific risk factors for PND (traumatic birth, adverse childhood experiences, and social isolation/loneliness) will be asked to take part in an optional interview at week 20 to explore their experiences of PND and how singing intersects with the specific context of PND.

9.12. Definition of End of Study

The end of the study for all participants will be upon completion of the week 36 (completed within weeks 35-37) follow-up assessment or participant withdrawal, whichever happens first. The end of study will be defined as the submission of the end of trial report to the REC.

The participants randomised to the control group will be offered the singing programme after 10 weeks (not for trial purposes). The intervention group, once the programme is completed will not be offered continued provision of the singing sessions, but this is the same approach offered to all women who attend this programme outside the study; however participants will be given a list of other mother-baby, singing and support activities they can take part.

10. INTERVENTIONS

10.1. The intervention group

M4M is a 10-week intervention for mothers with PND. The programme will be delivered face-to-face in groups of 8–12 mothers in weekly sessions lasting one hour. Mothers will start a block of 10-week classes together and continue with the same group and leader for the duration of the course. Classes are free to attend and will take place in Children's Centres or other community venues (or online via Zoom) on weekday afternoons. Mothers will attend with their babies and will be invited to sit in a socially distanced circle on the floor surrounded by soft play cushions and mats. Classes will start with welcome songs, introducing the babies and mothers to one another, and then involve a range of singing and music activities. These will include learning songs from around the world, ranging from short vocal exercises that use "motherese" style noises and sound effects (including sound baths where the mothers sing a sustained note providing a relaxation technique), to simple lullabies that can be picked up very quickly and sung in basic harmonies or rounds, to longer or more complex songs that will be learnt gradually over the weeks. Songs will be a mix of relaxing in style, with mothers encouraged to hug or stroke their babies as they sing, to energetic, with mothers standing and moving with their babies and bouncing their babies in their arms. Mothers will be required to respect social distancing guidelines and keep their babies within their reach to avoid physical contact with other mothers or their babies.
Some songs will be accompanied by maracas, drums, hand chimes and other simple instruments that the mothers and babies can play together. Instruments such as guitar and ukulele will also be used for a small number of songs. Instruments will not be shared between the participants and will be disinfected before and after the singing sessions with a COVID-19 validated disinfectant.
Mothers will also work to write some of their own songs over the weeks, developing lyrics together about their babies or experiences of motherhood and creating simple melodies. Recordings of the group singing the songs together will be made and uploaded to private online platforms or onto CDs for the mothers to listen to at home. Classes will be led by professional workshop leaders trained by Breathe, with support of assistants.

10.2. The control group

Our control group will be an 'active' control. During the first 10 weeks (during the study period), mothers in the control group will receive details of other non-music classes available to them in the community (either in-person or online, depending on the programs available at the time and government guidelines) and will receive the same schedule of texts and phone calls to encourage them to join these activities. They will still be seen by the researchers to collect clinical measures and biological samples (including the pre-post saliva samples) and to monitor engagement in other activities. Following the first 10 weeks, the mothers in the control group will be offered a place on the singing programme, but these data will not be part of the study, and they will not join groups with other women who are in the study.

10.3. Schedule of contact

Upon enrolment, mothers receive details of the classes (according to randomisation group they are allocated to) and are supported to join via texts and phone calls using the following protocol: a team member from Breathe will call mothers in the week before the start of a block of 10-week sessions; the day before the delivery of the sessions, mothers will be texted with session details as a reminder. This message will also include a reminder not to attend, and to notify the team, if self-isolating or experiencing symptoms of COVID-19. If two or more sessions are missed, mothers will be contacted (via phone or text) to assess any issues that prevent them to attend the sessions. A similar protocol will be used to encourage women in the control group.

11. STATISTICS AND ANALYSIS

11.1. The Number of Participants

The above mentioned initial RCT (see 6.2) show that both singing and control women improved in depressive symptoms (EPDS scores) by the end of treatment (Week 10), but the singing group had a numerically larger improvement: -5.2 (SD=2.8) in the singing group and -4.25 (SD=3.2) mean in the care-as-usual group (effect size = 0.32). To have 80% of power (at $p<0.05$, two-tails) to detect the same effect size difference, randomising subject 2:1, we will need 232 subjects in the intervention and 116 in the control group (total = 348). We aim to recruit 400 mothers and their babies to compensate for a 12% drop-out rates.

In total 800 participants, 400 women plus 400 babies will be recruited for the intervention/control groups. Babies will be recruited with mothers as participants to the study, but for statistical purposes all data analyses will refer to either mothers or mother-infant dyads. In the event that mothers have twins, one of the infants will be chosen as study participants for the different assessments but all children under 9 months at time of recruitment will be invited to attend sessions.

11.2. Planned recruitment rate

Participants (mothers) are going to be recruited in blocks of 40-50 women and their babies, screened and assessed prior to a 2:1 allocation randomisation (mothers and their respective babies will be allocated the same group). This process will be repeated 10 times, aiming to reach 800 participants (400 mothers and 400 babies) in total.

Wider stakeholders will be recruited during the trial, aiming to reach 3 stakeholders for each group by the end of data collection.

11.3. Description of statistical analysis

Descriptive statistics of quantitative effectiveness and implementation survey data will be provided. Primary analyses for main outcome data (EPDS), including for the association between the primary outcome (changes in the EPDS total score) and implementation survey data will be analysed using linear mixed models at 6, 10, 20- and 36-weeks post randomisation. A two-level hierarchical model will be employed when all time points will be included as repeated measures in the model (6, 10, 20 and 36 weeks) to improve power and take into account clustering of the observation at patient and level. These models utilise maximum likelihood estimation and thus allow for missing outcome data under the missing at random (MAR) assumption. Associations between post-randomisation variables and missingness will be dealt with by multiple imputation (MI), again under the MAR assumption. Departures from this assumption will be assessed with a sensitivity analysis. Associations between secondary outcomes (e.g. PSI, HDRS) and implementation survey data will be assessed with a similar methodology for the primary outcomes, using generalized linear mixed models depending on the type of outcome (normal, binary, count). In addition, mediation analysis with the use of structural equation models will also be employed to understand the potential pathways in which implementation has an impact on the effectiveness. An implementation by treatment interaction will be included to allow the effect of implementation to differ at each arm of the trial. To address confounding factors, we will additionally run sensitivity analyses including the venue and size of group as covariates within analyses and, if models suggest it is necessary, run further cluster analyses to explore if site variations influence outcomes results. All analyses will be conducted in STATA V.15.1.

11.4. Description of qualitative analysis

The focus groups led by the research team from UCL at the end of session 10 (weeks 10-12), will capture general feedback from sessions and experiences from mothers in the groups, focusing on the lived experience of PND and how this intersects with experiences in the singing group.

Following these focus groups, mothers will be asked if they would also like to be involved in individual or small-group interviews with three sub-groups of women self-reporting particular risk factors for PND: traumatic birth, adverse childhood experiences, and social isolation/loneliness. Mothers will self-select if they feel they are eligible for any of these groups and participation will be entirely voluntary. These interviews will focus in-depth on the phenomenology of PND and how singing intersects with the specific context of PND among the sub-groups.

The interviews led by the implementation research team at KCL at the end of week 10 (weeks 10-12), will capture feedback from stakeholders (including mothers and 'deliverers', 'referrers' and 'supporters' of the intervention) on perceived factors affecting the interventions uptake, adherence to, and long-term sustainability and wider roll-out.

All focus groups and interviews will be audio recorded and transcribed by a UCL approved external transcription company. Transcripts will be anonymised before analysis. Focus groups will be analysed using thematic analysis and interviews/small groups will be analysed using Interpretative Phenomenological Analysis. All analysis will be conducted using NVivo 12. Coding and organisation of codes will be cross-checked within the research team to ensure validity.

11.5. Description of health economic methods

An economic evaluation will evaluate whether evidence garnered from the current hybrid trial combined with existing clinical and economic evidence of relevance would support the economic case for the scale-up of M4M to the wider PND population of Lewisham, Lambeth and Southwark. The analysis will focus on estimating the incremental resource and cost implications of scale-up and spread from an NHS/social care perspective. Cost-effectiveness will be evaluated within a cost-per quality adjusted life year (QALY) framework. This will enable an estimate of the expected incremental cost of scale-up per gain in population QALYs to be evaluated against currently accepted cost-effectiveness thresholds (e.g. those adopted by the National Institute for Health and Care Excellence) that are used to appraise the value of investing of NHS resources in new health care technologies.

A robust economic evaluation of scale-up of M4M will require an understanding of: 1. the clinical impact of the intervention and the extent to which this is translates into improved quality adjusted years of life lived (QALYs) over time for participating mothers; 2. the price that local commissioners might be expected to pay for the intervention; 3. the effects over time of M4M participation on the cost of other health and social care services utilized by participant mothers; 4. the size of the population who could potentially benefit from M4M across the three south London boroughs; 5. Implementation outcomes, including anticipated levels of reach within the target population; 6. The resource implications and "fixed" costs borne by local NHS providers arising from embedding M4M within the existing care pathway for PND.

Our analytical approach will use economic modelling based on decision analytic methods. A synthesis of the relevant clinical, economic, and epidemiological evidence generated from the current trial and from existing sources combined with evidence on implementation outcomes will be used attach values to key modelling parameters and to quantify uncertainty and risk around cost-effectiveness estimates. Primary economic data will collected as part of the current study to support the economic evaluation, including self-reported use of health and social care services by mothers, use of structured activity logs and templates to quantity resources allocated to implementation activities, and short-term (with-in trial) quality of life outcomes using the established EQ5D questionnaire.

A key element of the economic evaluation will involve a quantification of the decision-making risks of using an economic analysis of scale-up to inform commissioning choices. This is important given the inherent statistical uncertainty that will surround the clinical and economic evidence-base and uncertainty in evidence on implementation outcomes that will be used to model the cost-effectiveness of scale-up. The economic analysis will also require assumptions that will also carry a degree of uncertainty - for example as regarding the sustainability of clinical effects on PND symptomology and participant quality of life beyond the immediate period of study within a trial. Quantification of uncertainty and risk will deliver insight into whether it would be optimal for commissioners to delay scale-up and conduct further evaluative research to reduce uncertainty around key parameters driving the benefits and costs of scale-up, a combination of both, or whether immediate implementation would be warranted from a health economic perspective.

Data collection will be done in phone interviews sometimes face to face, depending on what is practical and the circumstances within project resourcing.

12. DATA MANAGEMENT

12.1. Data collection tools and source document identification

There will be a combination of carbon and electronic CRFs, depending on the method of data collection. For home visits, NIHR/Wellcome King's Clinical Research Facility visits and specific group sessions (baseline, week 6 and week 10), researchers may be present and carbon copies of the CRFs will be completed by participants. When researchers do not need to be present, electronic versions of CRFs will be completed by trial participants.
Carbon copies for the PIS, ICF, questionnaires and sample collection CRFs that will be transported to KCL (Maurice Wohl) for storage and data input into the trial's database as soon as possible. All self-reporting questionnaires at Baseline, weeks 6, 10, 20 and 36 will be completed online using a secure service (REDCap) and they will be accessible to the research teams only. If participants have not completed the online CRFs for the respective week before the session, researchers will bring blank copies of the CRFs to be completed after the sessions take place. If participants cannot access a computer/laptop and/or if they are in the control group, questionnaires will be posted to them.

PIS and ICFs will be kept and stored separately from other carbon CRFs. They will be stored in lockable cabinets so that source data with identifiable participant information (PIS and ICF) will be kept separately from CRFs.

Focus groups and qualitative interviews will be audio recorded using password protected encrypted audio recorders. Audio files will be password protected and stored in the Data Safe Haven (certified to the ISO27001 information security standard and conforming to NHS Digital's Information Governance Toolkit). Anonymised transcripts will be stored on a secure shared drive only accessible to the research team.

All data will be kept in line with the GDPR preserving the confidentiality of all participants taking part in the study (M4M participants and professional stakeholders). All data, including the surveys and interviews will be de-identified (i.e., all personally identifiable information will be removed), kept safe and secure on encrypted and password protected folders and storage media, and separate from the research data.

Participants will be reassured that the data collected will remain strictly confidential, and that it will be de-identified, so that they will not be identifiable unless via code-breaking (see above). Participants will also be assured that their comments and survey responses will not be attributable

to them by the trial team and/or intervention delivery team. Any published data will be devoid of person identifiable information.

Confidentiality will be strictly adhered to at all times, and personal information will be discussed only with those individuals who have a need or right to know, or/and in those situations where it is deemed necessary in order to ensure safety of the participant and their family/carers.

Anonymised data may be shared with collaborating research projects that have been scientifically and ethically approved, within and outside the EU. Consent will be sought for this purpose.

12.2. Access to Data

12.2.1. Person identifiable data

Access to person identifiable data will be restricted to the research team, including the clinical research team. The access will be restricted to the strictly necessary data for the purpose.
Access to person identifiable implementation science data will rest with the data custodian(s) from the immediate study team and the implementation science team. Since the project seeks to explore in some depth women's experiences and barriers and facilitators to implementation, it is important to maintain strict confidentiality and facilitate openness in the interviews and survey responses thus optimal data quality. No patient medical records will be accessed for this study.

12.2.2. De-identified research data

De-identified research data will be kept on the secured network drive of the data custodian(s) in linked anonymised form, so data is not immediately identifiable. Consent forms and other identifiable paperwork will be kept in locked cabinets only accessible to the study team. Study data will be kept in a separate location from the person identifiable information. Access to the de-identified research data will be shared with the study management group for the purposes of review, analysis and dissemination. Only de-identified data will be analysed.

12.3. Data Recording and Record Keeping

Focus groups and interviews will be audio-recorded with permission, as will videos for the CCI (CARE-Index), according to the optional consent given in the ICF. After each focus group/interview, the recording will be permanently removed from the device and transferred as soon as possible on to the secured password-protected university network drive or external encrypted and password protected drive by the researchers involved in collecting these recordings. Audio recordings from the focus groups and interviews with subgroups of women will be sent for transcription via a secure server to an external transcription company. Transcripts will be anonymised and any person identifiable information in the transcripts replaced by an unrelated sequence of characters. The audio recordings will be confidentially destroyed as soon as possible, and any direct quotes from transcripts in subsequent publications and reports will not be identifiable. Furthermore, transcripts will be destroyed upon data analysis completion.

Identifiable data (i.e. name, address, telephone number etc) collected before the baseline assessment will be deleted at the end of the study, unless the participant has ticked the box on the ICF stating they authorise KCL to retain this data, in which case it will be stored securely on KCL SharePoint for 10 years.

After the completion of the study, study data will be kept for the King's College London's standard retention period of 10 years after the completion of the study, after which it will be destroyed. The

study data that supports published results will be deposited in a secure data repository (e.g. KCL's data repository called KCL Research Data Management System, an interdisciplinary open data repository service maintained by KCL). This will allow the data to be accessible for future reuse as per King's College London's policy on the management of research data long-term.

12.4. Archiving

Archiving will be authorised by the Sponsor following the submission of the end of trial. The documents and trial database will be kept for 10 years after the completion of the study.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

14.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

14.3. Peer Review and Ethical Approvals

The project has been funded by the Wellcome Trust after anonymous peer-review.

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to King's College London research ethics service and the NHS Research Ethics Committee (REC). The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.4. Reporting

An End of Study notification and final report will be submitted to the same parties and data uploaded to clinicaltrials.gov.
Participants will be notified of the published results via a newsletter.

14.5. Participant Confidentiality

There will be no access to patient medical records. Participants will be assigned unique identification codes. All documents will be stored securely and only accessible by study staff and authorised personnel.

15. FINANCE AND INSURANCE

15.1. Funding

The study is being funded by the Wellcome Trust. Additional infrastructure resources will be provided by the NIHR Biomedical Research Centre at King's College London and South London and Maudsley NHS Trust.

15.2. Insurance

Insurance arrangements will be made to ensure that the Sponsor will be covered in case of potential legal liability for any harm that may occur to participants, trial team members, investigators or collaborators arising from the design, participation or management of research.

16. PUBLICATION POLICY

Study results will be submitted for publication within 12 months of the publishing of the Final Trial report. Participants will be notified of the outcome of the trial via newsletter.

16.1. Authorship guidelines

Authorship will be determined according to Vancouver Protocol.

17. SIGNATURES

Carmine M Pariante _____ 04/02/21

Chief Investigator Date

Print name

Daisy Fancourt _____ 04/02/21

Chief Investigator Date

Print name

_____ _____

Statistician (if applicable) Date

Print name

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