Online singing interventions for postnatal depression in times of social isolation: a single arm study

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Study Title:	Online singing interventions for postnatal depression in times of social isolation: a single arm study
Chief Investigators:	Prof Carmine Pariante (King's College London) & Dr Daisy Fancourt (University College London)
Other Investigators:	Prof Paola Dazzan (King's College London)
Sponsor:	King's College London
Funder:	Wellcome Trust

Chief Investigators Signatures:

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

KCL REC Number:	19659		
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1.1. Chief Investigators

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2. SYNOPSIS

Study Title	Online singing interventions for postnatal depression in times of social isolation: a single arm study	
Internal ref. no. / short title	SHAPER-PNDO	
Intervention	Experimental: A 6-week singing programme for mothers and their babies delivered online	
Study Design	Single-arm clinical trial	
Study Participants	Trial participants: New mothers with babies from 0 to 9 months post-birth with postnatal depression	
Planned Sample Size	120 new mothers with babies up to 9 months old	
Planned Study Period	January 2021- March 2022	
	Objectives	**Endpoints**
Primary: effectiveness	To reduce symptoms of postnatal depression in mothers	Psychological scale: Edinburgh Postnatal Depression Scale (EPDS)

3. REVISION HISTORY

Document ID	Description of changes from previous revision	Effective Date

4. ABBREVIATIONS

BDI	Beck Depression Inventory
CCI	Crittenden Child-Adult Relationship Experimental (CARE)-Index
CECA-Q	Child Experience of Care and Abuse-Q
CI	Chief Investigator
DOB	Date of Birth
eCRF	Electronic Case Report Form
EPDS	Edinburgh Postnatal Depression Scale
GP	General Practitioner
GSE-6	Short General Self-Efficacy Scale
HDRS	Hamilton Depression Rating Scale
ICF	Informed Consent Form
KCL	King's College London
M4M	Melodies for Mums
MPAS	Maternal Postpartum Attachment Scale
MSPSS	Multidimensional Scale of Perceived Social Support
ONS	Office for National Statistics Wellbeing Scale
PIS	Participant/ Patient Information Sheet
PND	Post-Natal Depression
PSS	Perceived Stress Scale
REC	Research Ethics Committee
SCID	Structured Clinical Interview for DSM-IV
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 (CIs) will be taken by Professor Carmine Pariante and Dr Daisy Fancourt. Sponsorship is provided by King's College London (KCL).

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]. While there are still no scientific publications on postpartum depression at the times of coronavirus, the concerns about increases in domestic violence during the lockdown [3], and the well-known effects of social isolation on perinatal mental health [4,5], both indicate an almost certain increase in postpartum depression over the coming weeks or months, as already discussed in the lay press [6,7].

However, challenges surround the fact that there is still no complete treatment solution for PND in general, let alone during social isolation and a pandemic. Although pharmacological treatments have 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[2,8–10]. 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[11].

There is also a growing body of evidence demonstrating the effects of community group singing on mental health[12,13]. 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[14–16]. 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[17]. 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 participants 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[18]. 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 averages 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[19]. 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[20]. 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[21].

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).

While we have funding to upscale this group intervention as part of the SHAPER-PND programme, funded by the Wellcome Trust, the recent lockdown has so far not only halted the delivery of the programme in its face-to-face format, but also prompted our interest in developing an online version of the intervention that can be used (1) if the requirement for social distancing over the near future, even when the lockdown is relaxed, makes impossible the delivery of the programme; and (2) to broaden our reach to a nationwide delivery and extending to a wider population that may not have been able to attend in-person sessions due to geographical constrains or severity of depressive or anxiety symptoms.

In support of our approach, research on the emotional impact of online (or "virtual") singing as part of a choir has shown a high degree of personal engagement even using quite primitive 'virtual' settings [22]. For example, a study by Dr Fancourt has shown that attending a 'virtual choir', where participants record their performances in their own individual physical localities and then the performance is combined and presented back in cyberspace, can lead to equivalent feelings of social presence to participating in live choirs: the participants feel a sense of "connection" to the other people who are doing the same activity, even if they do not know them, and feel and part of "a community" and of "something bigger" [22].

7. TRIAL OBJECTIVES AND DESIGN

7.1. Aims and outcomes

This single-arm clinical trial aims, in a period of 12 months, **to pilot and evaluate an online delivery of Melodies for Mums** with the ambition:

1) To develop a remote intervention that can become a mainstream therapeutic tool not only at times of social isolation and distancing, but also for mothers who cannot leave their houses (e.g. because of mental health difficulties or medical comorbidities) or who live in areas where the intervention is unavailable;

2) To create a separate control group to the original face-to-face intervention, as we are still aiming to deliver the original SHAPER-PND when we will be able to start again; and

3) To make the best use of the expertise and experience available within the researchers and artists community brought together by the Wellcome Trust funding for the SHAPER-PND study, at a time where the originally planned activities are on hold.

7.2. Clinical outcomes

Objectives	Outcome Measures/Endpoints
Primary Objective To assess the effectiveness of group singing interventions on symptoms of postnatal depression (Baseline, 3, 6, 16 and 32 weeks)	Symptoms measured before, during and after the intervention using the Edinburgh Postnatal Depression Scale (EPDS). The primary outcome measure is change in EPDS total score between Baseline and Week 6 (end of treatment).
Secondary Objectives - clinical	**Outcome Measures/Endpoints**
To assess whether singing improves further aspects of mental health	Structured Clinical Interview for DSM-IV Disorders (SCID-IV), 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 changes in stress mechanisms underpinning the psychological outcomes assessed	Cortisol from saliva samples
To explore the experiences, mechanisms of effect, barriers and facilitators to taking part in online singing groups	Qualitative interviews with a sub sample of 20-30 women and the intervention deliverers

7.3. Trial design

In light of the limitations imposed by the current pandemic, we aim to deliver the M4M programme using a virtual platform to replace the in-person singing sessions. To achieve this, we will deliver a more advanced version of a 'virtual choir' but keeping to the framework of the existing M4M programme; we take the learnings by Breathe Arts Health Research from their Breathe Sing group for individuals with respiratory conditions. Prior to lockdown, this group met fortnightly in-person to use singing to benefit physical and mental health. During the COVID-19 pandemic, this group has moved online and is continuing to have excellent uptake with weekly attendance numbers higher than when the group was delivered in-person. M4M online will take a similar format, consisting of weekly sessions of one hour each, where women connect via Zoom at the designated date and time, and sing from their home *while following the singing leader*. To avoid the inevitable problems with Wi-Fi delays and instability, all participants are muted at certain times in the session but can all hear the singing leader throughout. The singing leader will also use a backing track that will be recorded specifically to support online singing delivery, and that has other voices and harmonies included to amplify the experience of singing with others. An additional Breathe member of staff will support participants to set up the online connection before the session starts and help them troubleshooting during the session. All participants are also connected via a WhatsApp group (monitored by Breathe), and there will be a space at the beginning and end of

the sessions where all participants are unmuted and can chat with the artist or their peers, in an unstructured way.

M4M online will be delivered as a single-arm clinical trial, without a control group. Participants will be recruited in the community, mostly via social media and other signposting methods according to the usual procedures carried out by Breathe for recruiting into the face-to-face M4M programme but with enhanced advertisement and social media reach nationally. Before entering the study, mothers will be assessed by the research team, and if found eligible, will be allocated to a singing group for 6 weekly sessions. Participants will remain in the group allocated to them to allow greater sense of community and familiarity with the artist, facilitator, and the other participants. Participants will be regularly assessed by the researchers and if they give consent, will provide biological samples. Follow up will be carried out at 16 and 32 weeks, that is, 10 and 26 weeks after completion of the trial.

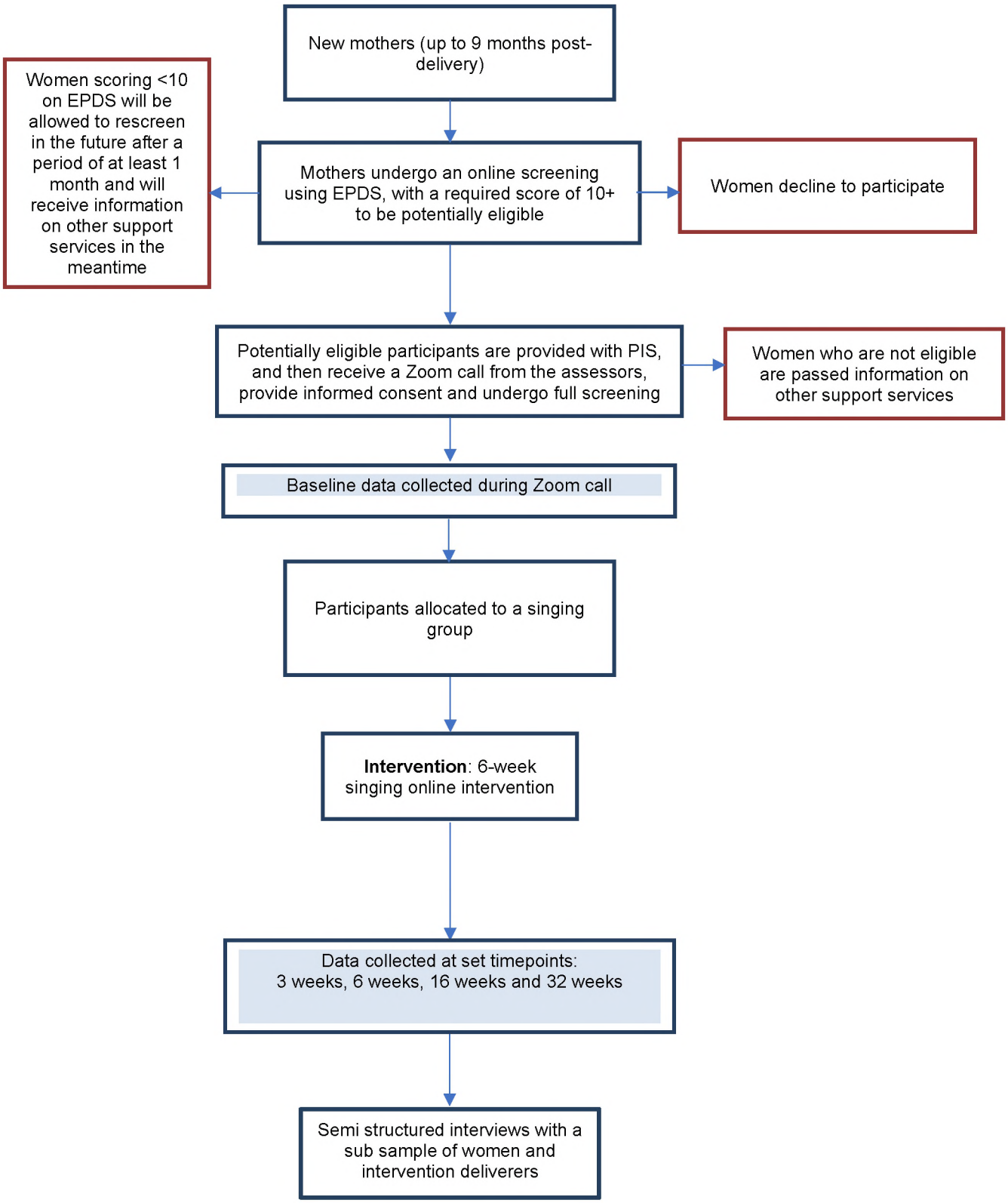
7.3.1. Team expertise

One of the CIs, Daisy Fancourt led the RCT on singing and postnatal depression, so has expertise in carrying out a large-scale clinical study with this population, using this intervention and a very similar data collection schedule. Two members of the team (Pariante & Dazzan) are perinatal 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 as well as online choir sessions, so have experience leading the sessions, recruiting the mothers, and handling relevant safeguarding issues.

8. STUDY DESIGN

This will be a non-randomised, single group trial using the following procedure:



Trial Setting

This is a single-centre trial that will be run online across the UK via the platform Zoom. In order to enrol a sufficiently large sample of women, there will be 4 blocks of the 6-week singing sessions in total. Women will be followed up at weeks 16 and 32.

8.1. Study Participants

8.1.1. Trial participants

Study participants will be new mothers with symptoms of postnatal depression defined as scoring 10 or above on the Edinburgh Postnatal Depression Scale (EPDS).

8.1.2. 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 EPDS, within two weeks of the start date of the intervention

8.1.3. 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
- Unable to access online sessions (i.e. internet connection, laptop or computer availability, etc.)

9. STUDY PROCEDURES

9.1. Recruitment and Informed Consent

9.1.1. Participants

Recruitment will be primarily done through:
- Posters and flyers in baby weigh clinics and other community and clinical centres for postnatal mothers and their babies, if lockdown rules allow that;
- Signposting via other health and social care professionals and in the community via email contacts;
- Social media and online forums
- Self-referral following general advertisement

Community services will be made aware of the study through a poster/flyer/e-mail campaign sent directly to them. Breathe has a database of contacts used to recruit for Breathe's Melodies for Mums in-person programme that will be used for this purpose.

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 first contact will be done by Breathe Arts staff over the phone, following social media/online self-referral/direct self-referral through posters and flyers in community and clinical centres. The

research team will only become involved once the potential participants have made contact with the Breathe Arts team, 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.

All potential participants will initially be directed to a pre-screening online form on Breathe's website. This will capture basic information including the mother's 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 trial in case their EPDS score is equal or higher than 10.

If a woman's EPDS score is lower than 10, she will receive a notification that she is not currently eligible to participate and will receive information on other support services in the meantime. 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, 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 when a new round of 6 singing sessions becomes available, the research team will arrange a call with potential participants to undertake the full screening interview against the inclusion/exclusion criteria outlined in section 8.1. This full screening will take place **in the 2 full weeks prior to the online classes starting (referred to as 'Baseline')**. If the participant is found to be non-eligible, they will be given information for other support services. If the participant is found to be eligible and has capacity to consent, the researcher will carry out the baseline measures. A contact point will be made available for participants in case they wish to ask further questions regarding the trial. If more women are found to be eligible for each 6-week programme than the sessions 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.

A copy of the ICF will be sent electronically to the participant once the baseline Zoom call has been arranged. The ICF will include a section detailing the samples to be collected (saliva) and others 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 9.7). A participant can opt out of the sample collections or babies' data collection and enter the trial for all other measures. 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.

9.1.2. Deliverers

During the course of the study, deliverers will be recruited by the research team from the pool of 1-3 artists trained by Breathe that deliver the Melodies for Mums sessions. We will approach deliverers of the intervention to ascertain their interest level in participating in our research study. Deliverers will be recruited to the study for the purpose of assessing the ways in which this 6-week online singing programme can ameliorate mothers' postnatal depression.

If deliverers express interest, we will provide them with the Deliverer participant information sheet, which will explain to them in better detail why we are interested in incorporating deliverer feedback on the programme into our study, and will explain what kind of information we are looking to collect from them. We will then electronically provide deliverers who are interested with the deliverer informed consent form to consent to their personal data being collected.

The ICF will explain that data will be collected and stored confidentially, and deliverers will have the option to opt-in to each consent point.

If deliverers consent to participation, the UCL researcher will arrange a Zoom call with them, during which we will interview them and collect feedback on how they felt the programme helped women's postnatal depression, with the aim to use their views and experiences to help inform upon the development of the programme.

9.1.3. Anonymisation – Participant IDs

Participants will be assigned a participant ID composed of letters and numbers to define the group and order of allocation (i.e first participant assessed to the first singing group: A-01).

9.2. Payment

Participants will be compensated with a £20 voucher to Love2Shop per timepoint assessment to compensate and thank them for their time. Participants will be emailed their vouchers upon completion of each research assessment.

9.3. 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 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[18].

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. 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.

Benefits
In light of the published data, participants are expected to improve their depressive symptoms by week 6 of the singing sessions. 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.

9.4. Monitoring and safety reporting

9.4.1. 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.

9.4.2. 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.

9.5. Protocol deviations and Serious Breaches to protocol

Protocol non-compliances such as changes to the delivery of the intervention will be reported first to the CI and then to the Sponsor.

9.6. Safeguarding

The research teams will have three safeguarding check points:

1. The UCL research team will check the EPDS scores of all participants as they come through online (that is, at baseline, 3, 6, 16 and 32 weeks) 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 research team thinks that the behaviour (or any responses to the questionnaires collected) of any participant during the online assessments or during any other contact (e.g. phone contact), is felt to be indicative that they are at immediate risk of harming themselves or their babies or others, the same process will be taken.

The clinical leads (the perinatal 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 72 hours of receiving the report. 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.

9.7. Assessments

Participants will be assessed via Zoom for baseline, week 6 and week 32 assessments. Week 3 and 16 assessments will be completed online by the mothers only, due to the self-reporting nature of the measures to be captured. It is expected that all mothers will have access to an internet-enabled device, as this is an essential inclusion criterion. For baseline online measures, participants will be encouraged to complete these a day either side of the first session. For week 3 measures, participants will be encouraged to complete these within 3 days of the 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 6, when the window will be weeks 6-8).

Individual qualitative interviews with a sub sample of women will take place after the final session of the intervention either by telephone or video call. Interviews will also be conducted with the intervention deliverers/singing group leaders. The interviews will explore the experiences, mechanisms of effect, barriers and facilitators to taking part and delivering online singing groups

Q=online questionnaire, Wk=week

		Baseline			Week 3		Week 6			Week 16	Week 32	
		Virtual assessment 1 (up to 2 wks before 1st session)	Q*	Session 1	Q*	Session 3	Virtual assessment 2 (up to 2 wks after 6th session)	Q*	Session 6	Q*	Q*	Virtual assessment 3 (wks 31-33)
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					

		Baseline			Week 3		Week 6			Week 16	Week 32	
		Virtual assessment 1 (up to 2 wks before 1st session)	Q*	Session 1	Q*	Session 3	Virtual assessment 2 (up to 2 wks after 6th session)	Q*	Session 6	Q*	Q*	Virtual assessment 3 (wks 31-33)
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												
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	5 min		x		x			x		x	x	

		Baseline			Week 3		Week 6			Week 16	Week 32	
		Virtual assessment 1 (up to 2 wks before 1st session)	Q*	Session 1	Q*	Session 3	Virtual assessment 2 (up to 2 wks after 6th session)	Q*	Session 6	Q*	Q*	Virtual assessment 3 (wks 31-33)
Support (MSPSS)												
BIOLOGICAL												
Diurnal saliva samples in mothers and babies[e]	5 min		x		x			x				
Pre- and post-session saliva samples in mothers and babies[e]	5 min			x		x			x			
QUALITATIVE												
Qualitative interviews with a sub sample of 20-30 women and the intervention deliverers (up to 2 weeks after the final session)								x				

*Questionnaires will be completed online by the mothers, ideally 3 days before or after the respective week sessions (1st, 3rd and 6th) or one week either side of the corresponding follow-up date (at 16 and 32 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 assessment.

[e]Salivettes absorbent swabs and SalivaBio Children's swabs will be provided to the mother before the 1st, 3rd and 6th sessions; samples to be collected by participants at home and posted by the participants using pre-paid postage materials provided by the researchers. All samples will be used to measure cortisol levels. Participants will be asked to collect diurnal samples up to 3 days prior or after to the session, and pre-/post-session samples on the day of the session. All samples for that time point can then be returned together, by post.

9.8. Biological samples

9.8.1. 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.

All saliva samples will be collected by Salivette absorbent swabs for adults and SalivaBio Children's Swabs for babies and used to measure cortisol levels. Mothers will be asked to collect samples to measure diurnal cortisol rhythm and cortisol reactivity to the sessions.

For diurnal samples, mothers will be asked to collect six saliva samples from themselves (awakening, +15, +30+ and +60 min after awakening, at 12 noon and 8 pm), and two samples from their baby (awakening and 8pm). Mothers will be asked to collect these samples up to 3 days prior to their session (baseline, week 3 and week 6), however, in order to allow flexibility in the schedule, a +/-5 day variation from session date will be accepted in the date of collection. We have extensively experience with this methodology and successfully collected such data before[23].

Mothers will also be asked to collect saliva samples from themselves and their baby immediately before and after their session (week 1, week 3 and week 6).

Mothers will be provided with pre-paid envelopes in which to return both diurnal and session samples together for each time point. All samples should be kept in the mother's fridge until ready to return by post.

9.8.2. Storage and processing of samples

Saliva samples for diurnal cortisol and pre-/post-session cortisol will be stored at the Maurice Wohl Clinical Neuroscience Institute at -20 degree C until analysis.

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.

9.9. Discontinuation/Withdrawal of Participants and Deliverers from Study

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

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening);
- Significant protocol deviation.

- Withdrawal of Consent.

If a participant or deliverer withdraws from the study, data already collected with consent will be retained if not requested to be deleted and will be used in the study analysis, 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 electronic case report form (eCRF).

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

9.10. Follow-up data collection

Upon termination of the 6 weekly sessions, participants will be contacted to complete follow-up questionnaires around weeks 16 and 32. An additional virtual assessment will be carried out around week 32. A sub sample of women will be invited to take part in a qualitative interview about their experiences of receiving the online intervention up to two weeks after their final intervention session.

9.11. Definition of End of Study

The end of the study for all participants will be upon completion of the week 32 (completed within weeks 31-33) 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.

Once the programme is completed, participants 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. INTERVENTION

10.1. The intervention

M4M online is a 6-week intervention for mothers with PND. The original M4M programme would be delivered face-to-face in groups of 8–12 mothers in weekly sessions lasting one hour. However, due to the current situation with COVID-19, we will therefore modify the original face-to-face intervention for this online study, as follows:
- Run groups of around 15-17 women to ensure that all participants can be visible on one screen during online delivery to create a stronger sense of community and connection
- Offer 6 weeks of intervention, also building on the evidence from the face-to-face intervention that by 6 weeks there is already a significant improvement in depressive symptoms compared with control interventions[24]
- Introduce a two-week lead-in period before the beginning of the six-session course, where mothers will be able to use WhatsApp and at least one (monitored) Zoom session to get to know each other.

Classes will start with a chat between mothers and the artist before the start of the singing session. The singing session will include 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 sang 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. Instruments such as guitar and ukulele will also be used by the artist for a small number of songs. 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 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. Schedule of contact

Upon enrolment, mothers receive details of the classes 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 6-week sessions; the day before the delivery of the sessions, mothers will be texted with session details as a reminder. If 2 or more sessions are missed, mothers will be contacted (via phone or text) to assess any issues that prevent them to attend the sessions.

10.3. Setting

This will be a single site study led by KCL and working with women and their babies across the country. The Sponsor is King's College London.

The intervention will be delivered by Breathe via the platform Zoom. In order to enrol a sufficiently large sample of women into this study, the 6-week blocks of singing classes will be run 4 times over a 12-month period.

11. STATISTICS AND ANALYSIS

11.1. The Number of Participants

The number of participants to recruit is defined by the maximum number of mothers that Breathe can place in an online singing session and the number of singing groups that logistically can be delivered in 12-months. There will be 4 groups in total of 30 participants each (split into two Zoom sessions), totalling to 120 participants recruited for the study.

11.2. Planned recruitment rate

Participants (mothers) are going to be recruited in blocks on 40-50 women, screened and assessed prior to enrolment. Each block of singing sessions will aim to have around 30 women divided into two sessions. This process will be repeated 4 times, aiming to reach 120 participants in total.

11.3. Description of statistical analysis

Primary analyses for this pilot study will be within-subject changes in the main outcome data (EPDS) using repeated-measures Analysis of Covariance. The within-person association between the primary outcome (changes in the EPDS total score) and secondary outcomes (for examples, changes in other psychiatric symptoms, in mother-infant interaction or in cortisol secretion) will be analysed using fixed effects regressions with data from 5 time points (baseline, 3-, 6-, 16- and 32-weeks post baseline). Missingness will be dealt with by multiple imputation (MI) under the missing at random (MAR) assumption. Departures from this assumption will be assessed with a sensitivity analysis using only available data. In addition, mediation analysis with the use of structural equation models will also be employed to understand the potential pathways in which changes in the secondary outcomes have an impact on the effectiveness. All analyses will be conducted in STATA V.15.1.

11.4. Description of qualitative analysis

Qualitative interviews with mothers receiving the online intervention 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. We will explore with both mothers receiving the intervention and those delivering the intervention, their experiences of receiving and delivering the intervention online, mechanisms of effect, barriers and facilitators to taking part.

All interviews will be audio recorded and transcribed by a UCL approved external transcription company (Way With Words). Transcripts will be anonymised before analysis. Interviews will be analysed using thematic analysis[25]. All analysis will be conducted using NVivo 12. Coding and organisation of codes will be cross-checked within the research team to ensure validity.

12. Data Management

12.1. Data collection tools and source document identification

De-identified research data will be kept on the secured network drive of the data custodians in linked anonymised form, so data is not immediately identifiable. All consent forms and other identifiable paperwork will be kept in electronic format in encrypted computers, and 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.

There will be a combination of carbon (if offices are available) and eCRFs, depending on the assessment: virtual assessment, self-reporting measures or biological samples. For the virtual assessments at baseline, weeks 6 and 32, the researcher will complete the questionnaire according to the participant's answer, either to a paper or electronic copy of the questionnaire. All self-reporting questionnaires at Baseline, weeks 3, 6, 16 and 32 will be completed online using a secure service (REDcap) and they will be accessible to the research team only. For biological sample collection, paper copies of the CRFs will be completed by participants and posted with the samples to the Maurice Wohl.

Paper CRFs will be stored in lockable cabinets so that source data with identifiable participant information (PIS and ICF) will be kept separately from other CRFs. Equally, electronic PIS and ICF will be kept in separate electronic folders to the folders where other eCRFs will be stored.

Audio files from the qualitative interviews will be stored in the Data Safe Haven (certified to the ISO27001 information security standard and conforming to NHS Digital's Information Governance Toolkit) and destroyed once data analysis is complete. 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.

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. Participants will also be assured that their comments and 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. Zoom calling

Zoom will be used as a platform of communications for delivery of the sessions and assessments. Zoom's comprehensive privacy policy (https://zoom.us/privacy) outlines the following data protection statements:

- Under EU's GDPR, Zoom is a "processor" of customer content and personal data and the customers are the data "controllers".
- Users' names, usernames, e-mail address and phone numbers are collected when a user accesses Zoom's services. These are used by Zoom to communicate with users.
- Cloud recordings, chat/instant messages, files and other information shared while using the service are stored in chat logs, video recordings are stored in Zoom's cloud or any other location specified by the meeting's host (if requested by the host/user).
- The system collects the IP address, MAC address, other device ID, type, operating system and other technical information to optimize experience in respond to request for support.
- The system also collects approximate location (nearest city) without tracking specific location.

The host of the Zoom calls will be Breathe (singing sessions) or the researchers (assessments) and only they will be able to record the call. Consent for the recordings will be sought from participants when they consent to the trial. For the videos of mother-baby interactions, instructions will be sent to the mothers ahead of the recordings. During the assessment call, instructions will be given to mothers to set up the layout of the room and interaction so that the video can be analysed by the researchers at a later date.

Video recordings of the singing sessions, assessments and mother-baby interactions will be de-identified and kept in in KCL's One Drive, accessible only by the research team via password-protected devices and backed up regularly. Videos of the singing sessions, since they may contain identifiable data, will be kept separately of the other videos where the participant ID will be used instead.

12.3. Record Keeping

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 authorised KCL to retain this data.

After the completion of the study, the anonymised study data will be kept for the King's College London's standard retention period of 10 years after the completion of the study. The study data that supports published results will be deposited in a secure data repository (e.g. Zenodo, an interdisciplinary open data repository service maintained by CERN, Geneva, where the data is stored in the CERN cloud infrastructure). 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.

Qualitative interviews will be audio recorded with permission. After each interview, the recording will be permanently removed from the device and transferred as soon as possible on to the UCL data safe haven as described in section 12.1. Audio recordings from the interviews will be sent for transcription via a secure server to an external transcription company (Way With Words).

Transcripts will be anonymised and the audio recordings will be destroyed following data analysis. Any direct quotes from transcripts in subsequent publications and reports will not be identifiable.

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, 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. Ethical Approvals

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

14.3. 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.

14.4. 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.

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

Chief Investigator	Date
Print name	
Chief Investigator	Date
Print name	
Statistician (if applicable)	Date
Print name	

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