Does "Mellow Babies" improve the psychosocial health of mothers and their children?
The Mellow Babies Trial

PROTOCOL

A UK Collaborative Trial funded by the NIHR PHR

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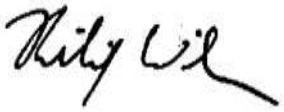
IRAS number:	235070

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above trial.

Prof Philip Wilson:  signature

Date: 13/09/18

Prof Graeme McLennan:  signature

Date: 13/09/18

VERSION HISTORY

Amendment no.	Protocol version no.	Description of changes (*incl. author(s) of changes*)	Date of protocol
	Version 0.1	New Document – content drafted - LT	18.05.2018
	Version 0.2	Amended based on comments from CRF nurses - LT	22.06.2018
	v 0.3	Amended PW	02.07.2018
	v 0.4	Amended LT	01.08.2018
	v 0.5	Amended LT	17.08.2018
	v 0.6	Amended in response to Sponsor comments. LT PW	13.09.2018
	v1	Amended in response to sponsor review LT	17.09.18
	v2	Amended in response to REC provisional opinion LT	23.11.18
	v3	Minor amendments to protocol. A sentence has been included in the 'Randomisation' section of the protocol HC – sponsor notified – PW signed	17.01.19

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PROTOCOL SUMMARY

Question addressed	Does Mellow Babies delivered to mothers who are anxious or depressed, along with their 6-18 month-old children, improve maternal mental health and the social, emotional and language development of their children at 8 months post randomisation and 30 months of age?
Considered for entry	Mothers with probable anxiety or depression and who have a child between 6-18 months of age
Inclusion/Exclusion criteria	***Inclusion criteria:*** (i) mothers aged 16 or over with principal caregiving responsibilities scoring ≥11 on the Hospital Anxiety and Depression Scale (HADS) Anxiety subscale (HADS-A) or ≥7 on the HADS Depression subscale (HADS-D) (ii) with a child who will be aged 6-18 months at the time of randomisation (iii) living in Highland Council region ***Exclusion criteria:*** (i) Current substance dependence (ii) Inability to complete questionnaires or participate in groups because of limited English language comprehension (iii) Child with learning difficulties sufficient to make outcome assessment impossible (iv) Mother has already participated in the trial (e.g., second eligible baby within life of the study)
Interventions	1. Mellow Babies 2. Usual Care
Outcomes	Primary: Maternal self-complete HADS at 8 months post-randomisation and when children are 30 months old.
Co-ordination	**Local**: by local research staff **Central**: by UoA research team at CRH (with support from Highland CRF and CHaRT in Aberdeen) (Telephone 01463 255xxx). **Overall**: by the Project Management Group, and overseen by the Trial Steering Committee and the Data Monitoring Committee.

GLOSSARY OF ABBREVIATIONS	
ADHD	Attention Deficit / Hyperactivity Disorder
AE	Adverse Event
ALSPAC	Avon Longitudinal Study of Parents and Children
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
EQ-5D	EuroQol Group's 5 dimension health status questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale – Depression subscale
HCRF	Highland Clinical Research Facility
HSRU	Health Services Research Unit
ISD	Information Services Division
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MB	Mellow Babies
NHS	National Health Service
NHSH	National Health Service Highland
NIHR	National Institute Health Research
NRES	National Research Ethics Service
NSS	National Services Scotland
PI	Principal Investigator
PHR	Public Health Research
PIL	Patient Information Leaflet
PMG	Project Management Group
PPI	Patient and Public Involvement
PCQ	Participant Cost Questionnaire
RCT	Randomised Controlled Trial
R&D	Research and Development
RA	Research Assistant
REC	Research Ethics Committee
RN	Research Nurse
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee
UC	Usual Care
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen
WoS	West of Scotland

TRIAL PERSONNEL
Chief Investigator

1 Philip Wilson

Grant Holders

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3	James Law	11	James McTaggart
4	Louise Marryat	12	Hugo van Woerden
5	Jing Shen	13	Clare Simpson
6	Graeme McLennan	14	
7	Angus MacBeth	15	
8	John Norrie	16	

Trial Office Team (UoA)

1	Chief Investigator (CRH)	7	Trial statistician (CHaRT)
2	CHaRT Director (CHaRT)	8	Quality Assurance Manager (CHaRT)
3	Senior Research Fellow (CRH)	9	Programmer (CHaRT)
4	Trial Manager (Research Fellow - CRH)	10	Research assistants (CRH)
5	Senior Trials Manager (CHaRT)	11	Trial secretary (CRH)
6	Senior IT Manager (CHaRT)		

Project Management Group (PMG)
This Group is comprised of the grant holders along with representatives from CRH and CHaRT.

Trial Steering Committee (TSC) Members
The membership of this Committee comprises independent members along with the Chief Investigator (CI) (Phil Wilson) or a nominated delegate. The other Mellow Babies Trial grant-holders and key members of the Trial Office team (e.g. the trial manager) may attend TSC meetings.

Data Monitoring Committee (DMC) Members
This Committee is comprised of independent members, and the trial statistician contributes as appropriate. The CI and/or a delegate may contribute to the open session of the meetings as appropriate.

1. INTRODUCTION

1.1 Background

Many long-term studies, particularly birth cohorts (1), have identified factors associated with poor mental health later in life. These may be:

- genetic (e.g. vulnerability to attention deficit / hyperactivity disorder (ADHD) or autism)
- antenatal (e.g. maternal stress hormones, smoking and alcohol consumption)
- located in the family/upbringing (e.g. postnatal depression, harsh or inconsistent parenting, parental discord)
- located in the wider environment (relative poverty, neighbourhood problems).

These factors may interact in different ways. Some factors may increase resilience to adversity: in particular there is a likely protective effect of positive parent-infant interaction against childhood psychological problems (2-6): secure infant-parent attachment, itself associated with resilience (7, 8) may be one mediating factor.

Early childhood social, emotional and behavioural problems are associated with increased risk of a wide range of poor outcomes associated with substantial cost and impact on society as a whole. Furthermore, childhood language, social and behavioural development predict long-term health. For example, early conduct problems predict antisocial behaviour, psychopathic personality traits, psychiatric problems, substance dependence, large family size, financial problems, work problems, and drug-related and violent crime at age 26 (9). Participants in the 1958 British birth cohort who were rated by their teachers as being in the highest quartile for emotional and behavioural problems had doubled mortality by age 46 years compared with the lowest quartile (10). ADHD predicts problem substance use (11) and smoking (12); and language delay predicts mental health problems at age 7 (13) and at age 34 (14). There is marked overlap between disorders of language development and psychopathology (15-18). Recent work (19) suggests a stable association between behavioural problems and pragmatic language impairments across childhood. It is thus essential to consider language and social, emotional and behavioural difficulties together. There is evidence for 'critical' or 'sensitive' periods in language acquisition, social-emotional development and behavioural regulation (20), so it appears reasonable to investigate ways to offer effective support early to families who most need it.

Parental emotional well-being is a major determinant of a child's social and emotional development (21, 22). Our work with data from the Growing Up in Scotland cohort (3, 4) and Avon Longitudinal Study of Parents and Children (ALSPAC) cohorts (2, 5, 6, 23, 24) demonstrates strong associations between parental mental health, parenting behaviours and children's psychiatric outcomes. The association between postnatal depression and child psychopathology has been long established (25) but the relationship between poor parent-child interaction and poor outcomes is probably stronger (26), and treatment of depression alone may be inadequate to achieve improvement in child outcomes (27). Interventions designed to improve both parental mental health and the parent-child relationship are thus likely to optimise benefits in terms of child development and are potentially valuable public health interventions (28).

<u>Effective interventions</u>

There are a number of systematic reviews of trials of group-based parenting programmes focussed on problem behaviours exhibited by children (29, 30) and one such review supported by the NHS National Institute for Health Research Public Health Research committee (NIHR PHR), focussed on the role of parenting programmes in reducing social inequality is in progress (12/3070/04). Other PHR studies have a focus on interventions aimed at families where there is a high risk of maltreatment (11/3007/01 & 11/3002/01). There is little doubt that group-based parenting interventions for preschool children with conduct problems can be highly effective and cost-effective in preventing later conduct disorders but such programmes have not been shown to be effective with younger children, where enhancing parental sensitivity is likely to be a more appropriate therapeutic aim than helping in management of challenging behaviour.

There are a number of small trials of parenting interventions with young preschool children, reporting impact upon parental sensitivity (31, 32) and attachment (33) and a number of useful systematic reviews and meta- analyses in the field (34-38). Barlow's 2012 Cochrane review of postnatal parenting interventions designed to improve child emotional and behavioural adjustment (39) identified no eligible trials with families whose children had a mean age of less than two years though a recent review of parent-infant psychotherapy (38) presented equivocal findings.

Our meta-analysis of the impact of the Mellow Parenting programmes (40) showed medium effects on maternal wellbeing and child behaviour problems, but there was a degree of heterogeneity and methodological weakness amongst the included studies. Overall the evidence to date supports the view that there may be beneficial effects of group parenting programmes both on parental mental health and child wellbeing in the early years.

1.2 Rationale for the trial

Problems in children's early social and emotional development are likely to have major long term consequences for the individual and society; parental emotional well-being is a major determinant of a child's social and emotional development (21, 22). Our work with data from the Growing Up in Scotland (3, 4) and ALSPAC cohorts (5, 6, 23) demonstrates strong associations between parental mental health, parenting behaviours (24) and children's psychiatric outcomes. Interventions designed to improve both parental mental health and the parent-child relationship are thus likely to produce substantial benefit in terms of child development and are potentially valuable public health interventions. (28)

As far as we are aware, this will be the first definitive trial of a postnatal group-based parenting programme specifically designed for mothers with psychosocial difficulties who have children aged under two years, although we are aware of ongoing Incredible Years for Babies studies (NIHR PHR-13/93/10; clinicaltrials.gov NCT01931917) and one on Circle of Security (clinicaltrials.gov NCT02497677).

Proportionate universalism. "*Focusing solely on the most disadvantaged will not reduce health inequalities sufficiently. To reduce the steepness of the social gradient in health, actions must be universal, but with a scale and intensity that is proportionate to the level of disadvantage. This is called proportionate universalism*" (41).

Universal provision of parenting programmes is unlikely to be cost effective (42-44), and our meta-regression using data from the Triple P programme suggests that targeted programmes are more likely to be worthwhile (45). This trial focuses on families with need directly assessed by health visitors (HV), social workers, GPs and paediatricians. This approach contrasts with trials of interventions spanning the antenatal and postnatal periods (eg Family Nurse Partnership (FNP)) which are generally delivered on the basis of demographic risk factors. Although FNP (as Nurse Family Partnership) has shown good outcomes in the USA, the recent large scale RCT in the UK failed to show improvements in the main outcome variables. We have already demonstrated that most mothers with psychosocial distress (and most children with language or behaviour problems) do not have high demographic risk (15, 46) and other work in Glasgow has demonstrated that many risks emerge over the first year of a child's life (47). Interventions based on demographic risk factors are thus likely to be delivered to many who do not need them while many who do need them are not entitled to receive the intervention. Health visitors are ideally placed to address these deficits in policy which can most easily be explained in terms of the ecological fallacy: usual care (UC) offered by HVs should be a proportionate universal intervention. In this study, UC will be augmented in the intervention arm through the offer of Mellow Babies to the more vulnerable families in the caseload of HVs and other health and social care professionals.

Recent pilot work

There are recently established norms for two of our major outcome measures among 420 children aged 30 months (15): the Strengths and Difficulties Questionnaire (SDQ) and Sure Start Language Measure (SSLM). Their predictive validity for psychiatric disorder, global developmental delay and language disorders 1-2 years later is good, with areas under Receiver-Operating Characteristic curves >0.8. (48) Vocabulary check lists equivalent to the SSLM have been shown to predict school readiness.

This proposal builds on a large number of before-and-after evaluations of Mellow Babies (Mellow Parenting for children under 18 months) as well as a small scale waiting list trial. The intervention is fully manualised and has been delivered to many thousands of families: we consider the intervention sufficiently mature to merit a definitive trial. We have been running a small exploratory trial with highly vulnerable mothers in Northern Ireland and have recruited and retained a high proportion of those women who were approached.

2. TRIAL AIM AND OBJECTIVES

This trial aims to establish whether MB delivered to mothers who are anxious or depressed, along with their 6-18 month-old children, improves maternal mental health and the social, emotional and language development of their children at 8 months following randomisation and at 30 months of age.

Specific objectives are:
To compare MB plus usual care with usual care alone in respect to:
Primary Outcome:

- Anxiety and depression of the mother on the Hospital Anxiety and Depression Scale (HADS) at 8 months post-randomisation and when the child is 30 months old

Secondary outcomes at 8 months post-randomisation:

- Brief Infant-Toddler Social and Emotional Assessment (BITSEA)
- SSLM
- Description of participants' service use and out of pocket expenses
- Maternal health-related quality of life (EQ-5D-5L)

Secondary Outcomes at 30 months:

- Child social and emotional development: Total Difficulties scale of the Strengths and Difficulties Questionnaire (SDQ) reported by the mother and subscale scores
- Language production: Sure Start Language Measure (SSLM)
- Directly assessed cognitive, social and emotional functioning: Bayley III Scales of Infant and Toddler Development with Behavior Observation Inventory
- Directly observed positive and negative parenting behaviours
- Within-trial cost analysis of participants' service use and out of pocket expenses
- Maternal health-related quality of life (EQ-5D-5L)
- Cost-consequence analysis of the MB intervention vs usual care

Longer term outcomes (school age and beyond):

- Model-based analysis of long-term efficiency of the MB intervention
- We shall inform participants of intention of later linkage to educational and NHS routine data

Process measures/secondary aims:

- Which eligible mothers agree and which decline to participate in the intervention, and what reasons do they give?
- How do effects on the child and mother at 30 months relate to:
    - level of participation in MB?
    - group composition?
    - changes in parenting behaviours?
    - maternal mental state at baseline and 8m post -recruitment?
    - child cognitive abilities
- What is the nature of usual care offered to participants?
- How do participants describe their experience of participating in MB, which elements of the intervention are considered most influential, and is participation stigmatising?
- Are there family characteristics associated with greater adherence to, and efficacy of, MB?
- How are the features (in terms of process and outcomes of care) of MB valued by mothers?
- What contextual factors facilitate or hinder delivery of, and engagement with, MB?

3. TRIAL DESIGN

This is a single centre randomised controlled trial comparing the Mellow Babies group-based parenting programme (MB) plus Usual Care with Usual Care alone for anxious or depressed mothers of children aged 6-18 months.

3.1 Intervention being evaluated

Mellow Babies (MB) is a group for mothers who are having difficulties in their relationship with their baby. The groups look at mothers' feelings of wellbeing (depression, anxiety, stress, etc). It also looks at the way mothers interact with their baby and aims to improve both. The MB programme involves attendance on 14 consecutive weeks within school hours and there is a reunion 1-3 months later. Groups can be offered at weekends, and transport (or transport cost), meals and a crèche are provided. MB aims to enhance close parent-infant attunement directly using a combination of video feedback and hands-on practice in baby-massage, interaction coaching and infant-focussed speech. Video material of mealtime interactions is shared, (34) and mothers are encouraged to discuss solutions to parenting difficulties. The MB programme has been used widely throughout the UK and internationally: over 2,000 practitioners have been trained and many thousands of families have participated. It has been used with women suffering postnatal depression and other social and psychological difficulties (49) and retention figures are high, even among those facing the greatest adversity.

Our pilot work found that video and audio recording for fidelity monitoring is unacceptable. Practitioner logs and records from supervision sessions will be used for this purpose.

The interventions will be carried out by experienced staff from a range of professional backgrounds who have worked with groups and who have received training in the MB intervention. The training to be provided to these staff lasts for three days. A key component of the MB programme is the need for expert supervision of the group facilitators by a psychologist. These supervision sessions, lasting 2 hours, will be provided monthly (i.e., three during the 14 week course of each group) by the Mellow Parenting organisation for all participating personnel, generally by Skype or videoconference, following strict confidentiality procedures.

Prior to the start of a Mellow Babies group, the group facilitator will visit the mother and child at home on at least one occasion. During one of these visits a video of a mealtime will be made for later use in the group, and key interactions in the video will be discussed on a one-to-one basis in preparation for the group. This video recording will be completely separate from that made by the research nurse at the baseline visit. It is important that the research and intervention elements are kept entirely separate, and that participants are reassured that the video taken by the group facilitator is only for use in the group intervention and will not be shared beyond that forum. The different uses of the video recordings will be clearly explained by both the research nurse at recruitment, and the Mellow Babies group facilitator at the pre-group home visit.

Comparison

All families will be offered Usual Care: the trial arms will be differentiated by whether or not MB is made available. Usual care will include normal care from the health visiting team and from the general practitioner, and in some cases a social worker or paediatric team. Where required, referral to additional services (hospital-, local authority- or third sector-based services) will take place. The nature of usual care (UC) will be varied, and could include simple practical support (helping mother at home) and advice (suggesting behaviour management strategies), individual psychotherapeutic support such as cognitive behaviour therapy, pharmaceutical intervention such as anti-depressant medication, assessment and intervention in child behaviour problems. The full range of types of UC and potential impact will be explored within the process evaluation.

Although UC is potentially complex and could include other parenting interventions, we have consulted with HV and GP colleagues and it is clear that restricting usual care to families in either arm of the trial would be considered unethical. Currently standard care would include scheduled HV visits at 8 months, 13-15 months and 27-30 months but with no formal assessment of maternal or child mental health (50). Following these visits HVs use their professional judgement to decide whether to revisit or to refer onwards to other services. Around 15- 20% of all families receive additional unscheduled visits between 12 and 30 months, and the proportion is likely to be higher

in participants eligible for this trial. Patterns of visits to GPs for support vary between families but we have recently published papers based on routine data (51) and on parent-reported data from the Growing Up in Scotland (GUS) cohort (52). Typically a family will consult a GP 3-4 times per year with a child between 13 and 30 months: in the GUS study, 6.1% of families reported using a GP and 17.8% a HV for information about children's behaviour in the third year of life. It is noteworthy that the control arm of the recently published evaluation of the Family-Nurse Partnership (53) received eight more HV visits than the intervention arm.

We intend to characterise the nature of usual care at the first follow up contact (8 months post randomisation) through a brief questionnaire to the HV and to the parent. We shall also review GP and health visitor records when the child is 30 months old to assess use of primary and secondary care services and the nature of any therapeutic interventions.

4. TRIAL RECRUITMENT

4.1 Trial population

Anxious or depressed mothers with principal caregiving responsibilities who have a child between 6 and 18 months living in the Highland Council region (where 34% of the population are in the urban centre of Inverness, and a further 35% within an hour's drive). Potential participants will be identified by HVs, GPs, social workers or paediatricians. Referred mothers will be asked to complete the HADS (54) by telephone, found to be a useful method in similar studies (55, 56). We aim to recruit families where the maternal score on the HADS exceeds either 10 on the Anxiety subscale or 6 on the Depression subscale, corresponding to the 85th centile for the UK female population (57).

We aim to recruit 212 families to achieve evaluable data on 170. This represents around 4% of families with children of 6-18 months in the area during the recruitment period. Given the strong health service and local authority management support for this trial, recruitment of around 3 families per week should be achievable. We calculate that the standard deviation of the total HADS score in this population will be approximately 7 points: in a normative population female sample the mean score is 10 points and SD 6 points (57). In a study using HADS as an outcome measure in a population similar to our proposed sample, mean change scores were 8.13 (SD 6.61) (58). The final sample size of 170 will give us 90% power to detect an effect size of 0.5 in the maternal HADS, corresponding to approximately 3 points. Although a Minimal Clinically Important Difference has not been clearly stated for the HADS (59), 3 points is likely to represent a clinically significant reduction based on the results of the Livingstone et al trial (58).

4.2 Inclusion and exclusion criteria

Inclusion criteria:

(i) mothers with principal caregiving responsibilities scoring $\geq$11 on HADS-A or $\geq$7 on HADS-D
(ii) with a child who will be aged 6-18 months at the time of randomisation
(iii) living in Highland Council region

Exclusion criteria:

(i) Current substance dependence
(ii) Inability to complete questionnaires or participate in groups because of limited English language comprehension
(iii) Child with learning difficulties sufficient to make outcome assessment impossible
(iv) Mother has already participated in the trial (e.g., second eligible baby within life of the study)
(v) Mother under 16 years

4.3 Identifying and approaching participants

Referrals will be made by health visitors, social workers, GP or paediatricians with concerns about the relationship between a mother and her child aged 6-18 months.

The referrer will briefly describe the Mellow Babies Study to the mother and ask her to complete an Expression of Interest (EoI) form including her preferred contact details to be passed to the Study's Research Nurse (at the Highland CRF). We will also allow a form of self-referral, where practitioners provide a study flyer (including the EoI form) to potential participants and they may contact the Study's Research Nurse directly. We also plan to use social media to publicise the study and include contact information for the CRF research nurse who is taking referrals to the study.

The Research Nurse will telephone the mother to seek permission to send her the Patient Information Leaflet and a Consent for Screening form. She will also make an appointment to call back and run through the HADS questionnaire within the following week (where feasible). Repeated attempts will be made where appointments are not kept, for up to one month, or if the baby reaches 18 months of age (and therefore moves out of eligible range).

4.4 Screening for eligibility

The CRF Research Nurse will contact the mother at the agreed time and run through the HADS with her. The HADS scores will be automatically generated within the eCRF so the Research Nurse can let potential participants know their score right away. If she scores above threshold on either subscale ($\geq$11 HADS-A; $\geq$7 HADS-D) the Research Nurse will then check the other eligibility criteria. If the mother is still interested in taking part, arrangements will be made for obtaining informed consent and baseline measures.

4.5 Informed consent

The Research Nurse will visit the mother at a pre-arranged mutually convenient time at her home. At the home visit the study's Participant Information Leaflet (PIL) will be discussed and the mother's questions answered. Then, if the mother wishes to proceed, written informed consent to participate in the trial will be obtained. Baseline measures will be taken either at this initial visit or at a subsequent visit according to the mother's preference. This will include completing questionnaires and taking a video of a mealtime or other interaction between the mother and child (although the video aspect is optional). Consent will be sought for contact details to be collected for two informants who would be likely to stay in touch with participating mothers, so that they could be contacted if tracing proves difficult during follow up. These informants will be sent a 'best contact' letter describing the intended use of their information and giving the opportunity to opt out.

4.6 Randomisation and allocation

The RN will use the online randomisation service (provided by the Trial Office) to randomise the participant, after the consent / baseline home visit. A random element will be incorporated into the randomisation algorithm. Eligible and consenting participants are randomised to either the intervention (MB) or control (UC) group using the proven 24-hour web-based application hosted by CHaRT. The Research Nurse will contact the mother, by telephone, and inform her of the randomisation result. The Chief Investigator, Co-Investigators and administrative staff will be blinded to the randomisation result. We shall use a minimisation design to reduce imbalance between groups in terms of maternal age (<25; $\geq$25 years), deprivation (working household yes/no) and age of child ($\leq$12 months; >12 months).

The maximum time allowable from randomisation to intervention commencement will be 3 months or if the baby reaches 18 months of age before the next available group commences. If a participant reaches 3 months of waiting time and her baby is still younger than 18 months (and the mother is still keen to participate), the HADS will be re-administered to confirm eligibility.

4.7 Code break/Emergency unblinding procedures

There is no requirement for emergency unblinding procedures. This is because knowledge of whether a participant is in the control or intervention group will not alter any management decisions should an adverse event occur.

4.8 Administration arrangements post recruitment

The Clinical Research Nurses in the Highland CRF will be responsible for the following:

- Notify the referrer and GP (if consent given) in writing that a participant has consented to participate in the Mellow Babies Study and their randomisation result. A summary of the trial will be included on the back of the GP letter.
- Enter trial data regarding the participant into the study website secure data portal.
- Maintain trial documentation at site.
- Return a copy of the signed consent form to the CRH.
- Ensure the signed informed consent form is filed within the Investigator Site File (kept electronically on the trial website and any paper copies within the CRH)
- Provide a point of contact for participants and Mellow Babies Intervention facilitators.

We intend to produce a yearly Newsletter for participants and collaborators to inform everyone of progress and maintain enthusiasm.

5. OUTCOME MEASURES

5.1 Primary outcome measure

Maternal self-complete HADS (54) at eight months post randomisation and when children are 30 months old.

5.2 Secondary outcome measures

At 8 months post-recruitment:

- Maternal HADS
- SSLM
- Brief Infant-Toddler Social and Emotional Assessment (BITSEA) (60-62)
- Caregiver accounts of the experience of interventions
- Participants' service use and out of pocket expenses
- Mothers' quality of life as measured by EQ-5D-5L
- Positive and negative parenting behaviours during a videoed family meal using the Mellow Parenting Observational System (MPOS) (2).

At 30 months of age:

- Social and emotional functioning as measured by the total difficulties scale of the maternally-reported SDQ (63) at age 30 months (15). We have recently published work on the predictive validity of the SDQ at this age (48).
- Emotional, conduct, hyperactivity/inattention and peer relationship problems, and prosocial behaviour (SDQ subscale scores).
- Expressive language performance in the 50-word Sure Start Language Measure (64) (SSLM).There is a substantial overlap between language delay and psychopathology (13, 15). We have recently reported excellent predictive validity for language disorder and global cognitive impairment (48). Parent completion questionnaire.
- The Bayley III Scales of Infant and Toddler Development (65) including Behavior Observation Inventory. Assessment by research assistant with some input by parental caregivers.
- Positive and negative parenting behaviours during a videoed family meal using the Mellow Parenting Observational System (MPOS) (2).
- Within-trial cost analysis of participants' service use and out of pocket expenses
- Cost-consequence analysis of the MB intervention vs usual care
- Mothers' quality of life as measured by EQ-5D-5L
- Satisfaction with intervention / usual care

Objective assessments will include the Bayley III scales at 30 months. Raters blinded to allocation will assess mealtime videos.

6. DATA COLLECTION AND PROCESSING

6.1 Measuring outcomes

Table 1 (below) summarises required research activities and visit timepoints. Further details about collection of outcome data are provided elsewhere in this section.

Table 1

Contact	Screening Telephone	Consent Home Visit	Baseline Visit *(may be combined with Consent Visit)*	6-monthly intervals	(Intervention arm) MB Intervention wks 1-14 1 day weekly	8 mths Post randomisation	Child 30 mths	End of Study
Consent	✓	✓						
Maternal HADS	✓					✓	✓	
BITSEA			✓			✓		
SSLM						✓	✓	
SDQ							✓	
EQ-5D-5L			✓	✓		✓	✓	
Bayley III							✓	
Socio-demographic questionnaire			✓					
Video interaction			✓			✓	✓	
Maternal account of service						✓	✓	
Participant Cost Questionnaire						✓	✓	
Attend Mellow Babies Intervention				✓	✓			
Contact with study results								✓

6.2 Baseline

Baseline measures will be the HADS (taken at screening stage), the Brief Infant-Toddler Social and Emotional Assessment (62) (BITSEA), the EQ-5D-5L and a video of parent-child interaction during a mealtime obtained from those families who will accept it, all administered by Highland CRF Research Nurses along with a brief demographic questionnaire. The demographic questionnaire will record ethnicity, age at leaving school, educational qualification level, employment status, socioeconomic status, household composition, substance use, obstetric history, social support (including partner support), and views on parenting support and confidence.

6.3 Follow-up

Participants are contacted by phone, post or email as appropriate. In case of non-attendance at follow-up appointments or non-return of questionnaires, attempts are made by Highland CRF staff or staff at UoA CRH Research Office to trace the participant directly using these means, through previously provided contacts or indirectly by contacting the GP.

To maintain contact throughout the trial, the study office will contact families on the birthdays of participating children by sending a card and a small gift (eg a small teddy bear with a study logo).

All participants will be offered a £10 voucher for completion of each follow-up visit.

Visit at 8 months Post Randomisation

The lead CRF Research Nurse will contact the mother and arrange for a home visit with the UoA Research Assistant. Required at this visit are a maternal HADS (Hospital Anxiety and Depression Scale), SSLM (Sure Start Language Measure), BITSEA (Brief Infant-Toddler Social and Emotional Assessment), maternal quality of life (EQ-5D-5L). In addition the Bayley III Scales of Infant and Toddler Development including Behavior Observation Inventory Assessment will be done (by the UoA Research Assistant) with some input by parental caregivers.
If the mother has consented, a video of the mother and child together will be recorded (in a caregiving situation, ideally a mealtime).

The Participant Cost Questionnaire will be completed to ascertain service use and any out of pocket expenses.

Visit when Child is 30 months of Age

The lead CRF Research Nurse will contact the mother and arrange for a home visit with the UoA Research Assistant. Required at this visit are a maternal HADS, SSLM, Strengths and Difficulties Questionnaire (SDQ) and maternal EQ-5D-5L assessments. In addition the Bayley III Scales of Infant and Toddler Development including Behavior Observation Inventory Assessment will be done with some input by parental caregivers.

If the mother has consented, a video of the mother and child together will be recorded (in a caregiving situation, ideally a mealtime).

The Participant Cost Questionnaire will be completed to ascertain service use and any out of pocket expenses.

End of Study

Participants will be contacted when the results of the study are published and provided with a summary of the results and publication details.

6.4 Change of Status/Withdrawal procedures

Study participants may choose to withdraw from the study intervention at any point without having to provide a reason. They are asked to consider if they wish to remain in the trial and be followed up as per trial schedule. All data collected will be retained and used in the study analysis unless the participant specifically withdraws consent for it to be retained. Participants may also withdraw or be withdrawn for clinical reasons. All changes in status with the exception of complete withdrawal of consent means the participant is still followed up using routine data.

Participants who do not attend for follow-up assessment but for whom any outcome data are available are included in an intention to treat analysis.

6.5 Data recording and processing

RNs or UoA Researchers will enter locally collected data into the eCRF. Staff in the Trial Office work closely with Highland CRF RNs to ensure the data are as complete and accurate as possible.

The electronic data capture system (eCRF) is validated, maintains a full audit trail of data changes, is secure (requiring unique user names and passwords), and has regular back-up within the University of Aberdeen servers. Participants have a unique participant identification number that allows identification of all data reported for each participant.

Access to the study websites where data are held is password protected. Site staff with access to the study website can only access the records for their own participants. Staff in the trial

office (CRH and CHaRT), as well as the senior RN in the Highland CRF, can access records for all participants. All Investigators and study site staff involved with this study must comply with the requirements of the General Data Protection Regulation (or subsequent legislation), with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Computers used to collate the data will have measure to limit access via user names and passwords. The study website data portal has limited access measures via user names and passwords. Staff at sites only have access to participant data for participants at their site. Within the study website, identifiable data are stored with a strong encryption algorithm (currently the key used is AES_256). Participants will be identified using a unique participant identifier.

CHaRT will transfer collected economic data in anonymised format to the study health economist (Dr Jing Shen) at the University of Newcastle for further analysis when required.

6.6 Long term follow-up

We plan to seek funding to follow-up participants (mothers and their babies) in the longer term using data from NHS and other government central registries. For example, we may seek to examine future use of health and social care services, or educational attainment of children. Any linkage of research data to health, social, education or criminal justice system data will be done confidentially within the NSS national safe haven (or relevant local safe haven). We shall inform participants of this intention at the outset of the trial, but in line with recent GDPR changes, we will not seek informed consent as very specific information on the nature of the linkage to be done would be needed up front precluding using novel datasets if/when they become available. Also, proxy consent obtained from parents could not be considered valid indefinitely/over the time period that linkage based follow up may be conducted as children grow up and attain competence. Therefore, any future linkage would be done on the legal basis of 'public task' rather than consent.

7. SAFETY

The Mellow Babies trial adheres to Good Clinical Practice guidelines on safety reporting in clinical trials. Mellow Babies is a non-drug trial and so participants will not receive medicinal products, although they will attend and participate in group programmes, one-to-one support and research interviews. There are structures in place for group practitioners and researchers to follow should incidents relating to the safety of participants, others in their household or staff themselves take place during group sessions or fieldwork. Where there is a health risk or medical emergency, appropriate procedures will be followed including alerting emergency services, GPs or social work services as appropriate. Incidents of this nature will always be reported to the Trial Manager who will inform the Chief Investigator (CI). All practitioners and researchers are trained in these procedures.

We will abide by the lone worker policy for Highland CRF. This means that no member of research staff, either employed by UoA or the CRF will attend participants' homes alone (for consent and data collection purposes). A member of staff in the CRF has been identified as the second worker who will attend all home visits with the research nurse or UoA research team member. If this person is unwell or otherwise unavailable on the day of a home visit, another member of the research team will be asked to attend, or the appointment rescheduled.

8. EMBEDDED PROCESS EVALUATION

8.1 Process evaluation: overview

Qualitative and quantitative data will be collected for a process evaluation. This will address the following secondary research questions:

- Which eligible mothers agree and which decline to participate in the study, and subsequently the intervention, and what reasons do they give?
- How do effects on the child and mother at 30 months relate to:
    - level of participation in MB?
    - group composition?
    - changes in parenting behaviours?
    - maternal mental state at baseline and 8m post -recruitment?
    - child cognitive abilities
- What is the nature of usual care offered to participants?
- How do participants describe their experience of participating in MB, which elements of the intervention is considered most influential, and is participation stigmatising?
- Are there family characteristics associated with greater adherence to, and efficacy of, MB?
- How are the features (in terms of process and outcomes of care) of MB valued by mothers?
- What contextual factors facilitate or hinder delivery of, and engagement with, MB?

8.2 Qualitative process evaluation: Data collection

Observation (N=1): the one group facilitator training course will be observed. ***Group facilitator self-complete questionnaires*** (N~8) will be administered with all facilitators pre-training (T1), immediately post-training (T2), again prior to delivery of their first intervention (T3) and following 12 months experience delivering the interventions (T4). ***Group facilitator semi-structured interviews*** (N=~8) will be conducted with all the MB practitioners at T1 and T4. ***Referring practitioners semi-structured interviews*** (N=6) will be conducted with six key professionals involved in referring women to the trial, to explore their experiences of identifying suitable women (and views on vulnerable groups). ***Protocol adherence checklists*** will be completed by practitioners at the end of every session, as well as ***participant attendance records***. ***Mother questionnaires*** (N=212) will be administered with all mothers after consenting and again at both follow-up points. ***Mother structured phone interviews*** (N=~60) will be conducted once only with each of a sub-sample of MB participants shortly after attending a MB session in order to check fidelity of delivery. These checks will be focused on those sessions most challenging to deliver. Our pilot work has indicated that video and audio recording for fidelity monitoring purposes is unacceptable to participants. ***Mother in-depth interviews*** (N=24) will be conducted pre- and post-intervention with a sub-sample of 16 intervention mothers, and post-intervention with 8 control mothers, selected to represent a range in terms of vulnerability, age, parity, and relationship status. There will be capacity to conduct <4 further in-depth interviews with mothers in response to emerging issues identified from monitoring data or preliminary research, e.g. difficult group dynamics or particularly problematic sessions. Similarly, we will conduct fewer than 24 interviews if a point of saturation has been reached.

8.3 Quantitative process evaluation: Data collection

Monitoring information will be gathered throughout the study. This will include dates of intervention groups, which groups have been attended by which practitioners, where the interventions take place, the uptake of supervision sessions per practitioner, and group attendance by participants.

8.3 Process evaluation: Data analysis

For the process evaluation, qualitative data will be transcribed (where necessary), coded and summarised systematically by charting according to key themes of implementation, mechanisms and context. Analysis will address the objectives set out above, and emerging hypotheses tested according to all the relevant data. Analysis of the qualitative data will start as soon as possible after collection so that emerging themes can be addressed in subsequent data collection. In order to minimise bias in interpreting qualitative process data we intend to document preliminary answers to the key process evaluation questions prior to analysing the outcome data by arm of the trial. It is anticipated that the process findings will generate hypotheses to explore using outcome data (e.g. are substantial variations in programme implementation between sites associated with different outcomes? (note that sample size is only likely to reveal trends)) and

vice versa (e.g. can variations in outcomes between sites be explained by differences in implementation or institutional contexts, or can variation in outcomes between different kinds of participants be explained by qualitative data on their engagement with the programme?).

9. SAMPLE SIZE AND PROPOSED RECRUITMENT RATE

9.1 Sample size

We plan to recruit 212 participants, aiming to obtain evaluable data on 170. Randomisation will be 1:1. A sample size of 85 per group will give us 90% power at 5% significance to detect an effect size of 0.5. This corresponds to a score of around three points on the HADS, which is likely to represent a clinically significant improvement (58). We shall use a minimisation design to reduce imbalance between groups in terms of maternal age (<25; ≥25), deprivation (working household yes/no) and age of child (≤12 months; >12 months). In terms of secondary child-based outcomes, we shall have approximately 80% power to detect an effect size of 0.4 at 5% significance after adjusting for baseline covariates. We have allowed for 20% attrition which is broadly in line with clinical and evaluation experience, and several design features (e.g., telephone collection of outcome data) will increase follow up rates.

9.2 Recruitment rates

We expect to recruit 2-3 families per week (10.6 per month). We have proposed a stop-go point at study month 8 related to recruitment rates. We will aim to have 70% of our targeted number of participants recruited at that stage (n=40) and to have established at least two intervention groups. Study month 8 will be 5 months into a 20 month recruitment period, and allows us to make a stop-go decision prior to recruiting the research assistant in month 15.

See Appendix for Gantt chart to describe recruitment projections and trial milestones.

10. STATISTICAL ANALYSIS

The statistical analyses will be governed by a comprehensive Statistical Analysis Plan (SAP) authored by the study statistician in the study data centre at CHaRT (a registered NIHR CTU) at the University of Aberdeen, and overseen by Professor Graeme MacLennan, an experienced medical statistician and trialist, and agreed by the independent oversight committees (the TSC and the iDMC).

The principal analysis will take place at the end of the study on the 30 month primary outcome. We shall adhere to the intention to treat principle, and use a statistical model appropriate to the design. The primary outcome is a continuous measure, and we shall use a normal theory multilevel mixed model using a GEE algorithm to compare the two randomised groups. We shall adjust for pre-specified baseline covariates, including the baseline measurement of the outcome, and fit therapy group as a random effect in the active group to adjust for this source of clustering (66). By adjusting for the design covariates (and other pre-specified baseline predictive factors) we should be able to recover lost power due to clustering effects (for example, if the increase in sample size required was 5% to allow for the clustering just in the intervention group, that would require a correlation between the baseline covariates and outcome of just over 0.2; for 10% it would be just over 0.3). The estimation of the treatment effect will therefore be fully consistent with the design used. The statistical analyses of the economic data will follow the same principles.

The SAP will also specify similar models will be used for the secondary outcomes appropriate to their distribution (including logistic regression for binary outcomes and negative binomial for count data). The SAP will also contain details of a limited number of pre-specified subgroup analyses – however, these will be exploratory since the study is not formally powered to address them, and we shall conduct them at a stricter level of significance ($p<0.01$) to avoid over interpreting the data through multiple comparisons. All other analyses will use a statistical level of significance at the conventional $p<0.05$.

Given the nature of the population and the intervention, we are anticipating some withdrawal and loss to follow up. Although we shall use evidence based strategies to minimise the level of attrition,

it is important in addition to such design / conduct strategies to have analysis strategies to assess how robust the findings are to any remaining attrition. The mainstay of our approach to these missing data will be a multiple imputation strategy under an assumption of missing at random, using likelihood based models, along with extensive sensitivity analyses (67). We shall also explore non-ignorable missing data mechanisms using pattern mixture models.

11. ECONOMIC EVALUATION

A formal economic evaluation will include a within-trial cost analysis, a cost-consequence analysis and a long term modelling exercise. The cost analysis will establish the cost of the intervention compared to standard care within the trial follow-up. The cost-consequence analysis will consider and present all possible costs and benefits associated with the intervention. The long term modelling will examine long term benefits and costs of the intervention.

11.1 Economic analysis

Within-trial cost analysis: The within-trial cost analysis will take a societal perspective to include costs that fall on the service provider (councils in this case), other relevant service providers (for example, social services or the NHS) and the affected mothers and their families. These costs will be presented for each cost generating area and overall. Costs of the intervention will be obtained from trial documentation and in consultation with intervention providers. The intervention costs will include staff cost for delivering the intervention, MB staff training cost, venue hire cost for hosting MB group sessions, psychologists' time cost, costs of consumables and reusable equipment required to deliver MB interventions, as well as costs of transport, meals and crèche provided for the attendees. The cost for the intervention group will be apportioned into a cost per attendance for each group with the cost per participant being the cost per attendance multiplied by the number of attendances for each participant. Costs of the usual care includes costs of current care to affected mothers provided by health visitors and general practitioners, and also the cost falling on other services (hospital-, local authority- or third sector-based services) through referrals. The costs of other use of health and social care services will be collected on the case report form (CRF) and a participant costs questionnaire (PCQ) developed specifically for this study. The PCQ will be designed to also include participants' out-of-pocket expenses during the trial's follow-up period, and the questionnaire will be collected every 6 months. These data will be combined with study specific unit costs or unit costs from publicly available standard sources (as listed below) to produce a total cost for both the intervention and control groups. Unit costs for healthcare services will be obtained from standard sources such as NHS reference Healthcare Resource Group (HRG) tariffs, the British National Formulary (68) for medications. Unit costs for personal and social care will be obtained from NHS National Services Scotland Information Services Division (ISD).

Within-trial cost-consequence analysis: Not all of the benefits of the MB intervention can be combined and represented within a single measure, so we shall conduct a cost-consequence analysis to include all possible costs and benefits of the intervention that not only fall on the health and social services, but also the wider society, such as the education sector. The within-trial cost analysis will provide costs information on the intervention both within and beyond the health sector. The potential benefits will be obtained based on information from the process evaluation, expert opinion as well as a literature search. Apart from changes in the child and maternal outcomes (listed in Section 9), there are likely to be wider benefits. These might include educational benefits for the affected mothers and their families, family bonding, increased social cohesion between the stressed mothers and their partner, and potential reduction of inequalities between socioeconomic groups, as well as better educational outcomes for the children involved. Those benefits may come about as a result of bringing affected mothers out of isolation into a group environment, increasing the interactions between mothers and their children and other family members, and helping them learn more about their problem, which may lead to enhanced family cohesion, and equip them with the knowledge and skills for continued improvement after the MB programme. The affected mothers are more likely to come from disadvantaged backgrounds, and by improving those mothers' mental states and their children's developmental outcomes, it is likely to lead to a reduction in inequalities between socioeconomic groups. Improvements in children's speech and

language skills and emotional outcomes will also likely to lead to better educational outcomes when they enter school. We shall also collect EQ-5D-5L data from mothers at baseline, every 6 months and at the end of the trial to capture potential improvement in maternal quality of life.

A sensitivity analysis will be undertaken to explore all possible variations of outcome measures, as there might be different estimates available for the wider benefits, depending on the characteristics of the patients, service providers and other relevant factors (e.g. source of reference) based on expert opinion. With the costs data, we shall present point estimates as well as confidence intervals for the different estimates. All relative changes in the outcomes will be included in the cost-consequence analysis with the results presented as a balance sheet. (69) The cost-consequence analysis is particularly useful in evaluating public health interventions as different decision makers can place their own weights on the different benefits and costs when all outcomes are presented separately.

Model-based analysis: It is possible that the intervention may lead to long-term benefits to society beyond the trial's follow-up period. Additionally, a longer time horizon will provide more time for the effects to accrue and potentially offset the initial costs of the intervention. The long-term benefits of the intervention are likely to include costs saved as a result of conduct and emotional disorders avoided, avoided criminal justice proceedings, reduced needs for special educational services, reduced mental health service use, and reduced productivity loss of parents and improved quality of life. To examine the long term efficiency of the MB intervention, a Markov model or other appropriate modelling approach chosen during the study will be used to extrapolate from the short-term trial outcomes into the longer term. The model will adopt a time horizon until the study children reach age 18 (or other appropriate time frame determined by the quality of data available to be decided during the project), where costs and effects (as measured by, for example, SDQ, SSLM scores) up to 30 months will be based on trial data and costs and effects (long-term benefits that go beyond the healthcare sector) in the remaining years will be based on evidence from the literature and data from the Growing Up in Scotland cohort through the application of econometric models. Parental outcomes as measured by EQ-5D-5L and HADS will also be incorporated into the model where quality data are available. A probabilistic sensitivity analysis will be undertaken to allow presentation of the level of variance around outcome measures. Deterministic sensitivity analyses will be combined with the probabilistic analysis to test for the effect of assumptions and variability, such as an exploration of changes in discount rate. Distributions will be attached to parameters where appropriate, and the shape and type of distribution will depend upon the data available. The output of the model will be presented as point estimates of costs, effectiveness, incremental costs, incremental effectiveness, and incremental cost per unit change in effectiveness at age 18. Results will be presented as an extended version of the cost-consequence analysis on a balance sheet, and be presented alongside the within-trial cost-consequence analysis result to provide both short-term and long-term efficiency of the intervention.

Long-term outcome forecasts for individual outcomes of interest, such as maternal mental and physical health, and the child's educational achievement, will be presented separately as well as being incorporated into the models described above.

12. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 Trial office in Inverness (UoA CRH)

The Trial Office is in the Centre for Rural Health (CRH), based within the Centre for Health Science, Inverness, and part of the University of Aberdeen. CRH will be supported by the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen. Together they provide day-to-day support for the clinical centre (the Highland CRF), and roles and responsibilities will be clearly marked as either CRH or CHaRT. The Trial Manager (CRH) takes responsibility for the day to day transaction of trial activities, for example approvals, site set-up and training, oversight of recruitment and follow-up rates etc. The Highland CRF organises all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal), liaising with the Trial Manager weekly. Both the Trial Manager and Highland CRF will receive clerical support from the Trial Secretary (CRH).

As per CHaRT's business and costing model, CHaRT base staff include the CHaRT Senior IT manager who will oversee all IT aspects of the study, while the CHaRT Senior Trials Manager will provide mentoring and guidance to the RF and advice to the team on generic coordination issues. The programmer will create, maintain and update all applications programmes for the trial, including the randomisation application and all administrative and analysis databases. The trial statistician will develop the statistical analysis plan and undertake the trial analyses. The CHaRT Quality Assurance Manager will provide guidance and advice to the team on CHaRT quality assurance and regulatory activities.

The Trial Office team meets formally at least monthly during the course of the trial to ensure smooth running and trouble-shooting.

12.2 Local organisation in sites

The Highland CRF will be responsible for recruitment of participants, arranging home visits for informed consent and baseline data collection, entering baseline data to the eCRF / secure data portal of the trial website, and liaising with the Trial Manager (CRH) on a regular (at least weekly) basis. The Trial office will coordinate recruitment, follow-up, and data collection. The Trial office will enter follow-up data to the eCRF / secure data portal of the trial website. Participant study data will be collected and recorded on study specific Case Report Forms and then entered onto a remote web-based data capture system. The study web portal will be the fulcrum of all trial documentation and facilitate communication between study personnel. The CI, study staff, research nurses, and CHaRT personnel will have undertaken ICH Good Clinical Practice training.

CHaRT will transfer collected economic data in anonymised format to the study health economist (Dr Jing Shen) at the University of Newcastle for further analysis when required.

A trial-specific delegation log is prepared, detailing the responsibilities of each member of staff working on the trial.

12.3 Project Management Group (PMG)

The study will be supervised by a Project Management Group (PMG). The chair of this group will be the CI and will consist of grant holders, representatives from the Study Office and CHaRT, and a representative from the advisory group of service users. The PMG will meet monthly for the first six months and last six months and every 2 months in between. In addition, the PMG will also meet at the annual Trial Steering Committee meeting. The participant advisory group will be formed within the first 3 months of the study and liaison will be managed by LT (with support from the RF). The schedule of meetings will be decided by the group, but are likely to be in line with PMG meetings for the first year and at key stages in the project (see Gantt chart).

12.4 Trial Steering Committee (TSC)

An independent Trial Steering Committee (TSC) will be convened. The role of the TSC is to monitor and supervise the progress of the trial. The membership will consist of an independent chair, together with at least two other independent members, and the Chief Investigator, a patient representative/service user and the National Head of Service for NSPCC Scotland. Other members will include the grant holders. Observers may also attend, as may other members of the Project Management Group (PMG) or members of other professional bodies at the invitation of the Chair.

12.5 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) oversees the safety of subjects in the trial. The DMC Charter documents the terms of reference of the DMC and the names and contact details and is filed in the TMF. The Committee meets regularly to monitor the trial data and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial. CHaRT has adopted the DAMOCLES Charter for DMCs. An independent DMC will be formed and agree its charter, and in light of the trial sponsor's risk assessment decide whether it needs to continue to meet.

The DMC will have an independent chair, and if it continues, will monitor accumulating trial data and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or closure of the trial.

13. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

13.1 Research Governance

CHaRT is a fully registered Clinical Trials Unit with particular expertise in running multicentre RCTs. The trial is run under the auspices of CHaRT based at HSRU, University of Aberdeen. This aids compliance with Research Governance and the principles of GCP, and provides centralised trial administration, database support and statistical analyses.

The CI ensures, through the TSC and Sponsor, that adequate systems are in place for monitoring the quality of the trial and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the trial. CHaRT SOPs are followed.

All research staff have been trained in GCP prior to commencing work on the trial. The Research Fellow and Research Assistants have not yet been employed, but will be given GCP training within the first two weeks of their posts commencing. The Mellow Babies practitioners will receive training in the intervention on 10-12th October 2018, and will attend GCP training provided by NHS Highland in November 2018.

13.2 Data protection

Data collected during the course of the research is kept strictly confidential and accessed only by members of the trial team, and may be looked at by individuals from the Sponsor organisation or NHS sites where it is relevant to the participant taking part in this trial.

Participants are allocated an individual trial number. Participants' details are stored on a secure database under the guidelines of the EU GDPR 2018. The CHaRT senior IT manager (in collaboration with the CI) manages access rights to the data set. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses.

The CI and study staff involved with this project will comply with the requirements of the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. The HRA recommended wording to fulfil transparency requirements under the GDPR for health and care research has been included in the PIS.

13.3 Sponsorship

The University of Aberdeen is the sponsor for the trial.

14. ETHICS AND REGULATORY APPROVALS

The East Midlands - Nottingham 1 Research Ethics Committee (REC) has reviewed this trial. The trial is conducted according to the principles of GCP provided by Research Governance Guidelines. Annual progress reports, end of Trial declaration, and a final report are submitted to the Sponsor and the East Midlands - Nottingham 1 REC within the timelines defined in the regulations.

14.1 Protocol compliance and amendment

The Investigators will conduct the trial in compliance with the Protocol given favourable opinion by the Ethics Committee. Any amendment to the project is approved by the Sponsor and funder before application to REC and R&D, unless in the case of immediate safety measures when the Sponsor is notified as soon as possible. Any deviations from the Protocol will be fully documented using a breach report form.

15. QUALITY ASSURANCE

The trial is monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of ICH GCP, and all other appropriate regulations. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate to the risk assessment of the trial. Investigators and their host institutions are required to permit trial related monitoring and audits to take place by the Sponsor and/ or regulatory representatives, providing direct access to source data and documents as requested.

15.1 Risk assessment

The risk to participants and researchers in this study is low. Some potential risks are detailed below, along with our assessment of potential harms and the steps taken to minimise these.

Participation in the research

Our quantitative data collection procedure consists of completing repeat questionnaires with trained researchers; all of whom have undergone criminal background checks and have significant experience of working with vulnerable groups. Whilst the questions being asked are well established and are not known to be problematic, it is possible that respondents may become upset whilst completing the questionnaires. All researchers will receive training in how to handle participant distress, and will follow NHS guidance relating to patient confidentiality and protection, including vulnerable adult and child protection procedure, at all times. All researchers will have access to the contact details for the women's health and social care professionals and will be able to contact them should they become concerned about women participating in the study. All researchers will carry a "useful contacts" sheet that can be used to signpost the women to relevant services should they request information about services. In the event of participant distress occurring, researchers will be asked to complete an incident report form outlining the steps taken. The same risks are present in conducting qualitative interviews with participants. All interviewers will have experience conducting qualitative interviews and working with vulnerable populations, and will follow the procedures outlined for dealing with distress that have been previously outlined.

Participation in the intervention

Since we will be working with vulnerable women, some activities such as being asked to reflect upon past experiences may have the potential to cause distress. However, we believe that this risk is minimal as the intervention is designed to reduce stress through positive action and the development of coping strategies.

In addition, the group facilitators will have undergone training to work with this group of women and will be able to provide empathic support and direct the woman to appropriate services when necessary. The group dynamics may help to reduce stress/distress to participants by providing a supportive and considerate atmosphere in which issues can be discussed. This will be laid out in the group rules and will be carefully monitored by the group facilitators. Additionally, the interventions will be delivered by trained facilitators who will be able to provide pastoral support and signposting to services should women require additional support.

The delivery of MB within a group setting carries a risk that participants might choose to discuss issues raised with others outside of the group setting. As the focus of the group sessions is more on activities and active discussion rather than disclosing personal histories, we believe the risk of this occurring is low. Nevertheless, to promote respect and confidentiality amongst participants the intervention facilitators will work with them to establish group rules about confidentiality, especially in relation to social media. In addition, the bringing together of vulnerable participants may result in the formation of positive or negative group interactions and social networks.

Group facilitators will adhere to NHS guidance relating to patient confidentiality and protection, including vulnerable adult and child protection procedure, at all times and report any concerns about participants to both the Mellow Babies Trial Manager and their line manager University of Aberdeen Centre for Rural Health.

Access to routine services

Participation in the research will not affect women's access to standard health and social care. The research team will ask permission from the women to notify their GP and/or other relevant

health/social care worker of their participation in the research. All of the women will be told during the consent process that if a significant risk of harm to themselves or their baby/child(ren) is identified, the research team will notify their GP and/or other relevant health/social care professional(s).

An independent risk assessment has been carried out by the Sponsor.

16. FINANCE AND INSURANCE

The trial is funded by a grant awarded by the NIHR Public Health Research programme. The necessary trial insurance is provided by the University of Aberdeen.

17. END OF TRIAL

The end of follow-up for each participant is defined as the final data capture on that individual. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the Sponsor and REC within 90 days, or 15 days if the trial is terminated prematurely. If terminated prematurely, the Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved, if appropriate.

A summary report of the trial will be provided to the Sponsor and REC within one year of the end of the trial. An end of trial report is also issued to the funders at the end of funding.

18. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Clinical data are entered into the database by the designated team members, together with data from completed questionnaires. Questionnaires returned by post to the trial office are entered there. Staff in the Trial Office work closely with local team members to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks further enhance the quality of the data.

The study documents will be archived in line with the Sponsor's archiving SOP. All essential data and documents (electronic and hard copy) are retained for a period of at least 10 years after close of trial according to the funder requirements and relevant Sponsor and CHaRT archiving SOPs. Electronic data will be archived by UoA.

19. AUTHORSHIP AND PUBLICATION

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the PMG.

Once the main trial findings have been published, a lay summary of the findings will be sent to all involved in the trial.

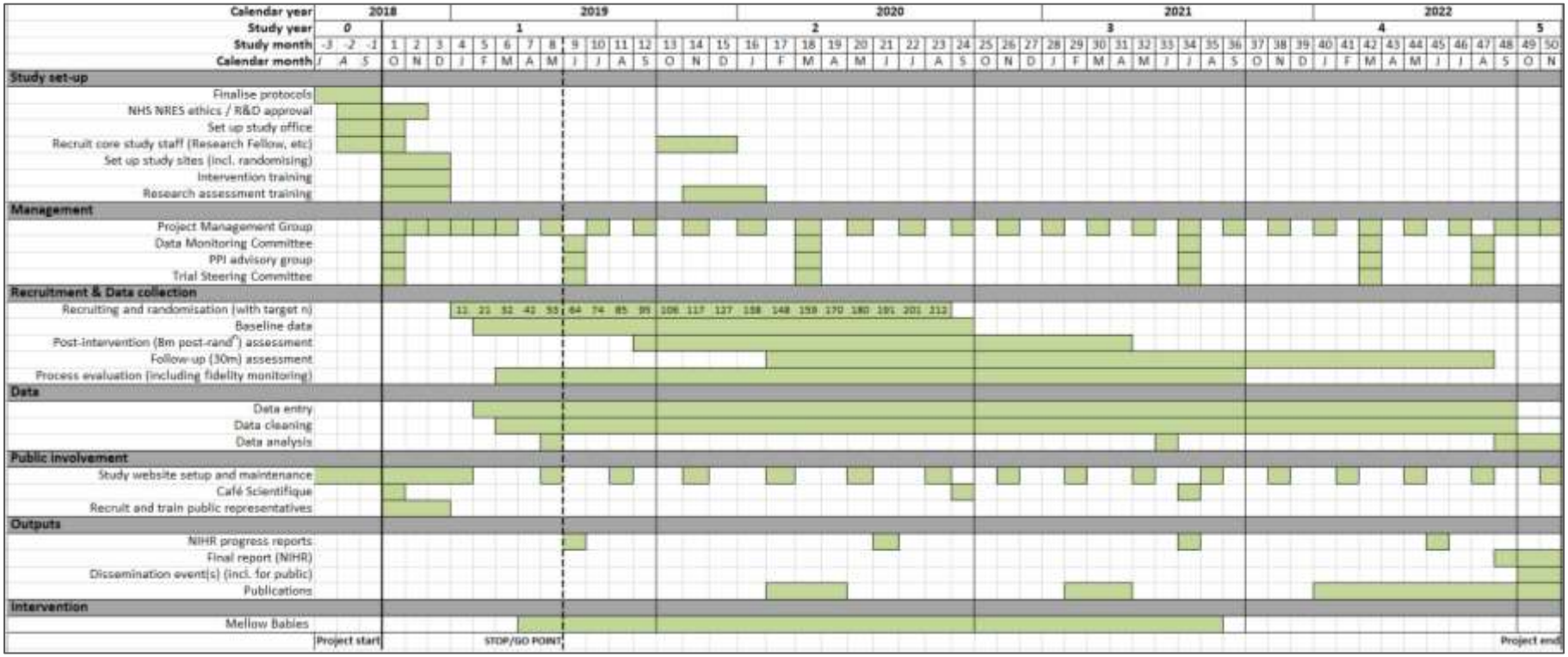
Please refer to the Appendix 2 (authorship policy) for full details on authorship.

APPENDICES

Appendix 1: Gantt Chart showing timescales and milestones

Appendix 2: Authorship Policy

Appendix 1: Gantt Chart showing timescales and milestones



Appendix 2: Authorship Policy for The Mellow Babies Trial

DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria[1]:

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

ii. Drafting the work or revising it critically for important intellectual content; AND

iii. Final approval of the version to be published; AND

iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

1. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals[2,3] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE)[1].

All contributors must fulfil the criteria detailed in section 1: DEFINING AUTHORSHIP in order to qualify for authorship.

Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or technical editing, language editing or proofreading the article is insufficient by itself to justify authorship[1]. Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.

a. Preferred CHaRT authorship

Where possible, all CHaRT studies should publish using all the named contributors who qualify for authorship in the byline i.e. Jane Doe, John Doe, John Smith and Ann Other.

However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstance, group authorship may be appropriate using bylines similar to “The Mellow Babies trial group” or “Jane Doe, John Doe, John Smith, Ann Other and the Mellow Babies trial group”. The article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group') [2]. Again, the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

b. Determining authorship

These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion numbers (ii) or (iii). Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript[1].

Tentative decisions on authorship should be made as early as possible[3]. These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

c. Ordering of authors

The following rules may help with the ordering of authors, particularly for publications with individual authorship:

i. The person who has taken the lead in writing may be the first author.
ii. The senior author may wish to be the last named author.
iii. Those who have made a major contribution to analysis or writing (i.e. have done more than commenting in detail on successive drafts) may follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.
iv. All others who fulfil the four authorship criteria described in Section 1: DEFINING AUTHORSHIP may complete the list in alphabetical order of their surnames.

2. ACKNOWLEDGEMENTS

All those who make a contribution to a publication, but who do not fulfil the criteria for authorship, such as interviewers, data processors, staff at the recruiting sites, secretaries and funding bodies, should be acknowledged by name, usually in an 'Acknowledgements' section specifying their contributions. Because acknowledgment may imply endorsement by acknowledged individuals of a study's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals[1].

3. DISCLAIMERS

All papers arising from CHaRT must include the full title of the Health Services Research Unit (HSRU) and the appropriate disclaimer specified by the Chief Scientist Office (CSO). For the current disclaimer please see Q-Pulse.

Authors should also ensure they include the study funder's disclaimer: refer to the funders website for details. Be aware that other disclaimers may also be required.

4. QUALITY ASSURANCE

Ensuring quality assurance is essential to the good name of the trial group. All reports of work arising from the Mellow Babies trial, including conference abstracts, should be peer reviewed by the Project Management Group. The Project Management Group will be responsible for decisions about submission following internal peer review. Submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

It is hoped that the adoption and dissemination of this policy will prevent disputes that cannot be resolved by informal discussion. However, any member off the study team with a concern about authorship should discuss it with the relevant Chief Investigator, TSC, Line Manager or Programme Director as appropriate.

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