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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Signatures

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

		signature
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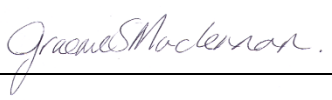
Date:	02.03.2023	
Prof Graeme McLennan:		signature
Date:	02.03.2023	

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
	v4	Minor amendments to protocol – updated contents page, addition of updated Gantt chart and all fields populated with reference numbers and relevant contact details	28.02.19
	v5	Substantial amendment – addition of new recruitment methods (allowing third sector organisations to become referring practitioners) – HC (p.13-14)	09.05.19
	v6	Substantial amendment – addition of a number of new recruitment methods and addition of a MPH research project	23.05.19
	v7	Minor amendment – addition of updated Gantt chart to reflect an updated STOP/GO point	14.11.19
	v8	Non-substantial amendment/minor amendment – amending study protocol to allow follow-up assessments to be carried out remotely	18.03.2020
	v9	Non-substantial amendment/minor amendment – COVID-related amendment. Retrospective approval for COVID letters sent to participating mothers. Also allowing for mothers to take their own research videos.	27.04.20
	v10	Substantial amendment – addition of PhD student project, new recruitment methods, and new study forms	02.11.20
	v11	Addition of alternative questionnaire measure to the Bayley III – the ASQ-3 + ASQ:SE-2	28.12.20

	v12	Substantial amendment – addition of new study document (letter sent out to participants alongside ASQ in advance of 30-month follow-up call)	16.02.21
	V13	Substantial amendment – addition of new study documents (ASQ-3 33-month version; ASQ-SE 36 month version; copies of SDQ and HADS to be sent out to participants prior to follow-up call). Minor amendment to study protocol, stating deadline of 30-month follow-ups.	16.4.21
	V14	Substantial amendment – use of Docmail mail communication service to send out PIC letters to potential participants	21.9.21
	V15	Substantial amendment – addition of add-on study evaluating Mellow Babies Online and addition of new stop/go point.	**REC Approved 24.05.22** **PENDING APPROVAL From NHSH RD&I**
	V16	Minor amendment MBO – intervention to be delivered and recorded via UoA MS Teams account rather than Mellow Parenting Zoom account.	**Sponsor Approved 13.10.22** **PENDING APPROVAL From NHSH RD&I**
	V17	Non-substantial amendment to extend study end date to 31.12.23	23.11.2022
	V18	Substantial amendment: change of Chief Investigator from Prof Phil Wilson to Dr Lucy Thompson (with clinical support by Angus MacBeth) as of 17.12.22.	01.12.2022
	V19	Addition of close down plan. Study end date revised to 30.06.2023.	17.02.2023
	V20	Removal of final group from close-down plan	

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PROTOCOL SUMMARY

Questions 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?
Mellow Babies Online Add-on study from 2022:	Does Mellow Babies Online delivered to mothers who are anxious or depressed, along with their 6-18 month-old children, improve maternal mental health and parent-infant relationships post-participation?
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) (v) Mother under 16 years old (vi) Mother of twins or other multiple births who would otherwise be of eligible age to take part in the study
Interventions	1. Mellow Babies 2. Usual Care
Mellow Babies Online Add-on study from 2022:	1. Mellow Babies Online 2. Usual Care

Outcomes	Primary: Maternal self-complete HADS at 8 months post-randomisation and when children are 30 months old.
Mellow Babies Online Add-on study from 2022:	Primary: Maternal self-complete HADS within 1-month post-participation.
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 255903). **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/eCRF	Case Report Form / electronic Case Report Form
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
DUFSSQ	Duke/UNC Functional Social Support Questionnaire
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
MBO	Mellow Babies Online
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
PIS	Participant Information Sheet
PMG	Project Management Group
PPI	Patient and Public Involvement
PRFQ	Parental Reflective Functioning Questionnaire
PSI-4-SF	Parental Stress Index-Short Form
PSOC	Parental Sense of Competence Scale
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 Lucy Thompson (with clinical support from Angus MacBeth)

Grant Holders

1	Philip Wilson	9	James McTaggart
2	Danny Wight	10	Tim Allison
3	Louise Marryat	11	Clare Simpson
4	Graeme McLennan	12	Laura Ternent
5	Angus MacBeth	13	
6	John Norrie	14	
7	Iain McGowan	15	
8	Bethan Murdoch	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) (Lucy Thompson) 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.

As a result of the COVID-19 pandemic and social distancing requirements in 2020-2021, the delivery of Mellow Babies groups was suspended. In response to this, Mellow Parenting developed an adapted version of the programme specifically for online delivery: Mellow Babies Online (MBO). This programme aims to provide parents with access to parenting support throughout ongoing COVID-19 restrictions and may also be particularly beneficial for parents who have limited access to in-person groups, for example those located in remote and rural areas.

Meta-analyses (Nieuwboer et al., 2013) have demonstrated that both self-guided and professional-guided online interventions can be effective in improving parenting outcomes. However, the majority of studies included in these reviews report on asynchronous, self-directed, or individual interventions. There is a paucity of research exploring the delivery of synchronous group-based parenting interventions in an online setting.

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.

As outlined above, the COVID-19 pandemic encouraged the development of MBO, which has not yet been fully evaluated. Recent pilot work demonstrates online delivery to be feasible and acceptable, and ongoing interview work is focusing on the experiences of participating mothers and group facilitators. The logical next step is to conduct a feasibility trial to inform a potential future definitive trial of MBO.

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 OR the Ages and Stages Questionnaire 3 and Social and Emotional Scale (where face-to-face observation is prohibited)
- 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?

MBO add-on study objectives are to compare MBO 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) within 1-month post-participation.

Secondary Outcomes (within 1-month post-participation):

- Maternal self-efficacy: Parental Sense of Competence Scale (PSOC)(49)
- Maternal reflective functioning: The Parental Reflective Functioning Questionnaire (PRFQ)(50)
- Maternal Stress: Parental Stress Index- Short Form (PSI-4-SF)(51)
- Maternal health-related quality of life (EQ-5D-5L)
- Directly assessed positive and negative parenting behaviours

Process measures/secondary aims:

- Recruitment and retention rates
- Which eligible mothers agree, and which decline to participate in the intervention, and what reasons do they give?
- What contextual factors facilitate or hinder delivery of, and engagement with, MBO?
- How do participants describe their experience of participating in MBO?
- What is the nature of usual care offered to participants?
- Directly assessed group processes and interactions during recorded MBO sessions.

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.

The add-on study is an extension of the main trial which will test the feasibility of MBO, comparing the online group-based parenting programme (MBO) plus Usual Care with Usual Care alone.

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 a mealtime 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 (52) 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 HCRF 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.

Add-on study: MBO comprises the same key components and group aims as MB. However, MBO groups run consecutively for eight weeks, and each session lasts 90 minutes. Sessions are delivered via video conferencing software by 2-3 trained facilitators. Throughout, mothers will participate in reflective activities and group discussion. They will be provided with a logbook to complete alongside the programme which includes 'Have a Go' tasks, i.e., activities for them to try with their baby between sessions.

Mellow Parenting are acting as a 3rd party in the study. MBO group sessions will be facilitated by Mellow Parenting practitioners rather than the trained practitioners at HCRF (as in The Mellow Babies Trial). These Mellow Babies Online groups will be exclusive to consenting trial participants.

Sessions will take place over, and will be recorded using, Microsoft Teams video conferencing software (UoA account). The MBO sessions will be hosted by UoA on Microsoft Teams. A member of the UoA trial team will invite Mellow Parenting practitioners and intervention participants into a Microsoft Teams meeting. The UoA researcher will initiate the session recording on Microsoft Teams (with consent) prior to leaving the call. Mellow Parenting practitioners will be left to facilitate the group.

The session recordings will be downloaded from the UoA Microsoft Teams account immediately following each session and stored on a secure UoA server. Recordings held by the UoA trial team will be destroyed once fully coded, no later than one year after the final study data collection. All data will be collected and stored within UoA systems.

Recording of MBO sessions is not standard practice for Mellow Parenting and is being conducted for research purposes only. These recordings are to allow our research team to analyse online group processes and interactions.

Comparison

All families will be offered Usual Care (UC): the trial arms will be differentiated by whether or not MB (or in the add-on study: MBO) is made available. UC will include normal care from the health visiting team and from the general practitioner (GP), 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 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 UC 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 (53). 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 (54) and on parent-reported data from the Growing Up in Scotland (GUS) cohort (55). 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 (56) received eight more HV visits than the intervention arm.

We intend to characterise the nature of UC 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 (57) by telephone, found to be a useful method in similar studies (58, 59). 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 (60).

We aim to recruit 212 families to achieve evaluable data on 170. 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 (60). 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) (61). 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 (62), 3 points is likely to represent a clinically significant reduction based on the results of the Livingstone et al trial (61).

Mellow Babies Online (MBO) will recruit a remote and rural population (i.e. those who will not be able to participate in the main trial due to location). The study population will also include those who would struggle to attend in-person groups regardless of location (e.g. those with symptoms of social anxiety, other health challenges or caring responsibilities). For this add-on study, we aim to recruit 32 families.

4.2 Inclusion and exclusion criteria

Inclusion criteria:

(i) mothers with principal caregiving responsibilities scoring ≥11 on HADS-A or ≥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 aged 16 years
(vi) Mother of twins or other multiple births who would otherwise be of eligible age to take part in the study

Participants in the MBO add-on study will meet the same inclusion/exclusion criteria as those in the MB trial but will face additional barriers to in-person groups.
MBO participants will reside in remote and rural areas out with the capacity of the main trial and/or will have other significant challenges to attending in-person groups (e.g. symptoms of social anxiety, other health challenges or caring responsibilities).

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. Referrals may also be made by nurseries and third sector organisations, whereby staff within these organisations will act as a referrer and have the ability to provide the mother with information about the study, before providing her with an EoI form so she can then be contacted by the study's research nurse if she is interested in taking part in the trial.

Alongside the acceptance of referrals from referring practitioners, both health professionals and third sector organisations, potential participants may also self-refer. Recruitment posters will be displayed around the community (e.g. libraries, shopping centre's display boards) and in locations where mothers and babies may gather (e.g. mother and toddler groups). Posters will also be displayed in GP and hospital waiting rooms. Through the use of social media recruitment posters will also be displayed on the trial Facebook page.

The trial team will also utilise a number of additional recruitment methods in order to maximise potential participant figures. The following methods will be noted below:

1. **Increased presence in the community**

Coffee mornings will be hosted by the trial team in central community locations that are easily accessible for mothers with young children. The aim of the coffee mornings will be to provide information about the trial and answer any questions mothers may have about their eligibility for the trial, or what participating in the trial may involve. The trial team also intends to begin attending local mother and toddler groups.
As a way to engage the public, the trial team also intend to host a mini-series of events, that will showcase the work being conducted by our partners NHS Highland Research Development and Innovation department, as well as providing more information to the public regarding the Mellow Babies Trial. In all cases it is hoped that by increasing our presence in the community, it will increase public awareness of the trial, which will subsequently increase participant numbers.

2. The use of Participant Identification Centre (PIC) sites

It has been highlighted to the trial team by the former Director of Public Health of NHS Highland, Professor Hugo van Woerden, that the use of PIC sites with the support of the Public Health department may also increase participant numbers. Professor van Woerden has provided assurances that this procedure is completely ethical. An invitation letter (includedamendment submission AM07) would be sent to any potential participants who fit the trial's eligibility criteria. Any interested participants would then be provided the relevant contact details should they wish to express interest in participating in the Mellow Babies Trial.

We will send out these PIC letters using the mail communication service Docmail (www.cfhdocmail.com). The addresses of potential participants will be accessed through Public Health records by a member of the research team under an honorary contract with Public Health and holding a Research Passport. Having an honorary contract with NHS Highland negates the need for a research passport. Participant names and addresses will then be uploaded to Docmail in an excel spreadsheet, along with the invitation letter, an expression of interest form and a response envelope. Docmail will then print and post out letters to all participants. Docmail has been used for patient communication by the NHS for over 12 years, and is an approved supplier on NHS Digital and procurement boards. It is GDPR compliant, accredited by the Data Security and Information Toolkit, and Cyber Essential Plus certified.

Given the success of the PIC sites (3% response rate), it is intended that the trial team also send out a follow-up letter to those parents who have received an initial PIC invitation and who still have babies in the eligible age range. This follow-up letter will act as a reminder and invite potential eligible mothers to get in touch with the trial team if they are interested in taking part in the trial (follow-up letter included in amendment submission AM013).We will also send out these follow-up letters using Docmail.

MBO participants will be recruited in a similar manner as Mellow Babies Trial participants. Potential participants will self-refer or be referred by health professionals (e.g. health visitors) and third-sector organisations. PIC letters will be the main recruitment strategy, along with social media advertisement of MBO. PIC letters will highlight the opportunity to join an online – rather than in-person – group should prospective participants be living in remote areas where attending (and feasibly running) an in-person group would be difficult or impossible (AM021). PIC letters will also highlight the opportunity for mothers to contact the study team to discuss MBO if they feel unable to attend face-to-face groups, regardless of location.

3. The use of vignettes

It is intended that anonymised vignettes from current participating mothers, both in the control and intervention arm of the trial, will be used to illustrate what it is like to take part in the trial. We hope that using this material may encourage other mothers to come

forward and express interest in participating in the trial. To reiterate, these vignettes will be anonymised and will only be used if the participating mother has given consent.

With this in mind, new consent forms will be developed to capture the use of vignettes for the trial. This will be included in the 'optional' section of the consent from (new consent forms can be found in amendment AM013). During follow-up visits (at 8-months post randomisation and when the participating child is 30-months old) we will ask mothers who gave consent using (2-086-18 Mellow Babies consent v1 17Sept18) if they wish to sign the amended consent from (2-086-18 Mellow Babies consent v2 13March20) in order to provide an anonymised vignette, they may do so.

The referrer will briefly describe the MB 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 Clinical Research Facility (HCRF). We will also allow a form of self-referral via PIC letter where the mother returns the EoI by post or expresses interest by contacting the HCRF nurse via phone or email. Self-referrals are also accepted 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 HCRF research nurse who is taking referrals to the study.

The Research Nurse will telephone the mother to seek permission to send her the PIL 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).

The referral process for MBO is similar to that of the Mellow Babies Trial. The referrer will briefly describe the MB study (including the option of MBO) to the mother and ask her to complete an Expression of Interest (EoI) form including her preferred contact details to be passed to the HCRF Research Nurse. We will also allow a form of self-referral via PIC letter where the mother returns the EoI by post or expresses interest by contacting the HCRF research nurse directly via phone or email. Self-referrals are also accepted where practitioners provide a study flyer (including the EoI form) to potential participants, and they may contact the study's Research Nurse directly. As of AM021 this EoI form highlights the opportunity to take part in Mellow Babies Online. We also plan to use social media to publicise the study and include contact information for the HCRF Research Nurse who is taking initial referrals to the study.

Any mothers who have expressed an interest in taking part in the Mellow Babies Trial, but who have been identified by the HCRF Research Nurse as unable to attend in-person MB groups due to challenges related to remote and rural living, will be asked whether they would want to take part in the MBO study instead. Potential participants for whom in-person groups are inaccessible regardless of location (e.g. those with additional caring responsibilities, health challenges or who experience symptoms of social anxiety) will also be asked if they would like to take part in MBO. If interested in MBO the Research Nurse at HCRF will ask for permission to pass the potential participants contact details to the UoA researchers involved in the MBO add-on study for future contact. A UoA researcher will contact the potential participant to conduct the screening process, providing more information about the MBO study and assessing eligibility for participation using the HADS.

4.4 Screening for eligibility

The HCRF Research Nurse (or UoA researcher for MBO participants) 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 the participant 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 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.

The following amendments have been made to the consent form:

- Participant also agrees to their Health Visitor being informed of their participation in the trial
- Participant has the option to also give consent to provide an anonymised vignette of their opinion of the trial and their participation in it.

For MBO add-on study participants – the UoA Researcher will send out a Participant Information Sheet (PIS) and consent form prior to a phone call with the potential participant. The researcher will talk through the PIS and answer any questions the participant may have. If the participant is happy to proceed, the researcher will read through each statement on the consent form and seek verbal consent from the potential participant. The researcher will also ask the participant to fill in the consent form electronically (entering their initials against statements and including their full name and the date of consent) and send it back to the research team via their personal email. The researcher will sign the consent form and send a completed copy for the participant to keep. A copy of the consent form will also be kept in the study's electronic site file on a secure UoA server. A UoA researcher will arrange a phone / video call with the participant to complete the baseline questionnaires.

4.6 Randomisation and allocation

The Research Nurse will use the online randomisation service (provided by the Trial Office) to randomise the participant, 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).

For MBO add-on study participants, randomisation will be conducted immediately following baseline measures by the UoA researcher during the baseline phone / video call using the same web-based application hosted by CHaRT. During this call the participant will be informed of which study arm they have been allocated to. The UoA researcher will inform the intervention team (at Mellow Parenting) of participants randomised to receive the intervention once the group is adequately populated. The UoA researcher will send the name and contact details of all consenting intervention participants to Mellow Parenting (one file per group via Zend-To file transfer) prior to the group start date. The Chief Investigator, Co-Investigators and project staff involved in outcome assessment will be blinded to the study arm allocation.

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 UoA Trial Team will be responsible for the following:

- Notify the GP (if consent given) in writing when a patient of theirs has consented to participate in the Mellow Babies Study. A summary of the trial will be included on the back of the GP letter.
- Send Letter to Best Contact to gain consent to contact if we are having difficulty reaching the participant for follow-up.

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

- Notify referrers (if consent given) in writing that a participant has consented to participate in the Mellow Babies Study and their randomisation result.
- 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 (57) 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) (63-65)
- 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 (66) 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 (67) (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 (68) including Behavior Observation Inventory. Assessment by research assistant with some input by parental caregivers. The Ages and Stages Questionnaire 3 and Social and Emotional 2 where face-to-face observation is prohibited – this is a questionnaire measure completed by the parent and then reviewed over the phone with the researcher. OBJECTIVELY objectively
- 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 (where permitted). Raters blinded to allocation will assess mealtime videos.

5.3 MBO add-on study outcome measures

We have tailored the measures included in the MBO study based on those likely to be sensitive to change over a much shorter period (i.e. parental wellbeing rather than child development).

Primary outcome measure:

- Maternal self-complete HADS within 1-month post-participation

Secondary outcome measures (within 1-month post-participation):

- Parental Stress Index (PSI-4-SF)
- Parental Sense of Competence Scale (PSOC)
- The Parental Reflective Functioning Questionnaire (PRFQ)
- 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)

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)*	(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 / ASQ[1]						✓	
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 (65) (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 HCRF 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.
All participants will be offered a £10 voucher for completion of baseline visit.

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 HCRF 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 (e.g. a small teddy bear with a study logo).

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

It should be noted that for both follow-up points (8-months post randomisation and when the child is 30-months of age) these follow-ups will ideally be carried out face-to-face in the mother's home. However, follow-up visits may also be carried out remotely. It should be attempted to maintain some form of face-to-face contact (e.g., to use skype or video call); however, if this option is not available then follow-up visits can be carried out over the phone. Researchers will be instructed to take participants through the questionnaires and complete the answers on the participant's behalf. Therefore, this will ensure 100% completion rate of questionnaire data.

Visit at 8 months Post Randomisation

A UoA Researcher will contact the mother to arrange a home visit and will attend this home visit with a second member of staff from HCRF or UoA. Required at this visit are a maternal HADS

[1] The ASQ will be used when it is not possible to conduct in-person assessments (i.e due to Covid-19 restrictions.)

(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).
If the mother has consented, a video of the mother and child together will be recorded (in a caregiving situation, ideally a mealtime). If the mother has consented, a video of the mother and child together will be recorded (in a caregiving situation, ideally a mealtime). In the event of a nurse/researcher being unable to come and film the participant in their home, the participant will be asked if they would be willing to complete their own recording and to send this securely to the research team via the University's ZendTo platform.

The Participant Cost Questionnaire (PCQ) will be completed to ascertain service use and any out of pocket expenses. It should be noted that the PCQ was edited as part of AM015. At 8-month post-randomisation participants are asked Part A of the questionnaire (service use), but not Part B (travel and time) to reduce respondent burden. The recall period here is 'in the last 8-months'.

Follow-ups at 8-months post randomisation must be completed within 28 days of the participant's randomisation date.

Visit when Child is 30 months of Age

A UoA researcher will contact the mother to arrange a home visit and will attend this home visit with a second member of staff from either HCRF or UoA. 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.

Where the ASQ-3 + ASQ:SE-2 must be employed in place of the Bayley III, the participant will complete the questionnaire and responses will be reviewed over the phone with the researcher. Participants will be sent a copy of the ASQ-3, ASQ:SE-2 and SSLM in advance of their 30-month follow-up, so that they are able to try the activities with their child before they review them with the researcher. They will also be sent a copy of the HADS and the SDQ so that they have it for reference during the follow-up call. If the follow-up is not completed by the time the child is 31 months and 15 days, we will use a version of the ASQ-3 suitable for children aged between 31 months 16 days to 34 months 15 days (inclusive). Similarly, if the follow-up is not completed by the time the child is 33 months, we will use a version of the ASQ-SE suitable for children between 33 and 41 months of age. Follow-up assessments when the child is 30-months of age must be completed by the time the child is aged 34 months and 15 days. If the follow-up is not completed by this time, it will be recorded as missing data.

If the mother has consented, a video of the mother and child together will be recorded (in a caregiving situation, ideally a mealtime). In the event of a nurse/researcher being unable to come and film the participant in their home, the participant will be asked if they would be willing to complete their own recording and to send this securely to the research team via the University's ZendTo platform. They will be sent detailed instructions about how to record and submit their video.
The PCQ will be completed to ascertain service use and any out of pocket expenses. It should be noted that the PCQ was edited as part of AM015. At follow-up when the child reaches 30-months of age participants are asked both Part A (service use) and Part B (travel and time) of the questionnaire. The recall period here will be unique to the individual respondent, based on the age of the child at the start of the trial.

6.5 MBO add-on study: measuring outcomes

Table 1 (below) summarises required research activities and timepoints for the MBO add-on project. Further details about collection of outcome data are provided elsewhere in this section.

Contact	Screening Telephone	Consent Telephone	Baseline Telephone or Video Call	MBO 8-week intervention	Within 1-month post-participation Telephone or Video Call	End of Study
Consent	✓	✓				
Maternal HADS	✓				✓	
PSI-4-SF			✓		✓	
PSOC			✓		✓	
PRFQ			✓		✓	
EQ-5D-5L			✓		✓	
Video interaction			✓		✓	
Socio-demographic questionnaire			✓			
DUFSSQ			✓			
Attend MBO Intervention				✓		
Contact with study results						✓

MBO Baseline:

MBO baseline measures include: the HADS (completed at screening stage), the Parental Stress Index Short Form (PSI-4-SF), the Parental Sense of Competence Scale (PSOC), the Parental Reflective Functioning Questionnaire (PRFQ), EQ-5D-5L, Duke/UNC Functional Social Support Questionnaire (DUFSSQ)(69) and a video of parent-child interaction during a mealtime or other caregiving situation obtained from those families who will accept it, all administered by a UoA researcher along with a streamlined version of the main trial demographics. The demographic questionnaire also includes questions tailored around remote and rural living, as well as satisfaction, accessibility, and participation with regards to community groups, services, and activities.

MBO Follow-up (within 1-month post-participation)

MBO follow-up measures include: the HADS, the Parental Stress Index Short Form (PSI-4-SF), the Parental Sense of Competence Scale (PSOC), the Parental Reflective Functioning Questionnaire (PRFQ), EQ-5D-5L and a video of parent-child interaction during a mealtime, or other caregiving situation obtained from those families who will accept it. Follow-up measures are completed by a second UoA Researcher, who is blind to study allocation, within 1 month of a participant completing the online intervention. We shall seek consent to follow-up at a later stage, should resources allow.

All contact on the MBO study will be remote, through telephone or videocall. Questionnaires will be posted out in advance of baseline and follow-up. Participants will be offered a £10 voucher for each parent-child interaction video provided (2x), for completion of both baseline and follow-up questionnaires and for interview completion (optional).

<u>End of Study</u>

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.

A letter will be sent to the participant's GP and HV (as long as appropriate permissions have been obtained) to inform them that the participant has withdrawn from the study. A copy of this letter will be submitted with AM015.

In addition, if participants who are currently enrolled in the trial (e.g., have been screened and are awaiting a home visit), or who are awaiting the commencement of an intervention group have their baby 'age out' (e.g., age past 18-months), they will also receive a letter stating that they are no longer eligible to take part in the trial with our apologies.

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 HCRF 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 usernames 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 HCRF, 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 usernames and passwords. The study website data portal has limited access measures via usernames 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 Laura Ternent) at the University of Newcastle for further analysis when required.

MBO add-on study: As this is a small-scale feasibility trial, we will only enter a participant's name, contact details and screening information onto the electronic data capture system (eCRF). We will also use this system to complete randomisation. All consent, baseline and follow-up data will be stored locally on the electronic study site files.

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.

Whilst we cannot incorporate long-term follow-up for the MBO add-on study participants within the current parameters of the trial, we shall seek consent to contact relevant participants in the future, should a longer study period / further resources become available. This will enable us to collect more substantial data on the potential long-term impact on mothers and their babies participating in a MBO group.

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 HCRF. This means that no member of research staff, either employed by UoA or the HCRF will attend participants' homes alone (for consent and data collection purposes). A member of staff in the HCRF 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.

The lone worker policy at HCRF has since been amended. Research staff employed by both UoA and HCRF are now able to attend participants' homes alone (for consent and data collection purposes). Continuous risk assessment will be conducted. Staff must contact a delegated staff member: (1) before travelling to a participants' home (2) on arrival, (3) on departure and (4) on arrival back to office. The delegated staff member should follow escalation procedures detailed in the lone worker policy should contact not be made.

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?).

8.4 MBO Process Evaluation

The following qualitative and quantitative data will be collected for a process evaluation.
Group attendance and technical difficulties will be recorded by practitioners at the end of every session, as well as protocol adherence checklists.
Group facilitator semi-structured phone / video call interviews will be conducted with all group facilitators (with their consent) after they have delivered MBO. Group facilitators interested in taking part will be asked to provide verbal consent to take part in the interviews. The researcher will also ask that they fill in the consent form electronically (entering their initials against statements and including their full name and the date of consent) and email it back to the research team.
Session recordings (with participant and group facilitator consent) will be analysed and used to check the fidelity of delivery, and explore patterns of interactions within group sessions, both between mothers, and between facilitators and mothers. This will include the number and duration of contributions, the nature of conversations (such as the level of sharing), eye gaze, interactions during the mid-session break, and facilitator techniques to promote participation and bonding (e.g. use of break-out rooms). Session recordings will be directly analysed using behavioural observation software (Noldus Observer). It will be explicit in the participant and group facilitator consent forms that session recordings are a necessary element of participation in the trial, but that there will be an option for deletion of recordings, or parts of recordings that are made at the end of each MBO session. After this point, recordings will be stored on the secure University of Aberdeen server and included in the study data analysis. The Mellow Parenting practitioners will reiterate the participants' rights to erasure of recordings at the end of each session (whilst still recording). The sessions are recorded by University of Aberdeen on a Microsoft Teams account so if a participant wishes for sections of recording to be deleted, the Mellow Parenting practitioner will arrange to meet virtually with a member of the trial research team (who is not involved in outcome analysis) to identify and delete the recording (so that the data is not included in the study analysis). The same procedure applies should a group facilitator request erasure of session recordings. The research team will keep session recordings on a secure University of Aberdeen network. All session recordings will be destroyed once fully coded, no later than one year after the final study data collection.
Mother semi-structured telephone interviews are optional and will be conducted with all consenting intervention and control participants following the final MBO session (N=32). Participants interested in taking part will be asked to provide verbal consent to take part in the interviews. The researcher will also ask that they fill in the consent form electronically (entering their initials against statements and including their full name and the date of consent) and email it back to the research team. The interviews will explore acceptability, technical issues and mothers' perceptions of interactions within the group sessions, as well as with group members in other contexts, if any.

8.5 Preliminary Process Evaluation – Masters in Public Health Student Project

Members of the trial team (LT and PW) are supervising a Masters in Public Health (MPH) student from the University of Aberdeen. This student will be conducting a preliminary process evaluation within the larger Mellow Babies Trial. The aim of this process evaluation will be to identify barriers to, and facilitators of recruitment of a difficult-to-reach, vulnerable population group. The process evaluation will be primarily a qualitative research project, involving interviewing key members of the trial team (including the principal investigator, co-Investigators, the trial manager and research nurses), as well as identified referring practitioners (including health visitors and GPs). It is intended that findings from the process evaluation will provide invaluable information prior to the implemented 'STOP/GO' point.

8.6 Process evaluation of the trial – PhD student project

Members of the trial team (LT and PW) as well as one of the trial's Co-Investigators (DW) are supervising a PhD student, who joined the team in October 2019. The purpose of the PhD will be to conduct an in-depth investigation into the group process dynamics of the Mellow Babies

intervention groups. The student will conduct the in-depth interviews referenced in 8.2 above and her project fits within the broader aims of the process evaluation.

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 (61). 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.

For the MBO add-on study we plan to recruit 32 participants (16 per arm). No formal sample size calculation is needed as this add-on study aims only to establish feasibility of evaluating MBO in a definitive trial.

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.

Following the pause to recruitment due to the covid-19 pandemic (March 2020 to October 2021), we have revised the projected recruitment rates. We have agreed a new stop-go point of 31 May 2022 (6 months into study re-start) by which point we expect to have recruited 55 new participants. This stop/go point was extended to July 31st 2022.

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

10. STATISTICAL ANALYSIS (see section 20.2 close down plan)

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 (70). 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 (71). We shall also explore non-ignorable missing data mechanisms using pattern mixture models.

MBO add-on study statistical analysis:
As well as descriptive data on the participants, the MBO study will involve pre/post analysis of the continuous primary outcome measure (HADS) using a generalised linear model adjusting for baseline covariates.

11. ECONOMIC EVALUATION (see section close down plan 20.3)

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. 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 (72) 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. It should be noted that following AM015 the EQ-5D-5L is no longer completed every 6 months, but is completed during follow-up at 8-months post-randomisation and when the child reaches 30-months of age. This is to reduce respondent burden.

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. (73) 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 (HCRF), 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 HCRF organises all aspects of the postal questionnaires at baseline (mailing, tracking, and entering returned data using the trial web data entry portal) and the UoA RA organises all aspects of the postal questionnaires at follow-up, liaising with the Trial Manager weekly. Both the Trial Manager and HCRF 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 HCRF 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 Laura Ternant) 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. All incoming and existing research staff within UoA CRH and HCRF that are named on the study's delegation log will be trained and regularly updated in GCP.

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.

<u>Participation in the research</u>

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.

<u>Participation in the intervention</u>

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.

20. CLOSE DOWN PLAN

Due to suspension of recruitment to the MB trial as a result of the Covid-19 pandemic, and in part due to slower recruitment rates than projected, a significant funded extension was required to complete the trial as originally planned. Our extension request was rejected, and funder has asked that we close-down the trial. As the trial will now be underpowered, we shall no longer be able to conduct an effectiveness analysis. Funder has encouraged us to use the data we have to maximise learning from the trial, and so supplementary questions have been added below.

Funder has approved a revised study end date of 30.06.2023 to allow for the close-down activities detailed below. The intention is to submit a "Draft Final Report" to funder by July 14th 2023 and to submit a manuscript for publication in a peer reviewed journal in parallel. A breakdown of the timescale for the close down of the trial is given in section 20.4 below.

20.1 Close-down procedures

Recruitment has been paused since October 2022, due to ongoing discussions with funder regarding the nature of the close down of the MB Trial. All other trial activity has continued as planned. During this period, participants taking part in the intervention group or scheduled for follow-up data collection have been verbally informed of the planned trial closure, that follow-up data collection will shortly cease and that we are no longer able to conduct effectiveness analysis of the MB intervention but will be able to use existing data to maximise learning from the trial. To uphold ethical and moral obligations all participants due to have a follow-up assessment will be contacted and offered a visit, fully informed of the trial status. Once the current change to protocol is approved, the final phase of close down will not involve any follow-up assessments. All participants will receive a formal letter from the CI (see below).

The few participants (screened for eligibility, but not yet recruited) interested in taking part in the final group have been informed by the RN at HCRF that the group may not go ahead and are accepting of this. The RN will contact these participants again to inform them that the group is not able to run and thank them for their interest in the study. All participants will be signposted to the Mellow Parenting charity who plan to offer online Mellow groups in the coming months. Qualitative interviews will continue as planned, as well as gathering any process data regarding the implementation of the intervention and the trial more broadly. The Mellow Babies Online add-on study will no longer take place.

Following REC approval a formal letter to communicate trial closure will be sent to:

- Potential participants who have expressed interest and been screened for eligibility, but have not yet been recruited and randomised;

- Participants recruited and randomised, but who have yet to start intervention (or concurrent control);
- Participants with outstanding follow-ups;
- Participants who have completed the trial;
- Referrers to the study;
- GPs/HVs of participants where consent to contact has been provided.

We shall also produce a newsletter to be sent to all potential referring practitioners (whether they referred or not) and a social media post to communicate closure of the trial more widely.

20.2 Revised analysis plan – close down

All outcome analyses in relation to effectiveness of the intervention listed in Section 2 will no longer be conducted. Characteristics of the sample at baseline, follow-up 1 and follow-up 2 will be presented descriptively. We shall also complete some subgroup comparisons based on a revised set of questions (see below).
Process evaluation data will be collected up until the end of March 2023 and analysis in relation to process evaluation questions (see Section 2) will proceed as originally planned (except for those questions pertaining to effectiveness). Thus, the process evaluation questions are now:

- Which eligible mothers agree and which decline to participate in the intervention, and what reasons do they give?
- Which recruitment methods were most effective and was there was any variation in participant characteristics with means of recruitment?
- How do sociodemographic characteristics and maternal mental health at baseline relate to:
    - level of participation in MB?
    - group composition?
    - changes in parenting behaviours?
    - maternal mental state at 8m post-recruitment?
    - child development at 30m, using ASQ rather than Bayley
    - whether recruited pre-pandemic (to March 2020) or post (since Nov 2021)?
- 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 MB?
- Are there family characteristics associated with greater retention to follow-up?
- 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?
- What specific impact did the COVID-19 pandemic have on the ability to run intervention groups and the trial

These added / alternative analyses will contribute to understanding of how to recruit underserved populations to trials, as well as whether any baseline information about participants indicates who is likely to complete participation in the intervention (where relevant) and the trial itself.

20.3 Revised Health Economics analysis plan – close down

Given the anticipated data available from the trial and the request from the funder that no outcomes data be presented we no longer plan to conduct the cost-consequence or model-based analysis. Our close down plan will consist of:

1) Provide descriptive statistics with the appropriate measures of variance for the EQ-5D-5L utility scores at baseline and 8 months and where available 30 months. These

will be presented overall and not by randomisation arm. QALYs will also be estimated and presented as descriptive statistics with the appropriate measures of variance for participants with utility data at each time point.

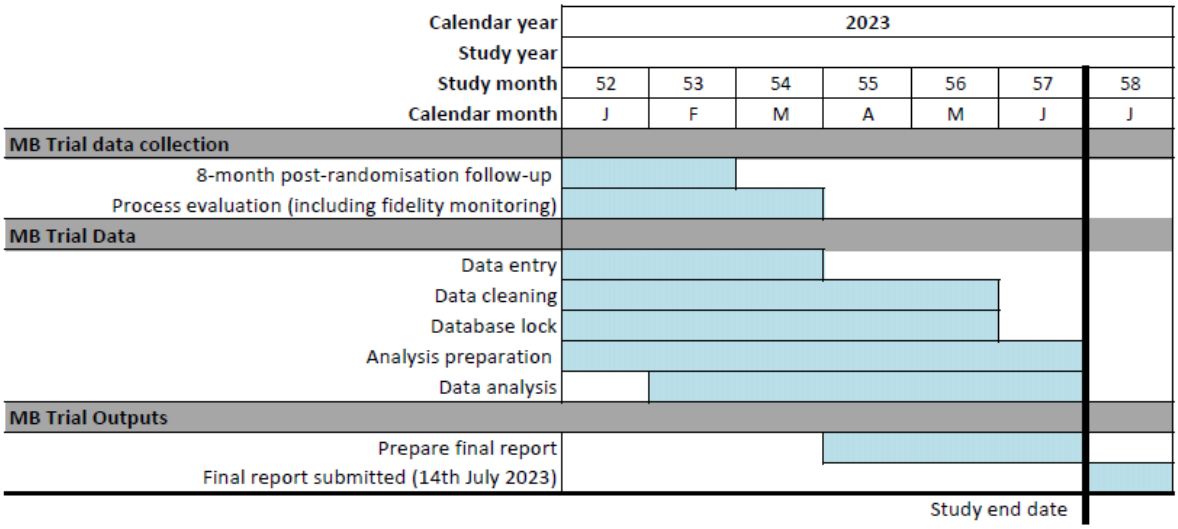
2) Using Case Report Form and Participant Cost Questionnaire data, provide descriptive statistics on completion rates and overall resource use by participants at 8 months and, where available, 30 months. Resource use will be broken down by service (e.g. primary care, secondary care, social services, mental health services etc) and presented as number/type of attendances. We will also describe out of pocket costs reported by participants.

3) Examine correlations between resource use and Quality of Life (EQ-5D-5L) and other outcomes e.g. mental health scores.

While deviating from the original analysis plan, the above work will provide information which may be used as a secondary data source in future work. These analyses will also support future study design by providing an understanding on the appropriateness and likely completion rates of these data collection tools for this participant group. A greater understanding of levels, and in particular, type of resource use, may allow refinement of future tools, such as health care utilisation questionnaires, where comprehensiveness of data and participant burden require balancing. These analyses will also provide insight into whether the EQ-5D-5L can detect changes in health status in this population.

20.4 Timescale for close down

See Gantt Chart for close-down activity and timescales



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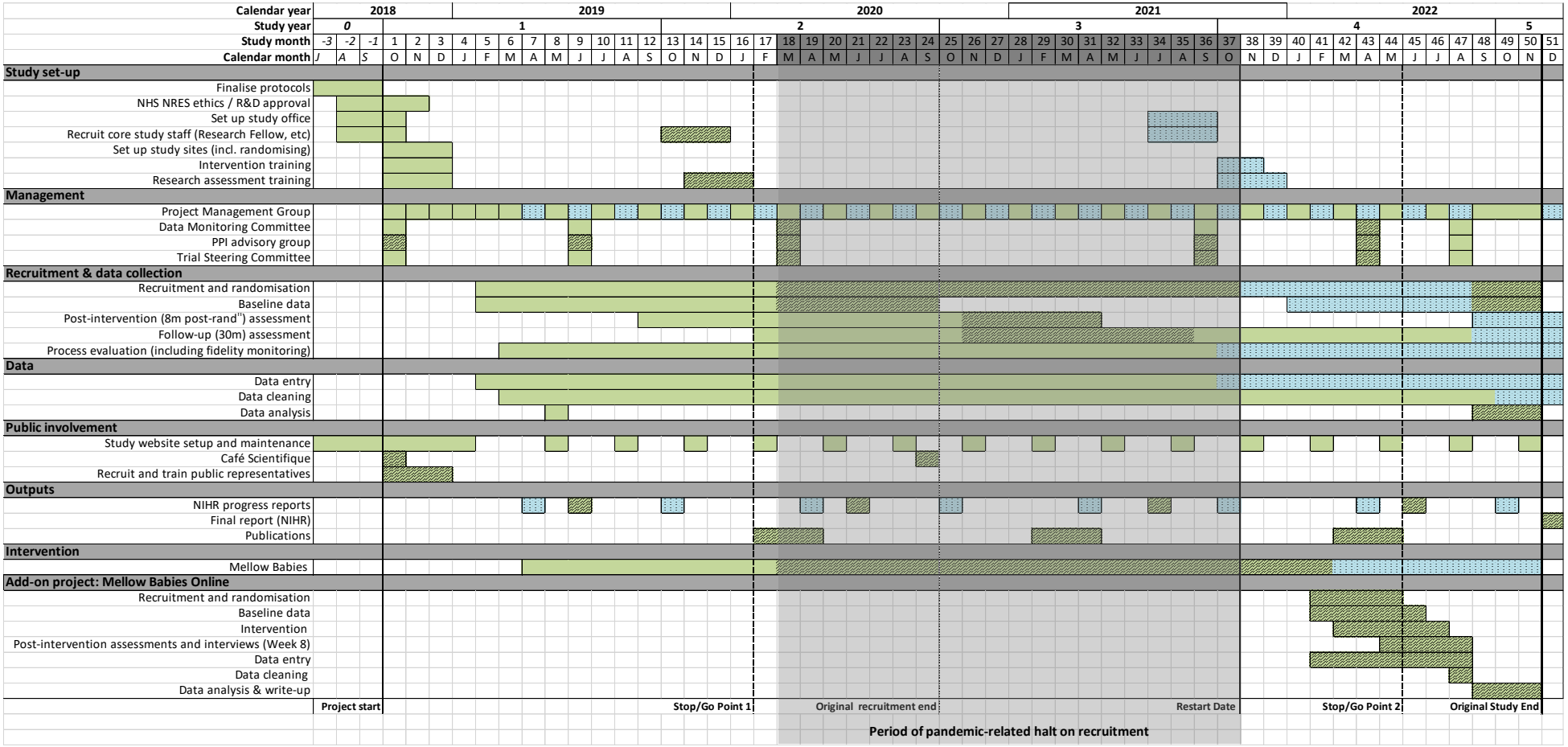
22. APPENDICES

Appendix 1: Gantt Chart showing timescales and milestones until end of 2022.

Appendix 2: Authorship Policy

Appendix 1: Gantt Chart showing timescales and milestones until end of 2022.
See close down Gantt Chart in section 20.4 for the period January 2023 to June 2023 (revised study end date).



Key:
Covid restrictions
Things that didn't / won't happen at that time
Proposed new timescales / extra things that happened

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 funder's 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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