Trial of Healthy Relationship Initiatives for the Very Early-years (THRIVE): A three-arm randomised controlled trial for mothers identified as vulnerable in pregnancy and their babies who are at risk of high maltreatment.

THRIVE

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This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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PROTOCOL APPROVAL

Trial of Healthy Relationship Initiatives for the Very Early-years (THRIVE): A three-arm randomised controlled trial for mothers identified as vulnerable in pregnancy and their babies who are at risk of high maltreatment.

THRIVE

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ABBREVIATIONS

REC	Research Ethics Committee
ANCOVA:	Analysis of Covariance
AWS:	Adult Wellbeing Scale
BSI-53:	Brief Symptom Inventory – a short version of Symptom Checklist-90-Revised: Measures the severity of any psychological distress across nine dimensions
CAU:	Care as Usual
CHI:	Community Health Index
CPO:	Child Protection Order
CSO:	Chief Scientist Office
EQ-5D:	EuroQol 5 Dimensions: a standardised instrument used as a generic measure of health
ETPB	Enhanced Triple-P for Baby
FNP:	Family Nurse Partnership
GP:	General Practitioner
HADS+I:	Hospital Anxiety and Depression Scale enhanced by the outwardly- directed irritability questions from the Adult Wellbeing Scale
HEHTA:	Healthy Economics and Health Technology Assessment
ICER:	Incremental Cost-effectiveness Ratio
MB:	Mellow Bumps
MIIQ	Mother-Infant Interaction Quality
MRC:	Medical Research Council
NHS:	National Health Service
NICE:	National Institute for Health and Clinical Excellence
RCB	Robertson Centre for Biostatistics
RCT:	Randomised Controlled Trial
SD:	Standard deviation
SNiPs:	Special Needs in Pregnancy
SPHSU:	Social and Public Health Sciences Unit
THRIVE:	Trial of Healthy Relationships Interventions in the Very Early years

STUDY SYNOPSIS

Title of Study:	**Trial of Healthy Relationship Initiatives for the Very Early-years (THRIVE): A three-arm randomised controlled trial for mothers identified as vulnerable in pregnancy and their babies who are at risk of high maltreatment.**
Study Centre:	UK multicentre, lead site NHS Greater Glasgow and Clyde
Duration of Study:	60 months
Primary Objective:	To establish whether participants receiving Enhanced Triple P for Baby (ETPB) or Mellow Bumps (MB), in addition to their routine antenatal care, show: 1) significantly lower anxiety, depression and outwardly directed irritability compared to those receiving receiving care as usual (CAU) when their babies are around six months old? 2) more sensitive interactions with their babies compared to those receiving care as usual (CAU) when their babies are around six months old?
Secondary Objective:	To establish whether: 1) any benefits to maternal mood, sensitive interaction style and quality of life continue or emerge when the women's infants are around 18 months old? 2) infants whose parents receive ETPB or MB show more cooperative behaviour signs than those whose parents received CAU? 3) ETPB or MB lead to changes in the number of children flagged as 'at risk' on the social services risk register, under a child protection plan, taken into local authority care or attending accident and emergency? 4) ETPB or MB lead to an improvement in the socio-emotional development of children at around 30 months old? 5) ETPB or MB lead to an improvement in language development in children at around 18 and 30 months? 6) ETPB or MB lead to an improvement in longer term educational and health outcomes for children? 7) either ETPB or MB is cost-effective for the NHS or society more broadly, in the long-term? 8) differences in programme fidelity; practitioners' characteristics and motivation; mothers' engagement; the intervention mechanisms; and contextual factors affect mother and infant outcomes. 9) fathers' involvement or support affect mothers' engagement with ETPB or MB?

Primary Endpoints:	Maternal mental health measured using the Hospital Anxiety and Depression Scale. Maternal outwardly expressed irritability measured using the outwardly expressed irritability measures in the Adult Wellbeing Scale. Sensitivity of mother-infant interaction measured using the CARE Index.
Rationale:	The UK scores badly on UNICEF child and adolescent wellbeing measures, highlighting a need for improvement in children's health and wellbeing in the UK. Neuroscience evidence suggests that the early years of development from conception to age six set the base for competence and coping skills that will affect learning, behaviour and health throughout life. Furthermore, evidence is growing that depression, stress and anxiety in pregnant women can permanently affect the baby's response to stress and disrupt the mother's ability to be sensitive to her baby. Both may adversely affect the mother-infant interaction. Postnatal interventions may not be able to undo some of the damage sustained by infants due to their mother's and/or parents' maladaptive coping in adverse circumstances during pregnancy. Poor mother-child interaction and maternal mental health are highly prevalent among mothers identified as vulnerable in pregnancy. These strongly predict child maltreatment and a disadvantaged trajectory for children in terms of their future social, emotional, cognitive development and health. Sensitive mother-infant interactions are characterised by reciprocal communication from an early stage. This may significantly reduce the risk of maltreatment as a result of mothers perceiving their infants as co-operating with them. Mother-baby/infant interactions that facilitate secure future attachments enable infants to be placed on improved pathways for their overall development, including language development. Limited language skills are a distinctive feature of children from disadvantaged, stressed or abusive backgrounds. Evidence demonstrates that early intervention is more cost-effective than intervening later, and most effective in the antenatal period. Antenatal and early childhood interventions, such as the USA Family Nurse Partnership (FNP) have had positive effects on a number of child development domains and on wellbeing and life success in adulthood. The FNP shares some similarities to the interventions we are proposing to evaluate, such as targeting vulnerable women and starting antenatally. The long-term impact of the FNP is currently being evaluated in the UK. However, short-term UK results have shown an improvement in maternal sensitivity and infant cooperation (as evidenced by video-tape analysis using the CARE Index), and an improvement in the identification of infants in need of child protection. There is little rigorous, UK-based evidence on the effectiveness of psychosocial parenting interventions delivered during the antenatal and early postnatal period. Whilst the evidence for the short-term effects of FNP in the UK appears to be robust, the intervention is expensive to implement, costing £3246 more per patient than routine care, is delivered on a one-to-one basis and may not be generalisable to different groups of vulnerable mothers, for instance those who are not first time mothers or teenagers. Therefore, the THRIVE trial aims to explore if participating in a group-based antenatal and early postnatal parenting intervention improves maternal and infant outcomes more than CAU. In particular, we aim to

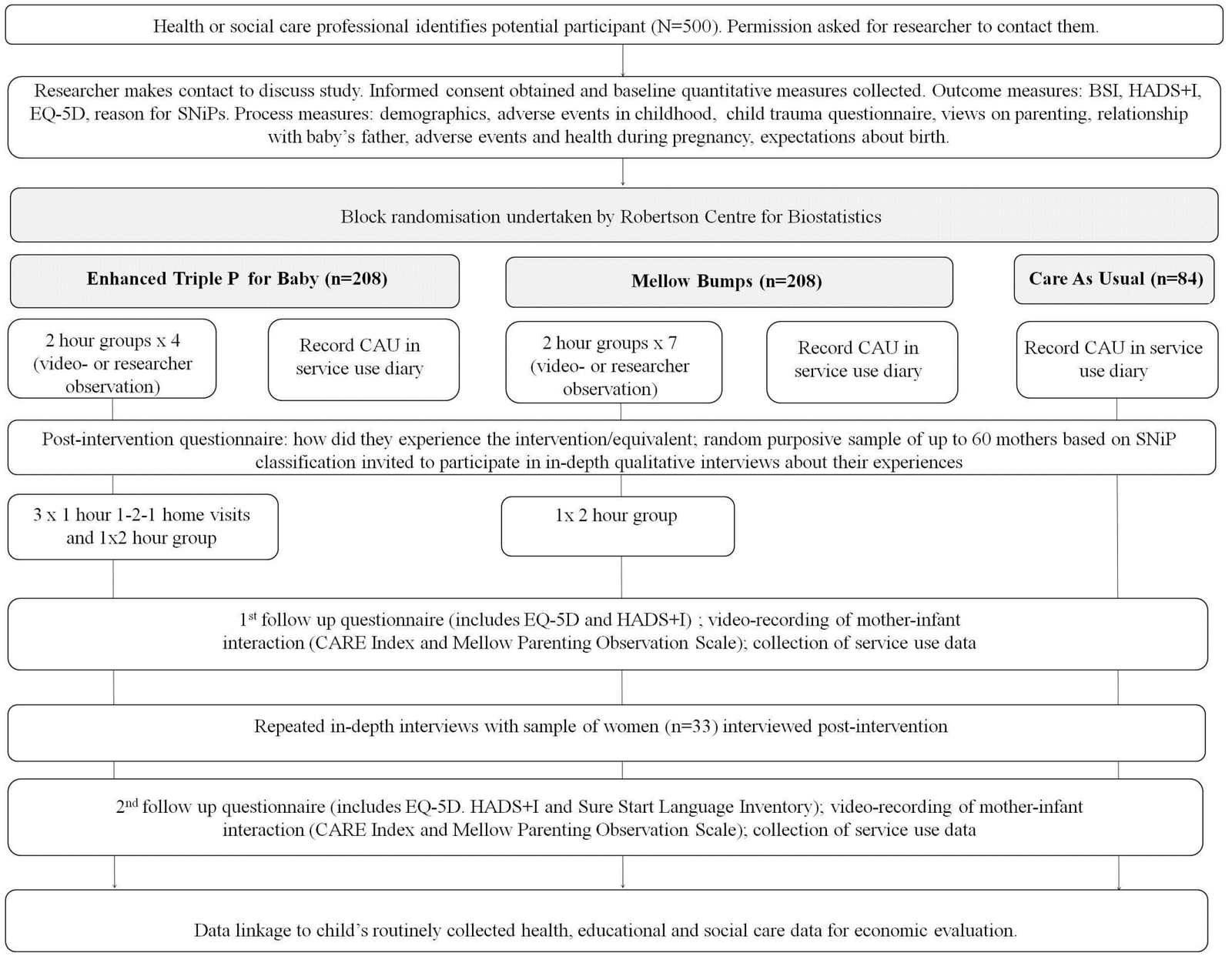
	investigate if receiving an antenatal and early postnatal parenting intervention in addition to CAU can improve maternal mental health, mother-infant relationships and child language development relative to receiving routine antenatal care alone. (See sections 1.2 and 1.2 for fuller discussion and references.)
Methodology:	Randomised controlled trial
Sample Size:	500 Women
Screening:	Participants who meet the trial inclusion criteria will be referred to the THRIVE trial by health and social care practitioners, or recruited directly in clinic settings by members of the THRIVE research team employed by the University of Glasgow, NHS Greater Glasgow and Clyde Clinical Research Facility or the Scottish Mental Health Research Network. Potential participants or the referring practitioner will be asked to sign and date a referral form to state that consent has been given for personal identifying information, including the patient's address, contact telephone numbers, CHI number and GP details to be provided to the THRIVE team. Once a referral form has been received by the THRIVE team, a member of the THRIVE research team will input the patient details into the study database and confirm with midwives based at the NHS Greater Glasgow and Clyde Clinical Research Facility whether the pregnancy is continuing. Once the pregnancy has been confirmed as continuing, a member of the THRIVE research team employed by the University of Glasgow will contact potential participants to verify eligibility and arrange an appointment at which they will be afforded the opportunity to ask questions about the research, and should they agree, be consented to trial and have baseline measures completed. A letter containing an appointment card confirming the date of the baseline assessments will be sent to the participant along with a copy of the THRIVE recruitment to trial information booklet. Appointments will be made 5-10 days in advance to allow participants to have at least 24 hours to read through the information booklet prior to being asked to consent to trial.
Randomisation:	Participating women with additional health and social care needs in pregnancy will be randomised into intervention and control arms after baseline data has been collected. The three arms will be treated identically in terms of data collection. The randomisation will be conducted by colleagues at the Robertson Centre for Biostatistics, University of Glasgow using randomised permuted blocks, with stratification for parity (number of children), severity of psychiatric symptoms and history of substance dependency. For every 12 participants randomised: two will receive CAU, five will receive ETPB and five will receive MB. The women will then be contacted and informed of their group allocation and, where appropriate, invited to attend the ETPB or MB group sessions.

Main Inclusion Criteria:	• Pregnant women aged 16+ (OR 14+ with social work support)
	• Living within NHS Greater Glasgow and Clyde
	• Living within NHS Ayrshire and Arran
	• Meets 1+ Criteria on NHS Greater Glasgow and Clyde's Special Needs in Pregnancy criteria which are:
	  ○ Asylum Seeker/Refugee
	  ○ Gender Based Violence
	  ○ Would benefit from Social Work Support
	  ○ Women who are resistant to professional intervention

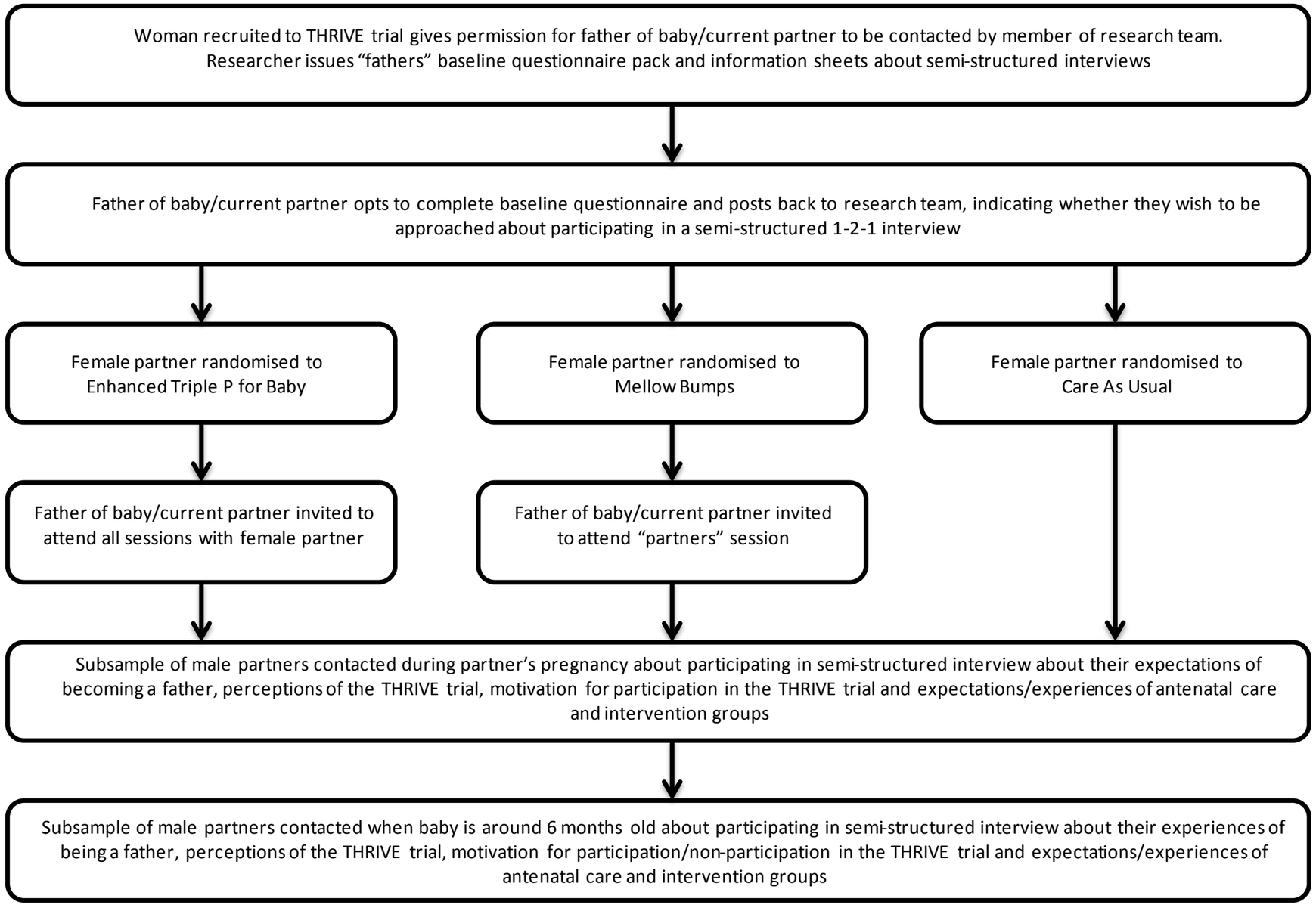
	○ Learning difficulties that could impact on parenting ○ Domestic violence with child protection issues ○ Homeless/Living in supported accommodation ○ Young mothers including: • Those living in supported accommodation • Looked after and accommodated services (LAAC) • Those of educational age but not in education • Lacking social support from family/socially isolated • Linked to leaving care services i.e. Throughcare • Those with learning disabilities • Those presenting with concealed pregnancy
Main Exclusion Criteria:	• Not living in NHS Greater Glasgow and Clyde OR NHS Ayrshire and Arran • Does not meet 1+ criteria on NHS Greater Glasgow and Clyde's Special Needs in Pregnancy criteria • Pregnant women who have passed 30 weeks of pregnancy prior to referral to trial • Lack of capacity to consent to participating in research • Insufficient English to participate in research or engage in groups • Lack of spoken English • Acute mental ill health, including active psychosis • Homelessness to the extent that the women are non-contactable • Receiving Family Nurse Partnership Scheme • Participating in another trial of antenatal interventions, e.g. NSPCC Minding the Baby • A decision has already been made that their child will be removed at birth
Interventions	Two interventions will be evaluated by THRIVE. These are Enhanced Triple P for Baby (ETPB) and Mellow Bumps (MB). Sections 6.1 and 6.2 contain fuller information and references on the interventions. All women receiving these interventions will also receive their routine antenatal care (see 2.5 for details). ***Enhanced Triple P for Baby*** The Positive Parenting program (known as Triple P) was developed at the University of Queensland, Australia and is informed by social learning theory. The efficacy and effectiveness of Triple P interventions have been demonstrated in numerous studies and randomised trials. ETPB is a variant specially developed for vulnerable families. It comprises four antenatal group sessions (two hours each session) and three postnatal one-to-one sessions delivered either face-to-face or by telephone (40-60 minutes each session) plus one final session (60 minutes) which can be delivered either individual or in a group. Thus, the intervention lasts approximately 16 hours. ETPB contains practical content around expectations and skills to meet the challenges of becoming a parent whilst ideally maintaining a happy family or at least reducing family discord. Mothers and their partners are introduced to positive parenting, guidance on to how to respond to common infant problems, how to interact with their infants in a nurturing, positive environment. They are introduced to a range of 'survival skills' and strategies for positive communication in order to facilitate adjustment to parenthood and reduce marital stress and social isolation. The postnatal sessions allow the woman/parents to practice these coping strategies and techniques once their baby is born. The foci for these sessions are determined by the parents who are encouraged to

	become their own coach throughout. ***Mellow Bumps*** MB was developed by Mellow Parenting. Trial data for Mellow Parenting programmes is encouraging. MB is underpinned by attachment theory and designed to target women who have are have additional health and social care needs in pregnancy. It involves seven antenatal group sessions and one postnatal group session (each two hours, i.e. 16 hours in total), focuses on mothers, although fathers are invited to one session; and the content focuses on encouraging nurturing, engagement and synchrony between mother and baby. In each session, a topic is raised that relates to maternal wellbeing. This includes healthy eating, exercise, relaxation and having fun for the mothers as well as exploring barriers to good parenting and sources of support which will benefit the mother and the baby. The infancy foci are the competencies of infants, infant brain development and the significance of very early interaction for shaping this development. The group dynamics and the development of safe relationships within the group play a key role in allowing mothers to address their current emotional state and its modulation. All activities are designed to require only the minimal literacy, with the emphasis on activity, viewing videos and discussion.
Duration of Treatment:	8 weeks to 1 year
Statistical Analysis:	Baseline-adjusted linear regression analysis (ANCOVA) will be used to compare primary statistical outcomes between intervention groups. Similar methods will be used for other outcomes (using data transformation and alternative regression methods, depending on the distribution of each outcome). Regression models will be extended to investigate the effects of baseline characteristics and the potential moderating effects of these variables and other measures of intervention compliance. Repeated measures methods will be applied to outcomes collected at more than one post-baseline assessment. Missing data will not be imputed in the first instance, but the sensitivity of key results will be assessed under alternative assumptions regarding missing values, such as imputation with the baseline value or with the average response in the alternative group. Multiple imputation, based on predictive regression models of study outcomes on baseline and intermediate outcome measures, will also be explored to account for the additional uncertainty in estimates of intervention effect differences due to missing outcome data. Whilst outcomes may exhibit clustering in the intervention arms of the study, due to being delivered in a group setting, this clustering will not be present in the CAU arm, and the anticipated benefits of the two interventions are expected to act in part through the group dynamic. Accordingly, since randomisation is performed at the individual, rather than at the group level, we will not make adjustment for the clustering of outcomes in the main analyses. We will, however, explore the extent of clustering of outcomes within each treatment arm as secondary analyses, in order to evaluate potential explanatory factors for any group-level variability in outcomes.

STUDY FLOW CHART FOR WOMEN RECRUITED TO THRIVE TRIAL



STUDY FLOW CHART FOR FATHER OF BABY/CURRENT MALE PARTNER



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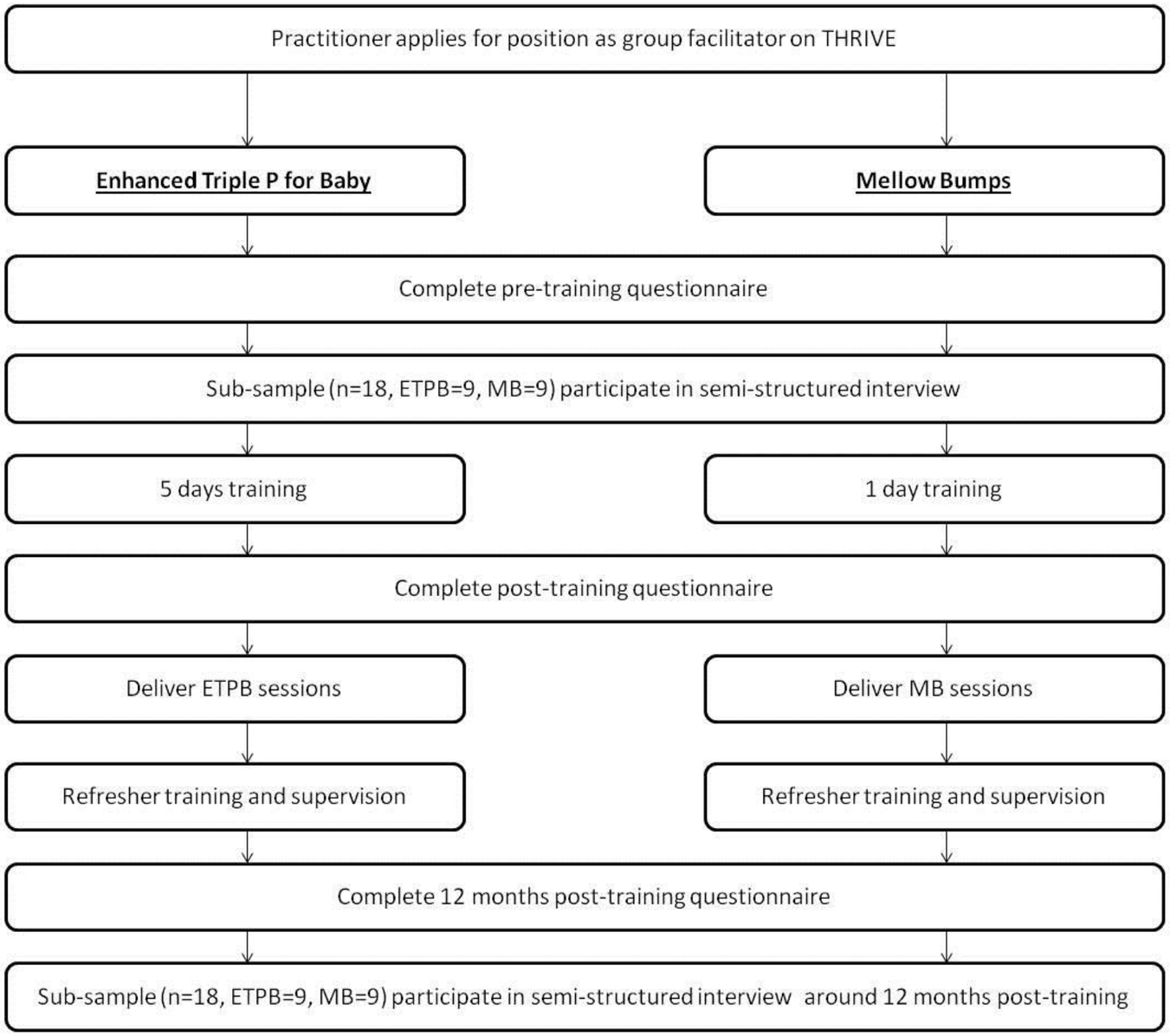
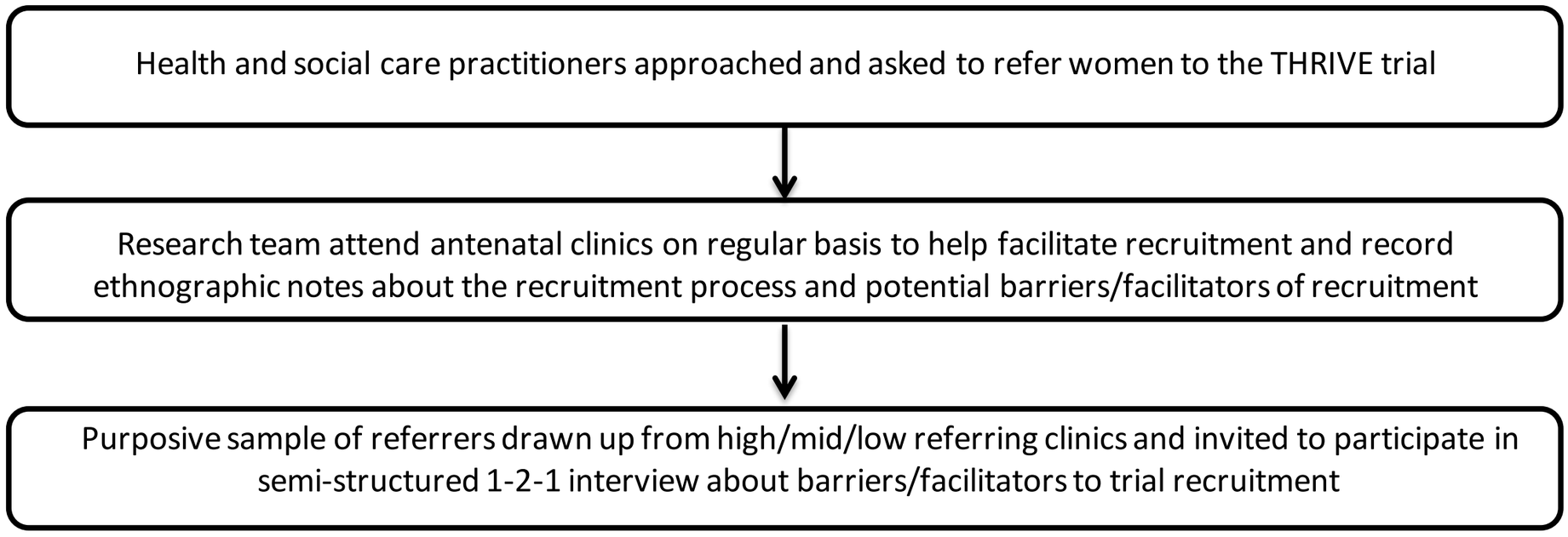


STUDY FLOW CHART FOR REFERRING PRACTITIONERS



SCHEDULE OF ASSESSMENTS FOR WOMEN RECRUITED TO THRIVE TRIAL <approximate date of assessment>									
Recruitment and screening <8-24 weeks antenatal>	**Consent and baseline assessment** <12-25 weeks antenatal>	**Randomisation** <14-27 weeks antenatal>	**Intervention or control** <20-38 weeks antenatal>	**Intervention or control** <6-24 weeks postnatal>	**Follow up 1 visit** <26-44 weeks postnatal>	**Follow up 2 visit** <78-92 weeks postnatal>	**Routine data access** <156 weeks postnatal>		
Review Inclusion and Exclusion Criteria	Obtain Informed Consent	Participant notified of trial arm	Participants randomised to ETPB invited to attend 4 antenatal group sessions, 3 postnatal one to one sessions and a final group session	Sub-sample of ETPB participants participate in telephone interview about postnatal sessions	Hospital Anxiety and Depression Scale (HADS)	Hospital Anxiety and Depression Scale (HADS)	Routine records access for 'at risk' registration at 6, 18 and 30 months postnatal		
Patient given 'at a glance leaflet'	Brief Symptom Inventory 53 (BSI-53)	GP notified of trial arm	Participants randomised to MB invited to attend 7 antenatal group sessions and a final postnatal group session	Sub-sample of MB participants participate in telephone interview about postnatal sessions	Outwardly expressed irritability questions from Adult Wellbeing Scale (AWS)	Outwardly expressed irritability questions from Adult Wellbeing Scale (AWS)	Routine records access for Child Protection Orders at 6, 18 and 30 months postnatal		
Permission given to provide THRIVE team with patient contact details, CHI number and GP details	Hospital Anxiety and Depression Scale (HADS)	Referring professional notified of trial arm	ETPB participants complete pre-intervention questionnaire, session evaluation forms and post-intervention questionnaire		EQ-5D-3L	EQ-5D-3L Sure Start Language Inventory	Routine records access for LAC status at 6, 18 and 30 months postnatal		
Recruitment to trial information sheet posted or given to participant by research team before visit 1 occurs.	Outwardly expressed irritability questions from Adult Wellbeing Scale (AWS)		MB participants complete pre-intervention questionnaire, session evaluation forms and post-intervention questionnaire		Questions on SES, labour and delivery experience, maternal health and wellbeing, infant health and wellbeing, child language development relationship history, father of baby, perceived support, parenting experiences and quality of mother-infant bond.	Questions on SES, labour and delivery experience, maternal health and wellbeing, infant health and wellbeing, child language development relationship history, father of baby, perceived support, parenting experiences and quality of mother-infant bond.	Routine records access for A&E admissions at 6, 18 and 30 months postnatal		
	EQ-5D-3L		Sub-sample of ETPB, MB and CAU participants invited to participate in semi-structured 1-2-1 interview about antenatal care, intervention attendance and parenting expectations		Participant returns completed service use diary	Participant returns completed service use diary			
	Childhood Trauma Questionnaire		Sub-sample of ETPB, MB groups audio- or video-recorded for fidelity monitoring		Video of mother-infant play interaction (CARE Index)	Video of mother-infant play interaction (CARE Index)			
	Questions on SES, childbirth history, health and wellbeing, relationship history, father of baby, perceived support and parenting expectations		Sub-sample of ETPB and MB groups observed by ethnographic researcher for fidelity monitoring.		Video of mother-infant care-giving episode (MPOS)	Video of mother-infant care-giving episode (MPOS)			
	Participant issued with service use diary				Sub-sample of ETPB, MB and CAU participants invited to participate in semi-structured 1-2-1 interview about postnatal care, intervention attendance and parenting experiences	Sub-sample of ETPB, MB and CAU participants invited to participate in semi-structured 1-2-1 interview about postnatal care, intervention attendance and parenting experiences			

SCHEDULE OF ASSESSMENTS FOR FATHER OF BABY/CURRENT PARTNER <approximate date of assessment>									
Recruitment and screening <8-24 weeks antenatal>	**Consent and baseline assessment** <12-25 weeks antenatal>	**Randomisation** <14-27 weeks antenatal>	**Intervention or control** <20-38 weeks antenatal>	**Follow up 1 visit** <20-38 weeks antenatal>	**Follow up 2 visit** <26-44 weeks postnatal>				
Recruited women asked to provide consent for father of baby/male partner to participate in study	Researcher leaves baseline questionnaire pack, including information sheets and questionnaire, for woman to give to father of baby/male partner	Women randomised to ETPB, MB and CAU	Fathers/partners whose female partners are randomised to ETPB invited by partner to attend all sessions.	Opt-in sub-sample of fathers/partners invited to participate in 1-2-1 semi-structured interview with THRIVE researcher	Opt-in sub-sample of fathers/partners invited to participate in 1-2-1 semi-structured interview with THRIVE researcher				
	Father of baby/male partner completes questionnaire and posts to MRC/CSO Unit using business reply envelopes		Fathers/partners whose female partners are randomised to MB invited by partner to attend "partners" session						
	Father of baby/male partner completes "please contact me" form indicating that they wish to take part in a 1-2-1 semi-structured interview and posts to MRC/CSO Unit using business reply envelopes		Sub-sample of ETPB, MB groups audio- or video-recorded for fidelity monitoring						
			Sub-sample of ETPB and MB groups observed by ethnographic researcher for fidelity monitoring.						

SCHEDULE OF ASSESSMENTS FOR ETPB AND MB PRACTITIONERS									
Recruitment and screening	**Consent and baseline assessment**	**Allocation**	**Follow up 1 visit**	**Intervention training**	**Follow up 2 visit**	**Delivery and supervision**	**Follow up 3 visit** <1 year after first group delivery>		
NHS Greater Glasgow and Clyde advertise for practitioners to deliver parenting support interventions as part of THRIVE Trial	Practitioners provided with recruitment to trial information and consent booklet and asked to provide consent for collection of research data across trial life course.	Practitioners without previous training in Triple P or Mellow Parenting interventions randomised to deliver either Enhanced Triple P for Baby or Mellow Bumps	Practitioners complete pre-training questionnaire	Practitioners trained in delivery of either Mellow Bumps or Enhanced Triple P for Baby	Practitioners complete post-training questionnaire	Practitioners invited to deliver around 3 intervention groups each.	Practitioners complete pre-training questionnaire		
NHS Ayrshire and Arran advertise for practitioners to deliver parenting support interventions as part of THRIVE Trial		Practitioners with previous training in Mellow Bumps or Mellow Parenting interventions allocated to deliver Mellow Bumps	Sub-sample of practitioners invited to participate in semi-structured interview with THRIVE researcher			Practitioners collect pre-intervention, session evaluation and post-evaluation questionnaires from participants attending groups	Sub-sample of practitioners invited to participate in semi-structured interview with THRIVE researcher		
		Practitioners with previous training in Triple P for Baby or Triple P interventions allocated to deliver Enhanced Triple P for Baby				Practitioners asked to write ethnographic notes about delivery of service			
						Sub-sample of practitioners observed delivering group by THRIVE researcher			
						Practitioners attend top-up training and supervision sessions as required.			

SCHEDULE OF ASSESSMENTS FOR REFERRING PRACTITIONERS									
Recruitment and screening	**Consent and baseline assessment**								
THRIVE team meet with senior midwifery and social care leads in order to gain permission to approach midwives about referring patients to THRIVE	Sub-sample of referring practitioners invited to participate in 1-2-1 semi-structured interview with THRIVE researcher								
Midwives refer practitioners to THRIVE trial with support from THRIVE research team members									

1. INTRODUCTION

1.1 Background

A recent UNICEF report, which compared 21 high-income countries across six dimensions of child and adolescent wellbeing, found that the UK was ranked worst, and obtained the lowest scores for three of these six dimensions (family and peer relationships, behaviours and risks, and subjective wellbeing). [1] Thus, there is an urgent need for improvement in children's health and wellbeing in the UK. "There is powerful new evidence from neuroscience that the early years of development from conception to age six, particularly for the first three years, set the base for competence and coping skills that will affect learning, behaviour and health throughout life." [2] Furthermore, nature and nurture interact in a way that can be harmful to the foetuses/babies of stressed mothers. Women who are vulnerable in pregnancy (for instance, due to domestic abuse, mental health issues, an addiction, having been in care) are likely to be more anxious, depressed and produce higher levels of cortisol than women who are not vulnerable. Evidence is growing that depression, stress and anxiety in pregnant women can i) create adverse epigenetic modifications to the foetus in utero that permanently affect the baby's response to stress [3, 4] and, ii) independently disrupt the mother's ability to be sensitive to her baby. [5] Both these pathways may adversely affect the mother-infant interaction. Thus, most postnatal interventions may not be able to undo some of the damage sustained by infants due to their mother's and/or parents' maladaptive coping in adverse circumstances during pregnancy.

Poor mother-child interaction and maternal mental health strongly predict child maltreatment [6, 7] and are highly prevalent among mothers identified as vulnerable in pregnancy. [7] In addition, poor mother-child interaction and maltreatment predict a disadvantaged trajectory for children in terms of their future social, emotional, cognitive development and health. [8-10] One of the early distinctive features of children from disadvantaged social backgrounds in general, and of those from very stressed or abusive backgrounds in particular, is that they commonly have very limited language skills. [11-16] Although the nature of the deficit is complex, it is assumed that the nature of the verbal input, interaction and range of positive learning experiences, whether in book reading or outside the home, is limited. [17-20] Although factors affecting early child development are very complex, there is reasonable evidence from the British Cohort Study that delayed language ability at school entry can have long term adult outcomes such as poor literacy, mental health and employment. [21] Recent research using the ALSPAC dataset has suggested that the early communication environment has a specific effect on early language development in the second year of life, over and above generic social risk, and language in turn is closely associated with performance on the Foundation Stage profile at school entry. [22] Thus, it is reasonable to see early language as a critical lynch pin between the infant's earliest experiences and their later achievements. Mother-baby/infant interactions that facilitate secure future attachments enable infants to be placed on improved pathways for their overall development, including language. Furthermore, sensitive mother-infant interactions are characterised by reciprocal communication from an early stage, which again facilitate language but also significantly reduce the risk of maltreatment thought to be due to mothers perceiving their infants as co-operating with them.

Evidence demonstrates that early intervention is more cost-effective than intervening later, and most effective in the antenatal period.[23] The evidence for the effect of early child development on health and wellbeing in later life is robust and widely accepted, and early childhood interventions, such as the High/Scope Perry Preschool Project,[24] the USA Family Nurse Partnership (FNP)[25], the Carolina Abecedarian Project [26] and the Chicago Child-Parent Programme [27] have had positive effects on a number of child development domains and on wellbeing and life success in adulthood. It is appropriate to exemplify this using the long-term results of the FNP trial [25], as it shares some similarities to the interventions we are proposing to evaluate. FNP targeted vulnerable mothers (albeit their definition was tighter than ours, for instance, they only worked with first time mothers), and started antenatally.

The FNP intervention group received antenatal and postnatal home visits from trained nurses until their child was two years old. When the children reached adolescence the intervention group (relative to the controls) were less likely to run away from home, had fewer convictions, fewer lifetime sexual partners, smoked less, drank less alcohol, and their parents reported fewer behavioural problems. The long-term impact of the FNP is currently being evaluated in the UK [28]. However, short-term UK results have shown an improvement in maternal sensitivity and infant cooperation (as evidenced by video-tape analysis using the CARE Index), and an improvement in the identification of infants in need of child protection. The FNP intervention costs society £3,246 more than standard treatment. [25, 29]

1.2 Rationale

Despite the considerable observational evidence summarised to date there is little rigorous, UK-based evidence on the effectiveness of psychosocial parenting interventions delivered during the antenatal and early postnatal period. Whilst the evidence for the short-term effects of FNP in the UK appears to be robust, the intervention is expensive to implement, costing £3246 more per patient than routine care, is delivered on a one-to-one basis and may not be generalisable to different groups of vulnerable mothers, for instance those who are not first time mothers or teenagers. Therefore, the THRIVE trial aims to explore if participating in a group-based antenatal and early postnatal parenting intervention improves maternal and infant outcomes more than CAU. In particular, we aim to investigate if receiving an antenatal and early postnatal parenting intervention in addition to CAU can improve maternal mental health, mother-infant relationships and child language development relative to receiving routine antenatal care alone.

Two interventions will be evaluated by THRIVE. These are Enhanced Triple P for Baby (ETPB) and Mellow Bumps (MB). All women receiving these interventions will also receive their routine antenatal care.

ETPB and MB are group-based antenatal and early postnatal parenting interventions. More information on intervention programmes and the control group are provided in Section 6, with prior study experience below.

1.3 Prior experience

THRIVE has been informed by two pilot studies conducted with women from similar socio-demographic backgrounds and diagnostic histories to those who will be recruited to the THRIVE trial.

1.3.1 Baby Triple P Open Prospective Trial

A three-arm open prospective trial, conducted by Dr. Anja Wittkowski and Prof. Rachel Calam, compared the effectiveness of Baby Triple P and routine postnatal care against baby massage plus routine postnatal care in order to assess which, if any intervention, is most effective at improving outcomes of mother and child. In particular, the trial assessed whether women who received Baby Triple P alongside routine postnatal care showed significant improvements in mental wellbeing, maternal sensitivity, parenting confidence and perceived relationship with their baby than women who received baby massage with routine postnatal care. 60 women diagnosed with postnatal depression and admitted to the Mother and Baby Unit in Manchester were recruited to the trial and allocated to receive either Baby Triple P and routine care, or Baby Massage and routine care. Due to the possibility of women discussing their care plans and causing contamination between arms of the trial, an open prospective trial design was used in which Baby Triple P plus routine care were offered for a period of time, and then withdrawn so that Baby Massage and Triple P could be evaluated. All participants completed questionnaires on mood, bonding and parenting confidence prior to the interventions beginning. These questionnaires were then repeated after completion of the two conditions, and at 6 and 12 months follow up assessments. Video-recordings of mother-

infant interaction were also made to allow for the quality of mother-infant relationships to be assessed using the CARE Index [30].

The Baby Triple P Open Prospective Trial has informed THRIVE by establishing procedures for the handling and coding of video-recordings of mother-infant interaction.

1.3.2 Mellow Bumps RCT

A three-armed randomised controlled trial, conducted by Prof. Phil Wilson and Dr. Lucy Thompson, Dr. Marion Henderson and Dr. Jane White, compared the effectiveness of Mellow Bumps (MB) against Chillout-In-Pregnancy (CHiP) and the routine antenatal care (CAU) received during pregnancy in order to assess which, if any, intervention was most effective at improving the outcomes of mother and child. The primary outcome measure was anxiety as measured by the Adult Wellbeing Scale. Participants who were identified by community midwives as having additional health and social care needs in pregnancy (SNiPs criteria) were invited to take part in the project. The interventions took place when they were between 20 and 30 weeks pregnant. In total 35 women were recruited and randomized in groups of six to one of three conditions: MB (designed to reduce maternal anxiety and improve maternal sensitivity) Chillout-In-Pregnancy (designed to reduce maternal anxiety only) or CAU. All participants were asked to complete questionnaires and give saliva samples (for cortisol assay) before the interventions began. The questionnaires were repeated on completion of the intervention and at a follow up occurring 8-12 weeks after birth. Consent was also sought to take saliva samples (for cortisol assay) from the baby before and after a routine blood test taken the baby was five days old.

The MB RCT has informed THRIVE by providing insight into recruitment, retention, and the handling and coding of video-recordings of mother-infant interaction. In terms of recruitment, the pilot study was conducted in the same NHS Health Board areas that THRIVE is being undertaken in, and recruited women using the same NHS Greater Glasgow & Clyde Special Needs in Pregnancy (SNiP) criteria. This has enabled the THRIVE team to build up local area contacts and understanding of the challenges of recruiting "hard to reach" and vulnerable women during pregnancy.

The MB RCT managed to retain about two-thirds of the women recruited for an average of six months (26.86 weeks, range 19-34, SD 4.6) from consent. To date 68% (n=21) of those who completed the baseline line measures (n=31) have completed measures at the three time points. Remuneration (£20 shopping voucher) was offered to participants at the last data collection point. In the THRIVE trial women will be provided with a £15 shopping voucher upon completion of each of the three outcome questionnaires. In addition, we plan to provide the women with a toiletry kit to take into hospital with them for the birth of their child and a baby bib with the THRIVE logo on it when the baby is 6 months. The MB RCT has also provided valuable insights into the retention of practitioners involved in delivering the interventions. Learning from these, THRIVE has successfully applied for funding from the Chief Scientist Office (Scotland) to provide the NHS with funds for each participant successfully recruited to THRIVE. These funds will allow the NHS to provide "backfill" for practitioners involved in the delivery of the interventions, as well as recoup 75-90% of the costs associated with the delivery of the interventions to each participant.

Finally, THRIVE has benefited from the piloting of video-recordings of mother-infant interaction with the target population.

1.4 Study hypothesis

We hypothesise that the provision of parenting support interventions, in addition to routinely provided antenatal care, during the antenatal and early postnatal phase, will be a cost-effective way of improving maternal mental health, increasing the sensitivity of mother-infant interactions, reducing child maltreatment risk and increasing child language and socio-emotional development.

2. STUDY OBJECTIVES

The overarching aim of THRIVE is to rigorously evaluate, using a three-arm randomised controlled trial, the impact of two parenting interventions against routine antenatal care or care as usual (CAU). In particular, THRIVE will assess whether women who receive either Enhanced Triple P for Baby (ETPB) or Mellow Bumps (MB) in addition to Care As Usual (CAU) experience improved mental health and wellbeing and develop positive, interactive and attuned mother-child relationships. The trial will also assess whether children whose mother received ETPB or MB show reduced incidence of child maltreatment and improved language development and socio-emotional wellbeing.

The primary research questions that will be addressed by THRIVE are:

1) Do participants receiving ETPB or MB show significantly lower anxiety, depression and outwardly directed irritability compared to those receiving CAU when their babies are around 6 months old?

2) Do women who receive ETPB or MB show more sensitive interactions with their babies compared to those receiving CAU when their babies are around 6 months old?

The secondary research questions that will be addressed by THRIVE are:

3) Do any benefits to maternal mood, sensitive interaction style and quality of life continue or emerge when the women's infants are around 18 months old?

4) Do infants whose parents receive ETPB or MB show more cooperative behaviour signs than those whose parents received CAU?

5) Do ETPB or MB lead to changes in the number of children flagged as 'at risk' on the social services risk register, under a child protection plan, taken into local authority care or attending accident and emergency?

6) Do ETPB or MB lead to an improvement in the socio-emotional development of children at around 30 months old?

7) Do ETPB or MB lead to an improvement in language development in children at around 18 and 30 months?

8) Do ETPB or MB lead to an improvement in longer term educational and health outcomes for children?

9) Are either ETPB or MB cost-effective for the NHS or society more broadly, in the long-term?

10) Do differences in programme fidelity; practitioners' characteristics and motivation; mothers' engagement; the intervention mechanisms; and contextual factors affect mother and infant outcomes.

11) Does fathers' involvement or support affect mothers' engagement with ETPB or MB?

2.1 Primary Endpoints

The study's primary endpoints are:

- Maternal mental health measured using the Hospital Anxiety and Depression Scale
- Maternal outwardly expressed irritability measured using the outwardly expressed irritability measures in the Adult Wellbeing Scale
- Sensitivity of mother-infant interaction measured using the CARE Index

2.2 Secondary endpoints

The study's secondary endpoints are:

- Number of children flagged as 'at risk' on the social services risk register, under a child protection plan, taken into local authority care or attending accident and emergency as measured using routinely collected NHS and Social Care Records
- Child language development measured using the Sure Start Language inventory
- Child socio-emotional development as measured using the Strengths and Difficulties Questionnaire
- Comparison of costs and outcomes associated with intervention delivery and routine antenatal care measured using routinely collected (NHS, social care, criminal justice and education) data, the EQ-5D-3L and self-reported patient service use
- Assessment of programme fidelity; practitioners' characteristics and motivation; mothers' engagement; the intervention mechanisms; and contextual factors affecting mother and infant outcomes using self-reported practitioner data, ethnographic observation and semi-structured qualitative interviews
- Assessment of whether fathers' involvement or support affects mothers' engagement with intervention delivery using semi-structured qualitative interviews

3. STUDY DESIGN

This three-arm randomised controlled trial compares the provision of two parenting support interventions, namely Enhanced Triple P for Baby and Mellow Bumps, with the routine antenatal care provided to women identified as having additional health and social care needs during pregnancy. THRIVE will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006).

3.1 Study Populations

The THRIVE trial will recruit participants from NHS, Social Care and Voluntary organisations located within the catchment areas of NHS Greater Glasgow and Clyde and NHS Ayrshire and Arran Health Boards. The following participants will be recruited:

- 500 pregnant women identified as having additional health and social care needs
- up to 500 partners of women recruited to the THRIVE trial
- up to 40 practitioners delivering group interventions for the THRIVE trial
- up to 20 health and social care practitioners in institutions who have been approached about referring women to the THRIVE trial

3.2 Inclusion criteria

3.2.1 Women who have additional health and social care needs in pregnancy

Inclusion criteria are as follows:

- Pregnant women aged 16+ (OR 14+ with social work support)
- Living within NHS Greater Glasgow and Clyde OR NHS Ayrshire and Arran
- Meets 1+ Criteria on NHS Greater Glasgow and Clyde's Special Needs in Pregnancy criteria which are:
    - Asylum Seeker/Refugee
    - Gender Based Violence
    - Would benefit from Social Work Support
    - Women who are resistant to professional intervention
    - Learning difficulties that could impact on parenting
    - Domestic violence with child protection issues
    - Homeless/Living in supported accommodation
    - Young mothers including:
        - Those living in supported accommodation
        - Looked after and accommodated services (LAAC)
        - Those of educational age but not in education
        - Lacking social support from family/socially isolated
        - Linked to leaving care services i.e. Throughcare
        - Those with learning disabilities
        - Those presenting with concealed pregnancy

3.2.2 Partners of women participating in the THRIVE trial

- Male partners aged 16+ (OR 14+ with social work support
- Living within NHS Greater Glasgow and Clyde OR NHS Ayrshire and Arran
- Consent given by female partner for being approached by a THRIVE researcher

3.2.3 Health and social care practitioners

- NHS Greater Glasgow and Clyde and NHS Ayrshire and Arran health and social care practitioners appointed and trained to run ETPB or MB groups for the THRIVE trial.

3.2.4 Referring practitioners

- NHS, Social Care or Voluntary Organisation Practitioner
- Employed within NHS Greater Glasgow and Clyde catchment areas
- Employed within NHS Ayrshire and Arran catchment areas
- Working in organisations approached by THRIVE trial to refer women to trial

3.3 Exclusion criteria

3.3.1 Women who have additional health and social care needs in pregnancy

- Not living in NHS Greater Glasgow and Clyde OR NHS Ayrshire and Arran
- Does not meet 1+ criteria on NHS Greater Glasgow and Clyde's Special Needs in Pregnancy criteria
- Pregnant women who have passed 30 weeks of pregnancy prior to referral to trial
- Lack of capacity to consent to participating in research
- Insufficient English to participate in research or engage in groups
- Lack of spoken English
- Acute mental ill health, including active psychosis
- Homelessness to the extent that the women are non-contactable
- Receiving Family Nurse Partnership Scheme
- Participating in another trial of antenatal interventions, e.g. NSPCC Minding the Baby
- A decision has already been made that their child will be removed at birth
- Women who miscarry after recruitment or during the delivery of the interventions

3.3.2 Partners of women participating in the THRIVE trial

- Female partner of mother recruited to THRIVE trial
- Partner meets 1+ criteria for THRIVE trial
- Not living in NHS Greater Glasgow and Clyde OR NHS Ayrshire and Arran
- Lack of capacity to consent to participating in research
- Insufficient English to participate in research
- Lack of spoken English

3.3.3 Health and social care practitioners

- Not employed by NHS Greater Glasgow and Clyde or Ayrshire and Arran Healthboards to deliver interventions for the THRIVE trial
- Lack of capacity to consent to participating in research
- Insufficient English to participate in research
- Lack of spoken English

3.3.4 Referring practitioners

- Not employed within NHS Greater Glasgow and Clyde catchment areas
- Not employed within NHS Ayrshire and Arran catchment areas
- Not working in organisations approached by THRIVE trial to refer women to trial
- Lack of capacity to consent to participating in research
- Insufficient English to participate in research
  Lack of spoken English

3.4 Identification of participants and consent

3.4.1 Women who have additional health and social care needs in pregnancy

The recruitment of women to the trial will commence in late summer 2013. In total, 500 women identified by the SNiPs protocol as having additional health and social care needs will be recruited. Participants who meet the trial inclusion criteria will be referred to the THRIVE trial by health and social care practitioners, or recruited directly in clinic settings by members of the THRIVE research team employed by the University of Glasgow, NHS Greater Glasgow and Clyde Clinical Research Facility or the Scottish Mental Health Research Network. Potential participants or the referring practitioner will be asked to sign and date a referral form to state that consent has been given for personal identifying information, including the patient's address, contact telephone numbers, CHI number and GP details to be provided to the THRIVE team.

Once a referral form has been received by the THRIVE team, a member of the THRIVE research team will input the patient details into the study database and confirm with

midwives based at the NHS Greater Glasgow and Clyde Clinical Research Facility whether the pregnancy is continuing. Once the pregnancy has been confirmed as continuing, a member of the THRIVE research team employed by the University of Glasgow will contact potential participants to arrange an appointment at which they will be afforded the opportunity to ask questions about the research, and should they agree, be consented to trial and have baseline measures completed. A letter containing an appointment card confirming the date of the baseline assessments will be sent to the participant along with a copy of the THRIVE recruitment to trial information booklet. Appointments will be made 5-10 days in advance to allow participants to have at least 24 hours to read through the information booklet prior to being asked to consent to trial.

At the consent and baseline visit, researchers will clearly explain all aspects of the study, and seek consent not only for participation in the study but also for the linkage of mother and infant data with routinely collected NHS health data, educational, social care and justice records. This will include asking permission to use the mother's and baby's NHS Community Health Index (CHI) number for tracing participants at follow ups 1 and 2 using electronic health records and data linkage using the NHS Greater Glasgow & Clyde's Safe Haven service. We will seek permission where applicable for the partners/fathers to be contacted in relation to research assessing male partners' involvement and influence upon mothers' involvement in group interventions and antenatal care. We will also seek permission to store the women's contact details on file so that we can re-contact them in the future should we be able to secure additional funding to follow up mother and child outcomes over a longer period. During the consent process it will be clearly indicated to potential participants that they do not have to participate in the research process, and that they have the right to withdraw from the study at any point without providing justification. All participants will be provided with the opportunity to ask questions and seek clarification about what participation in the THRIVE trial will involve.

3.4.2 Partners of women participating in the THRIVE trial

Women who agree that their male partners can be contacted about the linked partner research will be asked to provide them with a questionnaire pack containing information sheets about the questionnaire and interview elements, and a postal questionnaire that can be returned using a pre-paid envelope. At the back of the questionnaire there will be a tear of slip that men can complete and return if they are interested in participating in two semi-structured qualitative interviews about their attitudes to fatherhood, parenting and their partner's participation in the THRIVE trial. Male partners may also be directly approached by members of the research team about participation in the semi-structured interviews whilst attending ETPB or MB group sessions, or during a home visit to a participating woman. Men that show an interest in participating in the two semi-structured interviews will be contacted by researchers at the University of Glasgow or Glasgow Caledonian University at time points before and after the birth of their partners' child. At this visit the researchers will clearly explain all aspects of the study and seek consent for participation in the semi-structured interviews. Consent will also be sought to store the men's contact details on file so that we can re-contact them to participate in a second interview once their partner's child has been born. During the consent process it will be clearly indicated to potential participants that they do not have to participate in the research process, and that they have the right to withdraw from the study at any point without providing justification. All participants will be provided with the opportunity to ask questions and seek clarification about what participation in the THRIVE trial will involve. Data collected from partners by questionnaire and interview will be form the basis of addressing research questions for two linked PhD studies on attitudes to fatherhood and intergenerational transmission of parenting values, and will also contribute to the wider process evaluation being conducted as part of the THRIVE trial.

3.4.3 Health and social care practitioners

Advertisements for up to 40 health and social care practitioners to deliver the ETPB and MB interventions will be placed by NHS Greater Glasgow and Clyde and NHS Ayrshire and Arran Health Boards. After the practitioners have been recruited, we plan to randomly allocate them

to either the ETPB or MB arms of the trial. However, as some practitioners may already have experience delivering ETPB or MB it might not be feasible to use a fully randomised design as that could introduce contamination between arms of the trial. To avoid contamination we will allocate those practitioners to the intervention in which they have experience. We will still randomly allocate the other practitioners. Although employed to deliver the interventions, the practitioners will also be participants in the trial, with quantitative and qualitative data collected about their experiences of being trained in and delivering the interventions. As a result, all practitioners will be provided with information sheets about the research elements of the trial and asked to provide consent for participating in these elements. During the consent process it will be clearly indicated to practitioners that they do not have to participate in the research process, and that they have the right to withdraw from the study at any point without providing justification. All practitioners will be provided with the opportunity to ask questions and seek clarification about what participation in the THRIVE trial will involve.

3.4.4 Referring practitioners

A purposive sample of a maximum of 40 referring practitioners will be drawn up from practitioners based in high/mid/low referring practices and approached by a THRIVE researcher about participating in a semi-structured interview about the barriers and facilitators of referral to the THRIVE trial. All practitioners will be provided with information sheets about the research elements of the trial and asked to provide consent for participating in these elements. During the consent process it will be clearly indicated to practitioners that they do not have to participate in the research process, and that they have the right to withdraw from the study at any point without providing justification. All practitioners will be provided with the opportunity to ask questions and seek clarification about what participation in the THRIVE trial will involve.

3.5 Withdrawal of subjects

Participants will be withdrawn from the trial in the following circumstances:

- At their own request
- At the request of the Independent Data Monitoring Committee
- They become ineligible as the study progresses

All participants, regardless of reason for inclusion within the study, have the right to withdraw from the trial at any point for any reason. The investigators can also withdraw patients from the study or trial interventions in the event that they no longer meet trial inclusion criteria, if there has been a significant change in their cognitive circumstances which means participation in the research or intervention elements is no longer possible, or in the event of safety concerns and protocol violations arising.

If a participant is to be withdrawn a discussion will take place with the participant about the reasons for their withdrawal. Data collected till the point of withdrawal will be retained and this will be clearly documented in participant information and consent forms. The only exception to this is where participants contact the THRIVE team and request in writing that all data held upon them be deleted and destroyed.

It is likely that some women will become ineligible for trial participation after expressing an initial interest in participation due to spontaneous or medical termination of pregnancy. In the event of this occurring the researchers will handle this situation sensitively. To minimise the risk of patients whose pregnancies are non-continuing being approached about participation in THRIVE the researchers will check the progression of the pregnancy prior to scheduling the appointment during which consent and baseline measures are completed.

Withdrawal due to adverse event is unlikely as we anticipate there will be minimal risk to the women participating in the study from either the research measures or the interventions (see section 5 for further details on our assessment of the safety of both research measures and interventions).

4 TRIAL PROCEDURES

4.1 Study schedules

The schedule of assessments for each sub-group of participants is provided above. This section provides a description of research undertaken with each of the study populations.

4.1.1 Women who have additional health and social care needs in pregnancy

Outcome data will be collected from women at three time points. Baseline questionnaire data will be collected after the 12th week of pregnancy, whilst follow up data will be collected around six and 18 months after childbirth. In addition, video-recordings of mothers interacting with their infants in care-giving and play episodes, and answering 3 short questions about their relationship with their baby will be made when the infants are six and 18 months old. The following **outcome data** will be collected:

Baseline questionnaire
Includes questions on the reason for vulnerability in pregnancy; socio-demographic characteristics; previous childbirth history and parity; psychological distress, depression and anxiety, measured using the BSI-53 and HADS+I; women's health, measured using the EQ-5D; health in pregnancy; attitudes towards parenting; relationship with partner/father of child; and, recollections of childhood and childhood trauma.

First follow up questionnaire and service use diary (around 6 months postnatal)
Includes questions on childbirth experience; depression and anxiety, measured using the HADS+I; women's health, measured using the EQ-5D; antenatal care history; health after pregnancy; child's health and development; attitudes towards parenting; parenting self-efficacy; relationship with partner; peer, partner and family support; child's relationship with father; and use of health, social care, educational and criminal justice services by themselves and their baby between Baseline and Follow Up 1.

Second follow up and service use diary (around 18 months postnatal)
Includes questions on depression and anxiety, measured using the HADS+I; women's health, measured using the EQ-5D; child's health and development; attitudes towards parenting; parenting self-efficacy; relationship with father; peer, partner and family support; child's relationship with partner; child's learning environment; child's language development, measured using the sure start language questionnaire; and use of health, social care, educational and criminal justice services by themselves and their baby between Follow Up 1 and 2.

The outcome data collected from the women will be supplemented by process evaluation designed to interpret the trial outcomes and to answer secondary research questions designed to investigate the fidelity of programme delivery; practitioners' characteristics, perceptions and motivation; mothers' engagement; the importance of different intervention components; and contextual factors facilitating or inhibiting delivery and participation.

Process evaluation research involves:

Pre-intervention, session evaluation and post-intervention questionnaires
Women receiving ETPB or MB will be asked to complete a pre- and post-intervention questionnaire about their expectations and experiences of participating in the group sessions. The pre-intervention questionnaire will be completed at the beginning of the first session, whilst the post-intervention questionnaire will be completed within two weeks of the last antenatal group session being delivered. In addition, women will be asked to complete session evaluation forms after each group session. During the intervention programmes, we will seek permission from the women to physically observe or video-/audio-record a sample of the sessions in order to assess the fidelity of intervention delivery and the quality of practitioner-participant interaction.

Telephone interviews
In order evaluate the postnatal elements of both intervention a randomly selected number of women will be asked to participate in a telephone interview (between 20 -30mins in length) on their expectations and experiences of the session. One woman per group per postnatal session will be asked to participate, Therefore, for every ETPB antenatal group 4 women will be asked be contacted to take part and for every MB group 1 woman will be contacted to contribute. This method of data collection has been chosen as are concerns that women within the ETPB group who will receive individual session would not be comfortable completely evaluation forms in front of the facilitator that has delivered the material and therefore not be wholly honest with their views.

Semi-structured interviews
Up to 60 women (ETPB n=20, MB n=20, CAU n=20) will be invited to participate in a semi-structured interview about their experiences of participating in the trial and the support that they have received during pregnancy, including their experiences of ETPB, MB and CAU. These interviews will usually happen when the women are between 20 and 38 weeks pregnant. The same sample of women will be interviewed around 6 and 18 months after the birth of their child (and after outcome data has been collected) in order to explore the perceived lasting effects of the intervention upon their parenting. A nested purposive sample of young women with a history of being looked after and accommodated by local authorities (n=33) will also be invited to answer additional questions, as per the request of our funders, to explore the parenting experiences of young people who are in/have been in the care system.

We anticipate that further women will be identified by the THRIVE steering group and data monitoring committee to participate in semi-structured interviews to explore issues arising from the trial, this number will not exceed 30 women. These will be identified by the THRIVE steering group and data monitoring committee, and will be dependent upon the timing of emerging issues.

Routinely collected data and access to Guthrie Bloods
Consent will be sought from all women participating in the trial for linkage of mother and infant data with routinely collected NHS health data, educational, social care and justice records. This will include asking permission to use the mother's and baby's NHS Community Health Index (CHI) number for data linkage using the NHS Greater Glasgow and Clyde Safe Haven service. This data will be used to allow the health economics evaluation to assess the broader societal costs associated with receiving ETPB, MB and CAU.

Consent will be sought from all women to access and potentially use their infant's Guthrie Bloods for research purposes. At this stage we do not have funding in place for this, and further ethical approval will be sought from the REC should we decide to utilise the bloods for research purposes.

4.1.2 Partners of women participating in the THRIVE trial

The male partners of women participating in THRIVE will be provided with postal questionnaires via their partner or a member of the research team. These will include questions on socio-demographic background; relationship with partner; feelings about partner's pregnancy, motherhood, fatherhood and parenting; and, recollections of childhood and childhood trauma. In addition, up to 50 men will be invited to participate in two semi-structured interviews about the effects of fathers on mother-child interaction, mother's participation in trial and the men's perceptions of fatherhood and factors influencing parenting.

4.1.3 Health and social care practitioners

All practitioners delivering ETPB and MB will be asked to complete a questionnaire at three time points: pre-training, immediately post-training and following 12 months experience delivering the interventions. This will include information on their experience and qualifications, experience working with families, experience running parenting groups (including any previous training that they have undertaken to deliver groups), their perceived level of confidence and proficiency in running parenting groups in general and the specific intervention in particular. 18 practitioners, 9 per intervention, will be invited to participate in a semi-structured interview about their expectations of training; motivation for participating in the study; views on the specific parenting intervention and the need for fidelity; expectations of delivering the interventions; history working with, and perceptions of, families and vulnerable groups; previous training in parenting programs; and, expectations of supervision during delivery of interventions. The same practitioners will be interviewed after they have 12 months experience delivering ETPB or MB.

As previously noted, we will ask permission to observe the delivery of ETPB and MB using researcher observation or audio-/video-recordings. At the end of each session the practitioners will be asked to complete protocol adherence checklists. These will be requested from Mellow Parenting and Triple P to assess fidelity of programme delivery. Practitioners will receive routine supervision from practitioners more experienced in delivering ETPB or MB during intervention delivery. All supervisors recruited to the study will be asked to participate in two semi-structured interviews (before delivery of the first groups; 12 months after intervention delivery has begun) with the research team about their experiences of providing supervision.

4.1.4 Referring practitioners

A geographically purposive sample of 20 health and social care practitioners involved in the recruitment of women to the trial will be invited to participate in a semi-structured interview about their experiences of recruiting women to the trial, and the decisions that they make in relation to the inclusion/exclusion criteria provided. The sample of midwives invited to participate in the interview will be stratified by recruitment rates to allow us to compare the experiences of those with high and low recruitment rates. In addition to the semi-structured interviews outlined previously, practitioners involved in the recruitment of women to the THRIVE trial may be asked to participate in semi-structured interviews to explore issues arising from the trial. The samples sizes and the issues to be explored will be identified by the THRIVE steering group and data monitoring committee, and will be dependent upon the timing of emerging issues. Examples of topics that might be explored include attrition and difficulties recruiting specific types of women.

4.2 Study Outcome Measures

All outcomes will be compared in the ETPB, MB and CAU groups.

4.2.1 Primary Outcome Measures

The THRIVE trial has three primary outcome measures. These are:

- maternal mental health, in particular maternal depression and anxiety, measured at around 6 months postnatal using the Hospital Depression and Anxiety Scale

- maternal outwardly expressed irritability, measured at around 6 months postnatal using the outwardly expressed irritability questions on the Adult Wellbeing Scale

- sensitivity of mother-infant interactions, measured at around 6 months postnatal using the CARE Index

4.2.2 Secondary Outcome Measures

The THRIVE trial has nine secondary outcome measures. These are:

- maternal mental health, in particular maternal depression and anxiety, measured at around 6 months postnatal using the Hospital Depression and Anxiety Scale

- maternal outwardly expressed irritability, measured at around 6 months postnatal using the outwardly expressed irritability questions on the Adult Wellbeing Scale

- sensitivity of mother-infant interaction, measured at around 6 months postnatal using the CARE Index

- number of children flagged as 'at risk' on the social services risk register, under a child protection plan, taken into local authority care or attending accident and emergency, measured using routinely collected NHS and Social Care Records

- child language development at around 18 months, measured using the Sure Start Language inventory

- child socio-emotional development at around 30 months as measured using the Strengths and Difficulties Questionnaire

- comparison of costs and outcomes associated with intervention delivery and routine antenatal care measured using routinely collected (NHS, social care, criminal justice and education) data, the EQ-5D-3L and self-reported patient service use

- assessment of programme fidelity; practitioners' characteristics and motivation; mothers' engagement; the intervention mechanisms; and contextual factors affecting mother and infant outcomes, measured using self-reported practitioner data, ethnographic observation and semi-structured qualitative interviews

- assessment of whether fathers' involvement or support affect mothers' engagement with intervention delivery, measured using semi-structured qualitative interviews

Within the THRIVE baseline, follow up 1 and follow up 2 questionnaires we have also included a range of measures that will be used to provide descriptive statistics for the study population, and may also act as covariates or confounders in analyses exploring variations in outcomes across trial arms. The range of measures that we have chosen includes questions on SES, childbirth history, labour and delivery experience, maternal health and wellbeing, infant health and wellbeing, relationship history, father of baby, perceived support, parenting expectations, parenting experiences and maternal perceptions on the quality of mother-infant bond.

5. ASSESSMENT OF SAFETY

A number of risks have been identified for individuals participating in the THRIVE trial. These are listed below, along with our assessment of potential harms and the steps taken to minimise these.

5.1 Participation in the research

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

5.2 Participation in the interventions

Since we will be working with vulnerable women at a sensitive period in their lives, 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 both interventions are 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 woman and will be able to provide empathetic 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 ETPB and MB within group settings 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. A linked-PhD is currently being advertised that will explore potentially positive and adverse effects of relationships formed as a result of group participation.

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 THRIVE project manager and their line manager at NHS Greater Glasgow and Clyde's Clinical Research Facility.

5.3 Access to routine services

Participation in the research will not affect women's access to health and social care. All women will continue to receive their maternity care plan during and after pregnancy, and no care will be withheld due to participation in the study. 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).

5.4 Privacy of routinely held records and data linkage

All data linkage will be initiated by the Robertson Centre for Biostatistics (RCB) using the NHS Greater Glasgow and Clyde's Safe Haven that has been developed to support secondary research use of clinical data. Data from NHS Ayrshire and Arran will also be required and access to these data via Safe Haven will become available during the life of the THRIVE trial. If this does not occur then the research team will seek permission from ISD Scotland to link NHS records for NHS Ayrshire & Arran's patients into the Safe Haven. In addition to accessing routine NHS datasets we will ask permission from the participants to access routinely held social care, education, police and judiciary records about them and their child. We will request that these data are linked within the NHS Greater Glasgow & Clyde's Safe Haven during the life of the trial. Should this data not be made available during the lifespan of the trial the research team will liaise with the RCB to identify methods of linking this data in a manner that does not compromise patient confidentiality and privacy. The research team understands that data linkage at the individual level is sensitive and raises issues of privacy and will ensure that all data linkage undertaken adheres to the standards outlined by ISD Scotland. In addition, the NHS Greater Glasgow & Clyde's Safe Haven is subject to a local privacy advisory committee that will ensure that that privacy risks at the individual patient level are minimised.

5.5 Storage and anonymisation of confidential data

All data collected will be stored securely in accordance with University of Glasgow's Best Research Practice Guidelines in either locked filing cabinets or password-protected databases accessible only by members of the University of Glasgow research team and their research partners at Glasgow Caledonian University, the University of Manchester, University of Aberdeen and the University of Newcastle. Identifying information will be held separately at all times from non-identifying information. No names will be retained on any mother, father or practitioner questionnaires. Unique ID codes, and corresponding barcodes, will be used to identify all participants in order to link them throughout the study and identifying information linking participants to ID numbers will be stored securely in a database accessible only by the research team and Survey Office staff based at the University of Glasgow and Glasgow Caledonian University. Identifying information will be held separately from participant questionnaires and interview transcripts.

All quantitative data collected as part of the study will be securely transferred to the Robertson Centre for Biostatistics (RCB) for data entry and cleaning. Qualitative interview data and recordings of intervention delivery sessions will be transcribed by an external transcription agency, and securely stored by researchers based at the University of Glasgow and Glasgow Caledonian University. Video-recordings of mother-infant interaction will be securely transferred to the University of Manchester using a secure internet platform designed and maintained by the RCB for observer-rated coding using the CARE Index and the Mellow Parenting Observation System. The one expectation to this rule is to allow the transfer of a small number of anonymous video-recordings to Mellow Parenting for rater quality control checks.

In all cases data sharing and confidentiality agreements will be established per University of Glasgow regulations. All of the data collected as part of the study will be anonymised. Permission will be sought from participants for archiving purposes during trial consent, and the trial consent form will notify participants that their and their child's data will be made available to the funders in anonymised form.

6. INTERVENTIONS

Patients who eligible for the study will be randomised to receive either

- Enhanced Triple P for Baby
- Mellow Bumps
- Routine Antenatal Care

6.1 Enhanced Triple P for Baby (ETPB)

ETPB was developed at the Parenting and Family Support Center (PFSC) at the University of Queensland, Australia and is provided as a service to families by Triple P International. The efficacy and effectiveness of Triple P interventions delivered in five different levels of intensity have been demonstrated in numerous studies and randomised trials. [31, 32]

ETPB is informed by social learning theory. It comprises four antenatal group sessions (two hours each session) and three postnatal one-to-one sessions delivered either face-to-face or by telephone (40-60 minutes each session) plus one final session (60 minutes) which can be delivered either individual or in a group. Thus, the intervention lasts approximately 16 hours. ETPB's emphasis is on families and includes fathers, with very practical content around expectations and skills to meet the challenges of becoming a parent whilst ideally maintaining a happy family or at least reducing family discord. In the first two sessions mothers and their partners are introduced to positive parenting ideas and asked to reflect on their expectations about parenthood and knowledge of infant development. Then they are provided with guidance on to how to respond to common infant problems (i.e., crying, fussing) and how to interact with their infants in a nurturing, positive environment. They are then introduced to a range of 'survival skills' for dealing with psychological distress and how this impacts on their ability to appropriately interact with others, including their infants. The final two group sessions focus on partner support and strategies for positive communication in order to ensure practical and emotional support, facilitate adjustment to parenthood and reduce marital stress and social isolation. The postnatal sessions allow the woman/parents to practice these coping strategies and techniques once their baby is born. The foci for these sessions are determined by the parents who are encouraged to become their own coach throughout (and have their own workbook).

6.2 Mellow Bumps (MB)

MB was developed by Mellow Parenting. Trial data for Mellow Parenting programmes is encouraging. [33] MB is underpinned by attachment theory and designed to target women who have are have additional health and social care needs in pregnancy. It involves seven antenatal group sessions and one postnatal group session (each two hours, i.e. 16 hours in total), focuses on mothers, although fathers are invited to one session; and the content focuses on encouraging nurturing, engagement and synchrony between mother and baby. In each session, a topic is raised that relates to maternal wellbeing. This includes healthy eating, exercise, relaxation and having fun for the mothers as well as exploring barriers to good parenting and sources of support which will benefit the mother and the baby. The infancy foci are the competencies of infants, infant brain development and the significance of very early interaction for shaping this development. The group dynamics and the development of safe relationships within the group play a key role in allowing mothers to address their current emotional state and its modulation. All activities are designed to require only the minimal literacy, with the emphasis on activity, viewing videos and discussion.

6.3 Routine care (Care as Usual)

All women recruited to the trial will receive Care as Usual. Participants in NHS Greater Glasgow & Clyde will receive care in line with NHS Greater Glasgow & Clyde's Special Needs in Pregnancy protocol. Participants in NHS Ayrshire & Arran will receive care in line with NHS Ayrshire & Arran's Vulnerable Families guidelines. A Pre-Birth Case Conference may be arranged, between weeks 28-32 of the pregnancy, which may be followed by either a Child Protection Case Conference Post-Birth or a Post-Birth Planning Meeting. The CAU group will not be offered group based parenting interventions such as ETPB or MB, although contact with health visitors, Parents and Children Together (PACT) teams and any relevant specialist services such as the Community Addictions Team will be available.

7. SAFETY REPORTING

The THRIVE trial adheres to Good Clinical Practice guidelines on safety reporting in clinic trials. THRIVE 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 project manager who will inform the CI. All practitioners and researchers are trained in these procedures.

7.1 Definitions of adverse events

Adverse Event (AE) – Any untoward medical occurrence in a subject to whom a medicinal product/ intervention has been administered, including occurrences which are not necessarily caused by or related to that product.

7.2 Serious Adverse Event (SAE)

Any adverse event or adverse reaction that:

a. results in death
b. is life threatening
c. requires hospitalisation or prolongation of existing hospitalisation
d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect
f. is otherwise considered medically significant by the investigator
g. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

7.3 Recording and reporting of Adverse Events

Any SAE occurring to a research participant will be reported to the main REC (i.e. the REC that gave a favourable opinion of the study) where in the opinion of the Chief Investigator (CI) the event was:

"Related" – that is, it resulted from administration of any research procedures, and
"Unexpected" – that is, the type of event is not an expected occurrence.

Reports of related and unexpected SAEs will be submitted to the REC within 15 days of CI becoming aware of the event, using the report of serious adverse event form for non-CTIMPS published on the National Research Ethics Service (NRES) website.

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

7.4 Annual Safety Reporting

The CI is also responsible for providing an annual progress report to the REC using an NRES 'Annual Progress Report form for all other research'. This form is available at: http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/

A section on the safety of participants is included in this report.

8. STATISTICS AND DATA ANALYSIS

8.1 Statistical analysis plan

The study will have a comprehensive Statistical Analysis Plan, which will govern all statistical aspects of the study, and will be authored by the Trial Statistician and agreed by the Trial Steering Committee before any unblinded data is seen.

8.2 Statistical power

The THRIVE trial has been powered based upon the proposed primary outcomes. These are maternal mental wellbeing and mother-child interaction. In particular, THRIVE aims to assess whether women receiving ETPB or MB show:

1) significantly lower anxiety, depression and outwardly directed irritability compared to those receiving CAU when their babies are around 6 months old.

2) significantly higher maternal sensitivity scores in mother-infant interactions (compared to those receiving CAU when their babies are around 6 months old).

Maternal mental wellbeing will be measured using the Hospital Anxiety and Depression (HADS) and the outwardly directed irritability (I) questions from the Adult Wellbeing Scale (HADS+I), whilst mother-infant interaction quality (MIIQ) will be measured using the observer-rated child-centred component of the CARE index. Both of these measures are well established and validated. Video-recordings of mother-infant interaction will be analysed by researchers at the University of Manchester. These researchers will be blinded to the conditions that participants have been allocated, and will code the quality of mother-infant interactions using the CARE index [30] and the Mellow Parenting Observation System [41]. The raw coding scores will then be transferred to the Robertson Centre for Biostatistics to be used in the primary efficacy analysis.

The efficacy of ETPB and MB will be analysed at a significance level of 2.5% in order to maintain an overall Type I error rate of 5%. Two analyses, performed in a hierarchical fashion so no further p-value adjustment is necessary, will be undertaken. Analysis 1 will compare the two intervention groups (ETPB and MB) with CAU. If a positive result, at a significance level of 2.5%, is found then Analysis 2 will compare ETPB and MB. If Analysis 1 does not give a positive result, the focus of subsequent analyses will shift from testing whether ETPB and MB achieved different outcomes and determining which, if any, intervention was effective.

In order to have 90% power to detect an effect size of less than 0.5 for Analysis 1 and 0.4 for Analysis 2 requires 157 participants in both the ETPB and MB groups. Comparing these 314 subjects with CAU in Analysis 1 can be achieved with only 63 participants in the CAU group. Therefore, 377 participants are required. Due to the trial purposively recruiting women who are vulnerable in pregnancy, we decided to opt for a cautious attrition rate (25%) to minimise risk to the trial. To allow for 25% attrition at first follow up, 500 participants will be randomised.

The mother-centred primary outcome is the HADS+I. No data are available on the standard deviation (SD) of this measure in a comparable population. However, data from a similar sample of vulnerable mothers suggest the mean value on the Outwardly Directed Irritability (I) subscale of the Adult Wellbeing Scale (AWS) to be 4.7 points with a SD of 2.7.[34] Department of Health (DoH) Guidelines indicate that scores of 8 or more have a problem on this scale, with 5-7 being borderline; given the above mean and SD, we would expect 15% of mothers to have scores of 8 or more, and a further 38% to lie in the borderline range.[35] An effect size of 0.5 points (Analysis 1) would represent a mean difference of 1.35 points between the active intervention groups and CAU, and would results in a reduction in the clinical range to 6%, and in the borderline range to 28%. In addition, the anxiety subscale of the HADS has been found to have a SD of roughly 4.8 points in a population of non-

vulnerable mothers-to-be. [36] Effect sizes of 0.5 and 0.4 would therefore represent differences in mean HADS anxiety score of 2.4 and 1.9 points, which clinicians would consider to be clinically significant.

The child-centered primary outcome is the observer-rated child-centered component of the CARE index (Mother-Infant Interaction Quality, MIIQ) has a SD of approximately 3 points. A score in the range 0-2 suggests the need for psychotherapy for the parent, 3-4 suggests the need for a lesser parental intervention and score of 5-6 suggest the need for parental education only, whilst a score of 7 or over is considered normal. For Analysis 1, an effect size of 0.5 corresponds to a difference in mean MIIQ scores between the active interventions and CAU of 1.5 points; for Analysis 2, an effect size of 0.4 would equate to a 1.2 point difference, either of which would represent a clinically relevant difference. [28]

Although we have powered the study at 90%, we will also have good power to detect smaller effect differences. For example, we will have 80% power to detect an effect size of 0.35 between the two active interventions (Analysis 2), corresponding to a difference of 1.05 points on the MIIQ.

8.3 Primary and secondary efficacy analysis

Video-recordings of mother-infant interaction will be analysed by researchers at the University of Manchester. These researchers will be blinded to the conditions that participants have been allocated, and will code the quality of mother-infant interactions using the CARE index [30] and the Mellow Parenting Observation System [41]. Raw scores will be entered into a secure data platform maintained by the Robertson Centre for Biostatistics and integrated into the trial dataset.

Primary and secondary efficacy analyses will be undertaken by the Robertson Centre for Biostatistics. Baseline-adjusted linear regression analysis (ANCOVA) will be used to compare primary statistical outcomes between intervention groups. Similar methods will be used for other outcomes (using data transformation and alternative regression methods, depending on the distribution of each outcome). Regression models will be extended to investigate the effects of baseline characteristics and the potential moderating effects of these variables and other measures of intervention compliance. Repeated measures methods will be applied to outcomes collected at more than one post-baseline assessment. Missing data will not be imputed in the first instance, but the sensitivity of key results will be assessed under alternative assumptions regarding missing values, such as imputation with the baseline value or with the average response in the alternative group. Multiple imputation, based on predictive regression models of study outcomes on baseline and intermediate outcome measures, will also be explored to account for the additional uncertainty in estimates of intervention effect differences due to missing outcome data. Whilst outcomes may exhibit clustering in the intervention arms of the study, due to being delivered in a group setting, this clustering will not be present in the CAU arm, and the anticipated benefits of the two interventions are expected to act in part through the group dynamic. Accordingly, since randomisation is performed at the individual, rather than at the group level, we will not make adjustment for the clustering of outcomes in the main analyses. We will, however, explore the extent of clustering of outcomes within each treatment arm as secondary analyses, in order to evaluate potential explanatory factors for any group-level variability in outcomes.

8.4 Analysis of process evaluation data

A process evaluation will be conducted in order to interpret the trial outcomes and to answer secondary research questions related to process. The process evaluation has three main components which are designed to investigate the fidelity of programme delivery; practitioners' characteristics, perceptions and motivation; mothers' engagement; the importance of different intervention components; and contextual factors facilitating or inhibiting delivery and participation. Summary statistics will be generated from quantitative

data collected for sampling purposes, and to describe both participant groups and experiences. Qualitative interviews conducted with practitioners, women participating in the trial and their partners will be audio recorded and transcribed. An initial coding schedule will be piloted with a representative sample of transcripts. A revised schedule incorporating emergent themes will then be used to code all the data, using NVivo. The data will be summarized in chart form for each key research question, with rows of interviewees and columns of substantive topics, such as 'perceptions of programme' or 'factors encouraging participation'. This charting will allow hypotheses to be tested systematically against all the relevant data and, where they are not supported, for the phenomena in question to be redefined, or the hypothesis modified until all cases are accounted for.

All process data will be analysed independently of the outcome data and before the outcomes are known. Descriptive accounts of the data will be prepared in the order of completion of each key 'project' (e.g. pre-training interviews; observations; interviews with mothers-to-be) as far as is practicable. Report writing is likely to be a critical part of the process evaluation since it will enable us to: 1) keep clear records of which substantive themes were identified when; 2) present what we thought about the data at particular stages of the evaluation (as opposed to reinterpreting data retrospectively in light of later analyses); and 3) compare data more easily.

8.5 Analysis of health economics evaluation data

Health Economics and Health Technology Assessment (HEHTA) at the University of Glasgow has been commissioned to undertake a comprehensive economic evaluation. The majority of applied economic evaluations in the area of home visiting and parenting (many of which have been conducted in the USA) [37-40] have suffered from diverse economic objectives and methodological problems including the lack of a societal perspective and limited cost analysis. The THRIVE evaluation will assess the costs and outcomes associated with the delivery of each intervention and CAU from the NHS and Personal Social Services (PSS) perspective favoured by the National Institute for Health and Clinical Excellence (NICE). A broader societal perspective will be adopted to allow for the possibility of costs and outcomes beyond the NHS and PSS such as housing, education, employment and justice. Up-to-date unit costs will be attached to quantities of resource used to generate mean costs per study participant. The incremental costs and benefits of the treatment arms will be reported within an incremental cost-effectiveness ratio (ICER) where appropriate. Costs to participants and families will be examined as part of a sensitivity analysis. The cost-effectiveness will be assessed by comparing the additional costs associated with each of the interventions with the outcomes achieved in the study and those achievable in the longer term. These longer term outcomes will be assessed by linking the short term outcomes identified in the study to longer term impacts on health and wellbeing for both mother and child via relationships identified from the literature. Economic resource use forms developed for the economic evaluation carried out by McIntosh et al 2009 [29] for the Economic Evaluation of an intensive home visiting programme for vulnerable families were used as templates for the service use questionnaire and data collection forms. Diaries completed by the study participants will be used as an 'aide memoir' to inform the economic resource use data collection at the follow up points. The inclusion of the EQ-5D generic outcome measure will also allow the estimation of a cost-utility analysis (preferred evaluative technique of NICE). In line with current guidance, discount rates of 3.5% for costs and benefits will be applied where appropriate. Sensitivity analysis will be carried out on the perspective adopted as well as key cost-drivers and outcomes. As per recent economic evaluation guidance, missing data will be predicted as a function of relevant baseline covariates. [42]

The economic evaluation will incorporate available trial linked data, project cost and outcome data from baseline, 6 and 18 months and up to 30 months follow up. The cost-effectiveness will be assessed by comparing the additional costs associated with each of the interventions to the outcomes achieved in the study and those achievable in the longer term. The trial aims at collecting a number of long term variables including health measures, educational outcomes, children on the at-risk register, and children taken into care and attending

Accident & Emergency departments. Based on the availability of such routine data, longer term economic outcomes will be assessed by linking the short term outcomes identified in the study to potential longer term impacts on health and wellbeing for both mother and child via trial extrapolation methods including economic modeling techniques.[43] However, given the well-recognised limited nature of this exercise in terms of assumptions required to link intermediate costs and outcomes to long term economic costs and outcomes, relationships identified from the literature will also be used to guide and strengthen modelling scenarios and form the basis of a more robust, evidence-based long term modelling exercise. This long term modelling exercise will contain a base case scenario and incorporate a significant number of sensitivity analyses to allow for the likely variation around long term costs and outcomes. Hence, the long term model will be based on the best data available at the time, including short and long term trial outcomes, routinely available linked data, as well as best evidence from the published literature. In doing so, an evidence-based, realistic picture of likely cost effectiveness from a societal perspective over the long term will be generated. This approach fits with guidance of the methods for the economic evaluation of public health interventions. [44]

8.5 Safety analysis

Serious adverse events – both numbers of subjects and events – will be summarised by randomised group and overall using descriptive statistics. No formal statistical tests comparing the randomised groups will be pre-specified.

8.6 Software for statistical analysis

The statistical software to be used will be specified in the Statistical Analysis Plan.

8.7 Management and delivery

The Robertson Centre for Biostatistics, part of the Glasgow Clinical Trials Unit, a fully registered UK CRN Clinical Trials Unit, will manage and analyse trial data. All statistical analyses will be conducted according to a pre-specified Statistical Analysis Plan.

9.0 STUDY CLOSURE / DEFINITION OF END OF TRIAL

The study will end when the steering committee agrees that one or more of the following situations applies:

- Last patient last study visit;

OR

i. The planned sample size has been achieved;
ii. The Independent Data Monitoring Committee has advised discontinuation, e.g. because of safety concerns about the trial, or a statistically significant difference in clinical outcomes is evident between the two treatment arms;
iii. There is insufficient funding to support further recruitment, and no reasonable prospect of additional support being obtained;
iv. New information makes it inappropriate to continue to randomise patients to one or other arm of the trial;
v. Recruitment is so poor that completion of the trial cannot reasonably be anticipated.

10. Data Handling

10.1 Randomisation

A central randomisation facility will allocate the randomised therapy per patient. Randomisation outcomes will be available by email notification. Randomisation will be undertaken after collection of baseline questionnaire data, and researchers based at the University of Glasgow will be unblinded to trial arm allocation. Participants will usually be notified of trial arm allocation when they are between 20-30 weeks pregnant.

10.2 Case Report Forms / Electronic Data Record

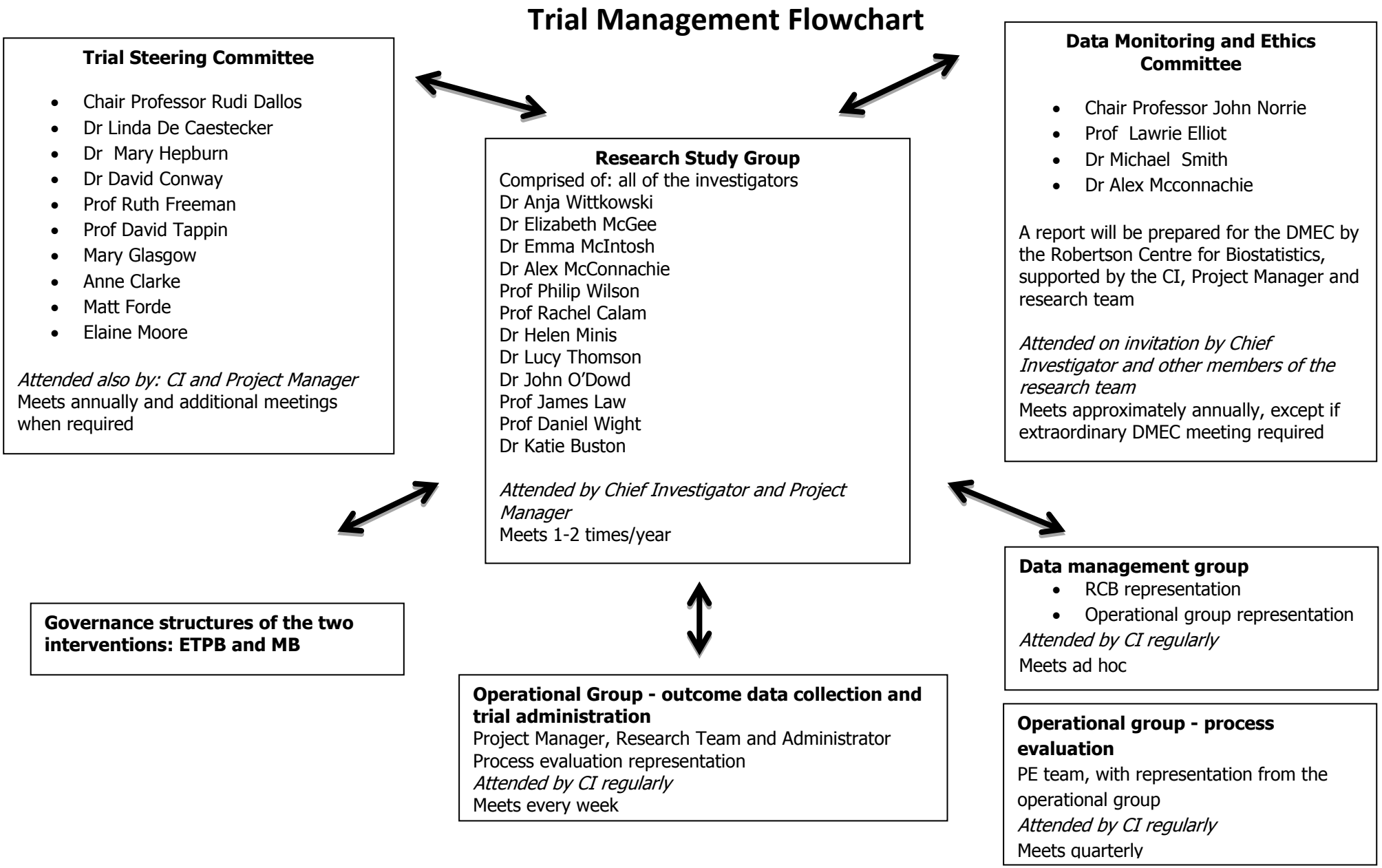
An electronic case report form (e-CRF) will be used to collect study data. The e-CRF will be developed by the study Data Centre at the Robertson Centre for Biostatistics, University of Glasgow and access to the e-CRF will be restricted, with only authorised site-specific personnel able to make entries or amendments to their patients' data. It is the investigator's responsibility to ensure completion and to review and approve all data captured in the e-CRF.

All data handling procedures will be detailed in a Study Specific Data Management Plan. Data will be validated at the point of entry into the e-CRF and at regular intervals during the study. Data discrepancies will be flagged to the study site and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

10.3 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. Data will be retained at the Data Centre for a minimum of 5 years.

11.0 TRIAL MANAGEMENT



11.1 Routine management of trial

The trial will be coordinated from the MRC/CSO Social and Public Health Sciences Unit, University of Glasgow by the Trial Management Group. The Trial Management Group normally includes those individuals responsible for the day-to-day management of the trial, such as the CI, statistician, trial manager, research nurse, data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

11.2 Trial steering committee (TSC)

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC should:

- agree the trial protocol and any protocol amendments
- provide advice to the investigators on all aspects of the trial
- have members who are independent of the investigators, in particular an independent chairperson.

Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the TSC.

11.3 Independent Data Monitoring Committee (IDMC)

The role of IDMC is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The IDMC will be independent of both the investigators and the funder/sponsor and will be the only body that has access to unblinded data. It will make recommendations to the TSC.

12. STUDY MONITORING/AUDITING

This study will undergo study set-up visit and site files will be provided. The study may be selected randomly for a routine study visit.

13. PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the TSC and any required amendment forms will be submitted to the regulatory authority, ethics committee and sponsor. The CI and the TSC will liaise with study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC and Research and Development (R&D) office(s).

14. ETHICAL CONSIDERATIONS

14.1 Ethical conduct of the study

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]).

Favourable ethical opinion was sought from the appropriate REC before patients were entered into this clinical trial. Patients will only be allowed to enter the study once either they have provided written informed consent.

The CI will be responsible for updating the Ethics Committee of any new information related to the study.

14.2 Informed consent

Written informed consent should be obtained from each trial participant. The Research Nurse or investigator will explain the exact nature of the study in writing, provision of patient information sheet, and verbally. This will include the known risks of participating in this clinical trial. Trial participants will be informed that they are free to withdraw their consent from the study or study treatment at any time. In the case of patients who were unable to consent at the start of the study, written informed consent will be sought once they regain capacity.

15. INSURANCE AND INDEMNITY

The THRIVE trial is sponsored by NHS Greater Glasgow & Clyde. The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

16. FUNDING

National Institute for Health Research (NIHR)
Public Health Research Programme
Evaluation, Trials and Studies Coordinating Centre
University of Southampton
Alpha House, Enterprise Road
Southampton SO16 7NS

NIHR Portfolio Number: (11/3002/01)
Total research funding: £1,086,244
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17. ANNUAL REPORTS

A biannual progress reports are submitted to the funder, the first being submitted 6 months from the date that all trial related approvals are in place. Annual reports will be submitted to the ethics committee and sponsor with the first submitted one year after the date that all trial related approvals are in place.

18. DISSEMINATION OF FINDINGS

The study team will develop a dissemination plan as the THRIVE trial progresses and nears completion. In summary, we will disseminate findings as follows:

Participants
THRIVE has a study website which will be regularly updated as the trial progresses. We will use this website to communicate key findings to participants in layman's terms.

Public
The CI will work with the communications office at the University of Glasgow to develop appropriate press releases to ensure effective public dissemination of the findings of the research.

Scientific Community
We will publish our findings in high impact peer reviewed journals including open access journals and the HTA series. We will also present at relevant high profile national and international scientific conferences.

Policy Makers
The CI will work closely with the SPHSU knowledge exchange manager to plan effective liaison with policymaking partners, with the aim of ensuring that the findings of the THRIVE trial are communicated effectively in a way that can help inform future policy development.

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