Manchester University
NHS Foundation Trust

MiNESS 20-28
Working together | Preventing Stillbirth

FULL TITLE: Mothers Working to Prevent Early Stillbirth Study 20-28

SHORT STUDY TITLE: MiNESS 20-28

PROTOCOL VERSION 1.4

DATE 18/10/2023

NCT06005272

Amendment History

Amendment No.	Protocol Version and date	Details of Changes Made
NSA01	1.2 01/08/23	Correction of typographic errors in participant information sheets
NSA02	1.3 21/09/23	Revision of inclusion/exclusion criteria and statistical analysis relating to control participants. Clarifies data sources to be accessed.
NSA03	1.4 18/10/23	Change in process for providing record of consent to participant. Clarifies electronic storage of potentially identifying data will be within access-restricted folders

RESEARCH REFERENCE NUMBERS

- IRAS 314658
- SPONSOR B01875
- FUNDER NIHR204398
- Clinicaltrials.gov NCT06005272

This protocol has regard for the HRA guidance and order of content

FUNDED BY
NIHR | National Institute for Health and Care Research

Signature Page

The sponsor signature on the IRAS form, acts as documented acceptance that the sponsor approves the protocol.

The Chief Investigator should sign below to confirm the following:

The Chief Investigator confirms the protocol has been agreed and accepted and agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: .... Date: 18/10/23

Name: (please print): Dr Lucy Higgins

LIST OF CONTENTS

KEY STUDY CONTACTS

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STUDY SUMMARY

Study Title	Mothers Working to Prevent Early Stillbirth Study 20-28
Internal ref. no. (or short title)	MiNESS 20-28
Study Design	Observational case-control study
Study Participants	Cases: recently pregnant people who have experienced baby loss during pregnancy, labour or immediately after birth between 20-28 weeks of pregnancy Controls: individuals still pregnant/recently delivered at same gestational age
Planned Size of Sample (if applicable)	948 participants, of whom: 316 cases, 632 controls
Follow up duration (if applicable)	Until delivery (up to 24 weeks for control participants)
Planned Recruitment Period	1st September 2023 – 31st August 2025
End of Study	Collection of final pregnancy outcome data (up to 24 weeks/6 months following recruitment of final participant).
Planned Study End Date	28th February 2026
Research Question/Aim(s)	Research question: Is early stillbirth associated with modifiable factors? Primary aim: to identify modifiable risk factors for early stillbirth that are amenable to public health campaigns or adaptation of antenatal care. Secondary aims: i. to confirm or refute whether the range of factors associated with late stillbirth are independently associated with early stillbirth, including (but not limited to) supine sleep position, caffeine intake and reduced fetal movement. ii. to explore interactions between maternal/parental characteristics (especially those relating to health inequalities including ethnicity and socioeconomic deprivation), fetal factors (including fetal growth restriction, reduced fetal movements) and early stillbirth risk.

	iii. to determine whether exposures associated with early stillbirth vary by cause of death.

FUNDING AND SUPPORT IN KIND

National Institute for Health and Care Research	Research for Patient Benefit scheme: £259,093

ROLE OF STUDY SPONSOR AND FUNDER

Manchester University NHS Foundation Trust is acting as sponsor for this study and is assuming overall responsibility for the initiation and management of the study. The Trust will provide permission to conduct the research and monitor the progress of that research. The research team all hold substantive or honorary contracts with the Trust and therefore the sponsor has influence over all aspects of the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results which are the responsibility of the research team.

National Institute for Health and Care Research (NIHR) are the funder. The funder is not involved in the study design, conduct, data analysis and interpretation, or manuscript writing. The funder has undertaken peer review of the study proposal prior to funding award.

Manchester University NHS Foundation Trust and the NIHR will undertake to assist dissemination of study results through highlighting the study findings on their communication channels.

Final decisions relating to all aspects of the trial design, management and interpretation are the responsibility of the Chief Investigator.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Design of the study has been informed by consultation with members of the public with relevant lived experience relating to pregnancy and/or early stillbirth. A study-specific public-participant involvement (PPI) group was convened to aid development of the research question, terminology, research design and matters relating to widening participation in this research (see section 7.4). The main group will be reconvened at the end of the initial data analysis period to inform interpretation and public dissemination strategies.

The Trial management group (TMG) comprises the study co-investigators, research midwife coordinator and sponsor representatives. It will be chaired by the Chief Investigator, meeting regularly at intervals

as determined by stage of study delivery (minimum six monthly) to review progress in study delivery and be collectively responsible for study management decisions.

External scrutiny is welcomed. An advisory group, comprising two subgroups (a stakeholder advisory subgroup and an expert advisory subgroup), has been recruited. The stakeholder group, comprises representatives from key charities/community interest groups who represent the interests of potential research users (those with healthy pregnancies and those bereaved through baby loss at this stage of pregnancy), as well as public contributors representing the study-specific PPI group who have personal experience of pregnancy/antenatal care, with and without personal experience of bereavement at 20-28 weeks' gestation. The expert advisory group comprises international experts in stillbirth epidemiological research who have considerable experience in the design, delivery and analysis of similar stillbirth studies in other settings. They advisory group will advise the TMG, having particular input in the interpretation of the study findings and recommendations, the public and scientific dissemination plan and providing advice in the event of experiencing participant recruitment challenges.

PROTOCOL CONTRIBUTORS

The protocol was drafted by Higgins and Heazell. All co-investigators have reviewed and approved the finalised version. Relevant sections of the protocol and associated documents have also been reviewed and edited by representatives of the study-specific PPI group. The study-specific PPI group members have informed of the study question, design, promotional materials and language used within the study documents. The Sponsor (Manchester University NHS Foundation Trust) has influence over all aspects of the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results which are the responsibility of the research team. The Funder (National Institute for Health and care Research) has had no role in study design, nor will they have a role (beyond that described on page vii-viii) in study conduct, data analysis, interpretation, manuscript writing or dissemination of results. The Chief Investigator retains final decisions regarding any of these aspects of the study.

KEY WORDS:

Early stillbirth
Perinatal death
Case control study
Risk factors
Sleep position

Abbreviations

Abbreviation	Definition
APR	Annual progress report
CI	Chief Investigator
Co-I	Co-Investigator
(e)CRF	(electronic) Case report form
DCC	Direct clinical care
GCP	Good Clinical Practice
IG	Information governance
IRAS	Integrated research application system
IT	Informatics team
HCRW	Healthcare research Wales
HRA	Health research authority
MBRRACE	Mothers and babies: reducing risk through audits and confidential enquiries across the UK
MFT	Manchester University NHS Foundation Trust
MiNESS	Midlands and north of England stillbirth study
MiNESS 20-28	Mothers working to prevent early stillbirth study 20-28
NHS	National health service
NICE	National institute for health and care excellence
NIHR	National institute for health research
PMRT	Perinatal mortality review tool
PPI	Patient and Public Involvement
PSP	Priority setting partnership
R&D	Research and development
REC	Research Ethics Committee
REDCap	Research electronic data capture
RFM	Reduced fetal movement
RM	Research midwife
Sands	Stillbirth and neonatal death society
SBL	Saving babies lives
SOP	Standard operating procedure
SMF	Study management file
TMG	Trial management group
UK	United Kingdom
USA	United States of America

STUDY FLOW CHART

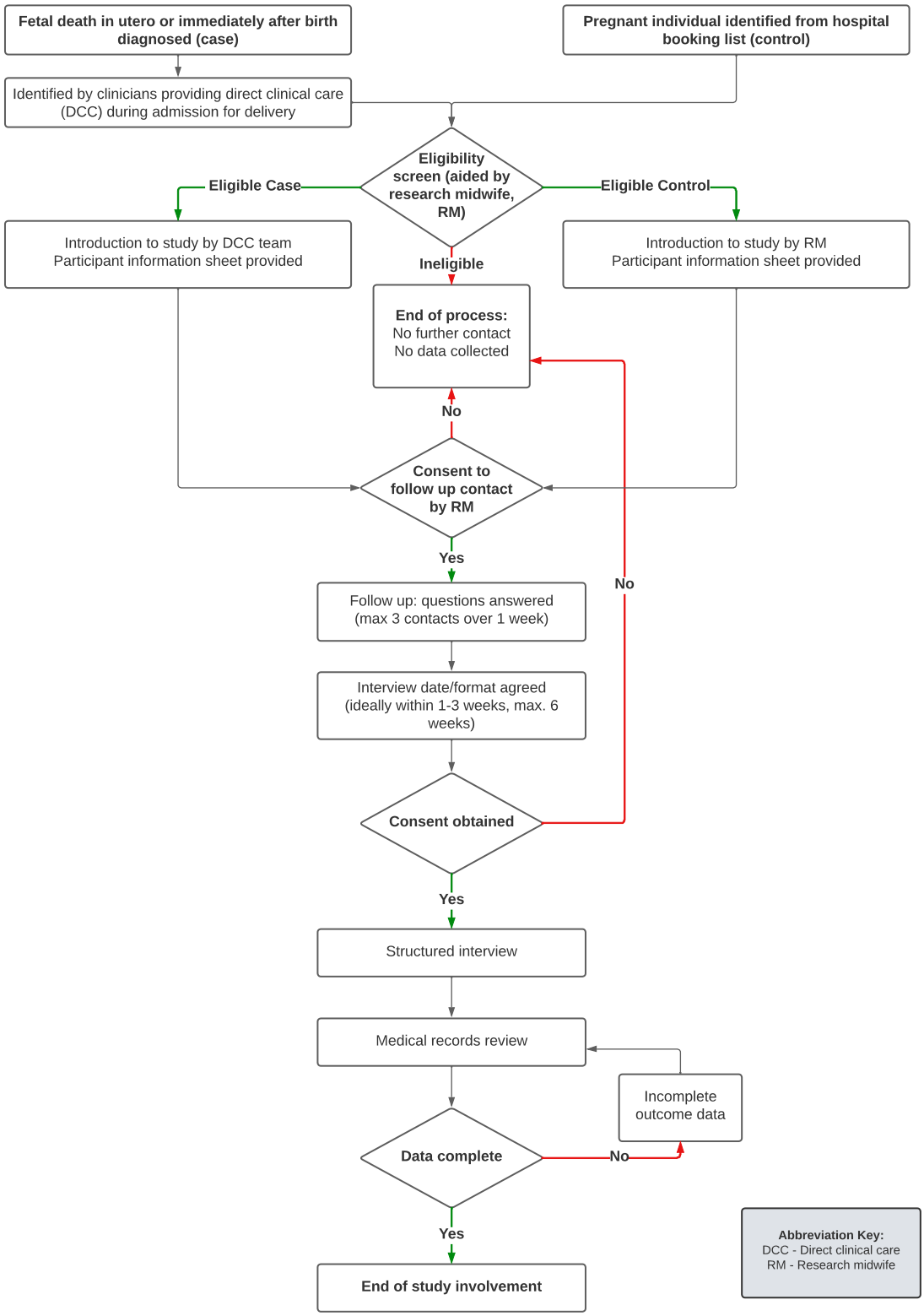

Figure 1: Study flow chart

STUDY PROTOCOL: MOTHERS WORKING TO PREVENT EARLY STILLBIRTH STUDY 20-28 (MiNESS 20-28)

1 BACKGROUND

Stillbirth, the death of a baby before or during birth, is associated with adverse psychological, social and economic outcomes for the mother, their partner, their wider family and society (1). Stillbirth costs >£27.2M per year in the UK in healthcare, workplace absence and funeral costs alone (2). Reducing stillbirth and neonatal death is a Government priority (3) and a primary concern for parents and families (4, 5). To prevent these deaths it is important to understand modifiable risk factors for baby loss, a topic identified as a research priority by the Stillbirth and Miscarriage Priority Setting Partnerships (4, 5).

In the UK, stillbirth (legally defined as death before birth of a baby ≥24 weeks' gestation) affects 4 in every 1,000 UK births (over 2,500 cases each year). However, this number is an underestimate in the true burden of baby loss, as most high-income countries (e.g. USA, Australia) record stillbirths from 20 or 22 weeks' gestation. Studies demonstrate that baby death between 20 and 24 weeks' gestation (an additional ~750 UK deaths/year) has a similar impact on parents' physical and psychological wellbeing (6). There is also evidence that births with signs of life occurring at pre-viable gestations (between 20-22 weeks' gestation) are variously reported as stillbirths or neonatal deaths in different maternity units around the UK (7). Therefore, in line with parents' requests and literature reviews, in this study we shall study baby deaths occurring between 20-28 weeks' gestation, whether occurring before or during labour or immediately after birth. For consistency, these baby losses (legally second trimester miscarriage / stillbirth / immediate neonatal death) will be referred to as "early stillbirth", in line with parents' wishes (6).

Previous and ongoing efforts to reduce stillbirth have principally focused on deaths occurring after 28 weeks' gestation. By understanding those at greatest risk of late stillbirth, effective healthcare interventions (e.g. Saving Babies Lives (SBL) Care Bundle V2 (8)) have been rolled out across England (and internationally). Consequently, UK stillbirths have reduced by 15% from 2014-2018 (9). The Midlands and North of England Stillbirth Study (MiNESS), the precursor of this current study, evaluated modifiable risk factors for stillbirth after 28 weeks' gestation, identifying an association with going to sleep on the woman's back, among other potentially modifiable exposures (10, 11, 12, 13, 14). These findings informed national and international education campaigns and policy. As a result, sleep position recommendations for pregnant people have been incorporated into NHS England SBL Care Bundle V2 (15) and NICE antenatal care guidelines (16). Dissemination of information about such modifiable factors in late pregnancy may be partly responsible for the recent reduction in late stillbirth in the UK and gives confidence in the ability of this study to produce a further reduction by doing the same for early stillbirth. Critically, there has been no reduction in the number of stillbirths occurring before 28

weeks – which account for 40% of losses (~1,600 losses between 20-28 weeks each year). In order to meet the UK Government's target of 50% fewer stillbirths by 2025 (and beyond), early stillbirths occurring before 28 weeks of pregnancy must also be reduced.

1.1 Trial design:

This is a non-interventional (observational) questionnaire-based case-control study. 316 mothers/parents who have recently been bereaved through early stillbirth at 20-28 weeks' gestation (before/during labour or immediately after birth), and 632 people who were still pregnant at the same gestation will complete one interview with a research midwife. The interview will take the format of a research midwife-administered (and completed) questionnaire which gathers information about the background, exposures and healthcare of the individual in pregnancy, in particular during the weeks immediately before the gestation at baby loss/interview. Supplementary information will be collected from the medical records relating to the pregnancy/birth.

1.2. Review of existing evidence:

Approximately 2 in every 1,000 pregnancies in the UK will end in early stillbirth at 20-28 weeks' gestation (~1,600 losses each year). A cohort study of the causes of early stillbirth in Australia (2013-2018) found ~10% were due to congenital anomalies, 30% due to preterm labour or antepartum haemorrhage, 20% were unexplained and the remainder were attributed to a variety of perinatal conditions (17). National MBRRACE-UK data for stillbirths at 22-28 weeks' gestation (co-applicant Smith, personal communication) shows similar patterns; 6% were attributed to congenital anomalies, 33% to placental conditions and 28% to unknown causes. To date, efforts to prevent early stillbirth are limited by a significant proportion of losses having no clear identified cause. Better understanding of early stillbirth causes can be used to ensure that appropriate preventative healthcare services are provided. However, there is an evidence gap relating to what factors are associated with increased or decreased risk of early stillbirth.

One example of the gap in information is caffeine consumption. A systematic review of 14 observational studies suggested caffeine consumption ≥300-350mg/day in pregnancy was associated with increased risk of pregnancy loss and late stillbirth (13, 18). However, only two studies included early stillbirth, meaning there are insufficient data on which to base education programmes aiming to assist individuals to modify caffeine intake in pregnancy. A lack of information on risk factors may also lead to inappropriate maternity service attendances. For example, the association between reduced fetal movements (RFM) and stillbirth after 28 weeks' gestation has been recurrently described (12, 19). However, 20% of women presenting with RFM do so prior to 28 weeks' gestation at a time when many pregnancies have not yet established a regular pattern of movement (20). Thus, extrapolating data from studies conducted later in pregnancy may lead to either over- or under-investigation (and intervention)

for this, and similar, common presenting complaints and may increase perceived stress in relation to this. Furthermore, six observational studies have demonstrated an association between going-to-sleep position (and other sleep habits) and risk of stillbirth after 28 weeks' gestation (21). However, the impact of supine going-to-sleep position on early stillbirths is unknown. Although the NuMom2b cohort study from the USA suggested no relationship with stillbirth, this analysis was underpowered (24 stillbirths / 8,706 participants) (22); a relationship to early stillbirth remains biologically plausible because uterine blood flow reduces in a supine position from 20 weeks' gestation onwards (23). Therefore, determining the relationship between modifiable factors and early stillbirth is important to enable public education campaigns or adaptations to maternity care to be targeted at the correct stage of pregnancy.

2 RATIONALE

Our research user engagement activities, and two relevant priority setting partnerships (4, 5) involving more than 1,000 individuals identifying as parents, family members or individuals with miscarriage experience highlights that pregnant people are highly motivated to improve their baby's health in pregnancy, and that understanding and addressing modifiable risk factors for baby loss is a key research priority for them. However, there is an evidence gap related to modifiable risk factors for early stillbirth. Consequently, expectant parents report an information void in relation to prevention advice and public awareness of early stillbirth is low.

Early stillbirths are likely to have different causes to those after 28 weeks' gestation. For example they may involve preterm birth processes or extreme early onset fetal growth restriction. Further, maternal and fetal physiology is different at this earlier stage of pregnancy with many babies not yet having an established fetal movement pattern, and less impact of supine sleep position on uterine blood flow. It is therefore likely that previously identified modifiable risk factors for late stillbirth (such as sleep position or fetal movement changes) may not impact on early stillbirth risk in the same way. It is also likely that there are novel additional factors specific to early stillbirth. This study will address the need for information on risk factors for early stillbirth, specifically identifying modifiable factors independently associated with baby loss occurring between 20 and 28 weeks of pregnancy. These factors may include 'exposure' factors (e.g. diet, sleep characteristics, physical activity), health inequalities (ethnicity, deprivation or exposure to domestic violence) and healthcare factors (e.g. timing and content of lifestyle advice, antenatal screening/care provided, management of extreme preterm labour).

Information about modifiable factors associated with early stillbirth is now urgently required to inform clinical practice, to assist expectant mothers/parents to reduce their baby's risk of stillbirth, and to help address inequalities in pregnancy outcome. This study will focus on what portion of early stillbirth risk may be mitigated by facilitating positive health exposures among expectant mothers/parents and their partners, or by adaptation of their environment or healthcare provision. Information obtained from this

study will enable antenatal care and education to be developed to reduce the risk of these earlier stillbirths.

3 RESEARCH QUESTION/AIM(S)

This study addresses the research question "Is early stillbirth associated with modifiable factors?" It specifically aims to:

1. Identify modifiable risk factors for early stillbirth that are amenable to public health campaigns or adaptation of antenatal care.
2. Confirm or refute whether the range of factors associated with late stillbirth are independently associated with early stillbirth, including (but not limited to) supine sleep position, caffeine intake and reduced fetal movement.
3. Explore interactions between maternal/parental characteristics (especially those relating to health inequalities including ethnicity and socioeconomic deprivation), fetal factors (including fetal growth restriction, reduced fetal movements) and early stillbirth risk.
4. Determine whether exposures associated with early stillbirth vary by cause of death.

3.1 Objectives

The study's principal objectives are:

1. To conduct structured interviews with bereaved mothers/parents or pregnant people to gain a deeper understanding of potentially modifiable risk factors which affect their baby's risk of early stillbirth
2. To describe associations of potentially modifiable risk factors for early stillbirth according to different causes of early stillbirth

The secondary objectives are to:

1. Confirm or refute whether factors associated with late stillbirth are independently associated with early stillbirth.
2. Explore interactions between maternal characteristics (especially those relating to health inequalities including ethnicity and socioeconomic deprivation), fetal factors (including fetal growth restriction, reduced fetal movements) and early stillbirth risk.
3. Determine whether exposures associated with early stillbirth vary by cause of death.

3.2 Outcome

The primary output from this research will be identification of novel modifiable risk factors for baby loss occurring during pregnancy/birth or immediately after birth between 20-28 weeks' gestation (collectively termed early stillbirth according to parental request). Specifically, this study will confirm or refute whether

risk factors for late stillbirth described above are relevant for early stillbirth. This will ensure evidence-based information for pregnant people, and those caring for them, to take positive steps to improve the health of their baby in the second trimester.

This approach extends the successful model used for the first MiNESS study to achieve similar breakthroughs in early stillbirth. Our findings will have direct impact on policy and practice through future iterations of the NHS SBL Care Bundle for dissemination by our stakeholder organisations. Assuming that a similar population attributable risk for early stillbirth to that seen in later stillbirths is attributable to identifiable modifiable factors, we would anticipate a 20% reduction in early stillbirth within five years (~320 fewer deaths/year). Our track record of translating research findings into national clinical policy indicates that our study findings would be clinically relevant and rapidly translated into parent information campaigns and national clinical guidance.

Secondary benefits would include an increased awareness of early stillbirth, a greater understanding of the factors that impact on inequalities in outcome, improved understanding of the causes of early stillbirth and potential reductions in the rate or severity of related pregnancy complications (e.g. preeclampsia and preterm birth) by early identification of pregnant people at risk, facilitation of lifestyle modification and improving access to evidence-based preventative healthcare. Reduction in these related pregnancy complications will realise cost savings (e.g. £9,000 excess healthcare costs per case of preeclampsia (24)). Population-based interventions to prevent early stillbirth are likely to simultaneously convey wider-reaching healthcare and economic benefits for pregnancy care. Our research user engagement activities indicate that giving bereaved mothers/parents the opportunity to talk about their baby, and their baby's life and birth, and by sharing those messages with healthcare professionals and other (future) parents, will assist in breaking down taboos surrounding (early) stillbirth and raise awareness of early stillbirth/early stillbirth prevention among pregnant people of the future and their family/friend support systems.

4 STUDY DESIGN AND METHODS OF DATA COLLECTION AND DATA ANALYSIS

4.1 Study design

The researchers will conduct a prospective case-control study of people who experience early stillbirth and those who have a contemporaneous ongoing pregnancy using approaches successfully employed in the original MiNESS (25). A schedule of events is found in Appendix 1. A case-control study is the most appropriate, efficient, design to study relatively rare disorders such as early stillbirth. This design also has the advantage of being able to study multiple exposures in the same study. Alternative study designs have been carefully considered but not pursued. Routine data studies lack detailed information regarding pregnancy exposures (e.g. sleep practices, caffeine consumption), while cohort studies of

pregnant people would be unaffordable and impractical as they would require >158,000 participants, assuming an early stillbirth rate of 2/1,000 pregnancies, in order to include sufficient cases (N=316) in which to detect clinically important exposures associated with early stillbirth.

This method also overcomes limitations of previous studies using gestation-matched live birth cohorts (which includes many infants who have risk factors for preterm birth). The study will exclude fetuses with serious congenital abnormalities, as these deaths are not amenable to prevention by interventions during pregnancy. While participating units will be welcomed from around the United Kingdom, it is anticipated that the majority of all participating units/participants will be within England, with a particular focus on units in the Midlands and North of England. This is because there is a network of maternity units established from the original MiNESS study and this area has maternity units serving a socially and economically diverse population. Traditionally, the Midlands and North of England has a stillbirth rate above the national average highlighting the need for improvements in this area.

The study will end upon collection of the final pregnancy outcome data for all enrolled participants. As control participants may participate as early as 20 weeks' gestation and may not deliver until 42 (or more) weeks of pregnancy, and/or bereaved participants' postmortem investigations may take (on average) 12 weeks to be reported, final study data collection may take up to six months following recruitment of the final participant.

4.2 Methods of data collection

Participants will be interviewed via Microsoft Teams or face to face (by mutual agreement) by trained research midwives, with an interpreter where required. Where interviews occur face to face these will be conducted in a suitably private location. For bereaved mothers/parents (cases), this will occur, where possible, within three weeks of loss (maximum six weeks) and people with ongoing pregnancies at the same gestation (controls) will be interviewed within the same time period of the target gestation (informed by that of historic losses in that unit according to the Standard operating procedure (SOP) for identification and approach of potential control participants).

Interviews will not be recorded. However, the process of obtaining verbal consent will be recorded according to the SOP for Documenting Virtual Consent. Standardised interviews, using an online study questionnaire administered and completed by research midwives, will be used to improve reliability of self-report measures and will stress the importance of giving honest answers, but also the option to decline to answer any question. Confidentiality will be emphasised, and interviews will be conducted by experienced interviewers who are not the caregiver (26),and have been trained by the coordinating midwife based in Manchester/co-investigator team in structured interview format and appropriate environment provision, from whom they will receive ongoing support.

The research midwife-administered study questionnaire used during the standardised interview will collect data on:

- Social and demographic characteristics of the participant and those of any partner including age, ethnicity, educational attainment, income, postcode (to allow calculation of deprivation indices), preferred language, immigration status and length of residence in the UK.
- Past obstetric history, including use of fertility treatment.
- Past medical history and medication/supplement use.
- Lifestyle determinants such as use of cigarettes, alcohol and street drugs prior to conception and during pregnancy. Information on caffeine consumption is included as this was associated with late stillbirth in MiNESS but lacks an evidence base in relation to early stillbirth.
- Exposure to stress and violence. The perceived social stress scale is used to obtain data on social stress experienced by participants (27), the multidimensional scale of perceived social support is used to obtain data on participants' support networks (28) and the presence of intimate partner violence is assessed by standardised questions.
- Sleep behaviour and perception of fetal movements.

Additional data will be collected from the participant's medical records for the current pregnancy including:

- Results from blood tests and ultrasound scans.
- Healthcare episodes in pregnancy
- Blood pressure and body mass index
- Baby's' birthweight

Separate medical records belonging to the infant will not be accessed.

Pilot interviews indicate that the majority of questionnaires will take 1-1.5 hours to complete (plus 5-10 minutes to record verbal consent). Interviews may take longer, particularly for bereaved individuals, where the participant may have more detail to communicate to the researcher; research midwives administering the questionnaires are encouraged to facilitate this where possible.

Where an individual participates in the study twice in the same pregnancy (once as a control and once as a case), a separate interview will be conducted for each participation as the range of questions asked differs depending on case/control status, and exposures (such as sleep position etc) may differ between control interview and subsequent early stillbirth. Research Midwives should discuss with the participant that answers from the previous interview can be re-used in order to prevent participants having to repeat themselves, where they do not change over time (for example background sociodemographic data).

However, where exposures may have changed over time (such as sleep position, substance exposures etc) these questions will be asked again. Data from the first interview (as a control) will be retained unless a specific request to withdraw data is received.

4.3 Standard care anticipated for participants

Participants (bereaved or those with ongoing pregnancies) will continue to be cared for by the health professional(s) responsible for their care. In the event of a participant (bereaved/otherwise) becoming upset/distressed by the questions asked the research midwife should follow the study distress protocol and give the option to pause or stop the interview, discuss local pathways to continuing care/counselling and offer referral to local support agencies. In the unlikely situation where an individual is identified as being a risk to themselves or an identifiable other, standard safeguarding practices (per local hospital policies) will be followed, obtaining consent to information sharing/disclosure where possible from the participant.

4.4 Data Management

The data sources for assessing eligibility of potential participants, and the sociodemographic background, exposures to potentially modifiable risk factors for early stillbirth and occurrence of the outcomes of interest (early stillbirth and broad category of stillbirth cause) are as follows:

I. Participant verbal responses during structured interview

II. Participant medical records including

- Paper or electronic documentation of healthcare encounters
- Paper or electronic reports from laboratory, radiology, and point of care investigations

III. Perinatal mortality review tool (PMRT)

Data will be entered directly onto an electronic case report form (eCRF; there will be no paper CRFs) and collated using a secure online database (REDCap). REDCap is a secure web application for building and managing online surveys and databases. In this study, it is being used to host online CRF/questionnaires. The system is specifically designed for research and data is stored on an MFT server (not shared with any third party). MFT servers are backed up at the end of each day and are maintained by MFT Informatics Team (IT). If data is lost, it can be recovered via the Trust IT back up service for the REDCap server. The Data Report can be downloaded from REDCap in the form of an Excel spreadsheet, this will be saved under a study folder with permissions based as to who can amend and view the data within the study team. The Data Report from REDCap will include participants' postcodes, dates of birth and medical history and is classed as identifiable. These will be stored, on a

Trust encrypted password protected device at MFT in keeping with the Information Governance (IG) arrangements.

In this database and data report participants will be allocated, and identified by, a unique study identification number. A separate log linking the unique study identification number to the participants' identifiable data (name, date of birth, hospital number) will be maintained securely at each participating hospital. During study recruitment/follow up this will be an electronic file, stored on the local NHS Trust server; a site file note will be made documenting where this file is stored. After the end of the study it will be printed, stored in the site file and the electronic copy deleted, being stored locally for a minimum of five years (longer if required according to sponsor SOPs/guidance at the time). After data collection is complete, the central research team will download all pseudonymised study data into a Microsoft Excel file and this will be stored securely on the MFT server. The central research team/Sponsor will not be able to identify participants from the data submitted centrally. This data will be processed to check for internal consistency (e.g. to ensure that the entered dates/gestations of certain antenatal events were not after the reported date/gestation of delivery/interview; data queries against potential data entry errors will be raised and resolved) and to derive variables from potentially identifying variables (such as indices of multiple deprivation or air pollution indices from postcode data and age from date of birth/delivery data) before they are removed to generate a fully anonymised dataset which will be saved as a .csv file to a restricted access area of the MFT server and stored for 5 years following completion of the project, or in line with MFT policies and in accordance with International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use Good Clinical Practice (GCP). Fully anonymised data may be made available to other researchers either through a central research data repository, or via request from other researchers, after publication of the initial study findings. Refer to the data management plan for further details.

4.4.1 *Consent to future contact*

During the process of obtaining participant consent, participants will be asked to indicate whether they are willing for the researchers to contact them in two circumstances: i) to receive a summary of the study findings, and ii) in the case of relevant future follow-on studies relevant to their pregnancy/birth. If permission is given, this will be recorded in the study recruitment log and contact details retained for these purpose(s). If consent for future research invitations is granted there will be a maximum of three invitations per participant to future research opportunities related to early stillbirth over the following five years (renewable for a further five year period if the participant wishes, as part of one of these contacts). There will be no obligation to take part in any future research study. Participants can request not to be contacted again in which case the research team will delete all details held.

4.5 Statistical analysis

Unadjusted associations between the outcome (early stillbirth) and each exposure will be estimated. Logistic regressions, adjusted for confounding variables, will consider multiple exposures in relation to early stillbirth. A separate logistic model, including a set of confounding variables (elucidated using causal diagrams (30)), will be used for each exposure variable to avoid spurious inferences (31). All models will include age, first pregnancy, self-declared ethnic group, smoking, obesity, diabetes, and hypertension. Both unadjusted and adjusted estimates and 95% confidence intervals will be presented for all exposure variables. Likelihood Ratio Testing will be used to test for an effect of each exposure. All analyses will be conducted for all cases; secondary analyses will be conducted by early stillbirth subtype (preterm delivery, unexplained *in utero*, explainable *in utero*) and repeated including only babies without any sign of life after birth. Missing data will be assessed, incorporated, and reported in line with recent guidance from the Strengthening Analytical Thinking for Observational Studies (STRATOS) Initiative (32). Participants who withdraw from the study after participation will not be replaced; data already collected will continue to be used, in line with the participant information sheet, unless a specific request to delete data is received before the data enters the public domain through publication and deposition in a central research repository. Where an individual participates as both a control and case participant, each collected dataset will be used independently, with appropriate adjustment made for repeat participation. Analyses will be conducted in Stata, R or other appropriate statistical analysis software. Study data will be compared with national data (MBRRACE UK; via co-applicant Smith) to assess generalisability (9).

5 STUDY SETTING

This is a multicentre study taking place in maternity units in the United Kingdom. The majority of research sites will be in England, but participating sites are welcomed from Northern Ireland, Scotland and Wales. In accordance with the recommendations of the study-specific PPI group, most data collection will occur by remote video call. Microsoft Teams is the sponsor-preferred video calling software and preferred format for study interviews. Some interviews may take place face to face, according to participant preference. Translators will be provided where necessary. Data extraction from source data, namely the (recently) pregnant individual's medical records pertaining to the pregnancy including medical investigations in pregnancy/around the time of birth, and PMRT (bereaved parents only) will occur at participating maternity units.

All individuals receiving antenatal care in participating maternity units will be made aware of the study through provision/display of promotional materials designed with the input of the study-specific PPI group; study awareness posters will be displayed in antenatal clinic and ultrasound department waiting areas and a study awareness leaflet will be provided at 16 week antenatal appointments to all pregnant

people with singleton pregnancies in participating maternity units. Self-referrals to the study are not accepted in order to limit sampling bias. Bereaved mothers/parents (cases) will be approached prior to discharge from the maternity unit by their midwife, bereavement midwife or doctor, and consent obtained to refer the individual to the study team and allow contact by a research midwife. Pregnant people (controls) will be randomly identified by the local research team from participating maternity units' booking lists according to the process described in section 6.2.2 and using the selection system described in the SOP for identification and approach of potential control participants, and will be approached in-person by a member of the research team at an appropriately timed routine antenatal appointment (usually the routine fetal anomaly scan). This methodology was successfully employed in the previous MiNESS study, and research user engagement indicates that this approach is favoured over other options.

6 SAMPLE AND RECRUITMENT

6.1 Eligibility Criteria

All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation except where the study inclusion and exclusion criteria explicitly state otherwise. Current or recent pregnancy/maternity is a required characteristic for inclusion due to the nature of the study question.

6.1.1 Inclusion criteria

Overall inclusion criteria:

[1] People receiving pregnancy care and/or giving birth in a participating maternity unit during the study period

[2] Singleton pregnancy/birth

[3] Baby without (evident) serious congenital abnormality*

[4] Between 20-28 weeks of pregnancy$

Specific inclusion criteria relevant to study group:

Cases participants only:

[A] Where baby was diagnosed to have died before/during or immediately after labour

[B] Where baby diagnosed to have died between 20-28 weeks of pregnancy

Control participants only:

[C] Ongoing pregnancy at the target gestation (as specified by the control identification tool between 20 to 28 weeks of pregnancy), even if no longer pregnant at the time of interview.

Where a control participant subsequently experiences early stillbirth after participating in the study, a sensitive re-approach to participate a second time as a case participant may be made, if deemed appropriate by the direct care team. There will be no obligation to participate a second time.

6.1.2 Exclusion criteria

All participants:

i. Presence of a known significant congenital anomaly (as informed by the NHS Fetal Anomaly Screening Programme (33))

Participants who give birth to liveborn baby with a significant congenital anomaly after participation will be excluded from data analysis

ii. Multifetal pregnancy

iii. Inability to give consent despite provision of translation services as required

iv. Participant age <16 years

v. Individuals not receiving care through a participating hospital

Case participants only

I. vi. Where signs of life were DETECTED after birth, attempted transfer of the infant to neonatal services

*Resuscitation attempts are **NOT** an exclusion if NO ATTEMPT TO TRANSFER TO NEONATAL SERVICES was made.*

6.2 Sampling

Cases: All bereaved mothers/parents meeting study inclusion criteria delivering in participating maternity units within the study recruitment period will be approached to participate. It is anticipated from previous research (11, 34, 35) that 50-75% of bereaved individuals approached will agree to participate.

Controls: Pregnant people with ongoing pregnancies, who meet the study inclusion criteria, will be recruited in a 2:1 ratio to the expected number of bereaved participants in that unit. It is anticipated that between 2-3 pregnant individuals will need to be approached to recruit one control participant (11, 34, 35).

6.2.1 Size of sample

Early stillbirth occurs in ~0.3% of births (22). Recruiting 316 cases and 632 controls (two controls per case) will detect associations with an odds ratio of 1.5 or greater (i.e. an associated fetal death rate of 0.45% or more) with 80% power and 5% significance level, where 30-60% of participants are exposed. Individual early stillbirth subtypes (preterm delivery, unexplained *in utero*, explainable *in utero*) are expected to occur in a 1:1:1 ratio. If these are differentially affected by certain exposures, the sample size is adequate to detect subtype-specific associations with an odds ratio of 2 or greater (same power and significance level, assuming 30-60% exposure). Larger effect sizes are expected in relation to subtype-specific risk factors compared to overall analyses, as subgroup effects will be attenuated by patient heterogeneity in the latter.

A 37% overall participation rate was observed in MiNESS (49% among bereaved mothers/parents) (11). Assuming similar rates of recruitment are achieved in the proposed study, we will need to approach 644 bereaved mothers/parents and 1,915 pregnant people to achieve the desired sample size. With ~1,450 UK early stillbirths without congenital anomalies per year, by recruiting in multiple locations we believe this recruitment target can be achieved within 24 months. However, we have adopted a series of approaches to improve participation rates from our experience of running the original MiNESS study, and from working with our study-specific PPI group. These approaches, including involvement of bereavement/usual care teams in the initial approach to bereaved/pregnant participants, raising awareness of the study among the general pregnancy population in advance of approach and provision of the option for online interviews including with translation facilities are expected to improve recruitment rates. In the Auckland Stillbirth Study, co-applicant Stacey achieved a 72% participation rate (35); this expertise will inform research midwife training in relation to study approach. The TMG will review recruitment rates quarterly; if a minimum recruitment rate of 50% is not achieved in each group at each site, we will examine patterns in recruitment data, investigate local/national barriers to recruitment and seek input of the SSG to overcome these. Thus, we are confident that a higher ratio of recruits to individuals approached will be achieved in the current study.

6.2.2 Sampling technique

Cases: All bereaved mothers/parents meeting study inclusion criteria delivering in participating maternity units within the study recruitment period will be approached to participate (total population sampling).

Controls: Self-referral to the study is not accepted. Individuals will be randomly selected from up to date (refreshed every 4-8 weeks) booking lists at participating hospitals by appropriate members of the local study team, adhering to the highest standards of research practice. Details of the sampling technique to be employed for control participants is provided in SOP for identification and approach of potential control participants; a bespoke control participant identification spreadsheet will be provided for each

site based on the gestation distribution of individuals delivering locally within the last three years who would have met the study "case" inclusion criteria, and birth rate at that unit. This identification algorithm will be applied by the local study team to each participating maternity unit's own booking list, so that all eligible pregnant individuals receiving care in participating hospitals have an equal chance of being approached. This will attempt to ensure that the "control" participants of the study are well-matched to the "case" participants in terms of key non-modifiable risk factors for early stillbirth. Should an individual approached to participate as a "control" participant decline participation, the selection SOP will be re-performed and the next individual will be approached, and so on, until a control participant of that demographic is recruited. This approach was successfully adopted in the original MiNESS study.

6.3 Recruitment

Recruitment is outlined in Figure 1 (flow chart). On the advice of the study-specific PPI group, all pregnant people receiving antenatal care at participating hospitals will be made aware of the ongoing study, its purpose, and that they may be invited to participate prior to any recruitment approach being made. This information will take the form of study awareness posters displayed in hospital/community antenatal clinic and ultrasound department waiting areas, and a brief study awareness leaflet to be distributed at/after the routine 16 week antenatal clinic appointment. Both poster and leaflet contain a QR code which can be scanned to view audiovisual content of research users talking about the study and why it is important. Thus, awareness of the study will already be high among individuals who may be invited to participate later in pregnancy.

Bereaved participants (cases)

Bereaved mothers/parents will be approached (ideally prior to discharge from the maternity unit) by a member of the clinical care team. A brief description of the study will be provided by their midwife, bereavement midwife or doctor, and consent to contact obtained to allow contact from a research midwife. Unless declined, a research midwife will either see the individual on the ward at a suitable time or contact the individual using their nominated preferred method of contact to discuss the study, provide the study information sheet, gain provisional consent and arrange an interview. Initial introduction to the study by a clinician known to the participant was viewed favourably by participants in MiNESS (36) and the study-specific PPI group. The co-investigators have extensive experience of recruiting bereaved parents to research studies. Our combined experience highlights that bereaved parents are keen to participate in research, even close to their time of loss. The co-investigators and coordinating research midwife will work closely with local research midwives to provide support for the local clinicians to minimise distress resulting from discussing the study. Bereaved individuals who attempt to self-refer direct to the study team will be advised to request referral by their midwife or doctor with whom the research team can confirm eligibility prior to recruitment.

Pregnant participants (controls)

Pregnant people will be approached at an appropriately-timed routine antenatal appointment; for most individuals this will be following the routine fetal anatomy scan (18+0 to 20+6 weeks' gestation (33)). This approach may be made by a clinician known to the potential participant or by a research midwife, many of whom recruited to the previous MiNESS study and are experienced in discussing stillbirth research with pregnant individuals. A brief description of the study will be provided and consent to contact obtained to allow follow up contact by a research midwife. If the individual declines participation or cannot be contacted (maximum three attempts over one week), another potential control participant will be identified and approached in the same manner until a suitable control participant is recruited. Self-referrals of pregnant individuals to the study team will not be accepted in order to minimise bias in control population recruitment. Individuals attempting to self-refer to the research team will be thanked and the random selection process explained.

Following approach

If the individual approached (bereaved or still pregnant) consents to being contacted by a research midwife they will be provided with a copy of the relevant participant information sheet (PIS) and consent form and asked to confirm their preferred mode of contact (telephone call, text message or email) and contact details using the study consent to contact (pre-recruitment) form.

If no response to attempted contact is obtained, a maximum of two further contacts will be attempted, over the course of the following week. If no response is received to any attempted contact, no further attempts will be made and the participant's contact details will be disposed of according to local NHS Trust procedures; if individuals subsequently self-initiate contact with the research team, the recruitment period can be resumed provided an interview can be arranged within the target time period.

Upon successful contact, the research midwife will check the individual's eligibility to participate, provide further details about the study and answer any questions the potential participant may have regarding the study. The individual will have up to one further week to decide whether or not to participate, if they are not ready to make that decision at the time of contact; this time is limited in order to attempt to preserve the accuracy of recalled information relating to their experiences and exposures around the time of fetal death diagnosis/target gestation. If the individual subsequently agrees to participate, a mutually agreeable date, time and format/place (e.g. Microsoft Teams call or face to face) for interview will be arranged. Interviews will be conducted by local research midwives. This builds on the model of recruitment in the original MiNESS study, which received positive feedback (36). Contact details will be retained until after interview, and only retained thereafter if specific consent to follow up contact is

received from the individual (see section 4.4.1), as there is no further participant involvement in the study after completion of the structured interview.

6.3.1 Sample identification

Bereaved mothers/parents (cases):

Bereaved mothers/parents will be identified by the direct clinical care team. The research team at each site will actively engage with all relevant clinicians including, but not limited to, midwives including bereavement midwives, gynaecology nurses including miscarriage specialist nurses, obstetricians and gynaecologists, as appropriate for the particular care arrangements in their unit. They will ensure that local clinicians are aware of the study, its eligibility criteria, purpose of the study and what it would involve for participants as well as how to refer a patient (with their consent) to the research team.

Pregnant people (controls):

Potential control participants will be identified by a clinician from the local maternity care team, and eligibility checked prior to approach. Those involved in participant identification and eligibility screening must have current Good Clinical Practice (GCP) and information governance training, have received study specific training from the local PI or delegated other, be listed on the site delegation log as participant identifiers and follow all relevant Trust policies. Potential participants will be identified from the maternity unit's booking list, according to the SOP for identification and approach of potential control participants in order to avoid recruitment bias. The exact implementation details of this SOP will depend on local maternity unit information systems and access controls. Study screening/approach, as well as recruitment, logs will be maintained at each study site and the number of potentially eligible individuals, number of people approached and number of people recruited will be reported. Recruitment ratios for each participant group will be monitored by the TMG.

The screening log will be cross-checked prior to approach of any potential control participants in order to avoid re-approach of individuals already approached/recruited. Where an individual was previously approached to participate in the study as a control participant, whether they participated or not at that time, and subsequently becomes eligible for inclusion as a bereaved mother/parent participant, the immediate clinical care team will sensitively provide a further no-obligation opportunity to participate under the new circumstances.

No participant identification centres or disease registries will be used. While awareness of the study will be raised among the general maternity unit population via study materials (poster, leaflet) and the study will be listed on a clinical trials registry, no participants will be recruited via such sources. No payments will be made to participants for their participation.

6.3.2 Consent

The majority of recruitment and interviews will be conducted remotely (Microsoft Teams call). Due to this, it will not be practical to obtain contemporaneous written informed consent from all participants.

All potential participants approached will be provided with a copy of the REC-approved PIS and study consent form in advance of the agreed interview. These documents will be professionally translated into Arabic, French and Urdu following REC approval; these languages have been chosen according to UK Census data (37) on first and second language skills and the known epidemiological distribution of (early) stillbirth (9). Telephone translation services will be available for other languages (or where the individual does not read that language) where appropriate to ensure that (potential) participants have appropriate understanding of the information contained in the PIS and consent form. The PIS and verbal information given to potential participants will emphasise that participation is voluntary and that they can change their mind if they wish. Researchers will ensure that participants have a good understanding of the pros and cons of participating, and what participation entails as well as answering any questions relating to the study to the participant's satisfaction before obtaining informed consent. It is recognised that individuals recruited to research studies in pregnancy, and particularly after bereavement, are particularly vulnerable and the highest standards of research practice will be ensured.

At the time of the interview, where conducted remotely, virtual consent will be sought according to the SOP for documenting virtual consent. The interviewer (research midwife) will obtain verbal permission to make a short audio(visual) recording of the participant's consent to participate using Microsoft Teams. Consent to recording will be stated before and also once recording starts. The participant and researcher (and interpreter if applicable) will verbally identify themselves. The researcher will then read the consent form item by item to the participant, and ask the participant to verbally indicate consent (or not) for each item, ending with confirmation of overall consent to participate in the study. The researcher will verbally confirm the end of the recording. The recording will then be stopped.

At the end of the Microsoft Teams call the research midwife will review the audio(visual) consent file to ensure it has saved correctly and stored securely on the local hospital secure data server according to the relevant Sponsor SOPs/Guidelines. A paper copy of the study consent form will be generated indicating the file storage location of the audio(visual) consent record on the local NHS Trust server (subject to at least daily back up); electronic records of consent will be named using the participant's unique study identification number. An electronic scan of this paper record will be sent by encrypted email to the participant from the research midwife's NHS Trust email address. A copy of the sent email

with attachment will be stored as a PDF along with the electronic consent recording. The email (containing the record of consent) will then be deleted from the research midwife's sent emails folder.

In the unlikely event of a failed recording, the participant will be contacted and the verbal consent process re-recorded (or arrangement made for a paper copy of the consent form signed and returned). The same process will be followed in the unlikely event of a lost/corrupted record of verbal consent during the study/data retention period. This is considered to be an unlikely scenario as all consent recordings will be stored on the local sites' NHS Trust servers which will be regularly backed up. In the event of not having been able to contact the participant to re-record consent, and in the absence of a request from the participant to withdraw from the study, informed consent to participate will be evidenced by meticulous contemporaneous records of the approach and consent process, and implied by virtue of the participant's active participation in the study interview.

Where the study interview occurs face to face, the participant will complete a paper consent form and be provided a paper or electronic copy of the consent form (according to the process described above) according to the individual participant's preference.

Where an interpreter is used for translating during consent procedures, whether in person or remotely their professional details (name and interpreter identification code as issued by their employing translation company) will be recorded in the same way as for researcher/participant; friends and family members will not be used to translate for the consent/interview process. Participants will be offered a copy of the completed paper consent form.

If an individual declines consent to participate in the study overall or in any non-optional consent clause (see consent form) any audio(visual) or paper record of the attempted consent procedure will be deleted/destroyed in line with the Trust's local policies. A record of the screening and attempted recruitment will be kept in the study screening log to prevent further approaches.

Individuals without capacity to provide informed consent to participate after the above steps (including translation) are taken, are not eligible to participate. Assessments of capacity will be made informally by the local research midwife who may seek support from the local Principal Investigator if needed. Any audio(visual) or paper record of the attempted consent procedure will be deleted/destroyed in line with the Trust's local policies if the individual is deemed to not have capacity to consent. A record of the screening and attempted recruitment will be kept in the study screening log to prevent further approaches.

7 ETHICAL AND REGULATORY CONSIDERATIONS

7.1 Assessment and management of risk

The interview will take place within the first few weeks following a bereavement (which is recognised to be an extremely traumatic and difficult period). If the recruitment process and the interview itself is not conducted in a sensitive and empathetic manner, there is the potential for participation in this study to exacerbate the grieving process. In order to mitigate this, the research midwives will be carefully selected and trained not only in the conduct of the interview, but also in aspects of bereavement support. Researchers will be trained to interview in a manner that upholds the dignity of participants at all times; while sensitive information is being collected, participants will be reassured that they can choose to not answer, to skip (a) question(s) or to stop the interview at any time. Similarly, while most interviews will take between 1-1.5hours to complete, sensitivity and flexibility is required, particularly when interviewing recently bereaved individuals who may need longer to adequately describe their experiences. Information will be made available to participants regarding local bereavement/counselling support as required. Feedback from participants in the original MiNESS, Auckland Stillbirth and Sydney stillbirth studies suggests that rather than finding the process a burden, participants appreciated taking part in the research, and appreciated the opportunity to talk about their baby and their experience. Bereaved members of the study-specific PPI group have emphasised that such participation may be viewed as a way to "make their baby's life count".

There is a risk that individuals approached to take part in the study in ongoing pregnancies (control participants) may be dissuaded from participating due to a fear of "tempting fate", and may experience some increase in distress in relation to mention of the potential of stillbirth in any pregnancy. However, significant proportions of individuals approached to participate as potential "control" participants in each previous similar study (Auckland Stillbirth Study, Sydney Stillbirth Study and MiNESS) did so and provided positive feedback on their experience of participation. Members of the study-specific PPI group have expressed that study materials emphasising the need to learn from healthy pregnancies in order to prevent stillbirths overall would be received as a positive message and would be more likely to encourage individuals approached to participate, particularly if they were made aware of the study in advance of being approached to participate. As a result we have co-produced a study information leaflet to raise awareness of the study and have named the study to emphasise the role of mothers/parents as experts, working with researchers to prevent stillbirths overall.

The majority of interviews are expected to occur via video call. However, if potential participants wish to have a face to face interview, it is appropriate that this can be facilitated in a location that is not likely to increase participant distress. The risks of lone working in an off-site location should be carefully risk assessed according to the local hospital Trust lone working policy which is already common practice in midwifery teams (for example community midwife home visits or home births). Recommendations for

safe lone working include review of any documented safeguarding issues, and use of a buddy system. Where significant risks are identified, online interview should be recommended; if not acceptable/possible for the potential participant the local research midwife should consider being accompanied at interview by another suitably trained research team member or, if serious concerns remain, consideration of non-recruitment.

7.2 Research Ethics Committee (REC) and other Regulatory review & reports

NHS Research Ethics Committee (REC) and Health Research Authority (HRA)/Health and Care Research Wales (HCRW) approval will be obtained prior to the study commencing. As it is unclear which sites will participate in the study after final approval, while overarching REC and HRA/HCRW approval is being applied for initially including research sites that have already expressed an intent to participate, other sites are expected to be recruited after approval. Thus, amendment(s) will be submitted to enable the REC and HRA/HCRW teams to review the intended additional recruitment sites when capacity to join the study is confirmed.

Before the start of the study, a favourable opinion will be sought from an NHS REC for the study and all the supporting documents including the protocol, information sheets, informed consent forms and other relevant documents. The study team will be responsible for the maintenance of a study site file, in which all current and superseded study documents will be retained. Also contained in the site file will be the approval documentation including correspondence with relevant authorities such as the HRA/HCRW and REC.

All correspondence with the REC and HRA/HCRW will be retained in the site file. The study team are responsible for producing progress reports throughout the study, including annual reporting (APR) to REC as required. The Chief Investigator will notify the REC of the end of the study, and will submit a final report with the results, including any publications, to the REC within 12 months of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

No participants will be enrolled into this research study at any site prior to the study being reviewed by the relevant regulatory authorities and receiving HRA/HCRW and REC approvals, as well as approval from the relevant R&D office. The study will be conducted in accordance with the Declaration of Helsinki, REC and HRA/HCRW approvals and the requirements of the Sponsor/local NHS Trust R&D department.

7.2.1 Regulatory Review & Compliance

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place.

7.2.2 Amendments

Any amendments to the to the study shall be reviewed by the Sponsorship Team prior to submission. Any non-substantial amendments shall be notified to the HRA and any substantial amendments, along with amended documentation, shall be approved by the REC, and HRA, prior to implementation as per nationally agreed guidelines. The Chief Investigator or designee will work with the R&I department to put the necessary arrangements in place to implement the amendment and to confirm their support for the study as amended. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

7.3 Peer review

The proposed study has been subject to rigorous internal and external independent expert peer review through the Manchester Academic Health Sciences Centre and the funding body, National Institute for Health and Care Research. The study has been modified in line with expert feedback.

7.4 Patient & Public Involvement

The research question - understanding the role of modifiable “lifestyle” factors in stillbirth prevention – was identified as top research priorities in the James Lind Alliance (JLA) Priority Setting Partnerships (PSP) for stillbirth (led by Prof. Heazell) (4), and for miscarriage (5). This question was proposed by individuals from all key stakeholder groups including those who identified as parents or family/friends. Stillbirth prevention and modifiable risk have also arisen as consistent themes in public engagement activities coordinated/participated in by Prof. Heazell and Dr. Higgins including the Still Born project, Before You Were Born event and Still Life workshops. Thus, the proposed project addresses a research user-defined research question.

A multi-ethnic study-specific PPI panel, representative of potential bereaved and pregnant study participants, was convened to inform the ongoing design of this study. Members provided input on the study question, scope (including expanding the case definition to include those bereaved by immediate neonatal death), study design (including specific input on study name, methods of approach/recruitment, widening participation and acceptability of proposed research areas/interview questions), terminology

and language sensitivity within the study interview and accessibility (including use of translators and translated study materials) which was used to inform the study protocol.

Key messages received from our PPI work to date include:

- The term “stillbirth” (rather than “miscarriage”) better describes baby loss at 20-28 weeks’ gestation as the baby is viewed as a “person” at that stage.
- The terms “bereaved mother/parent” and “pregnant woman/person” are the preferred terms to recognise the roles/identities of birthing people with and without bereavement through stillbirth.
- The second trimester of pregnancy is viewed as a time to “relax” having “avoided [early] miscarriage" and “before [the risks of] late pregnancy” kick in.
- Stillbirth risk reduction is rarely explicitly discussed with medically "low risk" prospective mothers/parents.
- Pregnant people are motivated to improve the health of their baby and would be willing modify their lifestyle to reduce stillbirth risk.
- Lifestyle modifications are preferable to pharmacological/other interventions in pregnancy.
- Pregnancy research involving lifestyle modification was viewed positively, but care must be taken to avoid inferring blame.
- Pregnant people receiving maternity care at participating hospitals should be made aware of the ongoing research study and its purpose before the time at which they may be approached to participate.
- Bereaved mothers/parents and pregnant women/people may be more likely to participate in the study if approached by an individual known to them/at a routine appointment, rather than by telephone call.
- Audiovisual study information leaflets/videos showing other mothers/parents of diverse backgrounds talking about the research are preferred to traditional or animated study promotional materials.
- Virtual interviews via video call are preferred to face to face meetings at hospital sites or having a stranger (researcher) visit their home; the option to have a face to face meeting should be available to those who want it.
- Bereaved parents are keen to honour their baby by telling their baby’s story; interviews should be allowed to continue to enable the participant to tell the researchers anything they feel is important.
- Baby’s name, where one has been given, should be used during the interview. Participants should be referred to by name and not as “Mum”.

- Potentially sensitive topics, such as personal hygiene practices, sexual activities and vaccination uptake are acceptable and important to be addressed in the study questionnaire; these should be asked along with other questions so as not to imply shame or "difference".

The study proposed has been directly informed by this PPI work, to address the specific needs of the current study population (those with baby loss between 20-28 weeks' gestation). The research study has been developed with, and refined by, Co-investigator Storey (Lay researcher and PPI co-lead). Members of the study-specific PPI group have reviewed and contributed to the study questionnaire wording/design, IRAS application and this study proposal and have accepted membership of the SSG.

The trial advisory group (comprising study-specific PPI group representatives, charitable/community interest organisation stakeholders and international advisors with expertise in stillbirth research as equal members) will meet as required to oversee the successful conduct of the study. Study-specific PPI group representatives' expertise will be sought to understand, and overcome, any barriers encountered in study recruitment/participation, and to determine/create a lay accessible public dissemination strategy for the study findings.

The study-specific PPI group members will be kept engaged throughout the study period with regular progress updates and will reconvene after initial data analysis is completed to discuss study findings, gain research-user insight and finalise the dissemination strategy.

7.5 Protocol compliance

The research team will be vigilant in protocol deviations and will record them on a study specific deviation log which will be regularly assessed by the PI

Deviations that may affect the safety, physical or mental integrity of participants or scientific value of the study will be reported to the study sponsor via research.sponsor@mft.nhs.uk by the MFT research team.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach and should also be reported to the sponsor without delay.

Compliance with the study protocol will be ensured by a number of procedures:

7.5.1 Set-up and training

The local midwives will already be experienced in obtaining informed consent for research studies and hold current GCP certification. They will be trained and supported by the coordinating research midwife and co-Investigator team to obtain study-specific informed consent from participants, in the study-specific interview process and in use of the eCRFs. The local midwives will extract data from clinical

notes and enter data from the interviews and medical notes reviews onto a customised online study REDCap database; training will be provided on how to use the study database eCRFs. The coordinating research midwife can be contacted by local research team members for day to day queries on these issues.

The Chief investigators and co-investigators can be contacted if there are any concerns regarding adherence to the protocol and to deal with any issues arising from the investigations (7.5.2-7.5.3).

7.5.2 Data processing and monitoring

Data will be collected directly onto bespoke eCRFs via the REDCap study database. Data extracted from the medical records will be checked for validity in 10% of records from each site every six months. Where errors are detected, these can be corrected at the time of cross-checking. If errors in more than 10% of data fields are detected at a particular site, all records created in that six month period will be locally cross-checked and amended as required; a file note will be made to detail changes made and shared with the Chief Investigator so that any need for targeted local staff training can be assessed.

7.5.3 Monitoring

The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust in line with applicable MFT SOPs and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the research team.

7.6 Data protection and patient confidentiality

- All investigators and study site staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.
- Audio(visual) recordings of verbal consent and electronic study logs will be uploaded direct to a restricted access folder on the local secure research data server of the recruiting NHS Trust at the time of recruitment.
- Hard copies of consent forms (where applicable) will be stored in a locked cabinet, in the local site research office with access controls (swipe card, passcode or key).
- Consent records (records of verbal consent or physical consent forms), consent to contact details printed study log documents will be retained in local site files and stored according to the Sponsor's SOPs/guidelines at the time of study completion.
- All participants will be allocated a coded, depersonalised study identification number upon entry to the study. All data recorded on eCRFs and submitted to the central research team at

MFT will be identified only by this unique study identification number. The link between the study identification number and participant identity will be stored on:

- The local study recruitment log: during study recruitment and follow up this will be an encrypted, password protected electronic file, which will be uploaded to a restricted access folder on the local NHS Trust server (a site file note will detail where this file is stored). After study follow up ends, the log will be printed and stored in the ISF, and the electronic file deleted.
- The paper/electronic record of consent: paper consent forms will be stored at the local research site where they will be subject to physical access controls. Electronic consent records will be stored in a restricted access folder on the local NHS Trust server with access restricted to only those who require it for their study role.

- Access to pseudonymised data, study screening/recruitment logs, contact details and consent forms will be restricted to the minimum number of individuals necessary for quality control, audit, and analysis. In particular, local research teams will only have access to records pertaining to recruits from their own NHS Trust.
- All electronic records containing patient identifying information, including audio(visual) consent records, will be stored only on NHS Trust servers with a minimum of daily back up. No electronic study data should be stored on USB sticks or laptops prior to complete anonymisation.
- The coordinating research midwife and chief investigator will have access to all study records in REDCap for the purpose of supporting local research site staff with eCRF data entry issues and data monitoring. They will have the ability to raise data queries (e.g. in the case of internal contradictions/inconsistencies, missing data or out of range/incorrect format data within individual eCRFs).
- Direct access to pseudonymised data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections in line with participant consent.
- The study data will remain the property of Manchester University NHS Foundation Trust. The Chief Investigator will be the data custodian. A complete copy of the study pseudonymised data will be kept on the MFT secure IT server at the end of the study. Local sites' individual site files will be stored locally.

7.7 Indemnity

The NHS indemnity scheme will apply to this study to ensure it meets the potential legal liability of the Sponsor, participating NHS Trusts, employers and Investigators/Collaborators for harm to participants

arising from the management, design and conduct of the research. No arrangements will be made for the payment of compensation in the unlikely event of harm.

7.8 Access to the final study dataset

At the end of the study data collection period, the pseudonymised electronic data set (including unique study ID numbers, but not the key to de-anonymise this) will be downloaded from the secure REDCap database and stored on a single data spreadsheet at MFT. It will be accessible only to the Chief Investigator and coordinating research midwife (until after resolution of all data queries and creation of derived indices e.g. indices of multiple deprivation and air pollution exposure [from postcodes], ages and gestations [from dates of birth] at which point the file will be locked and coordinating research midwife access removed). A record of patient's names and their unique subject identifier will be kept as an electronic study file that will be stored within the confines of each participating site, behind a firewall on password protected IT server to allow for the study investigators, if needed, to query original records. The study statistician will not have access to this record or any identifiable patient data, they will receive a fully anonymised data set for analysis. The study identification number and identifiable information will be removed prior to analysis to anonymise the database and be replaced with a unique sequential number commencing at 1.

Local researchers and co-investigators will not have access to the full dataset until after publication, after which point the full dataset, without study identification numbers and with all directly/indirectly identifiable data removed (completely anonymised), will be made available to all co-investigators and made freely available via a central research data repository upon publication of the primary research findings. Other researchers will be free to use this data to verify the research findings of this study and to answer related research questions, with appropriate attribution, under a creative commons licence.

8 DISSEMINIATION POLICY

8.1 Dissemination policy

- Data arising from the study will be owned by Manchester University NHS Foundation Trust. The funders (National Institute of Health and care Research) will be acknowledged in all publications arising from this study, but will have no role in the conduct, analysis or interpretation of the study.
- The study protocol, including statistical analysis plan, will be published.
- The study-specific PPI group, will be consulted during analysis stages to determine an appropriate research dissemination strategy.

- On completion of the research, the data will be published in peer-reviewed journals. It is anticipated that this will be accompanied by publication of the completely anonymised data in an online research data repository.
- Following completion of the research, the findings will be submitted for presentation at national and international conferences.
- Study participants are advised within the PIS that they will be contacted with a copy of the study results if they give their consent for their contact details to be used for this purpose, and are advised of several social media accounts belonging to the study team and charitable stakeholder partners who will disseminate lay-accessible summaries of the study findings.
- Key charitable partners, as well as the Maternal and Fetal Health Research Centre at University of Manchester will include lay summaries of the research findings on their social media channels. A study-specific twitter account will be established to share public study updates. Participants are advised to follow these channels for study updates.
- The central study team will provide research updates to all participating sites, informing them of the study findings after analysis.
- Any study manuscripts will follow the REDCap publication requirements (https://projectredcap.org/resources/citations/).

8.2 Authorship eligibility guidelines and any intended use of professional writers

In accordance with guidelines created by The International Committee of Medical Journal Editors, all authors will have:

- Made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
- Performed drafting of the work or revised it critically for important intellectual content;
- Approved the final version of the article prior to publication;
- Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Anyone meeting the above criteria for work contributing to any publication will be included as authors. The study co-investigators are anticipated to be included as authors on all primary academic papers arising from this study. As appropriate, students working under supervision with anonymised data performing secondary analyses, and/or the lead research midwife may also meet criteria for inclusion as authors for certain primary academic papers and will be appropriately acknowledged. There is no intended use of professional writers.

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10 APPENDICIES

10.1 Appendix 1- Schedule of Events

Procedures	Screening	Interview	Case note review	Pregnancy outcome
Confirmation of eligibility	x			x
Local approach of participant	x			
Informed consent		x		
Questionnaire		x		
Demographics		x	x	
Medical history		x	x	
Outcome assessment				x

10.2 Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A				