STUDY PROTOCOL

Methods of Assessing Perinatal Anxiety: The Acceptability, Effectiveness and Feasibility of Different Approaches

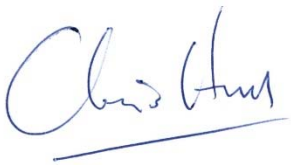
Short Title	Methods of Assessing Perinatal Anxiety
Acronym	MAP
Version number	Version 1.5 05 October 2020
Funder	NIHR Health Services Delivery and Research
Funders Reference	17/105/16
Sponsors Number	To be confirmed
IRAS Number	Work Package 2 only: 274901
Chief Investigator	Dr Susan Ayers
Host Institution	School of Health Sciences, City, University of London
Start date	1st June 2019
Project duration	42 months

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator 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.

For and on behalf of the Study Sponsor:			
Christopher Hull	Associate Dean for Research	Date: 30 April 2019	
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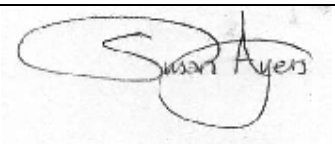
Susan Ayers	Chief Investigator	Date: 30 April 2019	

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SCIENTIFIC ABSTRACT

Background: Mental illness affects 1 in 5 women in pregnancy and after birth with a cost to society of £8.1 billion for every annual cohort of births. Anxiety is one of the most common mental illnesses, affecting around 15% of women, and is associated with increased risk of adverse outcomes for women and their children. Despite this, there is no validated method of screening or assessing anxiety to identify women who need treatment.
To be useful, any assessment tool for antenatal anxiety must meet a number of criteria. It must be: (1) acceptable to women; (2) effective at identifying women who require treatment; (3) acceptable and feasible to use in different context of the NHS and other services across the UK; (4) acceptable and easy to use by health professionals.

Aims: This study aims to identify the most effective, acceptable and feasible method for assessing anxiety in women during pregnancy and after birth.

Methods: This will be achieved through 3 work packages (WP) that compare 4 different tools for assessing anxiety: 2 anxiety-specific measures and 2 mental health measures (GAD-7, SAAS, CORE-10, Whooley questions) selected on the basis of research and clinical evidence that suggest they may be effective. To ensure relevance to different UK health services all WPs will be conducted in NHS services in England and Scotland.
WP1 will identify which assessment tools are acceptable to women using a purposive sample of 40 pregnant and postpartum women. Cognitive interviews and in-depth qualitative interviews will be used to determine which assessment measures are most acceptable, and obtain women's views and experiences of perinatal anxiety and mental health assessment.

WP2 will identify which assessment tool best identifies women who need treatment, as well as the optimal time to assess women during pregnancy. A systematic sample of 1915 women will be recruited in pregnancy and complete assessment tools by 15 weeks, and at approximately 22 weeks and 31 weeks gestation and 6 weeks postpartum. Effectiveness of measures will be examined in terms of identifying women with poor daily functioning, quality of life, or those who need treatment. Potential confounding factors such as psychological treatment will be controlled for. Diagnostic accuracy will be established using gold standard clinical interviews on a randomly selected subsample of 407 women who score positive or negative for perinatal anxiety.

WP3 will determine which assessment tool is acceptable and feasible to use in health services by implementing anxiety assessment in 2 services and evaluating the acceptability and feasibility of use in these services. A theoretically-informed implementation guide will be developed, with targeted versions for maternity, psychological and primary care services to enable wide scale implementation of assessment of perinatal anxiety.

Anticipated impact: This research will identify and implement evidence-based assessment of perinatal anxiety in health services, which is acceptable to women and health professionals. This will help identify women early, which will increase the chances for early intervention to improve maternal and child outcomes.

This research was developed through our partnerships with women who have experience of perinatal mental illness, health professionals and service managers. They have identified this as a priority problem and will work with us through the project to ensure its relevance to women and families and the NHS.

PLAIN ENGLISH SUMMARY

Mental illness affects one in five women during pregnancy and the first year after birth, costing UK society £8.1 billion for every year of births. Depression and anxiety are most common but there is very little research on anxiety. Perinatal anxiety affects around 15% of women and leads to greater risk of premature birth, postnatal depression and long-term mental health and behaviour problems in their children. It is currently recommended that women are asked two questions about anxiety by their midwife. However, it is not known if these are the best questions to identify women who need treatment.

We aim to solve this by finding the best questionnaire to identify women with perinatal anxiety. This will help us treat women early - reducing the number of women who experience long term anxiety and improving health of women and their babies. To be useful the anxiety questionnaire must be: (1) acceptable to women; (2) effective at identifying women who require treatment and those who do not; (3) acceptable, practical and easy to use in the NHS and other UK health services.

We will address each of these important points through three connected projects. We will compare four different anxiety questionnaires in NHS services in England and Scotland. We selected the questionnaires by looking at reviews of all the available evidence, and conducting our own research.

Project 1 will identify what questionnaires are most acceptable to women. We will interview women who are pregnant or recently gave birth. We will find out their views and experiences of being asked about anxiety during and after pregnancy.

Project 2 will identify the most effective questionnaire to identify women who need treatment. It will also establish the best time in pregnancy to ask women about anxiety in order to prevent long term problems. Women will complete the questionnaires three times in pregnancy and once after birth together with other questions about their health. Longer interviews will be carried out with some women to compare interview responses with questionnaire scores for accuracy.

Project 3 will determine which questionnaire is acceptable and practical to use in health services by implementing the most effective and acceptable questionnaire in two NHS Trusts. We will do this by asking healthcare professionals about their experience of using the questionnaire in these services.

We developed this research with women who have experience of perinatal mental illness, midwives and mental health professionals. They identified this as a priority problem and will work with us through the project to ensure it is relevant to women and the NHS. The research team includes midwives, obstetricians, health visitors, GPs, nurses and mental health professionals.

This research will identify an acceptable and effective questionnaire for pregnant women and women who have recently given birth that is practical to use in UK health services. We will work with women and health professionals to develop guides for services on how to put screening into practice which should enable wide scale implementation of screening for perinatal anxiety. Two events will be run by the NCT and Maternal Mental Health Change Agents to raise awareness and encourage uptake by services.

KEY WORDS: Pregnancy, Anxiety, Postpartum, Screening, Depression

AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Section amended	Details of change
1	1.1	11/03/20	MAP research team	Study logo (page 1)	Addition of MAP study logo. University logos removed
2	1.1	11/03/20	MAP research team	Table of contents	Addition of section 'Selecting the optimum tool for WP3'
3	1.1	11/03/20	MAP research team	Scientific abstract	"At 12 weeks" was amended to "by 15 weeks" and "approximately" added to subsequent time points (22 weeks, 31 weeks, 6 postnatal weeks)
4	1.1	11/03/20	MAP research team	Roles and responsibilities of study management committees	Addition of Research Fellow in England - Williams
5	1.1	11/03/20	MAP research team	Glossary of abbreviations	Addition of "MINI - Mini International Neuropsychiatric interview"
6	1.1	11/03/20	MAP research team	WP2 - Sampling	Section amended (as per tracked changes) to reflect: - Increase in number of study sites - Inclusion of "scan clinics" where women will be recruited "by a midwife, research midwife, or a research team member"

7	1.1	11/03/20	MAP research team	WP2 – Data collection (page 22-23)	Section amended to provide clarifications and add details regarding: - Initial approach of potential study participants - Different options to take part in the study and complete questionnaires - Addition of BadgerNet Maternity Notes to access the study - Follow up of study participants
8	1.1	11/03/20	MAP research team	WP2 – Data collection (page 24-25)	Section amended to add details regarding: - MINI modules used for diagnostic interviews - Procedure to monitor and respond to serious adverse events (SAEs)
9	1.1	11/03/20	MAP research team	Research timetable	Gantt chart removed
10	1.1	11/03/20	MAP research team	Various sections	Other minor changes in wording/clarifications throughout the protocol are not listed here but are visible as tracked changes
11	1.2	19/03/20	MAP research team		Revisions to protocol agreed with the NIHR
12	1.3	01/05/20	MAP research team		WP2 questionnaires to be returned securely by Business Reply Plus
13	1.4	05/08/2020	MAP research team		COVID-19 addendum added

14	1.5	05/10/2020	MAP research team	WP2 – Sampling (page 23) and Data collection (page 23)	Minor addition to reflect the option of the study being introduced to women by remote methods

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
National Institute of Health Research University of Southampton, Alpha House, Enterprise Road, Southampton, SO16 7NS Telephone: 0238 059 7501 E-Mail: netspostawardsetup@nihr.ac.uk	Financial support
City, University of London School of Health Sciences, Northampton Square, London, EC1V 0HB	Non-financial support: part-time administrative support for WP2.

ROLE OF STUDY SPONSOR AND FUNDER

City, University of London, is the sponsor for this research programme (WP1, WP2 and WP3) and will assume overall responsibility for the initiation and management of the study. City, University of London, as research Sponsor indemnifies its staff, research participants and research protocols with public liability insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

The programme is funded by the NIHR Health Services & Delivery Research. The NIHR HS&DR will monitor progress and be informed of all changes to the protocol. The NIHR HS&DR will be sent all outputs at least 28 days before publication/dissemination. All published outputs will acknowledge funding and include the following disclaimer:

'This project is funded by the National Institute for Health Research (NIHR) Health Services Delivery and Research programme (project reference 17/105/16). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.'

The NIHR HS&DR will have control over the final decision of whether to progress from WP2 to WP3. All other decisions about the study design, conduct, data analysis and interpretation, manuscript writing and dissemination of results will be made by the Chief Investigator and study management groups (see below) and will not be within the responsibility of the sponsor or funder.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

The trial is funded by the National Institute for Health Research (NIHR) Health Services Delivery and Research Programme (17/105/16). City, University of London will be the project sponsor and the host organisation, with Ayers as the Chief Investigator. Subcontracts will be put in place between City, University of London and other partner organisations, detailing the budget resources allocated, the responsibilities and the expected contributions of each party. There will also be site agreements between the sponsor and the NHS Trusts for the recruiting hospitals. Ethical approval has been obtained for WP1 from City University of London Research Ethics Committee (reference ETH1819-0689). Application for Ethical Approval for WP2 will be made to the Health Research Authority (HRA), and to City University of London Ethics Committee for WP3, following the award of the grant.

The Study Steering Committee (SSC) will provide independent oversight of the trial on behalf of the trial sponsor. The SSC will meet (in person) a minimum of once yearly (to be decided by the Committee according to NIHR guidelines and outlined in the Charter). The SSC comprises independent members to provide oversight of the project and ensure that the project is conducted to the standards set out in the Department of Health's Research Governance Framework for Health and Social Care (79) and the Guidelines for Good Clinical Practice.

The Programme Management Group (PMG) will meet at least twice a year and will report to the SSC at their meetings. The Programme Management group includes all co-investigators and collaborators to ensure milestones are achieved, oversee progress, trouble shoot if problems arise, plan the next stage and agree timelines. This will include all co-applicants

and collaborators to ensure we have expertise and representation from disciplines including midwifery (Jomeen), obstetrics (Walker), general practice (Shakespeare), psychiatry (Gilbody), health visiting (Salmon), perinatal psychology (Alderdice), and health services research and mental health (Maxwell).

A Core Programme Group (CPG) will meet at least every month (and more frequently as needed) to oversee day-to-day running of the programme. The CPG includes the Chief Investigator (Ayers), lead for Scotland (Cheyne), research fellows (Coates, Sinesi, Williams), research administrator (Uddin) and will draw on other expertise in the team when needed (e.g. PPI, statistics).

The Chief Investigator has overall responsibility for the study and will oversee all study management. The Chief Investigator will be responsible for monitoring of safety outcomes and reporting arrangements. The data custodian will be the Chief Investigator.
The project therefore has a clear management structure with the most appropriately qualified research team member taking responsibility for each aspect, and representation from the most relevant stakeholders.

GLOSSARY OF ABBREVIATIONS

CORE-10	Clinical Outcomes in Routine Evaluation-10
CORE-OM	Clinical Outcomes in Routine Evaluation-Outcome Measure
CPG	Core Programme Group
FYFV	Five-year Forward View
GAD	Generalised Anxiety Disorder
GAD-2	Generalised Anxiety Disorder 2-item scale
GAD-7	Generalised Anxiety Disorder 7-item scale
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
HS&DR	Health Services and Delivery Research
IAPT	Improving Access to Psychological Therapies
ID	Identity Document
IRAS	Integrated Research Application System
MINI	Mini International Neuropsychiatric interview
NCT	National Childbirth Trust
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NSPCC	National Society for the Prevention of Cruelty to Children
MMHCA	Maternal Mental Health Change Agents
PMG	Programme Management Group
PPI	Patient and Public Involvement
PTSD	Post-Traumatic Stress Disorder
PAR	Participatory Action Research
PARIHS	Promoting Action on Research Implementation in Health Services

RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROC	Receiver Operating Characteristic
R&D	Research and Development departments
SAAS	Stirling Antenatal Anxiety Scale
SIGN	Scottish Intercollegiate Guidelines Network
SSC	Study Steering Committee
TBC	To Be Confirmed
UK	United Kingdom
UK NSC	UK National Screening Committee
WP	Work Package

STUDY PROTOCOL

Background and Rationale

Perinatal mental health problems affect one in five women and cost the NHS and social services £1.2 billion for every annual cohort of women. The total cost to the UK is estimated to be £8.1 billion for every annual cohort of women, with 72% of this cost attributable to the long-term impact on the child (1). The most common disorders are depression and anxiety. Although depression has been extensively researched, research on anxiety is critically needed. Perinatal anxiety affects 15% of women (2) and is characterised by intense symptoms of anxiety and fear. Anxiety disorders include generalised anxiety disorder, panic, phobias, social anxiety, obsessive compulsive disorder, and post-traumatic stress disorder (3).

Evidence of the impact of perinatal anxiety on women and their infant includes increased risk of preterm birth, postnatal depression and poorer developmental outcomes for the infant (4,5). Evidence also shows that moderate symptoms which do not meet diagnostic thresholds can be distressing and debilitating for women (6).

Robust methods of assessing perinatal anxiety are essential if services are to identify and treat women with perinatal anxiety, including those who do not meet clinical thresholds for mental health services. Assessment methods need to be acceptable to women and healthcare professionals, feasible for services to use, and effective at discriminating between women who need intervention and those experiencing normal anxiety associated with pregnancy and birth. However, there is little evidence on the effectiveness of different methods of assessing perinatal anxiety.

In most countries universal screening is not in place for any mental illness in the perinatal period (7). Instead expert groups compile guidance with varying degrees of recommendation for perinatal screening or assessment (8). Anxiety is now recognised as being important to assess in itself and as a predictor of depression (9,10). In the UK, NICE clinical guidelines suggest healthcare professionals ask two questions to identify anxiety (GAD-2 (11)) and two questions to identify possible depression symptoms at appointments with perinatal women (Whooley questions (12)). However, the measure recommended for anxiety has not been validated for use with perinatal women so there is no evidence it is effective. There is also no information on the acceptability of different methods of assessing anxiety to women and health professionals, or on how methods of assessment can be best implemented and used in practice. This may account for variation in the implementation of screening in current practice e.g. Scotland only recommends assessment of depression (13).

This research therefore addresses the NIHR HS&DR call to ‘produce rigorous and relevant evidence on… robust methods of assessment that can be used by health and social care services, and are acceptable to potential service users, to identify those in need of intervention for perinatal mental health problems, including those who may not meet a clinical threshold for mental health services’ (14).

This research is essential to achieving the aims of UK health care services. A key aim of the NHS England Five-year Forward View (FYFV) is that at least 30,000 more women each year will access evidence-based specialist mental health care during the perinatal period by 2020/21 (15). Similarly, the Scottish Mental Health Strategy aims to improve the recognition and treatment of perinatal mental health problems (16).

Evidence explaining why this research is needed now

The most effective method of assessing perinatal anxiety is not known. Scottish SIGN guidelines acknowledge the need to identify the most effective assessment tools for perinatal anxiety (13) and the measure recommended by NICE guidelines (GAD-2) lacks evidence for its clinical effectiveness with perinatal women (11). A review of measures of perinatal anxiety conducted by members of the research team found very few self-report measures of anxiety had been validated for use with perinatal women (17).

It is therefore clear that methods for assessing perinatal anxiety currently in use are not evidence-based. In healthcare more generally, it is often the case that methods of assessing psychological outcomes, such as satisfaction and wellbeing, become widely used because they are acceptable to healthcare practitioners and the norm, sometimes despite little evidence they are effective.

Systematic reviews of assessment of perinatal anxiety (17), pregnancy-specific anxiety (18), and depression (19) evaluated the psychometric properties of various methods of assessing perinatal anxiety (17), depression (20, 21), mental health (22) and wellbeing (23) and indicated that no definitive research has been conducted that tests different methods of assessing anxiety in clinical practice. Research on women and health professionals' views on assessment (24-28) and the potential problems that arise in perinatal care pathways that act as barriers to women accessing treatment (24, 25, 27) has highlighted that this is a high priority for research.

The proposed research programme builds on this work to consider and address fundamental issues in the effective assessment of perinatal anxiety and how it fits into care pathways:

Conceptualising assessment of perinatal mental health

How assessment of perinatal mental health is conceptualised is central to the approach taken in research and clinical practice. The UK National Screening Committee (UK NSC) define screening as "the process of identifying healthy people who may have an increased chance of a disease or condition. The screening provider then offers information, further tests and treatment." The UK NSC do not recommend screening for postpartum depression due to lack of clarity on the population to be identified and lack of evidence that current screening tools identify risk with sufficient accuracy (29). The UK NSC do not consider assessment of perinatal anxiety. Despite this, clinical guidelines recommend routine assessment of perinatal depression (8, 13) and anxiety (8).

The distinction between screening and case detection is also important because it has implications for the type of measure used, how we evaluate the effectiveness of the measure, and whether we use a 1-stage or 2-stage process to identify disorders. For example, if we take a screening approach we would use a broad tool and look for high sensitivity (i.e. identify most women with any form of psychological distress) but specificity is less important (i.e. the tool does not need to be highly specific to anxiety). A second, more detailed assessment would then be conducted to diagnose and refer women for appropriate treatment. This distinction also has implications for the relative importance of false positives and false negatives (i.e. false negatives are less concerning for screening tools but more concerning for diagnostic tools).

In this research programme we take a screening approach in that we have chosen non-diagnostic measures that are likely to be more sensitive and we envisage these would be used as part of a 2-stage process. However, we recognise the UK NSC reasons for not labelling perinatal mental health assessment as screening, particularly because of the lack of evidence in this area, which this research will help address. We therefore refer to perinatal mental health assessment rather than screening.

General mental health vs. anxiety-specific assessment: Women develop a range of perinatal mental health problems so it may be more effective and clinically feasible to use general screening questions to identify women with any type of psychological problem, rather than disorder-specific assessments (30). There is some evidence the Whooley questions (12) recommended by clinical guidelines for assessing depression may do this (31). Alternatively, the Clinical Outcomes in Routine Evaluation-10 (CORE-10) (32) is a brief measure widely used in psychological services and some maternity services. It provides broad assessment of anxiety, depression, PTSD, insomnia, suicidal ideation and poor coping. Research by our group found the CORE-10 performs better than the Whooley questions and GAD-2 at identifying women with moderate and severe distress in pregnancy who are worried about their psychological wellbeing (22). However, general measures are unlikely to be as high in specificity as anxiety-specific measures.

General anxiety versus pregnancy-specific anxiety: General anxiety and pregnancy-specific anxiety both predict poor maternal and child outcomes and, in some cases, pregnancy-specific anxiety is more predictive (18, 33). Thus, a measure of perinatal anxiety that includes general and pregnancy-specific symptoms may be more effective in terms of identifying women at risk of poor outcomes. The Stirling Antenatal Anxiety Scale (SAAS) was developed by our team with funding from the Scottish Government Chief Scientist Office to include general and pregnancy-specific items and to be clinically relevant and acceptable (34).

Clinically derived vs. psychometrically derived measures: Self-report measures of anxiety developed for use in the general population have been used with perinatal women, some of which have been validated psychometrically (17). However, these measures are rarely clinically derived and it is not clear how appropriate they are for use with perinatal women (35, 36, 37). The SAAS was carefully developed by our team to be clinically relevant and acceptable through a literature review, stakeholder interviews, Delphi consensus study and psychometric testing (34).

Feasibility and acceptability of assessment in different clinical contexts: For assessment to be successful it needs to be acceptable to women and health professionals (35, 38) and feasible to implement in different healthcare contexts. Furthermore, there is a lack of training in perinatal mental health for the multiple healthcare professionals in contact with perinatal women and confidence is low in identifying women in need of support in the UK and other Western countries (26, 39, 40). This research therefore looks at acceptability and feasibility of assessment measures in both English and Scottish NHS services.

Effective assessment and identification of perinatal anxiety: Identifying the most effective method of assessment is vital for health and social care services working with perinatal women. The need for this is evident in UK strategy and policy (15, 16), clinical guidelines (8, 13) and calls for research (14). Recent prioritisation of perinatal mental health and rapid expansion of NHS services in this area, including development of a Scotland-wide perinatal

mental health managed clinical network, mean this research meets an urgent need which is likely to be sustained over the next 10 years.

This research addresses these issues by comparing the effectiveness, acceptability and feasibility of four measures: two that assess perinatal anxiety and two that assess broader distress:

1. Clinically recommended method of assessing perinatal anxiety (GAD-2/GAD-7).
2. Clinically derived measure that includes general and pregnancy-specific anxiety (SAAS).
3. General assessment using a broad measure of distress, including anxiety (CORE-10).
4. General assessment as per clinical recommendations and research (Whooley questions).

These measures have been identified on the basis of research and clinical evidence as 'front runners' in terms of the likelihood of being effective methods of assessing perinatal anxiety or mental health problems. They are consistent with a 2-stage approach to screening. Most of them are included in recent UK clinical guidance documents on perinatal outcome measures (8, 13) (41) and care pathways for perinatal mental health (42).

The first measure is the NICE recommended method of assessing perinatal anxiety. The Generalised Anxiety Disorder scale (GAD-2) consists of 2 items taken from the 7-item version (GAD-7) (11). The two items ask whether during the previous 2 weeks the woman has felt (i) nervous, anxious or on edge, and (ii) not able to stop or control worrying. NICE guidelines propose that women who score positively on the GAD-2 are then asked to complete the GAD-7 as part of the assessment pathway. As there was limited evidence of effectiveness for perinatal anxiety the NICE guidelines drew on evidence of case identification in non-perinatal populations. The GAD-2/GAD-7 appears to be effective in primary care populations (11, 43), adolescents with generalised anxiety disorder (44), and elderly populations (45). Since publication of the NICE guidelines, acceptable validity and reliability of the GAD-7 have been reported in perinatal women in Peru (46) and Canada (47). The GAD-7 is recommended by the Royal College of Psychiatrists and NHS England as one of a few measures to use with perinatal women (41, 42). The potential suitability of the GAD-2/GAD-7 for assessing perinatal anxiety therefore lies in its effectiveness in other populations and that it is currently the only clinically recommended tool for assessing perinatal anxiety. However, the current evidence for the GAD-2/7 with perinatal women is limited.

The second measure is a measure of psychological distress which includes anxiety. The Clinical Outcomes in Routine Evaluation (CORE-10) (48) is a 10-item measure of psychological distress derived from the larger CORE-OM, a well-established measure used in counselling and clinical psychology services in the UK (49). The potential suitability of the CORE-10 for assessing perinatal anxiety and mental health more generally lies in its broad coverage of a range of symptoms of distress and associated functioning. It includes items to assess anxiety, depression, physical problems, trauma, suicide risk, close relationships, social relationships and general functioning. The CORE-10 has been used to evaluate distress in studies of interventions for psychosis (50, 51) (52), severe mental illness (53), and is a preferred outcome measure in the Improving Access to Psychological Therapies (IAPT) services in England (54). A study conducted by the research team found the CORE-10 had good psychometric properties with pregnant women and performed better than the recommended measures of anxiety (GAD-2) and depression (Whooley questions) at

identifying women who were worried about their psychological health (22). The CORE-10 is recommended by the Royal College of Psychiatrists and NHS England as one of a few measures to use with perinatal women (41, 42). The potential suitability of the CORE-10 for assessing perinatal anxiety is therefore that it is clinically recommended and assesses anxiety in the context of other symptoms and psychosocial vulnerability. However, the current evidence for the CORE-10 with perinatal women is limited.

The third measure is the NICE recommended method of assessing perinatal depression. The Whooley questions (12) are two questions widely used in maternity services to assess depression. The questions ask if during the last month the woman has (i) often been bothered by feeling down, depressed or hopeless, and (ii) has had little interest or pleasure in doing things. Clinical guidelines recommended using the Whooley questions on the basis of evidence from other populations, as there was no evidence at that time for their validity and reliability in perinatal populations. Studies have since shown high sensitivity and variable specificity in identifying perinatal depression (55, 56, 57). There is some evidence that the Whooley questions may also be appropriate to assess perinatal anxiety and other mental disorders. A recent study in England comparing Whooley questions to psychiatric interviews in pregnant women found the Whooley questions also identified women suffering from other disorders, including anxiety (31). Consistent with this, a meta-analysis in adult populations found the Whooley questions were efficient at ruling out depression when the population prevalence is low (e.g. <20%) but less specific to depression, suggesting it identified other disorders in addition to depression (19). The potential suitability of the Whooley questions to assess perinatal anxiety and mental disorders is therefore based on its widespread clinical use and indication that it identifies women with other mental disorders. However, current evidence for the Whooley questions to assess perinatal anxiety is limited.

The fourth measure is a clinically derived measure developed specifically for perinatal anxiety that includes general and pregnancy-specific anxiety. The Stirling Antenatal Anxiety Scale (SAAS) (34) is a 10-item measure that includes both general and pregnancy-specific anxiety symptoms. The SAAS was developed by members of our research team based on a systematic review of the psychometric properties and content of existing anxiety scales and semi-structured interviews with women who had experienced antenatal anxiety. An initial pool of items was formulated based on these two sources (i.e. research literature and target population). The wording and clarity of items was also reviewed by women with lived experience of perinatal mental health problems and their feedback used to modify the wording. The initial pool of items was subsequently reviewed, through a Delphi study, by clinicians with expertise in perinatal mental health who indicated which items they considered were the most reliable and valid clinical indicators. A preliminary 30-item version of the SAAS was then tested on 62 pregnant women and psychometric properties examined and used to create the final 10-item version. The potential suitability of the SAAS for assessing perinatal anxiety is that it is a clinically derived measure developed specifically for this purpose on the basis of evidence from the research literature, the target population and experts in the field. It is also the only measure that includes both general and pregnancy-specific anxiety items. However, there is no evidence on the accuracy and acceptability of the SAAS. A pilot is currently being conducted to examine this which will be completed this year and the learning from this has informed the proposed research. However, the current evidence for using the SAAS to assess perinatal anxiety is limited.

It can therefore be seen that all four measures of assessing anxiety have strengths but the evidence base is limited. The proposed research addresses this.

Aims and objectives

RESEARCH QUESTION: What is the most effective, acceptable and feasible method of assessing perinatal anxiety?

OBJECTIVES:
1. Determine the acceptability of different methods of assessment to women and understand women's experiences of routine assessment of perinatal anxiety (WP1).
2. Determine which assessment measures are most psychometrically robust (WP2).
3. Determine the most effective assessment measure to identify women in need of intervention (WP2).
4. Determine the optimal timing of assessment to identify women in need of intervention (WP2).
5. Determine the acceptability of assessment measures to health professionals and healthcare services (WP3).
6. Determine the feasibility of implementing assessment in different healthcare services in Scotland and England (WP3).
7. Develop a theoretically informed guide to implementation in NHS services in England and Scotland (WP3).
8. Disseminate the assessment tool and guide to implementation to key stakeholders in England and Scotland to facilitate implementation into clinical services.

This research uses mixed methods of qualitative research, a prospective longitudinal cohort study, and participatory action research in three work packages (WP) conducted in maternity services in England and Scotland. An overview is given in **Appendix 1**. Work packages are described below.

WP 1: ACCEPTABILITY OF ASSESSMENT MEASURES

Aim
WP1 will determine the acceptability of different assessment measures to women and understand women's experiences of routine assessment of perinatal anxiety.

Objectives are to:
1. Assess the acceptability of the four assessment measures for women.
2. Explore women's views on the effectiveness and appropriateness of the four measures in relation to their current and previous symptoms.
3. Understand women's processes of completing each questionnaire considering their understanding of questions and comfort in responding.

Design
Cognitive interviewing and in-depth qualitative interviews with women.

Sampling
A purposive sample of pregnant and postnatal women. Women must be aged 16 or over. Women must speak adequate English but will not be excluded for reasons of literacy as the researcher will read information and questions to women who need this. Sample size will be guided by data saturation and is expected to be approximately 40 women (20 each at London and Glasgow sites). The sample will be purposively selected to achieve variation in perinatal time point (12 weeks, 22 weeks and 31 weeks gestation, and 6 weeks after birth)

because assessment measures must be acceptable on all occasions they are used. It is also currently unclear whether levels of mental health symptoms during the perinatal period affect acceptability (58). The sample will also be selected by Whooley and GAD-2 scores (those scoring positively or negatively) because a measure must be acceptable with the general population being screened as well as with the smaller target population. We will also sample to achieve variation in age and ethnicity.

Data Collection

Pregnant and postnatal women will be recruited through service user representative organisations and social media. Women who are interested in participating will be contacted by research staff and given a participant information sheet. If women are interested in participating in the study their contact details and consent will be obtained and they will be asked to complete the Whooley questions and GAD-2 and provide basic sociodemographic and obstetric information such as age, ethnicity, occupational status, parity, and previous mental health history. It will be made clear that not all women will be invited for interview. Demographic information and Whooley/GAD-2 scores will be reviewed by the research team and women who meet inclusion and sampling criteria will be contacted and invited to interview.

Women will be interviewed at a convenient time and place (e.g. home, health centre or the university). Women will also be given the option of a video interview should face-to-face not be possible. Interviews will be scheduled within 3 weeks of recruitment before any referral for treatment is likely to have affected mental health. At the start of the interviews the study will be explained and consent re-confirmed. Interviews will take up to 90 minutes.

The interview consists of two parts. In one part cognitive interviewing will be used to examine the process of completing the assessment tools from the perspective of women. This will identify problematic questions which may need to be adapted, acceptability of individual items and the questionnaire as a whole, confidence in being able to answer the questions and comfort doing so (59, 60). Specifically, a ‘think-aloud’ interviewing technique asks participants to think aloud as they complete the questionnaire to highlight how they interpret and comprehend the items and come to formulate a response (59). Women will be shown the assessment measures one at a time and asked to complete each one as they would normally but to ‘read aloud’ each question and to ‘think aloud’ their thoughts as they write their answer (60). This will be explained and demonstrated by the interviewer to ensure that women are comfortable and understand the process. The interviewer will also probe any verbal and non-verbal occurrences of hesitation, reluctance, confusion, or indecision. The order in which assessment measures are presented will be randomised to avoid order effects.

The other part of the interview will be an in-depth interview examining women’s experiences of perinatal mental health assessment and acceptability of assessment measures they have experience of. Participants’ experiences and views on acceptability of the different measures will be explored using a topic guide developed from a theoretical framework of acceptability (61). This includes affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs and self-efficacy. Interviews will be conducted by researchers trained and/or experienced in cognitive interviewing and qualitative interviews.

Data Analysis

Interviews will be audio-recorded, transcribed and fully anonymised before analysis. Inductive systematic thematic analyses will be conducted separately on each part of the

interview. Transcripts will be read multiple times to identify aspects of being assessed for anxiety that are important to the participant. These identified sections will be coded by two researchers. Once coding is complete for the first interview, all codes and themes will be examined and discussed with the leads for England (Ayers) and Scotland (Cheyne) to develop a coding schedule. All interviews will then be coded using this schedule and comparisons will be made across interviews to determine weight, range and prevalence of themes. Data will be analysed using NVivo software. Credibility will be ensured by regular meetings of the research team where problematic issues are discussed and resolved.

Outputs

Results of this WP will enable us to make recommendations about the assessment measures that are most acceptable to women. We will also be able to make recommendations on possible alterations and/or development of existing measures to assess perinatal anxiety.

WP 2: IDENTIFYING THE MOST EFFECTIVE ASSESSMENT MEASURES

Aim

WP2 will determine which assessment measures are psychometrically robust, most effective at identifying women in need of intervention, and optimal timing of assessment to identify women in need of treatment.

Objectives are to:

1. Determine the accuracy of assessment measures in identifying women who meet diagnostic criteria for an anxiety disorder. This will be achieved by comparing the four assessment measures to expert assessment using a gold standard clinical diagnostic interview at four time points during pregnancy and postnatally.
2. Assess a range of other psychometric properties of the assessment measures, including forms of reliability (i.e. internal consistency) and validity (i.e. convergent validity and factor structure).
3. Evaluate the effectiveness of assessment measures in identifying women in need of intervention by comparing scores from the four assessment measures with measures of poor daily functioning, poor quality of life, perceived need for treatment, and accessing treatment.
4. Establish the optimal timing of assessment. This will be achieved by assessing the temporal stability of assessment measures over the four time points and by examining the accuracy of earlier assessment points in predicting later mental health problems.
5. Provide information on the prevalence of anxiety disorders in the antenatal period, its effects on birth outcomes and comorbidities in perinatalwomen in the UK.

Design

Prospective longitudinal cohort study of 1915 women in pregnancy and postpartum.

Sampling

A systematic sample of women will be recruited at NHS sites in England and Scotland. A total of 1915 pregnant women will be recruited into the study, half (n=958) from English sites and half (n=957) from Scottish sites. Sites include Barts Health NHS Trust in England and Greater Glasgow & Clyde Health Board in Scotland, which were chosen because they have the largest maternity departments in England and Scotland with over 15000 and 12000 deliveries each year respectively. The populations served by these NHS Trusts are also

highly ethnically and socioeconomically diverse (62). The remaining NHS sites were chosen based on considerations related to location, socio-demographic characteristics and potential for recruitment.

Participants will be recruited at antenatal clinics, scan clinics or by remote methods at the same point of pregnancy by a midwife, clinical research network staff, or a research team member. Additionally, women will be able to access the study questionnaire and all participant documents directly via BadgerNet Maternity Notes, at sites where this is available (see also Data Collection section). Women will be eligible for inclusion in the study if they meet the following inclusion criteria: (i) aged 16 years or over (ii) less than 15 weeks pregnant at the time of recruitment (iii) able to provide written informed consent to take part in the study (iv) with a level of English sufficient to understand and complete questionnaires in lay language.

Potential participants are pregnant women (nulliparous and parous) attending antenatal clinics (e.g. dating scan or booking appointments) at the English and Scottish NHS sites who meet the inclusion criteria. In order to reduce the risk of sampling bias, we will aim for consecutive sampling at each site until the target number for each time point is met. Given the considerably large sample size and the consequent heterogeneity of potential participants, we expect the selected samples at participating sites to be a relatively accurate representation of pregnant women in England and Scotland.

To establish diagnostic accuracy of the assessment measures, clinical interviews will be conducted on a subsample of 25% of women (total n=407; 204 in England and 203 in Scotland; n=102 at each time point) to establish whether they are currently experiencing an anxiety disorder according to formal diagnostic criteria (63). This will enable us to determine the diagnostic accuracy of the assessment measures and to identify the optimal cut-off scores to distinguish cases from non-cases. A consecutive sample will be used to minimise bias as recommended by guidelines for studies of diagnostic accuracy (QUADAS-2 (64).

Data Collection

Women will complete self-report methods of assessment at 3 points in pregnancy which coincide with routine antenatal care (up to 15 weeks, approximately 22 weeks and 31 weeks) and 1 postnatal time point at approximately 6 weeks.

Each site will have a study set-up meeting between the research team and staff to provide information about the study, governance, recruitment procedures and issues to consider in relation to obtaining informed consent from study participants.

Women identified as eligible will be approached by site staff (Clinical Research Network funded research staff [England] / clinical midwife [Scotland] / central research team member [England and Scotland]) face to face or remotely, around the time of their antenatal booking or dating scan appointment. All potential participants will be given a brief explanation of the study. It will be made clear that participation in the study involves completing questionnaires at four time points and potentially taking part in a brief telephone interview. Women will have the option to complete and return questionnaires by post, online or through their electronic notes (BadgerNet) at available sites, depending on their preference. Flexibility in relation to method of response (paper or online) for follow-up assessments will be emphasized. We estimate this recruitment process will require approximately 3 to 5 minutes. All women interested in participating will be asked to indicate their preferred contact method. At this stage, if possible, the midwife/researcher will also obtain women's name and key contact

details (email address and/or phone number), and her preference for completing the questionnaire by paper, online, or via BadgerNet.

Women who opt for paper completion of the questionnaire at the initial time point will be provided with a study pack containing a cover letter, information sheet, two consent forms (one to be kept by the study participant, one to return to the MAP office), the study questionnaire (further details are provided below), comprehensive contact details sheet, and a secure Business Reply Plus envelope for return of completed documents. The name of the NHS study site will be stated on the front of the questionnaire.

For online completion, site staff will collect the participant email address/telephone number and women will be given a study leaflet with a URL link/QR code to access the questionnaire online. The women will be able to read and download the participant information sheet, and if happy to proceed will then consent before completing the questionnaires online. If it is not possible to provide the electronic link immediately, site staff will let women know that the central research team will be in touch as soon as possible to provide the study link and answer any questions.

At some sites, BadgerNet Maternity Notes, an online system, is available for women to access the study. A study invitation letter will be displayed in women's notes and women will be directed to it by a generic 'Push notification' sent by the BadgerNet system. The invitation will link to the study information sheet and to the questionnaire and women will be able to complete this online. At sites where BadgerNet is available, midwives/researchers will inform women of this option.

All women who have provided their contact details will be followed up, up to two weeks after their first questionnaire was due back. A week before follow up questionnaires are due (22 weeks, 31 weeks, 6 weeks after birth) central research staff will contact the participant via email / text message, depending on preferred mode of contact, to let them know to expect their next pack/link to the online survey soon. If completed questionnaires are not received women will be followed up with reminders up to two weeks later. This should preserve the uniformity of the four time points and thus allow meaningful comparisons among participants. If participants have not completed the questionnaires three weeks after they were due to, they will be given the opportunity to complete a short version of core measures with a central researcher by telephone. Completion of each questionnaire will be followed by a thank you email/letter.

Both the paper and online version of the study questionnaire will include the four assessment measures, measures of daily functioning, quality of life, perceived need for treatment and socio-demographic and obstetric information. The order of presentation of the four assessment methods will be counterbalanced in order to minimise any risk of bias in response patterns (65). Women will also be asked whether they consent to long term follow up (beyond the end of the study) and the possible use of their anonymised, clinical and questionnaire data for other research.

Measures of potential confounding factors that are likely to influence anxiety will also be taken so they can be controlled for when analysing effectiveness. These include psychological treatment, obstetric risk and existing health conditions, and sociodemographic risk. Women will be asked whether they are receiving treatment for psychological problems and, if so, the type of this treatment. Obstetric information will be collected on the current pregnancy and birth (e.g. gestation, p arity, obstetric risk factors, neonatal complications).

Sociodemographic characteristics will be assessed at baseline. In follow up questionnaires, women will be also asked whether anything has happened in their life since they completed the last questionnaire that may have changed the way they feel or responded to the current questionnaire. Where possible, we will aim to record information on the number of women who are approached, eligible, recruited into the study, declined or dropped out. We will then be able to examine whether there are differences in demographic or obstetric characteristics between women who take part and those who drop out.

A selection of participants will be interviewed using a gold standard diagnostic interview, the anxiety modules of the Mini International Neuropsychiatric Interview (66). Specifically, the following MINI modules for anxiety disorders will be administered to women to establish whether they are currently experiencing an anxiety disorder according to formal diagnostic criteria: Panic Disorder, Agoraphobia, Social Anxiety Disorder, Obsessive-Compulsive Disorder, Posttraumatic Stress Disorder, Generalised Anxiety Disorder and Specific Phobia. Furthermore, the MINI Module for Major Depressive Episode will be administered to women. Diagnoses of depression will be treated as a secondary outcome and analysed to examine the prevalence of comorbid anxiety and depressive disorder at the four time points. Diagnostic interviews will be administered by three psychologist members of the research team who will be blind to the results of the assessment measures. Women will be interviewed by telephone and all interviews will be audio-recorded to check for inter-rater reliability and monitor whether there is any cause for concern regarding study participants.

With regard to ethical considerations and the safety of women taking part in the study, serious adverse events (e.g. miscarriage, stillbirth) occurring after time point one will be monitored through the following procedure. Two weeks before the next questionnaire, central research staff will contact relevant site staff with a list of women due to take part. Site staff with access to participant medical records will check for pregnancy loss or maternal death. If a serious adverse event has occurred the central research team will write to women to express sympathy and give the options of leaving or remaining in the study, asking women to contact the research team if they would like to remain in the study. This approach has been effectively used in previous studies. We will include a resource sheet giving details of organisations who may be able to provide support.

With regard to women who meet diagnostic criteria for a disorder in the clinical interview, or who report clinically significant symptoms in questionnaire assessments, please see section on ‘Ethical issues’ on pages 31-32 of this protocol. A named clinician will be available to be contacted at each site in the event that risk to self or others is identified during the clinical interview. The relevant Research Ethics Committee and Management approvals will be obtained before the study commences.

Data Analysis

A data analysis plan has been developed by the statistician (Best). This plan will be refined in collaboration with the research team in light of results of WP1 before recruitment to WP2 commences. Analysis will include:

Diagnostic accuracy of the four assessment measures: In studies of diagnostic test accuracy, the result of the index test (i.e. the assessment measure under evaluation) is compared against the reference standard, which can be defined as the best available method for determining the absence or presence of the target condition. For the identification of psychological problems, the reference or gold standard is commonly considered to be a

structured clinical interview based on well-established diagnostic criteria. The comparison between the results of the index test and the results of the reference standard in the same subjects provides an indication of the test's diagnostic accuracy, also known as its criterion validity (67).

We will initially determine rates of true positives, true negatives, false positives and false negatives for the assessment measures at a range of cut-off scores. Based on this, we will calculate a number of parameters of test performance as detailed below (sensitivity, specificity, positive and negative predictive values, likelihood ratios and ROC Curves) by using 2x2 contingency tables. These are used to summarise the relationships between results on an assessment measure and the reference standard at a given cut-off score (67).

For the purpose of calculating the parameters above for the four assessment measures, outcomes from the structured clinical interview (reference standard) will be collapsed into a dichotomous variable indicating the absence or presence of an anxiety disorder as determined by formal diagnosis. Examination of the Area under the ROC curve for the four assessment measures will subsequently allow us to determine the appropriate cut-off scores for each of the measures and select those with the best performance in terms of diagnostic accuracy for implementation in WP3. This will be the first time that cut-off scores for most of these measures will be psychometrically established and validated in a large UK perinatal population

Internal consistency: This form of reliability is a measure of the degree of interrelatedness among items in a rating scale, and provides information on the extent to which items included in a given scale measure the same latent variable. Cronbach's alpha will be used as index of internal consistency for each measure.

Convergent validity: Measures assessing the same or similar constructs are expected to have at least a moderate positive correlation. Convergent validity is a measure of the extent of this correlation. We will determine the convergent validity of the four assessment measures by calculating Pearson's correlations.

Structural validity (factor structure): In psychometrics, factor analysis is used to reduce variables (i.e. single items or questions within a scale) that share common variance into set of clusters (i.e. factors). We will determine the factor structure of assessment measures using factor analysis, except for the Whooley which has only 2 questions so is not suitable for factor analysis. The correlation between the Whooley questions will be examined instead.

Effectiveness of assessment measures in identifying women with poor daily functioning, poor quality of life and perceived need for treatment: A mixed effects model will be fitted for each of the assessment measures to examine the relationship between scores on the measures and postnatal measures of daily functioning, quality of life and perceived need for treatment. Measures of quality of life will be treated as continuous outcomes and need for treatment as a binary outcome. Comparisons of the model coefficients (and their 95% confidence intervals) for each of the assessment measures across nested models will allow us to determine which of the assessment measures is most effective in predicting these outcomes. Analyses will be adjusted for potential confounding factors such as pre-existing health conditions, birth complications and sociodemographic characteristics. Analyses will also include a random effect of participant to ensure appropriate adjustment for repeated measures on individuals.

Optimal timing of assessment: We will establish the optimal timing of assessment for the four measures by looking at the antenatal and the postnatal time points and determining which timing of assessment provides the best diagnostic accuracy. We will also examine the predictive value of the measures at earlier assessment points in identifying women who are referred for treatment or state they need treatment for mental health problems. A mixed effects model will be fitted as described above for each of the assessment measures but will also include an interaction term between scores on the measures and the time point at which they were assessed. We will examine the magnitude of the effect of the interaction term for each time point on probability of subsequent diagnosis of a mental health condition. This analysis will enable us to examine the relative effect of the timing of observations for the different assessment measures and so determine which observation point has most utility in predicting later outcomes.

Additional analyses: Further analyses will be conducted to describe the sociodemographic and obstetric characteristics of the sample, as well as to determine whether any socio-demographic or obstetric characteristics are associated with perinatal anxiety. Estimates of the prevalence of different anxiety disorders and the overall prevalence of clinically significant anxiety in perinatal populations will be provided based on diagnoses from the structured clinical interviews.

Sample size calculations: In studies of diagnostic accuracy, the sample size necessary to achieve acceptable statistical power is dependent on the estimated prevalence of the condition (anxiety disorders) in the target sample (perinatal women), expected values of sensitivity and specificity, and a clinically acceptable precision for the estimates of sensitivity and specificity (68, 69). Based on an estimated prevalence of approximately 15% of all women experiencing clinically significant anxiety in the perinatal period (2, 9), for sensitivity and specificity of 0.80 and a maximally clinically acceptable width of the 95% confidence interval of 0.10 we calculated that a total sample size of 407 will be required to achieve 80% power. A quarter of the women will be given the clinical diagnostic interview at each measurement point. Therefore, we will need to have 1628 women available. Assuming attrition over the study period of 15% we will need to recruit 1915 pregnant women at baseline (12 weeks' gestation).

For the mixed effects models investigating the effect of observation time on the predictive value of the different assessment measures in estimating the probability of poor functioning in the postnatal period, data on which to base sample size estimates for a mixed effects model are scarce. We employed the following estimates for sample size determination: an estimated mean of 4.7 and standard deviation of 4.8 on the CORE-10, an overall prevalence of 15% for antenatal anxiety, an estimated odds ratio of 1.15 for the effect of CORE-10 on probability of postpartum perceived need for treatment, and interaction effect between observation time and CORE-10 of 1.04 on later difficulties and an autocorrelated error structure for repeated measures on participants. For a sample of 1600 this would give power of 80% to detect that the coefficient for the interaction of the observation point and score was significantly different to 0 in a mixed effects logistic regression on postnatal perceived need for intervention. This estimate is derived by simulation using Stata V.15.

Outputs

Results of this WP will enable us to make recommendations about the most robust, effective method of assessing perinatal anxiety, as well as the optimal time of assessment.

PROGRESSION FROM WP2 to WP3

Clear progression criteria have been included so that, in the event that none of the assessment measures are effective, WP3 will not be undertaken.

These are that at least one assessment measure meets all of the following criteria:

- Acceptable to women (WP1).
- Meets the minimum acceptable level of the area under the ROC curve of 0.70 (70, 71).
- Has a positive likelihood ratio of more than 10 and a negative likelihood ratio of less than 0.1 at the optimal cut-off point (72).

If at least one assessment measure meets all of the above criteria the study will proceed to WP3. If all of the measures meet none or one of the three criteria this will be reported to NIHR and a decision will be made not to progress to WP3. If one or more of the assessment measures meets two of the criteria this will be discussed with the SSC and NIHR and a decision made about the appropriate course of action.

SELECTING THE OPTIMUM TOOL FOR WP3

If more than one measure meets the above criteria, the following second level criteria will be used. These criteria are more subjective so will be determined in consultation with PPI and clinical collaborators. Results will be collated and considered by members of the research team and collaborators to decide which tool to take forward to WP3.

- Acceptability and inclusiveness. This will be determined through a wider PPI consultation with at least 30 women who will be asked to rate each tool on a number of scoring criteria including readability, comprehension, ease of completion, acceptability, relevance and inclusiveness.

- Clinical feasibility. This will be determined through consultation with at least 30 clinicians who will be asked to rate each tool on a number of feasibility criteria including ease of explanation, time to administer, perceived clinical utility, ease of understanding and scoring.

WP 3: IMPLEMENTATION CASE STUDIES

Aim

Determine the acceptability and feasibility of implementing assessment in healthcare services and develop a theoretically informed guide to implementation.

Objectives are to:

1. Determine the acceptability of assessment to health professionals and healthcare services.
2. Determine the feasibility of implementing assessment in different healthcare services in Scotland and England.
3. Develop a theoretically informed guide to implementation in NHS services in England and Scotland.

Design
Case studies of implementation of assessment in NHS services in England and Scotland using participatory action research.

Sampling
Two case studies will be undertaken. Each case study will encompass maternity services, psychological services and primary care. At each site a purposive sample of health professionals to include all roles who may undertake assessment (e.g. GPs, midwives, health visitors), managers, commissioners and other stakeholders working in maternity, primary care, and other relevant services will be recruited.

Data Collection
Case studies of implementation of assessment using Participatory Action Research (PAR) in 2 NHS sites in England and Scotland. PAR is a group of research methodologies which aim at implementing change with active engagement of the co-participants. Change is implemented and evaluated at the same time in a cyclical way following a PAR-cycle (Plan, Act, Observe, Reflect). A PAR methodology developed specifically for health services research is the Promoting Action on Research Implementation in Health Services (PARIHS) approach which offers a theoretically informed framework to guide implementation of new initiatives in health services and use PAR to evaluate these (73). In the PARIHS theoretical perspective, successful implementation is a function of (i) the nature of the evidence; (ii) the quality of the context for initiating and sustaining change, and (iii) the type of facilitation needed for change to be successful. Qualitative interview data collection will involve two stages:

1. *Baseline data collection and adaptation of recommendations to local setting*: Qualitative focus groups and interviews will be conducted with approximately 40 healthcare professionals and stakeholders (20 in each NHS site) to gather baseline data to understand the state of assessment of perinatal anxiety in services and the view of stakeholders on the proposed practice change. The (potential) recommended change in assessment practice will require adapting for implementation in the local settings. Therefore, interviews will involve exploring stakeholder perceptions of the specific needs, priorities, policies, resources, and problems of the setting and whether the change in practice is perceived as sustainable based on priorities of the setting. Perceived barriers and facilitators of implementing assessment will be explored using the revised PARIHS framework for a task-oriented approach to implementation which considers evidence-based practice characteristics of the setting, contextual readiness for targeted evidence-based practice implementation, and appropriate facilitation of implementation (73, 74). Interviews will be conducted until data saturation is achieved – anticipated to be around 40 participants. Analysis of documents pertinent to perinatal mental health assessment such as local policies will also be undertaken.

Based on these findings we will:

- Determine which implementation strategies are most conducive to successful implementation (i.e. strategies that are effective, that address the identified barriers and utilise facilitating factors, and which do not exceed available resources). Strategies may include: educational outreach, paper or electronic reminders, interactive educational meetings and workshops, and engaging local opinion leaders (75).
- Develop an implementation package to be put into practice in both services, and piloted for a five-month period using the strgies identified above.

2. *Evaluation of implementation:* 5 months after initiation of the package into practice, focus groups and interviews will be repeated with participants from the baseline phase. Focus group and interview questions will be based on the three factors of the PARIHS framework and will consider views on experiences of initiating a change in practice, contextual enablers and barriers experienced in implementing the tool, and usefulness of the implementation strategy in enabling change. Acceptability of the assessment measure and feasibility of using the assessment measure in practice will be explored. Verbal responses as well as subtleties of language and emotional responses will be documented. Discussions will be audio-recorded with consent and transcribed verbatim. Interviews will be conducted until data saturation is achieved.

Data Analysis

The Framework Method (76) will be used to provide a structured summary of the data. This type of thematic analysis is suitable for work with multidisciplinary teams and can be used with documentary sources of data as well as interview or focus group data (77). A combined inductive-deductive approach will be used which enables specific research questions to be addressed as well as identifying unexpected or new themes related to implementation of the assessment measure. Specifically, framework analysis will allow us to identify and compare key barriers and facilitators to implementing assessment at the two sites. Analysis will be conducted in six steps: (i) transcripts will be re-read for familiarisation with the data; (ii) data will be coded line by line for meaning by two researchers; (iii) researchers involved in coding and the project leads will meet to develop a working analytical framework of agreed codes to apply to subsequent transcripts; (iv) the analytical framework will be applied to remaining data; (v) the data from each transcript will summarised, by importing data for each category, into a matrix; (vi) data will be analysed for characteristics and differences, and connections between categories and relationships will be mapped. To establish credibility, members of the research team will keep a research diary in which they record reflection and impressions of the data and thoughts about analysis throughout the process; analytical findings will be shared with stakeholders at regular meetings and feedback incorporated into the analysis; and the systematic framework approach will be adhered to.

Outputs

Results of this WP will enable us to determine how evidence from WP1 and WP2 may best be implemented and then applied in practice. We will recommend the optimal method of assessing perinatal anxiety and develop a guide to implementation to facilitate the implementation of assessment in maternity and other relevant health services.

ETHICAL AND REGULATORY COMPLIANCE

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority if required. Ethical approval has been obtained for WP1 from City University of London Research Ethics Committee (ETH1819-0689). Application for ethical approval for WP2 will be made to the Health Research Authority, and to City University of London Ethics Committee for WP3, following the award of the grant.

Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

Research will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice and the UK Department of Health Policy Framework for Health and Social Care, 2017. GDPR regulations will be adhered to.

Ethical Issues

This project does not involve medical intervention so major ethical issues are unlikely to arise. However, it is likely that a proportion of women who participate in the research will report anxiety or depression, and a small proportion will report suicidal ideation.

Women who report clinically significant symptoms in questionnaire assessment in WP1 and questionnaire assessment or clinical interviews in WP2 will be contacted to say their scores suggest they might be suffering from anxiety or depression and they will be strongly encouraged to talk to their GP, midwife or health visitor about this. In case women do not feel comfortable discussing this with their GP, midwife or health visitor we will also provide them with a list of other support organisations, including the NCT helpline and psychological services (IAPT) they can access through self-referral. Clinically significant symptoms will be defined according to established cut-offs used for the GAD-2 and the Whooley questions.

Women who report suicidal ideation in questionnaire assessments will be contacted within 24 hours by email or phone to conduct a suicide risk assessment. If women report suicidal ideation in interviews the risk assessment will be conducted at that time. Action will be taken on the basis of the risk assessment and consultation with study clinicians as to whether a referral to specialist services is appropriate. In all instances a risk assessment form will be completed.

In WP2 measures are taken at four time points so women who report anxiety, depression or suicidal ideation will be monitored across time points and contacted as necessary to ensure they are accessing support or treatment as needed.

PATIENT AND PUBLIC INVOLVEMENT (PPI)

This project has been developed with PPI representatives from the National Childbirth Trust (NCT) in England (McMullen/Hann) and the Maternal Mental Health Change Agents (MMHCA), a group of women in Scotland with lived experience of perinatal mental ill health (Thompson). We also work closely with the PPI Research Advisory Group at the Centre for Maternal and Child Health Research, City University (advisors).

These organisations will continue to ensure we have PPI input from perinatal women generally as well as those affected by anxiety and other perinatal mental health problems. The research team have collaborated with the NCT and MMHCA for a number of years so have very good, productive and valuable relationships. Representatives from the NCT and MMHCA will co-ordinate PPI input throughout the research and will lead the Dissemination phase of the project. PPI members have been, and will continue to be involved in the project at every step including training researchers and practitioners, input into research materials, supporting recruitment, analysis and interpretation of the data, and dissemination.

DISSEMINATION AND IMPLEMENTATION

To ensure uptake of the recommended assessment method we have a comprehensive 6-month output and dissemination phase at the end of the research programme which will be led by the PPI representatives with input from the clinical and service leads in England and Scotland. The first part of this phase will focus on outputs and develop targeted implementation guides for different service contexts (e.g. maternity, primary care and psychological services). These will be made available online so that services and individuals can access them easily.

The second part of this phase will focus on engagement and facilitation activities to facilitate uptake and implementation of perinatal assessment in relevant healthcare services across the UK. These include:

- Launch events in England and Scotland for stakeholders, commissioners, service managers and health care professionals working with perinatal women.
- Disseminating results to the public through social media and press releases.
- Dissemination through clinical networks i.e. the National Managed Clinical Network for Perinatal Mental Health in Scotland (Clark) and England.
- Dissemination to perinatal mental health leads at the Royal Colleges of Psychiatrists, Midwives, General Practitioners, and Obstetrics and Gynaecology.
- Dissemination to NHS England's perinatal mental health team who are looking at perinatal assessment and outcome measures.
- Dissemination to the Scottish Government Health and Social Care Directorate Mental Health Division.
- Dissemination to services and service users through Maternity Voices Partnerships or Maternity Services Liaison Committees.
- Dissemination to third sector organisations e.g. the Maternal Mental Health Alliance, NSPCC, NCT, Children in Scotland, Aberlour Child Care Trust.

The research team is well placed to ensure wide spread dissemination to the NHS and wider population, and to facilitate implementation of assessment tools into health and social services. The NCT and MMHCA have active and successful campaigns for perinatal mental health (e.g. the NCT's Hidden Half campaign) so are very experienced at disseminating information and raising public awareness.

The research team has a strong clinical background with significant roles in local and regional healthcare services. Each member of the team will ensure the results are disseminated widely within their own hospital, trust or speciality. The research team are also well connected with professional, third sector, and policy organisations so will use these connections to ensure wide-spread dissemination.

The research team has a good track record of dissemination to other researchers through conferences and publishing in high-impact psychology, obstetric, midwifery and medical journals. Results from each WP will be published in open access journals to ensure maximum reach and impact. Results will be disseminated at key international conferences.

These dissemination strategies will ensure the recommended method of assessment is widely disseminated to the NHS, wider public and researchers.

Possible barriers to adoption and implementation of assessment may be organisational or individual. Certain healthcare services or individuals may be reluctant to replace existing assessments with a new measure, or may not want to add new measures if there are implications for time and resources. It may be particularly difficult to implement perinatal mental health assessment in services where clear referral pathways are not available. Most of these barriers should be identified and addressed though WP3, however, the research team will work closely with clinical networks and service delivery managers to identify and mitigate against potential organisational and individual barriers.

If the current research is successful in identifying a measure of anxiety that is acceptable, effective and feasible to implement then it is important to conduct future research on the effectiveness of screening for anxiety in reducing morbidity and improving maternal and infant health outcomes. To do this, a high-quality cluster randomised controlled trial is necessary to establish whether such a screening programme can reduce morbidity or mortality and justify its implementation (78). The present research is an important pre-requisite for an RCT by identifying an acceptable and effective method of assessment that is feasible to implement in different service contexts, and therefore appropriate to examine in an RCT. The current evidence base does not support use of any one measure so an RCT at this point testing multiple measures would be premature and an inefficient use of funding.

RESEARCH TIMETABLE

The project timeline is 42 months from June 2019 to November 2022 There is a 3-month pre-award period of work setting up the study e.g. approving contracts, recruiting staff and obtaining ethical approval. In the first 24 months we will complete WP1 and WP2 then progression criteria will be examined to determine whether to proceed to WP3. Providing criteria are met we have allowed 12 months for WP3 and developing the implementation guide framework, then 6 months for developing targeted guides, dissemination and implementation.

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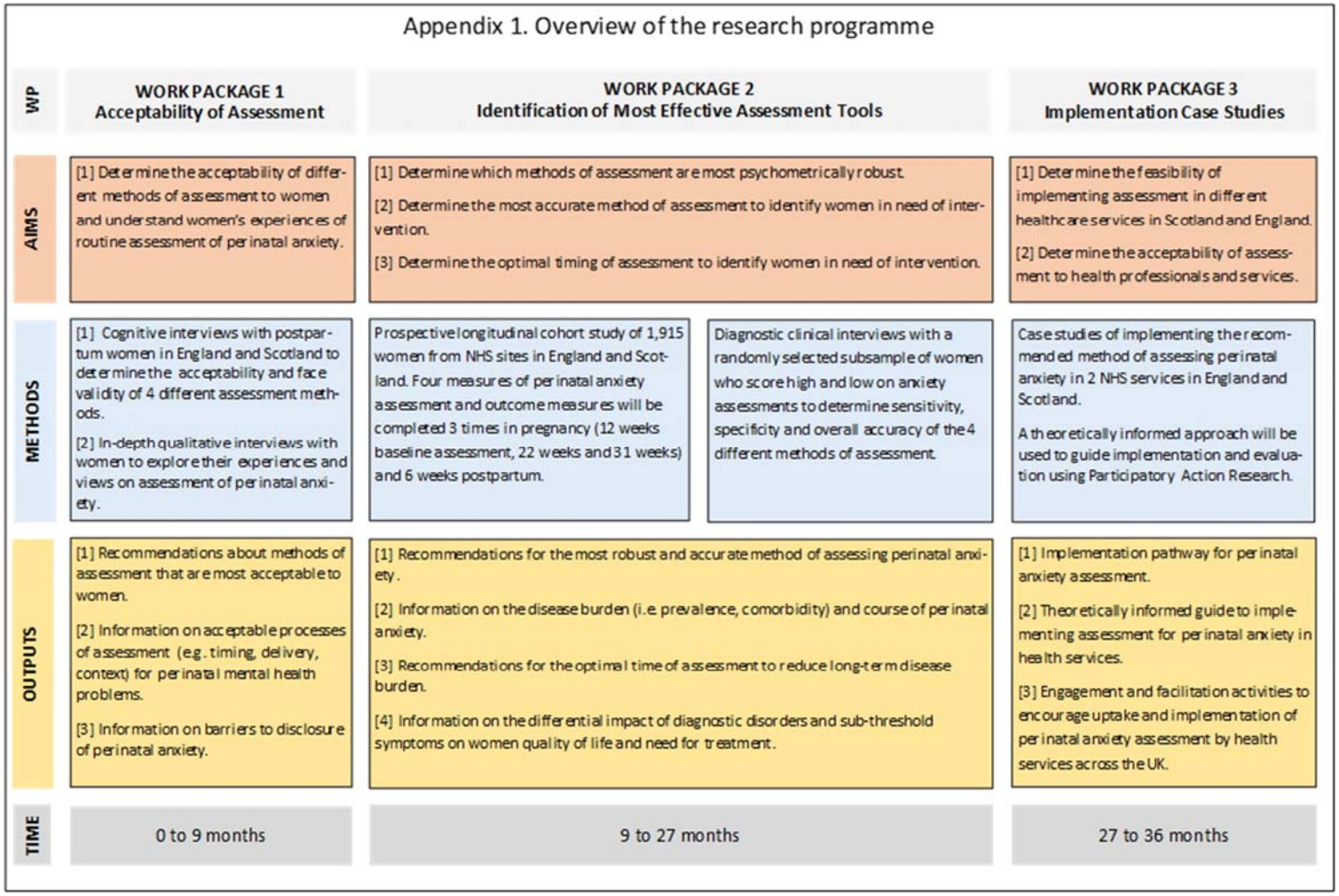
APPENDIX 1. OVERVIEW OF THE RESEARCH PROGRAMME



COVID-19 ADDENDUM

Synopsis

The aim of this additional research is to determine the impact of COVID-19 on women's mental health during pregnancy and after birth. This will be done by adding COVID-19 measures to the MAP longitudinal cohort study (WP2).

WP2 is a longitudinal cohort study of 1915 women looking at symptoms of anxiety, depression and other mental health problems at three times during pregnancy (up to 15 weeks, 22 weeks and 31 weeks) and 6 weeks after birth. Prevalence of perinatal anxiety disorders will also be established using clinical diagnostic interviews. Measures will be added to examine: (i) the impact of COVID-19 on mental health symptoms throughout pregnancy and postpartum; (ii) determine COVID-19 related predictors of poor birth outcomes and poor mental health later in pregnancy and after birth; and (iii) explore perinatal women's adherence to COVID-19 related public health guidance.

Background and rationale

The coronavirus disease 2019 (COVID-19) pandemic has resulted in wide-ranging changes to how people live, work and socialise in the UK and around the world. The anxieties caused by this unprecedented situation are likely to be exacerbated in pregnancy and the postnatal period. The MAP study is an NIHR funded study of perinatal anxiety and mental health, and as such is in a position to add valuable insights in three areas of COVID-19 research: mental health symptoms and mental health services; maternity services; and public health and communications.

Mental health

Tracking mental health

During the COVID-19 pandemic, increased anxiety is likely and expected in the general population. There is also a risk that there will be an increase in the number of people with clinically relevant anxiety and depression and who engage in self-harm and suicide (I). Additional anxiety in pregnancy is likely to arise because of the virus itself and the possibility of becoming physically unwell, as well as social and mental health concerns, which have ranked higher than physical concerns in a rapid national survey of the general population (II). In the postnatal period, potential stressors involved in the adjustment to parenthood including a woman's relationship with her partner, caring for the infant, maternal social interactions and establishing new routines are likely to be interrupted during the pandemic (III). Monitoring mental health and psychosocial variables throughout pregnancy and the early postnatal period can help understand the effect of COVID-19 on mental health outcomes. Tracking loneliness and social isolation has been highlighted as a research priority because reducing sustained loneliness can protect against mental health problems (I; IV). MAP has been designed to track mental health symptoms during pregnancy and the early postnatal period.

Effects of lockdown on mental health

The effects of lockdown or quarantine for everyone are likely to include reduced support from family and friends which may lead to increased social isolation and loneliness which in turn have a strong association with anxiety and depression. These effects may be increased for mothers with a new baby who may be expecting to have increased support from family members (V).

Furthermore, changes to sleep and lifestyle behaviours impact mental health and pregnant and postnatal women will have to cope with changes to sleep and lifestyle caused by COVID-19 in addition to those inherent in the perinatal period. Reduced finances, and changes to NHS care with a move away from face-to-face appointments are also likely stressors that will impact perinatal mental health (VI).

Evidence of the psychological effects of infectious disease outbreaks on pregnant and postnatal women is scarce. A recent unpublished rapid review found only 13 research studies in this area, and only two with participants from the UK (VII; VIII; IX). The review suggested that pregnant women experienced increased anxiety and other negative states, lived with uncertainty about effects of infection on themselves and their baby, and concerns about risk of infection led to women postponing or cancelling appointments, and fears about disrupted health care (VII). It will be important to understand whether the COVID-19 pandemic has similar effects, as a first step in addressing such problems.

Longitudinal research (WP2) can track COVID-19 specific mental health symptoms and psychosocial variables at population level, and can enable understanding of causal factors associated with poor mental health, enabling future development of effective interventions.

Maternity

Effects of lockdown on pregnancy and birth outcomes

Evidence suggests that heightened anxiety in pregnancy can result in poorer pregnancy behaviours such as increased sedentary activity and increased smoking (XI). Furthermore, women experiencing increased anxiety in pregnancy are at higher risk of poor birth outcomes. Different forms of anxiety are implicated with different outcomes, for example pregnancy specific anxiety is a risk factor for preterm birth, and life events and chronic stress contribute to low birth weight (X). The COVID-19 pandemic is a unique potentially threatening experience for perinatal women, in which the effects of different types of anxiety on birth outcomes can be examined. With the addition of variables specific to COVID-19 related anxiety, the MAP project can add evidence to understand this.

Changes to maternity services

It is suggested that maintaining access to midwifery services, accessing sources of self-help for anxiety and stress, and self-referral to IAPT (Improving Access to Psychological Therapies) services in England and equivalent services in Scotland can help to contain some of the anxieties related to COVID-19 (VI). As well as their role in supporting mental health, women may have particular concerns about place of birth, support during birth, support for breastfeeding, and availability of formula during COVID-19 which maternity services will need to respond to (XII). There is some evidence suggesting that pregnant women and those with young children are more concerned than other groups about transmitting or contracting the virus (XIII). It is not known whether perinatal women are willing and able to access these services, what the barriers and facilitators to access are, and how women have experienced services in their new format. Understanding women's experiences of appointments in telephone, door-step or video-consultation format can aid decision makers and healthcare professionals to tailor their approaches to appointments in these new formats. This will be relevant both during COVID-19 and in the post-pandemic health service which may decide to retain some of these new ways of working and could contribute to inform planning and delivery of services in future public health crises.

Public health and communications

The likely increase in anxiety in pregnancy during COVID-19 has been recognised by organisations supporting perinatal women including the Royal College of Obstetricians and Gynaecologists (XIV), the Royal College of Psychiatrists (VI), Maternal Mental Health Alliance (XV), and Women's Aid (XVI) who have all published guidance and/or links to resources to support pregnant women. In addition to the new experiences and challenges of pregnancy and the transition to parenthood, perinatal women are now expected to obtain, understand and rapidly apply this health information to avoid spreading or getting the infection. Understandable and accessible information is necessary, but complex, contradictory and false information is also available (XVII). Official guidance is clear in suggesting that COVID-19 is unlikely to cause problems with birth and with a baby's development based on current evidence. However, in the UK pregnant women were classified as being in a vulnerable group by the Chief Medical Officer on 16th March (XIV). This may be potentially confusing to pregnant women and media-fuelled distress can lead to poor mental and physical health consequences (e.g. not leaving the house for exercise as permitted).

Adherence to public health guidance

Guidance suggests the most important thing perinatal women can do is follow Government protocols on social distancing. If quarantine and social isolation are essential, then it will be vital to understand how to encourage people to adhere to this guidance, as adherence can be highly variable (XVIII). Evidence suggests that a clear rationale for, and public information about the necessity of quarantine for public health, emphasising social norms and altruistic behaviour may minimise the risk of non-adherence but that adherence will depend on psychological and practical factors (XVIII).

It is likely that pregnant and postnatal women will have specific requirements during outbreaks. There is some evidence that pregnant women are more concerned than the general population about contracting or transmitting the disease, and will adopt behavioural strategies such as increased physical distancing in response (XIX; XX). It is possible that the situation for postnatal women will be different, as the responsibilities for caring for a new baby and associated requirements such as emotional and practical support may lead to less support for and engagement with quarantine protocols. Further, the unprecedented nature of 'lockdown' in the UK means that there is no research with UK pregnant and postnatal women to understand whether results from previous contagious disease outbreaks with differing government-imposed restrictions applies to the current situation.

The MAP project is in a unique position to address COVID-19 research priorities for a number of reasons. First, the MAP team is a multidisciplinary team with representation from midwifery, psychology, health visiting, psychiatry and health services research; all are perspectives which are needed to address research priorities of understanding the psychological and social effects of the pandemic in perinatal women. Second, the MAP cohort study (WP2) is in a position to track symptoms of mental health and diagnostic disorders during the COVID-19 pandemic in a large sample of perinatal women. It has NHS Research Ethics Committee and Health Research Authority approval (IRAS reference 274901), sites have been selected and research infrastructure is in place for this study to begin as soon as possible subject to minor amendments. Third, this work can be conducted by the existing MAP research team so does not require funding at this point.

Research question:

What is the impact of COVID-19 on women's mental health during pregnancy and after birth?

OBJECTIVES:

1. Determine the impact of COVID-19 on mental health throughout pregnancy and after birth.

2. Determine COVID-19 related predictors of poor birth outcomes.

3. Explore perinatal women's adherence to COVID-19 related public health guidance.

This research will be embedded within a prospective longitudinal cohort study (WP2) conducted in maternity services in England and Scotland. Work package two is described in more detail below.

WP2 Addition of COVID-19 questions:

Monitoring rates of anxiety, depression, self-harm and other mental health issues by establishing new cohorts has been highlighted as an immediate research priority (I). Episodes of mental illness are expected to increase as they are likely to be triggered by periods of social stress (VI). The MAP WP2 cohort study of approximately 1915 women is large enough to demonstrate population-level changes in perinatal anxiety during the COVID-19 pandemic and its aftermath. WP2 has already been designed to measure symptoms of anxiety, depression and other mental health problems using surveys at three times during pregnancy (up to 15 weeks, approximately 22 weeks and 31 weeks) and approximately 6 weeks after birth. Prevalence of perinatal anxiety disorders will also be established using clinical diagnostic interviews. With the addition of COVID-19 specific questions at each time point we will be able to identify whether COVID-19 specific factors predict later mental health and birth outcomes.

The MAP cohort is funded by the NIHR, sites have been identified, and the study has received a favourable opinion from the NHS Research Ethics Committee (IRAS project ID 274901). As recruitment has not yet started, we are in a unique position to address COVID-19 mental health priorities on a population-level scale as soon as recruitment is possible in the NHS. Questions related to COVID-19 can be added before recruitment begins, and women can be followed through pregnancy and the beginning of the postnatal period. Subject to further funding, the longer-term consequences for children and mothers of pregnancy and birth in the aftermath of the pandemic could be established.

Given the uncertainty of when and if life will return to pre-COVID-19 routines, and the likelihood of long-term restrictions of some kind on people's lives, this research will add to knowledge about levels of anxiety and other mental health symptoms and disorders in pregnant women, associated birth outcomes and postnatal mental health, in an unprecedented time.

Design

Addition of COVID-19 questions to existing prospective longitudinal study of 1915 pregnant women in England and Scotland (WP2). All other elements of design and sampling remain as originally approved.

Data Collection

Measures of mental health, psychological treatment, obstetric factors, birth outcomes and sociodemographic variables have already been approved by the NIHR and have received HRA and NHS REC approval. In addition to these variables, we propose to include items specific to COVID-19, including exposure to and experience of COVID-19; COVID-19-related anxiety; perceived risk; adherence to and perceived efficacy of public health instructions; loneliness / social isolation due to COVID-19.

Data analysis

Mental health

Analyses will be conducted to determine whether any COVID-19 specific variables (experience of/exposure to of COVID-19; perceived risk; COVID-19 related concerns) are associated with later mental health symptoms and diagnoses. Analysis will be by mixed effects models evaluating the association between the mental health outcomes at each time point and COVID-19 related measures evaluated at previous time points (lagged effects).

Birth outcomes

Analyses will be conducted to determine whether COVID-19 related anxiety predicts low birthweight and/or preterm birth. Analysis will be logistic regression of COVID-19 anxiety during pregnancy on binary indicators of poor birth outcomes.

Public health

Analyses will be conducted to describe adherence to public health instructions, and associations with mental health variables. Cross-sectional analyses of the correlation between these public health related measures and mental health will be conducted at each time point.

Outputs

Results of the additional analyses will enable us to determine the impact of COVID-19 on perinatal mental health in a population-based sample. It will also enable understanding of perinatal women's experiences of following public health guidance.

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