Study Title: Defining, Recognising and Escalating Maternal Early Deterioration (DREaMED): Decreasing inequality through improved outcomes.

Internal Reference Number / Short title: DREaMED

Ethics Ref: X

CAG Ref: 24/CAG/0060

IRAS Project ID: 337633

Joint Research Office Ref: PID17763

ClinicalTrials.gov: X

NIHR Project: NIHR131227

Date and Version No: 3rd June 2024 Version 2.0

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Funder: National Institute for Health and Care Research (NIHR)

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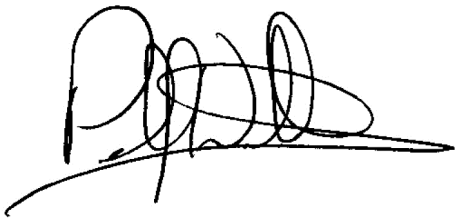

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Conflicts of interest:

PW declares significant grants from Wellcome and Sensyne Health (now Arcturis Data). He undertakes consultancy for Arcturis Data.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1 KEY CONTACTS

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Committees	*Study Management Group*

	The study management group will consist of the Chief Investigator, Lead Investigator and the named investigators listed under Key Contacts, and individuals directly funded by the project. *Project Oversight Group* The project oversight group will consist of independent members as approved by the funder. Their role will be to provide ongoing oversight of the project, to ensure that it achieves the study objectives.

INCLUSIVITY STATEMENT

We use the term 'women' throughout this protocol to refer to those who are planning to become pregnant, are pregnant, and give birth. We acknowledge that not all people who are pregnant and give birth identify as women, and it is important that evidence-based care for maternity, perinatal and postnatal health is inclusive.

2 LAY SUMMARY

Every year more than 700,000 women give birth in the United Kingdom. Of these at least 8700 nearly die – called a “near-miss”, and 70 die. Many more women suffer harm, often with effects lasting for life. Women from less wealthy areas and particular ethnic groups are more likely to come to harm.

"Vital signs" include measurements of blood pressure, heart and breathing rates. Doctors and midwives use tools that score vital signs to spot women becoming unwell. These tools are called “Modified Obstetric Early Warning Scores” (MOEWS). Despite their use, poor outcomes still occur. This may be because MOEWS use only the most recent vital signs. Using extra data like blood tests may help spot unwell people earlier.

We aim to reduce poor outcomes for women giving birth. We will find better ways of describing, spotting, and treating women becoming unwell.

We plan four linked projects to develop an electronic advanced maternal obstetric early warning system (eMOEWS). Patient and Public (PPIE) collaborators have developed this work with us. We will work closely with them throughout this project.

Once we have completed these four projects, we plan to carry out a trial to assess whether the new eMOEWS leads to better outcomes than the existing tools. This trial will be described in a separate protocol.

Project One

We will develop new definitions of worsening illness in women giving birth. We will work with our PPIE colleagues and other experts, reviewing published work. This will help staff use routinely collected health data to spot early illness, before a woman becomes very unwell. We will check that the new definitions reliably identify women becoming unwell.

Project Two
Using the new definitions, we will test how well current MOEWS pick up worsening illness. We will use data from eight to twelve NHS maternity units serving diverse women, and our national maternal review programme.

Project Three
We will develop an advanced, electronic MOEWS (eMOEWS) working with our PPIE collaborators and other experts. This will use extra information known to affect the risk of poor outcomes. We will test how well the eMOEWS spots worsening illness, using our new definitions.

Project Four
We will develop a way to digitally display eMOEWS on maternity units. We will work with staff who use computers along with experts in NHS computer systems. This will allow staff to understand quickly which women are at risk, and why. We will design guidelines for how to use eMOEWS on maternity units with women and staff. This will make sure our new system helps give women the right care at the right time.

3 SYNOPSIS

Study Title	Defining, Recognising and Escalating Maternal Early Deterioration (DREaMED) Phase 1: Decreasing inequality through improved outcomes
Internal ref. no. / short title	DREaMED1
Study registration	The study will be registered on clinicaltrials.gov
Sponsor	University of Oxford
Funder	National Institute for Health and Care Research (NIHR), Programme Grants for Applied Research (NIHR204430)
Study Design	Longitudinal Cohort study
Study Participants	Women aged 16 or over who are pregnant
Sample Size	Total: 459,160 Retrospective cohort: 293,200 Prospective cohort: 164,300 MBRRACE-UK cohort: 1,300 Patient interviews (escalation pathway): Up to 60 Staff interviews/focus groups (escalation pathway): Up to 100 Staff interviews/focus groups (eMOEWS interface development): Up to 100 Staff training (simulation scenarios): Up to 100
Planned Study Period	Funded study period: 02/05/2023 until 01/05/2029 Total funded study period will be 6 years Planned study period: 01/05/2024 until 01/05/2029

Planned Recruitment period	Retrospective cohort: 01/01/2021 to 28/02/2025 Prospective cohort: 01/03/2025 to 30/06/2027 MBRRACE-UK cohort: 01/01/2009 to 31/12/2022 Staff interviews/focus groups (eMOEWS interface development, WS4a): 01/04/2025 to 31/03/2026 Patient interviews (escalation pathway, WS4b): 1/06/2024 to 30/08/2025 Staff interviews/focus groups (escalation pathway, WS4b): 01/06/2024 to 30/11/2025 Staff training (simulation scenarios, WS4c): 01/11/2026 to 30/11/2027		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To develop, and validate an electronically-embedded, data-enhanced Maternal Early Warning Score (eMOEWS) with clinical escalation pathways	Predictive performance of new early warning scores, assessed by: discrimination, calibration, and clinical utility.	During pregnancy or in the immediate postpartum period.
Secondary:			
	To define 'near-miss' and 'pre-near-miss` criteria for use with routinely-collected data to measure maternal outcomes	'Near-miss' and 'pre-near-miss' outcome criteria measurable using routinely available electronic data, assessed in NHS hospitals	During pregnancy or in the immediate postpartum period.
	To assess performance of the new near-miss and pre-near-miss outcome criteria in 3 hospitals and MBRRACE-UK in: • a stratified random sample of 100 sets of records of near-miss and pre-near-miss cases across the three sites. • clinical serious maternal events recorded in hospital serious event systems. • MBRACCE-UK cases	Descriptive statistics to describe whether the electronic criteria used correctly identified the conditions. Descriptive statistics of missed and captured events according to electronic criteria Descriptive comparison to published rates	During pregnancy or in the immediate postpartum period.
	To develop a large representative eight to twelve maternity unit cohort for model development and assessment	Cohort developed and ready for assessment	05/2029
	To investigate the performance of existing MOEWS/MEWS in the new maternity cohort and in women who have died or had a near-miss or pre-near-miss event in pregnancy	Evidence-based assessment of existing MOEWS, both in new retrospective (assessed by discrimination, risk of our key events at each MOEWS/MEWS level) and nationally recognised mortality/morbidity (assessed	05/2029

		by sensitivity and duration of prior warning) cohorts	
	To develop and validate an optimal vital-signs-only-based MOEWS	Relative performance of new MOEWS, best published MOEWS and NHSI national MOEWS for prediction of near-miss or pre-near-miss	05/2029
	To develop and validate an eMOEWS to improve detection in comparison to existing MOEWS/MEWS	Relative performance assessment of eMOEWS, new validated vital-signs-based MOEWS, best published MOEWS and NHSI national MOEWS for prediction of 'near-miss' or 'pre-near-miss'	05/2029
	To design and deliver an eMOEWS interface	User co-designed eMOEWS implemented within 4 NHS sites. System Usability Scale performance	05/2029
	To develop treatment escalation pathways	Escalation and response pathways protocolised iterated and tested in a simulated environment	05/2029

4 ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
eMOEWS	Electronically-embedded, data-enhanced Maternal Obstetric Early Warning Score
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
MEWS	Maternal Early Warning Score
MOEWS	Modified Obstetric Early Warning Score
MBRRACE-UK	Mothers and Babies: Reducing Risk through Audit and Confidential Enquiries, United Kingdom
NEWS	National Early Warning Score
NHSE	National Health Service England
NHSI	National Health Service Improvement

RES	Research Ethics Service
PI	Principal Investigator
PIERS	Preeclampsia Integrated Estimate of Risk
PIL	Participant/ Patient Information Leaflet
PPIE	Patient and Public Involvement and Engagement
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance, University of Oxford
SOP	Standard Operating Procedure
WS	Workstream

5 BACKGROUND AND RATIONALE

5.1 What is the problem being addressed?

Of over 700,000 women giving birth in the UK annually, one in every 10,000 women dies during or up to six weeks after pregnancy (1). For every woman that dies, 120 will have a 'near-miss' (8,700 women annually) often with lifelong sequelae (2). Recent data from the United States using adapted Centre for Disease Control definitions found even higher rates (2%) (3). There are significant disparities in maternal and perinatal outcomes between ethnic, age and socioeconomic groups (1,4). Maternal mortality has been consistently shown to be more than four-fold higher among women from Black ethnic groups, and two-fold higher among women from Asian ethnic groups compared to women from White ethnic groups (5). Mortality rates are similarly two-fold higher amongst women who live in the 20% most deprived areas compared to those who live in the least deprived areas (5). Women aged over 40 are four times more likely to die during or after pregnancy compared to women aged 25-29 (5). Substantial disparities also exist in severe maternal morbidity; a recent analysis by our group (manuscript submitted) using Hospital Episodes Statistics data has shown that severe maternal outcomes at the time of a childbirth event, measured using the English Maternal Morbidity Outcome Indicator (EMMOI) are up to 70% higher amongst women from Black Caribbean and Black African ethnic groups. This disparity persists across all English regions and is driven primarily by sepsis and complications related to haemorrhage or pre-eclampsia. This variability, along with the major underlying causes, suggest a high degree of avoidability, a suggestion strongly supported by MBRRACE-UK mortality reports (5).

Current published morbidity criteria (6–9) represent near end stage (near death), rather than early deterioration and are not reliably derivable from routine data, preventing both development of early warning systems to detect early maternal deterioration and effective routine quality assurance.

The detection of women at risk of severe maternal morbidity or mortality is currently limited by the use of expert opinion-based Modified Obstetric Early Warning Scores (MOEWS). These MOEWS are based only on the most recent set of vital signs (heart rate, blood pressure, oxygen saturation, respiratory rate,

and conscious level), ignoring other highly relevant risk information used by clinicians. Current MOEWS have very limited assessment of detection performance (10–12).

5.2 Why is this research important?

It is internationally recognised that new definitions for early deterioration ('pre-near-miss' definitions) in maternity are required to avoid severe adverse maternal outcomes and for effective quality assurance (13). Recent work demonstrates that these are also essential for effective prediction model development (14). In our programme of research, we will develop these new definitions for early maternal deterioration (outside the current ethics/CAG application), ensuring that they can be operationalised to allow electronic extraction from routine clinical data.

Underlying these adverse maternal outcomes is persistent failure to recognise early deterioration. Adverse maternal outcomes investigations consistently show the severity of women's illness is not recognised and women are not listened to (15–17). This has been brought to the fore in the recent Ockenden report of the investigation into maternity care at Shrewsbury and Telford Hospitals (18). Developing robust pathways for managing women with complex pregnancies is an essential action recommended by the Ockenden report (18). Recent research examining the care of women from different ethnic groups who died identified that current structures were unable to provide care for women with multiple complex clinical, social, and cultural conditions whose needs crossed the expertise of multiple specialist teams (18,19). Failure to provide timely care was linked to a lack of understanding of the altered physiology in pregnancy and an inability to recognise disease severity, emphasising the importance of explaining why our proposed advanced eMOEWS identifies a woman as at risk. Women are entering pregnancy older, with increasing multi-morbidity, making recognising deterioration even more imperative and potentially more challenging. Earlier deterioration recognition should lead to early intervention, preventing progression to severe morbidity or mortality (3).

Significant deterioration is both common and has substantial immediate and long-term outcomes for the women affected. A prospective study of women giving birth in Wales, for example, reports that up to 3.3% of women (23,000 in the UK each year) have a postpartum haemorrhage of 1500ml or greater (20). Early detection and escalation through an enhanced MOEWS would prevent haemorrhage reaching higher levels, preventing early consequences of anaemia such as need for transfusion, maternal fatigue and depression (21,22). Long-term consequences of adverse maternal outcomes are also common. For example, a hysterectomy, which leads to consequent lifelong infertility, is used as a lifesaving intervention for severe haemorrhage. Severe uncontrolled blood pressure due to pre-eclampsia can lead to stroke and long-term disability. Women who have experienced life-threatening complications in pregnancy also highlight the mental health consequences, including post-traumatic stress disorder for both them and their partner and long-term impacts on their relationship with their baby (23–25).

The UK government aims to halve maternal mortality by 2025 (26), yet mortality rates have altered little across successive MBRRACE reports. Better early detection, escalation and management are essential.

Current methods for detecting deteriorating women are not fit for purpose. In the general hospital population, The National Early Warning Score 2 (NEWS2) (27) is used for deterioration detection. NEWS2 is not intended for use in pregnant women where physiological changes in pregnancy substantially change the normal vital sign ranges underlying such scores (28,29). Despite this, investigations into maternal deaths, including women dying in the recent pandemic, have repeatedly identified that NEWS2

is being used in pregnant women, and failing to identify critical illness (30,31). Alternative, expert opinion-based Modified Obstetric Early Warning Scores (MOEWS) have been developed, with limited assessment of performance (10–12). A wide variety of different MOEWS are in use in the UK, resulting in substantial practice variation (32), with little evidence of effective implementation (33). The urgency of this problem is illustrated by the care of pregnant and postpartum women who died during the COVID-19 pandemic (2). Women who were clearly in extremis were assumed to be hyperventilating, their care was not escalated, the maternal medical team were not involved, and women received potentially life-saving treatments late or not at all. These systemic deficiencies occurred despite current early warning tools.

We will assess current vital-signs-based MOEWS and externally validate an optimised vital-signs-based MOEWS. This will provide a reliable, evidence-based MOEWS tool in environments where a more advanced, multivariable, electronic MEWS (eMOEWS) is not feasible.

Outside maternity, advanced, multivariable, electronic MOEWS incorporating predictors beyond fixed vital sign thresholds substantially improve detection of deterioration (34–37). The variation in vital signs throughout pregnancy and postpartum (28,29,38), the need for non-vital sign measures to define World Health Organisation (WHO) near-miss events (9) and prior work in specific maternal conditions such as pre-eclampsia (39) and maternal sepsis (40) suggest an electronic advanced, multi-variable score will substantially improve early deterioration detection in maternity. We will therefore develop an eMOEWS for clinical testing within the programme.

Though specified response pathways have shown benefit outside the UK(3), evidence of design or implementation of escalation pathways and the organisational and behavioural science of successful care escalation is limited (41). For our eMOEWS to have clinical impact, a robust implementation strategy, with evidenced escalation pathways is required. The system is designed to work within UK healthcare systems whilst minimising workload and is required to ensure effective action in the event of early deterioration to prevent ‘near-miss’ or ‘severe morbidity’ events. Again, the Ockenden report recommendations emphasise the importance of this work, stating that the hospital ‘must strive to develop a safe environment and culture where all staff are empowered to escalate to the correct person’ and that the hospital’s ‘escalation policy must be adhered to and highlighted on training days to all maternity staff’ (18).

Our research will fill four important evidence gaps:

1. the lack of validated early deterioration definitions in maternity.
2. an optimally developed vital-signs-based MOEWS for use where eMOEWS is not feasible.
3. an optimally developed eMOEWS.
4. evidenced eMOEWS and escalation pathway implementation methodology.

Our research is targeted to reflect the Department of Health and Social Care’s priorities, supporting the healthcare workforce by using transformative technology (eMOEWS) to target more efficient care at the right time, improving healthcare outcomes and reducing the major health disparities seen in adverse maternal outcomes. Although the 2018 national Maternity Digital Maturity Assessment report (42) found only 29% of organisations used electronic vital signs systems, the accelerated electronic patient record implementation set out in the NHS long term plan (43) and NHS Digital’s Digital Maternity Record

Standard Requirements Specification (44) present an unrivalled opportunity to implement a world-leading, technologically-advanced eMOEWS deterioration detection system NHS-wide.

Beyond this protocol, our research programme will implement our eMOEWS and escalation pathways within a study designed to provide the clinical and health economic evidence to support wide-scale implementation. Learning from this implementation will be used to maximise eMOEWS performance for future use. We will seek additional funding to establish our electronic databases as a national resource for future use, extending the duration of data collection and use in subsequent applications.

6 OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To develop and validate an electronically embedded, data-enhanced Maternal Early Warning Score (eMOEWS) with clinical escalation pathways	Predictive performance of new early warning scores, assessed by: discrimination, calibration, and clinical utility.	During pregnancy or in the immediate postpartum period.
Secondary Objectives:		
To define 'near-miss' and 'pre-near-miss' criteria for use with routinely-collected data to measure maternal outcomes.	'Near-miss' and 'pre-near-miss' outcome criteria measurable using routinely available electronic data, assessed in NHS hospitals	During pregnancy or in the immediate postpartum period.
To assess performance of the new near-miss and pre-near-miss outcome criteria in 3 hospitals and MBRRACE-UK: • a stratified random sample of 100 sets of records of near-miss and pre-near-miss cases across the three sites. • review hospital serious event systems for serious maternal events • Proportions of women meeting criteria	Descriptive statistics to describe whether the electronic criteria used correctly identified the conditions. Descriptive statistics of missed and captured events according to electronic criteria Descriptive comparison to published rates	During pregnancy or in the immediate postpartum period
To develop a large representative eight-twelve maternity unit cohort	Cohort developed and ready for assessment	05/2029

for model development and assessment		
To investigate the performance of existing MOEWS/MEWS scores in the new maternity cohort and in women who have died or had severe morbidity in pregnancy	Evidence-based assessment of existing MOEWS, both in new retrospective (assessed by discrimination, risk of our key events at each MOEWS/MEWS level) and nationally recognised mortality/morbidity (assessed by sensitivity and duration of prior warning) cohorts	05/2029
To develop and validate an optimal vital-signs-only-based MOEWS	Relative performance of new MOEWS, best published MOEWS and NHSI national MOEWS for prediction of near-miss or pre-near-miss	05/2029
To develop and validate an eMOEWS to improve detection in comparison to existing MOEWS	Relative performance assessment of eMOEWS, new validated vital-signs-based MOEWS, best published MOEWS and NHSI national MOEWS for prediction of 'near-miss' or 'pre-near-miss'	05/2029
To design and deliver an eMOEWS interface.	User co-designed eMOEWS implemented within 4 NHS sites	05/2029
To develop treatment escalation pathways	Protocolised escalation and response pathways iterated and tested in a simulated environment	05/2029

7 STUDY DESIGN

7.1 Overview

This study consists of a programme of work that is centred around a UK-based, multi-centre cohort study of women who are pregnant or have recently been pregnant.

The overall research question is: "Can an electronically-embedded, enhanced Maternal Early Warning Score (eMOEWS) with behaviourally-informed escalation pathways prevent maternal 'near-miss', 'severe morbidity' events and mortality?"

The overall research aim is to prevent maternal morbidity and mortality and reduce inequalities in outcomes by developing, refining, validating, embedding, and testing an eMOEWS with clinical escalation pathways.

The initial programme of work, covered by this protocol, is divided into four workstreams as below. The work described in this protocol is intended (subject to funder agreement) to be immediately followed by a prospective study to assess the clinical and health economic effects of implementation of the eMOEWS and the associated escalation pathway (for which a separate protocol will be written and separate approvals sought).

7.2 Workstream 1

Workstream 1 will develop 'near-miss' and 'pre-near-miss' (indicating deviation from normal pregnancy such that intervention is required to avoid progression to a 'near-miss' event) definitions electronically derivable from routine data by a literature review, followed by an international Delphi process. The identification performance of these definitions will be assessed using data from MBRRACE-UK and three NHS hospitals. See Figure 1 for an overview of the workstream 1 workflow.

We will convene an expert clinical panel to define the pathological pathways to "near-miss" as defined by the World Health Organisation near-miss events and other published criteria. We will include multi-professional expertise (e.g., midwifery, obstetrics, anaesthetics, obstetric medicine, pathology, clinical epidemiology, critical care). We will use these pathways to identify candidate specific pre-near-miss maternal complications that could lead to "near-miss" events (or death).

We will identify consensus definitions of "pre-near-miss" criteria where possible from existing core outcome sets (such as the HDR UK Phenotype library and others (45,46)), along with methods to identify these outcomes from routinely collected data. Where there is any uncertainty regarding the definition of "pre-near-miss" criteria, we will conduct targeted literature reviews. Where consensus definitions are not available, they will be determined by the expert panel.

We will map definitions to the Maternity Services Dataset (MSDS), Hospital Episode Statistics and routinely available electronic patient record data in our partner hospitals, identifying where and what routine data augmentation may be required for specific definitions and where surrogates are available.

Definitions (consensus or expert panel), methods for their identification and any required routine data augmentation or surrogate available data fields will inform a three-round international consensus Delphi process, including the patient voice. The Delphi process will follow guidance from the Core Outcome Measures in Effectiveness Trials (COMET) Initiative (47). In round 1, participants will also be asked to identify missing important definitions. A Delphi facilitator will curate Round 1 results. Delphi participants will be asked to rate definitions on a 9-point Likert scale from 1 (not important) to 9 (critically important) in round 2. Following further curation, the results from Round 2 (all definitions, along with summary statistics of their respective scores (mean, median, range) will be fed back to the Delphi panel, allowing each member to see how the panel had voted on each definition. Using this information, each member will be asked to re-score each definition using the same 9-point scale as used in Round 2. Definitions rated 7-9 by 70% or more of the panel or 1-3 by less than 15% in at least one stakeholder group will be included in the final list (47).

The final list will again be assessed by our expert panel and mapped against routine data reviewed to achieve 'near-miss' and `pre-near-miss' for identification performance testing.

We will use retrospective data from three representative collaborator NHS hospitals (who will form part of the retrospective cohort) and from MBRRACE-UK, reviewing deaths, near-miss and pre-near-miss cases to estimate identification performance using the new definitions.

7.2.1 Objectives

In the three collaborator hospitals we will:

- Report the proportion of women meeting each of the new criteria and in total in WS2 retrospective datasets – comparing these proportions relative to the hospital populations with published rates for our individual criteria. Where the criteria definitions appear to under or over-capture events, we will undertake record review to inform definition adjustment where required (approximately 10 case records per event of over/under capture).
- Undertake validation of the coded criteria through examining a stratified random sample of 100 sets of records of these cases across the three sites to assess whether the codes used in the electronic data correctly identified the conditions – again if necessary, allowing criteria definition adjustment.
- Review hospital systems for recording serious events in the time period, reviewing cases identified as maternal serious incidents (maternal serious incident cohort) but not identified by our criteria to establish whether criteria definition adjustment is required.

From MBRRACE-UK we will report the proportions of women who meet the new definitions.

- Learning will be fed back to the expert panel to generate final definitions.

Further details of the statistical analyses related to workstream 1 are given in Section 11.2.1.

7.2.2 Permissions and data flow

For both retrospective case record reviews detailed above we will need to review specific (uncommon) cases of adverse events in each of three hospitals, precluding individual consent. An application to the Confidential Advisory Group will be made (see Section 9.1.2 for further details).

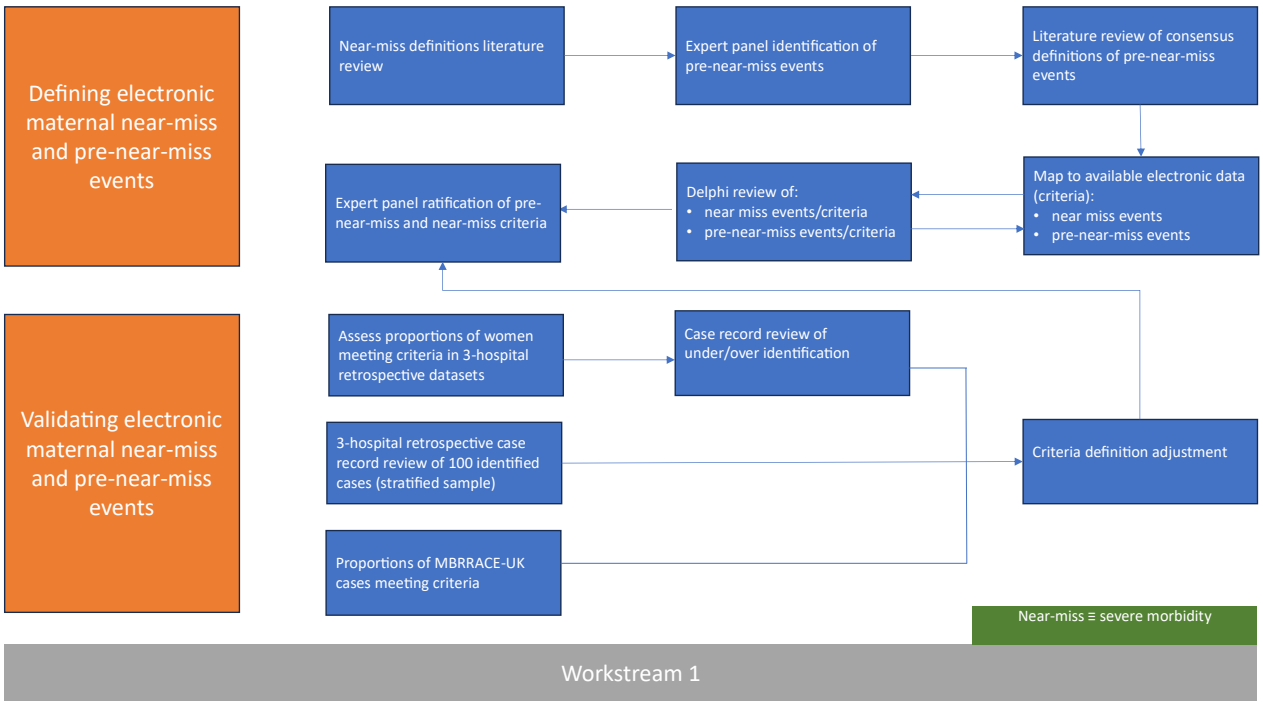

Figure 1 Overview of Workstream 1

7.3 Workstream 2

Workstream 2 will, in collaboration with the NIHR Health Informatics Collaborative, develop an eight- to twelve maternity unit dataset. Current MOEWS' ability to identify newly defined 'near-miss' and 'pre-near-miss' events will be assessed using this data and data from the MBRRACE-UK dataset.

7.3.1 Identification of existing MOEWS

Existing MOEWS will be identified by updating an existing systematic review (see WS3a for methods) along with checking with experts in the field (11), and will include Irish, Scottish and American published tools along with the new NHSE/I tool (11,48–50).

7.3.2 Workstream 2a

We will curate retrospective datasets from routine NHS maternity unit electronic data to encompass the work in section 2b and 3b. Data will encompass variables required for prediction and data required for maternal and neonatal outcomes (to allow assessment of the predictive ability of the scores for adverse neonatal outcomes). For data types see section 12.1.2.

The output of this workstream will be the external validation performance of existing MOEWS. Details of the methods that will be used to carry this out are reported in Section 11.2.2.

7.3.2.1 Data collection and data flow

Retrospective whole maternal unit data from available electronic patient records for multiple sites is required (see statistical analysis) precluding individual patient consent. Databases will be built by automated electronic extraction with manual augmentation (including from paper records) where necessary. All data will be pseudonymised prior to analysis by the study team. An application to the Confidential Advisory Group will therefore be made to undertake this work (see Section 12 for further detail). A data flow diagram is included in the study documentation.

7.3.3 Workstream 2b

7.3.3.1 Participants

MBRRACE-UK undertakes confidential enquiries into maternal deaths and specific severe morbidities. We have already extracted event and vital sign data for 205 women who died or suffered severe morbidity (from pulmonary embolism and severe haemorrhage). In this work stream, we will additionally extract available re-laparotomy (n=32) and diabetic ketoacidosis cohorts (n=80) to complete representation of the available major reversible events. We will also extract additional outcome data to define when women meet the new 'near-miss' and 'pre-near-miss' criteria (WS1). This will require an extended output request to the Healthcare Quality Improvement Partnership. All women in the cohort are likely to have had one of the near-miss or pre-near-miss events (as defined in WS1) or death.

7.3.3.2 Data collection and data flow

We aim to replicate the data in WS2a. Anonymised data will be collated into research datasets onto University of Oxford secure servers where the MBRRACE dataset already resides. In the case of thromboembolism and major haemorrhage datasets, these have already been curated, but will require addition of pre-near-miss events and times as defined in WP1.

7.3.3.3 Outcome measures

The primary outcome for MOEWS assessment for both data sources (WP2a&b) will be a combination of maternal death, 'near-miss' and 'pre-near-miss' events (as defined in WS1). Secondary outcomes will be maternal death, 'near-miss' and 'pre-near-miss' events, individually. For more details on the analysis methods see Section 11.2.3.

7.4 Workstream 3

Workstream 3 will develop an eMOEWS candidate variable list by literature review informing a further Delphi process. An optimal vital-signs MOEWS and a multivariable eMOEWS will be developed and validated, exploring regression models and machine learning (ML) approaches.

7.4.1 Workstream 3a – developing the candidate variable list

7.4.1.1 Systematic review

We will undertake a systematic review and critical appraisal of routinely collected, electronically available variables which affect the risk of sustaining a 'near-miss' or 'pre-near-miss' event as defined in WS1. This will include noting key interactions between variables. We will include existing prediction models and associated publications. We will follow guidance by the Cochrane Prognosis Methods Group (51,52). We will search bibliographic databases including MEDLINE and EMBASE. We will snowball to identify any further relevant studies. Searches will be developed with an academic librarian (with whom we have previously worked). The literature between 01/01/1993 and 30/06/2023 will be identified without language restrictions. Data will be extracted in duplicate. Authors will be contacted by e-mail where additional information is required.

7.4.1.2 Review strategy

We will undertake quality assessment of included studies, where possible using the QUIPS tool for prognostic factors, recommended by the Cochrane Handbook for the appraisal of studies of risk factors (53,54). The piloted data extraction form will follow the prognostic factors adaptation (CHARMS-PF) of the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies

(CHARMS) guidance (52). We will further synthesise available data using a semi-quantitative method previously described by Zaal et al. (55) and adapted by Dettmer et al (56).

7.4.1.3 Delphi strategy

We will assess the variables identified during our systematic review against those recorded in our partner maternity sites to inform availability for inclusion. We will use this information to inform a 3-round international Delphi process to compile a list of existing, electronically available variables which affect the risk of 'near-miss' and 'pre-near-miss' events (as defined in WS1). This will generate a candidate variable list. Our strategy will follow a similar process to that in WS1.

The Delphi participants will again be identified from author lists of articles included in our review of the literature to ensure diverse expertise and selection objectivity. We will also involve our PPI colleagues. In round one, variables identified from our literature review will be presented to the Delphi participants along with their purported effect on risk (protective vs predisposing). To provide structure, variables will be grouped into a small number of domains including but not limited to demographics, vital signs, and laboratory variables. Participants will again be asked to identify any variables felt to be important but not included, and whether these are felt to represent protective factors or predisposing factors. Round 1 results will then be collected and curated by a Delphi facilitator.

Subsequent rounds will follow the processes described in WS1.

The final candidate variable list will then be assessed against availability in the 8-12 sites followed by data extraction of available candidate variables as part of WS2a. For likely variable types see section 12.1.2.

7.4.2 Workstream 3b – developing an optimal vital-signs MOEWS and multivariable eMOEWS

We will develop and externally validate (see Section 11.2.4 for further details):

- A vital-signs-based MOEWS for use in environments where connection to an EPR is not available.
- A multivariable electronic maternal early warning score (eMOEWS) for use in digitally mature environments

We will extract a separate, more recent 2-year validation cohort from eight-twelve sites to allow external validation (containing relevant variables) of the optimal vital-signs MOEWS and multivariable eMOEWS.

7.5 Workstream 4

In Workstream 4 we will:

- Build working eMOEWS web interfaces following user-centred design principles (Workstream 4a).
- Develop escalation and response pathways for women identified as at risk by the eMOEWS (Workstream 4b)

7.5.1 Workstream 4a

7.5.1.1 Requirements identification

To ensure a bespoke eMOEWS user interface we will undertake evaluation of end-user needs for user interfaces using focus groups, with topic guides underpinned by Normalisation Process Theory and informed by the NASSS framework to identify barriers and facilitators, local adaptions and unintended consequences influencing implementation and hence potential effectiveness across the implementation sites. We aim to conduct 2-3 focus groups with up to 20 professionals per site (we anticipate this number will allow representation of the views of a range of professionals of different seniority – but will continue focus groups until saturation has been achieved).

7.5.1.2 Interface design

We will develop the key design elements and functionality for the web-interface through work including Applied Cognitive Task Analysis Interviews (57) with multi-disciplinary staff (including obstetricians, midwives and anaesthetists) and "card sorting" (58) exercises in implementation sites (59) to prioritise categories of information (e.g., demographics, vital signs, laboratory tests, eMOEWS risk score) displayed in the interface. We estimate approximately thirty cross-implementation site meetings with clinical staff will be required but will continue until no major new information is being obtained.

After installation of the eMOEWS system, we will trial the user interface with key stakeholders. We will encourage staff to use the eMOEWS to display information from patients currently under their care. As clinicians are likely to be familiar with these patients' recent clinical data, we will use this to discover minor omissions and local adaptions that could be addressed to enhance the system. We will continue trials until saturation occurs – but again estimate around 30 meetings with key stakeholders across sites. Learning from eMOEWS use within WS4b will also be iteratively incorporated into the final interface. We will document the time and equipment consequences of eMOEWS installation and maintenance at each site and centrally to inform WS5c.

Testing metrics will include task-based efficiency and effectiveness, user satisfaction and workload.

7.5.2 Workstream 4b

We will develop escalation pathways using:

- Secondary analysis of interviews with women who experienced near-miss morbidity.
- Interviews with women and partners who have recently experienced maternity complications.
- Focus groups
- A response pathway co-design group.

We will conduct secondary analysis of interviews with 36 women who experienced near-miss morbidity and 11 of their partners who were interviewed through the 'healthtalk' series (Health Experiences Research Group) to capture women and partners' perspectives relating to the recognition and management of acute illness in a maternity setting.

In addition, we will conduct a further 10-15 interviews or focus groups with women and partners from diverse groups who have recently experienced maternity complications to ensure we are capturing any specific barriers identified amongst women from diverse ethnic groups and amongst those who are vulnerable. Costs for translation services during these interviews (where required) are included in the budget. We will identify participants using posters in our partner hospitals and through our contacts with

trusted community support and patient groups. To maximise participation, we will offer a choice of on-line and face-to-face interviews and accessible community venues. A topic guide for interviews will be developed from previous work and secondary analysis of interviews above. Additional semi-structured questions will be asked, using a topic guide. A list of questions will be submitted as a study amendment prior to interviews/focus groups commencing.

Consensus best practice MOEWS responses to the NHSE/I MOEWS have been identified through a Delphi process using example clinical scenarios conducted by the co-applicant team with NHSI. These, with other published response pathways (3), and findings from our interviews, guided by Normalisation Process Theory underpinned by key NASSS domains, will inform topic guide content for focus groups, to identify barriers and facilitators, local adaptions and unintended consequences influencing response implementation and effectiveness.

We will apply inter-related social and behavioural science theories and frameworks to address the individual, socio-cultural and organisational factors influencing escalation responses. We will particularly explore factors influencing decision making and intentions around whether or not to escalate, and factors influencing appropriate and timely response as failure to escalate and respond appropriately could influence the effectiveness of the eMOEWS to prevent deterioration. Following the Behaviour Change Wheel approach to intervention design (60), we will use the findings from this behavioural analysis as a basis for systematically co-designing a response pathway to target the key factors facilitating or hindering escalation on the basis of an eMOEWS trigger in this context.

Response pathway co-design will then be undertaken with relevant stakeholder group representatives (e.g., pregnant women, healthcare professionals, experienced mMOET course leaders – see below – again including translation where necessary) paying particular attention to information from women whose voices and concerns find it harder to be heard and responded to (61,62). Key staff from intervention sites will be involved in escalation pathway development, ensuring a core intervention applicable across sites (and across the NHS), and identifying minor adaptions outside the core intervention to allow individual site integration. We will focus on minimising the perceived opportunity costs of implementation, working with the focus groups and local champions to foster the internal (within NHS) view (63,64). We envisage two meetings will be required with preparation work undertaken prior to each meeting, with initial pathways designed by the research team between meetings.

7.5.3 Workstream 4c

The research team will develop three simulated scenarios informed by the brief clinical scenarios used for development of the NHSE/I National MOEWS. These will be designed to refine the clinical escalation and response pathways developed in WS4b for representative near-miss and pre-near-miss events. Local champions from intervention sites will be involved in scenario development and manualisation of the escalation pathway to ensure that the core intervention remains applicable across sites (and across the NHS) and that minor adaptions outside the core intervention allow individual site integration.
We will then run and record scenario simulations at four mMOET training centres, building on pre-existing scenarios (e.g. post-partum haemorrhage and sepsis). Simulations will include a mixture of medical staff and midwives at representative levels of experience (8 in each of the implementation sites). Findings will inform escalation protocol review prior to repeat (potentially adjusted) scenario testing.

From our prior experience of this process, we estimate two iterations with decreasing participant time will be required to finalise recommended escalation protocols.

8 PARTICIPANT IDENTIFICATION

8.1 Study participants

8.1.1 Patient Retrospective cohort

All women who are treated by maternity services at study sites.

8.1.1.1 Overall Inclusion criteria

- All women aged 16 or over who are pregnant
- At any of the study sites

8.1.1.2 Overall Exclusion criteria

- Patients who have requested that their data not be used for research (e.g., NHS Opt-out, see Section 9.3.1)

The model development dataset sits within this cohort.

The case review dataset sits within this cohort. We will extract a stratified sample of 100 records for case review identified by our new criteria. The case review data set will comprise records:

- At one of three partner sites
- Electronically coded to meet a pre-near-miss/near-miss criterion.

The maternal serious incident dataset sits within this cohort. We will review up to 100 maternal serious incidents recorded in local serious event systems at the three partner hospitals not identified by our new electronic criteria. The maternal serious incident data set will comprise records:

- At one of three partner sites
- Not electronically coded to meet a pre-near-miss criterion.
- Recorded in local serious incident reporting systems.
- With a clinical rather than “operational” serious incident

8.1.2 Patient prospective cohort

All women who are treated by maternity services at study sites.

The model validation and real-time platform testing datasets sit within this cohort.

8.1.2.1 Inclusion criteria

- All women aged 16 or over who are pregnant.
- At any of the study sites

8.1.2.2 Exclusion criteria

- Patients who have requested that their data not be used for research (e.g., NHS Opt-out, see Section 9.3.1)

8.1.3 MBRRACE-UK cohort

All cases of maternal death and morbidity (for the cohorts described above) collected by MBRRACE-UK (see (65)). This cohort will be used in WS1 and WS2b.

8.1.3.1 Inclusion criteria

- See (65)

8.1.3.2 Exclusion criteria

- See (65)

8.1.4 Patient interviews/Focus groups(escalation pathway)

Women and their partners who have experienced near-miss events or other maternal complications.

8.1.4.1 Inclusion criteria

- Women and their partners aged 16 or over who have experienced near-miss events or other maternal complications.

8.1.4.2 Exclusion criteria

- Women or partners who do not consent.

8.1.5 Staff interviews/focus groups (escalation pathway)

Staff members will be involved in focus groups, interviews and testing the eMOEWS user interface.

8.1.5.1 Inclusion criteria

- Staff members aged 16 or over in a partner hospital.
- Involved in the care, management and escalation of hospitalised women who deteriorate in maternity services.

8.1.5.2 Exclusion criteria

- Staff who do not consent

8.1.6 Staff interviews/focus groups (eMOEWS interface development)

Staff members will be involved in focus groups, interviews and testing the eMOEWS user interface.

8.1.6.1 Inclusion criteria

- Staff members aged 16 or over in a partner hospital.
- Involved in the care, management and escalation of hospitalised women who deteriorate in maternity services.

8.1.6.2 Exclusion criteria

- Staff who do not consent

8.1.7 Staff training (simulation scenarios)

Staff will also take part in scenario simulations (MOET).

8.1.7.1 Inclusion criteria

- Staff members aged 16 or over in a partner hospital.
- Involved in the care, management and escalation of hospitalised women who deteriorate in maternity services.

8.1.7.2 Exclusion criteria

- Staff who do not consent

9 PROTOCOL PROCEDURES

9.1 Recruitment

9.1.1 Patients

For the retrospective and prospective cohorts, we will apply for Health Research Authority approval (HRA), under advice from the Research Ethics Committee and the Confidentiality Advisory Group (CAG) to allow access to confidential medical records without specific written consent (Section 251 support).

9.1.2 Staff and public participants

For medical staff we will use purposive sampling to ensure a diverse range of clinical experience, backgrounds, and training. For example, we will work with medical and midwifery leads, and local champions at each trust to identify and invite eligible staff members to participate, along with key NHS IT personnel. We will then snowball from these participants to ensure we are reaching all relevant staff groups.

For public participants we will identify interested women and their partners using posters in our partner hospitals and through our contacts with trusted community support and patient groups.

9.2 Screening and Eligibility Assessment

9.2.1 Patients

- Retrospective and prospective cohorts - there will be no screening in this study.
- Case review cohort – a stratified random sample of cases for review will be computer-generated from each of three partner sites using WP2 pre-anonymisation datasets (post application of the NHS opt-out and patients who have made requests to study sites for their data to be excluded).
- Maternal serious incident cohort – serious incident databases at partner hospitals will be screened for women with clinical maternal serious incident reports.

9.2.2 Staff and public participants

- No screening will occur for staff or public participants – with recruitment occurring as described above.

9.3 Informed Consent

9.3.1 Patients/Public participants

For the retrospective and prospective cohorts, the case review cohort, and the maternal serious incident cohort we will apply for Health Research Authority approval (HRA), under advice from the Research Ethics Committee and the Confidentiality Advisory Group (CAG) to allow access to confidential medical records without specific written consent (Section 251 support).

For the MBRRACE cohorts approvals to use anonymous data for research are already in place.

For public participants in interviews or focus groups, informed consent will also be taken. Women and partners who contact us through our posters or through our written communications or presentations to trusted community support and patient groups will be approached by telephone or in person by an experienced researcher who will explain the purpose of the interviews within the programme of research and provide public participant information. Public participant study documentation will detail the content of the interviews and what interviews will involve for the participant. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. The participant(s) will personally sign and date the latest approved version of the Informed Consent form. The participant will be given sufficient time up to 28 days to consider the information, and the opportunity to question the Researcher, or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the researcher who presented and obtained the Informed Consent Declaration. The person who obtained the consent will be suitably trained and will have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent declaration will be given to the participant. The original signed form will be retained at the study site.

Face to face interviews will be held in a quiet meeting room. Videoconferencing (using Microsoft Teams or Zoom software) or telephone interviews will be conducted in a private office. The audio from Face to face, telephone and video conferencing interviews will be recorded to allow for transcription.

9.3.2 Staff

For each of eMOEWS interface development, escalation development and simulation scenarios, staff will undergo informed consent. Staff identified through the medical and midwifery leads, and local champions will be approached to take part by telephone or in person by an experienced researcher who will explain the purpose of the interface development groups focus groups, interviews and trialling, escalation focus group or scenario simulation within the programme of research and provide staff participant information. Study staff participant study documentation will detail the content of the component and what the component will involve for the participant. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. The participant(s) will personally sign and date the latest approved version of the Informed Consent form or Consultant. The participant will be given sufficient time up to 28 days to consider the information, and the opportunity to question the Researcher, or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the researcher who presented and obtained the Informed Consent Declaration. The person who obtained the consent will be suitably trained and will have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent declaration will be given to the participant. The original signed form will be retained at the study site.

Participants will be interviewed or join focus groups at a convenient time and location to them. Participants will privately confirm their identity to the researcher (e.g., full name, date of birth) at the start of the interview/focus group.

Face to face interviews/focus groups will be held either in a meeting room away from the clinical area or in a quiet room within the clinical care, as chosen by the participant. Videoconferencing (using Microsoft Teams or Zoom software) or telephone interviews will be conducted in a private office. Face to face, telephone and video conferencing interviews will be recorded to allow for transcription.

Audio video recordings of participants may be required to track how participants interact with test user interfaces during eMOEWS interface development.

Audio visually recordings of participants during eMOEWS simulation scenarios will occur in four different training centres across the UK. The video recorded from the four centres will then be sent to a central location. Recordings will then be analysed by at least two members of the research team.

9.4 Randomisation

There will be no randomisation in this study.

9.5 Blinding and code-breaking

There is no blinding or code-breaking in the study.

9.6 Description of study intervention(s), comparators and study procedures (clinical)

There is no intervention in this study.

9.7 Baseline Assessments

Not applicable.

9.8 Subsequent Visits

Not applicable.

9.9 Sample Handling

No sample will be taken during the course of this study.

9.10 Early Discontinuation/Withdrawal of Participants

This is an observational study. Participants can request their data to be deleted at any time in accordance with GDPR and the study privacy policy.

9.11 Definition of End of Study

The end of study described in this protocol is the point at which all the study data has been entered, the eMOEWS built and checked and any post-implementation changes to eMOEWS algorithm have been added to the final derived and validated eMOEWS.

10 SAFETY REPORTING

This is a non-interventional study, so safety reporting is not applicable.

11 STATISTICS AND ANALYSIS

11.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here, with details fully described in a statistical analysis plan that will be publicly available from the time the first retrospective dataset is extracted from a minimum of 3 hospitals. The SAP will be finalised before any statistical analysis takes place.

11.2 Description of the Statistical Methods

11.2.1 Workstream 1

We will report descriptive statistics describing the proportion of women meeting each of the new criteria and in total in WS2 retrospective datasets – comparing these proportions relative to the hospital populations with published rates for our individual criteria,

We will use descriptive statistics to report the proportions of events correctly captured by our new electronic definitions in the stratified sample cohort and events missed in our review of hospital systems for recording serious events.

Similarly, from MBRRACE-UK we will report the proportions of women who meet the new definitions.

11.2.2 Workstream 2a

We will describe the characteristics of the study population and compare to national figures to ensure it is appropriately diverse and representative. To assess the predictive performance of each MOEWS/MEWS (11), we will report sensitivity and specificity at pre-defined thresholds, and overall score discrimination (c-statistic). Calibration, the level of agreement between observed outcomes and a model's predictions, is a key aspect of assessing predictive performance for prognostic models. However, a weakness of existing MOEWS is that they generally do not provide an estimate of risk, therefore, assessment of calibration will not be possible. We will, however, calculate the risk of our key events according to each level of MOEWS. We will also compare how early each MOEWS alerts prior to events. We will use the new multi-site dataset to calibrate the centile-based national MOEWS we developed with NHSE/I.

We will also explore whether MOEWS performance varies between key sub-groups (e.g., age, ethnicity), to identify where groups could be disadvantaged, or where the MOEWS could be improved. We will report the rates of missing vital sign data and use different approaches to account for these missing values during analysis (e.g., complete cases, assuming all missing values are normal or abnormal, and multiple imputation), to check the robustness of our estimates.

11.2.3 Workstream 2b

We will summarise key characteristics of women who experience these events, including demographics, clinical characteristics, vital signs measurements, and type of event. We will describe when women in MBRRACE-UK meet the new outcome criteria, prior to the extreme outcomes that result in inclusion in

the MBRRACE-UK dataset. For each existing MOEWS/MEWS, we will calculate sensitivity at pre-defined thresholds and assess how early women alert prior to the events occurring, if at all. Where sufficient data exist, we will examine performance in key subgroups. Missing vital sign data will be handled similarly to WS2a.

11.2.4 Workstream 3b

11.2.4.1 Model development

We will explore both regression and machine learning (ML) approaches for model development. We anticipate at least 5800 'near-miss' or 'severe morbidity' events, with higher rates using our new definitions.

For approaches using regression models (e.g., logistic or Cox regression if censoring is an issue) we will assess pre-defined pairwise interactions and include non-linear relationships for continuous predictors (e.g., using fractional polynomials or restricted cubic splines) (66). Pairwise interactions may be used to address apparent discrepancies in model performance for specific subgroups, identified in WS2. We will investigate whether accounting for trends of repeated measurements within individuals (e.g., blood pressure) can be incorporated to improve predictive accuracy. We will additionally explore how performance varies when using a composite outcome versus developing different models for individual outcomes (e.g., sepsis, pre-eclampsia). This may be informed by the results from WS2. Where appropriate, we will consider using a least angle selection and shrinkage operator (LASSO) penalty (67).

In parallel we will investigate and compare ML approaches to developing a prediction model, including methods such as random forests, deep neural networks, Bayesian Gaussian processes and gradient-boosted decision tree survival models (37,68). Such models allow consideration of interactions between available variables providing "latent variables" (complex, non-linear transformations of the original input variables) that may improve prediction performance over the non-transformed input variables. We will prioritise principled, probabilistic methods that permit the incorporation of prior clinical knowledge, such that results are "interpretable", avoiding the "black box" nature of much ML-oriented research in this area (68,69) .

MOEWS are typically calculated several times during a woman's pregnancy, and other candidate variables will also be measured repeatedly (for example, blood tests). The best way of accounting for these repeated measures in model development (and validation) is not well defined. Therefore, we will explore different options for how best to incorporate this.

Where applicable learning from the regression and machine learning approaches will be combined to achieve a final deliverable model.

11.2.4.2 Missing data

Missing data will occur in all medical research with not all patients providing data on all predictors of interest. To avoid excluding patients and reducing the sample size, multiple imputation will be used to impute missing values, under a missing at random assumption.

Identifying the true underlying missing data mechanism from the available data is rarely possible. Assumptions need to be made on the plausible mechanism, and approaches needed to be used. Under a missing completely at random mechanism (MCAR), the missingness mechanism does not depend on unobserved (unseen) data. Carrying out a complete case analysis will produce unbiased estimates (but

with a loss precision if full data are observed) but will reduce sample size. Under the missing at random (MAR) assumption, the missingness after conditioning on the observed data does not depend on the unobserved (unseen) data. Under this approach, we can apply approaches such as multiple imputation, by fitting a joint model to the observed data and impute the missing data, taking account of the uncertainty in the estimated parameters of this joint model. We feel this, MAR, approach makes a less strong and more realistic assumption than the MCAR approach. The MAR imputation model will include all variables considered for the multivariable model building, the outcome and any auxiliary variables that will help explain the missingness. When imputing missing values for predictors that are repeatedly measured (for example, vital signs) we will use methods that account for (and take advantage of) this structure in the imputation model. The assumption of a missing not at random (MNAR) approach whilst not implausible is considerably more complex to investigate – there is a dearth of research investigating MNAR in the context of prediction model research. We will nevertheless explore whether the MAR assumption holds by comparing the imputed values (after accounting for the observed values) and the missing values to identify if there are any systematic differences to suggest a MNAR assumption. We will explore patterns of missing data in key sub-groups (e.g., ethnicity) to detect any potential bias in data recording. We will also explore whether patterns of missingness (e.g. clinicians electing to perform specific blood tests) could be utilised to aid prediction (70).

11.2.4.3 Assessment of model performance

The performance of both new models will be assessed through internal and external validation. The performance of a model in the development data is usually over-estimated. Internal validation techniques will be used to adjust for this 'optimism'. The internal validity of the final models will also be assessed by the bootstrap re-sampling or k-fold cross validation techniques to adjust for over-optimism in the estimation of model performance. To ensure a meaningful comparison we will use the same internal validation procedures to compare statistical and machine learning models. The internal validation will quantify and be used to adjust the performance measures (e.g., discrimination, calibration) for any optimism. Heterogeneity in model performance will be explored across different hospitals using internal-external cross-validation (71).

We will use the performance metrics used in WS2 (i.e., discrimination, sensitivity, specificity, and the degree of advanced warning prior to an event). As discussed above, the performance of a prediction model is typically characterised by assessing both its calibration and discrimination. With our new models we will be able to assess model calibration as the new development models will provide risk estimates. Calibration reflects how close the predictions from the model are to the observed outcome frequencies, so represents a major step forward in assessing eMOEWS performance. It is a key performance metric recommended in TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) guidance (72). Calibration will be assessed graphically, using a calibration plot, plotting observed outcomes against predictions using smoothing techniques. The plot will also be supplemented with results for individuals grouped by similar probabilities (tenths) comparing the mean predicted probability to the mean observed outcome. Calibration will also be quantified by calculating the calibration slope and intercept. The discrimination of the prediction models will be summarised with the concordance statistic (equivalent to the Area Under Receiver Operating Characteristic curve) with 95% confidence interval. Validation will include assessing for variation in performance between key sub-groups, as per WS2.

We will explore risk thresholds to identify high risk (such that we predict poor outcome) and low risk (such that we predict good outcome) groups. We will compare performance of our models to those of published MOEWSs established in WS2a, including decision curve analysis. We will externally validate our models using new data from our collaborator sites collected in the two years following the derivation cohort. We will assess the model performance within key pre-defined sub-groups (including maternal age and ethnicity).

11.3 Sample Size Determination

11.3.1 Workstream 2a

We estimate the WHO "near-miss" event rate will be at least 10/1000 (2,3) and the severe morbidity event rate will be at least a further 10/1000 maternities (2,73) . Although rates of our less severe new 'pre-near-miss' will be higher we have calculated our sample size based on these severe event rates alone. The retrospective cohort will include four years and two months' worth of data from up to 12 sites. We anticipate that there will be 5875 births on average per site per year. Therefore, we will have approximately 293,200 births in the retrospective cohort, of whom 2932 will have a near-miss and at least a further 2932 will have pre-near-miss events. Guidance suggests that at least 100 events are required for model validation (74). Therefore, our sample size (which is driven both by the need for adequate representation in subgroups and the requirements of WS3, see below) should be more than sufficient to generate robust performance metric estimates, including in key subgroups and for the secondary outcomes (see model performance in key subgroups WS3b below – note that the retrospective cohort is larger than the prospective cohort and therefore the number of events per subgroup will be even higher).

11.3.2 Workstream 3b

We will use the full augmented WS2a data set (the retrospective cohort) for model development, which will be approximately 293,200 women. Assuming a conservative event rate of 2% (as in WS2a), a c-statistic of 0.8, and a shrinkage factor of 0.9, we will be able to include more than 850 parameters in our model if using logistic regression (which is more than adequate) (75).

After development we will assess the performance of our model in the prospective cohort within key sub-groups (including maternal age and ethnicity). The prospective cohort will include the births from up to 12 sites over a period of two years and four months, and therefore will be approximately 164,300 in total. The national MBRRACE report shows the proportion of women in the different ethnic groups (White 79.5%, Asian 10.3%, Black 4.3%, Chinese 4.1%, Mixed 1.8%) (17). Working with the NIHR HIC, we will ensure that we have at least this degree of representation in our research database. We would therefore expect event rates of greater than 100 (the minimum recommended in TRIPOD guidance and quoted papers) (74) for all groups other than "Mixed" (White 2611, Asian 338, Black 141, Chinese 134, Mixed 59) assuming a flat 2% event rate. If higher event rates are seen in the different groups as reported (relative risk Asian 1.8 95% CI (1.2-2.7), Black 4.9 (3.3-7.3), Mixed 2.0 (0.7-4.9)) (5) we will have over 200 events in major groups.

11.3.3 Workstream 4b

Transcripts from interviews will be read and re-read, a coding frame constructed, and the data coded. Anticipated and emergent themes will then be examined across the whole data set as well as in the

context of each person's interview. A qualitative interpretive approach will be taken, combining thematic analysis with constant comparison. NVIVO will be used to facilitate the analysis.

11.3.4 Workstream 4c

Recordings will be dual-coded. We will use the TOAsT framework to identify and categorise observable inter-professional teamwork behaviours that occur during the simulated clinical scenarios implementing eMOEWS and the escalation pathways. Anticipated and emergent themes will be examined across the whole data set and a qualitative interpretive approach taken, combining thematic analysis with constant comparison.

11.4 Analysis populations

The analysis populations will generally include all eligible participants in each study data set.

11.5 Decision points

Not applicable.

11.6 Stopping rules

Not applicable.

11.7 The Level of Statistical Significance

The level of statistical significance will be set at 5%.

11.8 Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data approaches are described as part of the statistical methods in Section 11.2, for each work package (where relevant).

11.9 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation from the statistical analysis plan will be described and justified in all study publications.

11.10 Health Economics Analysis

No health economic analyses are planned for in this study.

12 DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate Data Management document in use for the study.

12.1 Source Data

Source documents are where data are first recorded, and from which participants' data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and

concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Creation of the NHS Trust data set requires accessing and linking confidential health care records. Access to these data will be subject to approval from a REC and Section 251 support from the CAG. All data will be pseudonymised prior to analysis.

The following source data resources will be accessed without explicit consent:

12.1.1 Workstream 1

Hospital patient records will be the source data for record review from which data will be abstracted into limited piloted case reports.

MBRRACE-UK will be the source for MBRRACE data (also in workstream2)

12.1.2 Workstream 2/3b

Electronic patient record data for datasets in workstream 2 and 3 will include both inpatient and outpatient data, with sources including:

- Patient administrative records (e.g., admission times, medical/surgical speciality, age, gender, ethnicity, ward locations/transfers)
- Diagnostic (ICD-10) and procedure coding (OPCS4)
- Vital signs/early warning score recording systems (e.g., blood pressure, heart rate, early warning score)
- Intensive care patient record systems
- Laboratory management systems (e.g., haematology, biochemistry, pathology, and microbiology)
- Electronic prescriptions/administrations
- Point of care testing (e.g., blood gas analysis)
- Electrocardiogram systems
- Echo cardiogram systems
- Diagnostic imaging data reports
- Peripartum monitoring (e.g. Cardiotocography)
- Maternal records from maternity electronic record systems (including the digital “red book”) and local maternity data sets submitted to NHS England (e.g., Maternity Services Data Set), including information on current and previous pregnancies and maternal (e.g., weight/height/BMI, smoking status) and neonatal outcomes/characteristics (e.g., APGAR, requirement for additional care)

12.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

Creation of the NHS Trusts data set requires accessing and linking confidential health care records. All members of the data extraction team involved in this process will undergo appropriate local governance training.

A pseudonymised data set will be accessed by authorised members of the study team at the University of Oxford for analysis purposes. Excluding age, sex, and ethnicity (necessary to investigate model bias) we will not be accessing data on protected characteristics (e.g., religion, civil status, sexual orientation).

12.3 Data transfer and analysis environment

Pseudonymised data will either be analysed within Oxford University Hospitals NHS Foundation Trust Secure Data environment (or equivalent) or the Data Safe Haven within the University of Oxford's Critical Care Research Group (DSH-CCRG). The choice of analysis environment will depend on where appropriate computing resources are available. All study data transferred to the CCRG-DSH will be encrypted using AES-256 before being transferred using either the secure OUH file download service or the OUH Citrix environment.

Whilst stripped of all direct identifiers, all pseudonymised data will still be considered personal, controlled sensitive data, as it will still contain indirect identifiers such as date-time stamps. Data-time stamps are required to calculate the study's primary outcome.

In the case pseudonymised data are transferred to the CCRG-DSH, they will be loaded onto specialist secure hardware held and maintained by the CCRG. The CCRG-DSH is a computing environment designed to store and analyse complex datasets in a manner that is safe and secure. The CCRG-DSH conforms to NHS Digital Security Toolkit and Cyber Essentials Plus accreditation. The environment is designed so that patient level data never leaves the analysis environment.

12.4 Data Recording and Record Keeping

All study data and electronic correspondence will be stored securely on Trust or University password-protected systems as appropriate only accessible by study staff and authorised personnel. Any paper-based documentation will be kept in the Kadoorie Centre in the research area, behind two access-controlled doors and in locked filing cabinets. All documentation will be archived at the end of the project. Any paper correspondence will be archived at an off-site secure archive facility.

12.4.1 Electronic data

All records will be subject to quality assurance polices both at the University and research group level. These are designed to guarantee the accuracy and validity of the study data. All participants will be identified by a unique study number (pseudonymous study key). Participants names and any other direct identifiers will NOT be included in any study data electronic file used for analysis.

For the retrospective and prospective cohorts, the ledger(s) that link the source Clinical Information System (CIS) data and the unique study specific number will be held within secure NHS Trust systems and destroyed at the end of the study period. All study data will be stored in a dedicated storage facility and retained for a minimum of 25 years after the end of the study in keeping with current MRC guidance. Personal data such as contact details that could identify a participant will be destroyed as soon as it is practical to do so and no later than 12 months after the end of the study.

12.4.2 Staff/Patient interviews/focus groups/simulation scenarios

For each sub-study, an electronic study log of baseline data will be maintained. This data will be entered and validated by the researchers. Transcripts (conducted internally by the research team) from interviews/focus groups/simulations audio files will be stored and processed in NVIVO (Lumivero.com). The name and any other identifying detail will NOT be included in any study data electronic file. Audio files will be destroyed once transcription is completed and checked.

All interview/focus group data will be securely stored and password protected. The video footage will be held for up to 3 years after publication of the work.

13 QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1 Risk assessment

We will undertake and document a formal risk assessment of the project for each component of the project. Risks and management strategies for all participants in interviews/focus groups/simulations will be considered and RAG-rated with mitigation strategies prior to each component of work being undertaken.

In the retrospective and prospective datasets, researchers will not interact directly with patients or intervene in their care.

This study requires access to confidential patient records. Eligible patient records will be identified by the participating organisations. Directly identifiable data will only be required for record linkage and will not be available to the Sponsor.

To mitigate the risk of reidentification of participants and the risk of data loss we will undertake the following:

- All records will be accessed and de-identified at each participating site, using a dedicated computer that will conform to NHS information security standards.
- Only pseudonymous personal data will be transferred via secure/encrypted protocols to the coordinating centre (Critical Care Research Group (CCRG), Nuffield Department of Clinical Neurosciences, Oxford University).
- Only pseudonymous personal data will be held by the CCRG.
- Pseudonymous personal data will be held inside the Sponsors “Data Safe Haven” which conforms to the same NHS standards of information security and cyber security.

Where clinicians trial the study system using real patient data of patients for whom they are caring they will follow standard clinical practice where new insight occurs.

13.2 Study monitoring

All research team members will be fully trained in Information Governance, data protection and confidentiality. The study may be monitored, or audited in accordance with the current approved

protocol, GCP, relevant regulations and standard operating procedures.

13.3 Study Committees

13.3.1 Study management group (SMG)

The study management group will consist of the Chief Investigator, Lead Investigator and the named investigators listed under Key Contacts, and individuals directly funded by the project. The study management group will be primarily responsible for the running and conduct of the study. They will be responsible for ensuring that standard operating procedures are followed and that regulations are adhered to. Where appropriate public patient involvement will be gained in any changes or amendments that are needed during the study.

13.3.2 Project Oversight Group (POG)

A project oversight group will include an independent chair, at least two other independent members, a PPI representative(s), and the Chief investigator. The POG will review the progress of the research programme and report on progress to the funder.

14 PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g., consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15 SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

If a serious breach is suspected the Sponsor must be contacted within one working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3 Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4 Other Ethical Considerations

The main ethical issues occur in a) use of confidential patient data without explicit consent, b) patient interviews, c) staff interviews.

16.4.1 Use of confidential patient data without explicit consent

16.4.1.1 Issue

The study requires a large, unbiased representative population to develop and test our predictive models. The acceptability of using patient data without consent for this study was discussed with patient and public representatives.

16.4.1.2 Steps taken

The patient notification statement and the data privacy statement were discussed with a PPI group. These documents will help to ensure patients admitted to participating NHS Trusts are aware that their data is being used for the purposes of this study and are provided with information on how to opt out. An application will be made to the Confidentiality Advisory Group (CAG) to access to relevant patient health records of patients that meet the study eligibility criteria.

16.4.2 Interviews with patients

16.4.2.1 Issues

Access, exploring issues which may cause distress to participants, uncovering poor practice that requires action.

16.4.2.2 Steps taken

We will address access issues by also offering telephone interviews as an alternative to face-to-face interviews. Where poor practice is identified, the researcher has a duty to report this. Any concerns about individual practice will be discussed with the line manager of that individual, where they can be identified, or the manager of the clinical area.

16.4.3 Interviews with staff

16.4.3.1 Issues

Access, uncovering poor practice which requires action, exploring issues which may cause distress to participants.

16.4.3.2 Steps taken

Staff members may find it difficult to allocate time for interviews. This is particularly difficult for clinical staff who struggle to leave their clinical area during shifts and often work unsocial hours. As well as offering flexibility in timings of interviews, we will also offer telephone interviews as an alternative to face to face. This will allow all staff members to participate if they wish. The project includes funded time for staff to participate. Where poor practice is identified, the researcher has a duty to report this. Any concerns about individual practice will be discussed with the line manager of that individual, where they can be identified, or the manager of the clinical area. Occupational health will be made aware that we are conducting this study. Any participant who is distressed by topics discussed in the interviews will be signposted to occupational health. They will also be encouraged to discuss their concerns with their line manager or seek support from other colleagues where appropriate.

16.5 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor, and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6 Transparency in Research

The study will be registered on a publicly accessible database.

Where the study has been registered on multiple public platforms, the study information will be kept up to date during the study, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the study.

16.7 Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8 Expenses and Benefits

We will send a card (that will also include a £25.00 voucher) thanking patient/public interview or focus group participants for taking part in the study at the completion of their involvement. The card will include the public-facing study website details to increase opportunities for participants to hear about the final project results. The contribution of participants will be recognised in all publications, presentations and publicity associated with the study.

FINANCE AND INSURANCE

16.9 Funding

This study is funded by the National Institute for Health and Care Research (NIHR), Programme: Programme Grants for Applied Research, Call: PGfAR Competition 37 Stage 2 Panel A, Reference number: NIHR204430.

16.10 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

16.11 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

17 PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute for Health and Care Research (NIHR). Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

18 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the study.

19 ARCHIVING

At the end of the study, electronic files containing the anonymised retrospective and prospective study datasets will be stored and retained in the CCRG, (University of Oxford) on secure severs (referred to as the Data Safe Haven). This environment stores data in a manner that it can be securely analysed without removing or copying the data from its systems. The data will remain here for 25 years in keeping with the MRC Research Framework for studies involving pregnant participants. After the archiving period has ended, the paper documents and electronic files will be confidentially and securely destroyed in line with University of Oxford guidelines.

The video footage from the simulation scenarios will be held for up to 3 years after publication of the work.

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21 APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2	3Jun24	Peter Watkinson	CAG reference added and new PPI co-applicant, Zenab Barry, name added to the protocol

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / HRA submission.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).