Academic and Clinical Central Office for Research and Development

Study Protocol

Cervical Ripening at Home or In-Hospital - prospective cohort study and process evaluation (CHOICE Study)

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CEA	Cost effectiveness Analysis
CI	Chief Investigator
GCP	Good Clinical Practice
IHC	International Conference on Harmonisation
IOL	Induction of Labour
HTA	Health Technology Assessment
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute of Healthcare Research
NNU	Neonatal Unit
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operating Procedure

SUMMARY OF RESEARCH

RESEARCH QUESTION

Is it safe, effective, cost-effective and acceptable to women to carry out home cervical ripening during induction of labour (IOL)?

AIMS & OBJECTIVES

Our aim is to compare home versus in-hospital cervical ripening to determine whether home cervical ripening is within an acceptable margin of in-hospital cervical ripening for the safety outcome of neonatal unit (NNU) admission, whether it is more acceptable to women and whether it is cost-effective from both NHS and patient perspectives.

We will perform

i) a prospective multicentre observational cohort study, with internal pilot phase, using data obtained from hospital electronic health records

ii) a cost-effectiveness analysis

iii) a questionnaire- based survey and nested case studies evaluating process and women/partner experiences

SETTING

At least 14 maternity units offering only in-hospital cervical ripening and at least 12 offering dinoprostone home cervical ripening. We will concurrently collect data from at least 4 maternity units offering balloon catheter home cervical ripening to allow initial exploratory comparison of these two different methods of cervical ripening.

PICO

- TARGET POPULATION

Women with singleton pregnancies having IOL at or beyond 39 weeks gestation

- INTERVENTION

  Home cervical ripening with dinoprostone

- COMPARATOR:

  In hospital cervical ripening with dinoprostone

- OUTCOME

  NNU admission (within 48h of birth, for 48h or more)

SAMPLE SIZE

Our primary analysis sample size is 8,533 women with uncomplicated pregnancies at 39 weeks or more undergoing IOL. To achieve this, and to put our findings into context,

we will collect data on a much broader cohort of around 41,000 women having IOL after 37 weeks.

DATA COLLECTION AND ANALYSIS

De-identified data will be extracted from the BadgerNet Maternity system data on all women having IOL from 37 weeks onwards, from multiple existing data fields, supplemented by new bespoke, data entry fields enabled in participating sites. Unless women opt-out of secondary data use (from similar studies we estimate <1% will opt out), de-identified data will be transferred from BadgerNet Maternity systems in participating sites to a secure University of Edinburgh server for analysis.

NNU admission data will be obtained from the National Neonatal Research Database (NNRD). We will use mixed effects logistic regression for the non-inferiority comparison of NNU admission and propensity score matched adjustment to control for treatment indication bias.

COST-EFFECTIVENESS ANALYSIS

The economic analysis will be undertaken from the perspective of the NHS & Personal Social Services and will include a within-study cost-effectiveness analysis and a lifetime cost-utility analysis to account for any long-term impacts of the cervical ripening strategies. Resource use data will be obtained from electronic health records combined with unit costs to calculate the within-study cost for each strategy. Outcomes will be reported as incremental cost per NNU admission avoided and incremental cost per quality adjusted life year (QALY) gained. A secondary analysis will consider the patient perspective, including costs incurred by women and their families relating to IOL. Tailored questions will be added to the process evaluation survey (see below) to gain information on patient related resource use and expenditures.

PROCESS EVALUATION (qCHOICE)

We will perform a nested process evaluation study to identify contextual influences on implementation of cervical ripening protocols and outcomes, assess the acceptability of home cervical ripening to women, their families, and other key stakeholders and explore women's experiences of IOL. We will undertake a questionnaire-based survey across at least 12 participating study sites to assess women's experience of IOL, psychological sequelae, and associated costs. In five sites, we will also conduct interviews with women, partners and health professionals analysed using a thematic framework approach. We will audio record a sample of consultations where IOL is discussed, analysed to assess the extent to which practitioners involve women in decision making processes. At the final stage of data analysis, we will share and discuss emerging findings with a group of service users to develop a revised logic model and explanatory framework.

TIMELINES

The study will run for 36months. The first 6 months will be the initial set up with recruitment following on for 20 months. Outcome data collection analysis is planned for 4 months with the final analysis timetabled for the last 6 months.

ANTICIPATED IMPACT AND ANALYSIS

The findings of the study will be used to inform national guidelines on the best setting for cervical ripening and how this should be implemented.

EXPERTISE IN TEAM

The team performing the study includes midwives, doctors, and clinical trial and complex interventions research specialists, as well as women who have experienced induction of labour. We will collaborate with a leading UK provider of electronic maternity record systems (BadgerNet). This will enable us to collect the detailed information we need in an efficient way, leaving a platform in place for future studies.

1 INTRODUCTION

1.1 Background

IOL is the most common obstetric intervention, offered to women when risks of continuing the pregnancy are thought to outweigh risks of delivery. Rates of IOL were above 40% in the 1970s, but halved over the next decade, before increasing again from the late 1990s (1). Current IOL rates mean that 30.6% of pregnant women in the UK, have their labour induced (2). Elective IOL at term, when compared to expectant management of pregnancy, reduces caesarean delivery and maternal hypertensive disease (3), as well as being associated with a reduction in perinatal mortality and maternal complications (4, 5). It thus seems likely that demand for IOL will continue. Maternity services are struggling to accommodate increasing rates of IOL (6). Although IOL (compared to expectant management) reduces overall hospital stay, it increases the amount of time spent on antenatal wards and on labour wards (3), with a major impact on maternity resources and staffing, and women's experience of labour (7-9).

Cervical ripening is a key component of IOL (10), whereby application of a drug or mechanical method over a number of hours, causes softening, shortening, and opening of the cervix in preparation for labour. Cervical ripening may itself initiate labour, but is often followed by artificial rupture of membranes +/- intravenous infusion of oxytocin (both inpatient procedures). NICE guidance (11) recommends *all* women having IOL have prior cervical ripening, unless there is a contraindication.

Traditionally cervical ripening has been performed entirely in-hospital, to allow monitoring of maternal/fetal wellbeing and recognition of complications such as uterine hyperstimulation (frequent/sustained contractions that increase the risk of hypoxic birth injury; incidence 2-3% (12)). However, an increasing number of maternity units offer home cervical ripening, whereby women attend hospital for initial assessment and administration of cervical ripening agent; and then return home (to her own home, or that of a friend/relative/birth partner) for a period of time (usually 24 hours), before reassessment in hospital. Home cervical ripening has the potential to reduce hospital stay during IOL, reducing costs to health services. However, the safety and acceptability of home cervical ripening has not been fully evaluated. Potential NHS cost savings could be offset by increased costs of any additional morbidity resulting from home cervical ripening, costs to parents may be increased; and acceptability of home cervical ripening is unknown. Health services need to balance the full resource impact of IOL with the need to provide safe and acceptable care.

In the CHOICE study we address the question "Is it safe, effective, cost-effective and acceptable to women to carry out home cervical ripening during induction of labour (IOL)?" We will also perform additional descriptive analyses about the process and outcomes of IOL, and validate and refine risk prediction models for caesarean birth after IOL (13). These analyses will provide information to help women and their caregivers make informed decisions around when and how to have IOL.

1.2 Rationale and justification for study

As the rate of IOL is increasing, home cervical ripening may provide opportunities to reduce the burden on the NHS. However, there are evidence gaps in whether home cervical ripening is safe, acceptable to women, reduces hospital stay and cost-effectiveness. NICE (11) identified the need to assess the safety, efficacy and clinical and cost-effectiveness of outpatient and inpatient IOL in the UK setting, taking into account women's views. Maternity service users have identified IOL as an important research topic (14) and women have reported specific negative experiences such as increased pain and anxiety and lack of support which may be alleviated by home cervical ripening (9).

Home cervical ripening has potential to reduce separation of women from their families and increase choice regarding the timing and setting for labour and delivery. Existing evidence suggest that home cervical ripening is feasible and adverse outcomes appear to be rare, but trials have been underpowered to confirm safety (15, 16). Importantly, studies have not confirmed anticipated reductions in length of hospital stay or cost-effectiveness (4, 17). However, no studies have investigated the acceptability to women or their families, or whether choice is increased in a UK setting, apart from a small feasibility study conducted by some of the investigators in qCHOICE (Coates et al. in preparation). This study will provide much needed evidence on women's and partners experiences of home cervical ripening, IOL and costs from the service user perspectives.

Despite the lack of evidence on home cervical ripening, the practice is becoming increasingly common in UK practice. In preparation for this study we obtained information on IOL policies from 128/167 (77%) obstetric units in Scotland, England, and found that 54% (69 of 128) of units now, or soon will offer home cervical ripening (Aug-18). This is a large and rapid increase - a 2014 survey found only 17% of UK maternity units offered home cervical ripening (18).

There is variation in the population of women offered home cervical ripening between hospitals. However, most units only offer home cervical ripening to women with 'low risk' pregnancies (i.e. women with uncomplicated pregnancies). The majority of units that offer home cervical ripening (>90%) use topical prostaglandins applied intravaginally as a slow release pessary of 10mg dinoprostone, which stays in place for 24 hours. This is in line with NICE guidance, which recommend prostaglandins as the primary method of IOL for all women (11). Balloon catheters, which involve inserting either the balloon from a foley catheter or a specially designed cervical ripening catheter into the cervix and inflating it with saline to mechanically open the cervix, have also been shown to be effective (12). Compared to prostaglandins, balloon catheters have a lower incidence of uterine hyperstimulation (2% versus 3%) and operative delivery indicated by fetal heart rate abnormalities (12% versus 18%) (12). However, they may be less acceptable to women (19). Whereas in 2014 no units offered home cervical ripening with balloon catheters (18), our survey suggests that at least 6 UK units currently, or soon will, offer balloon catheters as the primary method of home cervical ripening. Other methods of cervical ripening are not currently used at home. Oral misoprostol has high rates of uterine hyperstimulation (20) and is not used outwith hospitals in the UK. Osmotic dilators (an alternative mechanical method) are under evaluation in hospitals (SOLVE trial; ISRCTN20131893) but have not yet been shown to be effective or established in UK practice.

Our main research question relates to the setting of IOL, however, additional analyses, particularly regarding method of IOL will add value to the project. Our preliminary work and site scoping have shown that there is considerable variation both in the rates and methods of IOL used throughout the UK. Data collected for the CHOICE study can be used to describe this variation, and to explore the impact on resource use and health outcomes for mother and babies of alternative methods of IOL. We will also be able to describe the outcomes relating to the success of IOL (i.e. achieving vaginal birth) in women and babies having IOL for different indications, and by week of gestational age. We will use this data to externally validate a risk-prediction model for caesarean birth following IOL developed in the USA (13) (and others if they become available), and, if necessary refine these for NHS use. A risk predictor that stratifies chances of success of IOL will help women and their caregivers make decision whether or not to undertake IOL.

2 STUDY OBJECTIVES & OUTCOMES

2.1 Aims & Objectives

We aim to perform a prospective multicentre observational cohort study, using real-world data obtained from hospital electronic health records (CHOICE prospective cohort study) linked with a process evaluation using a questionnaire-based survey and nested case studies (qCHOICE).

The primary objective of the overall CHOICE study is to assess the safety, clinical effectiveness, cost-effectiveness and acceptability of home cervical ripening.

Within the CHOICE prospective cohort study we will address:

Is home cervical ripening

- as **safe** as in-hospital cervical ripening in terms of NNU admission (primary outcome), and other secondary outcomes of maternal and neonatal morbidity?
- **effective** in reducing the amount of time women spend in hospital during the IOL process?
- **cost-effective** from the NHS perspective?

Our primary comparison will be will be home dinoprostone (intervention) versus in-hospital dinoprostone (comparator). A secondary exploratory comparison will be undertaken to explore home cervical ripening with balloon catheter (intervention) vs home cervical ripening with dinoprostone (comparator).

Additional research questions applied to the cohort study are:

How do

- IOL rates and methods and outcomes vary across the UK
- What are the outcomes of IOL in different subgroups of women (e.g. women with multiple pregnancy; women with IOL after a previous caesarean section) and at each week of gestation (37,38,39,40 and 41+ weeks)

- Can we predict which women will have caesarean section after IOL?

Within the qCHOICE process evaluation we will address:

Is home cervical ripening

- **acceptable** to women and their families, clinicians and health professionals?
- Cost effective from the perspective of women and their partners?

We will explore the **contextual influences** on the implementation and fidelity to cervical ripening protocols, and outcomes of cervical ripening, in different settings (e.g. different size units, rural and urban settings).

Specific research questions within qCHOICE are

- In what ways does the service context influence cervical ripening approaches in hospital or out of hospital settings?
- What is the acceptability of home or hospital and different methods of cervical ripening to women (and their birth partners) and implication for their experience of IOL & care?
- What is the acceptability of home cervical ripening from the perspective of clinicians and health professionals?
- What are the cost implications from the service user perspective?
- What information and outcomes are important for pregnant women and their partners?
- What are the psychological correlates of cervical ripening setting?
- What potential factors mediate women's experience; for example, rurality, distance from hospital, information provision, professional support?
- What are the service barriers and enablers of adoption of home cervical ripening?
- Are there any unintended consequences associated with home cervical ripening, for individuals, families and or services involved?

2.2 Primary outcome

Admission to a neonatal unit (NNU) within 48 hours of birth for 48 hours or more.

2.3 Secondary outcomes

Safety Outcomes:

-Baby

Any neonatal unit admission (any level of care)

Neonatal intensive care unit (NICU) admission

Duration of neonatal unit stay

Duration of NICU stay

APGAR score <7 at 5 minutes

APGAR score <4 at 5 minutes

Arterial Cord Blood pH <7.1

Arterial Cord base excess >12mmol/L

Neonatal Seizures

Hypoxic Ischaemic Encephalopathy (as recorded by care givers)

Level 2 or Level 3 Hypoxic Ischaemic Encephalopathy (as recorded by care givers)

Meconium aspiration syndrome

Mechanical ventilation

Intracranial haemorrhage

Stillbirth after admission/first attendance for induction of labour (excluding deaths from congenital anomalies)

Early neonatal death up to 7 days after birth (day 0-6; excluding deaths from congenital anomalies)

Treatment for neonatal sepsis [defined as positive blood, cerebral spinal fluid, or urine culture or cardiovascular collapse or X-ray confirming infection] *(Exploratory outcome)*

Treatment in neonatal unit for neonatal infection (defined as antibiotic treatment and Temperature ≥37.5 °C or <35.5 °C) *(Exploratory outcome)*

Treatment for neonatal jaundice [defined as peak total bilirubin of at least 15mg or the use of phototherapy] *(Exploratory outcome)*

-*Maternal*

Intensive care unit transfer

High dependency level care

Hyperstimulation or tachysystole (as defined by care givers)

Hyperstimulation or tachysystole causing CTG abnormality (as defined by care givers)

Umbilical cord prolapse

Birth outwith hospital

Postpartum haemorrhage 1000ml or more

Maternal pyrexia 38 °C or more after commencing cervical ripening (*Exploratory outcome)*

Effectiveness outcomes:

Time from first cervical ripening agent to admission to labour ward/birth unit

Time from first cervical ripening agent to birth

More than one cervical ripening agent used

Duration of antenatal hospital stay for cervical ripening

Duration of labour ward admission until birth

Duration postnatal hospital stay (mother)

Total hospital stay

Hours spent at home

Oxytocin use

Mode of birth

Birth in obstetric unit

Birth in alongside midwifery unit (if available at that site)

Mother-baby outcomes:

Breastfeeding at discharge from maternity care

Skin to skin at birth

Cost effectiveness

Primary economic outcomes

Incremental cost per neonatal admissions avoided (home versus in-hospital)

Incremental quality adjusted life year (QALYs) (home versus in-hospital)

Other (exploratory) economic outcomes

Incremental cost per hour prevented from hospital admission to delivery/birth

Incremental cost per neonatal admission avoided (home balloon catheter versus home dinoprostone)

Incremental cost per QALY (home balloon catheter versus home dinoprostone)

Incremental cost per hour prevented from hospital admission to delivery/birth (home balloon catheter versus home dinoprostone

Outcomes to check comparability of groups/matching

Birthweight

Birthweight centile

Small for gestational age (<10th centile for gestational age)

Large for gestational age (>90th centile for gestational age)

qCHOICE Process evaluation outcomes

Primary Outcome

Sense of control (agentry) in labour

Secondary Outcomes

Women's satisfaction with IOL care

Women's postnatal psychological wellbeing

Women's overall evaluation of their labour and birth experience (qualitative analysis)

Costs incurred by the woman and family

3 Design and theoretical/conceptual framework

We will carry out a prospective multicentre cohort study using de-identified clinical data from electronic hospital records with a process evaluation using a questionnaire-based survey and an interpretive case study design nested within the main cohort study. The description of the two component parts has been divided within the protocol for clarity. The CHOICE Observational Cohort study is described in section 4. The qCHOICE Process Evaluation is described in section 5. Sections 6 to 12 relate to the all aspects of the study.

4 PART 1: CHOICE Observational Cohort Study

4.1 STUDY DESIGN

4.1.1 Health technologies being assessed

Our main aim is to compare the setting of cervical ripening (home versus in-hospital). As the NICE recommended agent for cervical ripening is vaginal prostaglandin our primary comparison will be home dinoprostone (intervention) versus in-hospital dinoprostone (comparator). Dinoprostone is now most commonly administered as 10mg slow release pessary (Propess, Ferring) which stays in place for 24 hours. We will use this formulation in our primary comparison.

In order to future proof the study we will include a secondary (exploratory) comparison - home cervical ripening with balloon catheter (intervention) vs home cervical ripening with dinoprostone (comparator); using the same primary and selected secondary outcomes defined above. Although balloon catheters are only used for home cervical ripening in ~6 UK units at present, they are widely used in Europe, Australia and USA due to a potentially better safety profile (21); however, insertion may be more uncomfortable than prostaglandins (19). We aim to collect data from a minimum of 4 units which offer balloon catheter home cervical ripening. By including two different methods of home cervical ripening within our study, we will provide initial comparative evidence on these two methods of home induction.

If other methods of IOL are used (such as osmotic dilators e.g. Dilapan) we will collect data on these methods and also perform exploratory comparisons as to their safety effectiveness.

4.1.2 Design

We will carry out a prospective multicentre cohort study using de-identified clinical data from electronic hospital records.

In PICO terms, the principal research question for the study can be summarised as Population: women with singleton pregnancies having induction of labour at or beyond 39 weeks; Intervention: Home cervical ripening; Comparator: In-hospital cervical ripening; Primary Outcome: NNU admission (within 48 hours of birth, for 48 hours or more).

Our primary hypothesis is “Home cervical ripening is as safe as in-hospital cervical ripening, reduces the time women spend in hospital during IOL, and is more cost-effective and more acceptable to women”. We have thus chosen a non-inferiority design to determine whether home cervical ripening is within an acceptable margin of in-hospital cervical ripening for the umbrella neonatal safety outcome of NNU admission, and whether the acceptable margin of non-inferiority can be traded against increases in acceptability and reduction in costs due to less hospital delivered care.

NNU admission is an appropriate primary outcome as it is a marker of neonatal morbidity; is the number one core outcome defined for studies of IOL (22), devised with strong representation from maternity service users; and is supported by our own lay consultation. Admission of a term baby to a NNU separates mothers and babies and interrupts the normal bonding process (23), is expensive (23), and is associated with increased *postnatal* stay for mothers (offsetting any potential gains from reducing *antenatal* maternal inpatient stay).

Any increase in NNU admission of term babies is undesirable due to separation of mother and baby. However, we decided against using ‘any NNU’ admission as our primary outcome as NNU admission rates are highly variable between maternity units and are likely to depend on local policies and culture. We instead plan to use a primary outcome which represents more severe neonatal morbidity (admission to a NNU within 48 h of birth for 48 h or more). This is less likely to be influenced by site specific factors, so its use will minimise clustering of outcomes and the impact on analysis that this might have.

We will assess variation of the primary outcome at the pilot stage; along with that of other measures of neonatal morbidity included as secondary outcomes (e.g. any NNU admission, NICU admission). We may redefine the parameters of NNU admission used in the primary outcome after analysis of pilot data, choosing the one with the lowest intraclass correlation coefficient [ICC], or the one representing the least severe outcome which has an ICC of 0.01 or less. This decision will be made in consultation between the expert project management group, the trial steering committee (TSC) and the funder.

We have prespecified a number of secondary outcomes to assess the safety of home cervical ripening with respect to neonatal and maternal morbidity. We accept that some of these are rare individually, and thus our study is likely to be underpowered to show differences in these. However, as they represent serious harms we have included them as part of our safety assessment. We have also included low arterial cord pH and APGAR scores as safety outcomes. Both are routinely performed in the assessment of babies at birth. Low cord pH is strongly associated with neonatal mortality and hypoxic ischaemic encephalopathy (24). Low APGAR score is strongly associated with neonatal and infant mortality, particularly those attributed to anoxia in term babies. Given the strength and consistency of the association with serious harms, impacts on these surrogate markers of morbidity and mortality would likely be considered important enough to change practice (25).

In line with the commissioning brief for this study from the funder, we have also specified a number of secondary outcomes relating to effectiveness of home cervical ripening, to explore if the setting of cervical ripening influences subsequent labour and birth. Mother and baby outcomes were suggested by our lay consultation as important to include. We will use birthweight, birthweight centile, small for gestational age and large for gestational age as outcomes to check the validity of our matching procedures in analyses. Birthweight is an objective outcome that may represent pregnancy complications, but extremely unlikely to affected by the setting of cervical ripening. Comparison of birthweights should provide reassurance that we have minimised systemic bias in our analyses.

A large number of other core outcomes have been defined for studies of IOL (22). We will include these as secondary outcomes wherever feasible, along with additional outcomes suggested by our lay consultation/from commissioning brief. We will explore the use of maternal and baby temperature data as markers of infection, and our decision to use this will depend on data quality and completeness.

Our principal analysis will be restricted to women who have uncomplicated pregnancies having IOL at 39 weeks or more. This will include women having IOL for post-dates, but also women having IOL because of maternal or clinician preference, IOL for maternal age, IOL for discomfort or social indications. Feedback from potential sites and data from the most recent National Maternity and Perinatal Audit (NMPA) report (2) suggests that the proportion of IOL for post-dates is reducing, and numbers of IOL at 39-40 weeks increasing. If there are sufficient numbers we will perform subgroup analyses by the principal indication for IOL i.e. (Post-dates IOL; Maternal age; discomfort or social indications; maternal or clinician preference).

Further additional analyses may include IOL for other indications (e.g. reduced fetal movements; IOL in women with prelabour rupture of membranes). However, the

majority of proposed sites would only consider home cervical ripening for 'low risk' cases so it is less common for women with these circumstances to be offered home cervical ripening.

We will collect data from a much larger cohort of women having IOL to allow the analyses specified above. This is essential to put our findings into context, and allow us to explore and describe variation in practice across the UK, taking into account the demographics of the population having IOL at each site. This will help describe the generalisability of our findings, and will also add value to the study allowing a number of additional descriptive analyses relevant to UK practice. We will use the cohort to explore regional variation in IOL rates, settings, methods and outcomes in the UK. We will describe outcomes of IOL in different subgroups of women (e.g. women with multiple pregnancies; women with previous caesarean section) and outcomes at different gestational ages. We will also validate and refine a risk prediction model for caesarean section after IOL.

Future long-term outcome evaluation will be possible through data linkage to Hospital Episode Statistics and Scottish Morbidity Records, but this is outwith the scope of the current study and will require future funding.

4.2 STUDY SETTING

The CHOICE observational cohort study will be performed in a minimum of 26 obstetric units offering predominantly home cervical ripening, predominantly inpatient cervical ripening, or a mixture of both. De-identified data will be collected from electronic maternity records. The majority of participating obstetric units use the BadgerNet maternity electronic records system (BadgerNet Maternity, Clevermed, Edinburgh). However, if additional trusts would like to participate in the CHOICE study and are willing and able to provide data from other maternity data systems in accordance with the study protocols without incurring significant costs, we will include them.

We will ensure that sites are not confined to one geographical area, size or type of maternity unit. The BadgerNet maternity system is currently in use, or under implementation, in 38 obstetric units in Scotland and England (i.e. 20% of the 181 obstetric units in the UK [~17% of all deliveries in Scotland and England]; with more than 20 different systems in use across the remaining units). BadgerNet Maternity units range from London tertiary referral centres, through mid-sized urban district general hospitals, to small, isolated, rural units. We can thus select participating sites representative of the diverse range of maternity services in the UK.

4.3 STUDY POPULATION

Our primary analyses will be restricted to women with uncomplicated singleton pregnancies at 39 weeks gestation or more having IOL.

We will initially apply broad inclusion criteria and collect data from all women having IOL at 37+0 weeks gestation or more to create a cohort for analyses (see flowchart in Appendix 1). We will then apply more stringent inclusion and exclusion criteria at the analysis stage for suite of nested analyses. In our principal analysis we will create a cohort of women with "uncomplicated" pregnancies in whom there is no

contraindication to home cervical ripening, who are having IOL at 39 weeks gestation or more.

Secondary and additional analyses will be performed on data from women who have IOL for specific conditions or with concurrent conditions from 37 weeks onwards (e.g. reduced fetal movements; IOL in women with prelabour rupture of membranes; women with gestational diabetes).

4.3.1 Sample size considerations

See flow chart in Appendix 1.

The sample size is based on our principal analysis (women with singleton pregnancies having IOL for at 39 weeks gestation or more) and primary comparison (home cervical ripening vs in-hospital cervical ripening with dinoprostone), estimated 6% NNU admission rate for babies born to mothers having IOL at >39 weeks gestation [based on preliminary data from selected potential participating units on NNU admission from delivery suite for 48 hours or more, provided by BadgerNet], with 4% non-inferiority margin, at 90% power, 2.5% 1-sided alpha, and an estimated ICC of 0.01. We will require 160 women in each of 12 sites (clusters) with uncomplicated pregnancies at 39 weeks or more undergoing IOL (total 1,920 in each arm). To account for the fact that i) only around 50% of women eligible for home cervical ripening in the intervention arm will actually initiate home cervical ripening, and ii) a larger pool of women is required in the control arm to allow for propensity score matching, our required sample size is 1,920 *2 (number of arms) / 0.5 (numbers of women actually starting home cervical ripening and matching) / 0.9 (for missing data), giving an overall required sample size of 8,533.

We will collect de-identified data from a much larger cohort of women having IOL with broader inclusion criteria. The broad data collection criteria are important for three main reasons.

i) It will allow us to capture any changes in practice or the study period regarding criteria for eligibility for home cervical ripening, and change in method of IOL. Capturing this will help ensure generalisability of our findings.

ii) It will allow us to contextualise our findings on the background of unit practices for IOL and populations undergoing IOL. There is considerable inter-unit variation in both the rates of IOL and the risk profile of women giving birth, that need to be considered with our findings.

iii) It will allow us to perform additional analyses describing outcomes of IOL in subgroups, for example, by indication of IOL (eg Postdates IOL; Reduced fetal movements) or in the presence of specific risk factors (eg multiple pregnancy; previous caesarean birth).

De-identified data will thus be extracted from all women who have IOL at 37 weeks or more at participating sites. Current data from the NMPA for 2016/17 suggests that the national average rate of IOL after 37 weeks is 30.6% (2). As our proposed participating

units have about 90,000 births per annum, we anticipate collecting data on approximately 41,000 women having IOL at 37 weeks gestation or more.

4.3.2 Inclusion criteria

For data collection

- Gestation 37+0 weeks or more
- Undergoing IOL

For primary analysis

- Gestation of 39+0 weeks or more

4.3.3 Exclusion criteria

For data collection

- Opted out of data provision (checkbox)

Applied for primary analysis

- Grand multiparity (6 or more previous pregnancies)
- Previous caesarean section
- Antepartum stillbirth (before cervical ripening initiated)
- Class III obesity at booking (BMI 40 kg/m^2 or more)
- Prelabour rupture of membranes documented as primary or other indication for IOL (prolonged ROM; SROM; ?SROM)
- Maternal, fetal or medical condition that would/could preclude home cervical ripening documented as primary or other indication for IOL
- *Maternal conditions*: proteinuria; hypertension; antepartum haemorrhage; diabetes; obstetric cholestasis; past obstetric history; pre-eclampsia; PIH/PET (not defined); PIH; PET; thrombophilia
- *Fetal conditions:* oligohydramnios*;* reduced liquor volume*;* macrosomia*;* intrauterine growth restriction (IUGR)*;* static growth*;* congenital fetal anomaly*;* polyhydramnios*;* abnormal CTG/Doppler*;* breech*;* reduced fetal movements*;* termination of pregnancy for fetal anomaly

4.3.4 Co-enrolment

There will be no restriction on co-enrolment in other studies.

4.4 PARTICIPANT SELECTION AND ENROLMENT

4.4.1 Identifying participants

Participants will be identified from data recorded in specified fields in maternity electronic records. We will use data fields indicating, IOL, Estimated due date (EDD) and date of IOL to identify women having IOL at 37 weeks gestation or more. Further details on the fields used for identification are given in the Data Management Plan (DMP).

4.4.2 Opting out of the study

Women will be made aware of the CHOICE study through a variety of methods including posters in participating sites; business cards; information leaflets; online adverts on hospital/maternity websites and relevant social media sites; and information in maternal electronic maternity records (for women who can access their own maternity record).

Women will be able to opt out of data provision in one of two ways.

- They can notify their midwife or obstetrician of their preference to opt out

- They can opt-out by contacting the local study lead (CHOICE Champion). Contact details will provided within the study information leaflet.

Women's preference to opt out of the study will be marked on the electronic record by the local midwife or by the CHOICE Champion.

Currently less than 1% of women opt out of secondary data use from the BadgerNet Maternity records and none has opted out of inclusion of their baby's data in the National Neonatal Research Database (NNRD).

4.5 STUDY ASSESSMENTS

4.5.1 Study assessments

There are no participant study assessments within the observational cohort study. Women will receive standard care according to local policies and protocols. All analyses will be performed on routinely recorded de-identified data obtained from electronic maternity records, pertaining to clinical care given according to local clinical guidelines.

4.5.2 Long term follow-up assessments

This is an observational study of clinical care. There are no long term follow up assessments. We would anticipate that in future it may be feasible to evaluate longer term effects of IOL through data linkage with Hospital Episode Statistics and Scottish Morbidity Records, but this is out with the scope of current study. If we decide to do this it will require other funding and will have a separate protocol, ethical and governance approvals.

4.6 DATA COLLECTION

De-identified data will be collected directly from electronic maternity and neonatal records (in participants who had babies admitted to a neonatal unit). This data is recorded by clinical staff (midwives, doctors and neonatal nurses) during the course of antenatal, intrapartum and postpartum care.

The source documents will be the electronic maternity and neonatal records. There will be no specific study data collection forms, and study data will be securely transferred directly from sites to Edinburgh Clinical Trials Unit (ECTU) servers, which are managed by the University of Edinburgh.

4.7 DATA MANAGEMENT

De-identified data will be stored and analysed in the ECTU servers. Data held in ECTU is managed in accordance with the relevant University of Edinburgh Information Security policies, and applicable ECTU specific data management and IT policies. , Only approved members of the research team will have access to the study data.

The CHOICE DMP provides further details on how data will be collected, stored and analysed.

4.7.1 Personal Data

No personal data will be collected. Potentially identifiable data, such as baby date and time of birth, date and of events such as commencing cervical ripening, hospital discharge, will be converted into gestation at birth (Weeks, days); and antenatal and postnatal events into “t – x” and “t+x” hours and days respectively.

Ethnicity (as recorded in maternity record): This is a potential confounder that may influence likelihood of having home cervical ripening and risk of neonatal unit admission. We will also collapse ethnicity into groupings prior before writing the final report.

This is a study involving pregnant women and research records should be retained according to NHS Guidelines for the retention of documentation involving pregnant women. All medical records will be retained for at least 25 years, where possible, after publication of the final study report. Guidelines on retention of other research related documents are continually under review. We plan to retain all documents for 5 years and then review according to current guidance at that time.

4.7.2 Transfer of Data

Data collected or generated by the study will not be transferred to any external individuals or organisations outside of the Sponsoring organisation.

4.7.3 Data Controller

The University of Edinburgh is the data controller.

4.7.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh Data Protection Officer who will onward report to the relevant authority according to the appropriate timelines if required.

4.8 STATISTICS AND DATA ANALYSIS

4.8.1 Sample size calculation

As described above, the sample size is based on our principal analysis (women with singleton pregnancies having IOL for at 39 weeks gestation or more) and primary comparison (home cervical ripening vs in-hospital cervical ripening with dinoprostone), estimated 6% NNU admission rate for babies born to mothers having IOL at >39 weeks gestation [based on preliminary data from selected potential participating units on NNU admission from delivery suite for 48 hours or more, provided by BadgerNet], with 4% non-inferiority margin, at 90% power, 2.5% 1-sided alpha, and an estimated ICC of 0.01. We will require 160 women in each of 12 sites (clusters) per arm (total 1,920 per arm). To account for the fact that i) only around 50% of women eligible for home cervical ripening in the intervention arm will actually initiate home cervical ripening, and ii) a larger pool of women is required in the control arm to allow for propensity score matching, our required sample size is 1,920 *2 (number of arms) / 0.5 (numbers of women actually starting home cervical ripening and matching) / 0.9 (for missing data), giving an overall required sample size of 8,533.

Data will be extracted from approximately 41,000 women who have IOL at 37 weeks or more.

We will include at least 14 BadgerNet Maternity units offering only in-hospital cervical ripening and 12 offering dinoprostone home cervical ripening (~95,000 deliveries per annum). We will, however, invite all BadgerNet Maternity units to opt in to data provision, which will allow contingency in case of 'cross overs' due to sites changing their IOL protocols during the study period. Based on an estimate that 22% of all maternities have IOL at 39 weeks or more (from NMPA 2016/2017 data) and that ~29% of these would eligible for participation in our principal analysis (from scoping data from potential participating sites), and, in home cervical ripening sites ~50% of these will take up home cervical ripening, we anticipate achieving our recruitment targets within 20 months. If more women are eligible for inclusion we will reduce the recruitment period as necessary.

A superiority design for CHOICE was inappropriate because i) safety is a key concern to both clinicians and women, and was specified as the important outcome in the commissioning brief; ii) it is not plausible to hypothesise that home cervical ripening (intervention) is safer than in-hospital cervical ripening (comparator – the standard of care); and iii) it is not ethical to use a superiority design to test an intervention which may be worse (in terms of safety) than the established standard. Therefore, a non-

inferiority design was chosen with a non-inferiority margin of 4% for the primary outcome of neonatal unit admission.

Establishing the appropriate non-inferiority margin is complicated as the dimensions that are hypothesised to show benefit i.e. acceptability to women and partners, and a reduction in costs appeal to different audiences – women will be primarily interested in acceptability and largely indifferent to costs (in a free at point of care NHS), whereas the potential reduction in costs will likely be the primary focus for the healthcare provider. We were also conscious that due to the inflation of the sample size due to (a) clustering; (b) losses due to non-matching in the propensity analysis and (c) loss to follow up, the sample size for a smaller non-inferiority margin would quickly become not feasible within a realistic budget and timeframe. However, given that, regardless of a superiority or non-inferiority design, any specific sample size will estimate the treatment effect to a certain level of precision (e.g. the width of a 95% confidence interval), we are confident that with data collection ~41,000 women, a sample size of over 8,500 and a final comparison group of 1,920 in each arm (with ~ 230 NNU admissions), we will generate sufficient high-quality evidence to definitively answer the questions around safety, effectiveness, acceptability, and cost effectiveness for this important question. In addition, since data on the primary outcome is realized soon after delivery, and given the inclusion of an extensive internal pilot phase (see below), we are in a position to carefully monitor the assumptions behind this sample size and take corrective action if required.

4.8.2 Proposed analyses

All analyses will be fully specified in a comprehensive Statistical Analysis Plan and Health Economic Analysis plan authored by the study statisticians and health economists and agreed by the Trial Steering Committee. Analyses will be carried out in accordance with relevant guidance including RECORD (26), STROBE (27) and CHEERS (28).

For the principal analysis of the primary outcome we will use mixed effects logistic regression for the non-inferiority comparison of NNU admission within 48 hours of birth for 48 hours or more (Yes/No).

In maternity units which offer home cervical ripening, the risk of complications in women/babies having home cervical ripening (lower risk pregnancies) is inherently different to that of women/babies having in-hospital cervical ripening (higher risk pregnancies). To minimise this bias, in our principal analysis we will compare the outcomes of women undergoing cervical ripening at home, with women from maternity units that *only* offer in-hospital cervical ripening (See Appendix 1 Flow Chart).

For the principal analysis of the primary outcome we will use mixed effects logistic regression for the non-inferiority comparison of NNU admission within 48 hours of birth for 48 hours or more (Yes/No).

We will use a regression based approach rather than for example the popular approach of propensity score matched (PSM). As sensitivity analyses to demonstrate that the estimated treatment effects are robust to the chosen method, we will also explore propensity score weighting (PSW by inverse probability of receiving specified

treatment) and single-stage regression, without using any propensity scoring, adjusting directly for the baseline factors relevant for treatment indication. We will also use propensity score matched (PSM) adjustment to control for treatment indication bias. The logistic model underlying the PSM will include variables such as age, Bishop's score, co-morbidities, and relevant hospital level factors, with 1:1 matching. Potential confounding variables (see Appendix 2) will be identified before the start of the analysis, and these will be finalised after exploration of the data at the pilot stage.

Similar analyses will be used for analyses of secondary outcomes, using logistic, linear, negative binomial, and time-to-event regressions. For example, we will analyse duration of hospital stay during IOL, time spent at home, total hospital stay, and time to birth using linear models; while birth outwith hospital and breastfeeding will be analysed using logistic regression; and mode of birth using multinomial logistic regression.

For the remaining neonatal and maternal secondary outcomes, we will analyses umbilical cord prolapse, birth trauma, neonatal death, hypoxic ischaemic encephalopathy, therapeutic hypothermia, hyperstimulation, ≥1 induction agent, oxytocin, ICU admission, HDU admission, meconium aspiration syndrome, respiratory support, neonatal infection, haemorrhage, uterine rupture, pulmonary embolus, and cardio-respiratory arrest using logistic regression; and neonatal seizures using a Poisson or negative binomial regression, possibly inflated for excess zeros. For outcomes with a small number of events, we will use the appropriate exact regression procedure. As per the primary outcome, we will assess the influence of missing data for secondary outcomes using appropriate sensitivity-type analyses. We recognise that there are many secondary outcomes being analysed, as per the recommended core outcome set (21). We do not propose to make any formal statistical adjustment for the multiple comparisons. However, a caveat will be clearly expressed regarding the dangers of over interpreting these data, given the multiple comparisons made.

Subgroups Analyses

We propose the following subgroup analyses, if we have sufficient numbers to allow meaningful analyses.

- nulliparous and parous women
- indication for IOL (post-dates IOL; maternal or clinician preference; maternal age; discomfort or social indication)

Sensitivity Analyses

We propose the following sensitivity analyses, if we have sufficient numbers to allow meaningful analyses.

- Within-site comparison of home versus in-hospital cervical ripening (restricted to sites that offer home cervical ripening)

- Per protocol analysis (women who actually are discharged home after commencing cervical ripening)
- Complete case analysis to assess the effect of any strategies to deal with missing data.

Additional Analyses

We will use the data to externally validate a risk calculator to predict the risk of caesarean birth after IOL (13) which was developed in the USA. We may validate and compare other models if they become available (e.g. one that is being developed in UK), and refine models for NHS use. Multivariable logistic regression modelling will be the primary method of analysis. As the outcome is binary, a logistic regression modelling framework will be fitted to the CHOICE study data to validate the model. Measures of performance for the validated models will include discrimination (C-statistic), Calibration (calibration plot and calibration in the large) and fit (Nagelkerke's R^2).

4.8.3 Missing data

We anticipate missing data, but estimate that no more than 10% of women will not have a usable primary outcome, eligibility, setting of cervical ripening and/or have some part of the baseline data (age, co-morbidities, and any relevant identified hospital-level factors). We will use evidence-based strategies to minimise any such losses and recover any missing data that is possible. We will monitor levels of missing data as the study progresses, identifying any outcomes or exposures and/or sites that are prone to missingness, and take corrective action (e.g. additional feedback and support). We will conduct appropriate sensitivity type analyses, for example, using a multiple imputation approach assuming data are missing at random; and, if the data warrant (for example, if there is differential missingness between the in-hospital and at-home cohorts) non-ignorable (informative) missing data generating mechanisms.

We will also conduct an exploratory analysis comparing the two methods of home IOL i.e. dinoprostone vs. balloon. We will use the same methods as outlined above for the primary and secondary outcomes in the overall analysis.

4.8.4 Pilot phase

We propose a pilot phase to determine the parameters of the primary outcome and achievability of obtaining the required sample size for analysis. This is based on the evaluable comparison group of 1,920 women in each arm, so acts as an inherent check on home cervical ripening eligibility and uptake rates, the assumed level of missingness and attrition due to non-matching.

We will perform an analysis after 6 months of recruitment (evaluable target 600 women in each arm). We have based the threshold of an intraclass correlation coefficient (ICC) greater than 0.0125 being consistent with a required sample size of 320 for each cluster, double that of the currently specified requirement of an average cluster size of 160 (assuming an ICC of 0.01). If the observed ICC in the pilot is

substantially less than 0.01, then we can reliably reduce the sample size requirement for the specified power and level of significance; or for the same sample size detect a smaller non-inferiority margin. For example, an ICC of 0.006 would require an average cluster size of around 100. Stop/go criteria are specified in Table 1 below.

We will assess variation of the primary outcome at the pilot stage; along with that of other measures of neonatal morbidity included as secondary outcomes (e.g. any NNU admission, NICU admission). We may redefine the parameters of NNU admission used in the primary outcome after analysis of pilot data, choosing the one with the lowest ICC, or the one representing the least severe outcome which has an ICC of 0.01 or less. This decision will be made in consultation between the expert project management group, the trial steering committee (TSC) and the funder.

Table 1: Stop/go criteria for pilot phase

Criteria – 6month recruitment	**Stop**	**Change**	**Go**
Number of evaluable women in each arm	*<400* *(<4 SD of target)*	*400-549* *(2-4 SD of target)*	*550-650* *(2SD of target)*
ICC for neonatal unit admission	*>0.0125*	*> 0.01 but <=0.0125*	*<=0.01*
ACTION	*Discuss with funder feasibility of continuing study and/or design modifications to allow assessment of safety outcomes*	*Consult with funder for extension to data collection period*	*Continue study as proposed*

4.8.5 Economic Analysis

The economic analyses will explore the cost-effectiveness of at home versus inpatient cervical ripening for women having IOL from the perspective of the NHS and Personal Social Services (NHS & PSS), and the patient, adhering to good practice guidelines and the NICE reference case (29). Two separate cost-effectiveness questions will be addressed: (i) home cervical ripening with dinoprostone compared to in-hospital cervical ripening with dinoprostone and (ii) home cervical ripening with balloon catheter compared to home cervical ripening with dinoprostone. The evaluation will involve both a within study CEA and a lifetime cost-utility analysis to account for any long-term impacts (cost, morbidity and quality of life) of the alternative cervical ripening strategies. Resource use data will be obtained from the prospective multicentre observational cohort study using data obtained from the Maternity information system Badgernet Maternity and NNRD data (for babies admitted to NNU).

Relevant data items include time in hospital (time in triage/outpatient assessment, time in antenatal ward, time to and in labour ward, high dependence unit, intensive

care, etc), medications, hospital transfers, type of delivery (caesarean, vaginal, other operative), maternal complications (uterine hyperstimulation), as well as child related events such as perinatal mortality, neonatal complications (time in ward, neonatal intensive care unit, special baby care unit, etc). Resource use data will be combined with unit costs (30,31) to calculate the within study cost for each strategy.

Costs incurred by women and their families relating to IOL are relevant from the patient perspective and potentially important for the 'at-home' cervical ripening strategy. This data is not available from the observational datasets, and therefore tailored economic related questions have been incorporated into a process evaluation survey described in section 5 below. Through this we will gain data on patient related resource use and expenditures, e.g. number of trips and phone calls to unit, time, distance and mode of travel to and from hospital, birth partner role and time in hospital, time spent at home before admission, purchase of additional maternity items, additional expenditure on medications while at home, other visits to health care services that were made during IOL, and additional child care costs incurred (if any) while the mother is at home with IOL or in hospital. This will inform the resource use from the patient perspective.

To account for bias in the observational data methods such as multivariate regression and propensity scoring will be employed as recommended in guidelines for cost-effectiveness analysis based on observational data (32,33), which is consistent with the main study statistical analyses for this study. The within study analysis will include the primary study endpoint (NNU admission within 48 hours of birth for 48 hours or more) for a timeline up to one-month post birth, to capture any cost and morbidity events incurred in the neonatal period. Outcomes will be reported as the incremental cost per NNU admission avoided (in line with primary study outcome) as well as incremental cost per birth up to 28 days post-birth. We will assess the influence of missing data using appropriate sensitivity-type analyses, in line with the statistical analysis plan for the main dataset. If there is a large proportion of missing data (>10%), multiple imputation will be employed as per good practice guidelines. In line with the statistical analysis plan missing data will be imputed within each site separately, before analysis.

The lifetime analysis will account for longer term costs, quality of life and morbidity and disability from both the NHS & PSS and patient perspective and will report outcomes in terms of incremental cost per Quality Adjusted Life Years (QALYs) gained. If routine data allows, the lifetime model (or future analyses) could utilise data linkage to Hospital Episode Statistics (England), Scottish Morbidity Records and Patient Episode Database for Wales, to include more accurate estimates of long-term implications for operative pelvic floor repair, long term disability in children and future mode of delivery. Probabilistic sensitivity analysis will be undertaken to explore how uncertainty in the model inputs impact on the cost-effectiveness outcome (34).

5 PART 2: qCHOICE Process Evaluation

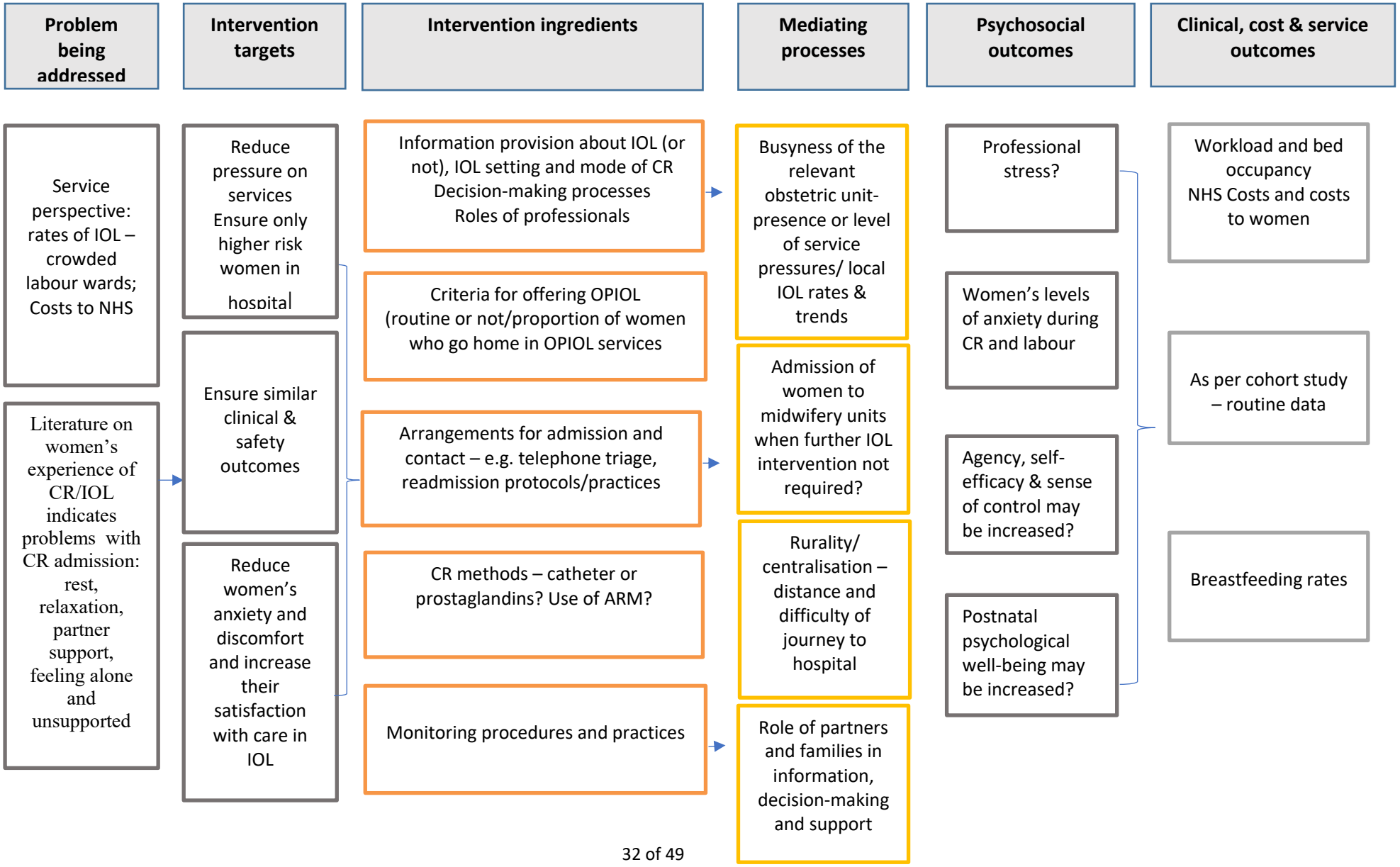
5.1 STUDY DESIGN

5.1.1 Design and theoretical/conceptual framework

We will undertake a questionnaire-based survey and case studies nested within the CHOICE observational cohort study. Both qualitative and quantitative data will be collected - specifically, a questionnaire, semi-structured interviews with women and birth partners, audio recordings of clinician/ women consultations, interviews and focus-group discussions with professionals. We will also ask sites to complete a COVID-19 Impact Assessment Form before they open to recruitment. This form will help to capture any changes in service provision in response to the virus, which will help contextualise our findings as services responded to the pandemic.

Figure 3 describes the initial process evaluation logic model that hypothesises the chain linking interventions and outcomes. This will inform data collection and analysis for the process evaluation.

Figure 3. Process evaluation logic model – V1 18/12/18



5.2 STUDY SETTING

The qCHOICE process evaluation questionnaire will be administered in at least 12 sites participating in the CHOICE observational cohort study. Case studies will be undertaken in five of the CHOICE observational cohort study sites.

5.3 STUDY POPULATION

5.3.1 Sample size

5.3.1.1 Survey sample

The sample size required to compare the experiences of women who had home and hospital cervical ripening is estimated to be 89 per group (178 in total) for a probability of type 1 error set at 0.05 for a two-tailed comparison and a 80% power. This is based on use of The Labour Agentry Scale (15) which will form part of the questionnaire where a change of 5.5 points is considered clinically meaningful. Mean LAS score for women having cervical ripening in hospital is estimated at 58 (standard deviation 13). Our previous experience of questionnaire-based surveys, and the UK's national maternity experience suggest a response rate of 40%, thus we will require to approach at least 445 women to achieve the required sample size. In order to ensure a sufficient number of responses from women eligible for home cervical ripening (those with uncomplicated pregnancies at 39 weeks gestation or more), who do and do not undertake this option (our principal comparison), we will invite a considerably larger number of women to complete the questionnaire survey. We will also report all responses in a descriptive analysis of women's experiences when undertaking IOL. As there have been no prior large-scale studies of women's experiences of an outpatient approach to cervical ripening, this presents considerable added value to the study.

We will invite all sites using the BadgerNet maternity portal (Badger Notes) to participate in the questionnaire-based survey; but they will be given the option of opting out of this part of the study. We will include at least 12 sites, i.e. a total of at least 43,200 births annually across the sites. With an estimated eligibility of 22% of all maternities having IOL at 39 weeks or more, and 15% of these having home cervical ripening. We will achieve our sample size within 4 months. We will monitor recruitment rates and if necessary extend the survey period to ensure the sample size is met.

5.3.1.2 Case study sample

The sample of five case studies is pragmatic and selection is designed to balance depth with breadth of information and analysis. The choice of case study sites forms a sub-study of the CHOICE sample of sites, to provide diversity and balance of service types on the basis of geography, service configuration and approaches to provision of IOL. Further sites will be added for qualitative data collection, using a theoretical sampling approach, if required to address emerging questions.

5.3.1.3 Qualitative sample

The sample sizes for the interviews, focus groups and recordings of visits are pragmatic and based on an estimation of numbers needed in a purposive sample to achieve data saturation. The sample is an estimation, based on typical sample sizes for enquiries of this type but will be increased where required to address specific and emerging questions. Further details of samples sizes for the different qualitative components of the study are given in section 6.3.

5.3.2 Inclusion criteria

For questionnaire-based survey

- Gestation 39+0 weeks or more
- Undergoing IOL

For case studies

- Gestation of 39+0 weeks or more

5.3.3 Exclusion criteria

For case studies

- Women who did not have IOL at 39+0 weeks of gestation
- Women who had IOL for medical reasons
- Women who had an elective cesarean section
- Women who have experienced intrauterine death, stillbirth or neonatal death

5.3.4 Co-enrolment

There will be no restriction on co-enrolment in other studies.

5.4 PARTICIPANT SELECTION AND ENROLMENT

5.4.1 Identifying participants

5.4.1.1 *Questionnaire-based survey*

Questionnaire data collection will take place early in the study over a 4-6 month period. We will invite all women at participating sites who use Badger Notes and who have IOL at 39 weeks gestation or more to complete a postnatal survey during this period. Sites will be given the opportunity to opt out of this aspect of the study – i.e. contribute routine data without recruiting women to the survey, but we anticipate receiving questionnaire data from at least 12 participating sites. At all participating sites women will be notified about the survey alongside general study information via posters, cards and information leaflets. Depending on usual clinical practice, women

will be invited to take part in the survey either through Badger Notes, or by invitation by a midwife.

(1) Women will be invited to take part either through Badger Notes, using their regular system of push notifications, or by invitation by a midwife (via a study card). We anticipate that the majority of women are able to opt out of push notifications on Badger Notes but monitoring of use indicates that a good proportion of women are using this and continue to access the portal postnatally, thus enabling a broad sample to be reached.

    Women who use Badger Notes will informed about the survey via a 'push or SMS notification' automatically sent to their accessible record when IOL is booked. The notification will direct them to view their maternity portal record which will contain a study leaflet providing brief information about the study and informing women that they will receive a second notification around 2-4 weeks after they give birth.

    A further notification will be sent 2-4 weeks postnatally, which will direct women to Badger Notes, which will contain a link to the study website where the participant information sheet, consent form and survey are held. Women will be able to request a postal version of the survey or to complete it via the telephone or with a translator if required. A reminder will be sent 2 weeks later and an additional reminder will be sent after a further two weeks if needed.

(2) In sites that are not using Badger Notes, or where engagement with the portal is poor, women may be invited to take part by a research midwife employed by the Trust/Board. The research midwife will select eligible women as per the criteria set out in section 5.3.2 and 5.3.3. Eligible women will be approached to take part, and given a study card which contains details of how to take part and the web address and QR code? for the online survey.

5.4.1.2 *Women and partner interviews*

As part of the questionnaire women will be asked to tick a box and provide their contact details if they give consent for a member of the research team to contact them regarding a possible interview. This will be on a detachable page, with linked questionnaire code to ensure that personal details of survey participants willing to be contacted further will be kept separately from survey responses.

5.4.1.3 *Key professionals, stakeholders and maternity professionals*

Key professionals and stakeholders will be identified with the support of the PI for each local case study service but will typically include: head of midwifery, clinical director, consultant obstetricians and midwives, chairs of local Maternity Voices Partnerships, representatives from local maternity service user groups and service commissioners or health board leads.

Both midwives and obstetricians will be invited to participate in focus group discussions. These will be organised to facilitate participation of a diversity of maternity professionals, by including in a local audit meeting or study day.

5.4.1.4 *Observations of maternity visits discussing IOL*

A small convenience sample of maternity visits will be included in each case study site in order to enable analysis of information provision and women's information needs.

5.4.2 Consent for participation study

5.4.2.1 *Questionnaires*

Eligible women will be approached to take part either via PUSH notification from Badger Notes or by invitation from a research midwife. Questionnaires will submitted online via Online Surveys https://www.onlinesurveys.ac.uk or posted and returned to University of Stirling or completed by phone with a member of the study team, with the support of an interpreter if needed.

The questionnaire landing page will include the consent questions, which women are asked to tick prior to completing and returning the questionnaire. It will include confirmation that the women have read the participant information sheet. A telephone number will be supplied for women to call if they have any questions about the survey or if they wish to complete it on paper or by telephone, to with an interpreter.

Women will have at least a week to consider their participation. Survey reminders will be sent as blanket notifications after two weeks. Participant contact details (telephone number or email address) provided by survey respondents who are happy to be contacted further about a possible interview will be on a detachable back sheet of the questionnaire or a separate online page. This page will also inform respondents that a £10 Love to Shop voucher will be offered to interview participants as a thank-you for the additional time spent.

5.4.2.2 *Women's Interviews*

A purposive sample of women who gave birth in one of the case study sites who have given consent for further contact on the questionnaire will be contacted by a study researcher to provide further information about the interviews. A sampling frame will be constructed within and across case study sites with the aim of including a balance of primiparous and multiparous women, women who were offered outpatient CERVICAL RIPENING but declined, women who experienced this and women who were not offered it. The sample size is estimated and will be guided by data saturation, but we anticipate interviewing between 10-15 women in each site (total 50-75 participants). The women approached will be given the opportunity to ask further questions and at least one week to decide whether to participate in an interview. For women who agree to participate in an interview, this will be arranged at a time and location of their preference (a private university or health premises room or at home). Written consent will be sought prior to the start of the interview. Verbal consent will be obtained if interviews are conducted over the telephone or on a video conferencing

platform (Microsoft Teams, Skype or Zoom). Verbal consent will be recorded and stored separately from interview data. Interviews will be either audio-recorded or recorded. No personal details of the participant will be included in the audio-recording and women will be asked to provide a pseudonym for themselves, if they wish to do this. Women who participate in interviews will be offered a £10 Love to Shop voucher as a thanks and acknowledgement of the additional time they have given to participation.

5.4.2.3 *Partner's Interviews*

All women who consent to participate in an interview will also be asked whether they give consent for their birth partner to be invited for interview. We anticipate interviewing between 10-15 women in each site (total 50-75 participants) and assuming that around half of participants may have a birth partner willing to participate we anticipate including around 25-38 birth partners. Partners will then be contacted and consented following the same process. If couples express a preference to be interviewed together, this will be accommodated. Birth partner will be defined by each woman invited to participate. Birth partners who participate in interviews will also be offered a £10 Love to Shop voucher as a thanks and acknowledgement of the time they have given to participation.

5.4.2.4 *Key professional/stakeholder interviews*

Key stakeholders may include: clinical directors, heads of midwifery, maternity commissioners, representatives from Maternity Voices Partnerships, consultant obstetricians and midwives. They will be sent a participant information sheet and given the opportunity to ask further questions. They will have at least a week to decide whether to participate and interviews will be arranged in a time, location and format which best suits each individual. Verbal or written consent will be taken at the start of the interview, by the researcher conducting the interview. Verbal consent will be recorded and stored separately from the interivew data. We anticipate undertaking around 10 individual interviews in each case study site.

5.4.2.5 *Professional focus group discussions*

Relevant professionals (midwives and obstetricians) in each site will invited to participate in focus group discussion and three focus groups comprising 6-8 participants (total 18-24 participants) will be held in each site. A participant information sheet for professionals will be distributed widely in case study services, supplemented by information posters about the study, at least a week before the focus group (usually at least two weeks in advance). Participants who attend for the focus group discussion will be given the opportunity to ask further questions at the outset and will be asked to complete a consent form or provide verbal consent before the focus group. All will be asked to respect the confidentiality of the discussion.

5.4.2.6 *Observations of maternity visits discussing IOL*

Up to five maternity professionals in each site will be provided with a digital recorder and given instructions on use and asked to record 3 consecutive interviews. Maternity professionals who conduct visits discussing IOL will be asked whether they consent to participate in this aspect of the study, via participant information sheets and posters. Each will have at least one week to decide and will then be asked to sign a consent

form for a short series of audio-recordings. Professionals will be asked to ensure that the audio-recording is commenced after any personal details are given, so that the recordings are anonymous. Prior to each relevant visit in a 'recording' clinic, the woman and accompanying persons will be asked whether they consent to the anonymous recording of the visit, followed by a brief (up to ten minute) interview to explore their understanding of the information provided. They will be given a specific participant information sheet and opportunity to ask questions of the researcher, who will be present in the clinic to support professionals with any questions about recording and to undertake the brief follow-up interviews. This will be done during time waiting for the visit, so potential participants will only have a short time to decide whether they consent to the recording as this is the only practicable approach. However, the main focus of the recording is on how professionals provide information to women and partners about IOL and their options, so the woman and her partner, where present, will not be the focus of the observation. All recordings will be anonymous. The brief follow-up interviews will be conducted in a private clinic room.

5.4.3 Withdrawal of Study Participants

Participants are free to withdraw from the qCHOICE process evaluation. Participants who withdraw will be able request their data are withdrawn subject to certain practical limitations, as follows.

Women who do not return the survey questionnaire will not be included in interviews. Women and their partners who return the questionnaire and give consent for further contact may still choose to decline the offer of an interview. It will be explained to participants that survey responses will not be withdrawn after study withdrawal if data analysis has already been conducted and likewise, interview transcripts will not be withdrawn after data analysis has commenced but will not be used to provide any quotations for study reports. Withdrawal of data for audio-recordings of visits can only be offered until the point the woman leaves the clinic as all recordings will be anonymous. The terms of withdrawal will be set out in the participant information sheets.

Key stakeholders and professionals will be able to withdraw from the study at any point. However, it will be explained that their interview data will not be able to be withdrawn after data analysis has commenced, although use of specific quotations can be excluded. Professionals will be able to decline participation in focus group discussions at any point up to and including the discussion, but will not be able to withdraw consent to use of focus group data following the focus group as no identifiers of participating professionals will be used and it will not be possible to extract their data from the recordings. Professionals will be able to withdraw consent to use data in recorded visits at any point during the relevant clinic, but it will be explained that withdrawal of data following the clinic will not be possible as the data will be anonymous.

5.5 DATA COLLECTION

5.5.1 Postnatal questionnaire- based survey of women's experiences and psychosocial outcomes

A postnatal survey of women who have experienced labour induction will be conducted to assess differences between setting +/- method of cervical ripening in terms of women's satisfaction, experience, and psychosocial outcomes. A consecutive sample of women who had any form of IOL involving cervical ripening, will be invited to complete the survey online or by post around 6 weeks postnatally. The questionnaire will comprise validated tools plus a small number of questions relating to service user costs, and some information about their IOL as follows:

1. The Labour Agentry Scale (short form) (16). The LAS is a well-established, validated measure of women's experience during labour and birth. The LAS measures perceived control during labour, which is the woman's sense of mastery over internal and environmental factors. The LAS score is highly correlated with satisfaction with care.

2. A modified version of the IOL satisfaction questionnaire (17) tested in the PROBIT-F trial [co-investigators' pilot RCT of home cervical ripening with balloon catheter vs dinoprostone NCT03199820]. This questionnaire focusses specifically on women's experiences of aspects of labour induction including information, anxiety and physical and emotional discomfort.

3. The Warwick-Edinburgh mental wellbeing scale WEMWBS (18). A 15 item (7 item short form) scale that measures mental wellbeing (as opposed to mental illness or disorder) representing positive attributes of wellbeing including feeling and functioning. WEMWBS addresses women's psychosocial outcomes. The 7-item short form will be used.

4. Additional questions which will inform the economic analysis from the patient perspective will cover patient related resource use and expenditures of CERVICAL RIPENING for women including number of returns and phone calls to hospital, time distance and mode of travel to from hospital, partner role, additional expenditure on maternity items and medication while at home, and additional childcare expenditure (if any) while at home. The questionnaire will include a question asking women to provide consent for data linkage of their survey with their clinical record and whether they would be willing to be contacted regarding possible participation in a semi-structured interview.

5. Women will be asked to provide their EDD; baby's DOB; baby's birthweight; the maternity unit where they gave birth; first method of cervical ripening used (prostaglandin, cervical ripening balloon), setting of cervical ripening (home or hospital). These variables are necessary for analysis and linkage to clinical record (if consent for linkage is provided).

5.5.2 Qualitative interviews with women/ partners and other key stakeholders

We will undertake semi-structured interviews with key stakeholders including women and birth partners and maternity professionals. These will be conducted by study researchers, and either audio-recorded or recorded on a video conferencing platform (Microsoft Teams, Zoom or Skype). No standardised tools will be used but a topic guide

and a care pathway visual map will be used to help guide and focus the discussion. Participants will be asked to adopt a primarily narrative approach, however, to recount the story of their induction, labour and birth experience, with focused questions introduced as prompts only when needed.

Maternity professional's interviews will explore how different IOL modes and protocols are applied by services and explore the acceptability of in or outpatient approaches to IOL from the service provider viewpoint. The interviews will involve mapping and discussion of local IOL pathways capturing the procedures and interactions involved with different services and staff. IOL pathways will initially be mapped for each site using local protocols and information gathered during the first few interviews with care professionals. The pathways will then be discussed and refined in subsequent interviews. Our previous research (19) has found that using care pathway maps can provide a focus for discussion, in particular of ways in which the ideal clinical pathway unfolds in real life practice at specific time points. Using the pathways in interviews with women and partners may also be useful in focusing discussion and assisting recall of particular aspects of their labour and birth experience, exploring experiences and feelings at specific points. This may be particularly important in exploring aspects of events that occurred in early or pre labour that may otherwise be overshadowed by subsequent birth experiences.

Interviews with professionals/stakeholders will be focused on perceptions about the service approach to induction, to information for women and their thoughts about the facilitators and barriers to using an outpatient approach to cervical ripening (to introduction in services not providing this or to increase in use in those providing at a limited level. Interviews will explore how local cervical ripening protocols have been implemented in practice, staff's experience of providing care. Focus group discussions will use a similar approach and will also focus on description of the service approach and will add the additional dimension of discussion between professionals about the service approach.

Individual interviews with stakeholders and senior professionals will be semi-structured, conducted face-to-face, on a video conferencing platform (Microsoft Teams, Zoom or Skype) , or by telephone and audio-recorded. Focus group discussions will be conducted with midwives and with obstetricians either on a video conferencing platform (Microsoft Teams, Zoom or Skype), or face-to-face. Where possible focus group discussions may be integrated within an audit meeting or training event to ensure a cross-section of professionals is included.

Interviews with women and birth partners will take place around 8-12 weeks postnatally and will be conducted face-to-face, on Microsoft Teams or Skype or by telephone. Research has shown that women have good recall of events and feelings relating to labour and birth even long after the birth, and this will be assisted by using pathway maps as a focus and to prompt discussion of feelings and experiences at specific time/ event points related to cervical ripening and IOL. Questions will explore the acceptability of in- or outpatient approaches to IOL, identify what information and outcomes are important for pregnant women and their partners and explore their experience of cervical ripening in a home or hospital setting. Our previous research on women's experience of early labour and of labour induction has highlighted the important role of birth partners and other family members therefore we will aim to include them in interviews where possible. However, some women may not have a

close family member or birth partner who is available for interview and this will not be a prerequisite for participation. In addition, consent for partner participation will be sought initially via the postnatal woman, giving the woman the opportunity to decline if she prefers that her birth partner is not contacted.

5.5.3 Audio observations and linked interviews

To provide more in-depth understanding of acceptability of home cervical ripening, and of the discussion and decision-making processes involved in potentially offering home cervical ripening to women we will audio record a sample of antenatal consultations between obstetricians or midwives and women/partners in which IOL will be discussed. Following the recorded consultation brief interviews (around ten minutes) will be conducted with women and partners involved, with their consent to explore their understanding of the information provided. The recordings will enable analysis of information provision to women about IOL and the different options available. The subsequent interviews will enable more in-depth exploration of information provision, decision making about IOL from the woman and her partner's perspectives. Audio recordings will be described and analysed thematically.

5.6 DATA MANAGEMENT

5.6.1 Personal Data

Women who choose to do so will complete a survey via Online Surveys http://www.onlinesurveys.ac.uk/. Women who request a postal survey will be required to provide their address.

Some women will provide further details on completion of the survey, for follow-up with researchers about possible interviews. These personal data will be maintained in a securely locked file separate from data files.

No personally identifying data will be kept for women or partners involved in visit recordings.

Professional participants personal data (usually email address and/or telephone number) will be kept for purposes of arranging interviews). No personal data of professionals participating in focus group discussions or visit recordings will be made, but notes will be made of professional category (midwife or obstetrician) and grade.

Personal data for all qualitative components will be stored by the research team at City, University of London. Survey data will be maintained on a database in the secure research server at the University of Stirling. The data management, retention and archiving policies of each respective university will be followed.

Personal data will be stored in accordance with the respective. University guidelines but will normally be retained in anonymised form for a minimum of ten years. Audio-recordings will be destroyed one year following study completion but copies of transcripts will be archived securely.

5.6.2 Transfer of Data

Anonymised qualitative and survey data will be transferred between the University of Stirling and City, University of London for anlaysis.

5.6.3 Data Controller

The University of Edinburgh and is the data controller.

5.6.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh Data Protection Officer who will onward report to the relevant authority according to the appropriate timelines if required.

5.7 STATISTICS AND DATA ANALYSIS

5.7.1 Survey analyses

Quantitative data: Survey data will be exported to Stata and analysed using descriptive and inferential statistics. Descriptive statistics with 95% confidence intervals will be reported for the total sample (by planned mode of cervical ripening – home or hospital, and by actual mode (as some women who plan one mode may in practice have a different mode) and by case study site. We will examine whether there are statistically significant differences in the primary outcome of sense of control (labour agentry) and by psychosocial outcome of postnatal psychological wellbeing score (WEMWBS) between women with home cervical ripening and women with in-hospital ripening. The covariates included will be clinical reason for IOL, gestational age, maternal age, parity, maternal BMI at booking, sociodemographic status, ethnic group and smoking status at booking.

In addition to anticipated outcomes (see logic model) the case studies will aim to capture unintended and unanticipated effects, whether positive or negative. These may occur at the organizational or individual level and could include issues such as normalization of IOL with outpatient approaches such that professional information giving or procedures change in ways that are not documented or planned clearly; changes in risk concepts or management.

5.7.2 Qualitative analyses

All qualitative data will be transcribed and entered into the analysis support software NVivo to support data management and analysis. Documentary sources will be added to the NVivo project file as PDF files. Visual models will be developed to support the discussion and analysis of the pathway and network maps using Visio. The Visio tool supports the development of a set of icons pertinent to maternity care providing a coherent, accessible language to describe the various steps in the care system and their interactions. Recordings of discussions will be analysed using a structured approach to conversation analysis. Interviews with women, partners and health professionals will be transcribed and analysed using a thematic framework approach, based on frameworks developed in recent work by the study team (PROBIT-F).

6 ADVERSE EVENTS

This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP), but an observational study of care carried out according to local policies and procedures so adverse events will not be formally reported.

However, it is possible that in recalling labour events during interviews, participants may experience some distress, or reveal concerns about the care provided. All participants will be reminded of the confidentiality of data collection in CHOICE and will be offered information about where to seek further advice, if appropriate. If any participant reveals signs of psychological distress or post-traumatic stress disorder, they will be advised to seek the support of their General Practitioner and Health Visitor.

7 OVERSIGHT ARRANGEMENTS

7.1 Inspection of records

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

7.2 Study monitoring and audit

The sponsor representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the sponsor Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the sponsor QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

8 GOOD CLINICAL PRACTICE

8.1 Ethical conduct

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

8.2 Investigator responsibilities

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

8.2.1 Informed Consent

The Investigator is responsible for ensuring that reasonable steps have been taken to inform women about the CHOICE study and that they are given the opportunity to opt out of data provision; and to ensure that data from women who have opted out of data provision will not be extracted from site or analysed.

Consent to participate in any aspect of the process evaluation study will be informed and voluntary. All participants will be provided with a relevant participant information sheet and written consent will be taken. In the case of the women's postnatal survey, consent will be managed via completion of consent questions on the first page of the questionnaire completed by the participant and returned by post or submitted online.

In all cases, information will be provided at least one week prior to seeking consent. The exception to this will be the recording of a small number of visits during which IoL is discussed. For pragmatic reasons, women will be asked for consent to recording of the visit while waiting for their appointment, shortly before the visit. However, the focus of these recordings is not on the woman and her birth partner but on the information provision by the professional providing care.

Written participant information sheets will in all cases be accompanied by the offer of verbal explanation and the researcher contact details will be provided for any further questions. In addition, posters about the study will be present in the case study maternity sites.

8.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their study related duties.

8.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded at each Investigator Site.

8.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files.

8.2.5 GCP Training

A GCP Certificate should be provided at the start of the study, if available, for all staff detailed on the delegation log. Although GCP is not a requirement for a non-CTIMP (i.e. non-drug) study, it is preferred that this is undertaken by the investigator and delegated team members prior to, or immediately after, the start of the study. All researchers are encouraged to undertake GCP training in order to understand the principles of GCP. GCP should be updated as per local requirements; when updates are undertaken, a copy of the certificate should be provided to the trial manager.

8.2.6 Confidentiality

All reports, and other records, must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access.

The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study.

Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

8.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords and will be encrypted.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place.

9 STUDY CONDUCT RESPONSIBILITIES

9.1 Protocol amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC and IRAS for approval prior to participants being enrolled into an amended protocol.

9.2 Protocol violations and deviations

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsor and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log maintained by sites and reviewed by the Trial Manager at specified intervals. Each protocol violation will be reported to the sponsor within 24 hours of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

9.3 Serious breach requirements

A serious breach is a breach that is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the sponsor (qa@accord.scot) must be notified within 24 hours.

It is the responsibility of the sponsorto assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

9.4 Study record retention

This is a study involving pregnant women and research records should be retained according to NHS guidelines for the retention of documentation involving pregnant women. All medical records will be retained for at least 25 years, where possible, after publication of the final study report. Guidelines on retention of other research related documents are continually under review. We plan to retain all documents for 5 years and then review according to current guidance at that time.

9.5 End of study

The end of study is the date that the baby of the last participant is discharged from NNU, or 30 days following the birth of the last participant's baby (whichever is earlier).

The end of study is defined as the completion of the last participant's questionnaire or interview.

The Investigators or the sponsor have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

9.6 Insurance and indemnity

The sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the sponsor responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The sponsor require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

- Sites will have the benefit of NHS Indemnity.

10 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

10.1 Authorship policy

Ownership of the data arising from this study resides with the Co-investigators and any others who fulfil the criteria for Authorship as determined by the Chief Investigator. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with GCP guidelines. Further details are given in the CHOICE publication and dissemination policy.

11 REFERENCES

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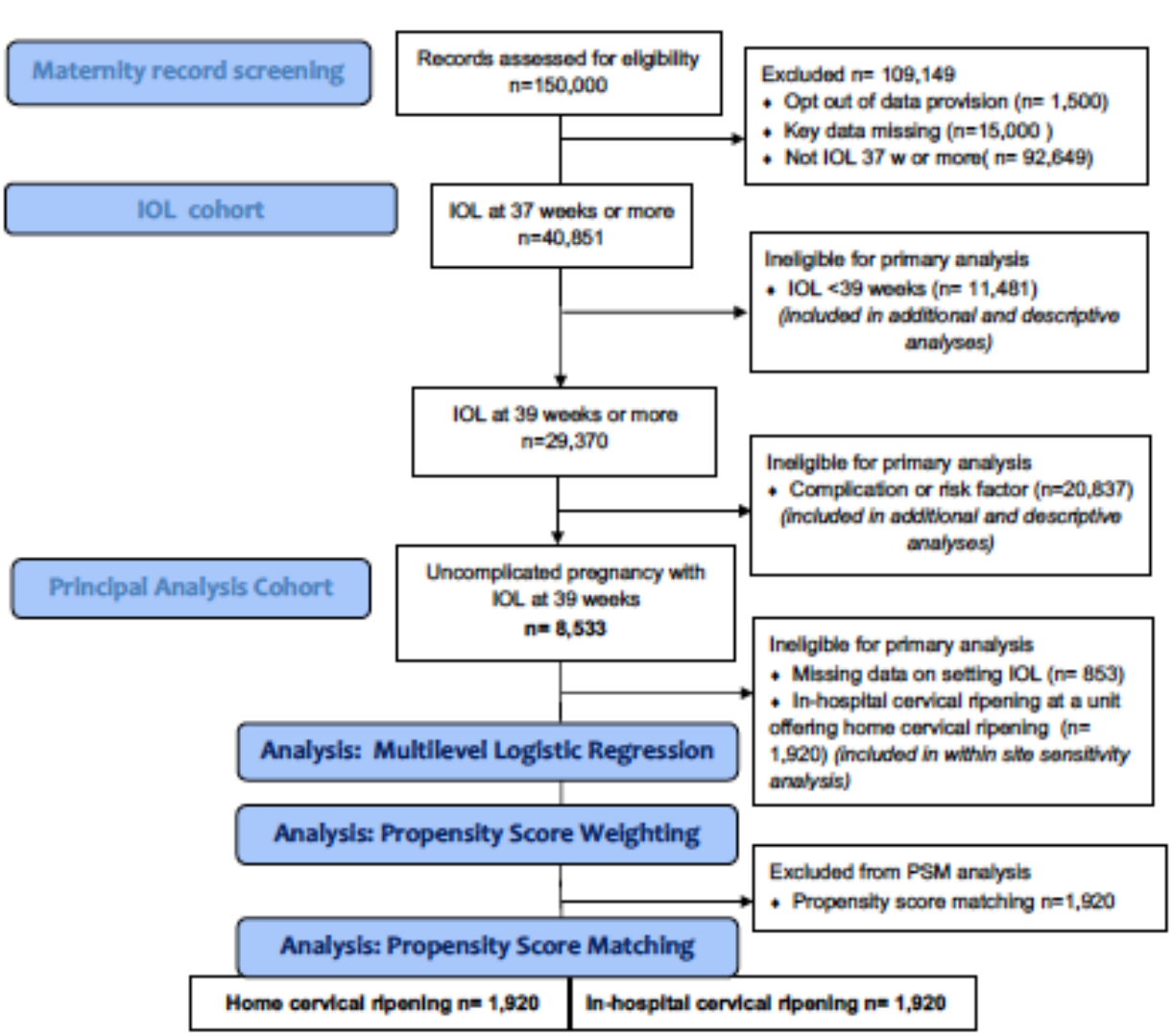
12 APPENDICES

12.1 APPENDIX 1 – FLOW CHART



Assumptions:
26 sites with 90,000 births pa
1% opt out from data
10 % data missing at screening stage
30.6% maternities IOL 37 weeks or more
22% maternities IOL 39 weeks or more *(data from NMPA 16/17)*
10% missing data on setting
29% of IOL 39+ weeks uncomplicated/suitable for home cervical ripening
50% of IOL 39+ weeks in centres offering home cervical ripening have home cervical ripening

12.2 PROJECT / RESEARCH TIMETABLE

- Months 0-6: Contractual agreements; development of study SOPs and materials; ethical approval and other approvals obtained (NRS, CSP, Caldicott); TSC appointment and meeting; test and refine data collection and transfer; confirmation and opt in of participating sites; submission of study protocols for publication.

- Months 6- 26: Data collection for prospective cohort; monthly data checks and feedback to sites; process evaluation

- Months 12-14: NNRD data download and linkage; analysis of pilot data and assessment according to stop/go criteria; database closed

- Months 27-30: Outcome data collection and queries; NNRD data linkage and download; finalise statistical analysis plan

- Months 30-36: Study closure, analysis, write up and dissemination; submission of report to HTA and publication of results