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Protocol and statistical analysis plan for the POOL study: establishing the safety of waterbirth for mothers and babies: a cohort study with nested qualitative component

Trial registration: ISRCTN registry [ISRCTN13315580](https://www.isrctn.com/ISRCTN13315580). Registered on 04 May 2018

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Abstract

Introduction: The POOL Study is a cohort study with a nested qualitative component examining the safety of waterbirths among women who are classified appropriate for midwifery-led intrapartum care.

Methods and Analysis: Data will be collected on 30,000 mother/infant dyads captured in electronic maternity and neonatal systems. The primary objective is to establish whether for low-risk women who use a pool during labour, waterbirth, compared with leaving a pool prior to birth, is as safe for mothers and infants. The maternal primary outcome is the rate of Obstetric Anal Sphincter Injury and for the infant, a composite of 'adverse infant outcomes or treatment' including: any neonatal unit (NNU) admission requiring respiratory support, antibiotic administration within 48 hours of birth, and intrapartum stillbirth or all deaths prior to NNU/postnatal ward discharge.

Two study populations will be used to address two clinical questions, reflecting the effect of waterbirth in both a 'real life' and 'pure' risk scenario. The maternal and infant populations will be characterised. For both maternal and infant primary outcomes, logistic regression models will be run and non-inferiority established at the 5% (one-sided) level, if the upper limit of the confidence interval for the difference between groups is below the margin. Continuous secondary outcomes will be analysed using linear models and count data analysed using Poisson models. Both crude and adjusted effect estimates will be presented, with the primary inference based on the adjusted estimates.

Ethics and Dissemination: The protocol has been approved by NHS Wales Research Ethics Committee (18/WA/0291); the transfer of identifiable data has been approved by Health Research Authority Confidentiality Advisory Group (18CAG0153). Study findings and methodology will be disseminated through peer-reviewed journals, conferences and events. Results will be of interest to the general public, clinical and policy stakeholders in the UK and will be disseminated accordingly.

Strengths and limitations of this study

- Using large retrospective and prospective datasets concomitantly provides six years data over a three year study period.
- Ability to look at all neonatal outcomes across a wide geographical range.
- Allocation is not random, so unmeasured confounding is possible.
- Rich maternal and neonatal characteristics to measure potential confounding of outcome.
- Study populations can be defined to address two clinical questions, reflecting the non-inferiority of waterbirth in both ‘real life’ and ‘pure’ risk scenarios.

Introduction

This paper details the proposed presentation and analyses for the main paper reporting results from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (Project number 16/149/01) funded multi-centre cohort study to establish the safety of waterbirth for mothers and babies among women who are classified appropriate for midwifery-led intrapartum care (The POOL Study) (1). This plan conforms to the published guidelines on the content for SAP in clinical trials and was finalised prior to completion of data collection from sites. Any deviations from this plan will be described and justified in the final report of the trial (2). The SAP is published and publicly available on the Open Scientific Framework (OSF) website: <https://osf.io/kwj53>. This manuscript was prepared by the trial statistician in accordance with Strengthening The Reporting of OBservational Studies in Epidemiology (STROBE) checklist (Supplementary table 1) (3).

Note on terminology

We use the terms ‘women’ and ‘mother’ throughout the document, but this document will also apply to people who do not identify as women and who are pregnant or have given birth.

Background information

In 1992, the House of Commons Health Committee recommended that hospitals should provide women with the use of a birth pool for labour ‘where this is practicable’ (4). In the intervening years the popularity of the use of water immersion for labour and birth in the UK has increased and the National Institute for Health and Care Excellence (NICE) guidance has recommended since 2007 that water immersion analgesia should be made available to all clinically appropriate women in labour (5).

The Cochrane review of water immersion during labour provided evidence supportive of pool use but could not answer the question relating to the safety of waterbirth or safety of delivery of the placenta into water (6). The review included 12 trials (3243 women), eight related to just the first stage of labour: one to early versus late immersion in the first stage of labour; two to the first and second stages; and another to the second stage only. Results for the first stage of labour found a significant reduction in the epidural/spinal/paracervical analgesia/anaesthesia rate amongst women allocated to water immersion compared to no immersion (478/1254 versus 529/1245; risk ratio (RR) 0.90; 95% confidence interval (CI) 0.82 to 0.99, six trials). There was also a reduction in duration of the first stage of labour (mean difference -32.4 minutes; 95% CI -58.7 to -6.13). There was no evidence of a difference in the rates of assisted vaginal deliveries (RR 0.86; 95% CI 0.71 to 1.05, seven trials), caesarean sections (RR 1.21; 95% CI 0.87 to 1.68, eight trials), use of oxytocin for augmentation (RR 0.64; 95% CI 0.32 to 1.28, five trials), perineal trauma or maternal infection. Of the three trials that compared water immersion during the second stage with no immersion, one trial found a significantly lower level of maternal satisfaction with the birth experience out of water (RR 0.24; 95% CI 0.07 to 0.80).

The outcomes for infants following waterbirth has more recently been reported in a systematic review of 29 studies (7). Whilst the review found no evidence of a difference in clinically important infant outcomes for infants born in water, it concluded that a large multi-centre study to address the question of the safety of waterbirth for infants is now a priority. Whilst there is sufficient evidence-based information and clinical guidance for women and clinicians to make appropriate decisions and recommendations about labouring in water, there is a distinct lack of evidence to inform decision making with regards to giving birth in water.

Objectives of the study

The primary objective is to establish whether for low risk women who use a pool during labour, waterbirth, compared to leaving a pool prior to birth, is as safe for mothers and infants. The secondary study objectives will set pool use and waterbirth in the context of NHS care. The study will establish:

1. The overall proportion and characteristics of women who use a pool for labour or birth, compared to those who do not use a pool.
2. The characteristics of, and outcomes for, women with identified risk factors at labour onset, who use a pool during labour.
3. The characteristics of and outcomes for, women who develop labour complications who use a pool during labour.
4. Factors associated with rates of pool use in individual maternity units.

Design

A natural experiment using a cohort design will answer study objectives using a combination of retrospective and prospective data in electronic NHS maternity and neonatal information systems.

Definitions of primary and secondary outcomes

Primary outcomes: The study has two primary outcomes.

The maternal primary outcome will be OASI. Such trauma is important to women and the NHS as it requires more complex repair and follow-up, and is associated with short term morbidity (pain, infection, incontinence) as well as longer term morbidity; (dyspareunia, urinary and faecal incontinence, future caesarean section).

The infant primary outcome will be composite of ‘adverse infant outcomes or treatment’ to include:

- (a) Any neonatal unit (NNU) admission requiring respiratory support;
- (b) Intravenous antibiotic administration within 48 hours of birth (with or without culture proven infection); and
- (c) Intrapartum stillbirth or all deaths prior to NNU/postnatal ward discharge.

Such outcomes are important as they cause distress to parents, are associated with potential long term damage to infants and with cost to the NHS. Composite infant outcomes combining mortality and morbidity are credible and provide more power to detect differences between groups, but the level of incidence of individual components will remain insufficient to detect differences in each outcome.

Secondary outcomes measure(s): Secondary outcomes of parental, clinical and financial importance have been identified. Data relating to maternal or infant readmission to hospital within seven days of birth are already reported by community midwives and captured in Wellbeing Software’s E3 systems at the point of discharge from midwifery care. Data relating to some primary and secondary outcomes are not currently captured in Wellbeing Software’s E3 maternity information systems and at site opening the Wellbeing Software’s E3 systems at sites will be amended to prospectively collect these data.

Maternal secondary outcomes:

Maternal Intrapartum:

- Shoulder dystocia and required management,

- Management of the third stage of labour (whether the placenta was intended to be, or delivered in or out of water),
- Obstetric involvement in care (including sepsis, treatment for haemorrhage),
- Incidence and management of perineal trauma,
- Maternal position at birth.

Maternal Postnatal:

- Duration of postnatal stay,
- Breastfeeding (initiation and continuation),
- Need for higher-level care,
- Maternal readmission to hospital within seven days of birth.

Infant secondary outcomes:

- Timing of cord clamping,
- Apgar scores (1, 5 and 10 minutes),
- Cause of intrapartum stillbirth or death prior to NNU/postnatal ward discharge,
- NNU admission requiring respiratory support,
- Antibiotic administration within 48 hours of birth (with/without culture proven infection),
- Intrapartum stillbirth or neonatal death prior to NNU/postnatal ward discharge occurring within seven days of birth,
- Neonatal resuscitation,
- Snapped umbilical cord prior to clamping,
- Skin-to-skin contact at birth,
- First breastfeed within first hour,
- Culture proven infection,
- Brachial plexus injury,
- Treatment for jaundice,
- Readmission to hospital within seven days of birth,
- Receipt of therapeutic hypothermia,
- Neonatal unit admissions,
- Respiratory support.

A further set of secondary outcomes were piloted at one site including highest C reactive protein (CRP) results, successful/attempted lumbar puncture and blood culture positive with a recognised pathogen (excluding skin commensal organisms). Data collection was successful and included in the dataset for all sites.

Hypothesis framework

This is a non-inferiority study and all comparisons will be analysed and presented on this basis.

Sample size and power

The non-inferiority of birth in water compared to birth on land on rates of OASIS will be examined by parity. The Birthplace in England study found that overall 4.6% and 1.6% of nulliparous and parous women respectively, sustained OASI (8). A sample size of 15,000 nulliparous and 15,000 parous low risk women (7,500 each water and land) is required to obtain 90% power, and a 95% one-sided confidence interval around a treatment difference of zero. A non-inferiority margin of 1% or

less, and 0.6% or less will be taken as clinically non-significant amongst nulliparous and parous low risk women respectively. Since nulliparous women birthing in water are regarded as the least prevalent of the four groups, a data collection period providing data on 7,500 would ensure adequate numbers in the other three, more prevalent groups.

These data will be combined to assess the effects averaged across both strata at an increased power, with a combined required sample size of 30,000 low risk women. We have assumed that 25% of the 6,600 waterbirths recorded in E3 in 2015 were nulliparous women (1650/annum). Allowing for staggered site set-up, six years of combined retrospective and prospective data collection would be required (January 2015 to June 2022). The exact ratio of nulliparous and parous women who give birth in water will be determined once the retrospective data are examined, but with increasing numbers of waterbirths, with 18 of the 35 E3 using sites, collectively undertaking 6,037 waterbirths in 2016, we are confident the study will have sufficient power to answer this important clinical question.

For the infant primary outcome, an estimate of 5% is used for the proportion of infants born to low risk mothers experiencing 'adverse infant outcome or treatment' (9). A non-inferiority margin of 1.0% or less will be taken as clinically non-significant. A sample size of 16,200 infants (8,100 per group water / land) are required to have 90% power, and a 95% one sided confidence interval around a treatment difference of zero.

Data collection

To answer the research questions, two datasets are used, extracted from Wellbeing Software's maternity information systems and the National Neonatal Research Database (NNRD).

1. Wellbeing Software's Maternity Information System, "E3", forms a comprehensive clinical data set and is currently used by 35 maternity NHS Trusts and Health Boards in the UK.
2. All 200 neonatal units in England, Wales and Scotland form the United Kingdom Neonatal Collaborative (UKNC) and contribute electronic health record data to the NNRD from 2014 to present (10,11). The NNRD is a national resource formed of the Neonatal Data Set (an NHS Information Standard), comprising 450 clearly defined variables extracted at patient level from the commercial Electronic Health Record used by all UK neonatal units (12).

To provide necessary denominator data, and to be able to compare characteristics of pool and non-pool users, a minimal data set will be extracted relating to women who did not use a pool in labour, whilst a more extensive dataset will be extracted for women who did use a pool in labour. An important clinical question is whether there is a differential effect of waterbirth on severe perineal trauma (OASI) amongst nulliparous and parous women. To undertake this subgroup analysis will require a necessarily large sample (N=30,000). As data relating to perineal trauma and waterbirth are already captured, and to avoid unnecessarily prolongation of the study, this analysis will use a combination of retrospective and prospectively collected data, including births from January 2015 to June 2022.

The sample required for the infant primary outcome is smaller (N=16,200) and, as all essential data are not currently collected for one component of this composite outcome (antibiotic administration within 48 hours of birth on postnatal wards) additional data fields will to be added to maternity systems at participating NHS sites. Therefore, we will collect these data on births prospectively during the period from site opening (around June 2018) to June 2022. Some infant outcomes of

interest, including hypoxia, respiratory support or mortality, are already held by study sites or by the NNRD. Where available and where the risk status, and pool usage of mothers can be determined, retrospective data will be utilised to increase the power of the analysis around secondary infant outcomes.

Data linkage and handling: To obtain detailed treatment and outcome information on any infant who required admission to a neonatal unit, following their mother's pool use in labour, the identifiers (NHS number) of all infants born to women who used a pool during the period of prospective data collection will be extracted and matched to any records held by the NNRD. Data will be received from Wellbeing Software and the NNRD at regular intervals and processed by the data manager. Cardiff University will receive only pseudonymised data.

Study population

Inclusion criteria: All women who meet NICE criteria for being at low risk of complications who use water immersion during labour as recorded from NHS maternity services using Wellbeing Software's E3 Maternity Information System between January 2015 and June 2022 are eligible (Figure 1).

Exclusion criteria: Data from women who opt out from the study will not be received. We will exclude women and infants recorded in E3 as being 'Born Before Arrival' (BBA), or recorded as freebirths. Women who do not use a pool (Group 5) are also excluded but will be described, as will women who used a pool but are not at low risk of complications (Group 4).

Defining the use of water

To capture data relating to women who use any form of water immersion during labour 'use of a pool' during labour, will pragmatically be any women for whom water immersion analgesia is recorded in Wellbeing Software's E3 system.

Defining women at 'low risk' of complications at the commencement of labour and use a pool during labour

The criteria of 'low risk' is one of exclusion of known risk factors; the NICE Intrapartum Care Guidelines will be used to identify these conditions (13). The intrapartum guidelines provide information on conditions that, if present, should be regarded as an indication to either advise birth in an obstetric unit, or that suggest individual assessment should be undertaken prior to making a recommendation on the planned place of birth. The guidelines do not specifically relate to use of a pool for labour or birth. Supplementary table 2 and supplementary table 3 lists medical conditions or situations in which additional observation or care would be recommended in an obstetric unit for the woman or baby during or shortly after labour, to reduce associated risks. The factors listed in Supplementary table 4 and supplementary table 5 are not reasons in themselves for advising birth within an obstetric unit, but indicate that further consideration of birth setting may be required.

Existing historic E3 fields (data between study start and end -January 2015 to June 2022) completed during the pregnancy, mapped to the NICE guidelines, and fields completed by the midwife following birth, but relating to the point of pool entry (from site opening in ~2019) will both be used to identify women with an identified risk factor. Women with identified risk factors will form Group 4, irrespective of whether they gave birth in water or not (Figure 1). Those with no risk factor identified in the antenatal records/or by the midwives at the time of pool entry will form Groups 1, 2 and 3.

Classification of risk may differ between these two sources:

- risk classification categorisation based on the existing E3 antenatal fields is likely to provide a lower threshold for risk, potentially identifying women who experienced a complication in the past or during pregnancy, but for whom this was no longer present at pool entry, e.g. a woman with an episode of hypertension during pregnancy, but who is later normotensive.
- risk classification categorisation used by the midwife at pool entry is likely to provide a more pragmatic definition and reflects the opinion of the midwife providing intrapartum care.

For all outcomes, risk will be defined using a combination of the existing historic E3 fields/ completed by the midwife following birth to ensure a consistent definition of risk in study populations across all outcomes. However, consideration of the potential differences in risk classification will be reflected by running sensitivity analyses based on the midwives' assessment at pool entry.

For women who gave birth prior to site opening, for whom the risk classification question relating to the time of pool entry is not available, if there is any record of risk factor in the antenatal notes, the woman will be classified as 'high risk' (Group 4).

For women who gave birth after site opening, if risk factors that cannot change over time are recorded in the antenatal notes, the woman will be classified as 'high-risk' regardless of whether this was also identified by the midwife providing intrapartum care, e.g. a previous caesarean section.

For women who gave birth after site opening, if risk factors that can change over time are recorded in the antenatal notes, but not identified by the midwife providing intrapartum care, the woman will be classified as 'low-risk' e.g. hypertension, suspected macrosomia.

Defining women who leave, or do not return to the pool due to a clinical need (a complication developed during labour with interventions that could not have been provided in the pool) – Group 3

Women leaving the pool due a clinical need i.e., develop a complication during labour, or by their own choice but subsequently developed a complication, will move to Group 3. These include women who received interventions including:

- caesarean section or instrumental birth,
- syntocinon augmentation of labour,
- pain relief incompatible with use in water (e.g., epidural, remifentanyl, pudendal block).

Defining women giving birth in water (Intervention - Group 1) or Women leaving the pool to give birth (Comparator – Group 2)

Intervention - Group 1

The primary study aim is to establish whether for low risk women who use a pool during labour, waterbirth, compared to leaving a pool to give birth (Group 1 vs Group 2 respectively), is as safe for mothers and infants. We will identify Group 1 - women who give birth in water, by using the Waterbirth field in E3.

To capture births commenced in, but completed, out of water, such as in the event of shoulder dystocia or previously unrecognised breech presentation, 'Waterbirth' will be defined in the study as 'A birth in which the fetus is partially or totally expelled under water'). This information will only be available from records after site-opening. For the period of data collection where this additional data

is not available, we will take any recording of waterbirth as such. We will examine rates of waterbirth using both definitions and be satisfied that there are no substantial differences.

Within this group will be mothers for whom staff recorded no clinical concerns prior to birth (Group 1a) but will also include women for whom staff recorded some clinical concern prior to birth (e.g. fetal heart rate concerns) but still gave birth to their baby in the pool (Group 1b). To identify women in Group 1b we will use a combination of existing fields (*'Maternal/Fetal intrapartum problems'*) and new E3 fields (*'Labour Complications'*).

Comparator group

Women who leave the pool prior to birth, will be categorised as having left either:

- a) due to their own choice and did not subsequently develop a complication (Group 2)
- or
- b) due to their own choice but who subsequently developed a complication prior to birth (Group 3).

Women leaving the pool due to their own choice who do not subsequently develop a complication prior to birth, will be allocated to Group 2 using a combination of new E3 fields (*'Left pool for vaginal examination/use bathroom and did not return'*, *'Maternal decision to leave pool and did not return'*, *'Left pool for further analgesia and did not return'*, *'Planned to labour but not give birth in water'*) and an absence of information in the existing E3 fields (*'Maternal/Fetal intrapartum problems'*).

Within Group 2 will be mothers for whom staff recorded no clinical concerns prior to birth (Group 2a) but will also include women for whom staff recorded some clinical concern prior to birth (e.g. fetal heart rate concerns) (Group 2b). To identify women in Group 2b we will use a combination of existing fields (*'Maternal/Fetal intrapartum problems'*) and new E3 fields (*'Labour Complications'*, *'Clinical reason for leaving pool or not getting back in'*) (including delay in 1st/2nd stage, abnormalities in fetal heart rate, meconium stained liquor, maternal pyrexia, tachycardia, or hypertension, breech presentation, or antepartum haemorrhage (APH)).

Women who leave the pool due to their own choice but who subsequently developed a complication prior to birth (making a pool birth contraindicated) can either remain in Group 2b (got out - some clinical concerns prior to birth) or move to Group 3 (got out due to clinical need). All women receiving obstetric interventions prior to birth will move to Group 3.

These two study populations will be used to address two different clinical questions, reflecting the intervention effect in both a real life risk and a pure risk scenario (table 1).

Table 1: Two study populations used in the analysis, alongside pros and cons.

Study population	Primary population	Sensitivity population
	Groups 1b and 2b* will remain in analysis	Group 1b and 2b excluded from analysis
Scenario	Reflects 'real life' practice	Reflects 'pure risk' of waterbirth
Intervention	Group 1a + 1b	Group 1a (birth in pool + no clinical concerns)

Comparators	Group 2a +2b	Group 2a (birth in /out of pool+no clinical concerns) as the 'pure' low risk
Pros	This study population reflects real life with some clinical concerns resulting in the woman leaving the pool but without time or subsequent indication for transfer for obstetric intervention. This answers the question, "what are the outcomes for babies born in /out of water whose mother used water immersion analgesia during labour?"	This study population excludes cases where outcomes are likely to be poorer but answers the question: "Does birth in water (in itself, and in the absence of any clinical concerns) influence maternal and neonatal outcomes?"
Cons	Potential bias in favour of waterbirth group	Potential to underestimate adverse neonatal events across whole primary analysis

** providing they did not undergo interventions incompatible with waterbirth (apart from episiotomy)*

Pooling of investigational sites

Records from all sites will be pooled for the analysis. Sites will be identified by their Site ID number (and not named) and will be included in the regression models as a random factor.

Withdrawals

- All mothers giving birth after site opening could opt out of the study; we will not receive these records from Wellbeing Software. We will however receive and report aggregate data on the number of opt outs per site over the time period.
- Sites ceasing to use Wellbeing Software (e.g. crossing over to a new system). Data relating to births recorded in the new maternity information system will not be extracted.

Outliers

Any outliers in the data will be discussed as part of the project team and, if necessary, the Study Management Team. In such scenarios, outliers will either be retained or deleted from the study database (and documented using syntax); there will be no opportunity to go back to sites to verify the data item.

Analysis Time Frame

Analysis will be performed when all data has been received and cleaned. No emerging results will be presented as the study proceeds. Maternal and infant outcomes will be reported concurrently.

Statistical analyses

Descriptive analysis

We will describe the numbers of records received from Wellbeing Software across all sites and depict in a flow chart the total number of women and babies for Groups 1 to 5.

We will describe the following by each NHS site:

- number and rate of opt-outs;
- number and rate of women not using a pool (Group 5);
- number and rate of women using a pool (Groups 1-4);
 - by risk status (low risk (Groups 1-3)/ underlying condition (Group 4));
 - rate of waterbirth.

Maternal and infant characteristics such as age, parity and ethnicity of all women giving birth in the study sites during data collection will be obtained and the characteristics of women who do and who not use a pool during labour, will be compared and described (see Table 2). Counts and percentages will be presented for binary and categorical variables, and mean and standard deviation or median and 25th to 75th centiles will be presented for continuous variables.

Table 2: Maternal and infant characteristics

	Group				
	5	4	3	2	1
Maternal characteristics					
Age at birth (years)*	✓	✓	✓	✓	✓
Maternal ethnicity	✓	✓	✓	✓	✓
Lead professional at labour onset	✓	✓	✓	✓	✓
Smoker at time of booking	✓	✓	✓	✓	✓
Issues with language/literacy	✓	✓	✓	✓	✓
Deprivation score quintile (Townsend)	✓	✓	✓	✓	✓
Risk factor	✓	✓	✓	✓	✓
Type of condition:					
Vaginal Birth after Caesarean (VBAC)	✓	✓	✓	✓	✓
Induction	✓	✓	✓	✓	✓
Previous OASI	✓	✓	✓	✓	✓
Gestational diabetes	✓	✓	✓	✓	✓
Para 4+	✓	✓	✓	✓	✓
Multiple pregnancy	✓	✓	✓	✓	✓
Thyroid disease**	✓	✓	✓	✓	✓
Other	✓	✓	✓	✓	✓
Complications per woman (none, 1, 2, 3,4+)	✓	✓	✓	✓	✓
Parity (primiparous / multiparous)*	✓	✓	✓	✓	✓
Body Mass Index (BMI) (Height/weight)*	✓	✓	✓	✓	✓
Gestational age at birth (weeks)*	-	✓	✓	✓	✓
Duration of labour*	-	✓	✓	✓	✓
Complications of labour	-	-	✓	✓	✓
Manual removal of placenta	-	✓	✓	✓	✓
Mode of birth	-	✓	✓	✓	✓
Meconium stained liquor at birth **	-	✓	✓	✓	✓
How was fetal heart rate (HR) monitoring performed?	-	✓	✓	✓	✓
CTG and syntocinon use in pool	-	✓	✓	✓	✓
Birth position	-	✓	✓	✓	✓
Reason for leaving pool prior to birth (maternal/infant intrapartum problems)	-	✓	✓	✓	✓
Perinatal deaths	-	✓	✓	✓	✓
Maternal and infant outcomes (for women with risk factors who use a pool)	-	✓	-	-	-
Infant					
Birthweight (g)*	-	✓	✓	✓	✓
Small for gestational age (<10th centile)**	-	✓	✓	✓	✓
Infant head circumference (cms)*	-	✓	✓	✓	✓
Sex of baby**	-	✓	✓	✓	✓
Duration ruptured membranes to birth**	-	✓	✓	✓	✓
Intrapartum fever**	-	✓	✓	✓	✓
Fetal heart rate concerns in labour	-	✓	✓	✓	✓

**potential confounders for maternal primary outcome; ** potential confounders for infant primary outcome*

Main comparative analysis: Group 1a+1b versus Group 2a +2b – ‘low risk’ mothers by birth in water or not, in whom there was no clinical concerns prior to birth.

Primary outcomes

The primary analyses are based on a non-inferiority test of births occurring in water versus births occurring out of water comparing:

1. the proportion of mothers that have OASI (based on retrospective and prospective Wellbeing Software data), and
2. the proportion of infants with a composite outcome of ‘adverse infant outcome or treatment’ (based on prospective Wellbeing Software and National Neonatal Research Database (NNRD) data).

A non-inferiority trial aims to demonstrate that birth in water is not worse than birth out of water by more than the non-inferiority margin and is established at the 5% (one-sided) if the upper limit of the CI for the difference between groups is below the margin.

Maternal outcome: Non-inferiority will be concluded if the upper limit of the 95% CI for the difference in the proportion of OASI between the groups is less than 1.0% (Odds ratio (OR) <1.23) in nulliparous low-risk women and less than 0.6% (OR<1.38) in parous women. The data will then be combined to assess the effects averaged across both strata.

Infant outcome: Non-inferiority will be concluded if the upper limit of the 95% CI for the difference in infant outcome between the groups is less than 1.0% (OR<1.21).

To test the primary hypothesis of non-inferiority between babies born in water versus leaving the pool before birth, both the maternal and infant primary outcomes will be evaluated for non-inferiority using logistic regression models. Three sets of ORs will be presented alongside one-sided 95% CIs: unadjusted OR, adjusted OR for selected confounders (no imputation), adjusted OR for selected confounders (with imputation).

For maternal outcomes, women will be the unit of analysis (denominator) and those leaving the pool to give birth will be used as the reference group for all comparative analyses. For infant outcomes, babies will be the unit of analysis (denominator) and those with mothers leaving the pool to birth will be used as the reference group for all comparative analyses. All analyses will use a mixed-effects two-level regression model to allow for clustering of outcomes by site. As we anticipated a very small number of twins, we will not be accounting for the clustering of infants within mothers within site.

Secondary analyses

If non-inferiority is shown, then a superiority analysis will be conducted as a secondary analysis of the primary outcomes using logistic regression and will again be presented as an (unadjusted and adjusted) OR, alongside a 95% CI.

An important secondary analysis of the infant primary composite outcome using both retrospective and prospective data Wellbeing Software and NNRD data will be examined, thus increasing the sample size and the power of this analysis. NNU admissions requiring respiratory support and intrapartum stillbirth or early neonatal death are captured over both periods of data collection in both

sources. However, this outcome will not include administration of intravenous antibiotic within 48 hours of birth among babies not admitted to a NNU.

Delivery of placenta in water

An important subgroup is that of women who birthed in water, by whether the placenta was delivered in water or the woman left the pool during the third stage. We will examine the primary maternal and infant outcomes and also postpartum haemorrhage of >1000ml between these two groups.

Secondary outcomes

Secondary outcomes will have non-inferiority testing as detailed above. All outcomes listed in Table 3 alongside the study population used, sensitivity analyses and analysis model. In addition, for mothers who give birth in water, we will examine the rates and management of postpartum haemorrhage (PPH) of >1,000 ml. We will also describe the rates and treatment of haemorrhage for the subgroup of ‘low risk’ women who, following birth in water (Group 1a + 1b), deliver the placenta underwater and for those that leave the water prior to delivery of the placenta.

The method of analysis is dependent on the outcome type e.g., binary (yes/no, presence or absence of events), continuous, and count data. Binary outcomes will be modelled using logistic regression models and effect estimates presented as ORs comparing the odds of an event in waterbirth compared to land. For continuous outcomes, a multilevel linear model will be fitted and results presented as difference in means (waterbirth minus birth on land). Count data will be analysed using a Poisson multilevel model. If the distribution of events displayed signs of over dispersion (greater variance than might be expected in a Poisson distribution), then a Negative Binomial model (NBM) will be used. Estimates will be presented as the incidence rate ratio (IRR) in waterbirth compared to on land. All parameter estimates will be accompanied by a 1-sided 95% confidence interval and p-value.

Table 3: All POOL outcomes, study populations used, sensitivity analyses and analysis model

Outcomes	Study population: Whole data (W) / from site open (P)	Outcome definition	Analysis
Maternal outcomes			
Primary			
Obstetric Anal Sphincter Injury	W	Presence/ absence	LO
Secondary			
Intrapartum			
Shoulder dystocia	W	Presence/ absence	LO
Required management of shoulder dystocia	W	See categories in Supplementary table 6	ORD
Planned and actual Management of the third stage of labour	P	Placenta delivered into water; Placenta delivered out of water	LO
Need for obstetric involvement in woman’s care including sepsis	W	Yes, need for obstetric involvement; No need.	LO
Reason for obstetric involvement in woman’s care	W	Categorical to include: Sepsis; caesarean section	ORD
Incidence of perineal and other genital trauma	W	Presence/absence	LO
Management of perineal and other genital trauma	W	See categories in Supplementary table 6	ORD

Outcomes	Study population: Whole data (W) / from site open (P)	Outcome definition	Analysis
Maternal position at birth	W	See categories in Supplementary table 6	ORD
Haemorrhage (PPH defined as blood loss>500ml)	W	Yes /no	LO
Treatment for haemorrhage	W	3rd stage drugs/3rd stage fluids	ORD
Maternal postnatal			
Duration of postnatal stay	W	Count of days	PO/NBM
Breast feeding initiation	W	Yes – Breast (expressed/maternal milk) No – artificial/breast (donor), No feed given	ORD
Breast feeding continuation (at community discharge of care)	W	Yes – Exclusively Breast (EBM) No – artificial milk feeding/combined	ORD
Need for higher-level care	W	Yes /no	LO
Maternal readmission to hospital (within seven days of birth)	W	Yes /no	LO
Infant outcomes			
Primary			
Adverse infant outcomes or treatment	P	Presence/absence	LO
Secondary			
Timing of cord clamping	W	Delayed cord clamping >60 seconds after birth or not	LO
Apgar scores @ 1, 5 and 10 min	W	Low score = <7 Healthy score = 7+	LO
Neonatal unit admission requiring respiratory support	W	Yes/No	LO
Neonatal unit admission length of stay	W	Count of days	PO/NBM
Antibiotic administration commenced within 48 hours of birth (with/without culture proven infection)	W (among babies admitted to a NNU) P	Yes/No/Attempted but unsuccessful	ORD
For babies receiving IV antibiotics above, duration of antibiotics	W (among babies admitted to a NNU) P	<48 hours, 5 days, 6-7 days, >7 days, Other	ORD
Intrapartum stillbirth or neonatal death prior to NNU/postnatal ward discharge occurring within 7days of birth	W	Neonatal death/ Stillbirth (Antepartum/Intrapartum resuscitation attempted /not attempted)	ORD
Neonatal resuscitation	W	Yes/No	LO
Snapped umbilical cord prior to clamping	P	Yes/No	LO
Skin-to-skin contact at birth	W	Yes/No	LO
First breastfeed within first hour	W	Yes/No	LO

Outcomes	Study population: Whole data (W) / from site open (P)	Outcome definition	Analysis
Culture proven infection	W (among babies admitted to a NNU) P	Yes/No	LO
Brachial plexus injury	W	Yes/No	LO
Treatment for jaundice	W	Yes/No	LO
Readmission to hospital within 7 days of birth	W	Yes/No	LO
Receipt of therapeutic hypothermia	W (NNRD only)	Yes/No	LO
NNU admissions	W (NNRD only)	Count of admissions	PO/NBM
Respiratory support	W (NNRD only)	Yes/No	LO
Highest C reactive protein (CRP) results	P	Continuous CRP result	LIN
Successful / attempted lumbar puncture	P	Presence/absence	LO
Blood culture positive with a recognised pathogen (excluding skin commensal organisms)	W (among babies admitted to a NNU) P	Presence/absence	LO

NNU=neonatal unit; NNRD= National Neonatal Research Database; LIN = Linear regression; LO = Logistic regression; ORD = Ordinal regression; PO/NBM= Poisson or negative binomial regression.

Subgroup analysis

A planned and powered subgroup of the primary maternal outcome will be conducted to compare rates separately for primiparous and multiparous women. The relationship between the proportion of women using a pool during labour, at individual sites and the incidence of adverse maternal and primary outcomes will be described and explored. A planned sub-group of the primary infant composite outcome will also be conducted to compare rates separately for infants born to primiparous and multiparous women. These pre-planned analyses will be conducted by the inclusion of appropriate interaction terms (waterbirth exposure x parity) in the regression models. Results will be presented using interaction coefficients, 95% CI and p-value.

Sensitivity analyses

For both maternal and infant primary outcomes a number of sensitivity analyses will be performed to assess the robustness of the results to factors which may introduce bias (i.e. definition of risk and the study populations, maternal characteristics associated with waterbirth, and fetal heart rate concerns).

Risk categorisation

To identify women with risk factors at the commencement of labour we will use both definitions of low risk using a) a combination of risk factors described in the existing E3 fields and the midwives' assessment at pool entry and b) using the midwives' assessment at the time of pool entry alone. We will quantify agreement in risk categorisation by source.

Clinical need

The study will also report outcomes for the study population reflecting 'pure' low risk:

- Group 1a (birth in pool+no clinical concerns) versus Group 2a (birth in /out of pool+no clinical concerns)

Propensity score analysis

Whether a woman who uses water immersion during labour remains in the pool for birth is likely to be influenced by their age, parity and other characteristics, resulting in imbalanced comparison groups. Incorporating propensity scores, i.e. the ‘propensity’ of a woman to choose a waterbirth, in the analysis is a way of controlling for this bias. Measurable maternal characteristics associated with both waterbirth and outcome will be pre-specified (e.g. age at gestation, parity). The balance of maternal characteristics will be examined by exposure groups by calculating standardised differences for all variables, with a standardised difference of 10% or more to be indicative of imbalance. If they appear to be different we will employ propensity score methods using logistic regression and a propensity score produced for all individuals to be used for matching purposes. Matching between treatment and controls will be done using a nearest neighbour (NN) method with a caliper (maximum permitted difference) of 0.2 of the standard deviation of the logit (14). If too many controls are excluded, we will re-weight on the propensity score (using inverse probability weighting), so that no controls are excluded.

Instrumental variable analysis

Instrumental variables (IV) are factors associated with outcomes only via their association with exposure (in this case to birthing in water) and are independent of other factors associated with exposure. IVs can deal with the unobserved factors in selection bias and can add potential value to a study dealing with just observable factors. Such variables might include midwifery practice, or other factor that encapsulates unit culture. The capture of denominator data to provide information on the proportion of women using water for labour or birth at each unit, and the qualitative component of the study, will be utilised in this analysis.

Missing data

We will distinguish empty cells by:

- (a) sites not collecting certain fields (partial or full study period) or entirely halting data collection (e.g. ceasing to use the E3 maternity information system);
- (b) cells that are expected but are empty (and coded as NULL).

For (b) we will distinguish between fields that are:

1. expected to be well completed (e.g., mode of birth, birthweight, breastfeeding). Empty cells will be defined as true missing and imputation will be considered.
2. likely to only be completed when an event has occurred (e.g., hypertension). Empty cells will be defined as absence of event.
3. only expected when relevant pre-screening questions are used (e.g., duration of antibiotics only applicable for those that receive antibiotics). Empty cells will be defined as ‘not applicable’, unless the screening question is positive in which case an empty field would be defined as missing.

We will use multiple imputation methods (using the mi command in Stata) if data are found to be missing (completely) at random (likely to be only applicable where data is truly missing). To assess the effect of missing data on the results of the primary analysis, a sensitivity analysis is planned using multiple imputation techniques to impute missing data for each of the potential confounders included in the adjusted regression models, under the assumption that the data were missing at random. This

assumes that the reason data are missing is not dependent on the value of the missing data if it were known. Missing outcome data would not be imputed since we cannot assume that these data are missing at random.

Bias

There is a potential for reporting bias of the risk categorisation at pool entry collected by midwives after site opening, as this will usually be recorded after the outcome of the baby/mother was known. To examine this bias we will examine trends in the incidence of overall risk and by categories over the study time period and by the data sources (E3 existing fields and midwives entry) to detect any increases caused by 'diagnostic drift'.

Patient and public involvement

Lay persons were involved in the original grant proposal, development of research questions, study design and outcomes. The study management group and the study steering committee have PPI representatives who were actively engaged in study design and study conduct and read through the statistical analysis plan.

Guidelines and software

The reporting of findings will be in accordance with the STROBE and RECORD recommendations for reporting observational studies using routinely collected data (3,15). Statistical analysis will be performed in Stata (version 17 or higher) (16).

Abbreviations:

AMU: Alongside Midwifery Unit; APH: Antepartum haemorrhage; BBA: Born Before Arrival; BMI: Body Mass Index; CI: Confidence interval; CTR Centre for Trials Research; DAG: Directed acyclic graph; FMU: Freestanding Midwifery Unit; HR: Heart rate; HTA: Health Technology Assessment; ICH: International Council for Harmonisation; IRR: Incidence rate ratio; IV: Instrumental variables; NBM: Negative Binomial model; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NIHR: National Institute for Health Research; NN: Nearest neighbour; NNRD: National Neonatal Research Database; NNU: Neonatal unit; OASI: Obstetric Anal Sphincter Injury; OBS: Obstetric Unit; OR: Odds ratio; OSF: Open science framework; PPH: Postpartum haemorrhage; RECORD: Reporting of studies Conducted using Observational Routinely-collected Data; SAP: Statistical analysis plan; STROBE: Strengthening the Reporting of Observational studies in Epidemiology; UKNC: United Kingdom Neonatal Collaborative; VBAC: Vaginal Birth after Caesarean.

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Current status: The POOL Study is currently still collecting data from sites.

Internal references: This plan adheres to the following CTR Standard Operating Procedure: Standard Operating Procedures for Statistical Analysis Plan SOP/008/2, Version 2.0, 14/02/2022

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Figure 1. Overview of the five groups of women within the study population

AMU=Alongside Midwifery Unit; FMU=Freestanding Midwifery Unit; OBS=Obstetric Unit.