The POOL Study

Establishing the safety of waterbirth for mothers and babies: A cohort study with nested qualitative component

PROTOCOL VERSION NUMBER AND DATE

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the relevant study regulations, GCP guidelines, and Sponsor's SOPs.

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

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

Director:		
Name	**Signature**	**Date**
Mike Robling		
Chief Investigator:		
Name	**Signature**	**Date**
Julia Sanders		

General Information This protocol describes the POOL study. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the study. Problems relating to the study should be referred, in the first instance, to CTR.

Contact details – Chief Investigator & Co-Investigators

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Study Co-ordination:

The POOL study is being coordinated by the Centre for Trials Research (CTR), Cardiff University.
This protocol has been developed by the POOL Study Management Group (SMG).
For **all queries** please contact the POOL study team through the main study email address. Any clinical queries will be directed through the Study Manager to either the Chief Investigator or a Co-Investigator

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Glossary of abbreviations

BBA	Born Before Arrival
CAG	Confidentiality Advisory Group
CI	Confidence interval
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
DAGs	Directed acyclic graphs
GCP	Good Clinical Practice
HTA	Health Technology Assessment
IG	Information governance
IV	Instrumental variables
MRC	Medical Research Council
NDAU	Neonatal Data Analysis Unit
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NNRD	National Neonatal Research Database
OASIS	Obstetric Anal Sphincter Injuries
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SMF	Study Master File
SMG	Study Management Group
SSC	Study Steering Committee
UKNC	UK Neonatal Collaborative

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No. *(specify substantial/non-substantial)*	**Protocol version no.**	**Date issued**	**Summary of changes made since previous version**

2 Synopsis

Short title	The POOL Study
Internal ref. no.	
Funder and ref.	NIHR HTA 16/149/01
Study design	A cohort study with nested qualitative component
Study participants	The main analysis will include women who use water immersion during labour at NHS study sites. Descriptive data will be reported on all women at study sites.
Planned sample size	30,000 women 16,200 babies
Inclusion criteria	Women who give birth in a participating site who do not opt-out.
Exclusion criteria	Women who have opted-out.
Treatment duration	N/A
Follow-up duration	To midwifery discharge
Planned study period	April 2018 – August 2021
Primary objective	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 babies.
Secondary objectives	Secondary study objectives are to: 1) Describe the indications and maternal and neonatal outcomes for women who use a pool during labour and who have risk factors at labour onset, or develop complications during labour; 2) Amongst women who left the pool prior to birth, describe the reasons birth occurred out of water. 3) Explore factors associated with high and low rates of pool use in individual maternity units; 4) Describe the demographic and obstetric characteristics, of women using a birth pool for labour and birth.
Primary outcomes	Maternal primary outcome: Obstetric Anal Sphincter Injuries (OASIS). Neonatal primary outcome: A composite of 'adverse neonatal outcomes or

	treatment' to include: (a) any neonatal unit admission requiring respiratory support (b) antibiotic administration within 48 hours of birth (with or without culture proven infection); and (c) intrapartum stillbirth or neonatal death.
Secondary outcomes	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 was, delivered in or out of water), need and reason for obstetric involvement in woman's care including sepsis, maternal position at birth, treatment for haemorrhage, incidence and management of perineal and other genital trauma. Maternal Postnatal: duration of postnatal stay, breast feeding, higher level care, and maternal readmission to hospital within seven days of birth. Infant secondary outcomes: Snapped umbilical cord prior to clamping, resuscitation, Apgar scores. Incidence of: culture proven infection; brachial plexus injury; treatment for jaundice; readmission to hospital within seven days of birth; therapeutic hypothermia; neonatal unit admissions; cause of neonatal death; respiratory support.
Intervention	Birth in water following water immersion during labour

3 Study summary

The POOL Study is a cohort study with a nested qualitative component. The primary study aim 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 babies. The criteria for women being 'low-risk' will follow criteria set out in the NICE Intrapartum Care Guidelines (1). Pool use during labour includes all forms of water immersion including permanent and temporary birth pools and conventional baths.

Primary study objectives are to:

1. Evaluate if waterbirth is associated with an increase in adverse neonatal outcomes or treatment, to include asphyxia, infection, respiratory difficulties, and mortality; or maternal morbidity, particularly complex perineal trauma (Obstetric Anal Sphincter Injuries (OASIS)) and haemorrhage.
2. Assess the primary safety outcomes amongst the subgroups of nulliparous and parous women who were low risk at labour onset.
3. Describe rates and treatment of haemorrhage for low risk women who, following birth in water, deliver the placenta underwater. This will also be described for women who leave the water prior to delivery of the placenta.

The secondary study objectives will set pool use and waterbirth in the context of NHS care. The study will describe:

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. Explore factors associated with high and low rates of pool use in individual maternity units.

3.1 Study lay summary

It is estimated that up to 60,000 (9 in every 100) babies are born into water annually in the UK and with encouragement from NICE for maternity units to provide birthing pools for women, this

number may increase further. Women use a birth pool during labour for pain relief, and some women choose to remain in the pool for the birth of their baby.

Over the years there have been reports of babies that had breathing difficulties or infection following birth in water, and there is a concern that women that have a waterbirth more often sustain severe trauma to their vaginal area or have unrecognised heavy bleeding. Despite concern, and some reports in the press, to date there have not been studies large enough to show whether or not waterbirth causes an increase in these poor outcomes for mothers or their babies.

This study plans to answer the question about the safety of waterbirths. The study will collect data on the births of all women in around 30 maternity units during 2015-2020. The study will determine how many women are using birth pools, how many women give birth in water and whether mothers or their babies come to any extra harm as a result of waterbirth. The study will include women giving birth to their first baby and women giving birth to a subsequent child.

The study needs to collect information on 15,000 waterbirths and 15,000 births out of water. To do this without disturbing women in labour or just after birth, when they are looking after their new baby, the study will use information collected as part of each woman's and linked baby maternity record stored at hospitals in computerised systems. For babies that need specialist care after birth, the study will also use data held by the National Neonatal Research Database (NNRD). Some of the data needed for this study is already collected by maternity units, so data from births from 2015 onwards can be included in the study. However, as some important information needed to fully answer the study questions, such as how many babies have antibiotics, and how many women deliver the placenta underwater, is currently not collected, some new items will be added to maternity computer systems when the study starts in 2018. To keep women's information confidential, the data stored in existing maternity information systems will have identifying information, such as names, addresses and NHS numbers removed before the information is sent to the research team in Cardiff for analysis.

Professionals and parents have strong opinions on waterbirth. Some are great advocates, who promote the potential benefits of waterbirth to women, whilst others remain concerned that women may be taking additional unnecessary risks by giving birth in water. The diversity of opinions towards waterbirth makes it particularly important that the study team have representatives from all interested groups. The professionals on the study team include midwives, an obstetrician and a neonatologist as well as the experts needed to deliver this large complex study. The NCT is the

largest parenting organisation in the UK and have joined the study team as have the Royal College of Midwives.

The study will produce academic papers and evidence based information for women and their partners on waterbirth. The study findings will be of great interest and would be expected to generate much press interest, and quickly influence the information provided to pregnant women throughout the UK.

4 Background

During labour and birth water immersion is facilitated by use of a conventional bath or more frequently a specialist birthpool. All birthpools offer sufficient depth of warm water for the woman to be immersed to above her breasts when sitting and sufficient space for ease of movement and change of position. Simple inflatable pools are available, but NHS maternity units frequently now have pools which are plumbed in, some of which are more complex with inbuilt lighting and heating. Women enter the warm water in established labour, leaving the pool either prior to birth due to clinical concerns or maternal choice, or remaining in the pool until after birth of the baby. Some mothers remain in the pool until after delivery of the placenta. For mothers the potential benefits of waterbirth are considered to be pain reduction, relaxation, reduced labour interventions and reduced perineal trauma whilst for babies, a gentle birth and transition to life. It is suggested that waterbirth may also improve longer term outcomes; mother infant bonding, increased breastfeeding and enhanced maternal postnatal mental health.

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*'[2]. In the intervening years the popularity of the use of water immersion for labour and birth in the UK has increased[3] and NICE guidance has recommended since 2007[1 4] that water immersion analgesia should be made available to all clinically appropriate women in labour. The Cochrane review[5] of water immersion during labour provided evidence supportive of pool use but could not answer the question relating to the safety of waterbirth. 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 babies following waterbirth has more recently been reported in a systematic review of 29 studies[6]. Whilst the review found no evidence of a difference in clinically important neonatal outcomes for babies born in water, it concluded that a large multicentred study to address the question of the safety of waterbirth for babies is now a priority.

The analgesic properties of water immersion during labour make the option attractive to women and the relatively low cost of the purchase and installation of birthpools, at around £5,000 per pool, makes this a reasonable facility to be provided within NHS premises. Whilst the provision of birthpools are desirable in order to provide women with comfort in labour, if waterbirth is associated with an increase in adverse maternal or neonatal outcomes the potential economic and social costs, could be very high. Several case reports have highlighted potential safety issues for babies that are manifest in the days after birth. Some potential adverse outcomes of clinical interest are specific to waterbirth such as neonatal water inhalation, whilst for other outcomes, being in a pool has the potential to adversely influence outcomes, such as in the time-critical emergency management of shoulder dystocia, which could potentially be delayed due to the need to move the woman from the pool. Such adverse outcomes, in addition being devastating to families are costly to the NHS with a daily tariff for neonatal intensive care at £1,081[7] and settlements for cerebral palsy resulting from clinical negligence with potential values of over £10m[8]. Whilst water immersion is accepted to provide effective labour analgesia, evidence continues to be lacking as to whether women should be encouraged to leave, or remain in, the pool for birth.

5 Study objectives/endpoints and outcome measures

The primary study aim 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 babies.

5.1 Primary study objectives

1. Evaluate if waterbirth is associated with an increase in adverse neonatal outcomes or treatment, to include asphyxia, infection, respiratory difficulties, and mortality; or

maternal morbidity, particularly complex perineal trauma (Obstetric Anal Sphincter Injuries (OASIS)) and haemorrhage.

2. Assess the primary safety outcomes amongst the subgroups of nulliparous and parous women who were low risk at labour onset.
3. Describe rates and treatment of haemorrhage for low risk women who, following birth in water, deliver the placenta underwater. This will also be described for women who leave the water prior to delivery of the placenta.

5.2 Secondary study objectives

The secondary study objectives will set pool use and waterbirth in the context of NHS care. The study will describe:

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. Explore factors associated with high and low rates of pool use in individual maternity units.

5.3 Primary outcomes measures

The study has two primary outcomes.

The maternal primary outcome will be Obstetric Anal Sphincter Injuries (OASIS). 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)[20].

The neonatal primary outcome will be composite of 'adverse neonatal outcomes or treatment' to include: (a) any neonatal unit admission requiring respiratory support (b) antibiotic administration within 48 hours of birth (with or without culture proven infection); and (c) intrapartum stillbirth or neonatal death. Such outcomes are important as they cause distress to parents, have potential long term damage to babies and are associated with cost to the NHS. Composite neonatal outcomes combining mortality and morbidity are credible[21] 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.

5.4 Secondary Outcomes

Secondary outcomes of parental, clinical and financial importance have been identified. Data relating to maternal or neonatal readmission to hospital within seven days of birth is already reported by community midwives and captured in EuroKing® systems at the point of discharge from midwifery care. Data relating to some primary and secondary outcomes are not currently captured in EuroKing® maternity information systems and at site opening the EuroKing® 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, need and reason for obstetric involvement in woman's care including sepsis; mode of birth, maternal position at birth, treatment for haemorrhage, incidence and management of perineal and other genital trauma. Maternal Postnatal: duration of postnatal stay, breast feeding initiation and continuation, higher level care, and maternal readmission to hospital within seven days of birth.

Infant secondary outcomes: Snapped umbilical cord prior to clamping, skin to skin contact at birth, timing of cord clamping, resuscitation, Apgar scores, administration and duration of intravenous antibiotics. Incidence of: lumbar puncture, culture proven infection, brachial plexus injury; treatment for jaundice; readmission to hospital within seven days of birth; therapeutic hypothermia;

neonatal unit admission and duration; cause of neonatal death; respiratory support. Where available, and where the risk status and pool usage of mothers can be determined, retrospective data will be used in addition to prospective data, to describe the occurrence of these infant outcomes.

Additional data items with accompanying background development required to fully answer the research aims will be added to E3 systems at study sites, and will include:

- Maternal risk factors at pool entry
- Maternal risk factors developing during labour
- Time of entry into pool
- Time of last leaving pool
- Reason for leaving pool if prior to birth
- Partial birth in water (breech / shoulder dystocia)
- Birth position in pool
- Conversion from planned physiological to active third stage labour management.
- Delivery of placenta in or out of water
- Treatment for haemorrhage
- Reason for obstetric involvement in woman's care
- Snapped umbilical cord prior to clamping
- Duration of antibiotics administered to neonates
- Lumbar puncture (Neonatal)
- Culture positive sepsis (Neonatal)

6 Study Intervention

The health technology being assessed is giving birth in water: 'waterbirth'.

7 Study design and setting

A natural experiment using a cohort design with a qualitative component will answer the study objectives by using a combination of data captured retrospectively and prospectively in electronic NHS maternity and neonatal information systems. The qualitative component will explore factors associated with high and low rates of pool use; data will be gathered in online discussion groups, focus groups and one-to-one interviews with key stakeholders, including mothers/to be.

To answer all research objectives approximately 600,000 individual computerised maternity records held on secure NHS servers at around 30 NHS sites, covering the period January 2015 – November 2020 will be accessed. To provide necessary denominator data, and to be able to compare characteristics of pool users 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 (OASIS) amongst nulliparous and parous women. To undertake this subgroup analysis will require a necessarily large sample (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 2015 to 2020.

The sample required for the neonatal primary outcome is smaller (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 June 2018 to November 2020.

Some neonatal outcomes of interest, including neonatal hypoxia, respiratory support or neonatal mortality, are already held by study sites or by the National Neonatal Research Database (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 neonatal outcomes.

The NNRD holds individual patient level data on all babies admitted for National Health Service neonatal care in England, Scotland and Wales[18] [19] from 2014 to present. To obtain detailed treatment and outcome information on any baby who required admission to a neonatal unit, following their mother's pool use in labour, the identifiers of all babies 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.

The primary study aim is to compare maternal and neonatal outcomes for 'low risk' women who gave birth in water (Group 1) against 'low risk' women who left the water prior to birth for reasons other than clinical need (Group 2) Figure 1.

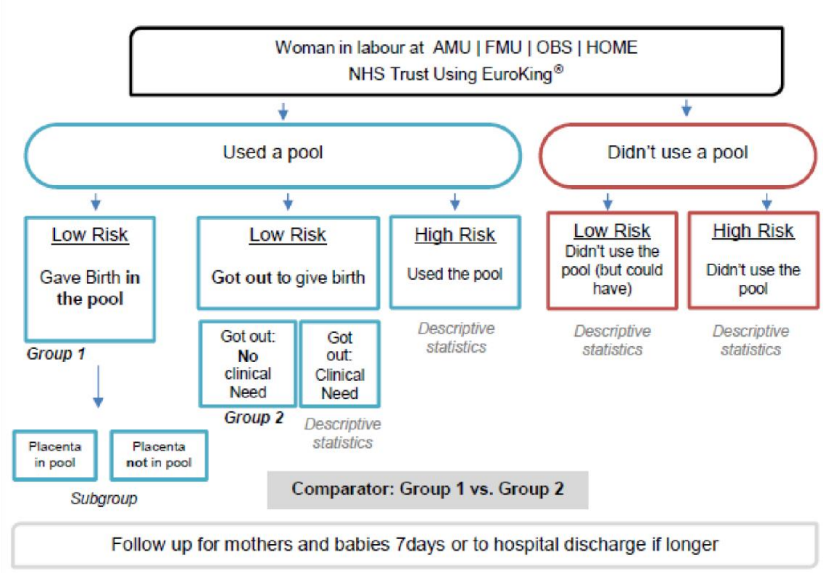

Figure 1 Study population groups

8 Site and Investigator selection

The study will include maternity units in the UK that use the EuroKing® E3 maternity information system. The sites will also have to have functioning birthing pools to be included within the study.

Before any Site can begin recruitment a Principal Investigator (PI) at each site must be identified. The following documents must be in place and copies sent to the POOL Study email account (see contact details on page 4):

- The approval letter from the site's R&D Department
- Favourable opinion from Main Ethics committee
- A signed Study Agreement

Upon receipt of all the above documents, the Study Manager will send written confirmation to the Principal Investigator detailing that the centre is now ready to open. This letter/email must be filed in each site's Site File.

Occasionally during the study, amendments may be made to the study documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It

is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be by attendance at a national POOL launch meeting / site visit/ or by teleconference if attendance of key personnel is unfeasible.

9 Cohort Study

9.1 Population

The target population is all women with an uncomplicated pregnancy, who meet NICE[1] criteria for being at 'low risk' of complications at labour onset and who use water immersion during labour.

9.2 Data sets

To answer the research questions, it is planned to use two datasets, data extracted from EuroKing® maternity information systems and data held by the National Neonatal Research Database.

EuroKing'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. All 200 neonatal units in England, Wales and Scotland form the United Kingdom Neonatal Collaborative (UKNC) and contribute electronic health record data to the National Neonatal Research Database (NNRD). The NNRD is a national resource formed of the Neonatal Data-Set (an NHS Information Standard), comprising 450 clearly defined variables[24] extracted at patient level from the commercial Electronic Health Record used by all UK neonatal units.

9.3 Study Procedures

To answer the research questions, demographic and clinical data relating to all births at participating sites during the period of retrospective and prospective data collection will be extracted as follows:

1. Maternity sites will be recruited by Cardiff University and all required permissions obtained.
2. Data relating to births from January 2015 onwards and captured in EuroKing® prior to site opening will be extracted and transferred to Cardiff University. This retrospective data will be identified by EuroKing® mother and baby numbers only and contribute to the maternal outcomes for the study.

3. Additional data items essential to the study, but not currently in the E3 system, including a screening question to identify women with complicating factors on pool entry, will be added to the system at each participating site.
4. Following three months of prospective data collection, and each quarter thereafter, data relevant to the study and captured in E3 systems at each study site will be extracted by EuroKing®.
5. EuroKing® will allocate each mother and baby a linking identifying number, remove NHS and hospital numbers, and other identifiable variables and forward the data to Cardiff University.
6. On a quarterly basis, the NHS and EuroKing® numbers of all babies born at units during that period, and whose mother used a pool in labour, will be extracted and passed onto the NNRD for matching. The transfer process will be managed by EuroKing® throughout the duration of the study. E3 systems are installed locally on premises at each NHS Trust / Health Board therefore each set of data extractions must be managed on a site by site basis by EuroKing®.

To Note. Data extraction from sites on a quarterly basis is required as less frequent extractions may result in challenges for sites with less powerful servers, and ensures timely matching of maternal and neonatal data between EuroKing® and the NNRD.

9.4 Creation of pseudonymised dataset in Cardiff University

Each phase of data extraction syntax can be run remotely from study sites by EuroKing®. Cardiff University will receive only pseudonymised data. For EuroKing® data transferred directly to Cardiff University from study sites, we will utilise a secure method of case labelling which will involve generating a unique study number for each mother and baby recoded from their NHS number, which also facilitates a link between each mother / infant dyad. This unique study number will be generated prior to data leaving the study sites. A separate syntax, will direct the NHS number of babies born to all women who used a pool during labour, after site opening, to the NNRD on a quarterly basis. Any NNRD matched data will undergo the identical secure method of case labelling of the babies NHS numbers prior to data being transferred back to Cardiff University. Use of this method of case labelling will enable Cardiff University only to hold pseudonymised data, whilst facilitating the identification of mother / infant dyads and enable the matching of the neonatal unit admission record onto to the EuroKing® mother and baby record. See Figure 2.

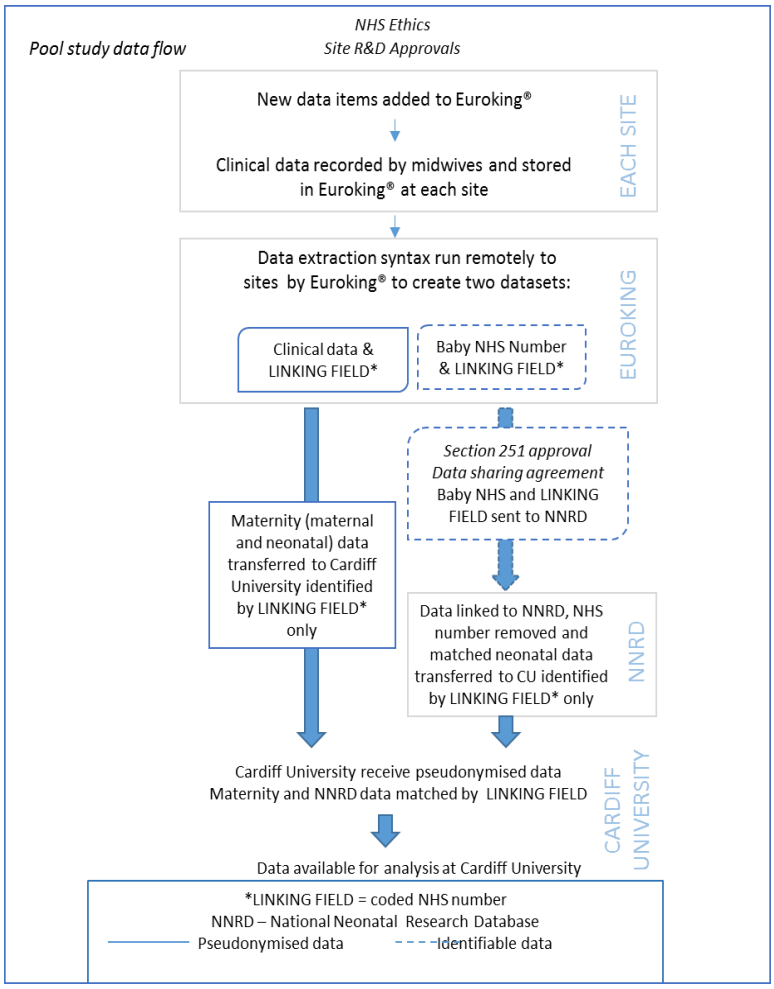

Figure 2 Data Flow

9.5 Data management

All procedures for data storage, processing and management will comply with the Centre for Trial Research's Standard Operating Procedures and the Data Protection legislation. No identifiable data will be stored or linked to the clinical data received. The study statistician will carry out all analysis. All electronic data will be stored on fire walled university servers. Access to files will be through password protected PCs and only accessible to named researchers responsible for the running of the study and the Chief Investigator. EuroKing® and NNRD both have established procedures for the

transfer and receipt of patient-level NHS data. Data will be transferred by these organisations in line with their current procedures to ensure data security and confidentiality.

The online focus groups with professionals and lay members will be hosted on a Cardiff University secure server (sewtudb.cf.ac.uk) and access password protected. A member of the research team will act as administrator for the online focus groups. Individuals expressing interest will be provided with an electronic participant information sheet (PIS) explaining what participation will entail and what measures will be taken to protect their identity. Participation in the discussion will be taken as consent. Focus group participants will be provided with a password, enabling them to view and contribute to only the focus group to which they are affiliated.

Consent forms and transcripts of interviews and focus groups, conducted at NHS sites, will be stored in a locked filing cabinet, with keys available only to researchers and the Chief Investigator. Voice recordings from focus groups and interviews conducted at study sites will be made onto password protected encrypted memory cards and only transported between study sites and Cardiff University with an individual member of the study team or, if needed, by courier. Voice files will continue to be password protected and only accessible to relevant members of the study team following transfer to Cardiff University. Recordings will be transcribed in line with CTR's SOPs either within the department or by an approved transcription service. Participants of the qualitative component will be assigned a participant ID which will be used to label the transcripts. Transcripts will be anonymised and stored on the secure university server with access rights given only to those study members who require access.

All other essential documents generated by the study will be kept in the Study Master File (SMF) and/or the electronic SMF.

Cardiff University demonstrates compliance with current information governance (IG) requirements, as set out in the Department of Health Policy, with an IG toolkit score valid from 1 April 2018 of 88%. The IG Toolkit score for NNRD was 66% in 2016-17. The IG Toolkit score for EuroKing® 2015/ 2016 Ref: ASS 159120 was 83%.

9.6 Cohort Study Statistical considerations

9.6.1 Sample size

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[22] found that overall 4.6% and 1.6% of nulliparous and parous women respectively, sustained OASIS. 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 EuroKing® in 2015 were nulliparous women (1650/annum). Allowing for staggered site set-up, five years of combined retrospective and prospective data collection would be required (January 2015 – November 2020). 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 EuroKing® 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 neonatal primary outcome, an estimate of 5% is used for the proportion of babies born to 'low risk' mothers experiencing 'adverse neonatal outcome or treatment'[22]. A non-inferiority margin of 1.0% or less will be taken as clinically non-significant. A sample size of 16,200 babies (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. The identification of women who leave and do not leave the pool prior to delivery of the placenta can only be captured by addition of new data items in the prospective cohort. As delivery of placenta in water, or postpartum haemorrhage of >1,000 ml following waterbirth are relatively uncommon events (17% and 1% respectively)[23] the proposed sample size of 30,000 women who use a birth pool will be underpowered to detect a difference in these outcomes, but will be described.

9.6.2 Missing, unused & spurious data

Detail provided in the Statistical Analysis Plan (SAP).

9.6.3 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP

9.6.4 Inclusion in analysis

Women, and their babies, will be included in the study if the woman used water immersion at a study site during the period of data collection. For the purposes of providing denominator data and

to fully answer the research objectives, a minimal data set will also be obtained on women at study sites who do not use water immersion.
To capture data relating to women who use any form of water immersion during labour 'use of a pool ' during labour, will pragmatically be being any women for whom water immersion analgesia is recorded in the EuroKing E3 system.

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*'.
Data relating to women and babies recorded in EuroKing as being 'Born Before Arrival' (BBA), or recorded as intentionally born without midwifery attendance, will be excluded from primary analysis.

9.6.5 Primary analysis

The primary analyses are based on a non-inferiority test of birth in water versus on land, comparing 1) the proportion of mothers that have OASIS, and 2)the proportion of babies with a composite outcome of 'adverse neonatal outcome or treatment'.
To test the primary hypothesis of non-inferiority between birth in water and on land, the two outcomes will be evaluated for non-inferiority using logistic regression models, in the first instance with no adjustment for covariates. Adjusting for potential confounders may result in a more precise treatment effect estimate. The potential confounders of both primary outcomes (listed in table 1) will be considered and the impact on bias through conditional associations when conditioning on these covariates will be assessed using directed acyclic graphs (DAGs). The main logistic model will incorporate these selected covariates through regression adjustment. Results will be reported as an (unadjusted and adjusted) odds ratio (birth in water compared to on land), and a two-sided 90% confidence interval (CI) for the (unadjusted and adjusted) odds ratio will be calculated. Non-inferiority will be concluded if the upper limit of the 90% CI for the difference in neonatal outcome between the groups is less than 1.0% (OR<1.21). Similarly, for the mother's outcome, non-inferiority will be concluded if the upper limit of the 90% CI for the difference in the proportion of OASIS between the groups is less than 1.0% (OR<1.23) in nulliparous 'low-risk' women and less than 0.6% (OR<1.38) in parous 'low-risk' women. The data will then be combined to assess the effects averaged across both strata.

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 be presented as an (unadjusted and adjusted) odds ratio of outcomes in the waterbirth group compared with the birth on land group. Parameter estimates will be provided alongside 95% CI and p-value. Secondary outcomes will have non-inferiority testing as detailed above.

Table 1. Potential confounders for both maternal and baby outcomes

	Maternal outcome: OASIS	**Adverse neonatal composite outcome**
Maternal age (years)	✓	✓
Maternal BMI	✓	
Parity	✓	
Duration of labour	✓	
Gestational age at delivery (weeks)	✓	✓
Child birth weight (g)	✓	✓
Child head circumference (cms)	✓	
Maternal thyroid disease (including hypothyroidism)		✓
Pre-labour ruptured membranes		✓
Intrapartum fever		✓
Fetal growth restriction		✓
Child gender		✓
Meconium stained liquor		✓

9.6.6 Subgroup analysis

Maternal: A planned and powered sub group of the primary maternal outcome will be conducted to compare rates separately for primiparous and multiparous women. One previous cohort study of women using a pool during labour found that delivery of placenta in water and postpartum haemorrhage of >1,000 ml to be relatively uncommon (17% and 1% respectively)[23]. It is likely therefore that the proposed sample of 15,000 women who will give birth in a pool during the period of prospective data collection (2018 – 2020) will be underpowered to detect a difference in rates of postpartum haemorrhage between women who remain in, or leave the pool, for delivery of the placenta, but these data and outcomes will be described. 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.

Neonatal: A planned sub group of the primary neonatal composite outcome will also be conducted to compare rates separately for babies born to primiparous and multiparous women.

15.3 Sensitivity analysis

For both primary outcomes a number of sensitivity analyses will be performed to assess the robustness of the results to factors which may introduce bias.

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. This will result 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. It also allows a more detailed examination of the impact of imbalanced comparison groups on the results. Differences in baseline characteristics before and after propensity score matching will be examined and analyses re-run.

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.

10 Qualitative Component

The qualitative component of the study will explore the influence of maternity unit culture on waterbirth and by placing the findings in the context of current NHS service provision will assist interpretation of the study's findings. Professional attitudes to waterbirth vary widely, with strong views held. It is therefore likely that aspects of unit culture may influence waterbirth rates. For example, differing professional perspectives may act as barriers or facilitators to birth in water, as may unit configuration and model of care (i.e. consultant-led or midwife-led), level of complexity of obstetric care provided, birth environment and facilities, staff training, local policies and procedures. There is currently no robust evidence describing these possible influencing factors.

The qualitative component will use a two-stage approach to identify and explore the influence of cultural factors, through collection and analysis of group and one-to-one interviews with a range of professional and lay stakeholders.

The key research questions are:

- What factors influence birth pool use in units with high and low waterbirth rates?
- What factors influence giving birth in water in units with high and low waterbirth rates?

The term 'unit' refers to all births taking place within the NHS Trust or Health Board, whether within an institution or at home.

The qualitative component design is informed by Realistic Evaluation, an approach which is well-suited for unpacking the causal web of factors that may affect a complex intervention such as waterbirth[29]. We will seek to identify 'what works in which circumstances and for whom' in relation to waterbirth. Stage one will focus on engaging with key senior professional stakeholders to hypothesise the generative mechanisms that explain how outcomes arise (i.e. the extent of pool use and waterbirth) and how these may be influenced by context. In stage two, these hypotheses will be tested in four case study sites, using the generative mechanisms and contextual factors identified in stage one to inform the development of interview and focus group schedules. Organisational case studies have been used to add a valuable qualitative component to other recent large-scale birth studies, for example within the Birthplace in England study[30]. By exploring organisational culture, insights can be gained into the effect of context on professional practice and service user experiences.

10.1 Qualitative component stage one

Design: Six closed online stakeholder discussion groups will be conducted, hosted on the Cardiff University website.

Participants: Proposed groups are:

1. Heads of Midwifery / Midwifery Managers from study sites.
2. Consultant Midwives from study sites.
3. Band 5 / 6 clinically focused midwives.
4. UK Obstetricians from within and outside of study sites (accessed via RCOG or another route).
5. UK Neonatologists from within and outside of study sites (accessed via the UK Neonatal Collaborative (UKNC) the RCPCH or another route.
6. Public including members of the RCOG Women's group, with participation open to women at study and non-study sites.

Participant Identification: Prospective participants will be recruited though various routes including potentially: participating units, professional and lay networks including social media, Royal Colleges. Those expressing interest will be provided with an electronic PIS explaining what participation will entail and what measures will be taken to protect their identity. Participation in the discussion will be taken as consent.

Online discussion group: Ground rules will be in place to ensure that the identity of individuals, departments or organisations are not disclosed and that participants act respectfully online. The groups will be administered and moderated by members of the research team, with access restricted to participants and the research team. Participants will be asked to discuss what cultural factors, in their experience, might contribute to the high and low rates of pool use and waterbirth.

Analysis: Framework analysis will be undertaken to generate key hypotheses for further exploration in stage two.

10.2 Qualitative component stage two

Design: In-depth organisational case studies will be conducted in four sites. The retrospective data extracted on site opening will be analysed to identify the range of the proportions of women using a pool for labour and birth. The four sites will be purposively sampled to represent sites with either high or low waterbirth rates.

Sites: The number of sites and time-frame is pragmatic; purposive site selection should provide breadth and depth of investigation within the resources and time available. To answer the qualitative research questions and address the secondary objectives of the study, it is proposed that the case studies be configured as follows:

- SITE A Obstetric Unit. High waterbirth rate;
- SITE B Obstetric Unit. Low waterbirth rate (excluding obstetric units without a bath or pool);
- SITE C Midwifery Unit. High waterbirth rate;
- SITE D Midwifery Unit. Low waterbirth rate, (excluding midwifery units without a bath or pool).

Data Collection: The aim of stage two is to explore the interplay between the generative mechanisms identified in stage one, organisational context and proportions of women that use water immersion for labour or birth. In each site, the following data will be collected:

1. Key documents relating to pool use and waterbirth (e.g. Guidelines, protocols, user information leaflets)

2. Three audio-recorded focus groups constituted as follows: i) Band 5 & 6 Midwives, ii) Band 7 Midwives, iii) Lay members of the local Maternity Voices / Maternity Services Liaison Committee.
3. Up to eight audio-recorded semi-structured interviews with key local stakeholders of which at least three will be with lay representatives. Key local stakeholders include: Head of Midwifery, Consultant Midwife, obstetricians, neonatologists, lay representatives from Maternity Voices / Maternity Services Liaison Committee, NCT or other local lay groups.

Sampling: Sampling will be purposive, to ensure a range of views are gathered from those with relevant experience.

Interviews: Interviews will be conducted face to face or by phone.

Participant identification: The study will be publicised at unit meetings and via local networks and potential participants requested to contact the research team or sign up to receive information. Prospective participants will be provided with participant information sheets and consent forms and invited to take part.

Analysis: Data will be thematically analysed initially, supported by NVIVO, in order to develop an analytic framework, which will then be used to code all data.

11 Risk assessment

A Study Risk Assessment has been completed to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This study has been categorised as a TYPE A, where the level of risk is no higher than the risk of standard medical care. A copy of the study risk assessment may be requested from the Study Manager. The study risk assessment is used to determine the intensity and focus of monitoring activity.

12 Withdrawal & lost to follow-up

12.1 Withdrawal – Qualitative Component

Participants have the right to withdraw consent for participation in the qualitative component at any time. The participant's care or employment will not be affected at any time by declining to participate or withdrawing from the study.

The withdrawal of participant consent shall not affect the study activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal.

In all instances participants who consent and subsequently withdraw should be requested to complete a withdrawal form or the withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant. A copy of the withdrawal form should be sent to the study manager by email. Any queries relating to potential withdrawal of a participant should be forwarded the POOL study manager.

18 Protocol/GCP non-compliance

The Principal Investigator should report (via CTR Protocol/GCP non-compliance and serious breach SOP [SOP/009/5]) any non-compliance to the study protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

19 End of Study definition

The end of the study at sites is defined as the date of final data capture to meet the study endpoints. In this case end of study is defined as the date of Cardiff University receiving final data extracts from EuroKing® and NNRD.

Sponsor must notify the main REC of the end of a clinical study within 90 days of its completion or within 15 days if the study is terminated early.

20 Archiving

The SMF and SSF containing essential documents will be archived at an approved external storage facility for a minimum of 15 years. The CTR will archive the SMF on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the study shall not be destroyed without permission from the Sponsor.

21 Regulatory Considerations

21.1 Ethical and governance approval

This protocol will seek approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This study protocol will be submitted through the relevant permission system for global governance review.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants and accrual of data commences within that host care organisation.

We will seek approval to use identifiable data in maternal and neonatal medical records held by the participating NHS sites and the National Neonatal Research Database, to form a linked pseudonymous research database, held by Cardiff University. This will require approval from the Health Research Authority's Confidentiality Advisory Group (CAG). The CAG is the independent statutory body established to monitor information governance in health and adult social care. The CAG reviews and advises the Secretary of State on requests to access confidential patient data under section 251 of the NHS Act 2006 (which allows identifiable patient information to be used without consent in specific circumstances). Approval for non-consented access to medical records of mothers and babies, held at NHS sites, and the matched neonatal records held by the NNRD will be required. The rationale for requesting to use identifiable data for data matching without consent is justified by several considerations: a) it is regarded as impractical to obtain individual level consent from the complete cohort of 600,000 women on whom data is required; b) the cost to the NHS cannot be justified when the study can been designed so that the data held at Cardiff University will be pseudonymous; c) obtaining individual consent from women would result in some inevitable distraction to them either during labour or the early neonatal period; and d) the requirement for individual consent to study participation would inevitably lead to an incomplete cohort and a potentially biased sample.

The data-set of the National Neonatal Research Database was created at the Neonatal Data Analysis Unit (NDAU), Imperial College London to NHS Information Standard (ISB1595). The NDAU holds all necessary regulatory approvals for the NNRD (Caldicott Guardian, NHS, Research Ethics, Confidentiality Advisory Group of the Health Research Authority). The Chelsea & Westminster NHS

Foundation Trust secures all data held in the National Neonatal Research Database.

21.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the Data Protection Legislation. The data custodian for this study is Cardiff University.

21.3 Indemnity

Negligent harm: The NHS organisation providing clinical care continues to have a duty of care to participants, whether or not the participant is participating in this study. Cardiff University does not accept liability for any breach of duty of NHS care, or any negligence on the part of employees of NHS organisations. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Study (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

Data will relate to women and babies receiving NHS care and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at study sites.

21.4 Study sponsorship

Cardiff University will act as Sponsor for study. Delegated responsibilities will be assigned to the sites taking part in this study. The Sponsor will be delegating certain responsibilities to the Centre for Trials Research, the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

21.5 Funding

This study is funded by National Institute for Health Research Health Technology Assessment (NIHR HTA) – Project number 16/149/01. The study will be eligible for adoption onto the NIHR portfolio and CLRN support.

22 Study management

The study will be delivered via two operational work packages (cohort study and qualitative component). Each work package group will be chaired by a co-applicant.

The cohort study work package will be chaired by Professor Julia Sanders (CI) and the qualitative component chaired jointly by Professor Billie Hunter and Dr Sue Channon. Each chair will convene work package group meetings as appropriate for the duration of the study. Each group will be responsible for deliverables within their work package and will convene task and finish groups to accomplish these as well as ongoing progress.

The lead applicant will assume overall scientific and financial responsibility for the study and with the study manager will be responsible for day to day overview of both work packages.

22.1 SMG (Study Management Group)

A Study Management Group will comprise the lead applicant, co-applicants, including work package chairs and patient representatives and will meet at least bi-monthly to regularly review study milestones. SMG members will be required to sign up to the remit and conditions as set out in the SMG Charter.

22.2 SSC (Study Steering Committee)

A Study Steering Committee (SSC) to include a midwife, an obstetrician, a neonatologist, a lay member and a statistician will be established to provide study oversight and report to funders. The first meeting will be prior to the commencement of data collection to review and approve the protocol. The SSC will then plan when it wishes to meet but as a minimum this will be at the end of the pilot phase and then annually to review study progress. As the study is evaluating outcomes associated with usual care provided by the NHS and does not intend to affect the care provided to individual participants it is not planned to have an independent Data Monitoring Committee.

SSC members will be required to sign up to the remit and conditions as set out in the SSC Charter.

23 Quality Control and Assurance

23.1 Monitoring

The study risk assessment has been used to determine the intensity and focus required monitoring of the POOL study. Low monitoring levels will be employed and will be fully documented in the study monitoring plan, saved in the SMF. Monitoring will be focussed on the data quality of the new data

items added to the system and will be assessed at the pilot extraction stage and reviewed to ensure these items are being completed correctly.

23.2 Audits & inspections

The study is participant to inspection by the Health Research Authority as the regulatory body. The study may also be participant to inspection and audit by Cardiff University under their remit as Sponsor.

24 Publication policy

Dissemination of the study results will include publication in a high calibre journal through open access agreement, a full report, a lay infographic summary aimed at pregnant women and available for use by NHS providers, and distribution though social media including pod casts or similar.

A publication policy, communication strategy and dissemination plan will be drafted for the study and circulated internally with the SMG and SSC. This will be detailed in the publication policy document and saved on the SMF.

All publications and presentations relating to the study will be communicated to the Study Management Group as per the publication policy.

25 Milestones

3 months prior to start	**Initial preparation** – Staff recruitment, protocol development, confirmation of study sites, development of required additional data items for the EuroKing® system and syntax for data extraction.
Months 1 – 6	**Continuing preparation and site set up** – protocol approval by Study Steering Committee, NHS ethical & R&D and Section 251 approval. **Open study sites** – including at each site the extraction of retrospective data and addition of required data items to maternity systems. First extraction of neonatal NHS numbers for NNRD.
Months 6-11	**Extraction of first three months of prospectively collected data from each site.** Test linkage between maternal and neonatal data from NNRD.
Months 4 – 21	**Qualitative work** Focus groups/ interviews / case studies of sites
Months 3 – 32	**Collection of prospective data** relating to maternal and neonatal outcomes – Extraction and transfer of data from participating sites to NNRD and Cardiff University every three months.
Month 33	**Final data extraction** and transfer to Cardiff of prospectively collected EuroKing® data from each site.
Months 34	EuroKing® **data cleaning**
Months 36	Final **NNRD** data transfer to Cardiff University
Months 35 – 40	Data analysis
Month 39 -41	Writing up results
Month 41	Complete reporting and dissemination

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