



Full/long title of study SNAPSHOT OBSTETRIC NATIONAL ANAESTHETIC RESEARCH PROJECT

Short title SONAR 1

Version and date of protocol Version 1.2
(12/12/2024)

Sponsor: University College London NHS Foundation Trust (UCLH)

Sponsor reference number: EDGE 129383

Funder (s): NIAA/OAA Large Grant. Application No.: WKRO-2019-0036

[NIHR Central London Patient Safety Research Collaboration](#)

IRAS Number: IRAS 265964

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PROTOCOL VERSION HISTORY

Version Stage	Versions Number	Version Date	Protocol updated & finalised by;	Reasons for Update
Initial submitted	Version 1.0	12/10/2023	Reshma Patel 12/10/23	Amendments to fit JRO protocol
Pilot	Version 1.1	20/4/2024	Reshma Patel 20/04/24	Amendments for REC/HRA resubmission
Current	Version 1.2	12/12/24	James O'Carroll	Amendments for national study

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DECLARATIONS

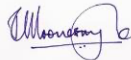
The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the U.K. Policy Framework for Health and Social Care Research 2017 (3rd edition) (as amended thereafter), the EU General Data Protection Regulation (2016/679) and the UK Data Protection Act (2018), Sponsor SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the research investigation without the prior written consent of the Sponsor.

I (investigator) agree to ensure that no research activity or recruitment will commence at participating research sites until the appropriate regulatory approvals and NHS confirmations of Capacity and Capability have been issued, and Sponsor green light confirmed.

I (investigator) also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given. Any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:



Signature:

Date: 12/12/2024

Print Name (in full): SR Moonesinghe

Position: Director, NIHR Central London Patient Safety Collaboration; Professor of Perioperative Medicine, UCL / UCL Hospitals

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On behalf of the Study Sponsor:

Signature: Date:/...../.....

Print Name (in full):

Position:

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STUDY SUMMARY

IDENTIFIERS	
IRAS Number	265964
REC Reference No.	
Sponsor Reference No.	EDGE 129383
Other research reference number(s) (if applicable)	
Full (Scientific) title	Snapshot Obstetric National Anaesthetic Research project 1
Health condition(s) or problem(s) studied	Incidence, risk factors and impact of inadequate neuraxial anaesthesia and intraoperative pain during caesarean section
Study Type i.e. Cohort etc.	Prospective cohort study
Target sample size	Feasibility study 100 Multicentre study <u>dependent on site number (circa 1500)</u>
STUDY TIMELINES	
Study Duration/length	15 months
Expected Start Date	July 2024
End of Study definition and anticipated date	October 2025
Key Study milestones	Feasibility study start: July 2024 Participant multicentre study start: <u>March 2025</u> Follow-up completion: <u>July 2025</u> Analysis and Write Up: <u>Q4 2025</u>
FUNDING & OTHER	
Funding	National Institute of Academic Anaesthesia (OAA Large Project Grant) £ 54,011.49 NIHR Central London Patient Safety Research Collaboration In kind support for statistician and leadership
Other support	UCL Centre for Perioperative Medicine Prof. Ramani Moonesinghe Charles Bell House 43-46 Foley Street Fitzrovia London W1W 7TS

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STORAGE of SAMPLES / DATA (if applicable)	
Human tissue samples	N/A
Data collected / Storage	<p>Data Custodian:</p> <p>Professor S R Moonesinghe</p> <p>ramani.moonesinghe@nhs.net</p>
KEY STUDY CONTACTS	
Chief Investigator	<p>Prof. Ramani Moonesinghe - Chief Investigator</p> <p><i>Address:</i> UCL/UCLH Surgical Outcomes Research Centre, Centre for Perioperative Medicine, University College London, Charles Bell House, 43-47 Foley Street, London W1T 7SG</p> <p><i>E-mail:</i> Ramani.moonesinghe@nhs.net</p>
Study Coordinator	<p>Dr. James O'Carroll</p> <p>Address: University College London Hospital, Department of Anaesthesia, 235 Euston Road, NW1 2BU</p> <p><i>E-mail:</i> james.ocarroll@nhs.net</p> <p>Dr. Reshma Patel – Trainee Lead Investigator</p> <p><i>Address:</i> University College London Hospital, 252 Euston Road, London NW1 2BU</p> <p><i>E-mail:</i> Reshma.patel21@nhs.net</p>
Sponsor	<p>University College London / UCL Hospitals Joint Research Office</p> <p>Uclh.randd@nhs.net</p>
Funder(s)	<p>NIAA/OAA Large Grant</p> <p>Application No.: WKRO-2019-0036</p> <p>£ 54,011.49</p>
Committees	N/A
Sub-contractors	N/A
Other relevant study personnel	<p>Dr Bo Hou – Statistician</p> <p>Centre for Perioperative Medicine, University College London, Charles Bell House, 43-47 Foley Street, London W1T 7SG</p> <p>Email: b.hou@ucl.ac.uk</p>

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KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also must be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals and confirmations of NHS Capacity and Capability are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the REC and JRO of the end of the study (including the reasons for premature termination, where applicable). Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC and JRO.

PRINCIPAL INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

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KEY WORDS

Anaesthesia, Regional Anaesthesia, Neuraxial Anaesthesia, Obstetrics, Surgery

LIST OF ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
GA	General Anaesthesia
GCP	Good Clinical Practice
ICF	Informed Consent Form
NA	Neuraxial Anaesthesia
NHS	National Health Service
NIAA	National Institute for Academic Anaesthesia
NIHR	National Institute for Health Research
PND	Postpartum Depression
PTSD	Post-traumatic Stress Disorder
PI	Principal Investigator
PIS	Participant Information Sheet
RCoA	Royal College of Anaesthetists
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SONAR 1	Snapshot Obstetric National Anaesthetic Research Project 1
UCL	University College London

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1 INTRODUCTION

There is limited high-quality information available about the quality of neuraxial anaesthesia (NA) during obstetric surgery, how intraoperative pain should be managed and what the outcomes are for participants who experience this adverse event.

SONAR 1 is a prospective, observational cohort study with a planned feasibility study to take place at a single centre followed by a national, multicentre study. The aim of SONAR 1 is to understand the incidence and risk factors for inadequate NA for patients undergoing caesarean section (CS), and to use patient-centred outcomes and qualitative methods to evaluate the physical and psychological impact on participants who experience NA failure.

The study cohort will encompass adult participants (aged 18 years and over) receiving NA for scheduled and unscheduled CS over the entire study period (daytime and out-of-hours). Data collection will comprise the use of three separate case record forms (CRFs):

1. The first of the three CRFs will be completed by the responsible anaesthetic clinician for each CS case and will consist of patient demographic, medical, anaesthetic and obstetric routine collected data (CRF1).

Following this, participants will be asked to complete two short questionnaires with study investigators:

2. The first patient questionnaire (CRF2) will ask questions regarding their experience, any discomfort they may have encountered during their CS, the overall satisfaction with anaesthetic care and the quality of recovery following their procedure. CRF2 data collection will occur within the first 24 hours (+/- 6 hours) postoperatively.
3. The second patient questionnaire (CRF3) will ask the same cohort of participants tick-box questions to identify the extent of the impact to those who may have had negative experiences of CS under NA, in order to compare this to those who did not. CRF3 data collection will take place at 6 weeks (+/- 3 days) postoperatively.

The results from this study will enable us to identify and understand the incidence, impact of intraoperative pain and neuraxial anaesthesia inadequacy, with a view to helping to develop standardised strategies to help reduce or better manage intraoperative pain during CS. It will also provide better information for future patients and healthcare professionals regarding this topic.

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2 BACKGROUND AND RATIONALE

CS is the most commonly performed inpatient surgical procedure globally, with approximately 30 million patients delivering via this route annually¹. In the UK alone, 28% of patients (approximately 178,000 yearly) deliver by CS, the majority of which are performed as emergencies.

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NA is the gold standard mode of anaesthesia for CS. It is regarded as superior to general anaesthesia (GA) and has a lower maternal morbidity and mortality associated with its use². Other advantages over GA include superior postoperative analgesia, improved recovery following surgery and an awake patient during childbirth - which is thought to improve maternal experience, satisfaction and facilitate neonatal bonding³.

The Royal College of Anaesthetists (RCoA) have proposed a quality improvement compendium for best practice in obstetric anaesthetic services which identify an NA rate of > 95% for elective CS (as opposed to GA) and > 50% for Category 1 emergency CS³ (defined as an immediate threat to life to patient or baby requiring immediate delivery). However, NA is not always successful - the incidence of inadequate NA varies widely and depends on factors such as urgency of surgery, type of NA (spinal vs. epidural vs. combined spinal-epidural), surgical approach and use of a pre-existing epidural that was previously inserted for labour analgesia. The incidence of severe breakthrough pain during obstetric surgery remains unknown.

A small number of single centre retrospective studies exist that discuss failure rates of regional anaesthesia for CS. Failure rates from these studies have a broad range from 1.7%⁴ to 19.7%^{5,6}. A recent systematic review including >3000 patients found that the overall prevalence of requirement for supplemental analgesia or anaesthesia was 14.6%⁷. One potential reason for this wide variation in failure rates is the lack of a standardised definition of what constitutes 'inadequate NA'. This has been defined as pain during surgery, requirement for intraoperative analgesia, the inability to achieve a desired sensory level of anaesthesia, poor maternal satisfaction and conversion to an alternative anaesthetic technique (including conversion to GA)^{3,7}.

Published audits, usually conducted in single centres, have reported rates of 9 – 23%⁸, although some studies have quoted rates of 2 – 10%^{8,9}. It remains unclear what percentage of these GA cases were converted from NA due to inadequate anaesthesia.

Kinsella et al. conducted the largest published study thus far, comprising of over 4500 neuraxial cases⁶. This was undertaken in a single UK institution over a 5-year period between 1999 – 2004⁶. The rate of conversion of NA to GA during emergency CS in this population was 5%, with a four times greater conversion rate reported for Category 1 CS cases. While the study identified factors associated with requirement for conversion to GA, the management strategies employed by anaesthetists and their corresponding success rates at mitigating requirement for conversion to GA were not reported. Furthermore, participants in this audit were not followed up to determine whether their experiences impacted their overall experience, maternal satisfaction, or subsequent quality of recovery from surgery. Finally, longer-term psychological effects (such as development of postpartum depression or posttraumatic stress disorder) were also not reported.

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Within the last decade, there have been no large prospective studies evaluating the rate of inadequate NA with the use of contemporary obstetric anaesthesia practices and techniques. During this time, there have been changes to staffing levels within delivery units (e.g. increased senior supervision out-of-hours, increased care by consultants who have undergone subspecialist training in obstetric anaesthesia), changes to practice. This is particularly relevant as labour epidural analgesia is frequently converted to surgical anaesthesia for emergency CS. Evaluation of current management strategies to deal with severe intraoperative breakthrough pain and the effect on subsequent maternal outcomes is required to help with decision making by clinicians in such challenging clinical scenarios.

“Preoperative anxiety” can be considered a form of state anxiety and is defined as an unpleasant state of discomfort or tension related to the condition of waiting to undergo anaesthesia and surgery¹⁰. Several studies have demonstrated that preoperative anxiety is associated with poor perioperative outcomes^{11,12}. Few studies specifically measure the impact of preoperative anxiety on intraoperative pain, as it is not common that patients are able to express their pain intraoperatively. However, measurement of preoperative anxiety is an appropriate choice for this study as it may impact the incidence of intraoperative pain and postoperative outcomes.

Recently published guidance emphasises the risk of adverse psychological sequelae as result of pain during CS and provides guidance on its management¹³ but does not elucidate on the scale of the potential impact.

The aim of this study is to initially evaluate the feasibility and inform a follow-on larger study which will determine the reliability, failure rate and incidence of inadequate NA in contemporary obstetric anaesthetic practice using a multicentre approach in the UK. Data will be collected and collated on how pain during obstetric surgery is managed in order to: (1) understand the scale of the problem, (2) how successful anaesthetists are in addressing these issues and (3) what the impact of inadequate NA and failure of NA is in the parturient population undergoing obstetric surgical intervention.

3 AIM(S) AND OBJECTIVES

- To evaluate the relationship between hospital level, patient, anaesthetic and obstetric risk factors, and short- and longer-term outcomes following caesarean delivery using neuraxial anaesthesia.
- To evaluate the relationship between hospital level, patient, anaesthetic and obstetric risk factors and the incidence of intraoperative pain following caesarean delivery using neuraxial anaesthesia.

3.1 Primary Objective

- To evaluate inpatient and outpatient outcomes related to intraoperative pain.

3.2 Secondary Objectives

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- To estimate the incidence of patient reported and clinician reported intraoperative pain during CS conducted under NA
- To evaluate the physical and psychological impact on patients of inadequate NA during CS

4 STUDY DESIGN & METHODS OF DATA COLLECTION

Type of Study

SONAR-1 is a prospective, observational cohort study. The initial feasibility pilot study at University College London Hospital (UCLH), will take place over 4-week period where we aim to recruit at least 100 participants. This is in order to identify any logistical difficulties in performing a multicentre study.

The subsequent multi-centre study will require participating sites to undertake one weeks of participant recruitment during a two-month window. Local study processes will be overseen by designated local study investigators. During the study, data will be collected from all caesarean deliveries using **CRF1** by the anaesthetist performing the case either during or immediately afterwards. Written consent will be sought from all participants in the perioperative period, followed by provision and completion of **CRF2** should consent be provided. At 6 weeks postpartum (+/- 3 days), local investigators will then aim to contact consenting participants for completion of **CRF3**.

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Study Population and Groups

All participants who meet the inclusion criteria are eligible to become participants.

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How has the planned number of participants been derived?

For the pilot study We plan to collect data from UCLH for a 4-week study period. UCLH has approximately 20 elective CS a week, and a similar number of non-elective sections. Thus, we aim to recruit approx. 100 participants. The subsequent multicentre study will take place over approx. one weeks (during a two-month time period), aiming to recruit 1500 participants

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Methods used to determine the sample size

The initial pilot feasibility study does not include a formal sample size calculation. However, we will aim to recruit 100 participants to draw conclusions with regards to feasibility and follow-up rates for the multicentre study. This will facilitate us to calculate a more definitive sample size. Currently for the multicentre component of the study the sample size is calculated for detection of intraoperative pain, which was estimated to be 15% with a 95% confidence interval and a margin of error of +/-3%. This gives a single centre total of 545 participants recruited. However, since there will be multiple centres in the study, a design effect has been used to account for between site variation and within site clustering. The design effect is $1+ICC*(n-1)$ and n is the number of subjects per cluster. If there is no empirical data of ICC we could use 2 as the design effect. So, the n is $545*2$ giving a total sample

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size of approximately 900 participants, and up to 10% will have incomplete data within their CRFs. At 6 weeks we anticipate approximately 70% of participants will be followed up, this therefore gives a total sample size of 1500 participants.

There is no specific sampling technique for the study, all eligible consenting participants will be included.

Definitions for the purposes of the study

For CRF 1, we will define inadequate neuraxial anaesthesia as: the need to convert to general anaesthesia where pain; the need to repeat or abandon a planned primary neuraxial anaesthetic technique following skin incision; the unplanned administration of intra-operative analgesia (excluding benzodiazepines); or unplanned epidural drug supplementation with local anaesthetic where an epidural catheter was in-situ (e.g., due to unexpected length of surgery or participant discomfort)

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What data will be collected and how?

There are two points of data collection during the inpatient stay. These will be **CRF1** and **CRF2** as detailed below.

CRF1 – Operating theatre data to be collected at the time of surgery or immediately after by the responsible anaesthetist and will compromise routinely collected intraoperative audit data. This includes baseline parturient characteristics, surgical indication and details, surgical complications, duration of surgery, subjective/objective measures of pain reported by patients and how pain was managed. Details regarding NA techniques will also be collected.

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CRF2 - Patients who provide consent will be asked to complete a paper-based CRF within 24 (+/- 6 hours) of their procedure. We will use two previously described and validated patient-reported outcome measures (PROMs). These include the current patient reported pain scores, and the Maternal Satisfaction Score¹⁷. In addition, we have developed a simple questionnaire to assess intraoperative pain and satisfaction with anaesthetic and analgesic therapies. During this time, patients will also be asked to provide their contact details to allow local investigators to contact them at 6 weeks for the purpose of completing **CRF3** (detailed below). In terms of patient data collection, inpatient follow-up will cease after completion of **CRF2**. Where the first language is not English, and the participant “Cannot speak English well or Cannot speak English”, we have provided patient facing documents in the 6 most spoken languages of Polish, Bengali, Urdu, Arabic, Mandarin and Panjabi. In addition, we have provided Welsh language documents

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There is one further point of data collection after hospital discharge:

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CRF3 – This CRF will be used to collect follow-up data at 6 weeks (+/- 3 days) from participants who provide consent. This will be the validated Generalised Anxiety Score (GAD7)^{15,16}, Edinburgh Postnatal Depression Scale (EPDS)¹⁸ and the Post-Traumatic Structured Checklist (PCL-5)¹⁹, Data collection by

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local investigators following discharge will be facilitated by the participant's contact details collected during completion of **CRF2**. Local investigators will telephone participants for **CRF3**, rather than using any other mode of contact (e.g., e-mail, letters). Up to a maximum of three attempts should be made to contact participants, with each attempt being noted on the study log. If no contact is made after three attempts, no further attempts should be made, and the participant should be deemed 'lost to follow-up' and recorded as such on the study log. If contact is made, but the participant asks to be called back at a later time, it is acceptable to make more than three phone calls. If contact with the participant is made, but **CRF3** is only partially completed (e.g., due to other time commitments), it is acceptable to make more than three attempts to recontact the participant in order to complete the CRF. However, recontact should be done with sensible judgement – local investigators should be dissuaded from an excessive number of attempts which could be deemed to be too intrusive by consenting participants.

Where the consenting participant "Cannot speak English well or Cannot speak English", and the participant's chosen language is Polish, Bengali, Urdu, Arabic, Mandarin and Panjabi, the participant should be telephoned using the trusts' local translation service.

Should a participant score more than 11 on the EDPS, more than 30 on the PCL-5 structured checklist, or more than 10 on the GAD-7 then a letter (as found in the study documents) should be sent to them and their GP. The participant should be informed that her score would suggest she may be suffering from anxiety, PPD or PTSD and encouraged to see her GP or health visitor. Specifically, if there is strong suspicion of patient risk or if the patient answers anything but "No, Never" to question 10 "The thought of harming myself has occurred to me" then the patient will be referred to the local safeguarding team and encouraged to seek urgent assistance.

In summary, during the data collection period, the following methodology will be followed: (Figure 1).

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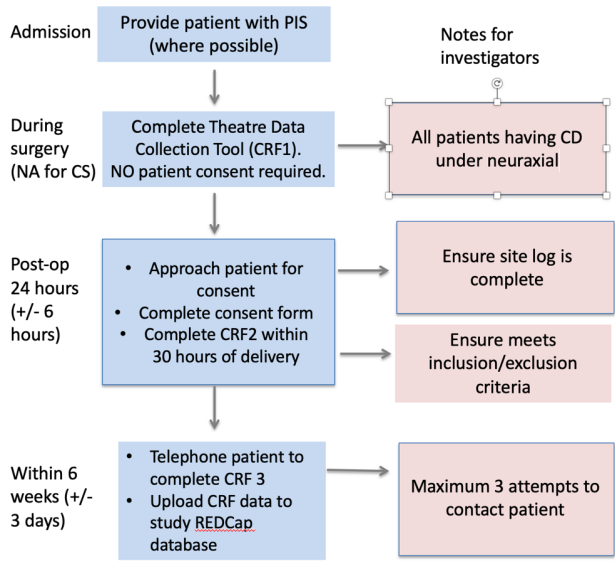


Figure 1. Flowchart of methodology for data collection and data upload to REDCap™

A pilot and feasibility study in a single centre will collect preliminary data, and assess feasibility and optimise the study protocol prior to a multi-site study.

Participating sites will need to provide evidence of:

- Consultant-led labour ward
- Appropriately trained Principal Investigator
- Availability of appropriate secure location for study log

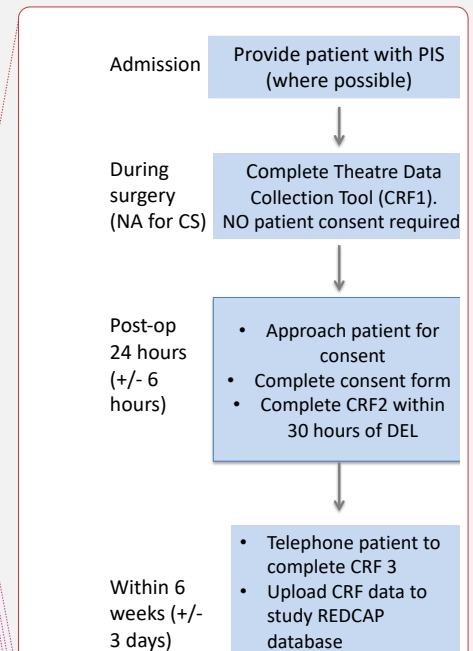
The same study activities will be undertaken at each site.

Approximate duration of enrolment and follow-up

For initial study, we plan to recruit 100 participants. UCLH has approximately 20 elective CS a week, and a similar number of non-elective sections. Thus, we will enrol for 4 weeks. They will be followed up by 6 weeks (+/- 3 days).

For the multi-centre study, we aim to run for one week (7days) at each site, within a two-month period. The participants at each site will also be followed up by 6 weeks (+/- 3 days).

Taking into account postoperative outcome data to be collected at 24 (+/- 6) hours (short-term) and six weeks (+/- 3 days) (medium-term) postoperatively, we anticipate an approximate 10-week total duration from participant enrolment to follow-up, allowing additional time for participants to provide data.



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Study Management

The project team, chaired by the CI, plan to oversee and deliver the day-to-day organisation of the study. All aspects of the study (inc. screening, data collection, follow-up) will be conducted by appropriately trained staff who should meet locally determined standards for these processes.

5 STUDY SCHEDULE

Enrolment, screening and follow-up

The planned outline for each potential participant participating in both the single centre feasibility study and the multicentre participant study is as follows:

- As early as possible following admission to a consultant-led labour ward, potential participants should be provided with information about the study via a Patient Information Sheet (PIS). Any member of clinical or research staff can give the participant a PIS and inform them that the study is occurring within the facility, but any specific participant questions regarding the study should be directed to a local investigator.
- In most cases, provision of information regarding SONAR-1 will occur shortly following admission and before delivery. However, in emergencies or for other local logistical reasons, some participants may only receive the PIS after delivery. In this case, local investigators are required to ensure that the participant is given at least one hour to consider the information on the PIS before being approached for consent.
- Potential participants should be approached for consent at the earliest feasible post-operative opportunity but not earlier than one hour after provision of the PIS. Patients who do not consent should be noted on a local study log. Audit data will be entered into the study database, but there will be no patient identifiable data entered; this data will be used for sensitivity analyses to compare patients who do and do not consent to study participation. We have chosen a minimum 1-hour timeframe as it is common for patients to move from recovery and post-natal wards and see many other health professionals during the immediate post-natal phase.

Patients who undergo CS under NA and who meet the inclusion criteria should have relevant intraoperative audit data collected on **CRF1** by the anaesthetist responsible for the case. Where possible, this should be done intraoperatively or immediately after the case. The participant is then entered on to the study log.

Patients should be consented at the earliest feasible opportunity post-operatively. If participants are too unwell to be included in the study during the immediate post-operative period (e.g. if they have received a large dose of opioids or a GA), local investigators should use their judgement about the appropriate timing of approach for consent. Recruitment and completion of **CRF2** should ideally within 24 hours (+/- 6 hours) of the CS. However, omission of recruitment during the 24-hour (+/- 6 hours) time window does not exclude participants from being recruited at any point up to their discharge from hospital, as long as this is recorded as a protocol deviation.

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Patients who consent should ideally complete **CRF2** no later than 24 hours (+/- 6 hours) postoperatively.

Patients should be contacted by telephone at 6 weeks (+/- 3 days) postoperatively for completion of **CRF3**. Three attempts should be made to contact participants (including a text message and email to check availability before the 3rd attempt). Following this, if no contact is possible after three attempts, these participants are 'lost to follow up'. Each attempt at contact should be noted on the study log.

Upon completion of **CRF3**, or following three failed attempts at contact, the participant record is closed, and their data should be uploaded to the central REDCAP™ database.

The process above is summarised as follows (Figure 2):

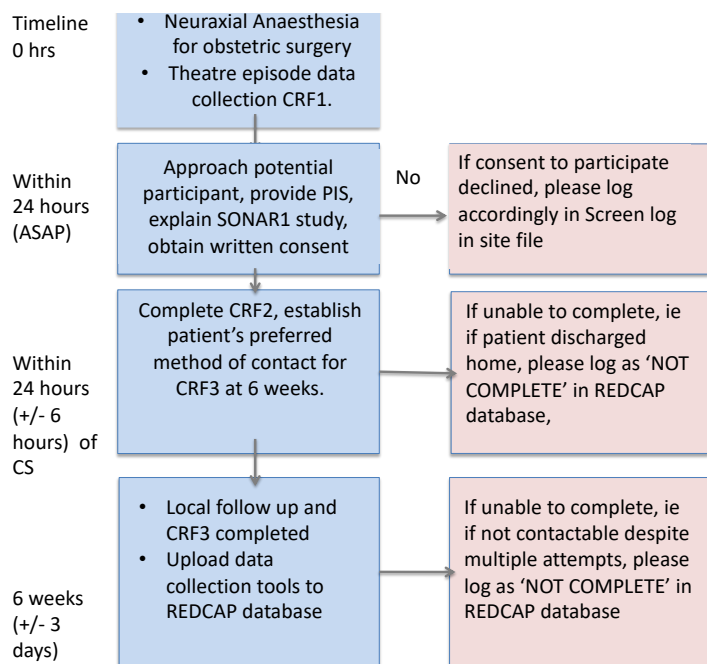


Figure 2. Flowchart of methodology for each potential participant

Enrolment Process

All patients will be informed about the study and given a study PIS. Additionally, the study will be openly advertised via posters. Contact details of the local investigative team will be made available on all study material to answer any enquiries which might arise from staff or participants.

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A synopsis of the enrolment, consent and data collection for each component of the study is as follows:

CRF1: Intraoperative audit data: completed by the responsible anaesthetist during the operative period on all patients who meet study inclusion criteria. As this comprises routinely collected audit data, this aspect of the study does not require participant consent.

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CRF2: completed within 24-hours of CS completion (+/- 6 hours). This visit should also be used to obtain contact details from each participant to facilitate completion of **CRF3** at 6 weeks (+/- 3 days) post-procedure following hospital discharge.

In all the above cases, consenting participants will be recorded on to a local site study log. Those who decline consent will also be recorded on this log to ensure that they are not followed-up. This logging will be for the purpose of reporting results according to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidance¹⁴.

CRF3: completed at 6 weeks following CS (+/- 3 days). In most cases, participants will have been discharged from hospital. An interval of 3 days either side of 6 weeks has been selected in order to provide maximum opportunity to select an appropriate time for the participant's convenience. Local investigators will be tasked with completing **CRF3** via telephone using contact details obtained during inpatient follow-up.

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Participant Withdrawal

Participants are free to withdraw from the study at any point and without reason. This should be recorded in the study log to prevent unnecessary follow-up and for reporting according to STROBE¹⁴. If they choose to withdraw before study recruitment is complete and the study closes, their data will be removed from the study database and not used during data analysis. Participants withdrawing consent will not be part of the database other than the screening log. However, if they choose to withdraw after recruitment is complete and the study closes, it will not be possible to remove their data as analysis will have already commenced. This will be stipulated on the PIS.

Study Closure

The feasibility study recruitment will end after once 100 participants have been recruited. The multicentre study will close at the end of the one-week study period at each site, within a 2-month window. The electronic database will be held for 10 years post-study end.

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Invitation to participate in future research or be contacted about study results

All consenting participants will be invited to give permission for their email contact details to be retained by local investigators, for the following two purposes:

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- To be sent (by email) information about the study findings
- To be sent (by email) details about further research on peri- and post-natal health and outcomes

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6 ELIGIBILITY CRITERIA

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6.1 Inclusion Criteria

- Aged 18 years old or above
- Gestation beyond 32/40 weeks
- Receiving NA (spinal, Epidural or combined spinal epidural as the primary mode of anaesthesia)
- Receiving a scheduled or unscheduled CS of any category.

6.2 Exclusion Criteria

- Patient refusal
- Patients who are unable to provide informed consent
- Other modes of delivery (e.g., instrumental delivery)
- De novo GA as an anaesthetic method
- [Intrauterine or neonatal demise](#)

7 RECRUITMENT

Hospital Recruitment

For the multicentre study the lead clinician for obstetric anaesthetic services will be contacted for agreement to participate. At the confirmed site, there will be a principal investigator (PI) and a trainee lead investigator will be nominated to oversee a local investigative team who will facilitate delivery of the study on the maternity unit.

Participant recruitment

- All participants who undergo a CS will be recorded on the local site screen log.
- Eligibility will be assessed based on the inclusion/exclusion criteria (as per *Section 2.2*).
- [We have provided translation of patient facing documents in the 6 most common languages when English is not spoken or spoken well, in addition to Welsh language translations, to facilitate broader recruitment.](#)
- A PIS will be provided asap upon admission to the maternity unit.
- Participants having elective CS may be consented for participation prior to surgery.
- All participants who meet the eligibility criteria (as per *Section 2.2*) in participating hospitals will have intraoperative data collected on **CRF1** by the responsible anaesthetist for the CS.
- Patients who have not already consented will be approached for consent after surgery.
- In cases where due to clinical pressures, **CRF1** was not completed at the time of surgery, Local investigators will be responsible for completing the participant's data retrospectively by accessing participant notes.

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Thus, for feasibility assessment and the STROBE flowchart, the site log will inform us of:

- Number of participants screened
- Number of participants eligible
- Number of participants consented
- Number of participants who complete **CRF2** and **CRF3**

8 CONSENT

Patients aged 18 or above who undergo CS conducted under NA and meet the inclusion/exclusion criteria will be approached to provide informed consent to participate. Consent should be sought by anyone who has completed the required training to obtain consent according to local R&D guidelines – this may include, for example, clinical staff, research nurses, research midwives or non-clinical research assistants. Potential participants must be given at least one hour to consider the information provided before they are approached for informed consent. The study will be openly advertised to patients and other members of the public through posters on relevant hospital areas. We have translated the patient facing documents into the 6 most commonly spoken languages where English is not spoken well or at all. These are Polish, Bengali, Urdu, Arabic, Mandarin and Panjabi. In addition, we will be providing Welsh language documents.

9 DATA ANALYSIS

Analysis of the intraoperative data (**CRF1**) and participant follow-up questionnaire (**CRF2**) will be predominantly based on providing descriptive epidemiology of the incidence of inadequate NA and strategies for its management. The descriptive epidemiology of decision-making with regards to analgesia supplementation and augmentation or conversion of NA will be described. Inferential statistics (regression modelling) will be used to understand modifiable and non-modifiable risk factors for inadequate NA and patient-centred adverse outcomes measured in **CRF2** and **CRF3**. This will also enable us to understand the relationships between patient and structural risk factors, care processes, short-term and longer-term outcomes. Free-text responses will be analysed thematically.

10 PATIENT AND PUBLIC INVOLVEMENT (PPI)

The themes of this study were prompted by Ms. Susanna Stanford's personal experience of neuraxial failure, as published in the International Journal of Obstetrics Anaesthesia²¹. This paper highlighted the paramount importance of communication between participant and anaesthetic provider. Following the lessons learned from Ms. Stanford's experiences, it is prudent to explore patient and structural risk factors of inadequacy of NA, as well as the impact on patients and their families. We have sought PPI from a community-based parent group in North London, comprised of people who have delivered at UCLH or their partner hospitals within the last year. This group have reviewed the protocol, patient information leaflet, participant information poster, letters to participant and GP, consent form and CRFs. In addition, we sought feedback from Ms Stanford, who has reviewed the study documents. Ms Stanford and the PPI group have provided valuable feedback and changes to the study documents. Our study team includes two patient representatives, one of which is Ms Stanford;

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they are full active members of the study team, have contributed to study design and will contribute to delivery, analysis and dissemination.

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11 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the UCLH/UCL Joint Research Office and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the Local Clinical Research Network.

The research costs for the study have been supported by the Obstetric Anaesthetists' Association through an award from the National Institute of Academic Anaesthesia. A total of £54,011.49 was awarded on the 26/06/2019. In addition, the NIHR Central London Patient Safety Research Collaboration is providing funding in kind for study costs including statistical and qualitative expertise, and operational support

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12 DATA HANDLING AND MANAGEMENT

The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the UK Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act's core principles. UCLH is the data controller; the UCLH Data Protection Officer is Alex Potts (a.potts@ucl.ac.uk, data-protection@ucl.ac.uk)

The data processors are [the investigators of the study. These individuals are all based at one or more of the following institutions.

- University College London Hospitals NHS Foundation Trust
- University College London (Centre for Perioperative Medicine, Research Department for Targeted Intervention, Division of Surgery and Interventional Science)

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The central team will have no access to personal identifiable data.

All investigators and study staff will be expected to comply with the requirements of the Data Protection Act 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Data will be collected on all participants who meet the inclusion criteria and who consent to the study (as detailed in *Sections 4* and *5*). Nominated staff that will be responsible for data collection and postoperative follow-up. No participant data will leave the UK, and all data analysis will be performed by the study group that is based in the UK. All CRFs are included as *Appendices*.

At a local level, completed paper CRFs for the participant study will be held in a secure location accessible only to the local PI and any named members of the site study team, in accordance with Good Clinical Practice (GCP) guidelines and local information and research governance frameworks.

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Information from the paper CRF will then be entered on to a central online database via a secure web-based portal.

Perioperative anaesthetic providers will complete **CRF1** for each participant that meets the inclusion criteria. Patient Identifiable data (name, hospital number) will be on **CRF1** in order to link the participant and their subsequent questionnaires, but no PID will leave the hospital or be made available to the central team. The information will comprise questions regarding participant risk factors, type of anaesthesia, surgical process data, and subjective and objective assessment of pain. Where a participant is handed over between anaesthetists, the most senior anaesthetist present at the end of surgery will be asked to review the responses to the questionnaire and amend if necessary.

For follow-up at 6 weeks (+/- 3 days), local investigators will ask participants during completion of **CRF2** for contact details and a preferred day/time to call. Patients will be asked to complete **CRF3** via telephone at 6 weeks (+/- 3 days) post-discharge from hospital, and this should be made clear when completing **CRF2** and gaining contact details from the participant. **CRF3** will be completed via telephone within 6 weeks (+/- 3 days) of the participant's procedure.

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Completed CRFs will be taken directly to a secure location accessible by the local PI or designated members of the local investigative team who will then enter data from the paper form for upload on to the central study database. Data will be entered electronically via a secure, encrypted connection onto an online portal hosted by University College London. The software used for data capture will be REDCap™ (Research Electronic Data Capture – <http://www.project-redcap.org>), a secure web application for building and managing online surveys and databases. Access to the REDCap™ data entry system will be protected by a username and password created during the local investigator registration process.

No PID will be transferred from the local site to the central study team. An anonymised dataset will be uploaded on to the centralised study database via UCL's REDCAP™ web-based portal hosted on secure UCL servers. No PID from the hospital CRF paperwork will be uploaded to REDCap™. REDCap™ will create a unique ID, not based on PID for central team logs. Local investigators will have access to enter and edit data from their own hospital only. Functionality of the CRFs and study database will be assessed as one of the objectives of this pilot study.

In order to facilitate follow-up of participants at six weeks, (+/- 3 days), the participant's name, contact details and relevant previous study questionnaire responses will be only shared within the site of recruitment and only between designated members of the local investigative team (which may include Clinical Trial Assistants/Research Nurses). PID will not be shared between recruitment sites, nor with the central study team. PID will be held only for the minimal necessary period. Once the 6-week (+/- 3 days) follow-up is complete, the site will destroy paper records in line with their local protocols. The electronic study data will be securely deleted after a specified time point (10 years after the end of the study).

Email address information may be gathered in the optional portion on the consent form to allow participant to receive a summary of the results of the study. The email addresses will not be used for any other purpose. It must remain at the local site only; no email address should be sent to the central

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study team. The collected email addresses should be kept in the secure location, along with the telephone contact details that will facilitate the 6-week follow-up data collection, the email addresses only on the optional part of the consent form, and not the CRFs, as the CRFs remain entirely anonymous.

13 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by UCLH.

The Sponsor considers the procedure for obtaining funding from The Obstetric Anaesthetists' Association to be of sufficient rigour and independence to be considered an adequate peer review.

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The study was deemed to require regulatory approval from the following bodies: Each approval will be obtained before the study commences.

1. The National Research Ethics Service
2. The Health Research Authority

Before any site can enrol participants into the study, the Chief Investigator/Principal Investigator or designee will ensure that the appropriate regulatory approvals have been issued, and NHS Confirmations of Capacity and Capability and Sponsor green lights are in place.

For any amendments to the study, the Chief Investigator or designee, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments as well as the study delivery team) to confirm ongoing Capacity and Capability for the study.

All correspondence with the Sponsor, REC and HRA will be retained. The Chief Investigator will notify the Sponsor and REC of the end of the study.

It is the Chief Investigator's responsibility to produce the annual progress reports when required; an annual progress report (APR) will be submitted to the Sponsor and REC within 30 days of the anniversary date on which the favourable opinion was issued, and annually until the study is declared ended.

If the study is ended prematurely, the Chief Investigator will notify the Sponsor and REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the Sponsor and to the REC and HRA.

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14 ASSESSMENT AND MANAGEMENT OF RISK

We do not consider this observational study to carry any significant risks to participants or investigators. Care of participants will be in line with local site policies and the at the discretion of local anaesthetic, obstetric, and midwifery teams at all times during inpatient stay.

It is possible that the study may follow-up participants who are at increased risk of postnatal depression and anxiety. A systemic review by Anderson et al²² found that, within the obstetric population, the two most important risk factors for the development of post-traumatic stress disorder (PTSD) were 'subjective distress in labour' and 'obstetrical emergencies'. By nature of the specific cohort of participants being studied in SONAR 1, those who either experience pain as a consequence of inadequate NA and/or who undergo an emergency CS are at increased risk.

Our research team has a wide breadth of experience of seeking post-operative patient reported outcomes. Our CI has led research where patient feedback has been sought after surgery in over 35,000 participants across the UK, often on multiple occasions up to a year after the initial procedure. Dr O'Carroll has experience leading multicentre observational studies in the obstetric population in the UK and US.

During our engagement with patient representatives and PPI groups, we have received feedback on this particular issue. In addition, we consulted recent papers by Lawton et al^{23,24}, and Hallowell et al²⁵. These authors conducted qualitative research during an observational study and wrote of their experiences of recruitment and consenting during emergencies in the peripartum setting. We have used these important findings, and our team experience to inform our protocol and our Standard Operating Procedures. (SOPs).

We will have the opportunity to discuss the project and its workings with Local Investigators. We will be clear in describing and discussing this potential risk with Local Investigators, with a view to ensuring they are informed and aware of any potential distress that may be caused. Based on team experience, and findings from Lawton and Hallowell et al, we will, amongst other issues, ensure we emphasise:

- Making a clear distinction between research and clinical care.
 - Consent is expedited by simplified verbal and written consent, and the importance of the PIS, and the opportunity to ask questions when given the PIS on admission.
 - Lawton et al showed that when given the choice, virtually all participants prefer to be contacted by phone, and we encourage this over other methods.
 - Lawton et al showed that taking part in interviews meant that participants felt as though their psychological health is also being looked after, and we are keen that this is reflected in follow up rates,
 - Patients valued revisiting information given antenatally in the early postpartum period, and thus visiting in recovery, and the 24-hour (+/- 6 hours) visit is key.
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- That even if participants feel satisfied with the consent process at the time of recruitment, their perspectives may subsequently change, highlighting the importance of following participants up post-trial, especially those identified as having negative

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experiences. We are keen that this is reflected in take up of the 6-week (+/- 3 days) follow-up trial.

As such, enrolled participants could potentially be identified as suffering from PTSD or anxiety earlier than conventional community-based methods during follow-up questioning. Local care teams at participating hospitals (or wherever is clinically most appropriate) will maintain responsibility for management and follow-up of clinical problems, including inadequate NA, that are identified through structured follow-up as part of the study; indeed, this will become increasingly key should the study become larger and be run in other centres.

Should a participant score more than 11 on the EPDS, more than 30 on the PCL-5 PTSD checklist, or more than 10 on the GAD-7 then they will be informed as such via a letter. This letter will encourage them to contact their GP or health visitor for further guidance. It will include a list of available resources for both urgent mental health help and specific resources for postpartum depression. A letter will also be sent to their GP to inform them that their patient has met these scoring thresholds. The letters are available in the study documents.

15 RECORDING AND REPORTING OF EVENTS AND INCIDENTS

All events and incidents (and near misses) that occur to participants and/ or staff that are **unexpected** and directly **related** to the research study will be reported to the Sponsor via UCLH sponsored: Trust Datix and host sites via their Trust reporting systems, and documented in the Trial Master File/Investigator Site File via study-specific incident logs (and related correspondence). This will be completed by the CI or PI. The Sponsor will be responsible for investigating, reviewing, or escalating to a serious breach if required.

15.1 Personal Data Breaches

Personal data breaches will be immediately reported to the UCLH Information Governance team and the UCLH Data Protection Officer Alex Potts (a.potts@ucl.ac.uk, data-protection@ucl.ac.uk) and to the Sponsor via <https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo> or Research-incidents@ucl.ac.uk. Sites will additionally follow their Trust incident reporting mechanisms and will document this within their ISFs.

15.2 Incidental Findings in Research

Incidental findings are not likely applicable to this study. All research staff must follow participating sites' incidental findings policies.

15.3 Protocol deviations and notification of protocol violations

Protocol deviations are usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the Sponsor. The CI will monitor protocol deviations, and if found to frequently recur, will discuss in the first instance with the Sponsor to determine re-classification and reporting requirements.

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A protocol violation is a breach which is likely to effect to a significant degree: –
(a) the safety or physical or mental integrity of the participants of the study; or
(b) the scientific value of the study

The CI and Sponsor will be notified immediately of any case where the above definition applies via Trust Datix and uclh.randd@nhs.net.

15.4 NHS Serious Incidents and near misses

A serious incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

- a. It is an accident or other incident which results in injury or ill health.
- b. It is contrary to specified or expected standard of patient care or service.
- c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
- d. It puts the Trust in an adverse position with potential loss of reputation.
- e. It puts Trust property or assets in an adverse position or at risk.

Serious Incidents and near misses will be reported to the Sponsor and Trust Quality & Safety department as soon as the study team becomes aware of them.

15.5 Complaints from research participants

In the first instance, research participant complaints (participants or healthy volunteers) will be reported to the CI/PI to investigate, as documented in the participant information sheet(s), and to the Sponsor via research-incident@ucl.ac.uk and the UCLH Complaints process; for participants who are NHS participants, complaints will be reported to the NHS Complaints Manager at the Trust where the recruitment and study procedures was undertaken. Complaints from NHS participants are handled under NHS complaints policies and procedures, with involvement from PALS and the Sponsor where necessary.

16 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the Sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

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17 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files for all central and local PIs and investigative team members. All researchers will have completed GDPR training.

18 INDEMNITY ARRANGEMENTS

UCLH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered, and Trust approved. Additionally, UCLH does not accept liability for sites such as GP surgeries in primary care; investigators/collaborators based in these types of sites must ensure that their activity on the study is covered under their own professional indemnity. Potential claims should be reported immediately to the Joint Research Office.

19 ARCHIVING

UCLH and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at UCLH for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents in line with all relevant legal and statutory requirements. Study documents will be archived for a minimum of 5 years from the study end, and no longer than 20 years from the study end.

The Trial Master File will be archived at UCL in accordance with the *JRO Standard Operating Procedure 10 Archiving of the UCLH Investigator Site File/Trial Master File*. It will be archived for a minimum of 5 years from the study end, and no longer than 20 years from study end.

20 PUBLICATION AND DISSEMINATION

We intend to present the results of SONAR₁ in peer-reviewed scientific journals and in the form of conference presentations. PIs and local investigators will be individually named as collaborators for their support. We will also provide specific summary reports for participants and the public, as well as for the participating NHS Trust and Health Board. Resulting publications and/or abstracts will be emailed to the JRO.

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