Research Protocol

1. Aims and Significance

The aim of this study is to compare the patterns of core temperature changes during antepartum elective caesarean section (CS) under subarachnoid block vs intrapartum emergency CS under epidural top-up, and to identify how this relates to maternal shivering. **The significance of this study** is that it will enhance practitioners' understanding of the changes in maternal core temperature during elective and emergency CS; it will help practitioners differentiate thermoregulatory and non-thermoregulatory shivering; it will demonstrate the importance of temperature monitoring during CS; and it will facilitate the development of personalised temperature regulation strategies.

Hypotheses

1. Elective caesarean section under subarachnoid block is associated with a reduction in core temperature, whereas intrapartum emergency caesarean section is associated with an increase or no change in core temperature.
2. The onset of shivering coincides with a reduction in core temperature during elective caesarean section under subarachnoid block and with an increase or no change in core temperature during intrapartum emergency caesarean section under epidural anaesthesia.

2. Background

In Australia, 1 in 3 (32-36%) births occur via caesarean section and in 2019, 87% of the women who had a CS received neuraxial anaesthesia (epidural or spinal).(1) Surgery and anaesthesia impair body temperature regulation. Hypothermia (<36.0 °C) is a prominent issue during non-obstetric surgery and is associated with an array of negative effects, including an increase in blood loss, and delayed wound healing. Consequently, active warming is recommended as part of Enhanced Recovery After Surgery (ERAS).(2, 3) The Society of Obstetric Anesthesia and Perinatology (SOAP) published the consensus statement for Enhanced Recovery After Cesarean Section (ERAC) in 2021.(4) The recommendations include active warming starting preoperatively, but the evidence supporting this recommendation was categorised as Level C (low-grade level of evidence).

Hypothermia occurs in up to 50% of elective caesarean sections under subarachnoid block when active warming is not used and takes 4.5 hours to resolve.(5-7) A recent audit at our institution (Fiona Stanley Hospital in WA) found that approximately a third of obstetric patients who underwent elective CS experienced hypothermia with or without shivering. This is because neuraxial blockade blocks the sympathetic fibres responsible for active vasoconstriction and the thermoreceptors responsible for cold sensation.

Consequently, cutaneous heat loss increases and the resulting fall in body temperature is not sensed or mitigated.(8) However, when active warming is used within 30 minutes of neuraxial block placement (either via forced-air warming or warmed fluid) the incidence of hypothermia decreases (RR 0.66), thermal discomfort improves, maternal shivering is less (RR 0.56), and umbilical artery pH is higher.(9)

By contrast, hyperthermia (>37.5 °C) is a side effect of labour epidural analgesia. This condition is often referred to as epidural related maternal fever (ERMF) and it occurs following 20% of labour epidurals.(10) Over a third of intrapartum emergency CS are performed under epidural anaesthesia.(11) In this scenario the labour epidural is "topped-up" with a more concentrated local anaesthetic solution to provide anaesthesia for the CS. A recent physiological study suggested that topping-up an epidural blocks active cutaneous vasodilation, limits cutaneous heat loss and thus results in a further increase in body temperature.(12) ERMF is associated with adverse maternal and neonatal outcomes, including sepsis evaluation and treatment (e.g. additional blood tests and antibiotic administration) and possibly neonatal brain injury (e.g. neonatal encephalopathy, cerebral palsy and early-onset seizure).(10, 13, 14) Therefore, it is important not to iatrogenically exacerbate hyperthermia during an emergency CS by instituting active warming inappropriately. A recent multicentre clinical study demonstrated that the prevalence of hypothermia, normothermia, and hyperthermia during CS differed between modes of anaesthesia; with hypothermia being more common following subarachnoid block and hyperthermia being more common following epidural top-up.(15) However, no clinical studies have investigated if the pattern of temperature change differs between antepartum elective and intrapartum emergency caesarean sections.

Shivering is a common (up to 87%) side effect of neuraxial blockade during both elective and emergency CS.(16, 17) It is an unpleasant experience which hinders monitoring of vital signs (non-invasive blood pressure, especially) and prevents early mother-baby bonding (skin-to-skin care and breastfeeding). Additionally, shivering increases oxygen consumption by up to 500% which may compromise patients with severe cardio-respiratory disease.(18) It is likely, however, that the cause of the shivering differs between elective and emergency CS. Physiological studies demonstrate that during elective CS shivering is usually preceded by hypothermia, and is therefore "thermoregulatory", and that during emergency CS shivering may occur at normal or increased body temperatures, and thus is "non-thermoregulatory".(12, 19) It is likely, therefore, that a "one-fits-all" approach to the management of shivering is inappropriate, but larger scale clinical studies have not investigated the generalisability of these physiological studies.

Preliminary data

Dr Mullington's (co-investigator) preliminary study which we used as pilot data for our study illustrated that inelective CS, hypothermia was observed post subarachnoid block and the shivering followed. The results suggested that shivering during elective CS under spinal anaesthesia is a normal thermoregulatory response.(20) [figure below]

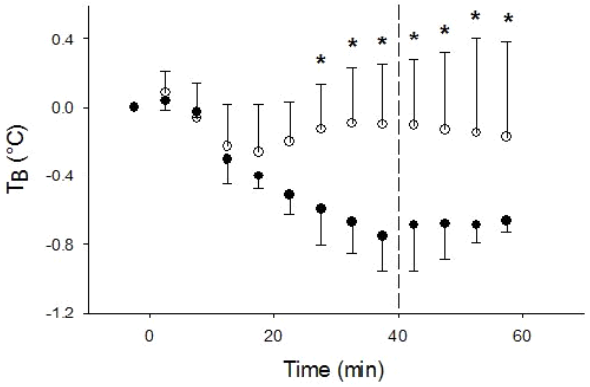

Figure: Mean T_B (SD) relative to baseline during caesarean section of shiverers (filled) and non-shiverers (unfilled). Induction occurred at 0 min. The dashed line indicates the mean onset of shivering. * indicate differences between shiverers and non-shiverers ($p < 0.05$).

On the other hand, in intrapartum emergency CS, another Dr Mullington's study showed that the mean core temperature before epidural top-up was 37.6 °C, and between the epidural top-up and the onset of shivering, the mean core temperature did not change.(12) [figure below]

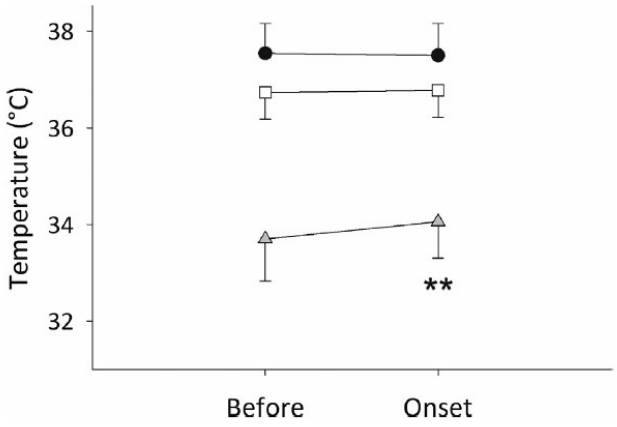

Fig. 3 Obstetric patients' mean core (black circles), skin (grey triangles) and mean body (white squares) temperatures before the epidural top-up dose and at the onset of tremor (n=16). Whiskers denote standard deviations. ** indicates significant difference to the before epidural top-up value (P=0.002)

Currently, it is not a routine practice to monitor core temperature during CS and, as a result, it is not possible for practitioners to tailor thermoregulation strategies to individual parturient requirements. This is largely because an accurate, non-invasive method of continuously monitoring core temperature has not been available.(21-24) Recently, however, an accurate, non-invasive forehead zero-heat-flux core temperature monitor (3M Bair Hugger™ Temperature Monitoring System; BHTMS) has been commercialised.(25) This has created the opportunity to examine between-parturient variation in core temperature during CS in clinical populations and to investigate the efficacy of goal-directed temperature management. It is anticipated that this study will demonstratethe importance of core temperature during CS and the need for personalised thermoregulation strategies.

Objectives

The study objectives are:

1. To record core temperature continuously throughout antepartum elective caesarean section under spinal anaesthesia and intrapartum emergency caesarean section under epidural anaesthesia.
2. To record the onset of shivering during antepartum elective caesarean section and intrapartum emergency caesarean section.

Primary outcome

1. Core temperature change from the baseline at the onset of shivering (shivering threshold delta: difference in core temperature between baseline and the onset of shivering) between elective vs emergency caesarean section.

Secondary outcomes

1. Maximum change in core temperature from the baseline between elective vs emergency caesarean section.
2. Maximum change in core temperature between those who shivered vs those who did not shiver,and elective vs emergency caesarean section.

3. Methods

3.1. Population and recruitment

Inclusion criteria

- Elective caesarean section under subarachnoid block (spinal/combined spinal and epidural anaesthesia)
- Intrapartum emergency caesarean section under epidural anaesthesia
- Age 18 or above

Exclusion criteria

- Patient refusal
- Inability to consent
- ASA 3 or over
- Morbidly obese (BMI 50 or over)
- Category 1 or “Code Blue” emergency caesarean section (due to an “urgent threat to the life of the woman or the fetus” as per RANZCOG)
- Antepartum haemorrhage requiring blood transfusion
- Active warming with air forced blanket and/or fluid warmer are planned to use from the beginning of the caesarean section

Withdrawal criteria

- General anaesthesia required
- Sedation required
- Massive postpartum haemorrhage (PPH): EBL>2L and/or required blood transfusion

3.2. Equipment

The 3M Bair Hugger™ Temperature Monitoring System (BHTMS) Zero Flux Thermometer is commercially available. This gives accurate core temperature without invasive monitoring devices (e.g. bladder probe, rectal probe, pulmonary catheter) continuously.(25) The previous published studies which looked at the accuracy of peripheral thermometers (e.g. tympanic membrane, temporal artery, axillary, or oral) emphasized the poor sensitivity of the peripheral thermometers and largely underestimated the temperature compared to core temperature (e.g. pulmonary artery catheter, urinary bladder, oesophageal, or rectal).(21-24) The sensor is single use and the control unit is reusable.

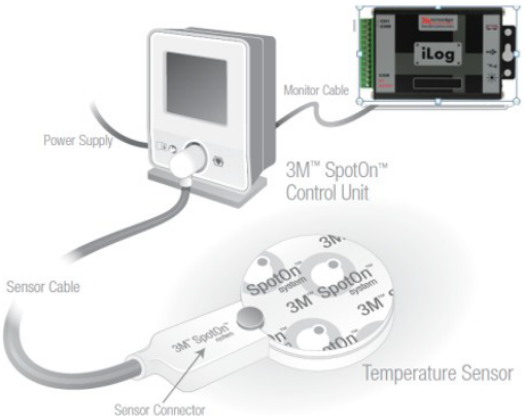

Figure 1. A sensor and a control unit of 3M Bair Hugger™ Temperature Monitoring System are connected to the logger

3.3. Experimental protocol

Antepartum elective caesarean section under subarachnoid blockade

Prior to their day of surgery, patients undergoing elective caesarean section will have project information mailed to them along with other important information regarding their surgery. This will be organised through the antenatal clinic (from which the caesarean information packs are sent out). Anaesthetists do not attend antenatal clinics, they are specifically for members of the midwifery and obstetric teams to discuss and consent patients for an elective caesarean section. Patients scheduled for an elective caesarean section only see an anaesthetist pre-operatively if they are deemed "high risk" by the obstetric team and referred to the High-Risk Obstetric Anaesthetic clinic. At this clinic, we do aim to invite patients to participate in the study at the end of their consultation with the anaesthetist, however most patients are seen via Telehealth, and written consent will not be possible.

On the day of surgery, patients arrive in the preoperative admission area, and are prepared for caesarean section (CS) according to the hospital standard protocol. They wear hospital gown and knee-height thromboembolic deterrent stocking. In the holding area, patients are approached by one of the anaesthetic department research team members (research member). Firstly, the patients are asked whether they have familiarised themselves with the study from the information sent to them preoperatively, and if they are happy for the research member to discuss an opportunity to participate in a study. If yes, then the details of the study involvement are explained verbally. All the questions will be answered by the research member, or principal investigators if any questions are unable to be answered by the research member. Written consent is obtained on the patient consent form (approved by local ethics).

After patients agree to take part in the study in the holding area, a sensor of BHTMS (figure 1) is attached to the patient's forehead (either right or left) and is going to be connected to the control unit. When temperature is showed up on the control unit screen, the logger is started to record the temperature. The first temperature logged by the BHTMS in the holding bay will be recorded as the patient's baseline temperature. When the patient is transferred from the holding area to operating theatre, the BHTMS unit is temporarily disconnected from power and re-plugged in operating theatre.

In theatre, firstly patients sit up on the operating table. A warmed blanket covers the front of the patient body. A large-bore cannula is inserted in a forearm or hand. Spinal anaesthesia or combined spinal and epidural (CSE) is sited. The spinal local anaesthetic with or without fentanyl and morphine is administered according to the departmental standard protocol. After the spinal medication is given, patients lay supine on the operating table with slight left tilt with the blanket covering their chest, abdomen, and lower limbs.

The administration of intravenous fluids, vasopressors, and uterotonics are applied according to the departmental standard protocol. When the anaesthetic level is satisfied, the CS is proceeded by obstetricians. Following delivery, the tilt on the operating table is removed and uterotonics are administered. All drugs and intravenous fluids were administered at room temperature. BHTMS continues to measure patient core temperature and the numbers are visible on the control unit. The logger continues to record and save the data.

During the CS, patients will be asked Shivering presence, shivering discomfort score, Thermal pleasantness score and Temperature sensation score every 5 minutes from the siting of neuraxial blockade until 1 hour after PACU arrival. Either the attending anaesthetist or a research member in theatre and a nurse or a research member in PACU will ask the questions. The attending anaesthetist will assess the shivering using a modified version of Horn's shivering grading system; 0(None) no shivering, 1(Mild) intermittent or low-intensity shivering, 2(Moderate) moderate shivering, 3(Severe) continuous and intense shivering, 4(Most severe) medical intervention required. The onset time of the shivering and other data items (Table 1) are recorded by the attending anaesthetist and/or research member. The temperature of the operating theatre air conditioning system is set at 22 °C. When the patient is transferred from operating theatre to recovery room, the BHTMS unit is temporarily disconnected from power and re-plugged-in recovery room.

Core temperature monitoring with BHTMS is continued in recovery room. The sensor will bedisconnected when patients discharge from recovery room.

Intrapartum emergency caesarean section under epidural extension

Recruitment of patients with an intrapartum epidural who eventually require an emergency caesarean section can occur at a few stages. The researchers aim to recruit potential participants before the decision is made by the obstetric team for an emergency caesarean section. It is beyond the scope of the researchers to be able to predict which patients with labour epidurals will progress to an emergency caesarean section, therefore recruitment of participants in this category must occur during the induction of labour phase, or during established labour, once the patient is comfortable, not distressed, with a good working epidural in situ.

Patients who are undergoing an induction of labour require up to 24 hours of cervical ripening before being transferred to the labour ward for further management. These patients are not in established labour during the cervical ripening process. During their stay on the induction ward, they will be approached by a member of the research team, to be invited to participate in the study, especially if they are considering requesting an epidural once in labour. Alternatively, if a patient is in established labour on the labour ward, they will only be approached by a member of the research team once a labour epidural catheter is in-situ and are they comfortable, not distressed, and have no immediate obstetric complications. Firstly, the patients are asked whether they are happy for the research member to discuss an opportunity to participate in a study. If yes, then the details of the study involvement are explained verbally. After the verbal explanation, the patient information sheet (approved by local ethics) is given and the time for patients to read it through is given. All patients will have a minimum of 1 hour to read the information sheet and consider participation. This has proved an adequate interval in previous studies. All the questions will be answered by the research member, or principal investigators if any questions are unable to be answered by the research member. Written consent is obtained on the patient consent form (approved by local ethics).

If the patients who consented to the study during labour, with an epidural in situ, require an emergency

caesarean section, then the study commences. Please note, it is an exclusion criterion of this study that any patient requiring a "Category 1" or "Obstetric Code Blue" emergency caesarean section - defined by RANZCOG as a caesarean required due to "an urgent threat to the life or health of a woman or fetus" - regardless if they have previously consented to participate.

Once the patient is transferred to the operating theatre for emergency caesarean section, the patients lay supine on the operating table with slight left tilt with a blanket covering their chest, abdomen, and lower limbs. A sensor of BHTMS is attached to the patient's forehead (either right or left) and is going to be connected to the control unit. When temperature is showed up on the control unit screen, the logger is started to record the temperature. Local anaesthetic with or without fentanyl is injected through an epidural catheter for top-up. The administration of intravenous fluids, vasopressors, and uterotonics are applied according to the departmental standard protocol. When the anaesthetic block level is sufficient, CS can be proceeded by obstetricians. Following delivery, morphine (Fiona Stanley Hospital) or diamorphine (St Mary's Hospital) can be given through the epidural catheter. Epidural catheter can be removed in the operating theatre before moving to recovery room. BHTMS continues to measure patients core temperature and the numbers are visible on the control unit. The logger continues to record and save the data.
During the CS, patients will be asked Shivering presence, shivering discomfort score, Thermal pleasantness score and Temperature sensation score every 5 minutes from the siting of neuraxial blockade until 1 hour after PACU arrival. Either the attending anaesthetist or a research member in theatre and a nurse or a research member in PACU will ask the questions. The attending anaesthetist will assess the shivering using a modified version of Horn's shivering grading system; 0(None) no shivering, 1(Mild) intermittent or low-intensity shivering, 2(Moderate) moderate shivering, 3(Severe) continuous and intense shivering, 4(Most severe) medical intervention required. The onset time of the shivering and other data items(Table 1) are recorded by the attending anaesthetist and/or research member. The temperature of theoperating theatre air conditioning system is set at 22 °C. When the patient is transferred from operating theatre to recovery room, the BHTMS unit is temporarily disconnected from power and re- plugged-in recovery room.

Core temperature monitoring with BHTMS is continued in recovery room. The sensor will be disconnected when patients discharge from recovery room.

Table 1 - data items		
Mother	Age (year)	
	Height (cm)	
	Weight (kg) - latest	
	BMI (kg/m2)	
	Parity	
	Gestation (weeks)	
	Pre-CS haemoglobin	
	Post-CS haemoglobin	
Labour	Onset mode of labour	Spontaneous/induction
	Onset time of labour	
	Cervical dilatation prior to CS	[cm]
	Rate of uterine contractions prior to CS	[per min]
	Total dose of oxtocin during labour (units)	[units]
	Duration of labour (the interval between the onset of labour and the time of birth)	
	The total volume of bupivacaine with fentanyl for labour analgesia	Bupivacaine [mg] Fentanyl [mcg]
CS	Category of CS	Elective/Cat 2/Cat3
	Indication for CS	Repeat CS/ Breech/ Failure to progress/ Fetal bradycardia/Other
	Mode of anaesthesia	SSS/CSE without epidural top-up/ Epidural top-up
	Interval between the spinal anaesthesia administration and the end of surgery (min)	
	Interval between the epidural extension and the end of surgery (min)	
	Duration of CS (from the time of arrival in OT till the time to leave OT) (min)	
	Operating room (ambient) temperature (°C)	[°C]
Spinal	Time of spinal anaesthesia administration	
	Bupivacaine dose for spinal anaesthesia (mg)	
	Intrathecal fentanyl dose (mcg)	
	Intrathecal morphine dose (mcg)	
Epidural	Time of commencement of epidural top-up	
	Total dose of Lignocaine (with/without bicarbo & with/without adrenaline) solution used in OT	[ml = mg]
	Epidural morphine/diamorphine dose (mg)	
IV-drugs	Total dose of Phenylephrine in OT (mcg)	[mcg]
	Total does of Ephedrine in OT (mg)	[mg]
	Total volume of fluid in OT (ml)	[ml]
	Uterotonics - Carbetocin	[mcg]
	Uterotonics - Oxytocin bolus	[units]
	Uterotonics - Oxytocin infusion	10 units/h or 20 units/h
	Uterotonics - Ergometrine	[mcg]
	Other Uterotonics	Syntometrin/Misoprostol/Carboprost
Symptoms	Hypotension (> 20% below baseline) in OT	Yes/No
	Tachycardia (HR>120 bpm)	Yes/No
	Bradycardia (HR<50 bpm)	Yes/No
	Nausea and/or vomiting	Yes/No
	Estimated Blood Loss in OT (ml)	[ml]
Temp & Shivering	Core temperature (continuous)	
	Core temperature at the onset of shivering	
	Shivering presence (by patient)	Yes/No
	Shivering presence (by practitioner)	Yes/No
	Onset time of shivering (by practitioner)	
	Shivering discomfort score (0-10) - how unpleasant the shivering is (0:no discomfort, 10: worst discomfort)	[ ] out of 10
	Thermal pleasantness score (0-10) - how pleasant thermal environments is (0: unpleasant 10: most pleasant)	[ ] out of 10
	Temperature sensation score (0-10) - how cold or hot patient feels (0: coldest 10: hottest)	[ ] out of 10

Baby	Baby's temperature at birth	
	Baby umbilical cord vein PH	
	Baby umbilical cord vein BE	
	Apgar score 1 min	
	Apgar score 5 min	
	Need for assisted ventilation at birth	Yes/No
	Need NICU admission	Yes/No

3.4. Statistics and Sample size estimations

Our primary endpoint is the core temperature change from the baseline at the onset of shivering (shivering threshold delta). The pilot data (12, 20) showed that the mean core temperature changes atonset of shivering from baseline were -0.62 °C (SD 0.12) in elective CS and -0.03 °C (SD 0.15) in emergency CS.

We powered our study to detect a true difference in mean shivering threshold delta between emergency caesarean group and elective caesarean group of 0.25 °C which is clinically significant. Further, we assumed a pooled standard deviation of 0.5 °C as the bigger population variance is expected with larger and more diverse sample. The study therefore requires a sample size of: 85 for each group (elective and emergency CS), a total sample size of 170 to achieve a power of 90% and a level of significance of 5% (two sided). We aim to recruit total 200 patients (100 for elective and 100 for emergency CS).

3.5 Data analysis

A two sample T tests, or non-parametric equivalent where appropriate, will be used to test if there is a significant difference between emergency and elective patients in the temperature drop between baseline and onset of shivering. Mixed effect ANOVA will be used to assess interactions between variables. Chi squared/Fisher/Barnards tests will be used to identify independence between categorical variables.

4. Feasibility

This is a joint funding project between Fiona Stanley Hospital (FSH) in Perth WA and St. Mary's Hospital (SMH) in London UK. The researchers from SMH in London will send their data to the researchers at Fiona Stanley Hospital for final data analysis, thereby increasing the validity, applicability and power of our final data analysis. No data collected from patients from Fiona Stanley will be sent to researchers not connected to this research proposal.

Fiona Stanley Hospital (FSH) is a tertiary hospital located inthe southern central area of Perth Western Australia. FSH holds approximately 3500 deliveries per year and the elective and emergency caesarean section rates are 14% and 21% respectively; a total of 1200 caesarean sections per year. FSH has an average of 35 elective caesarean sections and an average of 50 emergency caesarean sections per month. There are an average of 2 elective caesarean sections booked per day between Monday and Friday. This can give us an opportunity to recruit an average of 10 elective cases per week. There is an average of 1 emergency caesarean section during the hospital in-hours period per day between Monday and Friday. This can give us an opportunity to recruit an average of 5 emergency cases per week. We anticipate 20 percent of the patients are not eligible to be recruited to the study. Therefore, an average of 8 elective cases and 4 emergency cases can be eligible to be recruited to this study per week. Two sets of BHTMS and loggers will be available per day, hence maximum 10 participants including elective or emergency caesarean sections can be completed per week. The research nurse (0.45 FTE, 18 hours per week) will spend total of 3 hours per patient, this gives 6 patients will be the maximum number to be completed per week. In order to complete data collection from 100 participants (50 elective and 50 emergency), minimum of 19 weeks is expected to take. We anticipate slower recruitment for emergency caesarean sections compared to elective caesarean sections as the majority of emergency caesarean sections are performed outside of normal working hours. Hence we have extended the recruitment window by 2 months to accommodate this slower recruitment.

St Mary's Hospital (SMH), which is part of Imperial College Healthcare NHS Trust, is a tertiary hospital in Central London, UK. The maternity unit delivers approximately 4500 babies per year and the elective and emergency caesarean section rates are 24% and 12% respectively; a total of 1600 caesarean sections per year. Two sets of BHTMS and loggers will be available per day, hence data collection can be completed from a maximum of 10 participants (elective or emergency caesarean sections) per week. The research student (1.0 FTE, 40 hours per week) will spend a total of 3 hours per patient and therefore the maximum anticipated recruitment rate is 10 patients per week. It is expected to take a minimum of 15 weeks to recruit and complete data collection from 100 participants(50 elective and 50 emergency). We anticipate slower recruitment for emergency caesarean section scompared to elective caesarean sections as the average number of cases is small and approximately 50% of emergency caesarean sections occur outside of normal working hours. Hence we have extended the recruitment window by 2 months to accommodate this slower recruitment.

Project Time Lime	2022	2023				2024
Task name	Preliminary	Q1	Q2	Q3	Q4	Q1
Ethics						
Equip BHTMS, trial run						
Information to staff						
Patient recruitment						
Data collection						
1st interim analysis						
2nd interim analysis						
Final data analysis						
Manuscript preparation						
Manuscript submission						

5. Data storage and management

a. During the study the paperwork will be stored in a locked cupboard in the department research office. The only people with access will be the research team.
b. Digital data will be password protected, using the REDCap platform.
c. Paperwork will undergo confidential shredding and electronic data will be deleted from REDCap platform 7 years for adults and 25 years for the baby, post publication.

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