

STUDY PROTOCOL

Post-operative Emesis and Pain Outcomes after Cesarean delivery (EPOC)

UNIQUE PROTOCOL ID: EPOC01

CIRB NUMBER:

2017/2381

PROTOCOL VERSION: 1.0

PROTOCOL DATE: 1 Aug 2018

PRINCIPAL INVESTIGATORS:

Dr Farida Ithnin, Senior Consultant, KK Women's and Children's Hospital (KKH)

*Also refer to Section F9 on the sample size details.

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Section A: Protocol Title & Protocol Administrators

A1. Please enter the Full Protocol Title and Protocol Number (if available) for this Study

Protocol Title : Post-operative Emesis and Pain Outcomes after Cesarean delivery
Protocol Number (EPOC) : EPOC01
(Optional)

A2. You may assign Protocol Administrators for this study below

No.	Name	Institution/Organization	Department	Office No.	Email
1	Dr Han Nian Lin Reena	KK Women's and Children's Hospital (KKH)	Division of Clinical Support Services		Han.NianLin@khh.com.sg
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Section B : Study Sites, Study Team & Submission Board

B1. Please select the study sites

(i) SingHealth and Partner Institutions

KK Women's and Children's Hospital (KKH)

(ii) NHG and Partner Institutions

(iii) Other Local Sites and Overseas Sites

B2. Study Team Members

(i) Add Study Team Members

No.	Name	Study Role	Department	Institution	Designation	Involve in Informed Consent
1	Dr Ithnin Farida Binte	PI	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Consultant	[x]
2	Dr Chan Ju In Jason	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Resident	[x]
3	Dr Cheng Shang-Ming	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Associate Consultant	[x]
4	Dr Dabas Rajive	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Consultant	[x]
5	Dr Goy Wee Lip Raymond	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Consultant	[x]
6	Dr Lee Song En John	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Resident	[x]
7	Dr Leong Wan Ling	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Consultant	[x]
8	Dr Lew Eileen	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Consultant	[x]
9	Dr Lim Ming Jian	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Resident	[x]
10	Dr Mathur Deepak	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Consultant	[x]
11	Dr Nagarajan Singaraseelan	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Associate Consultant	[x]
12	Dr Oh Ting Ting	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	associate consultant	[x]
13	Dr Sng Ban Leong	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Consultant	[x]
14	Dr Tan Hon Sen	Co-I	Department of Anaesthesiology	Singapore General Hospital (SGH)	Resident	[x]
15	Ms Liu Juan	Study Team Member	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	clinical research coordinator	[x]

B3. Submission Board and other IRB**(i) Which CIRB is this application being submitted to?**

CIRB D Anaesthesia (including acupuncture)

(ii) Has the study been submitted to another IRB? No**(iii) Has the application been previously rejected by any IRB? (Including SingHealth CIRB) No****Section C: Conflict of Interest**

Does the Principal Investigator or any Study Team Member have any potential conflict of interest? The Declaration is also for the immediate family members of the Principal Investigator and Study Team Members listed below.

Name	Study Role	Department	Institution	Yes/No
Dr Ithnin Farida Binte	PI	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Chan Ju In Jason	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Cheng ShangMing	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Dabas Rajive	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Goy Wee Lip Raymond	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Lee Song En John	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Leong Wan Ling	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Lew Eileen	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Lim Ming Jian	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Mathur Deepak	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Nagarajan Singaraselvan	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Oh Ting Ting	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Sng Ban Leong	Co-I	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No
Dr Tan Hon Sen	Co-I	Department of Anaesthesiology	Singapore General Hospital (SGH)	No
Ms Liu Juan	Study Team Member	Department of Anaesthesiology	Women's KK Women's and Children's Hospital (KKH)	No

Submission Date: 31-May-2018

Section D: Nature of Research

D1. Please select one category that best describes your research activities. Clinical Research

NOTES:

Submission to HSA might be required if you are conducting clinical trials. You should check with HSA if you are unsure.

D2. Is this a US FDA IND/IDE study or data is intended to be reported to FDA in support of an IND/IDE Application?

No

Section E: Study Funding Information

E1. Please give information regarding the study's funding source or sponsor information.

Grant

i. Name of Grant Agency: Others, please specify

ANAESTHESIOLOGY & PERIOPERATIVE SCIENCES ACP

ii. Grant Name: Anaesthesiology ACP Pilot Research Grant **iii.**

Amount: 10000

iv. Deadline of Grant Application: 31 Jan

2018 **v. Has the grant been approved?** Yes

Reference Number ANAESPRG18/02

NOTES:

If you choose this option, the CIRB may only start reviewing the study when preliminary result for the Grant Application is available. Please contact the CIRB once you have received information on the grant results to start the CIRB review process. If your grant application was not successful, please advise the CIRB on your next course of action (e.g. withdrawal of the study, look for alternative funding etc.).

E3. Who will be responsible for the payment and compensation of injury or illness to participants arising from participation in the study?

The Hospital does not make any provisions to compensate study participants for research related injury. However, compensation may be considered on a case-by-case basis for unexpected injuries due to nonnegligent causes.

E4. Who will be responsible for research-related costs? For sponsored studies, please list the costs that will be borne by the sponsor.

Anaesthesiology ACP Pilot Research Grant

Section F: Research Methodology

F1. Please provide an abstract of your proposed research (Up to 300 words).

Approximately 1 in 5 women who undergo cesarean delivery would suffer from severe post-operative pain, which may further increase their risks from developing postpartum depression. Predictive factors such as pre-operative pain, age and anxiety could significantly contribute to post-operative nausea and vomiting (PONV) and pain in general surgery, however little information is available with regards to cesarean delivery. Previous studies demonstrated that pain scores upon local anesthetic injection is positively correlated to post-cesarean pain scores. Additionally, anxiety, anticipated post-operative pain score and anticipated medication need are also found to be promising risk factors to postcesarean pain management.

We aim to investigate the risk factors of causing post-operative emesis after cesarean delivery, and to reaffirm that there is a positive correlation between pain on local anesthetic injection, presence of mechanical temporal summation (MTS) and post-Cesarean pain scores. We will recruit 200 parturients undergoing cesarean delivery at KK Women's and Children's Hospital and requiring regional anesthesia. Pain and anxiety assessment will be conducted via visual analogue scoring (VAS), MTS assessment and a series of questionnaires. After the delivery, all patients will be given appropriate analgesia, and the pain score at movement will be recorded. Secondary outcomes include pain scores at rest, analgesia consumption, time-to-first-rescue analgesia, opioid-related side effects, patient satisfaction and postpartum depression.

This proposal will determine the clinical relevance of pre-operative determinants for post-cesarean pain management in local context. This would help us discover new risk management strategies and identify modifiable treatment. We hope that this will serve as a guideline for consistent and reliable delivery of care while enhancing the effectiveness and patient satisfaction in obstetrics pain management.

F2. What are the specific aims and hypothesis of this study?

Primary hypothesis: Women that undergo cesarean delivery at KK Women's and Children's Hospital, Singapore, who has higher pain score upon local anesthetic injection, will have higher risk of getting postcesarean pain.

Primary aim: To determine whether there is a positive correlation between pain on local anesthetic injection and post-Cesarean pain scores in women that undergo cesarean delivery at KK Women's and Children's Hospital, Singapore.

Secondary hypothesis (1): Women that undergo cesarean delivery at KK Women's and Children's Hospital, Singapore, who has mechanical temporal summation (MTS>0), will have higher risk of getting post-cesarean pain.

Secondary aim (1): To determine whether there is a positive correlation between mechanical temporal summation and post-Cesarean pain scores in women that undergo cesarean delivery at KK Women's and Children's Hospital, Singapore.

Secondary hypothesis (2): Women that undergo cesarean delivery at KK Women's and Children's Hospital, Singapore, who has higher anxiety score, anticipated pain score and/or anticipated medication need, will have higher risk of getting post-cesarean pain.

Secondary aim (2): To determine whether there is a positive correlation between higher anxiety score, anticipated pain score and/or anticipated medication need and post-Cesarean pain scores in women that undergo cesarean delivery at KK Women's and Children's Hospital, Singapore.

Exploratory Aim: To examine the correlation between medical history (presence of hyperemesis gravidarum, motion sickness, PONV etc.), demographical data and the incidence of post-operative emesis.

F3. Please briefly describe the background to the current study proposal. Critically evaluate the existing knowledge and specifically identify the gap that the proposed study is intended to fill.

Cesarean delivery is one of the most common surgical procedures performed in the United States, making up over 32% of all live births – about 1.3 million per year [1]. Similarly, cesarean delivery constitutes about 30% total delivery in our institution, contributing to 3000-4000 cases annually. Approximately 1 in 5 women who undergo Cesarean delivery will experience acute, severe postoperative pain[2]. This is important because the most significant predictive factor for the development of chronic pain after Cesarean delivery appears to be the severity of acute pain in the post-operative period [2, 3]. Thus, it is imperative to optimize pain management strategies during this time. The challenge for physicians is that inter-individual pain experience is highly variable, such that a “one-size-fits-all” approach is often inadequate for a large portion of patients with greater pain needs.

Many methods have been put forth to try to utilize preoperative measures to predict which patients will have greater post-operative pain needs, with varying levels of success. A systematic review of general surgery procedures found that preoperative pain, anxiety, age, and type of surgery were the most common variables consistently found to be significant predictors of postoperative pain, and that type of surgery, age, and psychological distress were the most commonly found significant predictors of analgesic consumption [4]. Although research has been done on this subject in the general surgical population, there is less information available with regards to Cesarean delivery.

Patients undergoing Cesarean delivery are unique in that in addition to their own recovery, they also must begin bonding with and caring for their newborns after delivery. The need for early mobilization and avoidance of over-sedation is also important in this population due to an increased risk for thromboembolic complications in the postpartum period [5]. It is also important to avoid under-treating this population, as acute, severe post-Cesarean pain triples a woman’s chances of developing postpartum depression [2]. Additionally, severe acute post-Cesarean pain greatly increases the risk of developing chronic pain [2], which occurs in 9.2% - 18% of women who undergo Cesarean delivery [6-8].

With the unique needs of this population in mind, prior research has focused on seeking out factors that may help identify patients who will have greater pain needs after Cesarean delivery. Previous studies have compared preoperative quantitative sensory testing (QST) and postoperative pain, with some encouraging results. Studies on preoperative pressure pain thresholds and pressure pain tolerance have shown modest correlation between these factors and postoperative pain and analgesic need [9-11]. Testing of preoperative pain using electrical stimulation has also yielded modest correlations with postoperative pain and analgesic consumption [9, 10, 12, 13]. Preoperative heat pain and sensitivity have likewise demonstrated correlations of varying strength with postoperative pain [14-16]. Finally, one recent study has found a significant correlation between patients’ pain scores in response to preoperative local anesthetic injection and post-Cesarean pain scores [17].

Other studies have been performed that utilize preoperative questionnaires in an attempt to predict postCesarean pain, again with encouraging results. One study used preoperative State-Trait Anxiety Inventory (STAI) scores and found that patient’s responses correlated with their total analgesic needs[15]. Another study employed a preoperative “Pain Catastrophizing Scale,” and found that patient’s responses were correlated with their post-operative pain scores [16]. Finally, a more recent attempt has used a simple, three question preoperative assessment and found that patient’s responses were correlated with postoperative pain on mobilization in both derivation and validation cohorts, accounting for up to 20% of the variance in post-Cesarean pain [18]. Following up these findings, the same group found that within a cohort of patients identified as having higher pain needs with the “three simple questions,” those who were randomized to receive higher doses of pain medication reported better postoperative pain management compared to a control group that received standard doses of pain medication [19].

Of the physical factors that have been studied, pain scores upon injection of local anesthetic seem to be the most promising in regards to clinical application, as the testing involved in the other methods (pressure, heat, and electric stimulation) are likely too time-intensive to be

clinically feasible, while local anesthetic injection is already part of the standard protocol for initiating spinal or epidural anesthesia. And although all of the questionnaires appear to have some potential for clinical use, the three simple questions appears to be the most useful due to its brevity while maintaining acceptable sensitivity and specificity for identifying patients who will fall in the upper 20th percentile of pain needs [18]. Local anesthetic injection and the “three simple questions” are both promising techniques that could lead to greater post-Cesarean pain management, but neither has yet to be validated outside of their respective institution of origin. Therefore, the purpose of this study is to evaluate the effectiveness of these two measures for the prediction of postoperative pain in women undergoing Cesarean delivery at KKH.

While numerous studies have investigated risk factors for postoperative nausea and vomiting in the general surgical population, there are relatively little data in the obstetric patient population. We will collect information about potential risk factors for post-operative nausea and vomiting (PONV), and assess for association with the occurrence of PONV. We will collect information about the following factors: history of PONV after CD, history of PONV after non obstetric surgery, history of morning sickness, history of hyperemesis gravidarum, history of motion sickness, smoking history, occurrence of intraoperative nausea and vomiting, and exteriorization of the uterus.

F4. Please provide a list of relevant references.

1. Hamilton, B.E., et al., Births: Final Data for 2014. *Natl Vital Stat Rep*, 2015. **64**(12): p. 1-64.
2. Eisenach, J.C., et al., Severity of acute pain after childbirth, but not type of delivery, predicts persistent pain and postpartum depression. *Pain*, 2008. **140**(1): p. 87-94.
3. Niklasson, B., et al., Risk factors for persistent pain and its influence on maternal wellbeing after cesarean section. *Acta Obstet Gynecol Scand*, 2015. **94**(6): p. 622-8.
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5. James, A.H., et al., Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol*, 2006. **194**(5): p. 1311-5.
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7. Nikolajsen, L., et al., Chronic pain following Caesarean section. *Acta Anaesthesiol Scand*, 2004. **48**(1): p. 111-6.
8. Sng, B.L., et al., Incidence and risk factors for chronic pain after caesarean section under spinal anaesthesia. *Anaesth Intensive Care*, 2009. **37**(5): p. 748-52.
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10. Buhagiar, L.M., et al., Pre-operative pain sensitivity: A prediction of post-operative outcome in theobstetric population. *J Anaesthesiol Clin Pharmacol*, 2013. **29**(4): p. 465-71.
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15. Pan, P.H., et al., Multifactorial preoperative predictors for postcesarean section pain and analgesic requirement. *Anesthesiology*, 2006. **104**(3): p. 417-25.
16. Strulov, L., et al., Pain catastrophizing, response to experimental heat stimuli, and postcesarean section pain. *J Pain*, 2007. **8**(3): p. 273-9.
17. Orbach-Zinger, S., et al., Severe pain during local infiltration for spinal anaesthesia predicts postcaesarean pain. *Eur J Pain*, 2015. **19**(9): p. 1382-8.
18. Pan, P.H., et al., Predicting acute pain after cesarean delivery using three simple questions. *Anesthesiology*, 2013. **118**(5): p. 1170-9.
19. Booth, J.L., et al., A Randomized Controlled Trial Comparing Two Multimodal Analgesic Techniques in Patients Predicted to Have Severe Pain After Cesarean Delivery. *Anesth Analg*, 2016. **122**(4): p. 1114-9.
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21. Carroll LJ, Cassidy JD, Cote P. Depression as a risk factor for onset of an episode of troublesome neck and low back pain. *Pain*. 2004 Jan;107(1-2):134-9.
22. Doan L, Manders T, Wang J. Neuroplasticity Underlying the Comorbidity of Pain and Depression. *Neural plasticity*. 2015;2015.

F5. Please provide an account of the Principal Investigator's preliminary studies and progress reports (if any) pertinent to this application.

We have an extensive research network collaboration with national and cluster funding, together with publications and conference presentations to illustrate collaboration, productivity and capability to execute large clinical trials. We have expertise in studies related to PND, persistent pain and childbirth pain, expertise in large clinical trials and focused pain publications.

Studies Related to Postnatal Depression

At KK Hospital, we have developed a strong collaborative multidisciplinary research team, with the principal investigator who has childbirth pain and PP management skills, co-investigators (Dr Helen Chen, Dr Chua Tze Ern) with expertise in PND and (Assoc Prof Tan Ene Choo) genetics, extending the work funded by the NMRC Exploratory Development Grant (NMRCEDG1006). The abstract was presented for the oral competition at the recently concluded Association of Anaesthetists in Great Britain and Ireland meeting in Edinburgh September 2015 and has been accepted for publication by the journal Neuropsychiatric Disease and Treatment (impact factor 1.8).

We conducted a pilot cohort study involving 479 women who delivered at KK Hospital from November 2010 to October 2013 who had psychological assessment. The analgesic outcomes were analysed retrospectively. PND diagnosis was made using psychiatrist diagnosis. PND was present in 12.9% (62/479). The incidence of PND was 10.0% (33/329) of women who received epidural analgesia and 19.3% (29/150) of those who choose non-epidural analgesia (p=0.0149). The independent risk factors included the absence of epidural analgesia being associated with increased risk of PND (OR 1.95, 95%CI 1.04-3.66, p=0.0367). Increasing age was associated higher risk of PND (OR 1.56, 95%CI 1.15-2.14, p=0.005, every 5 years increase). Psychological factors associated with PND were family history of depression (OR 11.1, 95%CI 4.23-29.75, p<0.0001), history of depression (OR 10.61, 95%CI 2.34-58.15, p=0.003) and previous history of PND (OR 9.42, 95%CI 3.7-24.54, p<0.0001). Though the findings of this observational study is intriguing, a more definitive trial is required to provide strong evidence for this observation. Furthermore, the outcomes for PP after childbirth were not available.

Submission Date: 31-May-2018

The principal investigator has recently published an invited review article as the senior author in a peer reviewed journal: Trends in Anaesthesia and Critical Care on 'Childbirth pain and Postpartum Depression'. The article illustrates the expanded role of the anaesthetists beyond pain relief and provides an argument for the discipline to take a greater role in patient care during childbirth. The accompanying commentary by Vuilleumier et al titled 'Is Birthing pain the trigger of postpartum depression? A commentary on Childbirth pain and Postpartum Depression' is evidence of the overwhelming interest in this topic. The authors suggested that further work is needed in order to understand how pain and depression relate to each other and that improved attention to helping women achieve desired pain control during and after childbirth may have far reaching benefits.

Studies Related to Persistent Pain and Childbirth Pain

The principal investigator was awarded the NMRC Transition Award (NMRC/TA/0017/2013) together with co-investigator (Assoc Prof Tan Ene Choo) and mentor (Prof Alex Sia). This ongoing study utilizes a comprehensive programme to investigate persistent pain after hysterectomy. Based on a preliminary study of the first 100 subjects, pain catastrophizing is a univariate analysis significant factor in chronic posthysterectomy, in particular women with increased rumination and helplessness. The independent risk factors were increased pain scores in the recovery room and lower risk in the Chinese race suggesting ethnic differences. The results were presented for oral presentation competition at the recently concluded Australian Pain Society Meeting at Brisbane March 2015.

Our pilot data using arterial spin labelling, a new MRI sequence allows objective quantification of relative cerebral blood flow. There is increased perfusion in the thalamus during heat stimulation (rising to 90mL/100g/min) that returns to baseline (60mL/100g/min) after stimulus is removed. Initial group analysis shows increased relative cerebral blood flow in multiple regions (frontal lobe, insula, temporal lobe, caudate) for those who develop chronic pain compared to those who are pain free.

We have also found that chronic or persistent pain after Caesarean section is associated with acute pain recalled in the immediate postoperative period after Caesarean section. The principal investigator presented the results as part of an invited speaker presentation at the Australian and New Zealand College of Anaesthetists Meeting at Singapore May 2014 on chronic pain in obstetrics.

The principal investigator and mentor specializes in obstetric anaesthesia and analgesia with productivity in publications on labour epidural analgesia and childbirth pain. The recent paper specifically addressed the role of breakthrough pain (unscheduled epidural supplementation by anaesthetist to treat pain whilst being on labour epidural analgesia due to inadequate pain relief) being associated with dysfunctional labour, reduced patient satisfaction and reduced successful patient bolus during epidural analgesia.

COLEUS: Clinical Trial Network Collaboration with PND and PP

COLEUS Clinical Trials Grant framework (NMRC/CTGIITL/0001/2014) investigates psychological and pain development associated with labour epidural analgesia as secondary outcomes in the setting of a randomized controlled trial of innovative epidural delivery systems developed between KK Hospital and industry. This research network establishes the close scientific collaboration between anaesthesia (Dr Sng Ban Leong, Dr Leong Wan Ling, Prof Alex Sia) and Women's Mental Wellness Service (Dr Helen Chen, Dr Chua Tze Ern). The trial is focuses on nulliparous women who requested epidural analgesia during labour only and aims to identify outcomes of PND, PP after childbirth and breastfeeding outcomes within women who receive epidural analgesia. The principal investigator is experienced in leading a large research trial with scientific rigor in innovative medical technology. The administrative and statistical setup includes electronic online randomization and data management through REDCAP electronic database.

From the COLEUS trial screening log (as of 18 November 2015), 814 women were screened. 667 women (81.9%, 667 out of 814) expressed that they were uncertain of their choice of pain relief during the screening phase. 98 women refused epidural analgesia and 49 women were certain of receiving epidural analgesia. The trial epidural regimens were administered to 199 women, 218 women received epidural analgesia but not part of the trial

(refusal, exclusion criteria) and 397 women (48.8%, 397 out of 814) chose non-epidural pain relief. Hence, there is clinical equipoise in randomizing the women who were uncertain of their choice of pain relief. Of the eligible 176 women with adequate follow up, 134 women (76.1%) responded to the postnatal survey at 6 to 10 weeks after delivery.

F6. Short Term Implications of Research

Our prospective group study will investigate the role of modifiable risk factors and develop a model that would take into account biological and psychological mechanisms to better understand PONV and pain after cesarean surgery. We will identify modifiable risk factors and explore the interplay of psychological and pain pathways will be investigated through targeted selected serotonin, monoamine and oxytocin candidate gene polymorphism with post-operative pain, PONV and postnatal depression. Our study will broaden the current understanding and basic neurobiological mechanisms especially in central sensitisation and central nervous system dysregulation in PONV and post-operative pain. We will validate the role of analgesic interventions and needs in reducing the risk of PONV and post-cesarean pain and change the current clinical practice in the care during cesarean delivery management. The proposed study will guide us in future studies on potential novel risk stratification and identify modifiable risk factors as therapeutic targets.

F7. Long Term Implications of Research

The long term goal of our project is to establish a collaborative care model according to each individual's risk factors and eventually to target specified interventions to minimize the risk of PONV and improve the pain experience after childbirth. The psychobiological model derived from this trial could be the basis of subsequent hypothesis testing in research into modifiable risk factors, as well as, validation of the model in a new population group such as other pain syndromes. This trial would aim to develop prediction and model validation in the long term. We plan to incorporate a longer term follow-up study (2 to 3 years) following this proposal to examine the sustained effect of these risk factors on post-operative pain and depression after childbirth including health sciences outcomes like cost-effectiveness analysis and longer term functional outcomes.

Ultimately, this trial will lay a strong foundation for subsequent prospective randomized clinical trials to determine whether rigorous risk stratification, psychological treatment and analgesic interventions can prevent PONV and improve pain after childbirth. This proposal will also be the basis of framework for future research in pain and related psychological disorders. Foreseeable applications may include functional brain imaging extending the capabilities of the NMRC Transition Award which is still being developed. Future research studies, based on the model, drug interventions, targets and psychological interventions would lead to better healthcare and patient outcomes.

F8. Discuss in detail the experimental design and procedures to be used to accomplish the specific aims of the study. If this study involves a retrospective medical record review, please specify the period of data collection.

The proposed study is an observational study in 200 women who undergo cesarean delivery at KK Women's and Children's Hospital, Singapore. Informed consent will be obtained from all subjects. Singhealth Centralised Institutional Review Board approval and Clinical Trials Registration will be obtained.

Before delivery

Women scheduled to undergo a cesarean delivery under spinal or combined spinal epidural anesthesia will be approached to participate in the study. After obtaining informed consent, patients will be asked about any history of PONV after CD, history of PONV after non obstetric surgery, history of morning sickness, history of hyperemesis gravidarum, history of

motion sickness, smoking history, and occurrence of intraoperative nausea and vomiting. The obtained data will be documented in Data Collection Form.

Patients will be asked to rate, using a 0-10mm visual analog scale (VAS), their surgical anxiety level ("On a scale of 0-100, with 0 being not anxious at all to 100 being extremely anxious, how anxious are you about your upcoming surgery?"), their anticipated pain (On a scale of 0-100, with 0 being no pain at all and 100 being pain as bad as you can imagine, how much pain do you anticipate experiencing after your upcoming surgery?"), and using a categorical scale, their anticipated pain medication need ("On a scale of 0 to 5, with 0 being none at all, 1 being much less than average, 2 being less than average, 3 being average, 4 being more than average, and 5 being much more than average, how much pain medication do you anticipate needing after your upcoming surgery?").

Study survey will be administered upon recruitment in antenatal clinic or delivery suite or till 5-14 days after discharge whenever patient is comfortable. It includes Edinburgh Postnatal Depression Scale (EPDS), Pain Catastrophizing Scale (PCS), Central Sensitisation Inventory (CSI), EQ-5D-3L and HADS. The estimated duration of the surveys is about 30 minutes.

Mechanical temporal summation (MTS) assessment using a 180 gram von Frey filament applied to the patient's arm, as demonstrated by Weissman-Fogel, et al.[20], will be done prior to surgery and results recorded. The anesthetic technique will be standardized using the current standards of care. All women will receive antacid prophylaxis with 30 ml sodium citrate. The spinal anesthesia administered will be standardized doses of intrathecal hyperbaric bupivacaine (10.5-12 mg), fentanyl (15 mcg), and preservative-free morphine (100 mcg). Before placing the spinal anesthetic, the skin at the site will be infiltrated with 2-5 ml 1.0% lidocaine as per standard practice. It has been shown that the words used during local anesthetic injection can influence patient's subjective experience of pain, so prior to local anesthetic injection we will use a standardized script to inform patients that local anesthetic is about to be given: "I am now giving you the numbing dose." After the injection is completed and the needle is removed, the anesthesiologist will use a standardized script, "From 0 to 10, where 0 is no pain and 10 is the worst pain imaginable, how much did this procedure hurt?" Patient's responses will be recorded.

During cesarean delivery: Surgery, intraoperative and postoperative management will be performed according to standard practice. Data will be collected on heart rate, blood pressure, oxygen saturation, presence of nausea and vomiting and use of wound infiltration. Acute pain in the postoperative care unit (PACU) will be treated at clinician's discretion.

After delivery and before discharge from the hospital: The woman is interviewed at 0 to 48 hours on the pain scores at rest and with movement (sitting up in bed from a supine position) and will be recorded in the nursing electronic records. Other data such as nausea scores, and occurrence of vomiting are also noted. Standard routine monitoring of haemodynamics parameters and pain relief will be done in the ward. Study surveys are continued while patient is comfortable before discharge or till 5-14 days after discharge. The survey for post-delivery health status (HADS, EQ-5D-3L) will take about 10 minutes to complete.

Six - Ten weeks after delivery: The patient will have a phone survey/ online survey at 6 -10 weeks post-delivery with: (1) EPDS (2) Pain Survey (3) Pain Vulnerability (PCS, CSI) (4) Breastfeeding Questionnaire (5) EQ-5D-3L and (6) HADS. Patients with scores on the depression scale consistent with postpartum depression will be referred to their obstetrician or primary care physician for further assessment and management.

F9. Please provide details on sample size and power calculation and the means by which data will be analyzed and interpreted (if applicable).

As an observational study, we will target to enrol for up to 200 consented subjects. The primary hypothesis will be assessed with a Pearson correlation test at $\alpha=0.05$ cutoff for statistical significance. The secondary numeric measures of pain, nausea, and satisfaction will be assessed for correlation with the preoperative measures using a Pearson correlation test. Anticipating that some patients will not require rescue oxycodone, we plan to analyze the time to rescue oxycodone via Kaplan-Meier mean time to event analysis. Dichotomous variables will be assessed via chi-square tests or fisher exact tests.

F10. List all activities that are carried out as part of research in this study. Please state/list all procedures involved in this research study and attach the data collection form (if any) which will be used for CIRB review.

The duration of study period for each participant can last about 17 weeks. Below are the main time points for the study activities:

Before surgery (duration: 4 weeks):

- Patient screening and recruitment before the surgery: gestational age week 36 and above
- Baseline Demographic data collection
- Survey and data collection (EPDS, pain score, vital signs, HADS score, EQ-5D-3L, MTS, "three questions", pain vulnerability (PCS, CSI))

After surgery (duration of labour till 5-14 days after discharge: ~19 days):

- Pain assessment, survey and data collection (pain score, vital signs, HADS score, EQ-5D-3L, analgesia usage, occurrence of vomiting, and nausea scores)

Follow up phone call survey at 6 - 10 weeks after delivery (duration: 10 weeks):

- Phone survey/ Online survey and data collection (EPDS, breastfeeding, HADS score, EQ-5D-3L, pain score, and pain vulnerability (PCS, CSI))

F11. Please describe the participant's visits (frequency and procedures involved). For studies with multiple visits, please attach study schedule.

There will be 3 visits in total. The duration of study period for each participant can last about 17 weeks. Below are the main time points for the study activities:

Visit 1-Before surgery (duration: 4 weeks):

- Patient screening and recruitment before the surgery: gestational age week 36 and above
- Baseline Demographic data collection
- Survey and data collection (EPDS, pain score, vital signs, HADS score, EQ-5D-3L, MTS, "three questions", pain vulnerability (PCS, CSI))

Visit 2-After surgery (duration of labour till 5-14 days after discharge: ~19 days):

- Pain assessment, survey and data collection (pain score, vital signs, HADS score, EQ-5D-3L, analgesia usage, occurrence of vomiting, and nausea scores)

Visit 3-Follow up phone call survey at 6 - 10 weeks after delivery (duration: 10 weeks):

- Phone survey/ Online survey and data collection (EPDS, breastfeeding, HADS score, EQ-5D-3L, pain score, and pain vulnerability (PCS, CSI))

F12. Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims.

There will be drop out in the follow up phone survey. However, the withdrawal rate has been accounted for.

F13. What are the potential risks to participants?

During the MTS pain assessment, a test would involve the repeated sensation of pinprick testing for increased sensitivity of pain to pinprick in some individuals.

Analgesic choices will be made upon patient request and routine hospital protocol, monitoring and recording will apply. If subjects are screened to have high EPDS (13 or more) or persistent pain, they would be advised to seek clinical psychiatric or pain assessment at KK Hospital. The assessment would be done as clinical work and not research funded.

No new research medications are involved by joining the study. The drugs being delivered are the same as what the patient shall receive as standard care.

F14. What are the potential benefits (direct as well as indirect) to participants? Indirect benefit may refer to the medical knowledge gained in the future, from the research.

As this will be an observational study, there will be no direct benefits or harms to patients who choose to participate in this study. On a population level, the data collected in this study may help to improve pain management for women undergoing cesarean delivery in the future.

F15. What is the estimated timeline for this study?

(i) Estimated start date 01-Jun-2017

(ii) Estimated end date 01-Jun-2019

Section G: Recruitment Details

G1. How will potential participants be identified? Please tick all the applicable boxes.

NOTES:

If you have selected that participants are “Patients of study team”, please select “Yes” for K6. If healthy volunteers are recruited for the study, please select the option “Other methods of participant identification” and describe your method(s) of participant identification.

- Referral by attending healthcare professional
- Patients of study team
- Databases
- Other methods of participant identification

G2. Who will make the first contact with participant?

Investigators and the clinical research coordinators in the study team will make the first contact with participant.

G3. How will the participant be contacted?

This study will be advertised with brochures. These will be distributed through KKH, and given to all patients who meet the inclusion criteria during antenatal period. Potential study patients may be invited to participate by study team members in the antenatal clinics/wards and preoperative rooms/wards at KKH. On admission to preoperative rooms/wards, they will again be given a study brochure. The investigators and study team will be available to answer any queries on this trial in the antenatal clinics/wards and preoperative rooms/wards, through phone and email correspondence.

Recruitment of patients from antenatal clinics/wards:

All potential patients who are expected to meet the inclusion/exclusion criteria at term and are seen in the KKH antenatal clinics/wards will be invited to participate in the study.

The informed consent process may be conducted at any time during prior to labour. Obstetricians and research team will approach the patients in the antenatal clinics/wards to provide information about the study. If a patient consents prior to labour, a copy of the consent form will be kept in the patient's case notes. The study investigator will recheck the inclusion/exclusion criteria when the patient is at the preoperative rooms/wards prior to the initiation of the study activities.

Recruitment of patients at preoperative rooms/wards:

The patients will receive the study brochure when they arrive at the preoperative rooms/wards if the patients have pain score of 3 or less (out of 10 using numerical rating scale) and not in distress. Screening for inclusion/ exclusion criteria will be performed and discussion of the study will be done by the study investigators.

G4. Will any advertising/recruitment materials be used to recruit research participants?

Yes

Brochures

Please state the location(s) where the brochures will be placed (e.g. in the general waiting area in Clinic X), and attach a copy of the brochure.

Brochures will be placed and distributed in Antenatal clinics/wards and preoperative

G5. Will any other recruitment strategies be used (e.g. talks in public places, societies etc.)? No

G6. What is the Recruitment Period (if applicable)? Please provide us with the approximate recruitment period.

Start Date: 01-Jun-2017

End Date: 01-Jun-2019

G7. How long will the participants be directly involved in the study (if applicable)? This includes the time from the screening procedures till completion of follow-up tests or examinations.

If applicable, please elaborate.

The duration of study period for each participant can last about 17 weeks. Below are the main time points for the study activities:

- Screening and recruitment time point: gestational age week 36 and above (duration: 4 weeks)
- Pain assessment and questionnaire completion time point (duration of labour till 5-14 days after discharge: ~19 days)
- Follow up phone call survey time point: 6-10 weeks after delivery (duration: 10 weeks)

Section H: Study Sites & Recruitment Targets

H1. Please state the target number of research participants to be recruited for each study site.

No.	Study Site	Total Recruitment Target
1	KK Women's and Children's Hospital (KKH)	200

Section I: Research Participants Characteristics

I1. Please list the inclusion criteria for research participants in this study.

- Aged between 21 – 50 year old;
- Pregnant and going to have caesarean delivery (36 weeks gestation or more; nulliparous and multiparous);
- Healthy or have mild medical problems that are well-controlled (ASA 1-2).

I2. Please list the exclusion criteria for research participants in this study.

- History of intravenous drug or opioid abuse;
- Previous history of chronic pain syndrome;
- Emergency cesarean section;
- Undergo general anaesthesia during cesarean delivery;
- Non-English speaking.

I3. Please state the age group of the research participants.

Lower Age limit 21

Upper Age limit 50

I4. Are there any recruitment restrictions based on the gender of the research participants (e.g. only males will be included in this study)?

Yes. Only female in labour and undergoing cesarean delivery will be included in this study.

I5. Are there any recruitment restrictions based on the race of the research participants (e.g. only Chinese participants will be included in this study)? No

I6. Do the potential research participants have a dependent relationship with the study team (e.g. doctor-patient, employee-employer, head-subordinate, student-teacher, departmental staff relationship)?

Yes

Describe how the study team will manage the dependent relationship to prevent coercion or undue influence.

The study participants are receiving analgesia during cesarean delivery by which the analgesia is performed by the study team members. The study team will be engaging the study participants during antenatal period (antenatal clinics/wards) and prior to analgesia (preoperative wards/rooms). The partner of the study participant will be present at the visits.

I7. Does the study involve any vulnerable research participants? Please select 'Yes' to view the options and select the applicable population(s). Yes

[x] If Pregnant Women, Foetuses and Neonates is selected, please respond to Section L.

[] If Children is selected, please respond to Section M.

[] If Prisoners is selected, please respond to Section N.

[] If a Cognitively Impaired Persons is selected, please respond to Section O. [] Others

I8. Does the study involve any of the following?

- Inpatients.
- Outpatients.
- Healthy Volunteers.
- Not applicable.

Research Participants – Pregnant Women, Foetuses & Neonates**I9. Please indicate if your research involves:**

- Pregnant Women and Foetuses.
- Neonates of Uncertain Viability and/or Nonviable neonates.
- Nonviable neonates.

I10. Describe if appropriate preclinical studies, including studies on pregnant animals and clinical studies including studies on non-pregnant women, have been conducted and data is available to assess risks to pregnant women and foetus.

Not applicable. This is an observational study, and the labour analgesia shall be performed as per hospital routine practice. No research medications or procedures are involved in this study. The risk to the fetus is the least possible as labour analgesia options are established and routine procedures in pregnant women with minimal effects on the fetus.

I11. Describe if the risk to the foetus is the least possible in order to achieve the research objectives.

The risk to the fetus is the least possible as labour analgesia options are established and routine procedures in pregnant women with minimal effects on the fetus.

I12. Describe the additional safeguards that will be provided to protect the rights, safety and welfare of these vulnerable participants.

The informed consent process will be conducted during recruitment at the antenatal clinic/wards and preoperative room/wards before their labour pain onset. It will take place in a single private room. They will be given time and space to make an informed decision with their partner or husband present at all times. They will be given verbal as well as written information.

I13. Special Informed Consent Requirements (Check all that apply).

- I will obtain consent from the pregnant women because:
 - Research holds out the prospect of direct benefits to the pregnant women.
 - Research holds out the prospect of direct benefits to both the pregnant women and the foetus.
 - Risk to the foetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.
- I will also obtain consent from the father because the research holds out the prospect of direct benefit solely to the foetus.
- The Informed Consent document(s) will provide information regarding the reasonably foreseeable impact of the research on the foetus or neonate.

I14. Assurances by Principal Investigator.

- There will be no inducements, monetary or otherwise, offered to terminate a pregnancy.
- Individuals engaged in the research will not have any part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
- Individuals engaged in the research will not have any part in determining the viability of a neonate.

Section J: Consent Process – Consent Required

J1. Describe when the consent process will take place with the potential participant.

Participants should be approached prior to the initiation of any study procedures and should not be approached in a situation where they may feel compromised (e.g. while in labour, just prior to a surgical procedure or under sedation).

This study will be advertised on study brochures placed in the antenatal clinics/wards and preoperative rooms/wards. They will be given to all parturients who meet the inclusion criteria during the antenatal period. On admission to preoperative rooms/wards, they will again be given a study brochure if the patients have pain score of 3 or less (out of 10 using numerical rating scale) and not in distress. The investigators and study team will be available to answer any queries on this trial in the antenatal clinics/wards and preoperative rooms/wards. With the activation of HBRA, informed consent will be obtained in the presence of a prescribed witness.

Recruitment of patients from antenatal clinics/wards:

All potential patients who are expected to meet the inclusion/exclusion criteria at term are seen in the KKH antenatal clinics/wards will be invited to participate in the study. The informed consent process may be conducted at any time during prior to labour. However, the patient will not be enrolled in the study until they have met all the inclusion criteria and exclusion criteria. If a patient consents prior to labour, a copy of the consent form will be kept in the patient's case notes. The study investigator will recheck the inclusion/exclusion criteria when the patient is at the preoperative rooms/wards prior to the initiation of the study activities. Obstetricians and research team will approach the patients in the antenatal clinics/wards to provide information about the study.

Recruitment of patients at preoperative rooms/wards:

The patients will receive the study brochure when they arrive at the preoperative rooms/wards if the patients have pain score of 3 or less (out of 10 using numerical rating scale) and not in distress.

Screening for inclusion/ exclusion criteria will be performed and discussion of the study will be done by the study investigators.

All patients who choose to enrol in the study will be counselled by the investigators about the study protocol, both verbally and with the patient information sheet. Adequate time will be given for discussion and with the investigators to clarify any doubts. The risks and benefits in joining this study will be clarified at recruitment prior to written consent.

J2. Where will the consent process take place with the potential participant (e.g. in room ward, outpatient clinic etc.)? Please justify why the place chosen for the consent process is suitable.

Informed consent will be taken place in the antental clinic/wards and preoperative rooms/wards in a private manner.

J3. Please describe the consent process as follows:

i. Explain if adequate time will be given to the participant to consider their participation.

This study will be advertised on study brochures placed in the antenatal clinics/wards and preoperative wards/rooms. They will be given to all parturients who meet the inclusion criteria during the antenatal period. The patients will receive the study brochure again when they arrive at the preoperative wards/rooms if the patients have pain score of 3 or less (out of 10 using numerical rating scale) and not in distress. Investigators or Clinical Research Coordinators will explain to the patients about the study and patients will be given ample time to read the informed consent form about the study before obtaining their consent.

ii. Please explain if the place where consent will be taken is suitable. This place should allow the participants to be comfortable and have the right frame of mind to consider participation.

Participants will be approached in the antenatal clinic/wards and preoperative rooms/wards. The discussion will be conducted in private manner with the patient.

iii. Please explain how the person taking consent would minimise the possibility of coercion or undue influence.

Participants will receive a patient information sheet. This will be discussed with them in private manner in the antenatal clinic/wards and preoperative rooms/wards. The subjects are able to withdraw from the study at any point. The contact details of the Principal Investigator will be provided in the information sheet. Patients are free to withdraw the study at any time (including timing after their delivery), should they decide not to participate.

J4. Does your study involve potential vulnerable participants whereby obtaining informed consent from the participant is not possible and informed consent is required from a Legal Representative (LR)? No

J5. Please describe the provisions to protect the "privacy interest" of the participants (e.g. consent will be obtained in a separate room, free from intrusion and participants are comfortable with the proposed settings).

Research personnel will conduct all the discussions about the study and answer any question in private manner.

J6. Will consent be documented in the form of a written and signed Research Participant Information Sheet and Consent Form?

Yes

File Name	Description	Version Number	Version Date
EPOC PIS Version 5 (tracked changes).doc	EPOC PIS (tracked changes)	5	24May2018
EPOC PIS Version 5 (clean copy).doc	EPOC PIS (clean copy)	5	24May2018

J7. Will research participants receive any monetary payments (including transportation allowances) or gifts for their participation in the study?

Yes

Participants will be reimbursed SGD20 for their time, inconvenience & transportation.

J8. Besides the Informed Consent Form, will any other materials or documents be used to explain the study to potential Research Participants (e.g. scripts, hand outs, brochures, videos, logs etc.)?

No

J9. Will the study enrol non-English speaking participants?

No

J10. Will the study be recruiting under emergency situations, when prior consent of participant is not possible, and the consent of the participant's legal representative, if present, should be requested?

No

J11. Do you have any additional comments regarding the Informed Consent process?

No

Section K: Research Data Confidentiality

K1. Will coded/anonymous research data be sent to the study sponsor (e.g. pharmaceutical sponsored studies)?

No, the study team would store all research data within the institution.

i. Please state where the research data (soft copy and/or hardcopy) will be stored and indicate if the location storage is secured (i.e Password Protected PC or Laptop, data stored in physical location with lock and key access.)

The soft copy of research data will be stored in a password protected PC. Hard copies of data collection forms are kept by the Principal Investigator under lock and key. The data is accessible only by Investigators for analysis purposes only.

Our recruited subjects/ participants can also do online survey (on Survey Monkey platform) 6-10 weeks follow up instead of only phone survey. The online survey data will be stored in Survey

Monkey's data center with reliable power sources and backup systems. Physical security controls are also ensured in their data center. The data will be encrypted using secure TLS cryptographic protocols. Participants' confidentiality will be protected as the online survey link will be sent to their email address only. No names or identification number that will identify subjects will be available on the online surveys and in the system. The survey data will then be extracted from the online system as password protected excel file. The soft copy of research data will be stored in a password protected

PC. The data is accessible only by Investigators for analysis purposes only.

ii. Who will have access to the research data, and how will access to the research data be controlled and monitored? (Please state the personnel who will have access to the study data eg.

Principal Investigator, Co-Investigator, study coordinator.)

An electronic database REDCap will be used for data entry into case report form (CRF). Password protected accounts will be created for relevant study personnel and the degree of database access granted to the each relevant study personnel (Principal Investigator, Co-Investigator and Clinical Research Coordinator) account will correspond to their trial responsibilities. The research data will be locked and soft copy will be under the computer security of Singhealth.

For the 6-10 weeks online survey, participants' confidentiality will be protected as the online survey link will be sent to their email address only. No names or identification number that will identify subjects will be available on the online surveys and in the system. Only the Principal Investigator and designated Clinical Research Coordinator will have the access to the online surveys by using the designated secured password protected survey monkey login account.

iii. Are there any other measures in place to protect the confidentiality of the research data?

For electronic database REDCap, No names or identification number that will identify subjects will be ensured. The subjects are only identified by study number.

For online survey, No names or identification number that will identify subjects will be available on the online survey and in the system.

iv. Are there any research data sharing agreements with individuals or entities outside the Institution, to release and share research data collected?

No

v. Describe what will happen to the research data when the study is completed.

The research data will be kept under lock and key and using computer security of Singhealth. The data will be destroyed after keeping for 6 years upon completion of the study.

K2. Will any part of the study procedures be recorded on audiotape, film/video, or other electronic medium?

No

Section L: Data & Safety Monitoring

L1. The purpose of the Data and Safety Monitoring Plan is to ensure the safety and well-being of participants, and the integrity of the data collected for the study. Depending on the type and risk level of the study, this may include the Principal Investigator, experts within the department or institution, independent consultants or a combination of the said persons.

Who will perform the data and safety monitoring?

The data is kept by the principal investigator under lock and key and using computer security of SingHealth. The data is accessible only by the investigators for analysis purposes only. The plan for adverse effect monitoring would include reporting to Health Science Authority and CIRB.

L2. Please describe the frequency of review (e.g. daily, weekly, quarterly) and what data (e.g. adverse events/serious adverse events) will be monitored for safety.

Safety data is monitored at all times by the investigators. There will be monthly meeting to review the trial.

Adverse events and serious adverse events will be reported to CIRB accordingly.

L3. How is data integrity monitored to ensure that study data is authentic, accurate and complete, and if the data correlates with the case report forms?

Data is extracted from data collection forms and random audits will be performed to make sure it is authentic, accurate and complete.

L4. Please describe the stopping criteria for the research study based on efficacy, futility and safety criteria.

The stopping criteria for the research study will be based on safety criteria. The review of serious adverse effects will be performed.

L5. Please state the route of dissemination of any data and safety information to the study sites, as well as the person/team responsible for doing so.

Face-to-face communication and email correspondence.

Other Attachments

Note: Please attach only documents that are not relevant to the above sections.

File Name	Description	Version Number	Version Date
EPOC PDPA.pdf	EPOC PDPA	1	-