

## Study Protocol

# Evaluation of central sensitization, fear-avoidance, and pain-pressure threshold with chronic pain in post-hysterectomy patients: A collaborative cohort study

EPOCH – Enhancing Post-operative Outcomes in Chronic pain after Hysterectomy

### Section A : Protocol Title & Protocol Administrators

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

Protocol Title : Evaluation of central sensitization, fear-avoidance, and pain-pressure threshold with chronic pain in post-hysterectomy patients: A collaborative cohort study (EPOCH – Enhancing Post-operative Outcomes in Chronic pain after Hysterectomy)

Protocol Number (Optional) :

#### A2. You may assign Protocol Administrators for this study below

No.	Name	Institution/Organization	Department	Office No.	Email
1	Dr Tan Chin Wen	KK Women's and Children's Hospital (KKH)	Department of Women's Anaesthesiology		Tan.Chih.Wen@khh.com.sg
2	Ms Teo Pei Chih Agnes	KK Women's and Children's Hospital (KKH)	Department of Women's Anaesthesiology		Agnes.Teo.PC@khh.com.sg

### Section B : Study Sites, Study Team & Submission Board

#### B1. Please select the study sites

(i) SingHealth and Partner Institutions (PI listed in Section B2(i) should be from any of the selected institution(s) under "SingHealth and Partner Institutions".)

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

(ii) NHG and Partner Institutions

(iii) Other Local Sites and Overseas Sites (The sites listed is for the IRB's information only. CIRB's approval will not include any of the sites. The sites should apply for their own IRB approval if required.)

**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)	Associate Consultant	[x]
3	Dr Lee Song En John	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Associate Consultant	[x]
4	Dr Lim Ming Jian	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Resident	[x]
5	Dr Sng Ban Leong	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Consultant	[x]
6	Dr Tan Hon Sen Paul	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Resident	[x]
7	Mr Yeam Cheng Teng	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Student	[ ]
8	Ms Liu Juan	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	clinical research coordinator	[x]
9	Ms Chen Jie	Co-I	KK Research Centre	KK Women's and Children's Hospital (KKH)	clinical research coordinator	[x]
10	Ms Gan Xin Ping Dora	Co-I	KK Research Centre	KK Women's and Children's Hospital (KKH)	Clinical Research Coordinator	[x]
11	Ms Wong Phaik Yen Emmerie	Co-I	KK Research Centre	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 Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	No
Dr Chan Ju In Jason	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	No
Dr Lee Song En John	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	No
Dr Lim Ming Jian	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	No
Dr Sng Ban Leong	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	No
Dr Tan Hon Sen Paul	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	No
Mr Yeam Cheng Teng	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	No
Ms Liu Juan	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	No
Ms Chen Jie	Co-I	KK Research Centre	KK Women's and Children's Hospital (KKH)	No
Ms Gan Xin Ping Dora	Co-I	KK Research Centre	KK Women's and Children's Hospital (KKH)	No
Ms Wong Phaik Yen Emmerie	Co-I	KK Research Centre	KK Women's and Children's Hospital (KKH)	No

### Section D: Nature of Research

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

Clinical Research

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: Ministry of Health (MOH)
- ii. Grant Name: Clinician Scientist Reidency Seed Funding
- iii. Amount: 50000
- iv. Deadline of Grant Application: 19 Oct 2018
- v. Has the grant been approved? Yes

File Name	Description	Version Number	Version Date
EPOCH LOA.pdf	EPOCH LOA		-

vii. Grant Reference Number MH14:18\13

#### 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?

If the patients follow the directions of the Principal Investigator of this research study and are injured due to the trial substance or research procedure given under the plan for the research study, our institution will provide them with appropriate medical treatment. Payment for management of the normally expected consequences of their treatment will not be provided by KK Women's and Children's Hospital.

The patients still have all their legal rights. Nothing said in the informed consent document on treatment or compensation in any way alters their rights to recover damages where they can prove negligence.

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

Ministry of Health Clinician Scientist Resident Seed Funding

## Section F: Research Methodology

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

Chronic post-surgical pain is persistent pain after a surgical procedure that lasts for at least 3 months with other causes of pain excluded. It is a major socioeconomic and healthcare burden, and has impact on quality of life, physical function, emotional wellbeing and healthcare costs. Locally, hysterectomy for benign indications incurs 32% risk of developing chronic post-hysterectomy pain (CPHP). CPHP can occur around the surgical site, lower abdominal or pelvic region. Based on the pathophysiology underlying chronic pain, we hypothesize that central sensitization, pain fear-avoidance and low pain-pressure threshold are plausible risk factors for CPHP. However, none of these three risk categories has been evaluated in patients with CPHP. We hypothesize that preoperatively abnormal central sensitization, pain fear-avoidance and decreased pain-pressure threshold are associated with increased risk of developing CPHP. We will evaluate these risk factors preoperatively, and follow-up study participants at 4- and 6-months after hysterectomy, to assess the associations between these risk factors and CPHP. We will perform a prospective study of 236 patients undergoing abdominal/laparoscopic hysterectomy for benign indications, recruited at KK Hospital, Singapore. Central Sensitization Inventory (CSI), Fear-Avoidance Components Scale (FACS), pain-pressure threshold and other known factors associated with CPHP will be assessed and recorded. Participants will be followed up at 4- and 6-months postoperatively to assess CPHP. Logistic regression analysis will be used to evaluate the associations between these factors and CPHP. Knowledge of risk factors for CPHP will guide future studies to identify high-risk patients for implementation of individualized targeted therapies to optimize surgical outcomes of this patient group, and to confirm the hypothetical pathophysiological processes of chronic post-surgical pain similarly applicable to CPHP.

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

### **Primary hypothesis**

60% of patients with preoperative increased CSI scores of >40 will develop CPHP at 4 months postoperatively. This is compared to only 20% of patients with preoperative CSI scores of ≤40 developing CPHP.

### **Primary aim**

To determine if increased preoperative central sensitization assessed by Central Sensitization Inventory (CSI score >40) is associated with increased post-operative CPHP incidence at 4 months.

Central sensitization is estimated using the Central Sensitization Inventory (CSI). CSI scores of >40 has been associated with increased chronic pain, and a previous study of CSI in chronic musculoskeletal pain sufferers demonstrated that 70% of the cohort had CSI scores >40.

CPHP is defined as pain that lasts for 3 months or more around the surgical site, lower abdominal or pelvic region, and determined by phone or online assessment at 4 months.

### **Secondary hypotheses**

1. Reduced trapezius pain-pressure thresholds are associated with significantly higher incidence of CPHP among post hysterectomy patients.
2. Increased FACS score is associated with significantly higher incidence of CPHP.

### **Secondary aims**

1. To determine the association between trapezius pain-pressure threshold and the development of CPHP. Trapezius pain-pressure threshold will be measured by applying an algometer to bilateral trapezius muscles to record the pressure that the patient first experiences pain
2. To determine the association between pain fear/avoidance and the development of CPHP. Pain fear/avoidance will be estimated using the Fear Avoidance Components Scale (FACS).

**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.**

Chronic post-surgical pain is defined as persistent pain developing after a surgical procedure that lasts for at least 3 months and after excluding other causes of pain<sup>1</sup>. It can occur after almost any surgery, with an estimated incidence of up to 60% for high-risk procedures<sup>2</sup>. Hysterectomy is one such high-risk surgery, with an estimated incidence of chronic post-hysterectomy pain (CPHP) ranging 14-50%<sup>3</sup>. The adverse impact of chronic pain on health-related quality of life and socioeconomic burden is consequential, with pain severity correlated with impaired physical functioning, emotional wellbeing, and healthcare costs<sup>4</sup>. Broadly, factors associated with increasing CPHP can be classified into three categories: pain vulnerability, psychosocial vulnerability, and patient/surgical factors.

**Pain vulnerability**

Pre-existing and severe postoperative pain are known risk factors for persistent post-surgical pain<sup>4</sup> and CPHP in particular<sup>5-10</sup>. Severe and uncontrolled perioperative pain increases the patient's susceptibility to the development of chronic pain; however, limited studies have been performed to show that improved postoperative analgesia decreases the incidence of CPHP.

The use of quantitative sensory testing and pain experimental modeling such as pain-pressure threshold (PPT) and mechanical temporal summation (MTS) provides robust and reproducible methods to elucidate pre-existing abnormal pain sensitivity, and may identify patients at risk for post-surgical pain<sup>11</sup>. There is limited evidence available on the use of these bedside tests in patients undergoing hysterectomy. For instance, PPT, measured using an algometer to determine the transition point where pressure is sensed as pain, has not been studied in patients with CPHP, but has been validated in myofascial pain<sup>12</sup>, pain sensitivity in osteoarthritic knees<sup>13</sup>, and has proven useful in quantifying hyperalgesia<sup>14</sup>. Conversely, MTS is a test for central sensitization (please refer to definitions in the next paragraph), and has been validated in our single-centre prospective study of 216 Asian women, showing increased preoperative MTS scores were associated with increased risk of developing CPHP<sup>9</sup>.

Central sensitization may be integral to the pathogenesis of chronic pain<sup>4</sup> and is defined as an increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent stimuli. Central sensitization can be assessed using several modalities including quantitative sensory tests such as MTS mentioned above, and validated questionnaires such as the Central Sensitization Inventory (CSI). CSI is designed to identify central sensitization via measuring the full array of related symptoms<sup>15</sup>. It has been found highly associated with central sensitization (measured by other means) in patients with persistent pain<sup>16</sup>, but has yet to be validated in post-hysterectomy patients. CSI demonstrated excellent psychometric properties, such as test-retest reliability of 0.817 and Cronbach alpha of 0.879<sup>15</sup>.

Other potential tests include (1) preoperative brush allodynia, which was associated with chronic pelvic pain after hysterectomy<sup>17</sup>, and (2) diffuse noxious inhibitory control that evaluates the endogenous analgesia system, but showed poor correlation with chronic pain after caesarean section and wide variability in our pilot study.

**Psychological vulnerability**

Psychosocial morbidity, particularly anxiety, depression, and pain catastrophizing are associated with chronic pain<sup>2</sup>. Anxiety and depression are known risk factors associated with CPHP<sup>5</sup>. Our group found that anxiety, as measured by the Spielberger State Trait Anxiety Inventory (STA), was associated with CPHP at 4 months<sup>9</sup>. A combination test for both anxiety and depression, called Hospital Anxiety and Depression Scale (HADS), has shown good internal consistency and concurrent validity<sup>19</sup>. It has been reported similar to measures using STA in a meta-analysis<sup>20</sup>. HADS > 8 has been associated specifically with increased CPHP<sup>5</sup>.

Another related psychological vulnerability, pain catastrophizing, defined as a negative cognitive-affective response to anticipated or actual pain, is associated with elevated acute and chronic pain, increased central sensitization, and increased healthcare costs and disability<sup>21, 22</sup>.

The Pain Catastrophizing Scale (PCS) assesses three domains of catastrophizing: rumination, magnification, and helplessness. The PCS has been associated with chronic pain patients<sup>23</sup> and CPHP specifically<sup>9</sup>.

The negative emotional perception of pain as terrorizing can generate catastrophic thoughts and vigilance; commonly seen in a morbidity known as fear-avoidance<sup>24</sup>, leading to overestimation of pain intensity, poor coping abilities, and delayed resumption of daily activities<sup>25, 26</sup>. Pain fear-avoidance behavior can be assessed with the Fear-Avoidance Components Scale (FACS), designed to elucidate related behavioral, cognitive, and affective components<sup>27</sup>. FACS demonstrated high test-retest reliability of 0.9, with good consistency of 0.89, and offers five severity levels, making it suitable for risk-stratification<sup>27</sup>. FACS has yet been used in post-hysterectomy patients. Other alternative measures such as the Fear-Avoidance Beliefs Scale and Pain-Anxiety Symptoms Scale may be limited in their specificity and lack important fear-avoidance components<sup>28, 29</sup>. Finally, lower preoperative quality of life has been associated with CPHP<sup>3</sup>, and conversely, CPHP was found to significantly impact on daily activities in 18% of patients a year after surgery<sup>8</sup>. Hence, quality of life is an important measure both as a risk factor of CPHP and to quantify impact of CPHP on the affected patients. Validated questionnaire EQ-5D assesses generic health-related quality of life.

#### Patient and surgical factors

Pinto et. al. found that **younger** and **pre-menopausal** patients were at increased risk of developing CPHP<sup>7</sup>. The **surgical method** of hysterectomy, and presumably representing the extent of injury, is another CPHP risk factor. Abdominal and laparoscopic hysterectomy exhibited similarly high CPHP incidence of 25-26%<sup>6</sup> and 20-31%<sup>5, 8</sup>, respectively. In contrast, only 12-18% of post vaginal hysterectomy patients had CPHP<sup>5, 8</sup>.

**The choice of anaesthetic does not significantly affect CPHP development.** Comparison of propofol (intravenous anaesthetic) versus sevoflurane (gaseous anaesthetic) anaesthesia have been studied in a non-randomized trial with no significant difference in the risk of CPHP<sup>8</sup>. Similarly, there was no difference in CPHP incidence rates between spinal anaesthesia versus general anaesthesia<sup>5</sup>. Epidural analgesia was initially shown to reduce CPHP in a non-randomized study<sup>30</sup>, but a subsequent randomized trial comparing epidural versus wound infusion of local anaesthetic found no difference<sup>31</sup>. Intraoperative dexmedetomidine infusion was reported to reduce CPHP only in a non-randomized trial in the Asian population<sup>5</sup>.

While evidence of **genetic predisposition** in the transition from acute to chronic pain exist, there is **no reliable genetic testing available** to quickly and cost-effectively risk-stratify patients and support the clinical decision-making process. Nevertheless, calcium channel polymorphism CACNG2 has been shown to increase spontaneous afferent stimuli in injured neurons in mice, and is associated with chronic pain after breast cancer surgery<sup>1, 32</sup>. We specifically target **post-hysterectomy patients** in contrast to other persistent post-surgical pain groups for the following reasons:

#### Clinical significance

KK Hospital alone performs more than **1,200 hysterectomies annually**, and more than **600,000 hysterectomies** are performed in the USA annually<sup>33</sup>. From a recent prospective trial conducted by our group, we found **CPHP incidence of 32.0% at 4 months and 15.7% at 6 months** among Singaporean women<sup>9</sup>. The combination of the large number of patients undergoing hysterectomy and high incidence of CPHP results in **significant economic burden and negative impact on quality of life** of the patients and their family.

#### Gaps in knowledge

In order to reduce the development of CPHP, knowledge of factors **underlying the acute-to-chronic pain transition** is essential. While several studies have suggested that chronic post-surgical pain is likely the culmination of factors in **multiple domains**, including genetic predisposition to pain vulnerability and psychosocial susceptibility<sup>4</sup>, many of these studies focused on orthopedic patients with different perioperative risk characteristics, and the knowledge gained may not be translated to post hysterectomy patients who experience predominantly visceral abdominal and pelvic pain. Furthermore, studies that specifically explored factors associated with CPHP are **limited by heterogeneity in study design**, and most **did not evaluate factors from the multiple domains** in chronic pain pathogenesis.

#### Research feasibility

The large number of patients undergoing hysterectomy, **high incidence of CPHP**, relative **homogeneity** of the surgical procedure and patient demographics ensure the **feasibility** of this study. Additionally, both the Singapore and USA centres have **established research capability and mentorship expertise in the field of chronic pain in women**. In order to evaluate the relative association of perioperative factors with development of CPHP, a **comprehensive set of variables** from multiple domains including pain vulnerability, psychosocial vulnerability, and patient/surgical information will be assessed in our **cohort study**. The selection of variables was based on previous studies of CPHP and supplemented with potential factors identified in other types of chronic post-surgical pain. By comparing the association of these factors with CPHP, we aim to establish perioperative somatic and psychosocial risk factors that can be used to **inform clinical decision-making** and permit targeted institution of **individualized therapy** to modify the specific risk of individual patients and improve the **risk-benefit and cost-effectiveness** of preventive treatment.

#### F4. Please provide a list of relevant references.

- 1 Nissenbaum J. From mouse to humans: discovery of the CACNG2 pain susceptibility gene. *Clin Genet* 2012; **82**: 311-20
- 2 Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; **367**: 1618-25
- 3 Bradsborg B, Nikolajsen L, Hansen CT, Kehlet H, Jensen TS. Risk factors for chronic pain after hysterectomy: a nationwide questionnaire and database study. *Anesthesiology* 2007; **106**: 1003-12
- 4 Chapman CR, Verck CJ. The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. *The journal of pain : official journal of the American Pain Society* 2017; **18**: 359.e1-e38

5 Han C, Ge Z, Jiang W, Zhao H, Ma T. Incidence and risk factors of chronic pain following hysterectomy among Southern Jiangsu Chinese Women. *BMC Anesthesiol*2017; 17: 103

6 Montes A, Roca G, Sabate S, et al. Genetic and Clinical Factors Associated with Chronic Postsurgical Pain after Hernia Repair, Hysterectomy, and Thoracotomy. A Two-year Multicenter Cohort Study. *Anesthesiology*2015; 122: 1123-41

7 Pinto PR, McIntyre T, Nogueira-Silva C, Almeida A, Araujo-Soares V. Risk factors for persistent postsurgical pain in women undergoing hysterectomy due to benign causes: a prospective predictive study. *The journal of pain : official journal of the American Pain Society*2012; 13: 1045-57

8 Pokkinen SM, Nieminen K, Yli-Hankala A, Kalliomaki M. Persistent posthysterectomy pain: A prospective, observational study. *Eur J Anaesthesiol*2015; 32: 718-24

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10 Theunissen M, Peters M, Schepers J, et al. Recovery 3 and 12 months after hysterectomy: epidemiology and predictors of chronic pain, physical functioning, and global surgical recovery. *Medicine (Baltimore)*2016; 95: e3980

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12 Ohrbach R, Gale EN. Pressure pain thresholds, clinical assessment, and differential diagnosis: reliability and validity in patients with myogenic pain. *Pain*1989; 39: 157-69

13 Fingleton C, Smart K, Mbloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage*2015; 23: 1043-56

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15 Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. *Pain Pract*2012; 12: 276-85

16 Neblett R, Cohen H, Choi Y, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *The journal of pain : official journal of the American Pain Society*2013; 14: 438-45

17 Brandsborg B, Dueholm M, Kehlet H, Jensen TS, Nikolajsen L. Mechanosensitivity before and after hysterectomy: a prospective study on the prediction of acute and chronic postoperative pain. *Br J Anaesth*2011; 107: 940-7

18 Hinrichs-Rocker A, Schulz K, Jarvinen I, Lefering R, Simanski C, Neugebauer EA. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) - a systematic review. *Eur J Pain* 2009; 13: 719-30

19 Brennan C, Worrall-Davies A, McMillan D, Gilbody S, House A. The Hospital Anxiety and Depression Scale: a diagnostic meta-analysis of case-finding ability. *J Psychosom Res* 2010; 69: 371-8

20 McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand* 2014; 58: 1199-213

21 Papaioannou M, Skapinakis P, Damigos D, Mavreas V, Broumas G, Palgimesi A. The role of catastrophizing in the prediction of postoperative pain. *Pain Med* 2009; 10: 1452-9

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25 Buer N, Linton SJ. Fear-avoidance beliefs and catastrophizing: occurrence and risk factor in back pain and ADL in the general population. *Pain* 2002; 99: 485-91

26 Flink IK, Mroczek MZ, Sullivan MJ, Linton SJ. Pain in childbirth and postpartum recovery: the role of catastrophizing. *Eur J Pain* 2009; 13: 312-6

27 Neblett R, Mayer TG, Hartzell MM, Williams MJ, Gatchel RJ. The Fear-avoidance Components Scale (FACS): Development and Psychometric Evaluation of a New Measure of Pain-related Fear Avoidance. *Pain Pract* 2016; 16: 435-50

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30 Bouman EA, Theunissen M, Bons SA, et al. Reduced incidence of chronic postsurgical pain after epidural analgesia for abdominal surgery. *Pain Pract* 2014; 14: E76-84

31 Fassoulaki A, Chassiakos D, Melemeni A. Intermittent epidural vs continuous wound infusion of ropivacaine for acute and chronic pain control after hysterectomy or myomectomy: a randomized controlled trial. *Pain Med* 2014; 15: 1603-8

32 Nissenbaum J, Devor M, Seltzer Z, et al. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. *Genome research* 2010; 20: 1180-90

33 Wu JM, Wechter ME, Geller EJ, Nguyen TV, Visco AG. Hysterectomy rates in the United States, 2003. *Obstet Gynecol* 2007; 110: 1091-5

34 Neblett R, Hartzell MM, Williams M, Bevers KR, Mayer TG, Gatchel RJ. Use of the Central Sensitization Inventory (CSI) as a treatment outcome measure for patients with chronic spinal pain disorder in a functional restoration program. *The spine journal: official journal of the North American Spine Society* 2017; 17: 1819-29

**F5. Please attach at least two relevant publications that support the conduct of the study.**

File Name	Description	Version Number	Version Date
2018_Sng BL_incidence an assoc factors CPHP.pdf	Known associated risk factors for CPHP	1	06-Mar-2019
nihms314358.pdf	CSI to assess central sensitization	1	06-Mar-2019

**F6. Please provide an account of the Principal Investigator's preliminary studies and progress reports (if any) pertinent to this application.**

We conducted a prospective cohort study in 216 Asian women who underwent abdominal or laparoscopic hysterectomy for benign conditions (CIRB ref: 2013/512/D, Clinicaltrials.gov NCT02025153). The incidence of persistent pain at 4- and 6-months were 32% (56/175) and 15.7% (25/159) respectively. Independent association factors for persistent pain at 4-months were higher MTS score, intraoperative morphine consumption, pain score in recovery room, pain score during coughing at 24-hours postoperatively, postoperative 24-hour itching and preoperative pain in lower abdominal region. Independent association factors for persistent pain at 6-months were preoperative pain during sexual intercourse, higher MTS score and morphine consumption at 24- and 48-hours postoperatively.

Additionally, we have an established collaborative relationship with Women's Anesthesiology at Duke studying chronic pain after breast cancer surgery.

**F7. Please state concisely the importance of the research described in this application by relating the specific aims to the long term objectives.**

**Short Term Implications**

A majority of evidence in CPHP comes from demographic profiling of differing quality and detail. While a number of prospective studies have attempted to characterize risk factors for persistent pain, such studies suffered from inadequate design lacking data on the continuum of patient care during the perioperative period. Therefore there is a need for well-designed studies to identify the risk factors of persistent pain and investigate the efficacy of preventive interventions targeted to those patients. We propose to address this gap in this prospective study.

**Long Term Implications**

The importance of identifying patients at high-risk of developing persistent post-surgical pain is essential to allow targeted efficacious interventions to be administered. However, many antineuropathic medications possess significant side effects such as sedation and drowsiness highlighting the importance to target those interventions only to high-risk patients. Potential pharmacological antineuropathic target medications include pregabalin and escitalopram. Hence, a randomized controlled trial targeted at the population with high-risk of persistent postsurgical pain will be conducted following the results of this prospective cohort study.

This collaborative grant will put forward the expertise of Duke, Duke-NUS, and KKH anesthesiologists and pain medicine specialists. This would form a common platform of pain experimental modeling and genomic capabilities, tapping on the cultural and socioeconomic differences that exists in understanding pain mechanisms. Chronic persistent pain has become an epidemic and this research collaboration has the vision to bring forth further understanding, reduce disease burden and bring value to intervention by improving efficacy and safety in pharmacological intervention in the future.

**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.**

This will be a **prospective study** in KK Women's and Children's Hospital (Singapore). Overall, we aim to enroll 236 subjects in total. All women scheduled for abdominal or laparoscopic hysterectomy are eligible, as the incidence of CPHP are similar.

**Screening for eligibility:** This study will be advertised on brochures placed in pre-operative assessment clinics and pre-admission areas. Patients planned for elective abdominal or laparoscopic hysterectomy will receive study information either at pre-operative assessment clinic or upon admission for surgery. Potential participants will be evaluated for both inclusion and exclusion criteria. If eligible, informed consent will be sought and psychophysical tests and questionnaires will be administered pre-operatively. Research personnel will conduct all discussions about the study and answer any questions in a private manner in the consultation rooms. Patients will be given the opportunity to ask questions / clarify doubts. Ample time will be given for written consent.

**Questionnaires:** Participants will be asked to complete the following questionnaires preoperatively:

- Hospital Anxiety and Depression Scale, HADS (4 minutes)
- Pain Catastrophizing Scale, PCS (4 minutes)
- Central Sensitization Inventory, CSI (4 minutes)
- Fear-avoidance Component Score, FACS (4 minutes)
- EQ-5D (3 minutes)

## Psychophysical test procedures

### Pain-pressure threshold

The test will be performed on bilateral trapezius muscles. Pressure will be applied at 90 degrees downward with an algometer, with the speed of pressure increase approximately 1kgf/s. Upon the sensation of pain, the patient will vocalize or raise her hand to terminate the test, and the highest reading will be recorded (up to maximum 6kgf). If two values are recorded within 0.2kgf of each other, the mean value will be recorded. If two values are greater than 0.2kgf of each other, a third test will be performed and the mean obtained.

### Mechanical temporal summation (MTS)

Pinprick hyperalgesia will be evoked using a Von Frey filament, applied to the volar aspect of the dominant forearm. Participants will report using the numerical rating scale the intensity of pain from the first stimulus. Subsequently, ten repetitive stimuli one second apart will be applied with the same filament within an area of 1cm diameter of the same forearm. Subjects will report the rate the pain intensity of the tenth stimulus. The magnitude of MTS is calculated as the difference between the last to the first pain scores. We will classify the participants according to "evoked MTS" if the last stimulus is rated higher than the first, or "no MTS" if the last stimulus is rated equal or lower than the first. The research team administering the test will follow a set script.

The above-mentioned bed-side tests for pain vulnerability (PPT, MTS) are chosen for the following reasons: (1) minimal discomfort, (2) quick and easy to perform at the bedside, (3) minimal equipment/training required, (4) tests are associated with central sensitization / post-surgical pain phenomenon, and (5) good psychometric properties.

**Medical procedures:** Anaesthetic and surgical providers will be blinded to the results of preoperative tests. Anaesthesia will be administered according to the current standard of care in both institutions – general anaesthesia with intravenous induction with propofol and maintenance with inhalational agents. Perioperative analgesia will be administered in a multimodal fashion, including opioids, non-steroidal anti-inflammatory drugs (NSAIDS), and paracetamol, at the anaesthesiologist/surgeon's discretion.

**Outcome measures:** Perioperative anaesthetic / surgical management and outcomes including analgesia, pain scores, and adverse events will be recorded at the post-anaesthesia care unit and postoperative days 1 to 3. Assessment will be performed in a private manner, and when the patients are not in distress or pain. Our primary outcome is the development of CPHP, defined as pain that lasts for 3 months or more around the surgical site, lower abdominal or pelvic region, and determined by phone or online assessment with the protocol used by Brandsborg et. al. and in our centre's previous study<sup>3, 9</sup> at 4 months via phone or online survey. We will repeat the phone or online survey at 6 months to assess for pain duration. The severity of pain, functional impairment, use of medications and mood disturbance associated with CPHP would be assessed.

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

**Sample size calculation:** Our primary aim is to assess the association between preoperative CSI scores >40 and development of CPHP. Our primary outcome is CPHP development assessed at 4-months post-hysterectomy. We planned to recruit 236 hysterectomy patients and estimated that 32% will develop CPHP<sup>9</sup>. Sample size is calculated based on the following assumptions: (1) among the patients with preoperative CSI >40, 60% will develop CPHP, (2) among patients with CSI ≤40, 20% will develop CPHP, (3) allocation ratio of 1:2, (4) level of significance of 5%, (5) power of the study is 80%, (6) two-sided Fisher's exact test used, and (7) loss to follow up of 20% at 4 months. To achieve the required sample size, 236 patients will be recruited at KK Hospital. In terms of feasibility, KK Hospital, Singapore alone performs more than 1,200 abdominal/laparoscopic hysterectomies annually.

**Statistical analysis plan:** The incidence of CPHP development (primary outcome measure), and CSI scores >40 (primary aim) will be treated as binary variables. Demographic, clinical and other anaesthetic variables will be summarized with respect to CSI > 40 and CSI ≤ 40. Categorical variables will be summarized as frequency (proportion) and while continuous variables will be summarized as mean (SD) / median (IQR). Difference between CSI groups will be compared using Fisher's exact test or Student's t-test. Secondary outcomes pain-pressure threshold and FACS will treated as continuous data. We will try to find reasonable cut-offs based on Youden's J-statistic in order to categorize pain-pressure threshold and FACS for easy use in practice, if it is found associated with risk of developing CPHP. All analyses will be done using SAS 9.4.

**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.**

**Visit 1: Before surgery (duration: up to 4 weeks):**

- Screening and recruitment, baseline demographic data collection
- Hospital Anxiety and Depression Scale, HADS (4 minutes)
- Pain Catastrophizing Scale, PCS (4 minutes)
- Central Sensitization Inventory, CSI (4 minutes)
- Fear-avoidance Component Score, FACS (4 minutes)
- EQ-5D (3 minutes)

**Visit 2-4: After surgery (duration: 3 days):**

- Pain assessment and data collection (pain score, analgesia usage, adverse events if any)

**Follow-up evaluation 5, 6: Follow up phone call or online survey at 4 months and 6 months respectively after surgery (duration: 4 months, 6 months):**

- Phone or online survey and data collection (EQ-5D-3L, pain score)

**Data Collection Form:**

File Name	Description	Version Number	Version Date
CSI_EPOCH.xlsx	CSI		-
PCS_EPOCH.doc	PCS		-
HADS_EPOCH_12Mar2019.docx	HADS		-
EQ-5D-3L_EPOCH_12Mar2019.docx	EQ 5D		-
EPOCH Data Collection Form.doc	EPOCH data collection form		-
FACS_EPOCH.xlsx	FACS		-

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

**Visit 1: Before surgery (duration: up to 4 weeks):**

- Screening questionnaire and recruitment (1 minute), baseline demographic data collection
- Hospital Anxiety and Depression Scale, HADS (4 minutes)
- Pain Catastrophizing Scale, PCS (4 minutes)
- Central Sensitization Inventory, CSI (4 minutes)
- Fear-avoidance Component Score, FACS (4 minutes)
- EQ-5D (3 minutes)

**Visit 2-4: After surgery (duration: 3 days):**

- Pain assessment and data collection (pain score, analgesia usage, adverse events if any)

**Follow-up evaluation 5, 6: Follow up phone call or online survey at 4 months and 6 months respectively after surgery (duration: 4 months, 6 months):**

- Phone or online survey and data collection (EQ-5D-3L, pain score)

**Visit Schedule:**

File Name	Description	Version Number	Version Date
Methodology (version 2).pptx	Visit schedule	2	27-Jun-2019

**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 or online survey. However, the withdrawal rate has been accounted for.

**F13. What are the potential risks to participants?**

During the pain assessments, a thin plastic tube will be used to mimic a pinprick sensation on your forearm (MTS test) and an instrument will exert pressure on your shoulder muscle, up to 6kgf of force. These tests may be uncomfortable to some patients. If you experience significant discomfort, please inform the investigator performing the tests.

Pain relief will be administered as per standard hospital protocol, and routine monitoring and recording will apply. If you are screened to be at risk of developing persistent pain from your surgery, you would be advised to seek pain assessment at KK Hospital. The assessment would be done as clinical work and is not research-funded.

As part of the study activities, screening of depression and anxiety will be performed through questionnaires conducted. You may also be inconvenienced on your time when you choose to take part in this study.

**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.**

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 hysterectomy in the future. If the patient is deemed to be developing persistent pain, she will be advised to return for consultation with a pain specialist.

**F15. What is the estimated timeline for this study?**

- (i) Estimated start date 08-Jul-2019
- (ii) Estimated end date 01-Jun-2021

**F16. Does this study have a Study Protocol?**

No

**NOTES:**

Investigators conducting Clinical Trials must submit a Study Protocol for CIRB review. You may refer to the CIRB website for the Protocol template (Clinical Trial) and Protocol Template (Clinical Research).

<http://research.singhealth.com.sg/pages/centralisedinstitutionalreviewboard.aspx>

**F17. The Principal Investigator is responsible for ensuring that all study participants give informed consent before enrolling into the study.**

Please select the applicable consent scenarios. Please select “Waiver of Informed Consent” if consent has been obtained for research purposes.

Informed Consent will be taken for all study subjects.

## Section H: Recruitment Details

**H1. 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

Investigators and the clinical research coordinators in the study team will approach patients in the antenatal clinics while they are waiting for their visits. Brochures will also be placed in the clinics so that patients can contact the research team should they express interest to join the study.

## H2. Who will make the first contact with participant?

Principal investigator, co-investigators, or clinical research coordinators

## H3. How will the participant be contacted?

Patients who are undergoing hysterectomy will receive study information either at pre-operative assessment clinic or upon admission for surgery if they have not attended the pre-operative assessment clinic. They will be screened for eligibility using the inclusion and exclusion criteria. If eligible for recruitment, the patients will be approached by the investigators for recruitment. Recruitment will be performed in the pre-operative assessment clinic or on the same day of surgery if they have not attended pre-operative assessment clinic. Research personnel will conduct all discussions about the study and answer any questions in a private manner in the consultation rooms. They will be counselled regarding the alternatives and given an opportunity to ask questions and clarify doubts. Ample time will be given to the potential patients for consent taking. Consent will be obtained in writing upon their willingness and agreement to participate in the study.

## H4. Will any advertising/recruitment materials be used to recruit research participants?

Yes

I Posters  
 II 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.

Pre-operative assessment clinics, pre-admission areas

File Name	Description	Version Number	Version Date
Brochure_EPOCH (Ver 3) CLEAN.docx	Brochure Ver 3 CLEAN	-	
Brochure_EPOCH (Ver 3) TRACKED.docx	Brochure Ver 3 TRACKED	-	

III Advertisements in Newspapers / Magazines / Publications

IV Advertisements on Radio / TV

V Letter of Invitation to potential research participants

VI Letter to Doctors requesting for referrals

VII Other types of materials will be used

## H5. Will any other recruitment strategies be used (e.g. talks in public places, societies etc.)?

No

## H6. What is the Recruitment Period (if applicable)? Please provide us with the approximate recruitment period.

Start Date: 08-Jul-2019

End Date: 01-Jun-2021

If this is a Medical Record Reviews, please indicate the period of the data that will be extracted for review.

## H7. 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.

Patients will be involved in the study before their admission to the hospital for surgery, which may take up

to 4 weeks. Questionnaires will be conducted during their hospitalization stay, i.e. from the time just before surgery until the patient is discharged from the post-operative observation area. This will take about 3-4 days. Phone or online surveys will be conducted at 4 and 6 months, respectively, after surgery. The total amount of time by which participants are involved in the study will therefore take about 7 months.

## Section I: Study Sites & Recruitment Targets

### I1. Please state the target number of research participants to be recruited for each study site in Singapore. If exact numbers are not available, please give an approximate number range in the recruitment target.

Please note that recruiting participants beyond the total number without CIRB's approval would constitute a non-compliance. If you intend to recruit beyond the total number, please submit a study amendment to increase the recruitment target.

No.	Study Site	Total Recruitment Target	Adults (Male)	Adults (Female)	Children
1	KK Women's and Children's Hospital (KKH)	236	0	236	0

### I2. Is this study part of an international study?

No

## Section K: Research Participant Characteristics

### K1. Please list the inclusion criteria for research participants in this study.

- Aged between 21 – 80 years old;
- Healthy or have mild medical problems that are well-controlled (ASA 1-2);
- Undergoing elective abdominal or laparoscopic hysterectomy;
- Benign gynaecological indications for hysterectomy, e.g. fibroids, adenomyosis.

#### NOTES:

For global studies, please modify the criteria according to local regulations (e.g. persons below the age of 21 and are unmarried are considered minors in Singapore and would require parental consent prior to participation).

Please also ensure that the symbols used are displayed accurately. Use “>=” or “<=” to represent “more than or equals to” or “less than or equals to” respectively.

### K2. Please list the exclusion criteria for research participants in this study.

- Vaginal hysterectomy;
- Uterine prolapse, endometriosis, malignant disease, or main indication of pelvic pain;
- Failure to determine mechanical temporal summation or pressure pain threshold;
- History of drug dependence or recreational drug use;
- History of chronic pain syndrome;
- Current chronic daily treatment with corticosteroids (excluding inhaled steroids).

**K3. Please state the age group of the research participants.**

Lower Age limit 21

Upper Age limit 80

**NOTES:**

Persons below the age of 21 and are unmarried are considered minors in Singapore and will require parental consent prior to participation.

**K4. Are there any recruitment restrictions based on the gender of the research participants (e.g. only males will be included in this study)?**

Yes

Female patients undergoing hysterectomy

**K5. 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

**K6. 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)?**

No

**NOTES:**

If you have selected that participants are 'Patients of study team' in Section H1, then the answer should be 'Yes'.

**K7. Does the study involve any vulnerable research participants? Please select 'Yes' to view the options and select the applicable population(s).**

No

**K8. Does the study involve any of the following?**

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

## Section P: Consent Process – Consent Required

### P1. 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).

With effect from 1 November 2017, for studies regulated under HBRA, please include a statement that informed consent will be taken in the presence of a witness (applicable to restricted human biomedical research and research that are ~~interventional~~ or invasive).

Patients will be approached in the preoperative clinic/wards or pre-admission areas. The Investigator will explain to the patients about the study and patients will be given time to read about the study before obtaining their consent. Adequate time will be given for patients' consideration of participation and discussion with the investigators to clarify any doubts. With the activation of HBRA, informed consent will be obtained in the presence of a prescribed witness.

### P2. 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 preoperative clinic consultation room or wards in a private manner.

### P3. Please describe the consent process as follows:

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

Patients will be approached in the preoperative clinic/wards or pre-admission areas and will be explained and given time to read 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.

Patients will be approached in the preoperative clinic or wards or pre-admission areas. The discussion will be conducted in a private manner with the patient.

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

Study participants will receive a patient information sheet. This will be discussed with them in private in the preoperative clinic consultation room or wards (private room). 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.

### P4. 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

### P5. 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.

**P6. 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
Consent_EPOCH (Ver 3) CLEAN.docx	consent ver 3 CLEAN		-
Consent_EPOCH (Ver 3) TRACKED.docx	consent ver 3 TRACKED		-

**P7. Will research participants receive any monetary payments (including transportation allowances) or gifts for their participation in the study?**

Yes

Remuneration of \$50 for research efforts and time inconvenience in participation and completion of the Research Questionnaires and pain assessment.

**P8. 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

**P9. Will the study enrol non-English speaking participants?**

No

**P10. Will the study be recruiting participants under emergency situations, when prior consent of the participant is not possible, and the consent of the participant's legal representative, if present, should be requested?**

No

**P11. Do you have any additional comments regarding the Informed Consent process?**

No

**Section R: Research Data Confidentiality**

**R1. 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.

**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.

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

No names or identification number that will identify subjects will be ensured. The subjects are only identified by study number.

**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 7 years upon completion of the study.

**R2. Will any part of the study procedures be recorded on audiotape, film/video, or other electronic medium?**

No

## **Section S: Biological Materials Usage & Storage**

**S1. Will any biological materials (such as blood or tissue) be used in the study? This includes both prospectively collected and existing biological material.**

No

## **Section T: Data & Safety Monitoring**

**T1. 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 CIRB.

**If the DSMB/DMC is an external committee, please include information/details of the composition of the external DSMB/ DMC. Kindly attach relevant file(s).**

**T2. 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 study. Adverse events and serious adverse events will be reported to CIRB accordingly.

**T3. 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.

**T4. 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.

**T5. 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
EPOCH PDPA.pdf	EPOCH PDPA		-
190627 Amendment Summary EPOCH.docx	Amendment summary		-