STUDY PROTOCOL

Development of an ultrasound guided automated spinal landmark identification system (uSINE study)

CIRB NUMBER:
2018/2021

PROTOCOL VERSION: 2.0

PROTOCOL DATE: 8 Aug 2020

PRINCIPAL INVESTIGATOR:
A/Prof Sng Ban Leong, Senior Consultant, KK Women's and Children's Hospital (KKH)

Refer to Section F9 on the statistical analysis.

A2. You may assign Protocol Administrators for this study below

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

National University of Singapore

B2. Study Team Members

(i) Add Study Team Members

No.	Name	Study Role	Department	Institution	Designation	Involve in Informed Consent
1	Dr Sng Ban Leong	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 Chimanlal Shah Mukesh Kumar	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Consultant	[x]
4	Dr Ithnin Farida Binte	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Consultant	[x]
5	Dr Lim Ming Jian	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Resident	[x]
6	Dr Mathur Deepak	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	Senior Consultant	[x]
7	Dr Oh Ting Ting	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	associate consultant	[x]
8	Ms Chen Jie	Co-I	KK Research Centre	KK Women's and Children's Hospital (KKH)	clinical research coordinator	[x]
9	Ms Gan Xin Ping Dora	Co-I	KK Research Centre	KK Women's and Children's Hospital (KKH)	Clinical Research Coordinator	[x]
10	Dr Lee Song En John	Co-I	Department of Anaesthesiology	Singapore General Hospital (SGH)	Resident	[x]
11	Dr Tan Hon Sen	Co-I	Department of Anaesthesiology	Singapore General Hospital (SGH)	Resident	[x]
12	Ms Sultana Rehena	Study Team	Office of Clinical Sciences	Duke-NUS	Associate (Biostatistician)	[ ]

		Member			

NOTES:

For multi-centre studies within SingHealth Institutions and/or institutions under the oversight of SingHealth CIRB or NHG DSRB, each institution must have a Site-Principal Investigator (Site-PI) who is responsible for the conduct of the study in his/her institution.

One of the Site-Principal Investigators should be designated as Principal Investigator (PI). The Principal Investigator will be the Site-Principal Investigator for his/her own institution, and will also be the primary contact person for the CIRB. The Principal Investigator should be a staff from SingHealth Institutions.

Co-Investigators (Co-Is) are members of the research/clinical trial team designated by the Principal Investigator to perform study-related procedure and/or make important research-related decisions. Study Team Members are personnel responsible for the design, conduct or reporting of the research. All personnel who have a responsibility for the consent process and/or direct data collection for this study must be listed as Study Team Members. Please specify their Study Role and Study Site from the dropdown list.

All Principal Investigators and Study Team Members from SingHealth Institutions or institutions under the oversight of SingHealth CIRB have to complete the mandatory minimum training requirement.

Study Team Members from SingHealth and CIRB's partner institutions should be added through their registered user accounts so that they will be notified of their participation in this study when the Application is submitted.

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 Sng Ban Leong	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 Chimanlal Shah Mukesh Kumar	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	No
Dr Ithnin Farida Binte	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 Mathur Deepak	Co-I	Department of Women's Anaesthesiology	KK Women's and Children's Hospital (KKH)	No

Dr Oh Ting Ting	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
Dr Lee Song En John	Co-I	Department of Anaesthesiology	Singapore General Hospital (SGH)	No
Dr Tan Hon Sen	Co-I	Department of Anaesthesiology	Singapore General Hospital (SGH)	No
Ms Sultana Rehena	Study Team Member	Office of Clinical Sciences	Duke-NUS	No

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: HiCura Medical Pte Ltd

ii. Grant Name: NA

iii. Amount: 30000

iv. Deadline of Grant Application: Jul 2020

v. Has the grant been approved? Yes

File Name	Description	Upload Date
2020.07.16 KKH-HiCura RCA (Oh Ting Ting).pdf	RCA-KKH-Hicura	16-Jul-2020 19:16

vii. Grant Reference Number 2020-0311

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 the treatment will not be provided by the KK Women's and Children's Hospital.

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

HiCura Pte Ltd

Section F: Research Methodology

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

Neuraxial ultrasonography has become popular in last decade in epidural space identification. It has been shown a safe and effective technique, with increasing use as an auxiliary to physical examination, enhances the overall success rate of lumbar puncture and reduces the number of injection attempts. Neuraxial procedures are commonly performed with wide range of therapeutic and diagnostic indications. Applications include neuraxial anesthesia for surgery, epidural labour analgesia, epidural steroid injections and lumbar punctures. The current blind palpation landmark technique is known to be highly inaccurate and may increase the risk of multiple insertion attempts, patient suffering and complication rates such as spinal cord injury.

The key challenges for neuraxial procedures are (a) to determine needle insertion and pathway to epidural space; (b) determine the spinal level of the lumbar spine; and (c) in anatomical complicated cases such as obese patients. Various clinical studies have confirmed the effectiveness of ultrasound imaging compared to the traditional palpation method. However, none of the present system can achieve real-time guidance.

The overall aim of this proposal is to develop an ultrasound guided automated spinal landmark identification system (uSINE) to improve patient safety and efficacy of neuraxial procedure needle insertion success. This will be achieved in a few phases of technology development and clinical trial phases. The first two phases recruited 70 patients to develop an automated spinal landmark identification algorithm using image processing to identify spinal landmarks in 50 obese patients. The third phase involve data collection and annotation of spinal ultrasonography in 65 obese patients, followed by a fourth phase to measure the uSINE identification accuracy and first-attempt puncture success rate in 65 obese patients.

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

The overall aim of this proposal is to develop an ultrasound guided automated spinal landmark identification system (uSINE) to improve patient safety and efficacy of neuraxial procedure needle insertion success.

The hypothesis is the ultrasound guided automated spinal landmark identification system would achieve at least 80% success rate of identification of neuraxial needle insertion on the 1^{st} attempt.

Third phase objective: To obtain clinical data, and evaluation and annotation of the clinical data of spinal ultrasonography in 65 obese patients (BMI > 30kg/m^2).

Fourth phase objective: To measure the uSINE identification accuracy and first-attempt puncture success rate of uSINE in a clinical study of 65 obese patients (BMI > 30kg/m^2).

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.

Neuraxial ultrasonography has gained increased popularity in last decade in regional anesthesia practice particularly in epidural space identification (1, 2). It has been shown a safe and effective technique, with increasing use as an auxiliary to physical examination, enhances the overall success rate of lumbar puncture and reduces the number of injection attempts. Lumbar ultrasonography has been recommended for clinical use when performing neuraxial anaesthesia and analgesia by the National Institute of Health and Clinical (NICE) guidelines and British Medical Journal systematic review in United Kingdom in 2008 (3, 4).

Neuraxial analgesia (including epidural analgesia) are commonly performed pain relief method which is effective in many therapeutic and diagnostic settings. Neuraxial anesthetics are employed for surgical anaesthesia, postoperative pain control, epidural labour analgesia and chronic pain management. Besides pain relief, lumbar punctures are performed to obtain cerebrospinal fluid as part of investigations to diagnose central nervous system infections. Therapeutic lumbar punctures are also performed to administer intrathecal chemotherapy drugs. Therefore, it is essential to make neuraxial procedure safe and reliable.

Lumbar neuraxial procedures are typically performed via a 'blind' surface landmark and palpation guidance, which was described in 1921 by Sicard and Forestier (5), and has remained largely unchanged since. Briefly, the anaesthetist has to identify needle entry point by the Tuffier's line derived from the palpation of the iliac crests that should correspond to L3/4 (lumbar) interspinous space.

In spite of its popularity, lumbar neuraxial procedure is associated with a significant failure rate that range from 27% to 32% to provide adequate anaesthesia (6, 7). This may due to various reasons including an inability to guide the needle through the interspinous or interlaminar gap into the epidural space, false-positive identification of entry into the epidural space, difficulty in advancing the epidural catheter into the epidural space, and malposition or subsequent dislodgement of the epidural catheter.

The identification of this space demands good knowledge of the anatomy and some skills due to its complexity (Figure 1). Unfortunately, surface landmark identification may be highly inaccurate in identifying the underlying spinal structures. Even in normal surgical patients, the neuraxial anaesthesia needle insertion first attempt success rate is relatively low using the palpation technique of about 50 to 60% (8, 9). The failure in palpation from patient factors such as obesity, abnormal spine or previous spinal surgery results in difficult needle placement, leading to higher rate of complications. Permanent neurological injury occurs when spinal anaesthesia is administered at or above the L2-3 inter-spinous space (10). Multiple attempts at achieving a successful neuraxial block are associated with an increased incidence of post-dural puncture headache, paraesthesia and spinal hematoma which eventually lead to a longer hospital stay and emergency room visits following discharge. The cost of epidural complications, which includes time lost due to a failed procedure, exceeds $1.5 billion annually in the US alone (11).

Epidural analgesia is the most common pain intervention in the world, with a significant increase in caseload of 120% over 10 years (12, 13). In United Sates, more than 1.4 million caesarean deliveries are performed with a majority using epidural anaesthesia (14). Epidural labour analgesia is utilized by increasing number of women in labour. 61% of women in the United States received epidural labour analgesia in 2008 and up to 98% of women received epidural labor analgesia in Barcelona (15). Use of epidural labour pain relief is increasing and locally in KK Hospital, more than 5000 procedures are performed yearly.

Obesity is a very fast increasing epidemic in the world. Neuraxial procedures are associated with higher risk of multiple attempts, difficult spinal landmark identification and higher risk of neuraxial anaesthesia failure (9). Ultrasound scanning in obese patients is more challenging with difficulty in landmark identification. Furthermore, pregnancy is associated with generalized weight gain, tissue edema and an increased lordosis which can make palpation and identification of surface landmarks very challenging. The hormonal changes of pregnancy cause ligaments to soften which can make the epidural space harder to identify. These changes make the epidural space narrower and cause the intrathecal space to become smaller, eventually increase the risk for inadvertent dural puncture (16). With the available new technology, it is clinician's responsibility to improve and ensure this common procedure to be safe and reliable.

Neuraxial ultrasound imaging is relatively cheap, compact, readily available for point of care testing. It can be used either for pre-procedural imaging of anatomical landmarks or for real-time imaging guidance of the procedure. Multiple clinical studies have concluded that neuraxial ultrasonography can be used to identify the intervertebral spaces, the midline for needle insertion, determine the depth from the skin to the epidural space, the best needle insertion point, and the best angle for needle insertion. A meta-analysis in 2013 demonstrated that ultrasound imaging can reduce the risk of failed or traumatic lumbar punctures and epidural catheterisation, as well as the number of insertion attempts (4). In addition, ultrasound imaging was especially useful for difficult patients with obesity, abnormal spine (scoliosis) and previous spinal surgery. Chin KJ et al (17) reported that neuraxial anaesthesia needle insertion first attempt success rate was improved from 32% (palpation technique) to 65% (ultrasound imaging) in these patients with abnormal spinal anatomy.

However, most of these clinical studies originated from highly skilled operators. The existing systems require a 2-operator technique with 1 anaesthetist performing the epidural procedure and 1 operator holding the probe. The difficulties include a steep learning curve and difficult pattern recognition of spinal structures may be challenging especially in novice learners and even in those experienced operators when difficult spinal anatomy is present. We have conducted a short online survey with 29 respondents. The results showed that more that 70% of anaesthetists (junior and senior levels) would like use to ultrasound imaging guidance to determine needle insertion point, determine the spinal level of the lumbar spine, and appreciate the use of ultrasound in assisting needle insertion in obese patients.

The objective of our project is to develop an ultrasound guided automated spinal landmark identification system (uSINE). uSINE is an AI-powered automated ultrasound spinal landmark identification system that would improve the accuracy of needle injection and improve the first-attempt puncture success rate of lumbar neuraxial procedure. Our previous study done on 100 normal-weight patients showed that uSINE is able to achieve 100% L3-L4 identification accuracy, and 92% first-attempt puncture success rate. A subsequent clinical study done on 48 obese patients showed 90% L3-L4 identification accuracy, and 79% first-attempt puncture success rate.

The workflow for pre-procedure needle site localization using uSINE's software is as follows. First, the anaesthesiologist starts scanning the patient's spine longitudinally from the sacrum and moves the probe upwards. By analysing images from ultrasound machine, uSINE's software identifies the location of relevant spinal features automatically, and displays their location on a graphical user interface (GUI) in real-time. The user interface guides the anaesthesiologist to move up along the spine until the ultrasound probe is at the optimal spinal level, the L3-L4 space. The software will prompt and alert the anaesthesiologist when this level has been achieved.
The anaesthesiologist then rotates the probe to the transverse view to search the best view without obstruction for the epidural space. The user interface guides the anaesthesiologist to adjust the angle of the ultrasound probe and fine tune the location until an optimal alignment for needle insertion is achieved. During this process, the depth of the epidural space is calculated automatically by uSINE and displayed on screen.

To further improve uSINE's success rate on challenging patients, such as patients who are obese, more annotated data on the anatomy landmarks of those patients need to be collected to build a bigger database for uSINE's machine-learning model. To this end, we will be building a labelling and annotation software to allow clinicians to easily annotate the images obtained during the lumbar ultrasound scans. We will use the annotated data to optimize uSINE's software to increase the identification accuracy and first-attempt puncture success rate for obese patients. Investigation in obese patients will be performed to measure the L3-L4 identification accuracy and first-attempt puncture success rate of the improved uSINE software.

F4. Please provide a list of relevant references.

References:

1. Perlas A. Evidence for the use of ultrasound in neuraxial blocks. Reg Anesth Pain Med. 2010 Mar-Apr;35(2 Suppl):S43-6.
2. Carvalho JC. Ultrasound-facilitated epidurals and spinals in obstetrics. Anesthesiol Clin. 2008 Mar;26(1):145-58, vii-viii.
3. Ultrasound-guided catheterisation of the epidural space: National Institute of Health and Clinical Excellence 2008.
4. Shaikh F, Brzezinski J, Alexander S, Arzola C, Carvalho JC, Beyene J, et al. Ultrasound imaging for lumbar punctures and epidural catheterisations: systematic review and meta-analysis. BMJ. 2013;346:f1720.
5. Sicard JA, Forestier J. Radiographic method for exploration of the extradural spce using lipiodol. Rev Neurol. 1921; 28:1264-6.
6. Hermanides J, Hollmann MW, Stevens MF, Lirk P. Failed epidural: Causes and management. Br J Anaesth 2012;109:144-54.
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8. Lim YC, Choo CY, Tan KT. A randomised controlled trial of ultrasound-assisted spinal anaesthesia. Anaesth Intensive Care. 2014 Mar;42(2):191-8.
9. de Filho GR, Gomes HP, da Fonseca MH, Hoffman JC, Pederneiras SG, Garcia JH. Predictors of successful neuraxial block: a prospective study. Eur J Anaesthesiol. 2002 Jun;19(6):447-51.
10. Reynolds F. Peripheral nerve injuries associated with anaesthesia. Anaesthesia. 2001 Feb;56(2):196.
11. 3D Ultrasound Epidural Guidance, Clinical Needs. Available from: https://rivannamedical.com/clinical-need
12. Friedly J, Chan L, Deyo R. Increases in lumbosacral injections in the Medicare population: 1994 to 2001. Spine. 2007;32(16):1754-60.
13. Manchikanti L, Pampati V, Boswell MV, Smith HS, Hirsch JA. Analysis of the growth of epidural injections and costs in the Medicare population: a comparative evaluation of 1997, 2002, and 2006 data. Pain Physician. 2010 May-Jun;13(3):199-212.
14. Ortner CM, Granot M, Richebe P, Cardoso M, Bollag L, Landau R. Preoperative scar hyperalgesia is associated with post-operative pain in women undergoing a repeat Caesarean delivery. Eur J Pain. 2013 Jan;17(1):111-23.
15. Alran S, Sibony O, Oury JF, Luton D, Blot P. Differences in management and results in term-delivery in nine European referral hospitals: descriptive study. Eur J Obstet Gynecol Reprod Biol. 2002 Jun 10;103(1):4-13.
16. Lee A. Ultrasound in obstetric anesthesia. Semin Perinatol 2014; 38: 349-58
17. Chin KJ, Perlas A, Chan V, Brown-Shreves D, Koshkin A, Vaishnav V. Ultrasound imaging facilitates spinal anesthesia in adults with difficult surface anatomic landmarks. Anesthesiology. 2011 Jul;115(1):94-101.

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

File Name	Description	Upload Date
Chin et al-Anesthesiology2011.pdf	Relevant publication	05-Dec-2017 17:05
Shaikh et al-Systematic Review-BMJ2013.pdf	Relevant publication	05-Dec-2017 17:07

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

Preliminary studies by our research group has been conducted for the software portion of the device which is responsible for selecting the optimal insertion point and angle for the introductory needle. The preliminary study funded by the SHF-NHIC joint medical technology grant was conducted on 100 patients who were about to undergo neuraxial anaesthesia. The system was able to identify the correct spinal level in all of the patients. Meanwhile, using the location and angle automatically determined by the device, the anaesthetists were able to successfully insert the needle into the epidural space in their first attempt in 92% of the patients with a short scan time (67 seconds). Meanwhile, the rest of the patients were able to be inserted in the second attempt with a small adjustment of the needle alignment.

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

Although the use of neuraxial ultrasonography to guide performance of neuraxial block is relatively new development, advances in technology have turned the shadows of the bony vertebral column into internal landmarks. Given millions of neuraxial blocks are performed across the world every year, it is critical to make this procedure safe and reliable.

Neuraxial ultrasound scanning may soon be considered the standard of care for neuraxial procedures. The NICE guidelines and systematic reviews have already recommended ultrasound imaging for lumbar spine procedures. Compared to other imaging modality, ultrasonography is a relatively cheap, compact, readily available for point of care testing to most of the patients. Our system will definitely fill the gap of current practice and offer a cost-effective and safe solution.

F8. Discuss in detail the experimental design and procedures to be used to accomplish the specific aims of the study.

NOTES:

If the study involves a retrospective medical record review, please specify the period of data collection.
If the study provides the provision for re-identification in the case of incidental findings, please describe the management of incidental findings.

This is a prospective cohort study to evaluate the efficacy and accuracy of ultrasound guided automated spinal landmark identification system (uSINE).

The subjects assume a seated position and the lower back is exposed. Ultrasound gel will be applied to the lower back lumbar spine and the investigator will place an ultrasound curved array probe around the sacral region. The graphical interface of the software, integrated with the wireless ultrasound probe and ultrasound machine, will inform the investigator when the software has positively identified the sacrum. The investigator will then move the probe in a steady vertical upward longitudinal direction until the L3/4 interspinous space is identified by the program. The ultrasound algorithm will identify the skin surface marking. The longitudinal section of the scan will be completed and the investigator will turn the probe 90 degrees clockwise around the probe center to the transverse view.

The transverse scan consists of minimal vertical movements by the investigator who will obtain images using the ultrasound probe. The software will signal when the correct identification of the ligamentum flavum is visualized. The scan sequence will be completed.

The first phase will involve 20 non-obese patients who are undergoing neuraxial anaesthesia or analgesia. The system is used prior and during needle insertion to provide real-time guidance for the anaesthetists. The neuraxial needle insertion is conducted manually by the anaesthetist as per routine practice.

In the second phase, 50 obese patients (body mass index more than 30) will be recruited to investigate and develop an "obesity" mode visualisation of the ultrasound guided automated spinal landmark identification. This will be to advance the technology to evaluate more difficult anatomy and more complex neuraxial needle insertion in future work plan. The patients' back will be scanned to obtain the images. The neuraxial needle insertion is conducted manually (i.e. independent of the ultrasound results) by the anaesthetist as per hospital routine practice.

For third and fourth phases, anaesthetist may determine the location of needle insertion via uSINE and standard care of practice. The third phase will involve 65 obese patients who are undergoing neuraxial anaesthesia. The conventional ultrasonography system is used prior to the needle insertion to provide guidance for the anaesthetists. The neuraxial needle insertion is conducted manually by the anaesthetist as per routine practice. The images collected in the system will be used for annotation and evaluation which serves as training material for uSINE to optimize its algorithm to improve landmark (sacrum, lumbar spinal segments, interspinal space) identification for obese patients. A labelling and annotation software will also be developed to allow clinicians to mark features including sacrum, spinous process, midline, articular process, transverse process, ligamentum flavum and vertebra body.

The fourth phase involves 65 obese patients whereby uSINE system is used prior to the needle insertion to provide guidance for the anaesthetists. The neuraxial needle insertion is conducted manually by the anaesthetist as per routine practice. The identification accuracy and first-attempt puncture success rate of uSINE will be determined.

De-identification of data: To comply with HBRA regulations, data as mentioned above and collected from participants recruited before 1 November 2018 will be de-identified through a trusted third party. De-dentification will be conducted in compliance with SingHealth cluster de-identification policy.

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

This is an ongoing project that will study device development for neuraxial ultrasonography. We have previously recruited 70 patients in Phases 1-2 to evaluate more difficult anatomy and more complex neuraxial need insertion. The third phase will involve 65 obese patients to obtain clinical data, and evaluation and annotation of the clinical data of spinal ultrasonography, of which these data will serve as the training data for the uSINE algorithm. Upon modification and refinement of algortihm, another 65 obese patients will be recruited to measure the uSINE identification accuracy and first-attempt puncture success rate of uSINE.

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 patient information sheet will be explained to every participant and informed written consent will be obtained from every participant by the investigators.

The subjects assume a seated position and the lower back is exposed. Ultrasound gel will be applied to the lower back lumbar spine and the investigator will place an ultrasound curved array probe around the sacral region.

The graphical interface of the software, integrated with the ultrasound machine, will inform the investigator when the software has positively identified the sacrum. The investigator will then move the probe in a steady vertical upward longitudinal direction until the L3/4 interspinous space is identified by the program. The ultrasound algorithm will identify the skin surface marking. The longitudinal section of the scan will be completed and the investigator will turn the probe 90 degrees clockwise around the probe center to the transverse view.

The transverse scan consists of minimal vertical movements by the investigator who will obtain images using the ultrasound probe. The software will signal when the correct identification of the ligamentum flavum is visualized. The scan sequence will be completed.

In the first phase each the attending anaesthetist will use the automated spinal landmark system for neuraxial needle insertion to place the neuraxial anaestehsia in non-obese patients. The number of spinal attempts will be recorded (number of spinal needle insertion points on the skin).

For the second phase, obese patient will have ultrasound scanning of their lumbar back only, which is non-invasive in nature. Once the scanning is completed, their neuraxial anaesthesia will be performed by anaesthetists as per routine practice (i.e. manual needle insertion without referring to the ultrasound scanning results, and is independent to this study).

Images produced are longitudinal and transverse images and videos of the scans, including the primary outcome of the L3/4 interspinous space in the longitudinal view and the ligamentum flavum in the transverse view. Images will be labelled and annotated using a customized labelling software.

Participants' necessary demographic data, e.g. age, weight, height, race and history of spine disorders, will be recorded, as demographic characteristics to the acquired ultrasound images. The study includes evaluation of the number of spinal attempts, correct identification of the L3/4 interspinous space in the longitudinal view (yes/no), correct identification of the ligamentum flavum in the transverse view. Other measurements that will be taken include the distance from skin to ligamentum flavum, ultrasound scanning durations for longitudinal and transverse scan, total duration of procedure from start of scan to successful insertion of spinal needle, complications relating to procedure if any.

We will record images and videos using study number and no identifiers will be used.

Data Collection Form:

File Name	Description	Upload Date
uSINE study Data Collection Form_Phase 3-4 Ver 1.docx	uSINE data collection form Phase 3,4 obese Ver 1	13-Jul-2020 16:12
ULTRA-SINE study Data Collection Form-Spinal Anaesthesia-V1-171206 SBL.docx	Data collection form Phase 1	07-Aug-2020 23:27
ULTRA-SINE study Data Collection Form-Spinal Anaesthesia-V2-240518 obese CLEAN SBL.pdf	Data collection form phase 2	07-Aug-2020 23:27

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

There will be no additional study related follow-up visits.

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

The purpose of the previous grant was to have a deliverable development plan to take an innovation to a commercialisable endpoint. Due to the time constraint of this previous grant (1 year), we could only conduct a preliminary test on 70 patients to develop ultrasound algorithm for obese patients. Nevertheless, we have secured additional funding to further refine the algorithm, which may serve as a foundation to extend this study to a randomized controlled trial in next stage.

F13. What are the potential risks to participants?

The process of using an ultrasound machine to scan the back of an obese patient is non-invasive and poses no additional medical risk and no ionizing radiation. For subjects who undergoing neuraxial anaesthesia, routine technique will be performed with guidance from the ultrasound automated spinal landmark identification.

NOTES:
It is not appropriate to provide a nil response as all research procedures have some risks or side effects. For retrospective medical records review or questionnaires study, although the risks are expected to be minimal, there may be a potential risk from the breach of confidentiality.

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.

Although the use of neuraxial ultrasonography to guide performance of neuraxial block is relatively new development, advances in technology have turned the ultrasound imaging into an automated process. Neuraxial anaesthesia is very commonly performed across the world every year, it is critical to make this procedure safe and reliable.

Neuraxial ultrasound scanning may soon be considered the standard of care for neuraxial procedures. The NICE guidelines and systematic reviews have already recommended ultrasound imaging for lumbar spine procedures. Compared to other imaging modality, ultrasonography is a relatively cheap, compact, readily available for point of care testing to most of the patients. Our system will definitely fill the gap of current practice and offer a cost-effective and safe solution.

F15. What is the estimated timeline for this study?

(i) Estimated start date 02-Apr-2018

(ii) Estimated end date 31-Dec-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 (Research Study).

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. For example:
- Select "Waiver of Informed Consent" if consent has been obtained for research purposes previously.
- Select "Informed Consent will be taken" if verbal consent will be taken or the study team is requesting waiver of documentation of informed consent.

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.

[x] Referral by attending healthcare professional
[ ] Patients of study team
[ ] Databases
[ ] Other methods of participant identification

H2. Who will make the first contact with participant?

Principal Investigator or the Co-Investigators will make the first contact with participant.

H3. How will the participant be contacted?

The potential patients are identified based on their age (between 21 to 75 years old) and body mass index who requires spinal anaesthesia. The potential patients 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 in the pre-operative assessment clinic or on the same day of surgery if they have not attended the 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 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?

No

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: 02-Apr-2018

End Date: 31-Dec-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.

The first phase patient participants will be involved from the time of consent taking and recruitment up to their day of surgery when neuraxial anaesthesia will be administered using ultrasound guidance using the automated spinal landmark guidance system. The expected duration of procedure will take about 20 minutes. There will be no further follow up thereafter.

The expected duration of ultrasound scanning for the second phase obese patients will take about 15 to 20 minutes, the whole procedure is non-invasive and participants will be released after the ultrasound scanning is complete, with no further follow-up.

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)	200	0	200	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.

First phase: Age 21 – 75 years old patients who require neuraxial anesthesia for surgical procedure. Normal body mass index (Weight 40-90 kg, Height 140-180cm).

Second -fourth phases: Obese patients aged between 21-75 years old, body mass index more than 30.

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.

The exclusion criteria are:

- History of scoliosis.
- History of spinal instrumentation.
- Drug allergy to ultrasound transmission gel.
- Visible wound or injury in the lumbar spine.

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.

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

Lower Age limit 21

Upper Age limit 75

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

Only Females who undergo neuraxial anaesthesia for surgical procedure will be included in the study.

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?

[x] Inpatients.
[x] 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).

The investigators will explain the informed consent in a private room to the participants and the participants are not in a situation where they may feel compromised. Patients will be approached in the preoperative clinic or wards.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.
Appropriate consent will be obtained in the presence of a prescribed witness who is 21 years of age or older, and has mental capacity. The witness will be present during the entire informed consent discussion and to sign on the witness section. The witness will be a member of the team carrying out the research.

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 take 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.

Adequate time will be given to the participant to consider their participation in the study.
Patients will be approached in the preoperative clinic or wards and will be explained and given adequate 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. 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.

Potential participant will receive a patient information sheet. This will be discussed with them in private manner 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 patient 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)?

Yes

The patients recruited will include parturients (vulnerable participants) who are undergoing spinal anesthesia for either obstetric or non-obstetric procedures. The participation is completely voluntary.

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	Upload Date
uSINE study CIRB PIS (Phase 3,4 Obese) Ver 1.doc	uSINE study CIRB PIS (Phase 3,4 Obese) Ver 1	14-Jul-2020 16:27
ULTRA-SINE study CIRB PIS (Phase 1) Ver 4 Clean.doc	PIS Phase 1 Ver 4 Clean	07-Aug-2020 23:25
ULTRA-SINE study CIRB PIS (Phase 2-Obese) Ver 3 Clean.doc	PIS Phase 2 Ver 3 Clean	07-Aug-2020 23:26

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

Yes
Remuneration of $50 for patient subjects in the first phase, $20 for obese patients in the second phase will be provided. $40 in third and fourth phases patients will be provided for research efforts and time inconvenience in participation.

P8. Besides the Research Participant Information Sheet and Consent Form, will any other materials or documents be used to explain the study to potential Research Participants (e.g. scripts, hand outs, brochures).

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?

Yes
Due to changes in HBRA, participants recruited on and after 1 November 2018 will be informed of the changes to the ICD and study protocol through re-consent. For those participants recruited before 1 November 2018, they will not be re-consented with the updated ICD. Instead, deidentification will be performed in this cohort of patients using trusted third party and will comply to the Singhealth cluster deidentification policy accordingly.

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.

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.)

Principal investigator and co-investigators. 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?

The study data will be anonymized. The subjects are only identified by study number. For patients recruited before 1 Nov 2018, deidentification will be conducted using trusted third party and will comply to the Singhealth cluster deidentification policy accordingly.

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 Health Science Authority and 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 trial. Adverse events and serious adverse events will be reported 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 ultrasound images and data collection forms and random audits will be performed to make sure the study data 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:
1. Additional documents may be attached here. Documents relevant to the respective sections should not be attached here.

File Name	Description	Upload Date
PDPA Declaration form [Ultra-Sine study].pdf	PDPS Self-Declaration Form	27-Dec-2017 16:21