IRB #	STU-2018-0096

Title: A Prospective, Randomized, PACU Blinded Study to Compare ANI-guided Analgesic Administration versus Standard Care in Surgical Patients Receiving Balanced Sevoflurane-Fentanyl Anesthesia

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IRB #	STU-2018-0096

PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

Specific Aim 1: To determine if intraoperative opioid administration guided by the ANI will decrease patient pain scores in the PACU compared to standard practice.

Primary Hypothesis: Patients who have intraoperative opioid administration guided by the ANI will have a 40% decreased incidence of severe pain (VAS ≥7) in the PACU compared to patients in the standard practice group.

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

Pain after surgery is one of the biggest concerns for surgical patients. A large percentage of patients experience severe pain in the recovery period, which increases the risk of developing chronic pain and contributes to an overall poor experience for the patient [1-3]. The Analgesia Nociception Index (ANI; MetroDoloris Medical Systems, Lille, France) is a non-invasive monitor that uses heart rate variability to determine the analgesic state of a patient. It calculates HR variation with respiration, which is mediated by the parasympathetic nervous system's effect on the sinoatrial node of the heart. Heart rate variability depends on the effects of the sympathetic and parasympathetic nervous systems. Studies suggest that pain leads to a decrease in heart rate variability in adults [4]. A painful stimulus increases sympathetic tone relative to parasympathetic tone, which causes the ANI number to go down. Alternatively, if the patient is at an adequate or abundant level of analgesia, the parasympathetic tone would be high and thus the ANI number would be high. The highest ANI is 100, which indicates maximum parasympathetic tone (no pain) whereas the lowest number is 0, which indicates minimum parasympathetic tone (significant pain).

The ANI may offer a method to administer intraoperative analgesics in a more objective manner compared to current standard clinical practice. It is important to provide sufficient analgesia during surgery, but it is also important to use the minimum dosage necessary in order to avoid unwanted side effects. Determining the optimal dosage of opioids during general anesthesia is difficult and traditionally has been guided by vital signs and the anesthesia provider's clinical judgement. However, inadequately treated pain can increase the stress response, increase sympathetic activity, predispose to postoperative myocardial ischemia, and lead to a suboptimal experience for the patient [7, 8]. The ANI may be able to more objectively guide opioid administration intraoperatively, which may result in decreased pain and improved patient satisfaction postoperatively.

The ANI Monitor has received 510k clearance in the US, but is not currently cleared for sale. It is being used for research purposes only at the time of this writing.

b. Current practice

The current practice is to administer intraoperative analgesics according to the anesthesiologist's best clinical judgment, based on surgical factors, patient factors, and changes in vital signs.

3. Study Design.
Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

This study aims to be a randomized, controlled study of ANI-guided opioid administration versus standard clinical practice in female patients undergoing abdominal hysterectomy. Patients will be randomly assigned to 2 groups- ANI vs. standard care. A member of the study team that is not involved in patient care (i.e., statistician) will make the randomization table based on a random number generator. The assignments will be written and sealed in opaque envelopes and not opened until each subject has signed all the necessary paperwork. The intraoperative and postoperative management of all patients will be standardized by protocol.

The PACU nurses and postop assessor will be blinded as to which group the patient is in. Patients will be followed in the PACU to assess pain scores and any adverse events.

The criteria for **inclusion**:

- 18-75 years' old
- American Society of Anesthesiology (ASA) physical status 1-2
- Patients undergoing surgery with general anesthesia with sevoflurane-fentanyl
- Planned abdominal or spinal surgery lasting 1-3 hours
- Willing and able to consent in English or Spanish
- No current history of advanced pulmonary or cardiovascular disease

The criteria for **exclusion**:

- Age less than 18 or older than 75
- Patient does not speak English or Spanish
- Patient refusal
- Monitored anesthesia care (MAC) or regional anesthesia planned
- Pregnant or nursing women
- "Stat" (emergent) cases
- ECG rhythm other than regular sinus rhythm
- Implanted pacemakers
- On antimuscarinic agents, alpha 2 agonists, antiarrhythmic, or beta blockers
- Presence of pacemaker
- Autonomic nervous system disorder
- Use of chronic opioids

All female subjects have a urine pregnancy test on the morning of surgery. The pregnancy test result will be reviewed as a part of the screening procedure.

IRB #	STU-2018-0096

4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,
2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.
3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

1) Order in which tests/procedures will be performed

Screening and Informed Consent

A member of the research team will use a screening form to look for surgical patients that meet all the inclusion and exclusion criteria. He/she will approach potential subjects in the preoperative area and the study will be explained in detail in a private room. Patients will be informed that they will receive no compensation for participating in the study and there will be no adverse consequences if they choose not to participate. If the subjects agree to participate, informed written consent will be obtained prior to any study procedures and this document will be sent to pmhresearchparticipants@phhs.org, for inclusion in the patient's medical record, per Parkland regulations. The study duration is one day.

Anesthetic Protocol

The anesthesia team that will be caring for the subject during surgery will be given the protocol for the study, which standardizes the general anesthetic technique. All patients will be monitored with standard ASA monitors and a BIS (bispectral index) for depth of anesthesia monitoring.

2) Setting and methods used to protect privacy

Setting

The study will take place in the pre-operative rooms, the operating rooms, and the PACU at Parkland Hospital.

Randomization

The research coordinator will make randomization envelopes by using a random number generator. A patients will be randomized to 2 groups:

1. Group 1- standard practice
2. Group 2- ANI-guided opioid administration

The ANI leads (2 non-invasive stickers that are placed on the anterior chest wall) will be attached to the patient's chest per manufacturer guidelines.

3) Plan for data analysis

The following parameters will be recorded intraoperatively: ECG, NIBP, ET sevoflurane concentration, ETO2, ETCO2, temperature, BIS readings.

Data Sources

Protected health information including name, medical record number, and date of birth will be recorded and stored securely in an IRB approved, secured REDCap database.

Parameters:

1. Protected health information (PHI): name, medical record number, date of birth
2. Demographic information (age, weight, height, BMI), medical and surgical history, ASA status
3. Intraoperative parameters
   - Baseline vital signs upon arrival to operating room
   - Intraoperative vitals (systolic, diastolic, and mean blood pressures, temperature, heart rate)
   - ECG rhythm

- ANI numbers

4. Adverse event monitoring
   - ANI malfunction
   - Patient movement
   - Delayed emergence
   - PONV
   - Respiratory depression
   - Prolonged hypoxia (SpO_2 less than 92% for > 1 min)
   - Critical respiratory adverse event including bronchospasm, atelectasis, pulmonary edema
   - Cardiovascular adverse events such as tachycardia, bradycardia, cardiac arrhythmias, hypotension, and hypertension

4) Statistics:

The study is powered to detect a 40% reduction in the incidence of severe pain (VAS > 6) with 80% power and a two-sided type I error rate of 0.05. Assuming an incidence rate of 75% in the standard of care group, the study would require a total of 80 patients randomized in a 1:1 ratio between the standard of care and ANI groups. Continuous outcomes will be summarized as mean and standard deviations or median and interquartile range. Categorical data will be summarized as frequency and percentages. Normality of the continuous outcomes will be assessed using normal probability plots and groups will be compared using Student's t-test or Mann-Whitney U test if gross violation of the normality assumption were found. Chi-square or Fisher's exact test will be used to compare groups in terms of categorical variables.

The primary efficacy analysis will be performed on the evaluable population of subjects who complete the schedule of assessments. Secondary analyses will be on all randomized subjects (the intent-to-treat population) with various methods of imputation of missing data. All statistical tests will be two-sided with a significant level of 0.05 unless otherwise specified. All confidence intervals will be two-sided with a confidence level of 95%, unless otherwise specified.

Sample size for this prospective validation was estimated using the following assumptions:

- Mean NRS for controls at each time point = 5.0
- Standard Deviation at each time point = 3.0
- Presumed difference in mean NRS between active treatment group and control at each time point = -2.0
- Primary Statistical test method: mixed effects, repeated measures
- Within-patient correlation is 0.55 or less
- Minimum Statistical Power = 80%

A minimum of 48 evaluable patients (24 per group) will be required for this two-treatment parallel-design study under the above assumptions.

An enrollment target of 80 (40 per treatment group) is proposed to account for potential drop-outs and uncertainty regarding the variability and intrapatient correlation of NPS pain scores, as well as to allow focused robustness testing.

IRB #	STU-2018-0096

4.b. List of the study intervention(s) being tested or evaluated under this protocol			
☐	**N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.		
#	**Study intervention(s) being tested or evaluated under the protocol** *Pain scores after surgery* *Nausea/vomiting after surgery* *Vital signs after surgery*	**Affiliate** Place a check next to institution(s) where the intervention will be performed	**Local Standard Practice?** Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	Analgesia Nociception Index (ANI; MetroDoloris Medical Systems, Lille, France)	☐ UTSW	☐ Yes
		☐**x** PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

IRB #	STU-2018-0096

4.c.
Study Intervention #1
Analgesia Nociception Index (ANI; MetroDoloris Medical Systems, Lille, France)

List each group exposed to this intervention on a separate line.	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
Experimental group	None

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

IRB #	STU-2018-0096

		4.d. List ALL other research procedures or components not listed in table 4.b. ***The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.*** Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)		
#	**Research component** • **Individual procedures** **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Insert component 1 here**		Monitoring of intraoperative analgesic state with non-invasive ANI monitor	
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			
2	**Insert component 2 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			
3	**Insert component 3 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			
4	**Insert component 4 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			

5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

There is minimal risk to subjects by participating in this study. The anesthetic management of subjects will not differ from the standard of care, with the exception of the intraoperative management of analgesic administration (e.g., opioids). The ANI is a non-invasive monitoring device that has no known adverse effects. There is minimal risk for psychological stress to the patient as a result of participation in this study. Subjects may refuse to answer any of the questions or take a break or stop participation in the study at any time.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

Procedures to Maintain Confidentiality:
A non-identifiable code will be assigned to the data collection sheet so that there is not a direct link to specific names. Patient IDs will be standardized in chronological order as patient 1, patient 2, etc. A key to the coding system will be maintained in a locked storage cabinet with limited access until all the data is collected and analyzed. Access to study data will be restricted to authorized study personnel only. Following the completion of the analysis and the project, the key to the coding system or subject identifiers themselves will be destroyed by shredding the documents so that there is no direct or indirect link to subject identifiers and information.

All data from the study will be kept on encrypted computers belonging to the University, which are stored in secured areas. All electronic study data will be password protected and passwords will be changed on a regular basis.

All data will be de-identified when exported from the REDCap database. Patient data will be analyzed without patient identifiers by assigning study ID subject numbers that are de-linked from patient identifiers. Signed consent forms, HIPAA forms, and study questionnaires will remain in a locked cabinet in the PI's office.

c. Will the safeguards be different between/among groups?

☐ ☒ **No**

If yes, describe here

References:

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2. Perkins FM, Kehlet H: **Chronic pain as an outcome of surgery. A review of predictive factors**. *Anesthesiology* 2000, **93**(4):1123-1133.
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7. Lovich-Sapola J, Smith CE, Brandt CP: **Postoperative pain control**. *Surg Clin North Am* 2015, **95**(2):301-318.
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9. Borsook D, Kussman BD, George E, Becerra LR, Burke DW: **Surgically induced neuropathic pain: understanding the perioperative process**. *Ann Surg* 2013, **257**(3):403-412.
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12. Gruenewald M, Ilies C, Herz J, Schoenherr T, Fudickar A, Hocker J, Bein B: **Influence of nociceptive stimulation on analgesia nociception index (ANI) during propofol-remifentanil anaesthesia**. *Br J Anaesth* 2013, **110**(6):1024-1030.
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14. Upton HD, Ludbrook GL, Wing A, Sleigh JW: **Intraoperative "Analgesia Nociception Index"-Guided Fentanyl Administration During Sevoflurane Anesthesia in Lumbar Discectomy and Laminectomy: A Randomized Clinical Trial**. *Anesth Analg* 2017, **125**(1):81-90.
15. Szental JA, Webb A, Weeraratne C, Campbell A, Sivakumar H, Leong S: **Postoperative pain after laparoscopic cholecystectomy is not reduced by intraoperative analgesia guided by analgesia nociception index (ANI(R)) monitoring: a randomized clinical trial**. *Br J Anaesth* 2015, **114**(4):640-645.
16. Dundar N, Kus A, Gurkan Y, Toker K, Solak M: **Analgesia nociception index (ani) monitoring in patients with thoracic paravertebral block: a randomized controlled study**. *J Clin Monit Comput* 2018, **32**(3):481-486.