HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Provide the full title of the study as listed in item 1 on the "Basic Information" page in CATS IRB (http://irb.psu.edu).

Efficacy of low-dose propofol infusion on postoperative nausea and vomiting in patients with prior history of postoperative nausea and vomiting (PONV) or motion sickness.

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Version Date:

Provide version date for this document. This date must be updated each time this document is submitted to the IRB office with revisions. DO NOT revise the version date in the footer of this document.

05.01.2025

Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable. See "HRP-103- Investigator Manual," under "ClinicalTrials.gov" for more information.

NCT05759481

Important Instructions for Using This Protocol Template:

This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.

1. **GENERAL INSTRUCTIONS[1]:**
   - Prior to completing this protocol, ensure that you are using the most recent version by verifying the protocol template version date in the footer of this document with the current version provided in the CATS IRB Library.
   - Do not change the protocol template version date located in the footer of this document.
   - Some of the items may not be applicable to all types of research. If an item is not applicable, please indicate as such or skip question(s) if indicated in any of the instructional text.
   - **GRAY INSTRUCTIONAL BOXES:** Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.
     - **Do NOT delete the instructional boxes from the final version of the protocol.**
   - The protocol should be written in lay language. Do **NOT** copy and paste grant proposal information into the protocol.

[1] This template satisfies AAHRPP elements 1.7.B, I.8.B, I-9, II.2. A, II.2.I, II.3.A, II.3.B, II.3.C-II.3.C.1, II.3.D-F, II.4.A, III.1.C-F, II.2.D

- Add the completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page.

2. **CATS IRB LIBRARY:**
   - Documents referenced in this protocol template (e.g. SOP's, Worksheets, Checklists, and Templates) can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

3. **PROTOCOL REVISIONS:**
   - When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the guides available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.
   - Update the Version Date on page 1 each time this document is submitted to the IRB office with revisions.

If you need help…

All locations:
Human Research Protection Program
Office for Research Protections
101 Technology Center
University Park, PA 16802-7014
Phone: 814-865-1775
Fax: 814-863-8699
Email: irb-orp@psu.edu
https://www.research.psu.edu/irb

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1.0 Objectives

1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested.

The purpose of this study is to clarify the effects of two different anesthetic techniques on post-operative nausea and vomiting (PONV)
1) low dose propofol infusion when combined with sevoflurane versus 2) propofol as sole anesthetic in patients who have a history of PONV and/or motion sickness.

Our hypothesis is that the incidence of PONV in patients with history of PONV and/or motion sickness will be higher when they receive low-dose propofol infusion at 25 mcg/kg/min as a supplement to sevoflurane compared to patients receiving only propofol infusion for their anesthetic.

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study.

Research typically has a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

The primary endpoint to be measured in this study is the percentage of PONV in patients who received a low-dose propofol infusion in combination with sevoflurane (Group A) vs patients who received a propofol-only infusion (Group B) for their anesthetic.

1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

Secondary end points measured will include the type and number of antiemetics needed to effectively treat postoperative nausea and vomiting and the frequency of hypotension related to propofol administration.

2.0 Background

2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

For clinical research studies being conducted at Penn State Health/Penn State College of Medicine, and for other non-PSH locations as applicable, describe the treatment/procedure that is considered standard of care (i.e., indicate how patients would be treated in non-investigational setting); and if applicable, indicate if the treatment, drug, or device is available to patient without taking part in the study.

Propofol is a commonly used anesthetic agent with some anti-emetic properties. In a 2009 review of propofol's non-anesthetic effects, it is described in detail how propofol may act on the dopaminergic, limbic, and serotonergic systems to elicit its antiemetic effects.[3] In the chemoreceptor trigger zone of the brain, propofol appears to predominantly interact with dopaminergic (D2) receptors, which can be observed via the appearance of dystonic movements immediately upon induction of anesthesia.[3] It is

briefly discussed that propofol may also possess an indirect inhibitory effect on the limbic system that ultimately produces a palliative effect on the vomiting center of the brain.[3] Additionally, the authors discuss propofol's interaction with serotonergic (5-HT_3) receptors.[3] The 5-HT_3 receptors are excitatory ligand-gated ion channels known to be associated with the modulation of nausea and vomiting. The authors refer to studies done in 1993 and 1995 which found that propofol elicits non-competitive and dose-dependent inhibitory effects on 5-HT_3 receptors.[3] This finding is consistent with the fact that commonly used, FDA-approved, antiemetic drugs antagonize the 5-HT_3 receptor (e.g. ondansetron and granisetron).

For this reason, propofol based anesthetic is commonly used for patients at high risk of PONV. Clinical trials and meta-analyses have shown that intravenous anesthesia with propofol is associated with significantly lower risk of PONV than volatile anesthetics.[4] Interestingly, sub-hypnotic (low dose) of propofol is also effective in preventing PONV.[4] However, these studies have excluded patients with history of PONV and/or motion sickness.

A retrospective cohort study in 2022 used multivariate regression models to determine the likelihood of observing PONV when using a propofol infusion for total intravenous anesthesia (TIVA) and combined intravenous anesthesia (CIVA).[2] In a total of 41,490 patients, PONV was reduced by 41% when using propofol infusion with TIVA and by 17% with CIVA. Both were statistically significant with $P < .001$. However, 1) the occurrence of PONV was limited to documentation by PACU nurses in the patients' electronic medical record, 2) PONV was only monitored for the brief duration that patients spent in the PACU, 3) postoperative administration of antiemetics was not considered evidence of PONV, and 4) the patient population also included individuals without a history of PONV.

A prospective randomized double-blinded study in 2022 compared the incidence of PONV following propofol infusion to the incidence of PONV following propofol infusion + sevoflurane after laparoscopic surgery.[1] The investigators found that PONV occurred in 33% of patients who received only the propofol infusion and in 38.7% of patients who received the propofol infusion + sevoflurane. They concluded the incidence of PONV was similar in both groups. This patient population included only female patients and excluded patients with a documented history of PONV and/or motion sickness.

Given the limited and unclear existing evidence, we plan to clarify whether or not one anesthetic technique is better than the other for PONV in patients with a history of PONV and/or motion sickness.

The standard of care for prophylaxis of PONV in patients with history of PONV and/or motion sickness is multimodal. Number of anti-emetics administered depends on the number of risk factors. Risk reduction measures include administration of propofol, avoiding nitrous oxide, reversal of neuromuscular blockade with sugammadex, lidocaine infusion, dexmedetomidine, supplemental fluids, opioid free analgesia, palonosetron, aprepitant, amisulpride, midazolam and acupressure/acupuncture. Any combination of agents can be chosen to mitigate the risk of PONV.

At Hershey Medical Center, prophylactic treatment of PONV includes intraoperative administration of ondansetron and dexamethasone with administration of other anti-emetics as needed postoperatively if patients are nauseous or are vomiting. In patients with history of PONV and/or motion sickness many anesthesiologists also in addition either modify the anesthetic technique to include propofol in low dose or as sole anesthetic while others choose to additionally administer aprepitant or scopolamine patch. All these measures will still be available to patients if they choose not to participate in the study.

2.2 Previous Data

Describe any relevant preliminary data.

No preliminary data available.

2.3 Study Rationale

Provide the scientific rationale for the research.

PONV is exceedingly common and occurs in approximately 30% of patients following general anesthesia. For some patients, the risk of PONV can be as high as 80%. When present, PONV can result in complications such as wound dehiscence, esophageal rupture, aspiration, increased intracranial pressure, pneumothorax, and severe dehydration. Given the body of evidence suggesting various ways in which propofol may elicit its antiemetic effects, and multiple studies demonstrating its efficacy in decreasing the incidence of PONV we seek to compare the difference in PONV when propofol is given in a low dose in combination with sevoflurane versus propofol only infusion for anesthesia in patients with a history of PONV and/or motion sickness. If one type of anesthetic technique is found to be more effective than the other its use in future may lead to fewer postoperative complications directly related to retching/vomiting, allow faster recovery and decrease length of hospital stay. It may also help to decrease the use of other agents to treat PONV in the postoperative period.

3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.).

Vulnerable Populations:

Indicate specifically whether you will include any of the following vulnerable populations in this research. You MAY NOT include members of these populations as subjects in your research unless you indicate this in your inclusion criteria because specific regulations apply to studies that involve vulnerable populations.

The checklists referenced below outline the determinations to be made by the IRB when reviewing research involving these populations. Review the checklists as these will help to inform your responses throughout the remainder of the protocol.

- **Children –**Review “HRP-416- Checklist - Children”
- **Pregnant Women** – Review “HRP-412- Checklist - Pregnant Women”
- **Cognitively Impaired Adults-** Review “HRP-417- Checklist - Cognitively Impaired Adults”
- **Prisoners-** Review “HRP-415- Checklist - Prisoners”
- **Neonates of uncertain viability or non-viable neonates-** Review “HRP-413- Checklist - Non-Viable Neonates” or “HRP-414- Checklist - Neonates of Uncertain Viability”

[Do not type here]

3.1 Inclusion Criteria

Create a numbered list of the inclusion criteria that define who will be included in your final study sample (e.g., age, gender, condition, etc.).

1. Undergoing general anesthesia for elective laparoscopic surgery
2. PONV or Motion sickness disclosed during Anes H&P pre-surgery

OR Patients self-disclosure of PONV and/or motion sickness during pre-screening call.

3. At least 18 years of age
4. The participant must be under the care of the attending anesthesiologist who is a member of the study team

3.1.1 Does this research involve collecting data from individuals residing outside of the US?

☒ No
☐ Yes – identify the countries where data collection will take place
[Type protocol text here]

3.2 Exclusion Criteria

Create a numbered list of the exclusion criteria that define who will be excluded in your study.

1. Any anti-nausea medication taken within 24 hours prior to surgery
2. Unable to provide consent independently
3. Allergy or adverse reaction to propofol or sevoflurane
4. Emergency surgery
5. Refusal to participate in the study

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

1. If, at any point, it is discovered that any form of anti-nausea medication was taken within the 24 hours prior to the patient's scheduled surgery, that participant will be removed from the study.
2. If a participant develops a severe reaction or allergy to propofol or sevoflurane, that participant will be removed from the study.
3. If the laparoscopic procedure is converted to an open procedure, the participant will be removed from the study.
4. If a participant decides to withdraw from the study, the participant will be removed from the study. No data from that participant will be used for the analysis of the study results.

3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the study; the type and timing of the data to be collected for withdrawal of subjects; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

If any of the above criteria for removal from study are met, the participants will be notified of their removal after their surgery. Additionally, they will not be asked to report any PONV. Since this is a prospective study, additional patients will be screened and selected to participate in this study on an ongoing basis.

4.0 Recruitment Methods

- Upload recruitment materials for your study in CATS IRB (http://irb.psu.edu). **DO NOT** include the actual recruitment wording in this protocol.

- StudyFinder: If StudyFinder (http://studyfinder.psu.edu) is to be used for recruitment purposes, separate recruitment documents do not need to be uploaded in CATS IRB. The necessary information will be captured from the StudyFinder page in your CATS IRB study.
- Any eligibility screening questions (verbal/phone scripts, email, etc.) used when contacting potential participants must be uploaded to your study in CATS IRB (http://irb.psu.edu).

[Do not type here]

4.1 Identification of subjects

Describe the source of subjects and the methods that will be used to identify potential subjects (e.g., organizational listservs, established recruitment databases, subject pools, medical or school records, interactions during a clinic visit, etc.). If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.

StudyFinder:
- If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, include this method in this section.
- Information provided in this protocol, including the description of study procedures, compensation, and recruitment, needs to be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Health submissions using Enterprise Information Management (EIM) for recruitment, and for non-Hershey locations as applicable, attach your EIM Design Specification form in CATS IRB (http://irb.psu.edu). See "HRP-103- Investigator Manual, Study Recruitment" for additional information. **DO NOT** include the actual recruitment material or wording in this protocol.

Potential Participants will be identified using the All cases + 30 surgery schedule.
The schedule will be scanned for Laparoscopic surgeries.
The study team member will look at the Anes H&P in the chart to see if the question of PONV and/ Motion Sickness was asked.

1. If noted PONV, denies, the patient will be not be called about the study.
2. If noted PONV, YES, the patient will be called to introduce the study.
3. IF no note about PONV, the patient will be called to ask if they have or have not had previous experience of PONV after anesthesia. If they respond Yes to PONV the phone script will be read. If they answer NO, they will be thanks and end the call

Using the All case +30 surgery schedule In Power Chart to review cases in advance. Form this list we can request an Anes Attending study member to be on the case. This will allow a better pool of patient that meet the inclusion criteria of PONV or motion sickness to be invited into the study. We will contact the patient in advance using the phone screen for interest in the study and approach the patient the day of surgery if they agreed during the pre-consent phone call.

4.2 Recruitment process

Describe how potential subjects first learn about this research opportunity or indicate 'not applicable' if subjects will not be prospectively recruited to participate in the research. Subject recruitment can involve various methods (e.g., approaching potential subjects in person, contacting potential subjects via

email, letters, telephone, ResearchMatch, or advertising to a general public via flyers, websites, StudyFinder, newspaper, television, and radio etc.). **DO NOT** include the actual recruitment material or wording in this protocol.

[Do not type here]

4.2.1 How potential subjects will be recruited.

The study team member will call the patient using the phone script to inquire if the patient has experienced PONV after anesthesia or has motion sickness. If the patient says yes, the research project will be explained. If the patient is interested then a study team member will approach then in the SDU on the day of surgery. If the patient states no, we will thank them for their time and the call will be disconnected.

4.2.2 Where potential subjects will be recruited.

Potential participant will be recruited in the same-day unit or other pre-operative area at Hershey Medical Center before their surgery.

4.2.3 When potential subjects will be recruited.

The patient will agree to have the study team talk to them while in SDU during the phone call. A study team member will approach the patient in SDU. The research study will be explained, any questions the patient has will be answered and the inclusion/exclusion criteria will be reviewed. If the patient agrees then consent form will be signed. The participant will receive a signed copy of the consent form.
Patients that appear unduly distressed about their surgery will not be approached.

4.2.4 Describe the eligibility screening process. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility.

☒ Eligibility screening is occurring *before* consent* - describe the process below
☐ Eligibility screening is occurring *after* consent - describe the process below
☐ Eligibility screening is occurring, consent is not being obtained in this research - describe the process below
☐ Not applicable - Eligibility screening is not being done in this research

The eligibility screening will take place using the All cased +30 surgery schedule. The study team will review Anes H & P for notes of PONV.

In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB.

*Unless informed consent is waived by the IRB, screening before consent is only permitted when screening activities are limited to the collection of information through oral or written communication

OR when identifiable private information or identifiable biospecimens is obtained by accessing records or stored identifiable biospecimens. Screening before consent is not permitted if data will be used for activities other than eligibility screening/recruitment (e.g., data analysis).

5.0 Consent Process and Documentation

Refer to the following materials:

- The "HRP-090- SOP - Informed Consent Process for Research" outlines the process for obtaining informed consent.
- The "HRP-091– SOP - Written Documentation of Consent" describes how the consent process will be documented.
- The "HRP-314- Worksheet - Criteria for Approval" section 7 lists the required elements of consent.
- The "HRP-312- Worksheet - Exemption Determination" includes information on requirements for the consent process for exempt research. In addition, the CATS IRB Library contains consent guidance and templates for exempt research.
- The CATS IRB library contains various consent templates for expedited or full review research that are designed to include the required information.
- Add the consent document(s) to your study in CATS IRB (http://irb.psu.edu). Links to Penn State's consent templates are available in the same location where they are uploaded. **DO NOT** include the actual consent wording in this protocol.

[Do not type here]

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form** *[Complete Sections 5.2 and 5.6; If this is the only box checked, mark Sections 5.3, 5.4 and 5.5 as 'Not applicable']*

☐ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent)** *[Complete Sections 5.2, 5.3 and 5.6; If this is the only box checked, mark Sections 5.4 and 5.5 as 'Not applicable']*

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).** *[Complete section 5.2, 5.4 and 5.6; If this is the only box checked, mark Section 5.5 as 'Not applicable']*

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement.** *[Complete Section 5.5; If this is the only box checked, mark Sections 5.2, 5.3, 5.4 and 5.6 as 'Not applicable']*

5.2 Obtaining Informed Consent

5.2.1 Consent Process

Describe the consent process, including when and where it will take place.

Informed Consent will be obtained in the same-day unit or other pre-operative area at Hershey Medical Center on the day of the patient's scheduled surgery.

5.2.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

Participants will be told explicitly, in plain language, that they may choose to participate or not to participate in this research. And, if they choose not to participate, there will be no penalty or loss of benefits to which they are entitled. Patients that appear unduly distressed about their surgery will not be approached.

5.3 Waiver of Written Documentation of Consent

Review "HRP – 411 – Checklist – Waiver of Written Documentation of Consent."

5.3.1 Indicate which of the following conditions applies to this research:

☐ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

For distinct cultural groups describe the alternative mechanism for documenting that informed consent was obtained:

Not applicable

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, or implied consent form)

Not applicable

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.4.1 Indicate the elements of informed consent to be omitted or altered

Not applicable

5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements

Not applicable

5.4.3 Describe why the research involves no more than minimal risk to subjects.

Not applicable

5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

Not applicable

5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

Not applicable

5.4.6 Debriefing

Explain whether and how subjects will be debriefed after participation in the study. If subjects will not be debriefed, provide a justification for not doing so. Add any debriefing materials to the study in CATS IRB.

Not applicable

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

Not applicable

5.5.2 Describe why the research involves no more than minimal risk to subjects.

Not applicable

5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

Not applicable

5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

Not applicable

5.5.5 Additional pertinent information after participation

Explain if subjects will be provided with additional pertinent information after participation.

Not applicable

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review “HRP-091 –SOP- Written Documentation of Consent” and “HRP-103 -Investigator Manual” to ensure that you have provided sufficient information.

Non-English speakers can be approached using hospital translator services and the IRB short form consent document from the IRB templates.

5.6.2 Cognitively Impaired Adults

Refer “HRP-417 -CHECKLIST- Cognitively Impaired Adults” for information about research involving cognitively impaired adults as subjects.

5.6.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

If there is any concern that a patient is not capable of providing consent, they will be excluded from the study.

5.6.2.2 Adults Unable to Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual's authority to consent to research.

For research conducted in the state of Pennsylvania, review "HRP-013 -SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "legally authorized representative."

For research conducted outside of the state of Pennsylvania, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013 - SOP- Legally Authorized Representatives, Children, and Guardians."

Patients who cannot provide consent for themselves, independently, will be excluded from the study.

5.6.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some, or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

Patients unable to consent will be excluded from the study.

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to provide permission. Describe the process used to determine these individual's authority to consent to each child's general medical care.

For research conducted in the state of Pennsylvania, review "HRP-013-SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "children."

For research conducted outside of the state of Pennsylvania, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013-SOP- Legally Authorized Representatives, Children, and Guardians."

Patients must be 18 years of age or older to be eligible to participate.

5.6.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

Patients < 18 years are excluded from the study

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See "HRP-103 -Investigator Manual" for a list of the 18 identifiers.

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

[Do not type here]

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used, or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal or implied authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable</u>.**

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol or in "HRP-598 – Research Data Plan Review Form".

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

Identifiers for participants that consent will be destroyed after the study has been completed and all papers have been authored. Identifiers from un-consented participants will not be retained.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Provide reasons why this research could not practicably be carried out without access to and use of PHI.

Access to PHI is also necessary to recruit patients for the study to determine eligibility before consent/authorization is obtained.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Provide reasons why this research could not practicably be carried out without the waiver or alternation of authorization.

Access to PHI is also necessary to recruit patients for the study to determine eligibility before consent/authorization is obtained. Screening a potential participant's anesthesia history and physical prior to approaching a participant will prevent approaching a person that does not meet the inclusion/excluding criteria.

6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable.</u>**

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

Data collection materials that will be seen or used by subjects in your study must be uploaded to CATS IRB (http://irb.psu.edu). **DO NOT** include any actual data collection materials in this protocol (e.g., actual survey or interview questions).

[Do not type here]

7.1 Study Design

Describe and explain the study design.

The study will be a prospective, randomized controlled trial. Patients will be actively recruited on an ongoing basis. Participants will be blinded to the anesthetic technique they receive—they will not know if they are receiving the low-dose propofol infusion in combination with sevoflurane (Group A) or a propofol-only infusion for anesthesia (Group B). Eligible Participants will be randomly assigned to either Group A or Group B. All potential study participants will be contacted via telephone prior to the day before surgery to verify history of PONV or motion sickness before surgery. All study participants will be contacted via telephone approximately 24 hours after their surgery by a member of the research team (who was not involved in the administration of anesthesia) to obtain information pertaining to PONV.

7.2 Study Procedures

Provide a step-by-step description of all research procedures being conducted (broken down by visit, if applicable) including such information as below (where and when applicable); describe the following:

- HOW: (e.g., data collection via interviews, focus groups, forms such as surveys and questionnaires, medical/school records, audio/video/digital recordings, photographs, EKG procedures, MRI, mobile devices such as electronic tablets/cell phones, observations, collection of specimens, experimental drug/device testing, manipulation of behavior/use of deception, computer games, etc.) For surveys, indicate if subjects are able to skip questions that they don't want to answer.

- WHERE: (e.g., classrooms, labs, internet/online, places of business, medical settings, public spaces, etc.)

Selection:

The participants in this study will be enrolled in the same-day unit or other pre-operative area at Hershey Medical Center.
Potential Participants will be identified using the All case + 30 surgery schedule.. The potential participant will be contacted by a study team member prior to the day before surgery to verify inclusion and to explain the research study.
The study team will verify the inclusion/exclusion criteria, explain the research and answer any questions the potential participant may have. If the potential participant agrees to be in the study, the research team will obtain informed consent from the potential participant.

Randomization/Group Assignment:
Eligible participants will be randomly assigned to one of two possible groups—Group A or Group B. Randomization of 1:1 will be done using https://www.randomizer.org/. Participants will have equal odds of being in either Group A or Group B. A concealed allocation schedule will be used so the group allocation will not be known when recruiting patients. The anesthesiologist performing the anesthetic (who will be a member of the research team) will be provided with a sealed envelope with the participants number on it. The anesthesiologist will open the envelope in the operating room before induction of the patient, which will contain a randomized number assigning the participants to either Group A or Group B.

- Participants assigned to Group A will receive a low-dose propofol infusion at 25 mcg/kg/min + sevoflurane titrated to a bispectral index (BIS) value of 40-60 for the duration of their surgery, starting at induction and ending at skin closure.
- Participants assigned to Group B will receive only propofol infusion at a rate titrated to a BIS value of 40-60 for the duration of their surgery, starting at induction and ending at skin closure.

Standard Anesthetic Plan. The rest of the anesthetic plan will be Penn State Health standard of care.

Blinding:
Participants will not be informed as to which group they have been assigned. In other words, participants will not be told if they received a low-dose propofol infusion + sevoflurane during surgery or a propofol-only infusion for their anesthetic. Study team members recruiting participants and conducting the follow-up data collection will also be blinded to which group (Group A vs Group B) participant was assigned. The attending who administers the anesthetic will be a member of the research team and will not be blinded.

After Surgery:
Once the surgery is finished and the patient is extubated, they will be transported to the PACU. Nursing staff will monitor and record any signs/symptoms of nausea and vomiting, as well as pain scores via visual analog scale (VAS), every 15 minutes for the first 2 hours and then every 1 hour until discharge from PACU. The nurse manager and PACU nurses will be asked to attend a training meeting about the study before the launch of the study. Research study team member will give a data collection sheet to the PACU nurse to record this information as well as the time of discharge from PACU and the hospital. This completed sheet (with patient sticker) will be placed inside the anesthesia research lock box located outside the PACU, which will then be collected later by the research team. The research team member providing the anesthetic will not tell the PACU nurse to what group the patient was assigned as a part of handoff process in order to avoid unblinding of the patient.

Once participants are discharged from PACU, they will be asked to keep track of any episodes of nausea (urge to vomit), retching (labored, spasmodic, rhythmic contractions of respiratory muscles without expulsion of gastric contents), or vomiting (forceful expulsion of gastric contents) experienced during the immediate 24 hours following their surgery by recording these events in the data collection form provided to them at the time of consent. Additionally, they will be instructed to record the times and any medications

used to treat their PONV. Approximately 24 hours post-surgery, each participant will be contacted via telephone by a blinded member of the research team to obtain the PONV data. A standardized data collection form will be used for each study participant. If unable to reach the participants, a second attempt (phone call) will be made up to 48 hours post-surgery. If still unsuccessful, the participants will be considered lost to follow up. If a participant remains in the hospital 24 hours after their surgery, a member of the study team may call the patient, or see them in person to collect their PONV data. Whenever a participant's 24-hour post-surgery PONV information is obtained, that participant's involvement in this study will conclude.

7.2.1 Visit 1 or Day 1 or Pre-test, etc.

Provide a description of what procedures will be performed on visit 1 or day 1 or pre-test in order of how these will be done. If your study only involves one session or visit, use this section only and delete 7.2.2.

Participants will be identified using the All cases +30 surgery schedule. The potential participant will be contacted by a study team member the day before surgery to verify inclusion and to explain the research study. The patient will be asked if they would like to be approached in the SDU before surgery.

7.2.2 Visit 2 or Day 2 or Post-test, etc. (If applicable)

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.). If your study involves only one session or visit, delete this section.

On the day of surgery, a study team member will explain the research and obtain informed consent to participate in this study from the potential participant that received a pre-consent phone call and agreed to be approached prior to surgery.

PACU nurse is to collect the following data, see PACU data collection form

1. Pain scores from arrival time to discharge.
2. Episode of nausea, retching and/or vomiting while in the PACU
3. Anti-nausea medication given to participant, name of drug and number of times used

The day following surgery, the participant will be contacted via telephone approximately 24 hours after their surgery by a blinded study team member to collect data regarding PONV. Every participant will be asked the same series of questions regarding PONV as well as the number of times any antiemetics were taken.

Participant self-record information, see participant data sheet

1. Episode of nausea, retching and/or vomiting after discharge from the PACU to the last 24 hours
2. Anti-nausea medication taken, name of medication and number of times used

The 24 hour post-surgery call will collect the following data, see 24 hour post-surgery

1. Number of episodes of Nausea, retching and /or vomiting
2. Anti-nausea medications used and how many times
3. Complications

Data collected from the EMR, see Information to be collected from EMR

1. Complication
2. ASA status
3. Participant weight
4. Duration of anesthesia
5. Duration of surgery
6. Was the patient in hypotension?
7. Number of time MAP<65
8. Agent used to treat hypotension
9. Adverse reaction to propofol or sevoflurane
10. Pain scores
11. MME
12. Time of PACU discharge
13. Time of hospital discharge
14. BMI
15. Participant Height
16. Participant Smoking history

7.3 Duration of Participation

Describe how long subjects will be involved in this research study. Include the number of sessions and the duration of each session - consider the total number of minutes, hours, days, months, years, etc.

Participants will be involved in this research study from the time they sign the research consent form (on the day of their surgery) until 24 hours after their surgery when they receive a call from the research team. Once the Participant's 24 hour PONV information is obtained, that participant's involvement in this study will conclude. The participation could last up to 48 hours if we are unable to reach the participant at 24 hour post-surgery.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Provide a brief description of all test articles (drugs (including any foods and dietary supplements), devices and/or biologics) used in the research including the purpose of their use and their approval status with the Food and Drug Administration (FDA). Include information about the form of the drug product (e.g., tablets, capsules, liquid).

Propofol and sevoflurane either alone or in combination are the drugs being studied in this study. Both drugs are FDA approved for induction and maintenance of anesthesia. Propofol is supplied as a solution for intravenous injection and sevoflurane is supplied as solution for inhalation.

7.4.2 Treatment Regimen

Describe dose, route of administration and treatment duration. Include information about dose adjustments.

Sevoflurane will be administered to patients via inhaled vapor. Propofol will be administered intravenously. All drug dosages are standardized or weight based; however, total amount of sevoflurane (for Group A) and propofol (for Group B) will vary between participants, as adjusted by titrating to a (BIS) of 40-60 (this is a monitor used to titrate depth of anesthesia). In group A the dose of propofol will remain fixed at 25 mcg/kg/min. Treatment will start at induction and end at skin closure. Actual length of time is dependent on the length of surgery.

7.4.3 Method for Assigning Subject to Treatment Groups

Describe the randomization process and how the associated treatment assignment will be made.

Eligible participants will be randomly assigned to one of two possible groups—Group A or Group B Randomization of 1:1 will be done using https://www.randomizer.org/. Participants will have equal odds of being in either Group A or Group B. A concealed allocation schedule will be used so the group allocation will not be known when recruiting patients. The anesthesiologist, a member of the research team, performing the anesthetic will be provided with a sealed envelope with the participants number on it. The anesthesiologist will open the envelope in the operating room before induction of the patient, which will contain a randomized number assigning the participants to either Group A or Group B, and a cheat sheet to standardize the anesthetic plan.

- Participants assigned to Group A will receive a low-dose propofol infusion at 25 mcg/kg/min + sevoflurane titrated to a BIS value of 40-60 for the duration of their surgery, starting at induction and ending at skin closure.
- Participants assigned to Group B will receive only a propofol infusion at a rate titrated to a BIS value of 40-60 for the duration of their surgery, starting at induction and ending at skin closure.

7.4.4 Subject Compliance Monitoring

Insert the procedures for monitoring subject compliance.

Not Applicable.

7.4.5 Blinding of the Test Article

Describe how the test article is blinded.

Participants will not be informed as to which group they have been assigned. In other words, participants will not be told if they received a low-dose propofol infusion + sevoflurane during surgery or a propofol-only infusion for their anesthetic. Study team members recruiting participants and conducting the follow-up data collection will also be blinded to which group (Group A vs Group B) each participant was assigned. The research team member providing the anesthetic will be unblinded to the study group assigned but they will not be involved in data collection of that patient.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Describe how the test article will be obtained and from what source. Describe how the study test article will be packaged along with amounts (e.g., number of tablets/capsules or volume of liquid) and labeling. If drug kits are used, describe all the contents of the kit and associated labeling.

All test articles and drugs will be received from existing OR stock, Pyxis machines (in OR), and/or OR pharmacy. Articles are packaged and received individually, are sterile, and only intended for one-time use. No special labeling is indicated for this research as the participants will be under anesthesia and amnestic to events that take place for the duration of treatment.

7.4.6.2 Storage

Describe the plans to store, handle the test article so they will be used only on subjects and only by authorized investigators. Describe storage temperature requirements and how temperature will be monitored and recorded.

Test articles/drugs will be stored in the OR and accessible only by authorized investigators who have access to the OR Pyxis machines. The drugs will be stored per their label requirements, using standard hospital and pharmacy practices and applicable SOPs. All test articles/drugs remaining at the end of treatment will be discarded into biohazard waste bins, drugs discarded into sharps containers, and opioids discarded via HMC's controlled waste management system.

7.4.6.3 Preparation and Dispensing

Describe how the test article will be assigned to each subject and dispensed. Describe the steps necessary to prepare the test article. Include where the test article preparation will be done and by whom. Fully describe how the study treatment is to be administered and by whom.

Test articles/drugs will be assigned to Participants based on their group designation, which is explained in Section 7.4.3. Drugs are dispensed via OR Pyxis machines, which require username and password to unlock. Test article/drug preparation will be done in the OR via the anesthesia resident or attending (member of research team) who will be administering the anesthesia for that participant

7.4.6.4 Return or Destruction of the Test Article

Describe the procedures for final reconciliation of the test article supply at the end of the study and whether the test article is to be shipped back to a source or destroyed on site.

All test articles/drugs remaining at the end of treatment will be discarded into biohazard waste bins, drugs discarded into sharps containers, and controlled drugs (opioids) discarded via HMC's controlled waste management system.

7.4.6.5 Prior and Concomitant Therapy

Describe what prior and/or concomitant medical therapy will be collected. Describe which concomitant medicines/therapies are permitted during the study. Describe which concomitant medicines are not permitted during the study.

Unless otherwise specified by their surgeon, participants have no restrictions on prior and/or concomitant medical therapy. To be eligible for this study, participants must not have taken any anti-nausea medication taken within 24 hours prior to surgery. The only medicines permitted during the study are those mentioned in Section 7.4.1.

8.0 Number of Subjects and Statistical Plan

8.1 Number of Subjects

Indicate the maximum number of subjects to be accrued/enrolled, to include all persons who sign consent for the study. If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

The minimum number of Participants needed to complete the research is 60. We aim at recruiting 90 Participants for the consideration of drop out, loss to follow up, etc.

8.2 Sample Size Determination

If applicable, provide a justification of the sample size outlined in section 8.1 to include reflections on, or calculations of, the power of the study.

Kawano et al (2016) shows that the incidence of nausea and vomiting were 62% in sevoflurane group and 21% in the combination group (sevoflurane + propofol). Using the likelihood test comparing the two independent proportions and assuming power to be 90% and alpha to be 5%, we estimated the effective (minimum) sample size to be 30 per arm (60 in total).

8.3 Statistical or Analytic Methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

We will perform tests on the equality of proportions of subjects experiencing nausea and vomiting over multiple time-points. We will apply Benjamini-Hochberg procedure to adjust for a false discovery rate of 5%. The coefficient is considered to be significant if the p-value is less than Benjamini-Hochberg critical value.

9.0 Data and Safety Monitoring Plan

This section is required when research involves more than Minimal Risk to subjects as defined in "HRP-001 SOP- Definitions."

Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Please complete each section below if the research involves more than minimal risk to subjects or indicate not applicable.

[Do not type here]

9.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

We will periodically evaluate the survey data on a monthly basis. We will specifically look at Participants' reports of PONV and if there appears to be any safety concerns among the study and control groups.

9.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

For both study and control groups, we will review the number of episodes of nausea, retching, and vomiting, as well as any instances of readmission or the need to be seen in the Emergency Department due to PONV. In addition, incidence of allergic reaction to propofol and /or sevoflurane**,** hypotension, and vasopressors received during the surgery will be reviewed.

9.3 Method of collection of safety information

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

Safety information will be collected via 24-hour post-operative phone call as well as electronic health record. During the phone call, Participants will be asked about any PONV complications, specifically, if they needed to be seen in the ED or required readmission due to their PONV.

9.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

All data (including safety data) will be collected via ongoing basis, 24 hours following each study participant's surgery

9.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

Both the principal and co-investigators will share the responsibility of reviewing the data.

9.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

We will periodically evaluate the cumulative survey data on a monthly basis.

9.7 Statistical tests

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

To be determined by the statistician

9.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

There are no foreseeable conditions that may trigger an immediate suspension of research.

10.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider all types of risk including physical, psychological, social, legal, and economic risks. **Note: Loss of confidentiality is a potential risk when conducting human subject research and must be listed here.**

- If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.
- If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.
- If applicable, describe risks to others who are not subjects.

1. The reasonably foreseeable risks include mild-moderate discomfort due to nausea, retching, and/or vomiting.
2. Risk for loss of confidentiality.
3. Risk of randomization - Participants will be assigned to a treatment program by chance. The treatment received may prove to be less effective than the other research treatment(s) or other available treatments.
4. Both propofol and the combination of propofol with sevoflurane are standard of care options currently available for use in this patient population at PSH
5. One anesthesia regimen may have more risks that the other.
6. Sevoflurane common side effects: Blurred vision; chest pain, tightness or discomfort; choking; dizziness, faintness or lightheadedness; fast, pounding or irregular heartbeat or pulse; low or irregular heartbeat; sweating; spasm of the vocal cords; coughing; agitation and airway obstruction; nausea; vomiting and drowsiness.
   Less common but more serious side effects include: malignant hyperthermia (drug induced dangerously high body temperature, rigid muscles or spasms, and a rapid heart rate); severe allergic reactions; and hypersensitivity.
7. Propofol common side effects: Hypotension (low blood pressure), hypertension (high blood pressure) or bradycardia (slow heart rate), itchy skin, a light-headed feeling; weak or shallow breathing; burning/stinging at injection site. Less common side effects include severe allergic reaction or hypersensitivity.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 13.0.

There is not guarantee that the participant will receive any benefits by being in the study. The potential benefit that Participants may experience from taking part in this research is reduced or absent nausea and vomiting after surgery.

11.2 Potential Benefits to Others

Describe the potential benefits to society or others.

This research has the potential to benefit other people in the future if low-dose propofol infusion is found to be effective. It would serve as an easy-to-implement, evidence-based, anesthetic technique for preventing PONV in patients with a prior history of PONV and/or motion sickness.

12.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how information will be shared.

The results of the study will not be shared with the participants.

13.0 Subject Payment and/or Travel Reimbursements

Describe the amount, type (cash, check, gift card, other) and timing of any subject payment or travel reimbursement. If there is **no** subject payment or travel reimbursement, indicate as not applicable.

Extra or Course Credit: Describe the amount of credit **and** the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered. It is not acceptable to indicate that the amount of credit is to be determined or at the discretion of the instructor of the course.

Approved Subject Pool: Indicate which approved subject pool will be used; include in response below that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

not applicable

14.0 Economic Burden to Subjects

14.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

not applicable

14.2 Compensation for research-related injury

If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

Identify and describe the facilities, sites, and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the principal investigator's experience conducting research at these locations and familiarity with local culture.

All recruitment and study procedures will take place at Penn State Milton S. Hershey Medical Center.

15.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

We have access to all patients presenting for surgery.

15.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Consider outside responsibilities as well as other on-going research for which the PI is responsible. Please only provide a response for the principal investigator – do **not** include information about any other study team members.

The PI will be able to devote 30 min each working day to conducting and completing the study. PI has three other ongoing studies. One is complete, manuscript is in press. The data collection of other studies is ongoing.

15.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subjects might need as a result of their participation in the study.

All resources needed for the protocol, as well as for any possible adverse event, are available at Penn State Hershey Medical Center.

15.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties.

Prior to initiating this project, all research study team members will meet either in-person or virtually to review and discuss the protocol, as well as each members' specific duties.

16.0 Other Approvals

16.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from engaged cooperating institutions IRBs who are also reviewing the research and other required review committees, community leaders, schools, research locations where research is to be conducted by the Penn State investigator, funding agencies, etc.).

Not applicable.

16.2 Internal PSU Ancillary Reviews

DO NOT ALTER OR DELETE:
Ancillary reviews are reviewed by other compliance groups or individuals within Penn State that inform the IRB's review of a new study or a modification to an existing study.

PSU IRB may set applicable ancillary reviews for your study. Please refer to the HRP-309 Worksheet – Ancillary Review Matrix for more information (found in the CATS Library).

[Do not type here]

17.0 Multi-Site Study

If this is a multi-site study (i.e., a study in which two or more institutions coordinate, with each institution completing all research activities outlined in a specific protocol) and **the Penn State PI is the lead investigator**, describe the processes to ensure communication among sites in the sections below.

[Do not type here]

17.1 Other sites

List the name and location of all other participating sites. Provide the name, qualifications and contact information for the principal investigator at each site and indicate which IRB will be reviewing the study at each site.

Not applicable.

17.2 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results, and closure of the study.

Not applicable.

17.3 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

Not applicable.

17.4 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

Not applicable.

17.5 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

Not applicable.

17.6 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

Not applicable.

18.0 Adverse Event Reporting

18.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction".

	• *Reasonable possibility*. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

18.2 Recording of Adverse Events

Address the frequency and process for eliciting adverse event information from research subject, e.g., "Research subjects will be routinely questioned about adverse events at study visits."

In the response, incorporate the following as written:
All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms

- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

Research Participants will be routinely questioned about adverse events at study visits.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of Participants participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

18.3 Causality and Severity Assessments

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 Written IND/IDE Safety Reports

For a drug study under an IND, incorporate the following from 21 CFR 312.32 as written – DO NOT ALTER OR DELETE:
The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

For a device study under an IDE, incorporate the following from 21 CFR 812.150 as written – DO NOT ALTER OR DELETE:
The Sponsor-Investigator will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500Awill be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the Sponsor-Investigator first receives notice of the adverse effect.

If the results of the Sponsor-Investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the Sponsor-Investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the Sponsor-Investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

not applicable

18.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

For a drug study under an IND, incorporate the following from 21 CFR 312.32 into the response, as written:
In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal, or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

Not applicable

18.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

18.6 Unblinding Procedures

Describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject's source document. Include example(s) here why someone might unblind a study. In most cases, the unblinding will be part of managing a serious adverse reaction and will be reported with the serious adverse event. However, in cases where unblinding was not associated with a serious adverse event, such actions should be reported in a timely manner.

In the event that the Participants has a concerning reaction or becomes unstable in any fashion, the Participants will be immediately unblinded and removed from the study.

18.7 Stopping Rules

In studies with a primary safety endpoint or studies with high risk to study subjects, provide the rules that define the circumstances and procedures for interrupting or stopping the study. If an independent Data and Safety Monitoring (DSMB) or Committee (DSMC) is set up for the study, the same stopping rules should be incorporated into the safety analysis plan as well.

The study will be stopped only if serious adverse events happen attributable to the study drug.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 Quality Assurance and Quality Control

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Describe how you will ensure that this study is conducted, and that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

Indicate who is responsible for monitoring the conduct of the study and specify how often the study will be monitored.

For single-site studies with low risk, it may be appropriate for the principal investigator to monitor the study.

For multi-center studies or single site studies involving significant risk, an independent monitor may be required (e.g., monitoring by the staff of the PSU quality assurance program office(s) or by a clinical research organization).

The Principal Investigator will monitor the study.

19.1.2 Safety Monitoring

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Indicate the process for identifying, recording, and reporting adverse events.

Specify roles for adverse event recording and monitoring. Indicate each staff member's role in the adverse event reporting process. Include the following if applicable:

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **Research Coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

The **Monitor** will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

The Principal Investigator will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

20.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting **identifiable** data and/or specimens that will be banked for **future undetermined research**, please describe this process in the sections below. This information should not conflict with information provided in section 22 below OR the "HRP-598 – Research Data Plan Review Form" regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly). If there are no plans to use identifiable data/specimens for future, undetermined research, then this section is **NOT applicable**.

[Do not type here]

20.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored, and the data associated with each specimen.

Not applicable.

20.2 Location of storage

Identify the location where the data and/or specimens will be stored.

Not applicable.

20.3 Duration of storage

Identify how long the data and/or specimens will be stored. If data and/or specimens will be stored indefinitely, indicate such.

Not applicable.

20.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

Not applicable.

20.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

Not applicable.

20.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

Not applicable.

21.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

1. Bansal T, Singhal S, Kundu K. Prospective randomized double-blind study to evaluate propofol and combination of propofol and sevoflurane as maintenance agents in reducing postoperative nausea and vomiting in female patients undergoing laparoscopic surgery. Med Gas Res. 2022;12(4):137-140. doi:10.4103/2045-9912.337994

2. Hoornstra E, Velagapudi N, Bryant JT, et al. Application of Data Science to Quantify the Effect of Propofol Infusion on Postoperative Nausea and Vomiting. AANA J. 2022;90(4):263-270.

3. Vasileiou I, Xanthos T, Koudouna E, et al. Propofol: a review of its non-anaesthetic effects. Eur J Pharmacol. 2009;605(1-3):1-8. doi:10.1016/j.ejphar.2009.01.007

4. Jin Z, Gan TJ, Bergese SD. Prevention and Treatment of Postoperative Nausea and Vomiting (PONV): A Review of Current Recommendations and Emerging Therapies. Ther Clin Risk Manag. 2020 Dec 31;16:1305-1317. doi: 10.2147/TCRM.S256234.

22.0 Confidentiality, Privacy and Data Management

IMPORTANT: The following section is required for all locations EXCEPT Penn State Health and the College of Medicine. Penn State Health and College of Medicine should skip this section and complete "HRP-598 Research Data Plan Review Form." In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all other sub-sections of section 22.

See the HRP-598 Research Data Plan Review Form"