

***TO SERENADE OR TO SEDATE? THAT IS STILL THE QUESTION – A FOLLOWUP
TRIAL ON ANXIOLYTIC OPTIONS BEFORE PERIPHERAL NERVE BLOCKS***

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Study Product *Patient choice of music*

IRB Number

Initial version **1.0**
Date **31 January 2020**

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Study Summary

Title	<i>TO SERENADE OR TO SEDATE? THAT IS STILL THE QUESTION – A FOLLOWUP TRIAL ON ANXIOLYTIC OPTIONS BEFORE PERIPHERAL NERVE BLOCKS</i>
Short Title	<i>TO SERENADE OR TO SEDATE?</i>
IRB Number	
Methodology	<i>A prospective, randomized controlled study</i>
Study Duration	<i>One year</i>
Study Center(s)	<i>Single-center, ambulatory surgical center, at a university hospital</i>
Objectives	<i>Primary:</i> <ul style="list-style-type: none"><i>To compare the change in preoperative anxiety scores between study groups from after to before placement of a peripheral nerve block.</i> <i>Secondary:</i> <ul style="list-style-type: none"><i>To evaluate differences in hemodynamics, block times, patient satisfaction scores, provider satisfaction scores, evaluation difficulty in communication between provider and patient, and adverse effects between both study groups</i>
Number of Subjects	<i>160</i>

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<p>Main Inclusion and Exclusion Criteria</p>	<p>Inclusion: patients who are >18 years of age who are able to give informed consent who are scheduled to receive any type of peripheral nerve block either for their primary anesthetic or for postoperative pain control in the preoperative bay at the ambulatory surgical center.</p> <p>Exclusion: patients who have an associated significant psychiatric disorder such as generalized anxiety disorder, panic disorder, depression, psychosis, bipolar disorder; individuals who were incompetent to give informed consent; pregnant and/or breast feeding patients; any underlying coagulopathy, infection or other factors which would be a contraindication to receiving a peripheral nerve block; hypersensitivity to midazolam; and history of renal impairment. Patients who were extremely anxious (scores 50 and greater on the State Trait Anxiety Inventory-6 (STAI-6) tool) as these patients typically require pharmacologic therapy to help reduce their anxiety and may confound the results of the study.</p>
<p>Intervention</p>	<p>There will be two study groups who will be randomized. 1. Music group: Music group – patients will select music of their choice to be played via non-noise canceling headphones. 2. Midazolam group: patients in this group will receive IV midazolam (1mg to 2mg max) after the golden moment has been completed.</p> <p>In our daily practice, it is the provider's preference to give patients medication for sedation while conducting the preoperative nerve block. Patients do not routinely get sedation medication during the preoperative nerve block placement.</p>
<p>Statistical Methodology</p>	<p>1:1 Randomized controlled study</p>
<p>Data and Safety Monitoring Plan</p>	<p>The PI, Dr. Graff and her MD collaborator Dr. Nabil Elkassabany will be responsible for data safety and monitoring. All data will be kept in a locked cabinet in the MD collaborator's office. The PI and collaborators will perform safety reviews after 25 subjects are enrolled. Any protocol-related problem or deviation will be reported to Dr. Graff and/or Dr. Nabil Elkassabany as soon as possible.</p>

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Background and Study Rationale

1 Introduction

This document is a research protocol and the described study will be conducted in compliance with the provisions set forth in the protocol as well as, Good Clinical Practice standards, associated federal regulations, and all applicable University research requirements.

Preoperative anxiety is common and can adversely affect a patient's perioperative course by elevating stress markers, promoting fluctuations in hemodynamics and negatively impacting on postoperative recovery.¹ Preoperative anxiety is routinely treated with pharmacologic agents such as midazolam, a benzodiazepine, which has known, undesirable side effects including respiratory depression, hemodynamic perturbations, and paradoxical effects such as hostility, aggression, and psychomotor agitation.^{2,3} The use of sedative medications requires continuous vital sign monitoring of patients by either anesthesia or nursing personnel and there is a question of whether midazolam helps reduce pre-procedural anxiety compared with placebo. Music is a non-pharmacologic intervention that has been shown to significantly decrease preoperative anxiety.^{1,4-6} This intervention can be used as an adjunct or even replace pharmacologic agents to help with preoperative anxiety. Music is a modality that is virtually harm-free and relatively cheap in cost. Patients who are unable to tolerate pharmacologic agents to treat preoperative anxiety can greatly benefit from non-pharmacologic options such as music.

Regional anesthesia procedures such as an ultrasound guided, peripheral nerve block is a common bedside procedure done preoperatively. Patients may have some anxiety prior to the administration of this nerve block procedure and may receive sedation for it. However, it is imperative not to over sedate them as constant feedback from the patient is necessary during the procedure. Commonly, midazolam is used to reduce this anxiety, but non-pharmacologic therapies can also reduce anxiety.^{1,5} In our recent published study, we evaluated the use of research-selected, relaxing music, to reduce anxiety before the nerve block is administered.⁷ In this study, we used noise-canceling headphones and played research-selected music as our anxiolytic music modality and compared this with midazolam.⁷ The findings showed no difference between both groups in the change in anxiety scores from after to before the nerve block, however patients had better satisfaction in the midazolam group and increased difficulty in communication in the music group. We attributed this to not allowing patients to choose their own selection of music and the use of noise-canceling headphones.

Therefore, in this follow-up study, we aim to evaluate the use of patient-selected music via non-noise canceling headphones as a preoperative anxiolytic prior to the administration of a bedside, peripheral nerve block procedure. This study will be conducted at an ambulatory surgical center in a university setting.

1.1 *Background and Relevant Literature*

Patients often feel a tremendous amount of anxiety prior to their planned surgical procedure and anesthetic. As a result, this can affect their perioperative period by elevating their stress markers, causing various fluctuations in their hemodynamics, and poorly impacting their postoperative recovery.¹ A significant number of patients have anxiety about the anticipation in their overall outcome and postoperative pain control.^{2,3} To treat preoperative anxiety, pharmacologic agents such as short-acting benzodiazepines and opioids are used as needed depending on an individual basis; however, there are known significant side effects from these medications such as respiratory depression, vital sign abnormalities, and possible apnea which limit the use of these medications and in some instances, prevent the use for preoperative anxiety. In addition to this, utilization of these medications for conscious sedation also require continuous monitoring of a patient by either anesthesia personnel or nursing staff.

Music is a non-pharmacologic intervention that has been shown to significantly decrease preoperative anxiety.^{1,4,6} This intervention can be used as an adjunct or even replace pharmacologic agents to help with preoperative anxiety¹. Music is a modality that is virtually harm-free and relatively cheap in cost. Patients who are unable to tolerate pharmacologic agents to treat preoperative anxiety can greatly benefit from non-pharmacologic options such as music.

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The Spielberger's validated tool, the State Trait Anxiety Inventory (STAI), is one of the best measured tools to evaluate preoperative anxiety. The STAI has been referred to as the "gold standard" in properly evaluating preoperative anxiety.⁸ There are two components to this tool; a state portion which evaluates the current state of anxiety a patient has in a clinical setting, and a trait portion which evaluates how the patient generally feels unrelated to the clinical setting. Each of these sections have 20 items to answer and approximately takes 10-15 minutes to complete. In preoperative anxiety testing, the STAI-S is commonly used in research to properly evaluate the level of preoperative anxiety in the current clinical setting. Marteau and her colleagues have developed a shortened STAI version, the STAI-6, that has also been validated.⁸ The shortened STAI-6 tool has six questions and may be more beneficial to use in a high turnover, ambulatory surgical center setting as it only takes a few minutes to complete.

We will be using the STAI-6 short form questionnaire to score the preoperative anxiety levels in our patient population.

2 Study Objectives

2.1 Primary Objective

To determine preoperative anxiety score differences between patients who receive music vs IV midazolam during their preoperative nerve block placement.

2.2 Secondary Objectives (if applicable)

To evaluate differences in hemodynamics, block times, patient satisfaction scores, provider satisfaction scores, evaluation difficulty in communication between provider and patient, and adverse effects between both study groups

3 Investigational Plan

3.1 General Design

This will be a prospective, randomized controlled study. Participants will be randomized to receiving research-selected music versus IV midazolam (1mg to 2mg max) during their preoperative peripheral nerve block placement.

3.2 Allocation to Interventional Group [if applicable]

Subjects will be randomized to either music or IV midazolam. Subjects will be randomized in a one to one fashion and the randomization will take place using a computer-generated algorithm.

3.3 Study Measures

There will be two study groups who will be randomized. 1. Music group – patients will select their choice of music via non-noise canceling headphones. 2. Midazolam group: patients in this group will receive IV midazolam (1mg to 2mg max) after the golden moment has been completed.

A pre-anxiety score will be obtained using the STAI-6 validated tool after the patient has signed the informed consent. After the golden moment is completed, the intervention will start. Once the nerve block is completed, a post anxiety score will be obtained using STAI-6 validated tool.

For our primary outcome measure, we will use the short form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI-6) to measure pre procedure and post procedure anxiety levels (see below). The shortened STAI-6 tool has six questions and may be more beneficial to use in a high turnover, ambulatory surgical center setting as it only takes a few minutes to complete. In the original 20-item STAI-State tool, the scores range from 20 to 80. A score greater than 50 on the original 20-item scale is associated with a high level of anxiety. The population normal score is approximately 35 (Spielberger 1983). In the STAI-6 tool, there are six questions with a Likert scale from 1 to 4. This gives a score range

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from 6 to 24. To create scores compatible with the original STAI-S scores, the STAI-6 scores will be divided by 6 and multiplied by 20 to give a range from 20 to 80.

Appendix A: Self-evaluation questionnaire (Y-6 item)

Name Date

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

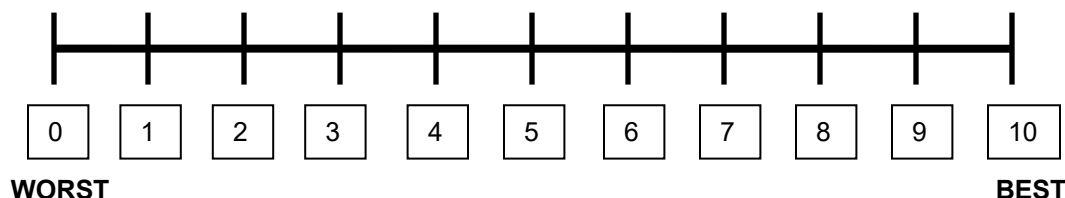
	Not at all	Somewhat	Moderately	Very much
1. I feel calm	1	2	3	4
2. I am tense	1	2	3	4
3. I feel upset	1	2	3	4
4. I am relaxed	1	2	3	4
5. I feel content	1	2	3	4
6. I am worried	1	2	3	4

Please make sure that you have answered *all* the questions.

For our secondary outcome measure, we will obtain the following information:

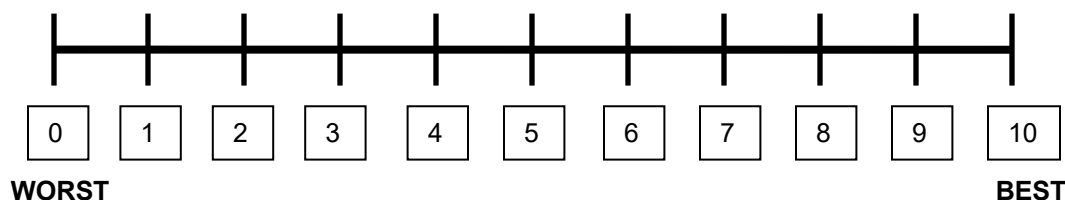
1. Patient satisfaction scores using a 10-point visual analogue scale (VAS) as follows:

"Using any number from 0 to 10, where 0 is the WORST experience possible and 10 is the BEST experience possible, what number would you use to rate your overall preoperative experience while getting a peripheral nerve block placed?"



2. Provider satisfaction scores using a 10-point visual analogue scale (VAS) as follows:

"Using any number from 0 to 10, where 0 is the WORST experience possible and 10 is the BEST experience possible, what number would you use to rate your overall preoperative experience while placing a peripheral nerve block for your patient?"



3. Evaluation of communication difficulties between provider and patient by asking one question on a 5-point Likert scale:

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From provider to patient:

"I found it difficult to communicate with the patient while doing the preoperative nerve block."

- A. *Strongly Disagree*
- B. *Disagree*
- C. *Neutral*
- D. *Agree*
- E. *Strongly Agree*

From patient to provider:

"I found it difficult to communicate with the physician while the preoperative nerve block was being done on me."

- A. *Strongly Disagree*
- B. *Disagree*
- C. *Neutral*
- D. *Agree*
- E. *Strongly Agree*

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The primary end point will be to determine change in the anxiety scores using the STAI-6 tool between the music group and the IV midazolam group.

3.4.2 Secondary Study Endpoints

The secondary end points will be to determine any differences in patient satisfaction scores, provider satisfaction scores, evaluation of difficulties in communication between provider and patient, hemodynamics, block times, and adverse effects including paresthesia's, patchy block, failed block, and serious adverse effects including bleeding, infection, paralysis, local anesthetic systemic toxicity between both groups.

4 Study Population and Duration of Participation

The study population will include patients who are >18 years of age, who will give informed consent in receiving a peripheral nerve block in the preoperative bay for their primary anesthetic and/or for their postoperative pain control.

We will exclude the following: patients who have an associated significant psychiatric disorder such as anxiety, panic disorder, depression, psychosis, or bipolar disorder; patients who are unable to give informed consent; patients who are pregnant; patients who have an underlying coagulopathy and infection.

4.1 Duration of Study Participation

The study duration will be from the time informed consent occurs to after the perioperative block has been completed. Once the post-anxiety STAI-6 score has been obtained, the study is complete.

4.2 Total Number of Subjects and Sites

Total number of subjects will be 160; 80 in the music group and 80 in the IV midazolam group. Study will take place at Penn Medicine University City, PMUC.

4.3 Inclusion Criteria

Patients who are >18 years of age, who will give informed consent in receiving a peripheral nerve block in the preoperative bay for their primary anesthetic and/or for their postoperative pain control.

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4.4 Exclusion Criteria

We will exclude the following: patients who have an associated significant psychiatric disorder such as generalized anxiety disorder, panic disorder, depression, psychosis, bipolar disorder; individuals who were incompetent to give informed consent; pregnant and/or breast feeding patients; any underlying coagulopathy, infection or other factors which would be a contraindication to receiving a peripheral nerve block; hypersensitivity to midazolam; and history of renal impairment. Patients who were extremely anxious (scores 50 and greater on the State Trait Anxiety Inventory-6 (STAI-6) tool)

4.5 Subject Recruitment

All patients will be screened initially at the preoperative surgical clinic visit. Any patient that cannot be reached will be approached in the preoperative bay during the preoperative period of their planned surgery. Subjects will be given the details about the study and given adequate time to read the consent form and talk the study over with family that accompanies them.

4.6 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Procedures

5.1 Screening

The general flow of the study will be conducted as follows:

1. Research coordinator will call or approach patients who are scheduled for a surgical procedure that is planning for a peripheral nerve block either for the primary anesthetic or for postoperative pain control to be placed in the preoperative bay in the ambulatory surgical center.
2. Research coordinator will discuss the purpose of our study and explain the study in detail for the patient. If a patient agrees to participate, then we will have the patient sign the informed consent for the study.

5.1.1 Visit

3. Once the patient signs the informed consent for the peripheral nerve block by anesthesia team. The patient randomized will be revealed to either music or IV midazolam. The pre-procedure anxiety score will then be obtained using the STAI-6 validated tool.
4. The golden moment will be conducted between the patient, provider, and nursing staff. Once this golden moment is completed, the anxiolytic intervention will start (music or IV midazolam)*
5. The preoperative nerve block will be conducted by the regional anesthesia block team.
6. Once the nerve block is completed, the post-procedure anxiety score will be obtained, and we will also obtain the patient satisfaction score, the provider satisfaction score, and the evaluation of any difficulties in communication between the provider and patient. After these questions have been obtained, the study is complete.

A minimum of 1mg and a maximum of 2mg of IV midazolam will be given in the IV midazolam group.

Peripheral nerve blocks are conducted under ultrasound guidance according to standard practice at PMUC.

Vital signs such as heart rate, blood pressure, respiratory rate, and oxygen saturation are routinely obtained as a part of standard of care if sedation medication is used and when peripheral nerve blocks are placed.

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Starting block time and ending block time are routinely obtained as a part of the patient record.

During this entire process, patient demographics, hemodynamics (heart rate, blood pressure, oxygen saturation, and respiratory rate), block times (start and end time), and any adverse effects including paresthesia's, patchy block, failed block, and serious adverse effects including bleeding, infection, paralysis, local anesthetic systemic toxicity will be recorded as the routine part of practice.

5.2 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or AEs. It will be documented whether or not each subject completes the study.

5.2.1 Data Collection and Follow-up for Withdrawn Subjects

Data will still be collected for subjects who withdrawal from the study. In cases where subjects wish to withdrawn PHI consent they will be able to do so by telling a study team member in person or through information provided on the ICF.

5.3 Safety Evaluation

When evaluating safety, the doctors will look at any reported AE's as well as patients who are unwilling or unable to adhere to the randomized allocation. If patients in either group have more than 25% deviation rate the inclusion and exclusion as well as block method will be reevaluated to better limit deviations.

6 Statistical Plan

6.1 Sample Size and Power Determination

Based on a previous study by Bringman et.al. the mean (SD) of STAI anxiety score is 34(8). ⁵A clinically meaningful decrease, as determined by the Cochrane review group was 0.5 of SD.^{1,5} Our sample size calculation to detect a 4-point change in pain score (p less than 0.05 significance level) was 64 patients ($\alpha=0.05$, power=80%). We will inflate our sample size by 25% to account for any missing data or any withdrawal from the study; therefore, our estimated sample size will be 80 patients per group.

6.2 Statistical Methods

Statistical analyses will be performed using STATA 13 statistical software (Dallas, TX). Demographic or other categorical data will be analyzed using T test or Fishers exact test as appropriate. Repeated measurements (STAI-6 scores) will be analyzed by using the t-test or Mann-Whitney U-test as appropriate. Normally distributed data will be presented as means \pm SE of the mean (SEM), non-normally distributed data are presented as medians \pm quartiles (interquartile range) and categorical data will be presented as raw data and as frequencies. The alpha level for all analyses was set as P less than 0.05.

6.2.1 Baseline Data

Demographic or other categorical data will be analyzed using T test or Fishers exact test as appropriate.

6.2.2 Analysis of Primary Outcome of Interest

Repeated measurements (STAI-6 scores) will be analyzed by using the t-test or Mann-Whitney U-test as appropriate.

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7 Safety and Adverse Events

This section provides the safety management plans for the study. This section should be consistent with the Penn IRB guidelines tailored to the requirements specific for each study. It should describe how safety reporting will be monitored and take place over the course of the trial.

7.1 Definitions

7.1.1 Adverse Event

Study definition of an adverse event (AE). Can include the Penn IRB definition of an adverse event unless there are some differences in the adverse event definitions for this particular study. Standard definition of an adverse event as follows:

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

7.2 Recording of Adverse Events

Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, procedures results will be recorded in the source document.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported.

7.3 Relationship of AE to Study

The PI will supervise the assessment of relationship of each adverse even to the study procedures. The adverse events, if such occurs, will be classified as definitely related, probably related, possibly related, unlikely or unrelated.

7.4 Reporting of Adverse Events and Unanticipated Problems

The Investigator will promptly notify the Penn IRB of all on-site unanticipated, Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to

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subjects or others will also be reported promptly. Written reports will be filed using the HS-ERA and in accordance with the Penn IRB timeline of 10 working days.

7.4.1 Follow-up Report

If an AE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

7.4.2 Data and Safety Monitoring Plan

The PI, Dr. Graff and her collaborator Dr. Nabil Elkassabany will be responsible for data safety and monitoring. All paper data will be kept in a locked cabinet in the MD collaborator's office. The PI and collaborators will perform safety reviews after 25 patients are enrolled. Any protocol-related problem or deviation will be reported to Dr. Graff and/or Dr. Nabil Elkassabany as soon as possible.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject

Study data will be stored on a Penn institutionally secured and managed server specific to the Anesthesiology Department in a locked folder only for this protocol.

8.2 Data Collection and Management

Demographic information will be collected from patient charts. Information about sedation onset, block start and stop as well as survey information will be captured on paper that will be stored on Penn campus in secured building in locked office in locked filing cabinets. Subjects will be given a study number at time of enrollment. De-identified data will be inputted into a department and folder password secured excel sheet.

Once study analysis is complete identifiable information linking subject to study number will be destroyed/deleted.

8.3 Records Retention

Records will be retained up to 3 years after the completion of research. Electronic records of directly collected data will subsequently be destroyed from electronic server.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study will be monitored by Dr. Graff and Dr. Elkassabany.

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9.2 *Auditing and Inspecting*

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities.

10 Ethical Considerations

Study will be submitted to the Penn IRB for approval before study enrollment begins. Any changes to the protocol will be preapproved by the IRB before any changes to study practice is made.

10.1 *Risks*

The risks of the study are related to the administration of midazolam which include tenderness and pain during injection at IV site. This risk is addressed in the local block consent form and thus is not putting subjects at a greater risk.

10.2 *Benefits*

The individual subjects may not receive any benefit from participating in this study. Potential benefit could be increased relaxation and lower anxiety from music sedation or midazolam. For the study population this study hopes to prove that non medicinal sedation is adequate for subject comfort and a decrease in anesthetics can be achieved.

10.3 *Risk Benefit Assessment*

The potential benefits are greater to the limited risks for patients thus this study should be conducted.

10.4 *Informed Consent Process / HIPAA Authorization*

All subjects for this study will be provided a consent form describing this study providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The subject, must sign the consent form, and the investigator-designated research professional obtaining the consent. Subjects will be consented by the study Principal Investigator, or appropriate designee, in perioperative holding room assigned at check in. Potential subjects will review the consent form in detail with the person designated to consent (either PI or CRC) and have the ability to review consent with family or friends that accompanied them to PMUC.

11 Study Finances

11.1 *Funding Source*

This study is not funded.

11.2 *Conflict of Interest*

No conflicts of interest have been noted by initial study team if conflict arises the IRB will be notified according to regulations. All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 *Subject Stipends or Payments*

Subjects will not be paid for study.

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