STUDY TITLE:
The effective dose of music duration for anxiolysis before elective cesarean delivery

STUDY SPONSOR:
Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center

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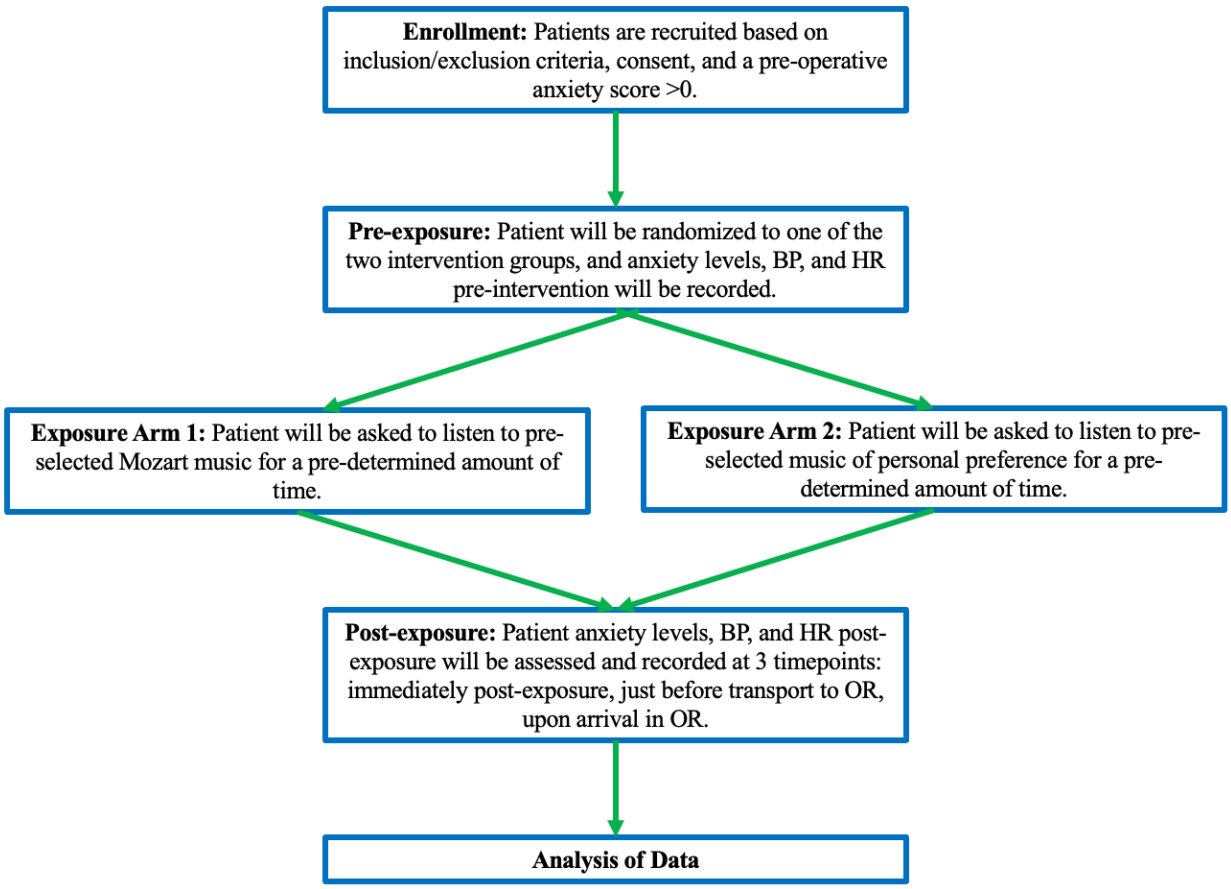
A. Study Schema

Include a diagram that provides a quick "snapshot" of the study. For examples of study schemas, refer to the FDA and NIH's Study Schema Examples document available on the IRB website:



B. Introduction

B.1 Background and Rationale

1. *Describe the relevant prior experience and gaps in current knowledge:*

2. In the current era of growing mental health awareness, it has become clear that patients have feelings of anxiety that can negatively affect the quality of their healthcare experience. Though pharmacological interventions are widely used to treat the symptoms of anxiety, these drugs often come with a risk of serious side effects and/or dependence. Alternatively, music has been used for centuries as a medium for healing, but only recently has it become a focus of research. To date, the beneficial effects of music for pain management, anxiety, and on various hemodynamic parameters have been demonstrated in several studies. Specific selections of Mozart sonatas have helped improve patient anxiety, reduce systemic stress markers, and lower blood pressure and heart rate in patients with cancer receiving chemotherapy and in patients and in patients in the ICU. In addition, it has been shown that listening to other genres of patient-preferred music can reduce preoperative anxiety and use of music intra-operatively has been associated with decreased anxiety in patients undergoing a cesarean section. Given the unique physiologic states and medical considerations surrounding pregnant individuals and their fetuses, parturients are a patient population in which non-pharmacological techniques for anxiety reduction can be particularly beneficial.

These beneficial effects can be particularly helpful in patients with histories of substance abuse who may not wish to use pharmacological interventions for anxiety reduction, regardless of the type of medication.

1. *Describe any relevant preliminary data:*
   Previous study, IRB #STUDY00001496, found preliminary results that indicated as few as 4 minutes of music listening time was sufficient to produce a 1-point reduction in anxiety on the 0-10 scale. This was found using the Mozart selections that we plan to use again for this study. We will base our starting point for music listening duration off of this preliminary data.
2. *Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how it will add to existing knowledge:*
   Though the effects of music exposure have been shown to be beneficial in parturients, the adequate "dose" to elicit an anxiolytic response or other health related benefits remains undetermined. Additionally, the previous literature has primarily focused on the health-related effects of intra-operative music during cesarean sections but has not addressed the use of music in the pre-operative setting. Dosing is one of the most important metrics for implementing clinical interventions to ensure an adequate response and a minimal risk of side effects; waiting in the pre-operative setting to undergo cesarean section can undoubtedly bring about a significant anxiety response. In anesthesia, it is agreed upon that the 95% effective dose (ED_{95}) is one of the most clinically meaningful metrics for dosing. Inasmuch, my proposed study aims to determine the ED_{95} of music listening duration for the reduction of anxiety in patients awaiting cesarean section. Further, the study will use both the beneficial selections of music by Mozart described in previous studies as well as music of patient preference to elucidate differences in dosing required to produce positive effects between intervention subtypes. If successful, this study could provide dosing estimates to help more precisely guide clinicians in their use of music for patients awaiting cesarean section and potentially for patients in other pre-operative settings.
3. *Describe the relevance and usefulness of the objectives:*
   If found to be effective, using music to combat pre-operative anxiety could reduce the variety and/or quantity of pharmaceuticals being administered to surgical patients, thus decreasing risk of adverse drug reactions.
4. *Specify whether or not this is the first time the study drug, device, or intervention/procedure will be used in humans. If there has been experience with the study drug, device, or intervention/procedure in humans, detail the experience to date:*
   ☒N/A, this is not the first time the study drug, device, or intervention/procedure will be used in humans
5. Is there an active control group?
   ☐ **Yes** ☒ **No**
   If **Yes**, respond to all of the following:
   a. ☐*Check to confirm that the active control is an established effective intervention. If it is not, clarify how it is ethically justified to use this control in the study:* Control is the equivalent of current standard practice
   b. *Describe any potential bias in the selection of the active control such that there will be an unfair advantage for the investigational intervention. For example, is the active control treatment known to be significantly less effective in this study population than another treatment:* or ☐N/A
   c. ☐*Check to confirm that the sample size and the randomization ratio for this active control study is ethically justified with regard to the number of participants who will be exposed to the risks of the study.*

B.2 Risks to Subjects

1. *List the reasonably foreseeable risks, discomforts, hazards, and/or inconveniences to the subjects related to their participation in the research, including risk of unintentional loss of confidentiality. Include a description of the probability, magnitude, duration, reversibility, and potential consequences of the risks. Consider physical, psychological, social, legal, and economic risks:*
   Participation in this study will include a risk of possible injury to the tympanic membrane if the music is too loud. This complication will be avoided with active participation from the patient to continually assess for improper volume status, and volume will be adjusted according to the patient's preference.

Other risks include the possibility of unintentional loss of participant confidentiality. To minimize that risk, all data related to the study will be stored in a secure location. Furthermore, all electronic data will be held in a password protected, encrypted, cloud storage account.

2. *State which study interventions may have unknown risks:* ☒N/A
3. *State which study interventions may have risks to an embryo or fetus (if a subject is or becomes pregnant) or to a nursing infant of a study subject:* ☒N/A
4. *Describe risks to people other than the participating subject, e.g., risks to family members, friends, others or risks to the community:* ☒ N/A
5. *Are there any risks to study investigators or staff performing the study procedures due to research with high risk populations (e.g. prisoners, intravenous drug users, patients with major psychiatric issues, etc.):?*
   ☐ **Yes** ☒ **No**

B.3 Potential Benefits to Subjects

1. *Describe the potential benefits that individual subjects may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research subjects:*
   ☒ N/A, there is no direct benefit. However, subjects may experience decreased levels of anxiety as a result of listening to music.
2. *Describe any benefit to the population from which the subject is drawn:*
   If proven effective, music could be offered to more patients in the pre-operative setting to help reduce their levels of anxiety and could provide more accurate "dosing" estimates of music duration for clinicians to use.
3. *Describe any benefit to science, society, and humanity in general:*
   The results of this study will help further reveal the effect characteristics of music on anxiety.

B.4 Alternatives

1. *Describe alternatives to participating in this research study (e.g. to decide not participate in the study, alternative treatments, no treatment (palliative care), etc.):*
   The alternative is not participating in the study.
2. *Describe the standard clinical care that may be an alternative:* ☒ N/A
3. *Describe how the subject can receive the research procedures/drug/device used in this study in a non-research setting:* The subject may use their own music-playing devices if so desired

C. Objectives

1. *Describe the purpose, specific aims, or objectives of the study (i.e. the reason for performing the study in terms of the scientific question to be answered):*
   The primary objective of this study is to determine effective dose of music duration for anxiety reduction in parturients awaiting non-emergent cesarean section.

   A secondary objective of this study is to compare the effective dose of music duration for anxiety reduction between classical pieces previously studied vs. patient-preferred music selection.

   An additional secondary objective is to analyze the physiologic impact from anxiety reduction pre- and post-study intervention.

   An exploratory objective of this study is to investigate the dose-duration relationship of music on anxiety reduction in patients awaiting non-emergent cesarean section.

D. Enrollment and Withdrawal

D.1 Inclusion Criteria

1. *Describe the criteria that define who will be **included** in the study as a numbered list:*
    1. Age: 18 years old or older.
    2. Planning a scheduled or urgent (non-emergent, i.e. for arrest of labor) cesarean section.
    3. Able to provide informed consent.
    4. American Society of Anesthesiologists (ASA) physical status rating of II-III. (Mild systemic disease; severe systemic disease that is not incapacitating)

D.2 Exclusion Criteria

1. *Describe the criteria that define who will be **excluded** in the study as a numbered list:*
    1. Patient refusal.
    2. Impaired hearing.
    3. Patient is taking at least one anxiolytic medication daily at baseline.
    4. No anxiety (a score of 0, on a scale of 0-10 of pre-music exposure anxiety) after consent is given.
    5. ASA physical status rating of IV or higher. (Incapacitating disease that is a constant threat to life; a moribund patient who is not expected to live 24 hours with or without surgery)
    6. Severe medical condition(s) of the fetus or other pregnancy complications (ex: congenital heart defects, physical malformations, pre-term delivery, etc.)
2. *Describe in detail how the eligibility criteria will be assessed and satisfied (e.g., medical record review, physical examination):*
   A brief medical record review, discussion with the patient, and pre-music anxiety assessment (after consent is given) will be performed.
3. *State who will determine eligibility. Note that those who are designated to determine eligibility must have appropriate training, expertise, and oversight, for example a physician PI or Co-I on a biomedical study:*
   Either the PI or Co-investigator will determine final eligibility.
4. *Can study subjects participate in another research study while participating in this research study:*
   ☒Yes ☐ No

D.3 Withdrawal of Subjects

1. *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent:*
   Participants who score a 0 on their pre-music anxiety assessment will be withdrawn from the study.
2. *Describe procedures that will be followed when subjects withdraw voluntarily **or** are withdrawn from the research, including the possibility of partial withdrawal from study intervention with continued data collection:*
   Participants who are withdrawn from the study will be provided the standard of care at Tufts Medical Center. All collected data and identifying information will be promptly destroyed.
3. *Describe any necessary safety precautions to be applied to subjects who withdraw or are withdrawn (tapering drug doses, evaluative x-ray, etc.):*
   ☒N/A

D.4 Recruitment and Retention

D.4.1 Local Recruitment Methods

Describe the following attributes of the recruitment plan for the local Tufts site:

1. *When, where, and how potential subjects will be recruited:*
    a. *Source of subjects (for example, patient population, local community, etc.):*
       Patients undergoing pre-operative clinic evaluation at Tufts Medical Center.
    b. *Methods that will be used to identify potential subjects:*
       Faculty and staff in the Obstetrics and Gynecology Department at Tufts Medical Center will be informed about the study at a departmental meeting. They will be asked to inform their patients about this study in their pre-operative clinic visits.
    c. *If potential subjects will be approached, specify where the recruitment discussion will take place to ensure subjects' privacy (e.g. a private clinic room):*

Once the patients arrive to the labor and delivery pre-op area, if the patient informs their provider that they are interested in participating, the provider will inform a study team member and a researcher will meet with the patients in a private room to discuss the study further with them. If the patient agrees to participate, informed consent will be obtained, and a copy of the consent form will be provided to subjects for them to retain.

2. *If potential subjects will be **recruited by telephone**, describe how many times the research team will attempt to call / leave a voice message:* ☒ N/A
3. *When subjects respond to recruitment material, describe the information that will be provided to them about the study and the information that will be collected from subjects (e.g. name, telephone number, etc.). Describe also, how many times you will attempt to respond to call the subject back / leave a voice message:*
4. N/A*Will potential subjects be recruited at institutions that are **not owned and operated by Tufts Medical Center, Tufts University, or MelroseWakefield Healthcare**:* ☐ **Yes** ☒ **No**
5. *Describe how the recruitment methods described will be effective in attracting the targeted subject population. Address both planned recruitment activities as well as any proposed engagement strategies for retention:*
   Recruitment will be done directly by the study team on the Labor and Delivery (L&D) Unit at Tufts Medical Center (TMC) in the pre-operative setting. The study team will recruit subjects daily for a period of roughly three months to ensure adequate sampling of the population at the L&D Unit at TMC. This will also ensure that only patients meeting inclusion criteria will be recruited to the study.

D.4.2 Study-Wide Recruitment Methods

Is this is a multicenter study where subjects will be recruited by methods not under the control of the local Tufts site (e.g., call centers, national advertisements)?

☐ Yes ☒ No

D.4.3 Projected Enrollment Numbers

1. *If the study involves prospective involvement or new contact with study participants, complete the projected enrollment table below by sex, race, and ethnicity. If applicable, participants at the U.S. (domestic) and non-U.S. (foreign) sites must be reported using separate tables, even if it is for the same study:*

	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
Racial Categories	Female	Male	Female	Male	
American Indian/Alaska Native	1	0	0	0	1
Asian	15	0	1	0	16
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	10	0	1	0	11
White	20	0	5	0	25
More than One Race	9	0	3	0	12
Total	56	0	10	0	66

2. *Inclusion of individuals across the lifespan:*
   a. *Specify how you will ensure the inclusion of individuals across the lifespan. If applicable, provide a scientific or ethical rationale for the minimum and maximum age of study participants and for limiting inclusion of any age group (e.g., children or older adults)*:
   Pregnant adults of all ages will be eligible for this study (18 years old or older). That said, recruitment distribution will likely depend on the age distribution of patients undergoing cesarean section delivery at the time.

b. *Include a description of expertise of the investigative team for working with individuals of the ages included, the appropriateness of the available facilities to accommodate individuals in the included age range, and how the age distribution of participants will contribute to a meaningful analysis relative to the purpose of the study:*
Adult patients of all ages are treated at Tufts Medical Center, so their care will not be compromised. Wider age distribution will allow for better generalizability of the findings in this study.

3. *Inclusion of women and minorities:*
   a. *Describe the projected distribution of subjects by sex/gender, race, and ethnicity. Provide the rationale for the selection in terms of the scientific objectives and proposed study design. Describe the proposed outreach programs for recruiting sex/gender, racial, and ethnic group members. If applicable, provide a reason for limiting inclusion of any group*:
   Subjects will be of female sex given the inherent study focus on pre-cesarean section parturients. Patient gender, racial and ethnic group distributions will match that of the populations typically treated in the Labor and Delivery Department at Tufts Medical Center.

4. *Inclusion of Populations affected by the Disease or Condition being studied:*
   Patients with anxiety before non-emergent cesarean section
   a. *Describe any population that is disproportionately being affected by the disease or condition being studied and any specific recruitment methods that would be used to promote their enrollment in the study*:
   There is insufficient evidence that specific groups or populations experience disproportionate anxiety while awaiting cesarean section, therefore there will be no specific recruitment methods for any such subpopulation(s).

D.4.4 Payment
Will subjects receive money, gifts, or any other incentive for participating in this study?
This does not include reimbursement for expenses, which is considered in the next section.
☐ Yes ☒ No

D.4.5 Reimbursement
Will subjects be reimbursed for their expenses, such as travel, parking, meals, or any other study related costs?
☐ Yes ☒ No

E. Costs to Subjects

Does the research involve any costs to subjects?
☐ Yes ☒ No
If **Yes**, describe any costs that subjects might be responsible for due to participation in the research: ☒N/A

F. Study Design

F.1 Study Timelines

1. *Describe the duration of an individual subject's participation in the study:* Study participation will range from 1-8 hours, depending on variable factors such as wait-time between study intervention and cesarean section surgery.
2. *Describe the duration anticipated to enroll all study subjects at the Tufts study site:* 3-4 months.
3. *Describe the estimated date for investigators to complete this study (complete primary analyses):* December 2023.

F.2 Procedures

1. *Summarize the research design and sequentially identify all procedures to be performed to accomplish the specific aims of the project. Clearly identify and distinguish procedures that are considered*

experimental, procedures that are performed exclusively for research purposes (including "extra" routine tests), and procedures that would occur regardless of the research (i.e., standard of care). Point out any procedures, situations, or materials that may be hazardous, and the precautions to be exercised to maintain subject safety:

- Participation begins upon review and completion of a written consent document and ends after completion of the final post-intervention anxiety survey. Participation duration will be around 3-4 hours on average but could be longer (up to 8 hours) depending on surgery timelines.
- Once consent is given, the study subjects will be asked to assess their anxiety level on a scale of 0-10, 0 being no anxiety at all. Additionally, they will be asked to complete 6 STAI questionnaire prompts to further assess their anxiety levels. If the score is 0, they will automatically be removed from the study (as per the exclusion criteria). If the score is greater than 0, a baseline heart rate and blood pressure will be recorded, and the participant will proceed to the study intervention.
- All study participants will be also initially asked to choose four songs of personal preference that they would enjoy listening to. These song choices will be written down on their pre-intervention screening questionnaire and later used if their pre-determined music selection falls into the "personal preference" study arm.
- If there are multiple support people present in the room, the participant will be asked to identify a maximum of one person to stay in the room for the study intervention.
- The study intervention includes listening to pre-selected music, randomized to selections either from Conrad, et al. or from their own preference list, for a pre-determined duration ranging from 1-30 minutes. This intervention is being performed exclusively for research purposes and is not part of the standard of care. The study subjects will listen to this music played from a speaker connected to an audio device, both supplied by the research team. The investigator and patient will collaborate on patient positioning (supine, semi-recumbent, seated upright, etc.) to optimize patient comfort during the study intervention. Active participation on the study subjects' part will be required to continually assess the volume of the music being played to avoid potential tympanic-membrane injury.
- Once the music play duration has lapsed, the study subject will be asked to then reassess their anxiety level on the same 1-10 scale as pre-music intervention. This reassessment will be performed at three event points: directly following completion of music duration, just prior to transport to the OR, and directly upon arrival in the OR. STAI questionnaire completion will be assessed only directly following completion of the intervention, not before transport to the OR or upon arrival in the OR. Heart rate and blood pressure measurements will be recorded at all three post-intervention assessments. After completion of the final post-music assessment, this will conclude the study subject's participation.
- Pre- and post-music anxiety scores will be recorded and correlated to the study subjects' assigned 3-digit codes.
- Once all 30 (or 33 maximum) subjects in each intervention group have undergone the study protocol, their pre- and post-anxiety data will be analyzed.

Please also describe the following concerning procedures:

a. *How individuals will be screened for eligibility. Specify screening that will take place prior to informed consent and screening that will take place after informed consent:*
   Patients will be screened for eligibility by the PI or Co-I and will be required to meet all inclusion criteria and none of the exclusion criteria. To do this, a brief chart review will be performed to assess age and ASA clinical status, and to ensure that daily anxiolytic medications are not taken at baseline. After informed consent, the first 0-10 anxiety rating and STAI questionnaire will be completed by the participant. If their anxiety score is rated as 0, then at that time they will be excluded from participating in the study.
b. *Procedures being performed to monitor subjects for safety or to minimize risks:*
   As stated above, the PI or Co-I will remain nearby to continually assess volume status of the music to prevent potential tympanic membrane injury.
c. *The source records that will be used to collect data about subjects. (Submit all surveys, scripts, and data collection forms.):*
   See attached data collection and anxiety-screening forms

2. *Is there a placebo control arm?*
   ☐ Yes ☒ No
3. *Describe the following concerning pregnancy testing and birth control:*
   a. *What type of pregnancy testing and how frequently will be conducted on women of reproductive potential. If testing will not be conducted provide the reason:*
   Pregnancy testing will not be conducted, as it would be redundant since only patients already admitted to the Tufts Medical Center Labor and Delivery Unit who are scheduled for cesarean section will be approached and recruited for this study.
   b. *What birth control methods **women** of reproductive potential will be instructed to use. If women will not be instructed about acceptable methods of birth control, clarify why:*
   Birth control methods will not be discussed as part of this study. These discussions will be left to be had between the patients and their OB/Gyn or primary care providers.
   c. *What birth control methods **men** of reproductive potential will be instructed to use. If men will not be instructed about acceptable methods of birth control, clarify why:*
   This study will only enroll participants of female sex. If female-sex-assigned-at-birth subjects identify their gender as male, their discussions surrounding birth control will be left to be had between them and their OB/Gyn or primary care providers.
4. *Describe the data that will be collected during the study and how the data will be obtained:*
   The data collected during this study will include patient age, race, ethnicity, height, weight, gestational age, gestational history, ASA status, blood pressure and heart rate measurements, and cesarean delivery type (scheduled vs. unscheduled). This data will be obtained through a combination of chart review, oral history taking from the participant, and physical measurement (for blood pressure and heart rate) by the investigator. Anxiety ratings on a 0-10 scale and an STAI scale will also be collected by the investigator.
   a. *If there are plans for long-term follow-up (once all research related procedures are complete), describe the data will be collected during this period:* ☒ N/A
5. *Specify which procedures, tests, visits, etc. described above are:*
   a. *Part of usual standard of care at Tufts:*
   Acquisition of heart rate and blood pressure measurements are part of the standard of care at Tufts Medical Center, as are the determinations of age, race, height, weight, ethnicity, gestational age, gestational history, and ASA status.
   b. *Performed solely for research purposes:*
   Anxiety ratings on the 0-10 scale and STAI scale will be performed solely for research purposes.
6. *For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures* ☒ N/A

F.3 Evaluations

Will you perform any laboratory tests for this study?
☐ Yes ☒ No

F.4 Collection, Storage, and Use of Human Biospecimens for Unspecified Future Research

(formerly referred to as "Tissue Banking")

Will biospecimens be collected and stored for unspecified future research?
☐ Yes ☒ No

G. Ethics and Protection of Human Subjects

G.1 Informed Consent Process

Will subjects be required to provide informed consent?
☒ Yes ☐ No
If **Yes**, respond to all of the following*:*

1. *Where the consent process will take place (e.g. a private clinic room):*
   The informed consent will be taken in-person in the pre-op area in a private room.
2. *Anticipated amount of time a potential subject will have to make a decision about participation in the study:*
   The patient is anticipated to decide within roughly 15 minutes. However, this is not a cutoff and it will be ensured that patients will not be coerced and will be given ample time to think about enrollment.
3. *Processes to ensure ongoing consent throughout the study:*
   The researcher will be present for the entirety of the study intervention and will be able to stop the intervention at any point if the patient wishes to discontinue their involvement. Patients will also be informed that they are able to withdraw from the study at any time.
4. *Role of each research team member involved in the informed consent process (Please note, in general, for studies designated by the IRB as greater than minimal risk, a physician PI or Co-I must perform the informed consent process with subjects. A study coordinator/clinical research associate may not consent subjects. A study coordinator/clinical research associate may assist with this process; however, the PI or Co-I should be present to discuss the study with the subject and answer questions, and the PI or Co-I should sign the ICF documenting that s/he has performed the informed consent process with the subject and the subject understands the study.):*
   Either the PI or Co-I will perform the consent process.
5. ☒ *Check to confirm you will follow "SOP: Informed Consent Process for Research (HRP-090)".*
6. ☒ *Check to confirm that Non-English speakers will be enrolled using interpreters and IRB approved Short Forms per the IRB's Short Form policy. If IRB approved Short Forms will not be used, describe which languages the consent will be fully translated into, who will conduct the consent interview, use of interpreters, use of IRB approved translated documents, etc.:*
7. *If non-English speakers are not eligible (excluded from enrollment) for this study, provide the ethical and scientific justification, including whether this would be equitable. For example, if non-English speakers are eligible for the study and could potentially benefit from participation, it would not be equitable to exclude them:* ☒N/A
8. ☒*Check to confirm you will follow "SOP: Written Documentation of Consent (HRP-091)". If* ***not****, describe how consent will be documented in writing:*
9. ☐*Check to confirm you will follow "SOP: Remote Consent Process (HRP-092)" if there is ever a situation where consent will* ***not*** *be obtained in person. If you will follow a different process if there is ever a situation where consent will* ***not*** *be obtained in person, describe:* ☒ N/A.

G.2 Waiver or Alteration of Consent Process

1. Is a waiver or alteration of the consent process being requested for this study?
   ☒ Yes ☐ No
   If **Yes**, respond to all of the following:
   a. *Provide the rationale for the waiver:*
      To ensure appropriate patient age and ASA physical status, and absence of use of anxiety medications daily at baseline, a pre-consent screening via brief chart review will be performed before approaching patients for recruitment.
   b. *How the waiver or consent alteration will* ***NOT*** *adversely affect the rights and welfare of subjects:*
      This alteration to the consent process will not affect the subjects' clinical care, nor will any PHI be recorded or kept before written patient consent is complete.
   c. *How the research could* ***NOT*** *practicably be carried out without the waiver or alteration:*
      Without this consent alteration, patient recruitment cannot be accurately directed towards candidates who meet inclusion criteria.
   d. *How, subjects will be provided with additional pertinent information after participation. If subjects will not be provided this information after participation, explain why:*
      After screening and verifying patients meet inclusion criteria, they will be approached by the investigator to receive the standardized consenting information for participation in the study. Subjects will not be provided additional information after participation in the study is complete, as this study is solely for research purposes and will have no impact on the subjects' clinical care.

2. Is a waiver of written documentation of consent being requested?

☐ Yes ☒ No

3. Is a waiver of the consent process being requested for parents for research involving children?

   ☐ Yes ☒ No

4. Is a waiver of the consent process for planned emergency research being requested?

   ☐ Yes ☒ No

G.3 Confidentiality

1. *State where the study records, both electronic and/or paper documents including signed ICFs/assent forms, will be retained during the study (state the location for original document plus any copies that are made, e.g., if a copy of the ICF will be retained in the subject's medical record):*
   All study-related materials, including ICFs and data collection forms, will be stored in the principal investigator's office. The ICFs will be kept in a separate filing area from the data collection forms. The principal investigator and co-investigators will have exclusive access to the forms. Electronic patient data will be held in Tufts CTSI REDCap. Data will be coded.
2. *If you are coding data with a key to identifiers, explain how you will keep the coded data and the key separate. (For example: storing them in two different locations, or using two different passwords):* The key for coded patient data will be created and kept in an Excel document stored in a secure cloud server separate from electronic patient data in REDCap.
   a. *State where study records will be retained when the study has been closed (long-term storage):*
      Records will be stored for 7 years after the study is closed with the IRB, as per IRB policy. Physical ICFs and data collection forms will be stored as detailed in G.3.1. Electronic data will be kept in Tufts CTSI REDCap with the exception of a coding key which will be stored as an Excel file in a secure cloud server. The coding key will be immediately destroyed once the required number of participants have been recruited and the data is compiled.
3. *State who, in addition to the research team, will have access to the study files, data, and/or specimens:*
   Only the research team will have access to the study files and data.
4. *In this study, will you be entering research data using a computer software application (on a computer or any other electronic device)?*

   ☒ Yes ☐ No

   If **Yes**, respond to the following:

   a. For **Tufts Medical Center** studies:
      Check to see if all software applications used in this study are already on the list of approved software. Please review the version type and/or described use-case of each application to confirm approved use. If the software you are using is not already on the list of approved software (or will not be used in accordance with the approval details on the list), you are required to complete this IT Security form so Tufts Medical Center can review the security of the software.

      ☐ *Check this box if the IT Security form has been completed and submitted.*

      ☒ *Check this box if you have confirmed that the software applications used in this study are already on the list of approved software (and will be used in accordance with the details on the list)*

      Please e-mail infosec@tuftsmedicalcenter.org with any questions about this institutional requirement.

5. *Will data (or specimens) be sent outside of Tufts Medical Center or Tufts University **and/or sent between Tufts Medical Center and Tufts University**?*

   ☐ Yes ☒ No

6. *Explain how data and/or specimens will be transported (e.g. fax, mail, delivery, email, etc.):*
   Data will be kept and transported by hand only by members of the investigator team. Electronic data will be accessed via secure internet and Tufts VPN usage with Tufts CTSI REDCap and Box cloud storage.
7. *If data and/or specimens will be coded, describe the coding mechanism in detail. Describe how the unique IDs (used to code the data) will be generated / assigned (sequential, random, other). If not sequential, explain how you will avoid duplicates:*

Each patient will be assigned a 3-digit numerical code. These codes will be from a randomly generated list of 66 codes (given the maximum target of 66 patients for the study) using an online randomizing tool, which will also separate these 66 values into two lists of 33 values (one for each treatment arm). A separate list of 66 values will be generated to randomize patients into one of the two treatment arms using the same online software. Patients will then be sequentially assigned their random 3-digit identifiers in the order of recruitment.

Note: The IDs used to code the data should not include initials, dates, or any identifiers.

8. *If there is a key to the code that matches the subjects' study identification number with their name, specify who, in addition to the research team, will have access to the key:*
   The key to the coded subject data will only be accessible to the research team and will be stored and handled in accordance with section G.3.1.
9. *Explain whether confidential genetic information will be collected from subjects:* ☒ N/A
10. *Explain whether audio/videotapes and/or photographs of subjects could potentially identify the study subject. If so, indicate who will have access to (be able to view) these item, in addition to the research team, and how long the videotapes or photographs will be retained for the study and what the plan is for their destruction:* ☒ N/A
11. ☒*Check to confirm that study records will be retained for the timeframe described in the record retention policy of the "SOP – Records Retention Timeframe – Investigators". If they will not, describe the record retention plan for this study:*
12. ☒*Check to confirm that you will follow the "Confidentiality and Data Security Guidelines for Electronic Research Data" for electronic data. If not, describe how your plan differs from these guidelines:*
13. *A Certificate of Confidentiality will be issued (for NIH studies) or obtained:* ☐Yes ☒N/A
    CoCs protect the privacy of research subjects by prohibiting disclosure of identifiable, sensitive research information to anyone not connected to the research except when the subject consents or in a few other specific situations. NIH funded researchers are automatically issued a CoC through their award. Other Department of Health and Human Services (HHS) agencies issue CoCs to researchers they fund. Researchers not funded by HHS can apply to NIH or the FDA as appropriate to request a CoC for HHS-mission relevant research, i.e., research involving collection of information that, if disclosed, could have adverse consequences for subjects or damage financial standing, employability, insurability, or reputation. For more information, refer to refer to the NIH website.

G.4 Screening Data Collection Form/Screening Log

This section specifically refers to data collected about potential subjects who are screened, but have not signed consent, for example potential subjects whose medical record is reviewed to see if they are potentially eligible, potential subjects who respond to a telephone screening call where the research team records information about the potential subject, etc. In this section "Screening Data / Screening Log" refers to any form of data collection on potential subjects who have not yet signed consent. For more information, refer to https://privacyruleandresearch.nih.gov/clin_research.asp.

Will a screening data collection form/screening log be used in this research study?

☐ Yes ☒ No

If **Yes**, respond to all of the following:

1. ☐ *Check to confirm you have submitted the Screening Data Collection Form / Screening Log to the IRB.*
2. *Review the following and provide information about the Screening Data / Screening Log and how it will be used (**check all that apply**):*
   a. ☐ *De-identified Screening Log will be provided to and/or viewed by the Study Sponsor (the log does not record any HIPAA identifiers or contain protected health information (PHI)).*
      i. *Explain how the Screening Log will be "distributed to" or viewed by the study Sponsor, i.e., how the Screening Log be e-mailed, sent to and /or viewed by the study Sponsor:*
   b. ☐ *Identifiable Screening Log that will **not** be distributed or viewed outside of the institution (although the Screening Log will record HIPAA identifiers, the Screening Log will **not** leave the institution.)*
      i. *Specify the identifiers that will be collected (e.g. date of admission or clinic visit, medical record #, and reason the person was not eligible for the study):*
   c. ☐ *Identifiable Screening Log that will be distributed or viewed outside of the institution.*

Consider whether these identifiers could be removed from the Screening Log. It might be possible to eliminate HIPAA identifiers or use a screened subject identifier code and maintain a separate key to the code so no PHI will leave the institution.
If it is necessary to include HIPAA identifiers in the screening log, address the following:

i. *The rationale for including HIPAA identifiers in the Screening Log:*
ii. *A plan for protecting the privacy and confidentiality of screened subjects. Screened subjects might or might not be enrolled in the research study, and since screened subjects will not have consented to the use of their PHI for research purposes, it is especially important to protect their privacy and confidentiality. The plan should include keeping identifiers to a minimum, and keeping the Screening Log in a secure location (password protected computer location only accessible by the research team or a locked file cabinet in a locked office, only accessible by the research team):*

Note: A Screening Data Collection Form / Screening Log that contains identifiers and/or PHI must NOT be sent to the study Sponsor UNLESS the IRB has granted a waiver of consent/authorization for this component of the study (or unless the investigator has obtained IRB approved consent and research authorization from each study subject whose name is on the log.)

G.5 Provisions to Protect the Privacy Interests of Subjects

1. *Describe the steps that will be taken to protect subjects' privacy interests (e.g. ensuring that discussion of the study will take place in a private area where subjects cannot be overheard):*
   Initial discussion of the study and informed consent will be held in a private area of the pre-op unit, either at the patients' bedside or in a private room, depending on individual circumstances.
2. *Describe the steps that will be taken to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might or might not experience in response to questions, examinations, and procedures (e.g. ensuring that subjects are comfortable with the research team members performing the study procedures):*
   The research subjects will be assured that their interaction with any member of the research team, as well as the information they share, is optional and confidential.

G.6 Provisions to Monitor the Study to Ensure the Safety of Subjects

1. *Describe the plan to periodically evaluate the data regarding both harms and benefits to assess subject safety as follows:*
   a. *The data that will be reviewed, including safety data, untoward events, and efficacy data:*
      Safety information and adverse events that will be collected includes patient agitation and ear injury/hearing issues.
   b. *Who will review the data:*
      For the purposes of this study, the principal investigator will periodically evaluate the safety data and assess the risks and benefits to assess subject safety.
   c. *How the safety information will be obtained and documented (e.g., case report forms, by telephone calls with participants, printouts of laboratory results, etc.):*
      The standard of care at Tufts Medical Center is to collect safety information on all patients undergoing surgery through an established computerized system called Anesthesia Touch. This study will also utilize this system to monitor research safety information.
   d. *The frequency of data collection, including when safety data collection starts:*
      Information will be obtained after subject consent with frequency of data collection aligning with the standard of care at Tufts Medical Center.
   e. *The frequency or periodicity of review of cumulative data:*
      Standard safety data review intervals per Tufts Medical Center protocols.
   f. *The statistical tests for analyzing the safety data to determine whether harm is occurring:*
      The statistical tests that will be performed on the safety data to determine whether harm is occurring will include a chi-squared test, to compare proportions between groups.
   g. *Any conditions that trigger an immediate suspension of the research or other action for the research:*
      In the unlikely event of serious patient harm or an unreasonable level of interference with the standard of care at Tufts Medical Center.

2. *Describe the entity responsible for monitoring the data, and their respective roles (e.g., the investigators, the research sponsor, a coordinating or statistical center, an independent medical monitor, a Data and Safety Monitoring Board (DSMB) /Data Monitoring Committee (DMC), and/or some other entity, and the timeframe for reporting events to this entity:*
   As mentioned above, the principal investigator will periodically evaluate the safety data and assess the risks and benefits to assess subject safety.
3. *A copy of the DSMB/DMC Charter if the study is enclosed with the submission:* ☐Yes ☒N/A

G.7 Subject Populations & Vulnerable Populations

1. Can or will pregnant women be enrolled?
   ☒ Yes ☐ No
   If **Yes**, respond to all of the following:
   a. *Describe any preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, that have been conducted that provide data for assessing potential risks to pregnant women and fetuses:*
      There are no additional known potential risks to pregnant individuals or their fetuses other than those described in section B.2.
   b. *Are there any risk to the fetus from the study interventions or procedures? If yes, describe:* or ☒No*, there are no risks to the fetus from the study interventions or procedures.*
   c. *Do the study interventions or procedures hold out the prospect of direct benefit for the woman or the fetus? If yes, describe:*
      Potential benefits for the pregnant individual are as described in section B.3. Benefits to the fetus are unknown, though may occur indirectly from benefits to the pregnant individual.
   d. *If there is no prospect of benefit to the fetus, clarify whether the risk to the fetus is NOT greater than Minimal Risk, and whether the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means:* ☒ N/A
   e. *The biomedical knowledge that is expected to result from this research for this population:*
      Potential anxiety-reducing effects of listening to music before non-emergent cesarean section.
   f. *How any risk of this research is the least possible for achieving the objectives of the research:*
      No increased risk over the standard of care.
   g. *How mothers providing consent are informed of the reasonably foreseeable impact of the research on the fetus or neonate:*
      Standardized verbiage that is consistent with the general consenting process for all potential participants.
   h. ☒*Check to confirm that no inducements, monetary or otherwise, will be offered to terminate a pregnancy and that in the case of a fetus, the fetus is not the subject of a planned abortion.*
   i. ☒*Check to confirm that individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy or in determining the viability of a neonate.*

2. Can or will the research involve neonates of uncertain viability or non-viable neonates?
   ☐ Yes ☒ No

3. Can or will subjects who are not yet adults (neonates, children, teenagers) be enrolled?
   ☐ Yes ☒ No

4. Can or will minors who are:
   i) married, widowed, divorced; or
   ii) the parent of a child; or
   iii) a member of any of the armed forces; or
   iv) pregnant or believes herself to be pregnant; or
   v) living separate and apart from his/her parent or legal guardian, and is managing his/her own financial affairs

   be approached for study participation for either themselves or their child?

☐ Yes ☒ No

5. Can or will wards of the state and/or children at risk of becoming wards of the state be enrolled (this includes foster children or any child that is in state custody)?
   ☐ Yes ☒ No

6. Can or will cognitively impaired adults (adults with impaired-decision making capacity) or adults who may lose the capacity to consent be enrolled?
   ☐ Yes ☒ No

7. Can or will prisoners be enrolled?
   ☐ Yes ☒ No

8. Can or will students and/or employees be **targeted** for enrollment in this research?
   ☐ Yes ☒ No

9. Transgender Subjects: Are you recording sex or gender for your study?
   ☐ Yes ☒ No

H. Adverse Event Monitoring

H.1 Definitions

Define adverse events (AEs), serious adverse events (SAEs), and unanticipated problems for your study:
☒ **N/A**, no physical risks are anticipated with this research study, and we will use the definitions in the Tufts Health Sciences IRB's **Reportable New Information policy**.

H.2 Reporting Procedures

1. *Describe the protocol-specific reporting procedures, including who will be responsible for each step (e.g., PI, Data Coordinating Center, Medical Monitor), which forms should be completed, timeframes for reporting, how reports will be distributed, and what follow-up is required:*

Patients are routinely monitored for development of adverse events as part of their anesthetic care. This occurs on a continuous basis from the moment the anesthetic is administered until the moment the patient is discharged home. Monitoring of patients during the study intervention prior to anesthetic care will be done by the co-investigator, Tristan Fong, who will coordinate with clinical staff to ensure patient safety. Specifically, the co-investigator will monitor for participant ear injury or agitation. A computerized system exists which alerts clinicians to the development of some adverse effects, which are recorded in the medical record. The co-investigator, will be alerted in these situations and all adverse events will be forwarded to the principal investigator. Clinicians are alerted to events immediately as they occur. Clinical staff are trained to deal with such events. The co-investigator, will be responsible for contacting the principal investigator to report the occurrence of adverse events. The principal investigator will then complete any necessary safety forms, including the Anesthesia Department's Quality Assurance form. The events will be reported within 24 hours to the QI director and the chairman of the department.

H.3 Reportable New Information

☒*Check to confirm that reportable new information will be reported to the IRB per the Tufts Health Sciences IRB's Reportable New Information policy. If your reporting plan to the IRB differs from the IRB's policies, please describe it in detail or specify where this information is in the protocol:*

I. Statistical Considerations

I.1 Study Endpoints

1. *Describe the primary and secondary study endpoints:*
   Primary endpoint: determination of the 95th percentile effective dose of music duration for anxiety reduction.

Secondary endpoint: compare the 95th percentile effective dose of music duration for anxiety reduction between the Mozart and personal-preference intervention arms.
Secondary endpoint: analyze and compare pre-and post-intervention heart rate and blood pressure measurements.
Exploratory endpoint: analyze and compare anxiety ratings at the three post-intervention event-point measurements.
Exploratory endpoint: analyze and compare anxiety ratings using the 0-10 scale with the STAI questionnaire.

2. *Describe any primary or secondary safety endpoints:* ☒ **N/A**

I.2 Sample Size Justification Statistical Analyses

1. *Describe the statistical analyses that will be performed for this study:*
   Statistical analysis to determine the ED_{95} will be conducted using the methods described by Pace, Stylianou, and Warltier (8).
2. *Provide a sample size justification:*
   The plan is to enroll up to 33 subjects per treatment group (up to 66 total), with a minimum goal of 30 per group (60 total). This is based on prior studies that suggest 20-40 study subjects are required for adequate statistical power in sequential allocation biased coin design studies, and we expect a ~10% attrition rate. A goal of 33 subjects per group will thus likely turn into an estimated sample size of 30 after attrition, which falls well within the acceptable sample size range.

I.3 Number of Subjects

1. *Specify the number of subjects to be enrolled in total across all sites:* ☒ N/A this is not a multicenter study.
2. *Specify the number of subjects to be enrolled at the Tufts site(s)[1]. Subjects who sign an ICF are considered "enrolled". For studies that have a separate screening ICF, this number is the number of subjects who sign a screening ICF:*
   a. *Specify the number of subjects expected to be enrolled at the Tufts site (i.e. sign the screening or study ICF):*
      Up to 66 subjects.
   b. *Estimate the number of subjects needed to complete the study at the Tufts site:* 60 subjects
   c. *Provide the rationale for enrolling this number of subjects at the Tufts site:*
      As mentioned above, previous sequential allocation biased coin design studies suggest that 20-40 subjects are required for adequate statistical power.
   d. *If a large number of withdrawals and/or dropouts is expected, explain why:*
      Withdrawal/dropout rate is expected to be roughly 10%.

I.4 Data Management

1. *Describe the data analysis plan, including descriptions of the data:*
   Data collection forms and an excel spreadsheet with all the analyzed data will be stored during the study period in the PI's private locked office and/or cloud account, where access is exclusive to the research team.
2. *Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission:*
   As mentioned above, physical data will remain in a locked private office to which access is restricted to research team members only. To separate and distinguish ICFs between this study and the previous, similar study (IRB STUDY #00001496), the physical forms will be kept in a folder/binder of a different color with clear labels. All electronic data will be held in a password protected, encrypted account within Tufts CTSI REDCap.Data will be coded. Each participant will be assigned a unique randomly generated three-digit number that will be linked with their medical record number on the key. Duplicates will be

[1] [1] If Tufts IRB is requested to be the Single IRB of Record for external sites (as per section **Error! Reference source not found.**), include all sites in these enrollment numbers.

prevented via software functions in the original generation of three-digit numbers. No part of the patient's information or MRN will be used to generate the randomly generated number. Once this unique, randomly generated 3-digit number has been assigned, all coded information will utilize this unique identification number. The 3-digit number will replace the patient's MRN on coded data. The only place where the patient's MRN and their unique 3-digit identification number will coexist is on the physical key that will be kept in the PI's locked office as detailed in section G.3.1. Coded data will be stored with a Tufts CTSI REDCap account. Records will be stored for 7 years after the study is closed with the IRB, per IRB policy. The key will be immediately destroyed once the required number of participants have been recruited and the data compiled.

3. *Describe any procedures that will be used for quality control of collected data:* continual collaboration between PI and Co-I on data collection and handling.

I.5 Randomization

Will subjects be randomized?

☒ Yes ☐ No

If **Yes** respond to all of the following:

1. *Describe the randomization procedures, including the ratio of subjects randomized to each study arm:* Randomization will be performed to assign study subjects to one of the two intervention groups using "randomizer.org" or a similar online program. This will also assign subjects to a random number to help blind later analysis. Ratio of subjects should be 50/50 in each study arm. Determination of music dosage (the duration of music played for participant listening) will be done using the biased coin up-down sequential allocation algorithm, which is not random.
2. *Describe the blinding procedures:* The PI or Co-I administering the study intervention will be unable to remain blind to the study intervention given the inherent nature of the protocol. This will also be true of the participants, as the intervention treatment arms will likely be easily distinguishable. However, the participants will remain blind to their randomized intervention group until the intervention begins. Given the nature of clinical workflow surrounding cesarean sections, blinding of anxiety level assessment will also not be feasible.

J. Drugs or Devices

1. Will the research involve drugs?
   ☐ Yes ☒ No

2. Will the research involve devices?
   ☐ Yes ☒ No

K. Study Administration

K.1 Setting

1. *Describe the sites / locations where your research team will conduct the research, **including recruitment activities**:*
   a. *Tufts MC / Tufts University locations (specify which facility/clinic if applicable):*
      Tufts Medical Center, Labor and Delivery Unit

K.2 Registration

1. *Describe the steps the research team will take to ensure that a subject is appropriately enrolled or registered in the study prior to receiving any study intervention (e.g. describe and submit any protocol eligibility checklist that will be used, specify who on the research team will confirm eligibility and that consent was documented, etc.):*
   The Co-I will ensure subject eligibility, perform the informed consent process, and subsequently perform the study protocol. Eligibility criteria will be consistent with those outlined above in Section D. Thus, there will be no risk of miscommunication between the informed consent process and the study interventions.

K.3 Resources Available

1. *Describe the roles/tasks of each research team member here (or alternatively, you may submit any current Delegation of Authority Log you may have which already has this information completed):*
   The research team is composed of the following members:
   - Principal investigator: Dan Drzymalski, MD Assistant professor of Anesthesiology. Primary investigator responsible for the preparation, design, conduct, and administration of the study.
   - Co-investigator: Tristan Fong, MS4 and Tufts CTS Research Fellow. Responsible for writing the study's protocol under the PI guidance, obtaining the informed consent, managing data collection, and coding and coordinating various sectors in the study.
   - Tufts Medical Center facilities will provide medical resources that might be needed by study subjects.
2. *Describe the qualifications (e.g., training, experience) of the PI and research team to perform their roles. Provide enough information for the IRB to determine the PI and research team are qualified to conduct the proposed research. Alternatively, you can submit the current CVs for the research team instead:*
   - Please see attached CVs
3. *Describe the coverage plan to address any issues (including subject safety issues) that occur while the PI is away and/or unavailable. The research team member designated to serve as the acting PI in the PI's absence should have similar training and expertise as the PI:*
   In the absence of the PI, the Co-I will perform duties as able but may temporarily halt research activity until the PI's return if necessary. This is due to the fact that the Co-I has some similar training to that of the PI but not to the same extent (less overall research and clinical experience). If patient safety issues arise while the PI is absent, the Co-I would temporarily halt research activity until the PI's return.
4. *Describe the process to ensure the research team members have adequate oversight and are adequately trained regarding the protocol, study procedures, and their roles and responsibilities:*
   There will only be two research team members, the PI and the Co-I, both of whom will be heavily involved and educated on the study protocol, procedures, and their respective roles and responsibilities.
5. *Medical or psychological resources that subjects might need, such as for emergencies or medical issues, are available for the study:* ☒Yes ☐ N/A

K.4 IRB Review

1. ☒*Check to confirm that an appropriate IRB, registered with the OHRP, will review and approve this study.*
2. ☒*Check to confirm that any amendments to the protocol or informed consent documents will be reviewed and approved by the IRB prior to use, unless required to eliminate an apparent immediate hazard to subjects.*

K.5 Multi-Site Research

Is this a multi-site study where Tufts IRB is requested to be the Single IRB of record for non-Tufts sites or collaborators, AND/OR where Tufts is the sponsor, primary grant recipient, or coordinating site?:

☐ Yes ☒ No

K.6 Community-Based Participatory Research

Can or will this study involve community-based participatory research?

☐ Yes ☒ No

K.7 Sharing Results with Subjects

Will results (overall study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) be shared with subjects or others (e.g., the subject's primary care physician or the subject's treating physician)?

☐ Yes ☒ No

L. Nursing Involvement

Will your study require the involvement of Nursing

☒ Yes ☐ No

If **Yes**, respond to all of the following:

1. Describe the research procedures Nursing will do for this study above and beyond their usual nursing practice:
   Nursing may assist in acquiring vitals for this study if it coincides with their usual nursing practices. Nursing is otherwise only asked to help coordinate clinical care with the research procedures that will be carried out by investigators.
2. Describe what measures have been taken to notify nursing, plan for nurse education, and mitigate the increase in nursing responsibilities:
   Nursing staff has been notified by email of our upcoming research plans.

M. References

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3) Dixon WJ, Mood AM. A method for obtaining and analyzing sensitivity data. J Am Stat Assoc 1948; 43:109-26. https://doi.org/10.2307/2280071.

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6) Jia N, Braun TM. The adaptive accelerated biased coin design for phase I clinical trials. J Appl Stat 2011; 38: 2911–2924. https://doi.org/10.1080/02664763.2011.573540.

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