STUDY PROTOCOL

Audiovisual interactive games to improve pediatric patient cooperation with induction of anesthesia and alleviate perioperative anxiety

Protocol Number

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Version 6

Synopsis

Purpose: To explore the utility of interactive audiovisual distraction games (AVGs) in alleviating perioperative anxiety in pediatric patients.

Objectives:

.1 To determine if AVGs improve perioperative anxiety in pediatric patients undergoing non-emergent surgery.

.2 To determine if AVGs result in a lower score on the Induction Compliance Checklist than control for pediatric patients.

.3 To assess if implementation of AVGs in the perioperative setting affects surgical and discharge timepoints and how operating room staff view the intervention.

.4 To explore if implementation of AVGs affects caretaker satisfaction and/or perioperative anxiety.

.5 To assess if implementation of AVG results in different perioperative administration of sedating pharmacologic agents by anesthesia providers.

Study Population:

Pediatric patients aged 4 to 14 years old undergoing non-emergent surgery requiring general anesthesia who choose inhalational induction for non-emergent surgery/procedures (including ENT, ophthalmology, orthopedics, dentistry, gastrointestinal, general surgery) at YNHCH. Caretakers of enrolled patients who elect to be present at induction will be eligible for inclusion. Any healthcare professional in an operating room where the study intervention is being utilized is eligible for inclusion.

Number of Participants:

Up to 178 subjects. 74 pediatric patients, up to 74 pediatric patient caretakers, 30 healthcare professionals. In calculating the sample size, we assumed that the randomization is successful and the mean difference (SD) mYPAS is 5.1 (4.5) for the standard care group at induction including standard child life services (ie. tablet, distraction techniques, etc) (Rodriguez et al, 2019). We assumed an intervention group mYPAS difference of 1.8 based on similar studies evaluating perioperative anxiety changes with use of handheld and VR games (Stewart, et al, 2019, Patel et al, 2006, Dwairej et al 2020, Marechal et al 2017). At a significance level of 0.05 and a power of 80%, it was determined that 29 subjects would be needed in each group. We increased this to account for dropout and dissimilarity of utilized studies, reaching a final target sample size of 37 per group (29/0.8 = 37).

Study Design:

This study is a prospective parallel randomized controlled trial. Due to the inherent intervention, it is difficult to blind the researchers or subjects for the entirety of the study. A subset of patients will be evaluated for the primary outcome in an attempted blinded fashion, using a video recording, as detailed below. The study uses multiple different evaluation tools, including observational and direct reports.

Study Duration:

Each subject will be actively involved in the study only for the duration of their perioperative surgery, specifically preoperative (consenting, baseline measures), early intraoperative periods, and post-operative (time in PACU). There will only be direct interaction with the study team during preoperative and induction of anesthesia; other data will be extracted from the electronic medical record. We expect the interaction duration to be approximately 1 to 2 hours for most patients. The study will last approximately 4 months to achieve the methods and accrue the desired sample size.

Outcome Variables:

.6 Modified Yale Perioperative Anxiety Score (mYPAS)[3]

.6.1 The mYPAS is the gold standard for measuring pediatric perioperative anxiety. It is an observational-based 22-item instrument divided into five categories: activity, emotional expressivity, state of arousal, vocalization, and use of parents. The score ranges from 23 to 100, higher scores suggest higher levels of anxiety. It was developed at Yale University. This will be used for patients only. The primary outcome measure will be the difference between the score at induction from the score at baseline.

.7 Short State Anxiety Inventory (STAI)[4]

.7.1 The STAI is a 6-item validated measure of anxiety in subjects aged 5 years and older. Subjects are asked to rate how they felt on a 4-point Likert scale in relation to feeling calm, tense, upset, relaxed, content, or worried. A score of 1 correlates to "not at all" and a score of 4 correlates to "very much." The final score is the sum of recorded values and ranges from 6 to 24, higher scores suggest higher levels of anxiety. This will be used for caretakers only.

.8 Health Professional Survey[5]

.8.1 This survey will obtain health care providers' opinions on the usefulness of AVG in reducing anxiety and the feasibility of such a program in a health care setting. Operating room staff that work in the unit where the study is occurring (Pediatric Operating Room West Pavilion 3, YNHCH) will be asked to enroll. Eligible individuals include: physicians, physician assistants/advanced practice providers, nurses, and other operating room staff.

.9 Induction Compliance Checklist (ICC)[6]

.9.1 The ICC is a validated 10-item observer-rated checklist of behaviors that interfere with induction of anesthesia. The ICC score is the sum of the items checked. A perfect induction (the child does not exhibit negative behaviors,

fear, or anxiety) is scored as 0, whereas the worst induction is a score of 9. A score greater than six is considered "poor" compliance.
Locations/Facilities: **.10 Yale New Haven Children's Hospital (YNHCH), New Haven, CT, USA: 3rd Floor, West and South Pavilion Operating Rooms and Perioperative Spaces**

Abbreviations

Abbreviation	Explanation
AVG	**Audiovisual games**
BERT	**Bedside Entertainment and Relaxation Theatre**
ICC	**Induction compliance checklist**
mYPAS	**Modified Yale Perioperative Scale**
OR	**Operating Room**
PACU	**Post-anesthesia care unit**
STAI	**Short state anxiety inventory**
VR	**Virtual Reality**
YNHH	**Yale New Haven Hospital**
YNHCH	**Yale New Haven Children's Hospital**

Glossary of Terms

Glossary	Explanation
Induction	**The initiation of the anesthetic period where the anesthesia provider administers medication to change the state of the patient from awake to less than awake.**

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Protocol Revision History

Version Date	Summary of Substantial Changes
5/19/2023	Initial submission
7/9/2023 (response to 7/7/23 comments)	Sample size calculation adjusted to 39 per group based on reviewer comments. Explicit operationally defined stopping rules for study at interim analysis defined. Standard of care further elaborated.
8/20/2023	Protocol edited per IRB reviewer recommendations. Clarifications made on study design, including: objective detail, data extraction, intervention mechanism, and survey timing.
10/6/2023	Specified that the REDCap platform that will be used is not validated for 21 CFR Part 11 compliance per request of Research Project Data Triage Team.
10/13/2023	Further specified that consent from patients and caretakers will be obtained in paper form.
12/1/2023	Changed video recording from the first 20 patients enrolled to all patients enrolled. Changed the surveying conditions for healthcare professionals.

Background

.1 Background

Surgery is an incredibly stressful and emotion-provoking time for all patients, especially those in the pediatric world. Pediatric anxiety upon induction of anesthesia is widely prevalent and can present in a wide range of behaviors, such as crying, trembling, and restlessness. Such behaviors can lead to negative patient psychological impact, hindrance to induction of anesthesia, and increased surgical morbidity.[7] Certain patient characteristics are known to be associated with higher levels of preoperative anxiety. These include: younger children, female gender, prior negative hospital experiences, prior anesthetic exposure, among others.[8] Understandingly, parents also exhibit anxiety in the perioperative period when their children are undergoing surgery, and increased parental anxiety is associated with increased pediatric patient anxiety in such circumstances.[8]

Historically, various techniques have been used to alleviate pediatric perioperative anxiety, including: premedication administration, presence of parent in the operating room upon induction of anesthesia, distraction therapy, scent administration to face mask, clowns, magicians, and many others. Audiovisual distraction, including virtual reality (VR) and interactive gaming, has been proposed as an additional modality to alleviate pediatric patient perioperative anxiety.

.2 Prior Experience

VR with use of a headset worn over the patients' eyes during induction of anesthesia has been shown to reduce pediatric perioperative anxiety in a prospective randomized controlled trial.[1] Patients engaged in a game designed for pediatric perioperative use featuring an animated animal character moving through a landscape. The game was not directly interactive in nature. In the same study, randomization to VR did not alter parental anxiety, parental satisfaction, or pediatric induction compliance.

Our department has recently obtained a set of previously developed AVGs (developed at Stanford University) tailored to assist with induction of anesthesia in children. This includes a projector that clips to the operating table and a projector screen that sits at the end of the bed – the equipment is commercially available and has been piloted at YNHCH since June 2022 and is called the *Bedside Entertainment and Relaxation Theatre (BERT)*[10]. The equipment has been used over this time in a minority of patients. It has been postulated that AVG utilization may preferentially lead to improved perioperative outcomes, such as: reduced patient/parent perioperative anxiety, shorter operating room duration, and time to discharge, among other measures. The games used are interactive in nature – no prior controlled evaluation has been conducted that evaluates the use of interactive audiovisual games in alleviating perioperative patient anxiety and improving the induction experience.

Rationale/Significance

.1 Rationale and Study Significance

Pediatric anxiety upon induction of anesthesia is widely prevalent and can lead to negative patient psychological impact and hindrance to induction of anesthesia. Studies have shown that more than 60% of children display anxiety at induction[9] and more than 30% of children ultimately resist anesthesiologists during induction[7].

Historically, various techniques have been used to alleviate pediatric perioperative anxiety, including: premedication administration, presence of parent in the operating room upon induction of anesthesia, distraction therapy, scent administration to face mask, among others.

Audiovisual distraction, including virtual reality (VR) and interactive gaming, has been proposed as a modality to alleviate pediatric patient perioperative anxiety. New interactive audiovisual distraction games have been developed by Stanford University. They have been noted to be highly effective, but they have yet to be tested in a controlled manner. We seek to address that gap in knowledge with this study.

.2 Risks

This is a minimal risk study, as the intervention has been used as a standard-of-care at YNHCH (more than 1 year) and at other children's hospitals for excess of three years. However, minimal risks are still present.

There is a slight risk of physical injury to the patient if the patient were to shift and hit their head against the AVG equipment though this has not been seen in our experience and this risk is roughly equivalent to the risk of injury from other standard operating room equipment. Additionally, there is risk for psychological distress if the contents of the games (dragons, batman, etc) are distressing to the child in the setting of an already stressful stimulus (surgery). There is risk of breach of confidentiality though all records will be stored in password-protected computers/iphones/online software that is licensed to Yale University for use in research (REDCap).

The potential benefits of this study outweigh these risks in our opinion, as the intervention of investigation has potential to notably improve patient and parent anxiety and other measures – this study may help others to learn about these benefits and either integrate the system under investigation and/or create their own. The study may also offer avenues by which we can improve the current intervention.

.3 Anticipated Benefits: This study can benefit subjects (patients and caretakers) by improving their perioperative anxiety and distress. It may also benefit patients by decreasing their time in the hospital and operating room. This study also has potential to benefit other patients should this therapy be seen to be effective. We believe that the therapy is likely to be seen as effective and anticipate publishing results to share with others.

Study Purpose and Objectives

.1 Purpose

The main purpose of this study is to evaluate the effects of interactive audiovisual games at improving pediatric perioperative anxiety and compliance with inhalational induction. This study can improve the perioperative experience for pediatric patients and their families. It may also influence which tools are used to improve pediatric patient anxiety and lead to improvement of currently used tools.

.2 Hypothesis

OBJ **Primary Hypothesis:** The mYPAS score difference from preoperative to induction time points will be significantly decreased (decreased relative anxiety) for the AVG group as compared with standard of care.

Secondary key questions:

1. Does AVG usage improve inhalational induction compliance?
2. Does AVG usage alleviate caretaker perioperative anxiety?
3. Does AVG usage on induction improve operating room and PACU time metrics?
4. Does AVG usage alter pharmacologic usage?
5. Does AVG usage affect perioperative flow and how is it perceived by perioperative staff?

.3 Objectives

Primary Objective

The primary objective of this study is to determine whether interactive audiovisual games reduce perioperative pediatric anxiety in patients aged 4 to 14 years old undergoing non-emergent surgery at YNHCH who elect inhalational induction.

Secondary Objective(s)

The secondary objectives of this study are to evaluate how interactive audiovisual games:

1. Affect pediatric patient induction compliance
2. Affect caretaker state anxiety associated with surgery (if caretaker is present on induction)
3. Influences operating room and hospital stay times
4. Alters perioperative pharmacologic administration
5. Are perceived by perioperative staff

Study Design

Study framework: Prospective, parallel assignment, quantitative randomized controlled trial

Intervention: Audiovisual interactive games[10]

Intervention Description[1]: The audiovisual interactive gaming system used in this study is projected via the Bedside Entertainment and Relaxation Theatre (BERT), developed at Stanford University[10] and utilized at YNHCH for more than 10 months. The interactive games were built to be used with the BERT platform. Upon entering the operating room, a plastic projection screen will have already been placed at the foot of the operating table by the study team and the game will already be displayed on the screen via a projector mounted to the operating table. Several games will be offered per available on the BERT system, including: “Sevo the Dragon” and others. The patient will be given verbal instructions for interacting with the game as an induction mask is placed over their face by the anesthesia provider and the game will commence as does induction with inhalational anesthesia per standard of care. If applicable, the subjects’ caretaker will be present and may help hold the mask or interact with the patient in another desired manner. The observer administering the quantitative scales will be observing in this process and interacting with the individuals present if indicated (ie. asked by clinical team to help in process).

Quantitative Measures Timing (see “Outcome Variables” for description of scales):

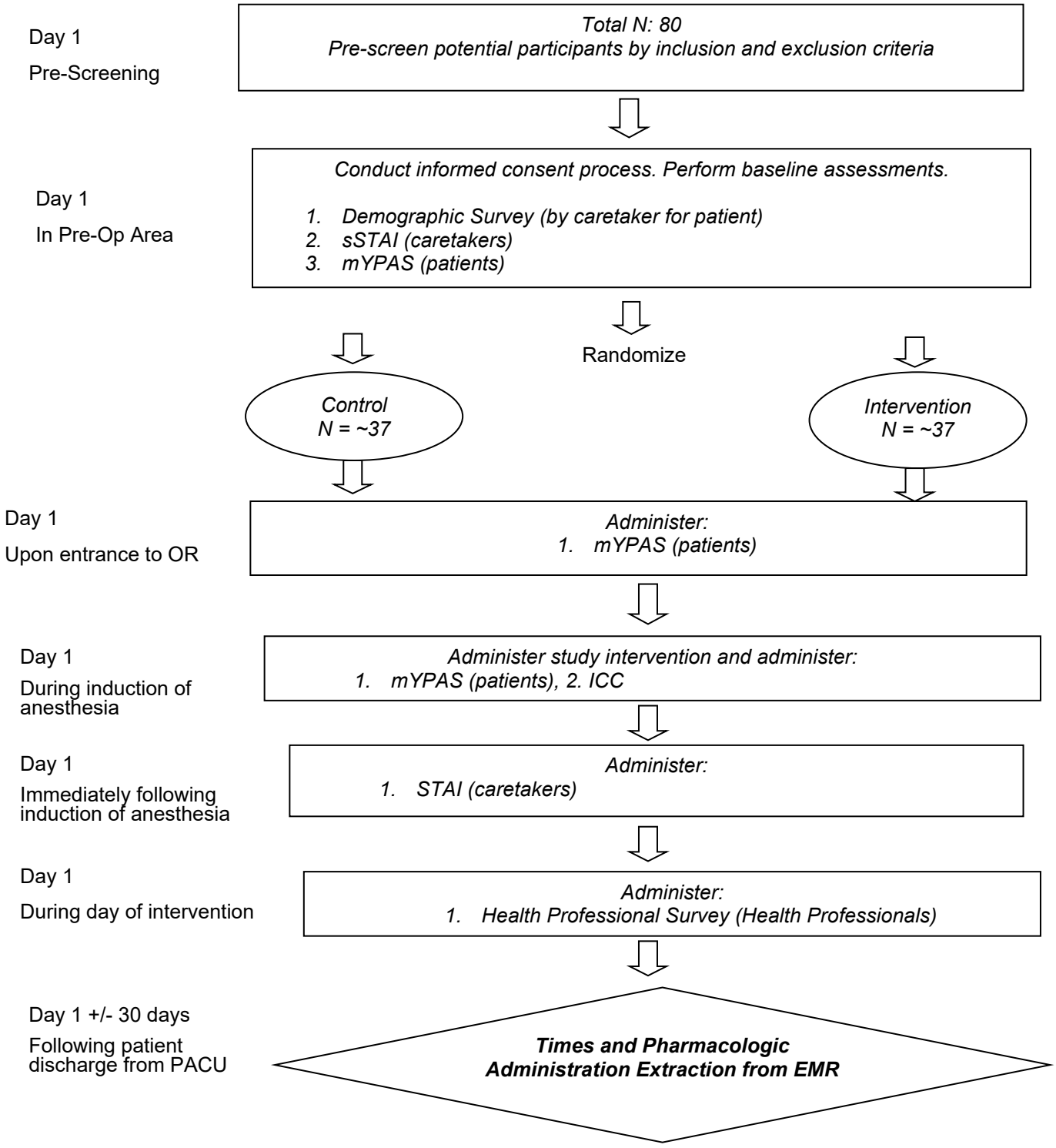
Preoperative administration (not in operating room): demographic survey, mYPAS (patient), STAI (caretaker)

Upon entering operating room: mYPAS (patient)

Upon initiation of induction in operating room: mYPAS (patient, score will be taken immediately after placement of mask), ICC

Upon completion of induction: STAI (parent; out of operating room), Health Professional Survey

Flow Diagram (patients and caretakers)



.1 Study Duration

We expect this study to last approximately one year. We anticipate that subject recruitment will last for four months with expected initiation Summer 2023. Individual subjects will be involved only during the day of surgery in the preoperative period and early intraoperative period (until induction is complete), a total time of roughly 2 hours (anticipated range 1 hour to 4 hours). Other metrics will be extracted from the electronic medical record after the patient's surgery. We anticipate that the data analysis and publication period may take an additional 8 months following data collection.

.2 Outcome Variables/Endpoints

.2.1 Primary Outcome Variables/Endpoints

i. mYPAS score change from preoperative to induction. The mYPAS is the gold standard for measuring pediatric perioperative anxiety. It is an observational 22-item instrument divided into five categories: activity, emotional expressivity, state of arousal, vocalization, and use of parents. The score ranges from 23 to 100, higher scores suggest higher levels of anxiety. A single observer (HP) will document the score at preoperative, introduction to the operating room, and induction of anesthesia.

.2.2 Secondary and Exploratory Outcome Variables/Endpoints (if applicable)

i. Short State Anxiety Inventory (STAI)

a. The STAI is a 6-item validated measure of anxiety in subjects aged 5 years and older. This self-report tool will evaluate parent state anxiety preoperatively and post-induction. It will help determine if the intervention improves parent anxiety. This was chosen because it is short, easy to administer, and highly validated. It will be used with caretakers and the difference between baseline and post-induction will be the outcome.

ii. Health Professional Survey Score

a. This survey will obtain health care providers' opinions on the usefulness of AVG in reducing anxiety and the feasibility of such a program in a health care setting. This will help us determine if the program is supported by OR staff and their thoughts regarding it, potentially leading to improvements.

iii. Induction Compliance Checklist (ICC)

1. The ICC is a validated 10-item observer-rated checklist of behaviors that interfere with induction of anesthesia. This tool will be used to evaluate pediatric patient compliance with induction. It was chosen because it is a simple observation-based tool that has been validated and is easy to administer.

Absolute scores will be the outcome measures used. A single observer (HP) will document the score at induction of anesthesia.

Study Participants

.1 Study Population

Pediatric patients aged 4 to 14 years old undergoing non-emergent surgery requiring general anesthesia who choose inhalational induction with certain operations (including ENT, ophthalmology, orthopedics, dentistry, gastrointestinal, general surgery) at YNHCH. Caretakers of enrolled patients who elect to be present at induction will be eligible for inclusion. Any healthcare professional in an operating room where the study intervention is being utilized is eligible for inclusion.

.1 Number of Participants

Up to 178 subjects. 74 pediatric patients, up to 74 pediatric patient caretakers, 30 healthcare professionals. We anticipate screening approximately 100 patients and enrolling 74. We anticipate screening 74 caretakers (parents/guardians/legally authorized individual of patients enrolled) and enrolling up to 74 of them.

.2 Eligibility Criteria

Eligibility will be determined by Co-Investigators who will screen all subjects and enroll. Vulnerable populations include children who must be included for this study, as the intervention under investigation was designed to benefit children and is being investigated as such.

To be eligible for inclusion in the study, an individual patient must meet all of the following criteria:

- 4 to 14 years of age
- Undergoing non-emergent surgery at YNHCH requiring general anesthesia
- Chooses inhalational induction as induction method
- Surgery qualified under one or more of the following fields: otolaryngology, ophthalmology, orthopedics, dentistry, gastrointestinal, general surgery

Any individual who meets any of the following criteria will be excluded from participation in this study:

- Altered mental status
- Significant audiovisual deficits (per parent report and at discretion of study team)
- Received pharmacologic premedication

.3 Recruitment Procedures

Potential subjects will be identified by prescreening in the EPIC electronic medical record based on the regular operating room schedule at YNHCH within 48 hours (weekdays only) of surgery. Per study team availability, efforts will be made to call the patient's caretaker in the

48-hours prior to arrival in the perioperative area to inform them of the study and discuss what it would entail. On the day of surgery, patient parents/legal authorized representatives (caretakers) will be approached in the pre-operative area for formal consent. The study will be discussed with patients and caretakers by a member of the study team in this area where enrollment and consent will be obtained by an investigator (HP or AL). Assent will be obtained from patients aged 10 years or older via verbal methods (see below) and notated if obtained. If a child is enrolled in the study, parents will then be offered enrollment in the same area.

Operating room staff will be approached after the surgery is completed and asked to complete a short survey.

No third parties will interact with subjects pertaining to this study.

.4 Consent/Assent Procedures/HIPAA Authorization

- Consent forms describing in detail the study intervention, study procedures, and risks are given to the patient's caretaker and written documentation in paper form of informed consent is required prior to starting procedures/administering study intervention.
- Consent forms will be Institutional Review Board (IRB)-approved and the participant/legally authorized representative (LAR) will be asked to read and review the document. HP or AL will explain the research study to the participant and answer any questions that may arise. This conversation will take place in a private room in the preoperative area.
- Participants/LAR will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants/LAR will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.
- Participants/LAR will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be available to the participants/LAR for their records.
- Assent will be obtained for pediatric patients aged 10 and older. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Assent will be documented with an initial of a study team member on the parental consent form.
- Parental permission will be obtained in the pre-operative area where children and their caretaker wait prior to surgery. Permission will be obtained from the caretaker of all children enrolled. All consent forms will be provided to parents/caretakers in paper form upon which signed (paper) consent will be obtained.

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APPROVED BY THE YALE UNIVERSITY IRB 12/28/2023

Study Methods/Procedures

.1 Study Procedures

	Pre-screening (Pre-consent)	*Visit 1 Day 1*	*Day 2*
EMR Review Eligibility	*X*		
Informed Consent		*X*	
Demographics		*X*	
Outcome Evaluation			
mYPAS, STAI, ICC, Health Professional Survey		*X*	
Randomization		*X*	
Control & Experimental Interventions		*X*	
Adverse Events Reporting		*X*	*X*
EMR Data Extraction		*x*	*X*

.1.1 Data Collection

Data via survey tools, demographic forms, and EPIC extraction will be collected on an iPad with direct input into Yale-licensed REDCap that is not validated for 21 CFR Part 11 compliance. A coded link to identifiers will be created and stored in REDCap.

If problems arise with the iPad/digital surveys, paper survey forms will be used. Paper surveys will be directly logged into REDCap on the day of enrolment. All paper documents will be discarded into YNHH-designated shred bins upon study completion.

Consent forms (with identifiable information) will be digitized on a YNHH-owned and password-protected device and uploaded to the REDCap study project.

All survey tools are included in the study package and the primary tools have all been previously validated externally. Per patient, all tools will be completed within an approximately 1-to-2-hour period from the preoperative area to the time after induction. The individual(s) administering the tools will be anesthesiologists or anesthesiology residents on staff at YNHH and on the study team.

No official training is needed to administer any of the used surveys. However, in order establish reliability statistics with the single observer administering the mYPAS, all patients enrolled will be videotaped during induction. This video tape will then be shown to an independent observer who will individually score the patients. The scores of the two observers will be compared.

Demographic information that will be collected for patient subjects includes: age, sex, gender, race/ethnicity, prior surgery (yes/no), and anxiety diagnosis via direct report of caretaker. Demographic information that will be collected for caretaker subjects includes: age, sex, relationship to child, prior surgery experience.

Procedures

Potential subjects will be identified by prescreening in the EPIC electronic medical record based on the regular operating room schedule at YNHCH within 48 hours (weekdays only) of surgery. Per study team availability, efforts will be made to call the patient's caretaker in the 48 hours prior to arrival in the perioperative area to inform them of the study and discuss what it would entail.

Upon arrival to the preoperative area on the day of surgery, consent and enrollment of subjects (patients with or without caretaker) will be completed by a member of the study team. Upon consent, an intake demographic form and two additional measures (mYPAS and STAI) will be administered by a member of the study team. The intake demographic form and STAI will be given to the caretaker to fill out on an iPad via REDCap survey. The mYPAS score will be documented by the member of the study team on iPad. At this time, the member of the study team will randomize the patient using an online randomizer module in REDCap. If the subject is randomized to the intervention group, expectations of the intervention will be briefly explained to the patient and caretaker.

When ready to proceed to the operating room for surgery, a member of the study team will follow the staff that is bringing the patient to the operating room. Upon entrance to the operating room, the study team member will document a mYPAS score. The patient will be placed on the operating table, monitors and other standard-of-care procedures will occur, and the AVG system will be setup by the relevant staff present (child life specialist, anesthesia resident, anesthesiologist, nurse, and/or study team member – if patient is assigned to intervention group) and initiated. After the game is initiated, the study team

member will score the subject with mYPAS and ICC. The games utilized are described below:

“Sevo the Dragon”: The child will be placed on the operating table after the game has been initiated. The patient will be able to choose the color of the dragon. It will be selected by a member of the study/clinical team using a remote attached to BERT. As the patient exhales through the anesthesia mask, the dragon breathes fire (the fire is triggered by a member of the study team/clinical team pressing a button on the remote). The game will be stopped and the BERT system will be removed by the study and/or clinical team once induction is complete.

“Batman”: The child will be placed on the operating table after the game has been initiated. A racing steering wheel that has already been connected to BERT will be given to the child and placed between their legs. On the screen will be a batman racer (similar to that seen in other racing video games) and the patient will use the steering wheel to “drive” the racer. While the patient is playing this game, the anesthesia mask will be introduced.). The game will be stopped and the BERT system will be removed by the study and/or clinical team once induction is complete.

If the patient is randomized to the non-BERT group, standard-of-care procedures on induction will occur. Standard of care anxiolysis procedures include: parent present on induction and/or additional distraction intervention, such as those initiated by a certified child life specialist, or no additional interventions as deemed necessary collectively by certified child life specialists and anesthesiology personnel. BERT will not be available to these patients. Interventions offered through child life include distractions, pet therapy, art therapy, and other therapeutic interventions. Standard of care directly relates to the needs of the patient. If the patient appears to have a low level of anxiety, minimal interventions will be employed as deemed necessary by the child life and anesthesiology teams, which is the current standard of care. Based on Anesthesiology Attending preference, standard of care slightly deviates as is standard for anesthesiology induction across sites – specific interventions present in the standard will be documented. The standard-of-care procedures will also be available to the BERT group, as determined by the clinical care team.

After induction is complete, the caretaker will be escorted out of the operating room as is standard-of-care – at this time, a study team member will administer a STAI on iPad with the caretaker. The caretaker will receive a copy of the signed consent form prior to the time that the patient is discharged from the perioperative area.

In the time after patient discharge, a member of the study team will extract relevant data from the EPIC EMR. All measures will be directly logged into RedCap. The measures extracted include:

1: “Anesthesia start” time, 2: “In Room” time, 3: “Induction” time, 4: “intubation”/”LMA placement” time, 5: “Anesthesia release” time, 6: “incision” time, 7: “Extubation” time, 8: “Out of room” time, 9: “Anesthesia stop” time, 10: “PACU discharge” time, 11: total opiates used during anesthesia time (morphine equivalents).

Healthcare professionals will be surveyed throughout the patient enrollment period. Surveys will be administered via an iPad using the Qualtrics platform or via paper form of the same survey and input manually into Qualtrics by the study team. Operating room staff (nurses, technicians, child life specialists, etc) will be asked to fill out a survey at the beginning or end of staff meetings outside of clinical commitments. Physicians and APPs will be asked to fill out the survey in-person or via direct email with a link to the Qualtrics study. Emails will only be sent to staff who have been directly involved with the care of a patient enrolled in the study as observed by a member of the study team.

.2 Method of Assignment/Randomization

Randomization will occur via REDCap randomization module. After consent and baseline assessment, a member of the study team will randomize subjects. Due to the nature of the study, it cannot be completely blinded after randomization.

.3 Adverse Events Definition and Reporting

An adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related.

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

If a serious adverse event is identified to meet the above criteria, it will be reported to the IRB within 5 days of occurring by the principal investigator and the study will be suspended until a complete review is performed.

.4 Reaction Management

All subjects will be evaluated by an attending anesthesiologist post-operatively per standard-of-care. If needed, a consult will be placed to the department of psychiatry for further evaluation of psychological distress per standard clinical procedures. This may occur at any time during clinical care as deemed necessary by the clinical team.

.5 Withdrawal Procedures

At the discretion of the subjects and/or their caretaker, subjects may withdraw from the study at any time. They may choose to have their data destroyed at any time after engagement in the study as well. Data will be maintained in a protected database (RedCap) following subject enrollment and involvement in the study.

.6 Locations/Facilities

The primary physical location is YNHCH, floor 3 in the operative area. Online locations used include the RedCap database – this is only used by the study team for logging and coding data.

Statistical Design

.1 Sample Size Considerations

Sample size: 74 pediatric patients. In calculating the sample size, we assumed that the randomization is successful and the mean difference (SD) mYPAS is 5.1 (4.5) for the standard care group at induction including standard child life services (ie. tablet, distraction techniques, etc) (Rodriguez et al, 2019). We assumed an intervention group mYPAS difference of 1.8 based on similar studies evaluating perioperative anxiety changes with use of handheld and VR games (Stewart, et al, 2019, Patel et al, 2006, Dwairej et al 2020, Marechal et al 2017). At a significance level of 0.05 and a power of 80%, it was determined that 29 subjects would be needed in each group. We increased this to account for dropout and dissimilarity of utilized studies, reaching a final target sample size of 37 per group (29/0.8=37 subjects).

.2 Planned Analyses

Baseline categorical data will be compared using the $\chi 2$ test of association; baseline continuous data will be compared using t tests for independent or paired samples as appropriate. A mixed model or generalized linear mixed model will be used to examine the mYPAS and other measures, as appropriate. Specifically, the model will include group, time, and group and time interaction as fixed effects. Group differences in the change from preoperative administration to subsequent time points will be evaluated to see if the IAG effect remains the same over time. The intraclass correlation among the raters will be reported. Because the study sample size is small, as a secondary analysis, the model will be repeated to include any baseline imbalanced covariate (defined as >0.2 standardized mean difference). Inter-observer variability will be reported. The analysis may be amended post-hoc.

.2.1 Analysis of Subject Characteristics

Baseline categorical data will be compared using the $\chi 2$ test of association; baseline continuous data will be compared using t tests for independent or paired samples as appropriate.

.2.2 Interim Analysis

An interim analysis will be conducted after 50% enrollment is attained (37 patients) to assess futility in completing enrollment in the allotted time frame. Forty-eight research days were allocated to HP for completion of this project. Thus, enrollment must be sufficient in this period to complete enrollment. During this analysis, we will calculate the average number of patients enrolled per day over the course of the study up to this time. We will then project the number of research days required to complete enrollment, using the same rate of enrollment. If this projection lies notably beyond the allowed research time (>50 days), the study will be halted, as the desired sample will not be attainable. This time will expire in June 2024. Safety events will not be reviewed at this time. Safety events will be periodically reviewed per this protocol as they occur as discussed in sections 6.3 and 9.5. No independent DSMB will oversee this project.

Example 1: 37 patients are enrolled at enrollment day 20. This equates to an average enrollment of 1.85 patients per day (37 patients/20 days). Thus, it will be estimated that it

would take approximately 20 days to enroll the remainder of the sample. The total projected enrollment days is 40, which is less than the allotted 48 days. Thus, research will continue.

Example 2: 37 patients are enrolled at enrollment day 30. This equates to an average enrollment of 1.23 patients per day (37 patients/30 days). Thus, it will be estimated that it would take approximately 30 days more to enroll the remainder of the sample. The total projected enrollment days is 60, which is more than the allotted 48 days. Thus, research will be halted.

.3 Data Relevance

All data collected will have direct relevance to the study questions (outcome measures) and ensure that randomization has been successful (demographic survey).

.4 Data Coding

A coding system will be utilized to link all surveys for repeated measure statistical analyses. The list linking the names to the code will be kept in a secured location (REDCap). Identities will not be revealed in any publication or presentation of the results of this research.

.5 Data Analysis Tools

SPSS Stata and Microsoft Excel will be used to analyze the data.

.6 Data Monitoring

Periodically, data monitoring will occur by the principal investigator and co-investigator.

.7 Handling of Missing Data

Missing data will exclude the relevant subject from the quantitative analysis relevant to the missing data. Other data will remain within the evaluation.

Data/Specimen Handling and Record Keeping

.1 Subject Data Confidentiality

Participant confidentiality and privacy is strictly held in confidence by the participating investigators, their staff, and the sponsor(s)/funding agency. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB), regulatory agencies or study sponsor/funding agency may inspect all documents and records required to be maintained by the investigator for the participants in this study. The study site will permit access to such records.

The study participant's contact information will be securely stored at each study site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, regulatory, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored online in the RedCap system. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. There will be a separate REDCap sheet that contains a linker between the patient MRN and study id. The study data entry and study management systems used will be secured and password protected. At the end of the study, the link between code and patient information will be destroyed.

Data will only be available to the principal investigator, co-investigator, and relevant statisticians on the study team.

.2 Data Quality Assurance

The first twenty patients will be video-taped and scored via mYPAS by an independent observer. These scores will then be compared to the study team member scores to ensure consistency.

.3 Data or Specimen Storage/Security

The individuals with access to data during the study have been trained on data management per the required Yale trainings and by prior institutions. All electronic data will be stored in a password-protected manner.

.4 Study Records

Study records include consent forms, surveys, and extracted EMR data. This data will be stored online in RedCap. The data will be maintained by Harrison Pravder and Anthony Longhini. This data will be available only to the co-investigators and study statisticians.

.5 Access to Source

Source documents include completed paper surveys and electronic medical record information. The electronic medical record information is maintained in the computer system and is not specific to the study. Thus, it will continue to be maintained in the electronic medical record system and managed at YNHH's discretion. Only co-investigators will have access to source documents.

.6 Retention of Records

Upon conclusion and publication of the study results, the coded/deidentified data will be maintained by Harrison Pravder indefinitely on a personal computer. This data will be available upon reasonable request by other study teams. All paper materials will be destroyed via authorized shred bins at YNHH.

.7 Data and Safety Monitoring Plan

This is a minimal risk study; however, the PI will conduct monitoring of research data. The PI will periodically communicate with the co-investigator (Harrison Pravder) who is maintaining the data to ensure that proper procedures are being followed.

Study Considerations

.1 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol will require an approved IRB amendment before implementation. The IRB will have final determination whether informed consent and HIPAA authorization are required.

Study closure will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale policies.

.2 Research Personnel Training

All study team members will complete Yale-mandated training for research with Human Subjects. No official training is needed to administer any of the used surveys. HP is responsible for carrying out survey collections.

.3 Study Monitoring

The principal investigator and co-investigator will meet at least once (1) monthly during enrollment to review study progress. These reviews will include reviewing enrollment, data collection, data storage, data coding, and any ongoing concerns.

.4 Unanticipated Problems and Protocol Deviations

A protocol deviation is any noncompliance with the protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to identify and report deviations within 7 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the study sponsor, and the reviewing Institutional Review Board (IRB) per their policies.

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the study team becomes aware of an unanticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB by the principal investigator and/or co-investigator via email and direct methods (ie. telephone, in-person).

The UP report will include the following information:

Protocol identifying information: protocol title and number, PI's name, and the IRB project number.

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB within 5 days of the investigator becoming aware of the event.

.5 Study Discontinuation

The study will be discontinued upon discovery of a serious adverse event. The study may also be discontinued upon interim data analysis if the study team deems the sample to be sufficient to evaluate the outcome measures of the study.

.6 Study Completion

The study is expected to be completed by June 2024. Upon request, all published materials and study methods will be available to the IRB. Study completion means completion of the study methods and final publication of results.

.7 Conflict of Interest Management Plan

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

All investigators will follow the applicable conflict of interest policies.

.8 Funding Source

No additional funding will be provided for this study.

.9 Publication Plan

The study team will be responsible for publication of the study results. We expect that results will first be presented in poster format at an academic conference and that ultimately results will be published in article form in a peer-reviewed journal. Data will be entirely de-identified in the publication. Primary responsibility for publishing the study results lies with the principal investigator.

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