Cover Page for Protocol

NCT Number:	NCT03980067
Official title of study:	Pediatric Procedural Sedation and the Relationship with Post-Discharge Negative Behavioral Changes in the Emergency Department
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INSTITUTIONAL REVIEW BOARD
SUMMARY

Children's Hospital and Health System™

STUDY TITLE: Pediatric Procedural Sedation and the Relationship with Post-Discharge Negative Behavioral Changes in the Emergency Department

A. PURPOSE OF THE STUDY:

Determine if an interactive virtual reality (VR) intervention will decrease post-sedation negative behavioral changes one week after ED (emergency department) sedation.

B. SPECIFIC AIMS/HYPOTHESES

1) Specific Aim: To determine whether a non-pharmacological virtual reality intervention (non-invasive, technology-based distraction via interactive digital game participation) will decrease the incidence of post-sedation negative behavioral changes in children undergoing procedural sedation with IV ketamine in the pediatric ED following their discharge home.
    i. Hypothesis: Fewer children in the intervention group will have post-sedation negative behavioral changes at 1 week follow up post-discharge as compared to the control group who receive standard of care.
2) Secondary Aim: To determine whether administration of a non-pharmacologic virtual reality intervention will decrease anxiety levels just prior to procedural sedation.
    i. Hypothesis: Children in the virtual reality intervention group will have less anxiety just prior to procedural sedation when compared to controls as evidenced by a reduction in their Modified Yale Preoperative Anxiety Scale (m-YPAS).

C. BACKGROUND, SIGNIFICANCE, AND RATIONALE

Procedural Sedation and Outcomes

Pediatric emergency medicine providers administer procedural sedation to minimize patient discomfort and anxiety during diagnostic testing and therapeutic treatments (Kannikeswaran et al., 2017). Institution-specific protocols, individual patient factors, and intended procedures to be performed impact the sedative and analgesic medications administered. Despite highly skilled practitioners and guidelines emphasizing safe and methodical practice, procedural sedations carry risk for adverse effects (Cote et al., 2016). Well-established anesthesia literature of post-operative patients and increasing pediatric emergency medicine literature demonstrates that the adverse effects of anesthesia and procedural sedations are not limited to respiratory, cardiovascular, or gastrointestinal signs and symptoms. Significant and lingering negative behavioral changes can be seen weeks to months post-sedation which have implications for patients and their families that extends beyond the walls of the hospital (Hilly et al., 2015).

Several studies have documented post-operative negative behavioral changes in children following anesthesia and surgery (Eckenhoff 1953, Pearce et al., 2017, Thompson 1993). Investigations have shown that hospitalization and anesthesia can impact children psychologically and behaviorally and contribute to post-operative negative behavioral (PONB) changes (Stargatt et al., 2006, Karling et al., 2006). PONB effects include increased anxiety, sleep disturbance, nightmares, apathy, and eating difficulty (Karling et al., 2005,

Keaney et al., 2004). Children with high anxiety prior to anesthesia or emergency department (ED) procedural sedation are even more vulnerable to develop PONB changes (Beringer et al., 2014, Kain et al., 1996, Kain et al., 1999, Pearce et al., 2018, Zavras et al., 2015). In one study, "very anxious" children were found to be 40% more likely to suffer these changes (Kain et al., 1996).

Children cared for in the ED are subjected to traumatic procedures and stress. It is important that their pain and anxiety are managed appropriately to avoid posttraumatic stress and developing a fear of doctors and hospitals (American Academy of Pediatrics 2006). The new behaviors can additionally have a negative impact on the child's health, social skills, development, and school work. Therefore, it is important to recognize anxious patients, understand the higher risk for adverse behavioral effects following procedural sedation, and explore remedies for improvement in PONB changes.

Risk Factors/Reduction in PONB Changes

A variety of risk factors have been associated with PONB changes. Parental anxiety and younger patient age (Stargatt et al., 2006, Fortier et al., 2010) are associated with increased risk for developing these changes (Hilly et al. 2015). Preexisting somatic conditions, anxiety, depression, and separation anxiety contribute to PONB effects in children (Fortier et al., 2010, Tripi et al., 2004). Children who have frequent temper tantrums are at an increased risk as well as children who have undetected sleep disorders prior to anesthesia and surgery (Tait et al. 2014). Non-white children are at an increased risk for PONB changes (Pearce et al., 2017). Spanish-speaking Hispanic parents reported lower negative behavioral changes in their children compared to English-speaking Caucasian parents, and these findings may be due to a difference in cultural practices and symptom reporting (Fortier et al., 2013).

A host of risk factors for developing PONB changes in pediatric populations following anesthesia or ED procedural sedation have been reported. There are studies primarily in the anesthesia/surgery literature that demonstrate activities that reduce PONB effects. A preoperative preparation workshop for patients and their family showed a reduction in new PONB changes in children and also preoperative anxiety (Hilly et al., 2015). In a double blind-control study, fentanyl given prior to lower abdominal surgery in children undergoing general anesthesia and regional anesthesia exhibited significantly lower negative PONB changes and decreased pain scores (Bortone et al., 2014). A preoperative informational video reduced preoperative anxiety and postoperative negative behavior changes in pediatric patients (Batuman et al., 2016). To our knowledge, similar studies have not been performed in the pediatric ED.

There is some evidence that distraction techniques may help alleviate pre-procedural anxiety and direct attention from the source of pain in certain procedures (Koller and Goldman 2012). Children engaging in medical play and distraction techniques and undergoing difficult procedures in the burn unit experienced less pain and distress (Moore 2015, Khadra et al. 2018). Play therapy as an intervention and the presence of parents reduced anxiety at the induction of anesthesia (Tan and Meakin 2010). Virtual reality has been used as a distraction technique to reduce anxiety and decrease pain (Jones et al., 2016, Mosso-Vazquez et al., 2014, Wiederhold et al., 2014, Gold et al., 2016). For instance, virtual reality which allows children to be immersed in an interactive and simulated world (Sharar and Patterson 2008) has been used in several dental studies to alleviate dental anxiety, and reduce pain associated with procedures (Wiederhold et al., 2014, Aminabadi et al., 2012, Elmore et al., 2016).

Virtual reality interventions have been shown to be well-tolerated by children. Virtual reality because of it immersive nature was used to teach children ages 6 to 12 years with autism spectrum disorder virtual reality safety skills for response to tornado and fire alarms. (Self et al., 2007). Virtual reality technology has been studied with favorable results in decreasing perceived pain via distraction in various pediatric patient clinical scenarios (Dahlquist, et al., 2009) including IV insertion for magnetic resonance imaging (MRI) or computer tomography (CT) (Gold, et al., 2006), burn patients requiring dressing changes (Das, et al., 2005), and oncology patients during port access (Gershon, et al., 2004).

Perceiving pain has a strong psychological component and requires conscious attention to the pain whereas distractions take away some of the attention focused on the pain (Noble et al., 2010). In a randomized controlled trial of 120 healthy children age 4-6 years old, investigators conducted three treatment sessions (Aminabadi et al., 2012). The first consisted of fluoride therapy. In the second treatment one group received restorative treatment without virtual reality eyeglasses and while the third group received therapy with virtual reality glasses. At the end of each treatment, pain was measured with the Wong Baker FACES Pain Rating scale and state anxiety was measured using the Modified Child Anxiety Scale. A significant decrease in both perceived pain and state anxiety was found with the use of virtual reality eyeglasses.

Several clinical benefits have been found using virtual reality. However, a few reports of side effects, such as nausea have been documented in the literature. Aminabadi et al. conducted a clinical trial using 120 children ages 4-6 years old to determine if a virtual reality distraction decreased pain and anxiety during dental procedures. Pain decreased during the restorative procedures and only 2.5% of the children failed to complete the study. Schneider et al. reported children ages 10-17 years old found virtual reality games provided temporary relief from the stress of chemotherapy treatment and nausea was measured in the study. Nausea was rated on a 1 to 5 scale. The average rating by the participants was low at 1.4. In another study, Gold et al. compared standard care to a virtual reality distraction in 20 children age 8 to 12 to determine if pediatric pain decreased during IV placement. Pediatric pain decreased and none of the children experienced simulator sickness (nausea, vomiting, headaches, etc.). The vast majority of patients experience no side effects and complete research investigations. The risk of bad side effects is extremely low due to redesign of the helmets and proper fitting of the devices (Newbutt et al., 2016).

To our knowledge, evaluating the use of a non-pharmacologic, virtual reality intervention and its effects on reducing PONB changes following patient discharge has not been evaluated. Our investigation may improve patient outcome, satisfaction, and experience due to decreased anxiety and PONB changes at home.

D. DESIGN AND METHODS

- Study Design: This is a randomized control trial.
- Site: Children's Hospital of Wisconsin (CHW) ED.
- Subjects: Subjects will be recruited during ED hours when research assistants (or other member of the research team) are available.
    - Inclusion criteria: Children ages 6 years to 17.5 years old receiving procedural sedation with IV ketamine in the CHW ED for long bone fracture reduction. See Appendix A. This age group is most likely to achieve positive effects, fit the VR headset equipment, and tolerate the device without adverse side effects.
    - Exclusion criteria: Patients with moderate to severe developmental delay will be excluded because the anxiety scoring tools have not been validated in this population. Non-English-speaking patients/families will be excluded because the parent survey questionnaire has not been developed and validated in languages other than English. Patients taking psychotropic medications will be excluded because these pharmaceuticals may affect measuring the primary outcome, PONB changes. See Appendix B. Patients with a history of severe motion sickness will be excluded. Patients currently experiencing nausea will be excluded. Patients who have severe visual impairment will be excluded as the VR intervention engages patients in an interactive game that requires navigation through visual content on the VR headset/screen. Patients with an expected admission to the hospital post-procedure will be excluded because outcome data may be affected by this. For a portion of patients this will not be known until after the fact. These patients will be excluded and considered screening failures.

- Demographic Data: The research assistant (or other member of the research team) will collect routine demographic data from the electronic medical record and/or from the patient's parent or guardian including age in years, gender, race, weight in kilograms, medical comorbidities, procedure type and history of sedation difficulty. Additionally, the parent/guardian will be asked to provide their phone number and select the best time of day for the research assistant (or other member of the research team) to call for phone follow-up, cell phone number to text, provide an email address, and mailing address. Parents will be contacted by the research assistant (or other member of the research team) at 1 week follow up via phone, text, email (via secured REDCap link) and/or mail to complete the post-hospitalization behavior questionnaire (PHBQ) and pain surveyOne PHBQ survey and pain survey is completed.. This information will be collected by the Research Assistants (or other member of the research team) on questionnaires on REDCap or by paper. See Appendix C.

- Measures:
    - Anxiety: To assess the patient's anxiety, the following assessment tool will be used.
        - Modified-Yale Pediatric Anxiety Score (m-YPAS): See Appendix D.

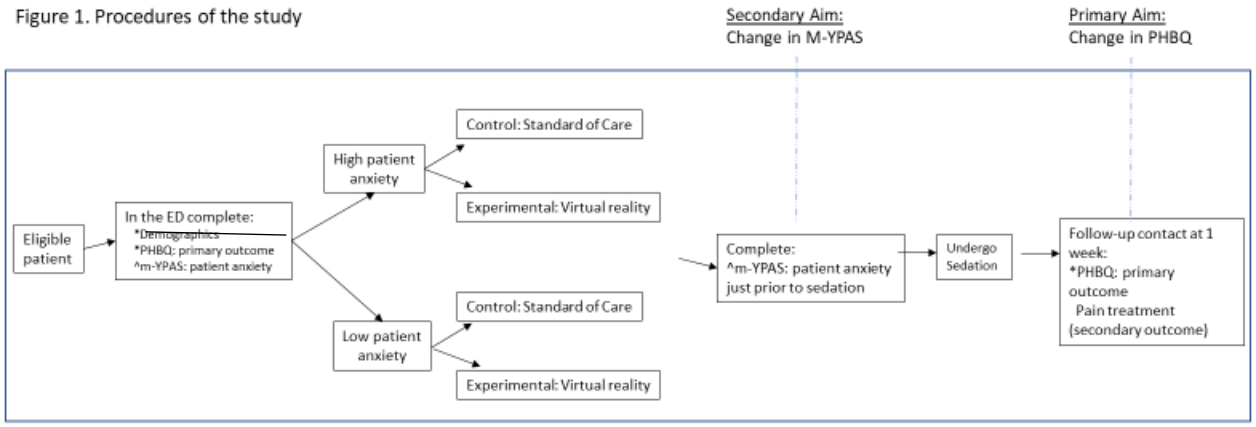
The m-YPAS is a widely used by medical providers to assess patient anxiety at the time of induction of anesthesia. It is designed to be completed in less than 1 minute. It was originally developed for use in children ages 2-6 years but has since been modified to include adolescents. It is reliable and its validity compares favorably to that of the gold standard, the STAI-C (Kain, Z. 1997). The patient's provider (attending physician or fellow physician) will assess the patient's anxiety using the m-YPAS twice during our study: 1st upon patient arrival and enrollment and 2nd immediately preceding sedation after VR intervention or standard of care (depending on which group patient has been randomized to). This will be given to the research assistant (or other member of the research team) to score. The score will not be shared with the physician.

- Procedure Measures: Variables that might be associated with the primary outcome will be collected. Following the procedure, charts will be reviewed to collect: 1) the type of pain medication given in the ED, 2) the dose (mg/kg and total number of doses) of pain medication given in the ED, 3) the anxiolytic mediation given in the ED, 4) the dose (mg/kg and total number of doses) of anxiolytic medication given in the ED, 5) the type of pain medication prescribed for home, and 6) the dose (mg/kg and total number of doses) of pain medication prescribed for home. See Appendices E and F.

- Outcome Measures:
    - Post-Hospitalization Behavior Questionnaire (PHBQ): See Appendix F. The PHBQ is a parent-report questionnaire with 27 items in six categories, comprising general anxiety, separation anxiety, sleep anxiety, eating disturbance, aggression towards authority, apathy, and withdrawal. This questionnaire has been used extensively since its development in 1966 to study negative behavioral changes in children post-surgery or hospitalization (Kain et al., 1996, Kain et al., 1999) and was recently used to evaluate the same after minor ED procedures (Brodzinski et et al., 2013). This questionnaire takes approximately 10 minutes to finish. This tool will be completed by a parent(s)/guardian(s) prior to the sedation and during phone or mail follow-up post-sedation.

Procedures of the study: The study procedure is outlined in the diagram below (Figure 1).

Figure 1. Procedures of the study



*Parent completes survey
^Medical provider completes survey (attending physician, fellow physician, or Advance Practice Provider

Patients will be identified by trained research assistants (or other member of the research team) and enrollment criteria will be reviewed. Parent/guardian consent will be obtained for all eligible patients. A separate assent form will be completed for patient's aged 7- 13 years. Demographic information will be collected from the parent/guardian.

Patient's anxiety measures using the m-YPAS will be completed at baseline by the patient's medical provider (attending physician or fellow physician). A PHBQ will be completed at baseline by the patient's parent. Patients will then be stratified into high and low anxiety groups based on their baseline m-YPAS score (score of 40 or greater being highly anxious) (Pearce, et al., 2017, Kim, et al., 2012, Kain, et al., 2006) and randomized in blocks of 4 by a computer to either the control or experimental group on a 1:1 ratio. See Figure 1.

The control group will receive standard of care. The experimental group will receive the standard of care in addition to our intervention (interactive VR game while waiting to undergo procedural sedation). This children in the control group receiving standard of care will have access to in room activity including TV distraction if desired, parent support and distraction at bedside, and quiet time like a typical emergency department visit for this type of injury. There would be no active intervention or virtual reality game initiated by the Children's Hospital of Wisconsin staff/Research team in the "Standard of Care" group. Children in the experimental group will receive standard of care as detailed above in addition to the virtual reality game intervention. Additionally, children who choose not to participate in the study and/or terminate the study (which is completely voluntary) early, will receive standard of care and resume their planned emergency department course with the medical team without any change to their healthcare. During the consent/assent process for the study, parents and children will be explained the possible groups they could be allocated to and that this determination is random using a computer software.

Virtual reality, a technology-based distraction device, provides the user with the sense of being present in a virtual environment (Waterworth and Riva, 2014). Distraction techniques can be safe and inexpensive and are commonly used to decrease pain in short invasive medical procedures (Sinha et al. 2006). Virtual reality is a distraction technique in which the participant-computer interface allows the user to interact dynamically using, kinesthetics, visual, auditory, and emotion cues within a computer-generated environment (Aminabadi et al. 2016, Silfer et al., 2002). It uses a head-set, three-dimensional displays, a wide field of view, and motion sensors. Immersive images are placed in front of the eyes of the participant and the headset blocks out outside stimuli as the user interacts with the virtual environment. Since the focus is on what is going on in the virtual world, less attention is focused on the pain or anxiety the patient may be experiencing. The decrease in pain may be due to the virtual reality headset taking attention from the painful stimuli thus taxing the patients limited attention capacity (Wismeijer and Vingerhoets, 2005). We hypothesize that there may also be a decrease in anxiety for these same reasons.

The research assistant, (or other member of the research team) will receive hands-on training from the study investigators per the protocol and device user manual on the operation and use of the VR device and software with the opportunity to use the device as a subject themselves/application onto another individual to ensure competence prior to study enrollment. The research assistant (or other member of the research team) will assist the patients in the VR intervention group by explaining the technology-based distraction device using a standard script provided. See Appendix G. The research assistant (or other member of the research team) will additionally set up the technology system to comfortably fit the patient's head, turn on the VR device, assist the patient in starting the game of their selection, and remove the device when VR intervention has been completed. The headset is thick like a pair of googles and can be adjusted to fit comfortably on children and to make sure the virtual image is sharp and in focus. Consistent with the procedures used previously by Aminabadi et al., participants will be introduced to virtual reality headset using a tell-show-do technique. The child will be told this is a virtual reality headset and it allows you to play a creative activity or game prior to sedation and this is how to work the headset. It goes on your head and you turn it on and the activity begins. If at any time the child does not wish to continue the activity or game, they will let the research assistant (or other member of the research team) know by raising their hand or saying so. The interactive tell-show-do approach establishes a rapport with the participant, so they are more comfortable and allows time for questions to be answered.

The VR headset, device, and software, created by Stanford's Childhood Anxiety Reduction through Innovation and Technology (CHARIOT)program/Weightless Studio, LLC will be utilized in this study. Patients in the VR intervention group will be allowed to select a distraction-based game to play with active VR content featuring interactive avatars and interactive experiences tailored to the pediatric population that allow players to do things such as control penguins sliding down a mountain while collecting pebbles for points, control puppies running in space to collect treats to the rhythm of music, and control an asteroid miner exploring an asteroid belt and collecting points based on color of asteroids collected, for example. See appendix H.

The game will last a minimum of 5 minutes in duration, provided patient tolerance. The patient may play longer if desired prior to receiving procedural sedation and the total length of activity played will be documented by the RA who will record patient's start and stop time. The VR device will not be applied until the pending time of the procedure is known, such that it will be removed from the participant no longer than 5 minutes before the sedation procedure is initiated, provided patient tolerance. The VR device will be removed when the X-ray technician team arrives to the room prior to the start of the sedation. The time from VR removal to the time of m-YPAS assessment and time of sedation medication administration will be collected and analyzed.

The VR intervention will require the use of the patient's head to navigate the characters in the game (i.e. looking left, right, up or down) and will not require the patient to get out of bed, move their arms, or legs. The research assistant (or other member of the research team) will initiate the VR intervention for patient, record the duration of intervention, and denote any reports of distress including nausea or dizziness (See Appendix I). Parents will be asked to remain at the bedside with the patient throughout the VR intervention, keep the rails of the bed up at all times, push the call light to notify the RA when the child has completed the game, and advocate for their child if the VR experience is poorly tolerated as an additional safety measure.

At the closure of the game the research assistant (or other member of the research team) will remove the headset. The headset will then be thoroughly cleaned with hydrogen peroxide wipes and/or replacement of facemask according to standard infection control recommendations for the CHARIOT VR device before the next study participant's use. See Appendix J.

After intervention and immediately preceding sedation, anxiety measures using m-YPAS will be reassessed by the medical provider (attending physician or fellow physician).

The physician will perform the sedation per CHW ED sedation policy. The sedation will be administered and as appropriate the patient discharged. Child life consultation by nursing staff or medical provider as an adjunct to patient care during ED course will be permitted per standard procedure and noted. See Appendix K.

Follow-up with the family will be performed by the research assistants (or other member of the research team) between 7-14 days after ED discharge consistent the procedures followed previously (Pearce et al., 2017). Phone, secured REDCap email/text, and mail surveys will be sent. One PHBQ and pain survey will complete the study. Follow up contact via email/text will include instructions for the parent to complete the PHBQ survey and pain questions via a link that will be provided through the secured REDCap database and record their responses electronically. Script content will be consistent with the example documented in Appendix L. The phone follow-up attempts will take place during the hours agreed upon by the parent(s)/guardian(s). The phone follow-up attempts will occur no more than two times per day during the follow-up period. During the phone, email, text or mail follow-up, the PHBQ post-sedation will be administered to assess the degree of change PONB changes post-sedation as well as 3 additional questions regarding post-discharge pain treatment: (1) Was your child prescribed an opiate medication (ie. oxycodone) prescription for pain control at home? (2) Did you fill this prescription? (3) Have you given your child an opiate medication for the pain following discharge from the ED? This phone survey was utilized in a prior study and took no longer than 5 minutes to complete. If the parent(s)/guardian(s) are not reachable by phone after the period specified above, then a paper copy of the follow-up survey will be mailed to him/her along with a self-addressed stamped envelope for return of the survey.

In anticipation of funding, a gift card in the amount of 25.00 will be provided to the child if their parent/guardian completes the study's follow up 1-week PHBQ, our primary outcome of interest. The Research Assistant will track study completion via REDCap and mail receipt of the PHBQ. The gift card will be provided within 1 week of receiving the survey results either via email or mail with the contact information provided upon study enrollment. If the parent/guardian does not complete the 1-week follow up survey, a gift card will not be sent. This incentive will be described to study participant and their parent/guardian at the time of enrollment and detailed in the assent/consent forms.

E. TOTAL NUMBER OF HUMAN RESEARCH PARTICIPANTS PROPOSED FOR

THIS STUDY AT THIS SITE AND GLOBALLY. WHAT ARE THESE NUMBERS BASED ON?
We will require 243 child subjects in the study. Allowing for a 20% dropout, we will have 97 subjects in each group. This will give us at least 80% power at a significance level of 0.05 to detect a difference of 15% (25% in the control group and 10% in the experimental group) in the proportion of patients with post-sedation negative behavioral change. This change was deemed a clinically relevant change by pediatric emergency medicine physicians.

F. DRUGS OR PROCEDURES
See appendices A-K.

G. RISK CATEGORY:
(1) 45 CFR 46.404 - Research not involving greater than minimal risk to the children.

H. RISKS AND THE PRECAUTIONS WHICH WILL BE TAKEN TO MINIMIZE RISK EXPOSURE
This research does not involve greater than minimal risk to children. The only risks to patients and their families are the 30-minutes required to complete the surveys, potential risk for nausea/dizziness or headache, the 5-minutes for follow-up contact (via phone call, secured REDCap email, text, or mail), and the risk of confidentiality outlined below. Patients with preexisting nausea, vomiting, dizziness, or a history of motion sickness are excluded from participation in the study. We expect a 2.5% or lower incidence of intolerability (primarily nausea and dizziness), in which case the VR headset can simply be removed and any follow up care can be assessed by the patient's medical provider (Aminabadi et al., 2012, Wismeijer and Vingerhoets, 2005, Gold et al. 2006). Treatment for the low but potential risk of dizziness and/or nausea is primarily to remove the device, as consistent with other studies. Medical providers will evaluate patient at bedside and determine if further intervention, such as an anti-emetic is indicated. The study does not cover the cost of nausea medication, should it be required. This is clearly explained in the consent/assent documentation for review prior to participation.

Per recommendations of the IRB administrative offices, VR, being implemented as a distraction tool in the form of an interactive game prior to sedation for pediatric patients in the Emergency Department, is considered a medical device. We are submitting the FDA form regarding the use of a device in a study because this is being considered a "medical device" at CHW due to the following description, "it is …intended for use in the potential mitigation of anxiety , in man, or other animals." The use of the device is hypothesized to reduce (mitigate) post-sedation negative behavior changes and pre-sedation anxiety as measured by PHBQ and m-YPAS scores, respectively. We contend that the device while viewed this way is at least a non-significant risk (NSR) device and can be ruled on by the IRB.

I. PROVISION FOR THE PROTECTION OF PRIVACY OF SUBJECTS AND TO MAINTAIN THE CONFIDENTIALITY OF DATA
Study data will be collected and managed using REDCap electronic data capture tools hosted at the Medical College of Wisconsin. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

J. PROVISIONS FOR MONITORING DATA TO ENSURE THE SAFETY OF SUBJECTS; AND ADDITIONAL SAFEGUARDS TO PROTECT THE RIGHTS AND WELFARE OF SUBJECTS WHO ARE LIKELY TO BE VULNERABLE
Each medical record number (MRN) will be assigned a study ID number. The study ID number will be used to identify all data. There will be one computer file that links the study ID and the MRN. This file will be locked and kept separately from the database. All data entered on paper forms will be labeled with the study ID. The data will be entered by a trained research assistant (or other member of the research team) into the database and then the paper will be destroyed.

K. ANTICIPATED BENEFITS ASSOCIATED WITH THE PROTOCOL TO HUMAN RESEARCH PARTICIPANTS AND SOCIETY

Participants may benefit from the use of an interactive virtual reality intervention prior to procedural sedation, but this is not guaranteed. Virtual reality is a safe technology, and it has been well-tolerated by most participants in a variety of different disciplines. Researchers have used virtual reality headset and activities to relieve pain and anxiety associated with dental procedures. For instance, Aminabadi et al. showed decrease pain during dental procedures in children ages 4-6, and only 3 of the 130 healthy children failed to complete the virtual reality treatment. Similarly, Wismeijer and Vingerhoet examined ten studies that utilized virtual reality to improve conditions in patients with phobias and panic disorders. Their research showed a significant analgesic effect using virtual reality when it was compared to the controls in the studies investigated, and very few negative side effects were reported. This study rated nausea and the side effect to the virtual reality intervention as negligible to nonexistent (Wismeijer and Wingerhoet, 2005)

Several other studies have also reported low or no side effects from the use of a virtual reality intervention in children. Parson et al. used virtual reality in children to study attention performance in children with attention deficit-hyperactivity disorder. None of the participants experience simulator sickness. In addition, virtual reality reduced chronic pain and no discomfort due to the headset was reported (Jones et al., 2016). Only one patient experienced nausea out of thirty and none of the patients dropped out of the study. Mosso-Vazquez et al. reported 3 of the 67 patients experiences nausea and vertigo which interfered with the cybertherapy to determine whether virtual reality decreases pain during cardiac surgery. During research involving Autism spectrum disorder patients experienced a low level of negative effects using virtual reality headsets (Newbutt et al., 2016). Children in a pilot study aged 10- 17 received virtual reality cybertherapy during painful cancer chemotherapy. All 11 patients responded that chemotherapy using virtual reality was better than previous chemotherapy treatment (Schneider and Workman 2000). All participants completed the study and would like to use the virtual reality head set for future studies.

Very few investigations involving children and virtual reality in emergency departments have been reported. Das et al. compared teaching residents procedural sedation using the traditional web-based educational module to a virtual reality environment. Students performed similarly although the virtual environment was reported to be more enjoyable (Das et al., 2016).

Since virtually reality can allow users safe, repeatable and a different intervention each time, it can be beneficial to typically developing children and also children with disabilities (Parson et al., 2017). Evidence indicates children do not experience more negative effects with virtual reality headset than they experience with other screen-based media (Parsons et al, 2007, Peli et al.,1998). Participants can immediately withdraw from the study at any point.

There is potential benefit to the public in greater understanding of sedation for the pediatric patient, potentially resulting in improved patient care, satisfaction, outcome and a less stressful medical environment.

L. STOPPING POINTS THAT WOULD NOT ALLOW THE STUDY TO CONTINUE AS PROPOSED

N/A

M. IS THERE A DATA SAFETY MONITORING BOARD IN PLACE? WHO ARE IT'S MEMBERS? HOW OFTEN DO THEY MEET?

N/A

N. DESCRIBE HOW THE CONSENT PROCESS WILL TAKE PLACE. INCLUDE A LIST OF APPROPRIATELY TRAINED PERSONNEL WHO WILL BE INVOLVED.

Patients will be identified by trained research assistants (or other member of the research team). Enrollment criteria will be reviewed and consent and assent obtained. Parental/guardian consent will be obtained for all patients. A separate assent form will be completed for patients aged 7 to 13 years. See attached consent and assent forms.

O. PROCEDURES TO BE EMPLOYED IN ANALYZING DATA AND THE ANTICIPATED SIGNIFICANCE OF THE PROPOSED STUDY.

- Missing data handling: Every effort will be made to avoid missing data. Using logistic regression, the assumption of missing at random (MAR) will be explored. In general, we will assume MAR, and multiple imputations will be used for items.

- Patient demographic and characteristics data: To evaluate comparability between treatment groups regarding patient demographic and baseline characteristics, descriptive statistics such as mean, median, standard deviation, range, frequency will be used to summarize the data. To compare the two groups, a student's t-test will be used for continuous variables. Where necessary, for parametric assumption, we will employ appropriate transformations with justifications. If data cannot be appropriately transformed, we will compare continuous variables between the two groups using a Mann-Whitney test. A chi-square or Fisher's exact test will be used for categorical variables.

- Analyses for Specific Aim #1: A chi-square or Fisher's exact test will be used to compare the proportion of negative behavioral change between two groups. Logistic regression analysis will be performed to compare the proportions after adjusting for covariates.

- Analyses for Specific Aim #2: The change of anxiety scores will be compared between two groups using a student's t-test or a Mann-Whitney test if the parametric assumption is not met and the data cannot be appropriately transformed. A generalized linear model will be used to compare the change of anxiety scores after adjusting for covariates.

- Statistical software SAS version 9.4 will be used for the analyses and a p-value < 0.05 will be considered as statistically significant.

P. FINANCIAL RELATIONSHIPS

Jon Vice Innovation Award funds will be utilized to complete this study.

Q. ADVERTISEMENTS / FLIERS

N/A

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