Feasibility and Acceptability of Technology-Based Interventions in the Perioperative Setting

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PROTOCOL TITLE:

Feasibility and Acceptability of Technology-Based Interventions in the Perioperative Setting

PRINCIPAL INVESTIGATOR:

Name: Vanessa A. Olbrecht, MD, MBA
Department/Center: Anesthesiology
Telephone Number:
Email Address: Vanessa.Olbrecht@nationwidechildrens.org

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	#2 – 08/31/21	IRB Requested Modifications	
2	#3- 01/12/22	Include Biometric identifiers in section#27	Y
3	#4 – 03/21/22	Change inclusion criteria from ≥ 2 days to at least one night in the hospital post-op and study duration to up to 3 months	Y
4	#5 – 04/25/22	Change device name to Oculus/Meta Quest; change in-person daily visit to in-person visit and as needed	Y
5	#6 – 05/18/22	Exclusion criteria regarding opioids or benzodiazepines changed from "currently using" to "chronically using" Addition of possible study communications via text under Economic Burden to Subjects	
6	#7- 06/17/2022	Changing Aim #1 enrollment from 20 to 32 and the overall enrollment number for the study from 90 to 102	Y
7	#8 – 08/18/2022	Include statement that de-identified data will be shared with a statistician at CCHMC	

1.0 Study Summary

Study Title	Feasibility and acceptability of technology-based interventions in the perioperative setting
Study Design	Feasibility/acceptability study; single-blinded, randomized, controlled trial.
Primary Objective	To develop and refine a VR-BF treatment protocol for preoperative education and training and postoperative delivery of VR-BF in children and adolescents undergoing surgery.
Secondary Objective(s)	To collect pilot data for R01 application and to gather data on outcomes that will be assessed in the future randomized clinical trial (pain, anxiety, opioid consumption, efficacy of VR-BF).
Research Intervention(s)/ Investigational Agent(s)	Biofeedback-based virtual reality (VR-BF, intervention), *Manage My Pain* application (active control)
IND/IDE #	NA
Study Population	Aim 1: up to 32 adolescents (12-18 years) undergoing surgery anticipated to cause moderate to severe pain requiring management by the Acute Pain Service; Aim 2: 70 adolescents (12-18 years) scheduled to undergo surgery anticipated to cause moderate to severe pain requiring management by the Acute Pain Service randomized to 1 of 2 treatment arms (VR-BF or *Manage My Pain* application).
Sample Size	Up to 102 patients (minimum 82)
Study Duration for individual participants	Up to 3 months Study duration: 3 years (12/2024)
Study Specific Abbreviations/ Definitions	VR, virtual reality VR-BF, virtual reality-based biofeedback VR-D, distraction-based virtual reality HR, heart rate HRV, heart rate variability BF, biofeedback NRS, numerical rating scale CCHMC, Cincinnati Children's Hospital Medical Center

2.0 Objectives

***Aim 1 (Phase 1)*. Refine a treatment protocol for preoperative education and training and postoperative application of VR-BF in children and adolescents undergoing surgery.** We will collect qualitative feedback (regarding content, usability, perceived benefits) via questionnaires and a semi-structured interview and sensitivity to change of key physiological parameters (heartrate variability, respiratory rate) from 12-32 patients (12-18 years) undergoing surgery anticipated to cause moderate to severe pain. Purposive sampling will be used to obtain a representative sample of a broad patient population. Treatment protocol refinement using iterative methodology will allow us to define the trial protocol, including frequency and duration of (**1a**) preoperative education and training and (**1b**) postoperative administration of VR-BF.

***Aim 2 (Phase 2)*. Conduct a pilot randomized controlled trial to assess the feasibility and acceptability of perioperative use of VR-BF in children and adolescents undergoing surgery.** Seventy children and adolescents (12-18 years) scheduled for surgeries anticipated to cause moderate to severe pain will be randomized to receive VR-BF or active control (commercially available *Manage My Pain* application). *Manage My Pain* is engaging but lacks specific instruction in behavior change techniques, a key feature of VR-BF. It is included as the control arm to confirm appropriateness for use in the future efficacy trial. Specifically, (**2a**) *Feasibility* will be assessed by rates of study recruitment, enrollment and randomization, retention, and adherence. Target goals will be set at 80% for each assessment. (**2b**) *Acceptability* will be assessed by treatment/study burden, satisfaction, treatment credibility, and tolerability. It is essential that both treatment arms are feasible and acceptable for use in an efficacy trial.

Our *central hypothesis* is that preoperative education and training combined with independent, self-directed, repeated postoperative use of VR-BF will be feasible and acceptable in this population. This proposal addresses key components necessary for the design of a large-scale, clinical efficacy trial.

3.0 Background

There have been many attempts to enhance analgesia by combining various groups of medications while deemphasizing the use of opioids. Despite these attempts, the percentage of patients experiencing severe pain after surgery has essentially remained the same for the last 20 years.[6,7] Many children are initially exposed to opioids to treat pain,[1] and surgery is typically the point of their initial opioid exposure.[58-60] Just five days of opioid use can increase the risk of persistent use, and use for more than eight days may increase that risk nearly 50-fold.[58,61]

Children and adolescents are at risk of persistent pain[5,60,62,63] and opioid use[65] after surgery. Chronic postsurgical pain (CPSP) is defined as pain extending beyond that expected from surgery. A recent study identified an approximate 20% incidence of CPSP in children.[5] While 80% of these patients recover without issue, about 20% maintain a reduced quality of life due to persistent pain.[5] Children are not just at risk of developing CPSP; they are also at risk of persistent opioid use after surgery,[58,59] as opioids have long been the cornerstone of postoperative pain management.[64] A study of opioid-naïve patients (13-21 years) who underwent one of 13 surgeries found persistent opioid use in 4.8% of adolescents compared to 0.1% in a matched, nonsurgical cohort.[58] In a study assessing patients with chronic pain using opioids, more than 25% of patients transitioned to chronic use after receiving opioids for surgery.[65] *Novel, nonpharmacologic strategies are needed to reduce the risk, adverse consequences, and long-term impact of persistent pain and opioid use.*

Mind-body therapies, like biofeedback (BF), provide sustained pain reduction,[8-18,22,66-71] and have the potential to reduce pain and opioid use after surgery, but there are barriers to their routine use in postoperative[72,73] and inpatient settings.[74] BF reduces pain[8,75] by teaching patients to modify the behavioral responses that influence their pain and by changing their brain's perception of that pain, resulting in improved physical, mental, and emotional health.[19,20] By slowing breathing during BF, patients increase their heartrate variability (HRV),[76] which activates the parasympathetic nervous system to increase vagal tone, resulting in pain reduction.[19,20] Implementation of BF, however, is fraught with barriers, particularly with respect to the availability of trained providers in inpatient and acute settings.[8,9,77] Further, application of BF uses various computerized instruments to provide instantaneous data to patients to teach and reinforce physiological self-regulation. Because BF is so resource-intensive, widespread application has not been possible.[78] As such, BF is not available to help manage pain in children

after surgery. In order to increase availability,[79] novel strategies are needed to deliver this effective therapy at point-of-care. *Biofeedback-based virtual reality (VR-BF) has the potential to reduce pain and opioid requirements and to fill the unmet need for alternative, effective mind-body therapy for children with acute postoperative pain by increasing accessibility and acceptability of BF therapy.*

Distraction-based virtual reality (VR-D) transiently reduces pain by redirecting attention but is insufficient to manage prolonged pain associated with surgery. VR has been used to temporarily reduce pain in multiple clinical situations.[25-28,32-34,36,46,49] Most studies assess the application of VR-D to minimize pain during acutely painful procedures in adults[33,34,36,40,41,48,80-83] and children[26,32,39,84-86] by redirecting attention. Without VR, distraction alone provides little benefit in pain reduction,[87] with no lasting or significant impact.[49,50] The improved efficacy of VR-D to temporarily reduce pain compared to distraction alone is related to the immersion created by VR.[44,88] Studies using VR to help manage postoperative pain shows pilot effectiveness in adults to transiently reduce pain after a single session.[89,90] Our unpublished pilot work marks the first study to assess the impact of VR-D on pediatric postoperative pain. Results of our study were similar to the results of these two adult studies.[91] *Although VR-D is more effective than distraction alone, transient pain reductions associated with VR-D are insufficient to treat prolonged pain experiences, including postoperative pain.*

VR-based delivery may enhance BF, making this therapy more engaging and relevant[92] and increase its accessibility.[78] Administering BF in diverse clinical settings has several challenges, including a lack of engagement, a dependence on administration by a trained clinical provider, and a lack of motivation for repetition.[78,93] Using VR to deliver mind-body therapies, like BF, can increase their accessibility while enhancing acceptability, motivation,[47] and adherence[52] compared to methods without VR.[78] Combined, these two therapies could be accessible and useful in many clinical settings,[78,92] including in the management of acute postoperative pain. *VR-BF has the potential to avoid many of the common challenges of administering conventional mind-body therapies, allowing its widespread dissemination for postsurgical care.*

VR-BF has not yet been employed in perioperative care, therefore no defined treatment protocols for preoperative training and postoperative application of VR-BF exist. The literature supports the use of education and training to master and optimize the success of mind-body techniques.[19,20,78,94] Studies of VR-based mind-body interventions support teaching patients about the role of the autonomic nervous system on stress and pain and teaching patients how to alter their physiological response *prior* to the VR sessions.[52,55,78] Classically, BF is done in weekly sessions with a clinical psychologist coupled with daily, 10-minute home practice sessions.[20] In studies of adult and pediatric migraine patients, home practice between formal sessions enhanced BF efficacy.[95,96] For postsurgical pain, our pilot work (**CCHMC IRB #2018-2892**) showed that initiating mind-body training after surgery, while the patient is experiencing considerable pain and fatigue, is not optimal. Providing preoperative education and training and enabling technique mastery prior to the pain and stress caused by surgery may improve efficacy and enhance acceptability of VR-BF.[19,20,56,57] *Aim 1a will refine a VR-BF preoperative education and training protocol and help define the number and duration of sessions needed before surgery.*

VR-BF is a new therapy. Optimal frequency and duration of therapy sessions have not been established. Although the standard duration of a BF session is about ten minutes,[20,97] VR-D sessions range from five[80] to ten[33,81,98] to 30 minutes.[82,90] Frequency of BF sessions have ranged from just one[97] to six weekly sessions.[20] Published studies of VR-D to manage pain primarily use VR during acute pain from procedures such as cystoscopy,[83] IV placement,[32] dressing changes or

acute burn care,[24,26,31,33,36,38,40,42,45,46,48,82] dental procedures,[34,35] episiotomy repair,[81] or during labor.[98] Like our unpublished pilot studies,[91,99] the single study applying VR-D in adults after surgery used one postoperative session.[90] The variability of treatment regimens used in the literature does not provide a model for VR-BF dosing. *Aim 1b will help determine the appropriate frequency and duration of VR-BF to help identify the appropriate "dose" of therapy following surgery*.

This proposed study seeks to establish measurable milestones that have not been addressed in prior studies. Aim 1 will refine a treatment protocol for preoperative education and training and postoperative application of VR-BF in children and adolescents for Aim 2, the pilot feasibility and acceptability trial. By understanding the key components of VR-BF and demonstrating feasibility and acceptability of the trial design, we will optimize design and execution of a large-scale, randomized, controlled efficacy trial comparing VR-BF to active control in this patient population. **Before conducting this efficacy trial of VR-BF versus active control, it is imperative to assess factors that will impact the VR-BF intervention[105] and, consequently, the efficacy of VR-BF to reduce pain and opioid use.** This study will answer "*whether the future trial can be done, should be done, and, if so, how*."[106]

PILOT DATA (CCHMC IRB #2018-2892)

Recruitment data. In FY2020, a total of 25,122 surgeries were performed at Cincinnati Children's Hospital. Of those, 952 patients were followed by the Acute Pain Service for management of moderate to severe postoperative pain. Between November 2018 and March 2020, we conducted two pilot studies using VR-D and biofeedback-based VR (VR-BF). We screened 550 patients. Based on eligibility criteria, 95 (17%) were ineligible. We approached 235 patients after surgery. Of those approached, 82% were interested in the study and 43% were successfully recruited and completed the study. Despite being interested, many eligible patients declined enrollment due to feeling tired, being in too much pain, or needing to participate in other clinical care. *This pilot data informed our decision to recruit patients preoperatively in efforts to increase recruitment and enhance buy-in for this therapy with preoperative education and training*. *Ultimately, we believe this strategy will also enhance efficacy as technique practice and mastery are likely necessary components of efficacy*.

Variables	VR-D	VR-BF
Age – mean (SD), years	15.6 (2.5)	14.6 (3.2)
Sex – male/female (n)	31/19	32/19
Race (%)		
Caucasian	88%	80%
Non-Caucasian	12%	20%
Surgery type (%)		
Abdominal	38%	37%
Pectus/chest	34%	41%
Orthopedic	28%	22%
Baseline NRS scores – mean (SD)		
Pain intensity (0-10)	4.68 (2.09)	5.11 (1.74)
Pain unpleasantness (0-10)	5.39 (2.50)	5.73 (2.30)
Anxiety (0-10)	1.79 (2.52)	2.05 (2.50)

Table 1. Characteristics of VR-D, VR-BF patients.

Reduction of pain and anxiety with VR-D. Children and adolescents (8-18 years) being managed by Cincinnati Children's Hospital Acute Pain Service for moderate to severe pain after surgery were screened for eligibility. Over seven months, we enrolled 50 patients to participate in a single, 10-minute postoperative VR-D session (Table 1). After consent, patients were asked to complete surveys for

trait measures: (a) pain catastrophizing (Pain Catastrophizing Scale for Children, PCS-C)[107] and (b) anxiety sensitivity (Child Anxiety Sensitivity Index, CASI).[108,109] Children played one of three games (all provided a similar distraction-based experience) for ten minutes. Patients were asked to rate their pain intensity, pain unpleasantness, and anxiety using the numerical rating scale (NRS)[110,111] immediately and 15 and 30 minutes after the VR session. Pain intensity decreased by about 1 point immediately following the session (p<0.0001), and this change remained significant at 15 minutes (0.4 points, p=0.02) but not at 30 minutes. Pain unpleasantness decreased significantly (1.5 points, p<0.0001) immediately following the VR-D session and this change remained significant at 15 (0.8 points, p=0.0008) and 30 minutes (0.33 points, p=0.0001) following session completion. We found only minimal associations of VR-D with anxiety. Anxiety decreased from baseline by about 1 point immediately following the session (p<0.0001) and remained lower at 15 minutes (0.4 points, p=0.0014) but was no longer significant at 30 minutes. Levels of pain catastrophizing and anxiety sensitivity were not associated with changes in pain and anxiety. No patients experienced adverse effects related to VR-D. *Small, transient changes in pain and anxiety were associated with a single, 10-minute postoperative VR-D session. These results informed our decision to explore integration of a mind-body therapy with VR using a commercially available VR application*.

Reduction of pain and anxiety with VR-BF. In a follow-up study, patients (n=51) were recruited from the Acute Pain Service over 8 months (Table 1) using the same eligibility criteria used in the VR-D pilot study. The same approach was used as described above but instead of receiving a single, 10-minute VR-D session, patients underwent a single, 10-minute session using *Mindful Aurora*, an application that engages patients in guided relaxation and slow breathing. Moderate changes in pain intensity and pain unpleasantness and small changes in anxiety were found to be associated with the VR-BF session (Figure 2). Pain intensity decreased by about 1 point immediately (p=0.002) and 30 minutes (p= 0.028) following VR-BF but was not significant at 15 minutes. Pain unpleasantness decreased by about 1.5 points immediately (p=0.001), 1.1 points at 15 (p=0.025), and 2 points at 30 minutes (p=0.001) following VR-BF. Anxiety decreased by about 0.9 points immediately following VR-BF (p=0.008); changes were not significant at 15 or 30 minutes. Anxiety sensitivity was associated with greater reductions in pain intensity (Beta (SE) = -0.06 (0.03), p=0.0426) and pain unpleasantness (Beta (SE) = -0.09 (0.04), p=0.0111). Pain catastrophizing was not associated with changes in outcomes. No patients experienced adverse effects related to VR-BF. *Small, transient changes in pain and anxiety were associated with a single postoperative VR-BF session. These results highlighted the need for preoperative education and training and multiple sessions after surgery to likely produce greater and more sustained reductions in pain*.[20,78,112]

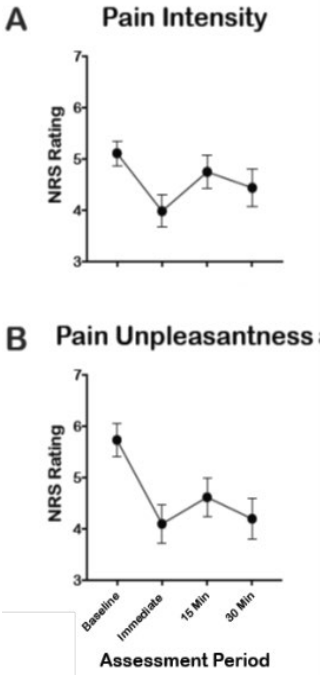

Figure 2. Changes in pain following VR-BF. Figure provided for graphical purposes only.

Patient and family satisfaction. Qualitative data from our pilot studies indicated high levels of patient and family satisfaction. Survey data showed 94% of patients in the VR-D pilot and 96% of patients in the VR-BF pilot would "*recommend friends or family to try VR during their visits*." Although the survey data clearly expressed the overwhelming positive attitude that patients had toward VR, it was unable to capture the magnitude of patient engagement and satisfaction best told through patient experiences. An

adolescent male completely bed-ridden due to abdominal pain was able to sit up for the first time while using VR in our study. Because he felt that VR was the only intervention to help his pain, his family purchased a VR headset for use during his rehabilitation. Acceptance and appreciation of VR treatment by families has been near universal. According to survey data of parents of enrolled patients, 95% of parents from the VR-D and 100% of parents from the VR-BF pilots would recommend VR to friends or family. Parents consistently exhibited tangible changes in emotion and disposition when watching their child use VR. Fatigue and stress were suddenly replaced by relief and excitement. In addition to enthusiastic patient and family feedback, surgeons have also been highly engaged, with one expressing that "*this innovative therapy will help transform how we deliver postoperative care at our institution*." Another, while initially skeptical, received so much positive feedback from his patients enrolled in our studies that he has engaged us to apply VR to patients in one of his NIH-funded trials. *These anecdotal reports of improvements in pain, mood, and positive reports from patients, families, and providers show high acceptance of VR therapy*. *This level of engagement will be crucial for integration of VR-BF into postoperative pain management*.

4.0 Study Endpoints

Primary endpoint: Successful accrual of patients and completion of study

Secondary endpoints: Refinement of VR-BF platform; protocol for preoperative education training in and postoperative delivery of VR-BF; feasibility and acceptability data for clinical efficacy trial design; preliminary assessment of efficacy trial outcomes.

Safety endpoints: NA

5.0 Study Intervention/Investigational Agent

Description: The VR headsets (Oculus/Meta Quest) used in this study are minimal risk devices, and because they are considered a relaxation device by the FDA, they are not regulated. The Oculus/Meta Quest have been used in prior studies without any reported adverse events (**CCHMC IRBs #2019-1090, 2020-0258, 2020-0612**). FOREVR VR is a device developed by the research team approved for research use by the Equipment and Standards Committee at Cincinnati Children's Hospital. It is a noninvasive device that measures respiratory rate (via chest movement) and heart rate using an ear clip. This device also bears minimal risk. It has also now been approved for clinical use at CCHMC by this same committee.

Back-Up Intervention: Should there be technical challenges with FOREVR VR, we will use HeartMath Inner Balance as a back-up means to collect heart rate and use data (www.heartmath.com), a commercially available biofeedback device. HeartMath Inner Balance is also considered a non-invasive device and uses an ear clip to collect heart rate data (analogous to FOREVR VR). There is minimal risk with the use of this device.

Drug/Device Handling: All equipment will be kept in a secured area in a locked cabinet/office to be used only on subjects by authorized study team members.

6.0 Procedures Involved*

Table 2 (below) summarizes the measures and goals of this proposal.

Overall experimental design. We *hypothesize* that the use of VR-BF in children undergoing surgery resulting in moderate to severe pain will be feasible and acceptable. Findings from this

pilot trial will inform design of a large-scale efficacy trial of VR-BF versus active control in this patient population. The *goals* of this study are to define the approaches for effective training in and delivery of VR-BF and to conduct a pilot clinical trial to assess the feasibility and acceptability of VR-BF in managing moderate to severe postoperative pain in children and adolescents. This pilot study will be conducted in two phases: Phase 1 (Aim 1) will refine our VR-BF intervention allowing us to create a treatment protocol for VR-BF. Phase 2 (Aim 2) will conduct a pilot clinical trial assessing feasibility and acceptability of the intervention. Phase 2 will inform development of a manual of procedures for efficacy trial design and provide key pilot data for future extramural grant applications.

		Measures	Goal(s)
Aim 1 (Phase 1)	**a**	Questionnaires, semi-structured interviews, use of VR-BF, sensitivity to change of physiological parameters (HR and respiratory rate)	Refined VR-BF treatment protocol VR-BF dose
	b	Questionnaires, semi-structured interviews, use of VR-BF, sensitivity to change of physiological parameters (HR and respiratory rate)	
Aim 2 (Phase 2)	**a**	Rates of recruitment, enrollment and randomization, retention, adherence; qualitative data assessed with questionnaires and semi-structured interviews; pain, anxiety, and opioid consumption; physiological parameter achievement (HR and respiratory rate)	Feasibility and acceptability of VR-BF and active control in perioperative setting VR-BF dose finalization Pilot data for R01 application
	b	Treatment/study burden, satisfaction, treatment credibility, and tolerability; qualitative data assessed with questionnaires and semi-structured interviews; physiological parameter achievement (HR and respiratory rate)	

Table 2. Proposed outcome measures and goals for Aims 1 and 2.

Study population. Subjects will be recruited when scheduled for surgery at Nationwide Children's Hospital. We will coordinate recruitment efforts with surgeons who perform surgeries that require pain management by the Acute Pain Service. We will screen patient lists provided by the surgical schedulers as well as operating room schedules to identify potentially eligible patients prior to their scheduled surgery. Messages assessing interest in the study will be sent through MyChart. We anticipate recruiting 1 patient per week. We are confident that we can successfully recruit and enroll our full cohort of up to 102 patients: up to 32 for Aim 1 (minimum 12 patients) and 70 for Aim 2.

Blinding. Although patients will not be blinded to the intervention they receive, patients and families will be blinded with respect to the study arms. Therefore, the consent will describe the study as assessing technology-based interventions for the management of pain without specific detail about VR-BF (FOREVR VR) or *Manage My Pain* or indicate the use of any device, such as a headset. Once assigned to a group, patients will receive a handout describing the intervention with instructions and information about what participation entails. We will also blind data collection by using a study number for each patient and will not indicate in which arm the patient is enrolled in data collection forms. The biostatistician will be blinded to the patient groups during analysis.

Study Materials

***Self-reported measures*.** Patients will be asked to complete a survey at the end of study participation as well as participate in a semi-structured interview. Parents will also be asked to complete a survey. The questionnaires will be completed through the Research Electronic Data Capture (REDCap) database.

VR headset. Participants will use the Oculus/Meta Quest VR headset with the FOREVR VR device. When necessary, we will use the software supplied by Invincikids (*Mindful Aurora* application) with the Oculus/Meta Quest.

The Oculus/Meta Quest VR devices are non-invasive, relaxation devices that are commercially and widely available to deliver mobile (untethered) VR content to the patient; they are not FDA regulated. Both devices are all-in-one headsets, so no additional hardware is required to deliver the VR experience. These devices have audio capabilities built into the headset to deliver instructions and application sounds, creating an immersive experience. We have used these devices in multiple IRBs since 2018 without any adverse events. Each VR headset will be cleaned with an alcohol or peroxide wipe according to infection control standards following use of the device by the patient as well as prior to use for each patient and may undergo further cleaning with UV light using the Cleanbox (https://cleanboxtech.com/).

VR session. All participants will receive a device tutorial at the start of the study which will entail teaching them how to use the device and introducing them to the VR-BF software. They will be taught how to sync their breathing with the application. Patients will be instructed to remove the device should any discomfort or side effects occur, such as motion sickness, dizziness, or nausea.

FOREVR VR. FOREVR VR is the result of the collaboration between our research team, engineers at the Digital Experience (DX) Center at Cincinnati Children's Hospital, and programmers at House of Moves, an animation and motion capture studio in Los Angeles, California. FOREVR VR integrates real-time patient physiological data into a gamified environment using a chest strap (to monitor respiration) and an ear clip (adapted from HeartMath, see below) to measure heart rate. This technique is effective in reducing respiratory rate, and consequently, increasing heartrate variability.[20,97] This increased heartrate variability increases vagal tone, resulting in activation of the parasympathetic response and decreased pain.[97]

VR-BF content. We currently have two game options for use with the FOREVR VR device. The first is a 360-video shot in Eden Park (a public park in Cincinnati, OH) that starts out as a stand-still, black and white image that adds color and eventually motion as the participant achieves target heart rate and respiratory rate targets. The second is a blooming flower scene that starts with a clean, blank scene that allows the participant to have a flower appear and fully bloom as he/she achieves target physiological parameters.

We are currently finalizing the *Mysterious Island* game with House of Moves which we plan on using for the study once it becomes available. In this game, participants will be transported to a beautiful tropical island in which the participant will use breath to explore the island. As the patient breathes in, they will make a small rise in the VR world upwards and breathing out will propel forward movement. The motions are small and gentle to minimize the risk of motion sickness. The entire VR space syncs with the patient's breathing. During the course of the experience, the participant will travel through a sunny island full of palm trees, caves, and tropical flowers. The user will move towards a beach to watch the sunset. The user will also encounter several tropical animals and birds. The VR world will combine a total of 3 locations: a tropical island and trail going to the entrance of a cave, the cave, and a beach. On the tropical path, the user will encounter a waterfall, up to 5 different tropical birds, and 2 different animals (hippo and monkey). This experience in its entirety will take up to 10 minutes.

Back-Up Technology. This is the first study to use FOREVR VR. Although we anticipate success with its use, we appreciate the difficulties of using any new technology. We therefore have a

back-up plan in place using existing technology. Should it be necessary, we will use the Oculus/Meta Quest with the *Mindful Aurora* application and monitor heart rate/heart rate variability with the commercially available HeartMath Inner Balance device (www.heartmath.com). HeartMath is a program that is used clinically at Cincinnati Children's Hospital to teach biofeedback and that can document a patient's use of the application and heart rate/heart rate variability. The Inner Balance device integrates directly with a participant's smart phone device. HeartMath products are currently used in over 500 institutions. From a research perspective, they have been used in over 11,500 subjects resulting in over 400 peer-reviewed publications. Analogous to FOREVR VR, it uses an ear clip to measure heart rate. It stores information about use and performance in an application that is accessible to the research team. Dr. Williams, one of the co-investigators, is an expert in the use of HeartMath for biofeedback.

In this scenario, the *Mindful Aurora* application would be used to deliver the VR content. This application acts as an escape for patients as well as a tool to help them learn slow breathing and relaxation techniques. It transports patients to an alpine meadow. With the help of a 10-minute relaxation narrative, study participants will observe the world transition from day to night while focusing on paced breathing. The goal of the application is to have participants mirror the rate of their breathing with the virtual world around them, which includes changes in floating butterflies and swaying trees to assist in the pacing of their breathing. This technique is effective in reducing respiratory rate, and consequently, increasing heartrate variability.[20,97] This increased heartrate variability increases vagal tone, resulting in activation of the parasympathetic response and decreased pain.[97] This is the same application that has been used to deliver VR-BF content in **CCHMC IRB #2018-2892, 2019-1090, and 2020-0258**.

***Manage My Pain*.** Control patients in Aim 2 will use the *Manage My Pain* application analogously to VR-BF per the protocol developed in Phase 1. This commercially available application is designed to assist patients with recognizing and reflecting on their pain and is highly engaging. It is available for iPhone, Android, and laptop download and is approved for children 12 years of age and older. In an assessment of commercially available pain applications, *Manage My Pain* was found to be appropriate for adolescents and had a high engagement score (4.2/5) as well as an excellent functionality rating (4.5/5).[114] While it scored high overall (application quality score 4.06/5), it lacks the immersion and specific instruction in behavior change techniques,[114] which are key features of VR-BF.

Device Tracking. Participants in Phase 1 as well as those randomized to the VR group in Aim 2 will receive a VR headset and FOREVR VR device to take home. During the first visit, these patients and families will be told that they will be given temporary possession of this equipment. To help increase our ability to retrieve these devices, they will be asked to sign a Device Agreement form. We will plan to collect the devices in the first postoperative clinic visit. If this is not possible, we will provide patients with a prepaid label and box to mail the device back to us. Other arrangements may be made with families for device retrieval as necessary.

Study Procedures

Aim 1: We will accomplish Aim 1 using an iterative study design eliciting data through questionnaires and semi-structured interviews of pediatric patients scheduled to undergo surgery anticipated to have moderate to severe pain with a length of stay at least one night in the hospital post-op. We will use a grounded theory[114,115] and thematic analysis[116] approach to study design, data collection, and analysis.

Research Design. We will recruit up to 32 patients (minimum 12 patients, 12-18 years) scheduled for surgery anticipated to cause moderate to severe pain with admission of at least one night in the hospital post-op to participate in Aim 1 (Figure 2). Purposive sampling will be used to select a representative patient group according to age, sex, and race. We anticipate recruiting about 1 patient per week. Patients will be identified when scheduled for surgery. They will receive scripted instruction on the Oculus/Meta Quest and a tutorial on the biofeedback application. Once device and content education are complete, patients will receive manual-based training on the benefits of HRV BF.[56] They will be given the appropriate equipment and instructed to complete an independent daily, 10-minute session (based on the standard duration of a BF session) and record each session in a log. Patients will bring the equipment to the hospital on the day of surgery for continuation into Aim 1b. After surgery, patients will have free use of VR-BF. They will be instructed to undergo, at minimum, one daily, 10-minute session. They will also be instructed to freely use VR-BF, particularly when in pain. They will use a log to record their VR-BF usage (date, time, and duration). Patients will be visited daily, or more or less frequently as applicable/needed, to assist with log completion and any issues. On the day of discharge, a study team member will conduct a detailed, semi-structured interview. Patients may take the VR-BF device home for up to two weeks for home pain management; a similar log will be used to document home use. We will enroll 4 patients at a time and analyze data to refine the protocol in an iterative fashion; this process will be repeated until 12 patients are enrolled. If further data is required for protocol refinement, we will continue recruiting patients in groups of 4 as necessary until a maximum number of 32 patients is reached.

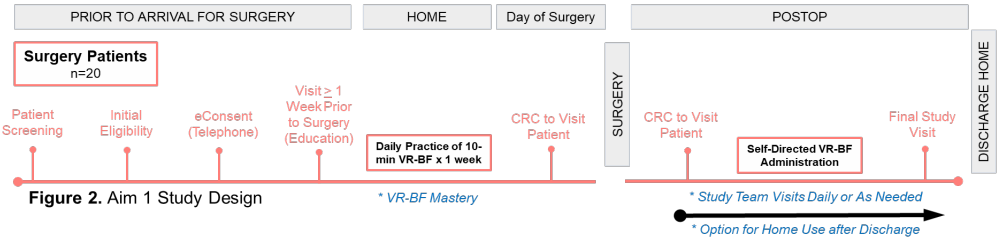

Figure 2. Aim 1 Study Design

Study measures. Qualitative data will be collected using questionnaires and a semi-structured interview to collect feedback on the FOREVR VR platform content and usability, preoperative VR-BF education and training, postoperative application of VR-BF, and perceived efficacy. Review of patient daily use obtained from FOREVR VR will provide quantitative data about frequency and duration of VR-BF use. As mentioned below, we will assess sensitivity to change of physiological parameters (HRV, respiratory rate) to different frequencies and durations of VR-BF use (dose).[117] This data will assist us in determining an appropriate dose (frequency and duration) of VR-BF for training and postoperative pain management to be trialed in Phase 2. Iterative refinements to the VR-BF treatment protocol will be made throughout Aim 1 based on this data. Refinements will be documented, tracked, and applied by the study team.

Aim 2: We will conduct a pilot clinical trial to assess the feasibility and acceptability of the VR-BF protocol defined in Aim 1. Feasibility will be assessed by rates of recruitment, enrollment and randomization, retention, and adherence. Acceptability will be assessed by treatment/study burden, satisfaction, treatment credibility, and intervention tolerability. Qualitative data will also be used to assess feasibility and acceptability.

Patient Groups. Seventy patients with the same inclusion/exclusion criteria described in Aim 1 will be randomized to 1 of 2 groups in a 1:1 ratio: VR-BF or attention control condition using a web-based application (www.randomizer.org). The randomization scheme will be generated prior to the start of the study and patients will be randomized based on subject number. We will use the

protocol generated in Phase 1 to apply either the VR-BF or control condition. Control patients will use the *Manage My Pain* application analogously to VR-BF per the protocol developed in Phase 1. Like the VR-BF group, patients will receive scripted instruction on the benefits of mind-body therapy. We will recruit a total of 70 patients to participate, with 35 in each group. Both patient groups will receive a handout detailing the intervention and what they can expect with participation in the study.

Research Design (Figure 3). Eligibility, recruitment, and study procedures will follow those described in Aim 1 but VR-BF or the control condition will be applied both pre- and postoperatively according to the protocol refined in Phase 1. Figure 3 summarizes Aim 2 design. During the preoperative visit with our study team, patients randomized to the control group will download the *Manage My Pain* application onto their device. If patients do not have a personal device, we will ask a parent to download the program onto his or her phone or computer. We will provide explicit instructions on how to use the application and what features should be used. Patients will also be instructed on how to create a daily report documenting each day's use of the application prior to surgery. These daily reports will be returned to our study team. Like the VR-BF group, patients will receive scripted instruction on the benefits of mind body therapy, will be instructed to use the application for at least 10-minutes per day for seven days prior to surgery, and will be asked to complete a daily report using the application each day. On the day of surgery, a study team member will visit each participant to document possession of the FOREVR VR platform (intervention group), to collect reports, and to any answer questions.

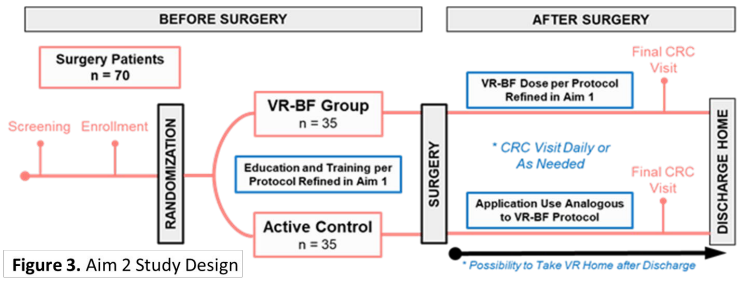

Figure 3. Aim 2 Study Design

After surgery, as in Aim 1, a trained CRC will visit patients daily or as needed while hospitalized. Control group patients will complete a daily application-generated usage report (date, time, duration); VR-BF patients will have this information, along with HRV and respiratory rate data, obtained from the device. To help determine what outcomes may be impacted by VR-BF for future trial development, patients will also be asked to document pain and anxiety scores before and after each VR-BF or application session using the NRS.[110,111] Patients will self-report and document these scores before each session and then immediately, 15 minutes, and 30 minutes after session completion. All pain scores and opioid consumption (in morphine equivalents mg/kg/day) will be collected from EPIC, the electronic medical record, for each 24-hour period during study enrollment; anxiety scores are not documented by the nursing staff so only self-reported scores will be used. Documented pain scores will also help finalize the "dose" of VR-BF to be used in the efficacy trial as we will assess for correlation, if any, between pain score and use of VR-BF. At the final study visit prior to discharge, patients will answer a questionnaire and engage in a semi-structured interview soliciting qualitative feedback about their experience with the intervention or control to finalize the study protocol for the clinical efficacy trial. Participants will be given the option to take the VR-BF platform home or continue using the *Manage My Pain* application for up to two weeks after discharge. If this option is selected, patients will complete a daily log/report documenting use, pain scores, and opioid consumption. During the first postoperative clinic visit, VR-BF and reports/logs will be collected and questions about home use will be asked, answered, and recorded. Parents will also be asked to complete a survey about their experience and opinions. If patients cannot be met during the first postoperative clinic visits, other arrangements will be made to collect the information and equipment.

Data Collection (Table 3). Feasibility. *Recruitment*: The number of patients screened per month will be recorded and assessed for eligibility; reasons for ineligibility will be recorded. If 80% of patients do not meet criteria, we will adjust criteria as necessary. *Enrollment and randomization*: Enrollment and randomization will be defined as agreeing to participate in the study and being willing to be randomized. We will record the number of eligible patients approached and enrolled each month. We will collect reasons for refusal to enroll, including unwillingness to be randomized. If rates are not maintained at 80%, we will adjust strategies accordingly. *Retention*: We will define retention as the number of patients who complete the study by participation in the last study visit for both arms. We will collect reasons for dropout. If ≥ 80% retention is not maintained, we will evaluate reasons for dropout. *Adherence*: We will define adherence to preoperative training as completion of the education and training session with the study team and completion of ≥ 5/7 daily sessions. Adherence to postoperative VR-BF/app use will be defined as completion of ≥ 5/7 daily sessions. Our target will be ≥ 80% completion. We will collect reasons for failure. Questionnaires and the semi-structured interview will also assess feasibility using measures based in the literature.[119] Acceptability. *Treatment/Study Burden*: Burden will be assessed by collecting data on daily log completion, data from questionnaires, and participation in the interview. We will collect reasons for drop out to better understand treatment and study burden.

	Measures	Definition	Benchmarks	Additional Data
Feasibility	**Recruitment**	Number of patients screened per month	≥ 80% will meet eligibility criteria	Reasons for not meeting criteria
	Enrollment and randomization	Number of patients approached who agree to enroll in the study and be randomized to a treatment arm	≥ 80% of those approached will agree to enroll and be randomized	Reasons for refusal, including unwillingness to be randomized
	Retention	Number of participants who complete the study as defined by participation in the last study visit	≥ 80% retention	Reasons for dropout
	Adherence	Treatment-specific adherence	≥ 80% will complete ≥ 1 session per day for ≥ 5/7 days (preop) and ≥ 1 session per day (postop)	Reasons for failure
Acceptability	**Burden**	Percent completion of daily logs/reports, percent completion of questionnaires and interview	≥ 80% completion of all study measures	Reasons for failures
	Satisfaction	Patient/parent satisfaction	NA	Questionnaires, semi-structured interview
	Credibility	Perception of efficacy	NA	Questionnaires, semi-structured interview
	Tolerability	Number and percent of patients experiencing AEs	< 1% will experience a serious AE	Reasons for not tolerating therapy, AEs

Table 3. Feasibility and acceptability outcome measures and benchmarks**.**

We anticipate ≥ 75% of patients will complete all study measures, with completion of daily logs defined as completion of ≥ 5/7 daily logs. *Satisfaction*: Satisfaction will be assessed by questionnaire and the semi-structured interview. Development of these qualitative assessments are based on reported measures of acceptability.[102,119] *Treatment credibility*: We will define treatment credibility as patient perception of treatment efficacy as measured by survey and interview. *Tolerability*: We will record the number of adverse effects (minor, moderate/severe)

from therapy. We anticipate a very low rate (<1%) of adverse events. We will collect qualitative acceptability data using questionnaires and the semi-structured interview using measures based in the literature.[102,119]

Additional Data Collection
The following data may be collected in the CRF: (a) type and duration of anesthesia and surgery where applicable; (b) anxiety and pain scores (both intensity and unpleasantness as well as pain medications used to treat the patient (including doses and number of rescues); (c) satisfaction with VR device/comments; (d) desire for study team to return; (e) any critical or adverse events. Survey data will be captured directly into REDCap or paper forms.
We will also collect descriptive data from the health record for each patient, such as age, sex, race, ethnicity, ASA status, type of surgery, diagnosis at surgery, underlying medical conditions, medications taken prior to surgery, and treatment history. We will record VR experience, presentation order, and any use of corrective lenses. Anxiety and pain will be collected with numerical rating scale (NRS) prior to and after the VR intervention for patients in all 3 cohorts. Additional outcome measures will be pulled from EPIC regarding narcotic/medication consumption during hospitalization, all pain assessments during the hospitalization, and length of stay. We will collect all heart rate, respiratory rate, and FOREVR VR usage from the FOREVR VR device (or HeartMath if necessary).

7.0 Data and Specimen Banking*
NA

8.0 Sharing of Results with Subjects*
NA

9.0 Study Timelines*
Each individual subject will have a participation period of no more than 3 months depending on timing of initial preoperative visit. Patients will be approached before surgery, have a study visit in person or virtual before surgery, and participate in practice sessions for 1 week prior to surgery. They will participate in the study during their hospitalization and may opt to continue participation for up to 2 weeks following hospital discharge.

We anticipate a total of up to 3 years to fully enroll all study subjects.

We anticipate completion of primary analysis by the end of year 3 (12/24).

10.0 Inclusion and Exclusion Criteria*
Screening: Surgery patient lists and the operating room schedules will be screened for eligible patients based upon basic eligibility criteria such as age and surgical procedure.

Inclusion/Exclusion:
Inclusion criteria. Patients will be eligible if they are:
- Between the ages of 12 and 18 years, inclusive
- Able to read, understand, and speak English
- Scheduled to undergo surgery at NCH anticipated to cause moderate to severe pain with staying at least 1 night in the hospital post-op.

- Require postoperative pain management by the Acute Pain Service
- Own or have access to a mobile device or computer for study participation

Exclusion criteria. Patients will be ineligible if they:
- Are less than 12 years of age or older than 18 years of age
- Are non-English speaking
- Have a history of significant developmental delay, psychiatric conditions associated with hallucinations or delusions, or significant neurological disease, especially epilepsy/seizure disorder
- Have a history of significant motion sickness
- Have a history of chronic pain
- Are chronically using opioids or benzodiazepines for the management of pain
- Are actively experiencing nausea or vomiting
- Have any conditions that preclude their ability to use the virtual reality (VR) headset, such as craniofacial abnormalities or surgeries of the head and neck
- Previous participation in this study
  Children (ages 12-18 years) will be included in this study. No other vulnerable populations will be included.

11.0 Vulnerable Populations*

We will include children, and will not include pregnant women, and prisoners as they are not part of our usual patient population.

This study presents no more than minimal risk as it only requires use of VR-BF or computer application and completing questionnaires and interviews.

Study staff will discuss the study with the parents and children together, review the consent form with them, answer any questions, and obtain parental permission and assent from those children able to provide it.

12.0 Local Number of Subjects

Total number of subjects to be accrued locally: up to 102
We anticipate a $\geq$ 80% recruitment and retention rate

13.0 Recruitment Methods

Patient Recruitment. Participants who are being managed by the Acute Postoperative Pain Service for the management of moderate to severe postoperative pain will be recruited continuously throughout the course of the study until enrollment numbers for each cohort are met. Once the family agrees that this is a study that they want to hear more about, a team member will describe the study procedures and verify eligibility criteria. Specifically, a team member will explain the study in greater detail and invite them to participate in the study. If the family is interested in proceeding to the consenting phase of the study, a team member will review the consent and assent in detail and cover all required elements of consent. The team member will answer any questions and verify understanding of the consent by asking questions about the study to the parent and child. The research coordinator will give the family adequate time to review the consent/assent form in full on their own. It will be made clear to the family that participation is

completely voluntary, non-participation will not result in any consequences to them, and they are free to withdraw at any time for any reason.

Consenting/Assenting Procedures and Considerations. Due to needing subjects to begin study participation prior to surgery, we are requesting permission to consent by phone. Consent for participation will be done via an e-consent platform conducted through an application (REDCap or another NCH supported application or with a paper informed consent form (ICF) provided ahead of time. A member of the study team will arrange for a time to discuss the study with the parent/LAR over the phone and answer any questions they may have about study participation. Informed consent will be documented by the person obtaining consent and parents/LAR will be asked to sign via the e-consent platform or if using the paper ICF, to bring the original version of the ICF with them to the training appointment. (see Section 12 for further detail). Subject/parent/guardian identity will be verified with documentation in EPIC.

Requirements. A signed consent form will be obtained from the participant. For participants who cannot consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the participant's assent must also be obtained if he or she is able to understand the nature, significance, and risks/benefits associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the signed consent form will be given to the participant, parent, or legal guardian, and this fact will be documented in the participant's record.

Procedure. The approved, HIPAA compliant informed consent/assent will be provided to the study participant and the parents for review. The consent will be completed through the Research Electronic Data Capture (REDCap) database or on paper forms (if eConsent is unavailable at the time of consent). After allowing adequate time for review, the participant and parents will have the opportunity to ask questions and receive answers. When all questions have been answered, the consent and/or assent will be signed, and a signed copy will be provided to the participant and parents. This will all be conducted before any study measures interventions are undertaken.

Phone Consent. Due to needing subjects to begin study participation prior to surgery, we are requesting permission to consent by phone in order to have time to have subjects be trained on the technology prior to the scheduled surgery. Potential subjects may schedule surgery over the phone or at an in-person visit however subjects who are in person may not be available for approach due time constraints or already being overwhelmed with information regarding the surgery.

Documentation of Ineligibility. Screen failures will be documented on the source worksheets with the supporting data accompanying the eligibility screening form. Documentation of ineligibility or non-participation for each consented participant will be maintained in an electronic database (e.g., REDCap). Reports detailing the reasons for screen-failure and non-participation of eligible participants will reviewed by the study team to determine if the exclusion criteria require revision in order to make the study accessible to families and study participants.

Payment. Patients may receive a stipend for participation, not to exceed a total of $100 per patient. For time and inconvenience, the subject will receive up to $100 - $50 for completing all pre-surgery activities and an additional $50 when the device is returned. There is no difference in how subjects will be compensated based on the phase of the study they are in.

Subjects will be issued a debit card specially designed for clinical research. When a study visit is completed, funds will be approved and automatically loaded onto the card.

14.0 Withdrawal of Subjects*

We do not anticipate any withdrawal of subjects or early termination.

15.0 Risks to Subjects*

There are minimal physical risks to participants and enrollment in this study will not alter their management. All patients will receive pain management per the Acute Pain Service during the duration of the study.

Clinical Care. Enrolled patients will receive the same care and attention in the postoperative period or during their hospital stay as those non-enrolled patients. Patients will be given the opportunity to end participation in the study at any time.

VR Headset. VR headsets used in this study are minimal risk devices, and because they are considered a relaxation device by the FDA, they are not regulated. Risks specific to this research study are minimal or absent with the greatest risk being motion sickness while the headset is in place[113] and a theoretical risk of inducing seizures (0.025% in pediatric data supplied by a similar Samsung device). Should motion sickness occur, the participant will be instructed to remove the device to ensure resolution of symptoms; we will exclude patients with a history of seizure disorder or other relevant neurological conditions. Other adverse events will be defined using standard criteria. The researchers shall monitor the patient while the device is applied. Serious adverse events, although unanticipated, will be reported using routine avenues. The Starlight Xperience device was used in our pilot study (**CCHMC IRB #2018-2892)** without any documentation of adverse effects. We have since purchased new headsets, the Oculus Quest and Oculus Quest 2, which have been used in prior studies without any reported adverse events (**CCHMC IRBs #2019-1090, 2020-0258, 2020-0612**). We will continue updating to newer versions of the Oculus/Meta Quest as they become available when new equipment is required.

FOREVR VR. This device has been approved for both research and clinical use by the Equipment and Standards Committee at Cincinnati Children's Hospital. It is a noninvasive device to measure respiratory rate (via chest movement) and heart rate using an ear clip. This device is also considered a minimal risk device. This is the first study to use FOREVR VR.

HeartMath Inner Balance. If FOREVR VR is unable to be used, we will use HeartMath Inner Balance as a back-up means to collect heart rate and use data (www.heartmath.com), a commercially available biofeedback device. HeartMath Inner Balance is also considered a non-invasive device and uses an ear clip (analogous to FOREVR VR) to collect heart rate data. There is minimal risk with the use of this device.

We do not anticipate any psychological, social, legal, or economic risks to this study. We also do not anticipate risk to others who are not subjects in this study.

16.0 Potential Benefits to Subjects*

Individual study participants may derive direct benefit from participation in the study as the addition of VR or Manage My Pain may enhance standard pain management strategies and result in decreased pain intensity and unpleasantness and anxiety at the time of participation in the study. Participants may also have a longer lasting benefits, but these are currently unexplored,

and this exploration will be part of future studies. Should VR show to be a useful tool to augment pain control, we hope that this technology will ultimately be offered to all pediatric patients coming in for surgery to assist with postoperative pain control. Participation in the study may also decrease medication consumption; however, this potential benefit will be assessed in subsequent studies using the treatment protocol developed in this proposed work. Patients may receive a stipend for participation, not to exceed a total of $100 per patient.

17.0 Data Management* and Confidentiality

Aim 1:

Data analysis. Statistical analysis will be done using SAS 9.4 (Cary, NC). Demographic and baseline characteristics will be summarized for all patients (*categorical variables*: frequency and percent; *continuous variables*: mean ± standard deviation (SD) or median and interquartile range (IQR)).

Qualitative analysis. Qualitative data will be collected via questionnaires and a semi-structured interview (see Appendix 1 for the interview guide and Appendix 2 for the questionnaires) conducted by a trained CRC. The interview script creates a framework for the discussion with further probing based on patients' responses to elicit a rich and informative description of their experiences and perceptions. Interviews will be recorded, assigned an identification number to anonymize content, and transcribed for coding. Each transcript will be independently reviewed by two trained coders and line-by-line content will be analyzed using *a priori* themes evaluating the acceptability and satisfaction with content (understanding, difficulty level, ease of use), feasibility of practice (both at home after preoperative training and after surgery), and perceived helpfulness in reducing pain and distress after surgery. Results will be analyzed and reviewed by the study team after each cohort of four patients has completed Aims 1a and 1b so that iterative changes can be made to refine the protocol (e.g., improvements to the education component, involvement of parents, device adjustments, recommendations for duration and frequency of use postoperatively, etc.) before the next group of four patients is enrolled.

Quantitative analysis (dose). Data will be collected on number of daily practice (preoperative) and therapy (postoperative) sessions completed by each patient, duration of each session, and changes in HRV and respiratory rate parameters over time. We will also assess the total daily dose of sessions by totaling the duration of all sessions per day and assessing the mean and variability of the daily dose. These quantitative data together with quantitative responses from the questionnaires and interviews will be summarized using frequency and percent for categorical variables and mean ± SD or median and IQR for continuous variables. For variables measured multiple times per participant (duration of each practice/therapy session, changes in HRV and respiratory rate), within- and between-subject summary measures of location and variability will be derived and examined.

Sample size. No statistical power analysis was done to determine the sample size for Aim 1. Rather, sample size determination was based on our extensive pilot work and clinical experience with the population along with the team's expertise in protocol refinement studies in intervention development.

Anticipated outcomes. At the end of Phase 1, we anticipate having a refined treatment protocol for preoperative education and training, and postoperative application of VR-BF. This protocol will be piloted in Phase 2. Results from Aim 1 will provide a preliminary study protocol and manual of procedures for the clinical efficacy trial that will be finalized at the end of Aim 2.

Aim 2:

Data analysis. Phase 2 is a single-center, randomized, two-arm, parallel-group, single blinded trial to assess the feasibility and acceptability of the treatment protocol designed in Aim 1. We will ensure study transparency, describing recruitment, enrollment, and outcomes in a Consolidated Standards of Reporting Trials (CONSORT) diagram[106,120] and provide detailed descriptions of the intervention and active control. Demographic and baseline characteristics will be summarized for all patients and within each study group (categorical variables: frequency and percent; continuous variables: mean ± SD or median and IQR).

Quantitative analysis. We will assess measures of feasibility and acceptability for each arm. *Feasibility*. We will calculate descriptive data on 1) How many patients are screened per month; 2) Percentage of patients meeting eligibility criteria; 3) Percentage of eligible patients approached, enrolled, and randomized; 4) Percentage of patients completing Phase 2; and 5) Percentage of patients adhering to preoperative education and postoperative application of VR-BF as defined in the study measures. For each measure, the rates, variances, and two-sided 95% confidence interval (CI) will be reported. Each CI will be examined to determine if the hypothesized value of 80% is contained within the interval. This data will also be used to generate a diagram of participant flow. Because this is a feasibility study, we will not conduct statistical tests on the clinical outcomes collected for exploratory purposes (pain and anxiety ratings, opioid use). We will analyze this data using descriptive measures stratified by treatment arm. *Acceptability*. We will calculate descriptive data on 1) Treatment/study burden: number and percentage of patients completing all study measures; 2) Tolerability: number and percentage of patients experiencing AEs; and 3) Any quantitative data of satisfaction and treatment credibility from questionnaires and semi-structured interviews. For each of these measures, the rates, variances, and two-sided 95% CI will be reported. The CI for treatment/study burden will be examined to determine if the hypothesized value of 80% is contained within the interval. Qualitative treatment credibility and parent/patient satisfaction data will be assessed qualitatively as described below.

Dosing. To finalize VR-BF dosing prior to the efficacy trial, data will be collected on the number of daily practice (preoperative) and therapy (postoperative) sessions completed by each patient, duration of each session, changes in HRV and respiratory rate, and achievement of target HRV and respiratory rate parameters. We will also assess the total daily dose of sessions by totaling the duration of all sessions per day and assessing the mean and variability of the total daily dose. Achievement of target physiological parameters will be assessed by calculating the percentage of time a patient spends within specified targets for each session. Consistency in achieving target HRV and respiratory rate parameters will be defined as a binary outcome (yes/no) when the target range is achieved ≥75% of the time during use (by session and by day). We will run descriptive statistics on duration of each session stratified by sessions achieving consistency (or not) and on frequency and duration of daily use by days achieving consistency (or not). Mean duration per session and mean duration and frequency per day in the group achieving consistency will be used to guide minimal dosing in the efficacy trial. Exploratory analysis. We will examine the association of VR-BF dose (frequency and duration of use) with the change in target physiological parameters to help identify the minimal dose (frequency and duration of use) required to reach consistency in achieving these targets. We will also examine the correlation between pain score reduction and VR-BF use (frequency and duration). We will calculate mean changes in pain score before and after VR-BF and mean frequency and duration of VR-BF use for each patient. We will visualize any correlation using a scatter or box plot and quantify the correlation using Spearman or Pearson correlation coefficients between two continuous variables

and two sample t-tests or Wilcoxon rank-sum tests, as appropriate, between a continuous and categorical variable. Regression on changes in pain score will be used to examine linear or nonlinear correlations between pain reduction and VR-BF use. The same analysis will be repeated for opioid use (mg/kg/day) and patient-reported anxiety scores.

Qualitative analysis. From the questionnaires and semi-structured interviews, we will compile data on satisfaction, credibility, and tolerability as well as additional feasibility data. This qualitative data will be analyzed in the same way as in Aim 1.

Sample size. Seventy subjects will be enrolled and randomized to one of two study arms: intervention and active control. As this is a pilot feasibility and acceptability study, no confirmatory hypothesis testing will be done. Our sample size is based on estimation of two-sided CIs for one proportion with exact formula of the binomial probabilities. To estimate a 95% CI with targeted width of 0.22 and an assumed proportion of 80%, we will need a sample size of 70 (35 per group), resulting in a total of 56 patients (28 per group) included in the analysis after 80% retention.

Anticipated outcomes. We anticipate creating a final VR-BF study manual that will define study procedures for an efficacy trial and provide key pilot data for future grant applications. By the end of Phase 2, we expect to have 1) A defined patient population with clearly delineated eligibility criteria; 2) A clearly delineated preoperative education and training protocol for VR-BF/active control; 3) A dosing strategy (frequency, duration) for postoperative administration of VR-BF/active control; 4) Feasibility and acceptability data for VR-BF/active control; and 5) A preliminary assessment of key outcome measures (pain, anxiety, opioid consumption) to be evaluated in the efficacy trial.

Data Safety:
Data confidentiality will be maintained by data being stored in a password protected computer and any hard copies of patient information stored in a locked office. Data will be transmitted to a password-protected Nationwide Children's computer for further analysis. Data held in REDCap is deemed secure. All individuals using and interacting with this data will be trained appropriately and a member of the study team. Any data transmission will occur via secure emails (not personal). Proper agreements have been executed to cover the sharing of de-identified data from REDCap with a statistician at CCHMC. Data will be de-identified by selecting the option to export data directly from REDCap with all known identifier fields (date, name, address, MRN, etc.) removed. The exported data set will then be shared with CCHMC. Data will be stored for the duration of the study and analysis/presentation up to the time period specified by the IRB.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*
Although this is considered a minimal risk study, we have created a Data Safety Monitoring Plan that has been approved by the NIH. It will be uploaded separately.

19.0 Provisions to Protect the Privacy Interests of Subjects
Subject information will not be given to any other investigators. Subjects and their information will be closely monitored and guarded by study staff; there will be limited access to patients and their information by trained study staff; and subject information will only be shared and discussed between study staff specific to this study.

20.0 Compensation for Research-Related Injury

NA

21.0 Economic Burden to Subjects

Some study communications such as appointment reminders may be done through text messaging and the subject would be responsible for any message and data rates may apply. Subjects will be given the option to communicate via email or phone if they could potentially incur costs due to text messaging.

22.0 Consent Process

Children will be identified from the operating room schedule and surgery patient lists. Parents and children will be provided with oral and written information about the research project and a signed consent will be obtained from the participant. For participants who cannot consent for themselves, such as those below the legal age, a parent or legal guardian must sign the consent form; additionally, the participant's assent will also be obtained if he or she is able to understand the nature, significance and risks/benefits associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks/benefits of participation. A copy of the signed consent form (including assent where appropriate) will be given to the participant, parent or legal guardian and a copy will be placed in the patient's medical record. Patients will be contacted prior to surgery and told about the study. If interested, consent may be signed electronically (see below) or may be obtained during the first preoperative study visit.

Participants may choose to complete an electronic consent by using an application (e.g., REDCap) supported by Nationwide Children's Hospital in compliance with HIPAA designed to protect PHI in the electronic transfer and storage of the consent form. Participants that choose to complete the electronic consent will have the opportunity to review the consent form and talk with research staff. If the potential participant agrees to participate, they will have an opportunity to check a box stating that that agree to provide their consent / parental permission / assent. There will also be fields for their typed name and their signature, along with witness fields. Once the electronic form has been submitted, a copy of the signed form will be provided to the participant. Electronic consents will be maintained within the application. In the event electronic consent is not available papers consent forms will be used.

Subjects and participants will be informed during the consent process (and included in written form) that their consent/assent in the study is fully voluntary and that they may withdraw at any time with no consequence or penalty. The consent process will follow the *SOP: Informed Consent Process for Research (HRP-090)*. Parental permission will be obtained from one parent, even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child as this is a minimal risk study. If a parent is not available or the legal guardian, consent may be obtained from one legal guardian or an individual with the ability to consent for the child. This ability to consent will be verified with documentation in the patient's medical record. As this study involves children of the age of assent, appropriate assent will also be obtained per the *SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)* and will be documented via signature of the subject participating in the study.

23.0 Process to Document Consent in Writing

We will follow *SOP: Written Documentation of Consent (HRP-091)* to obtain consent for this study.

24.0 Setting

All research will be conducted on Nationwide Children's Hospital premises.

25.0 Resources Available

The study team will devote an adequate amount of time each week to ensure recruitment and enrollment timelines and goals are met.
Most study visits will occur in the Clinical Research Services area, 6th floor, Tower Building which is dedicated clinical research space with 6 exam rooms, a CLIA waived lab for processing specimens, EKG, crash cart and all other necessary equipment to conduct a variety of study visits. Studies requiring ancillary services including but not limited to lab, radiology imaging, physical therapy, cardiac diagnostics and/or behavioral health assessments will be seen in those areas for those portions of the study.

Should a subject exhibit signs requiring medical attention, the study doctor will be called immediately to assess required follow-up. Any subject experiencing suicidal ideation (verbally or through a response on the CSSRS), the psychology on call service would be contacted for a more thorough evaluation and if necessary a referral for treatment.

A delegation of authority will be maintained for all studies involving informed consent. The delegation of authority clearly outlines each person's role and responsibilities in the study. All study staff listed on the delegation of authority will be trained on the protocol, procedures, duties and any subsequent amendments per ICH and federal regulatory requirements. Documentation of all training will be kept in the study administrative binder and managed by the regulatory coordinator or study coordinator assigned to the study.

26.0 Multi-Site Research*

NA

27.0 Protected Health Information Recording

1.0 Indicate which subject identifiers will be recorded for this research.

- ☒ Name
- ☒ Complete Address
- ☒ Telephone or Fax Number
- ☐ Social Security Number (do not check if only used for ClinCard)
- ☒ Dates (treatment dates, birth date, date of death)
- ☒ Email address , IP address or url
- ☒ Medical Record Number or other account number

☐ Health Plan Beneficiary Identification Number
☐ Full face photographic images and/or any comparable images (x-rays)
☐ Account Numbers
☐ Certificate/License Numbers
☐ Vehicle Identifiers and Serial Numbers (e.g. VINs, License Plate Numbers)
☐ Device Identifiers and Serial Numbers
☒ Biometric identifiers, including finger and voice prints
☒ Other number, characteristic or code that could be used to identify an individual
☐ None (Complete De-identification Certification Form)

2.0 Check the appropriate category and attach the required form* on the Local Site Documents, #3. Other Documents, page of the application. (Choose one.)

☒ Patient Authorization will be obtained. (Include the appropriate HIPAA language (see Section 14 of consent template) in the consent form OR attach the HRP-900, HIPAA AUTHORIZATION form.)
☐ Protocol meets the criteria for waiver of authorization. (Attach the HRP-901, WAIVER OF HIPAA AUTHORIZATION REQUEST form.)
☐ Protocol is using de-identified information. (Attach the HRP-902, DE-IDENTIFICATION CERTIFICATION form.) (Checked "None" in 1.0 above)
☐ Protocol involves research on decedents. (Attach the HRP-903, RESEARCH ON DECEDENTS REQUEST form.)
☐ Protocol is using a limited data set and data use agreement. (Contact the Office of Technology Commercialization to initiate a Limited Data Use Agreement.

***Find the HIPAA forms in the IRB Website Library, Templates.**

Attach the appropriate HIPAA form on the "Local Site Documents, #3. Other Documents", page of the application.

3.0 How long will identifying information on each participant be maintained?
Identifying data will be retained for 6 years after the research is complete as this meets both HIPAA & OHRP regulations.

4.0 Describe any plans to code identifiable information collected about each participant.
Each subject will be assigned a unique study number. Only subject initials and/or study number will be used when sending data for analysis.

5.0 Check each box that describes steps that will be taken to safeguard the confidentiality of information collected for this research:
X Research records will be stored in a locked cabinet in a secure location
X Research records will be stored in a password-protected computer file

X The list linking the assigned code number to the individual subject will be maintained separately from the other research data
X Only certified research personnel will be given access to identifiable subject information

6.0 Describe the provisions included in the protocol to protect the privacy interests of subjects, where "privacy interests" refer to the interest of individuals in being left alone, limiting access to them, and limiting access to their information. (This is not the same provision to maintain the confidentiality of data.)
Subject information will not be given to any other investigators. Subjects and their information will be closely monitored and guarded by study staff; there will be limited access to patients and their information by trained study staff; and subject information will only be shared and discussed between study staff specific to this study.

Confidential Health Information

1.0 Please mark all categories that reflect the nature of health information to be accessed and used as part of this research.

☒ Demographics (age, gender, educational level)
☒ Diagnosis
☐ Laboratory reports
☐ Radiology reports
☒ Discharge summaries
☒ Procedures/Treatments received
☒ Dates related to course of treatment (admission, surgery, discharge)
☐ Billing information
☒ Names of drugs and/or devices used as part of treatment
☒ Location of treatment
☐ Name of treatment provider
☐ Surgical reports
☒ Other information related to course of treatment
☐ None

2.0 Please discuss why it is necessary to access and review the health information noted in your response above.
This information is necessary to conduct the research and achieve the aims of the study.

3.0 Is the health information to be accessed and reviewed the minimal necessary to achieve the goals of this research? ☒ Yes ☐ No

4.0 Will it be necessary to record information of a sensitive nature? ☐ Yes ☒ No

5.0 Do you plan to obtain a federally-issued Certificate of Confidentiality as a means of protecting the confidentiality of the information collected? ☒ Yes ☐ No