STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: Randomized Pilot Crossover Study Comparing Virtual Reality (VR) and Non-VR Distraction (other Child Life guided activities) for Decreasing Preoperative/Procedural Anxiety as a Function of the modified Yale Preoperative Anxiety Scale (mYPAS)

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UTSouthwestern
Harold C. Simmons
Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

STU-2020-0607

Randomized Pilot Crossover Study Comparing Virtual Reality (VR) and Non-VR Distraction (other Child Life guided activities) for Decreasing Preoperative/Procedural Anxiety as a Function of the modified Yale Preoperative Anxiety Scale (mYPAS)

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Study Drug/Treatment: mYPAS scoring while playing VR device versus non-VR distraction for Port access

Funding Source: The University of Texas Southwestern Medical Center, Department of Anesthesiology and Pain Medicine

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Signature Page

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Amendment/Version # Version 6.0, 29May2024

STU-2020-0607

Randomized Pilot Within Groups Comparison of VR and Non-VR Distraction to Decrease Preoperative/Procedural Anxiety as a Function of the modified Yale Preoperative Anxiety Scale (mYPAS)

Principal Investigator (PI) Name: **Sarah Rebstock, MD**

PI Signature: _____

Date: _____

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LIST OF ABBREVIATIONS

AE	Adverse Event
CCBD	Center for Cancer and Blood Disorders
CHST	Children's Health System Texas
CMC	Children's Medical Center as an entity of Children's Health System Texas
DOT	Disease Oriented Team
DSMC	Data Safety Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IQR	Inter-quartile range
IRB	Institutional Review Board
IV (or iv)	Intravenously
LAR	Legally Authorized Representative
mYPAS	modified Yale Preoperative Anxiety Scale
Non-VR	Child Life Guided distraction not including Virtual Reality
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SOC	Standard of Care
UPIRSO	Unanticipated Problems Involving Risk to Subjects or Others
UTSW	University of Texas Southwestern Medical School
VR	Virtual Reality

STUDY SUMMARY

Title	Randomized Pilot Crossover Study Comparing Virtual Reality (VR) and Non-VR Distraction for Decreasing Preoperative/Procedural Anxiety as a Function of the modified Yale Preoperative Anxiety Scale (mYPAS)
Short Title	VR-mYPAS study
Protocol Number	**STU-2020-0607**
Phase	Pilot
Methodology	Cross Over Design
Study Duration	Up to two years
Study Center(s)	Single-center – Children's medical center, Dallas, Texas
Objectives	To use the modified Yale Preoperative Anxiety Scale (mYPAS) to evaluate children prior to and during Port access, to look for a decrease preoperative anxiety during distraction in pediatric oncology patients undergoing port access.
Number of Subjects	77 patients
Diagnosis and Main Inclusion Criteria	CCBD patients requiring port access twice within a year
Study Product(s), Dose, Route, Regimen	mYPAS scoring while playing VR device versus non-VR distraction for Port access
Duration of administration	~ 15 minutes maximum (observation and completion of questionnaires after 10-minute familiarization with distraction method, during port access)
Reference therapy	N/A
Statistical Methodology	Cross over study will be performed. Subjects will be randomized (1 to 1 randomization via Proc Plan in SAS 9.4) at their initial encounter to either VR or Non-VR. During their second visit patients will be given the alternative mode of care (i.e. patients who initially received VR distraction will be given Non-VR distraction, and patients who initially received Non-VR distraction will receive VR distraction)

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Pre-operative anxiety is common in children, with 50-70% of children experiencing it on
the day of procedure (1). Children undergoing cancer treatment need multiple procedures throughout their course of treatment. Preprocedural anxiety can be particularly high in this group as the disruption to daily life, physical appearance, and the nature of therapy to include procedures, is aggressive to preserve health and life.

1.2 Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities

The mYPAS observational scale will be used to assess VR and non-VR distraction for decreasing preoperative/procedural anxiety in pediatric oncology patients undergoing port access. It is an observational scale that consists of five domains (activity, emotional expressivity, state of arousal, vocalization and use of parents) and has shown good to excellent inter-observer reliability (2). It can be applied to children two years and older although it was validated for use in the 5-12 age group (2).

VR technology can be used as a distractor to decrease preoperative/procedural anxiety in pediatric oncology patients undergoing port access. Side effects of VR technology are minimal but include motion sickness and nausea.

1.3 Other Agents

Child Life guided activities for pre- and intraprocedural distraction for anxiety management.

1.4 Rationale

The purpose of the research study is to evaluate the use of VR as a distractor to decrease preoperative/procedural anxiety in pediatric oncology patients undergoing port access. In a study looking at the use of VR for needle-related procedural pain and distress in children and adolescents in a pediatric oncology unit, while the quantitative data did not show reduction of pain and distress in the VR group, results from observational pain scores showed a decrease, and the interviews indicated that using VR could be a positive experience (3). In a study of pediatric burn patients, another population that requires repeated procedures, the patients randomized to the VR group had significantly lower pain and anxiety scores as well as achieved faster healing rates (4).

Most of the studies on VR used pain assessment scales like faces pain scale, visual analogue scale and FLACC focusing on its effect on pain rather than anxiety (3-6). There have been few studies examining the use of VR as a tool to decrease preoperative/procedural anxiety and even fewer studies utilizing the

mYPAS to assess the effect of VR on preoperative anxiety in children. The mYPAS is now considered the gold standard in assessing preoperative anxiety in children (1,2)

VR can be a safe, non-pharmacologic way, of decreasing preoperative anxiety with minimal side effects, improving quality of care, patient experience and satisfaction. CHST currently uses the Kind VR device in house as a method of procedural distraction in various locations. Kind VR is a research-based company that has partnered with several research hospitals in the United States and Canada. Areas of research where the kind VR device has been used includes vaso-occlusive crisis in children with sickle cell disease, pediatric cancer patients needing port access procedures, Emergency Room patients needing IV placement or laceration repair and in children needing surgical procedures to help with preoperative stress.[7] A study of Virtual reality on children with sickle cell disease vaso-occlusive crisis concluded that The Kind VR Aqua software was able to provide distraction through total immersion.[8] Another study using Kind VR was able to demonstrate the safety of VR interventions in children and adolescents with cancer undergoing port access procedure.[5] CHST and this research group are not partnering entities with the Kind VR, and the Kind VR device is not being studied. The effect of virtual reality (VR) on preprocedural anxiety as measured by questionnaires and the observations of the modified Yale Preoperative Anxiety Scale (mYPAS) is being studied.

If VR proves clinically useful in decreasing pre-op anxiety, patients may potentially allow clinicians to treat them for any number of ailments using interactive VR in lieu of, or at decreased requirement for, medicinal anxiolysis or anesthesia. Avoiding and minimizing sedation can potentially decrease length of post anesthesia recovery room stay. In addition, physical therapy is a big part of rehabilitation for pediatric pain patients. By distracting patients from pain and anxiety, VR can help patients improve function and range of motion during physical therapy, decreasing days away from school and promoting return to normal activities faster. Looking at post anesthesia recovery room length of stay with and without VR and range of motion/outcome of physical therapy with and without VR are areas of potential further studies.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To utilize the modified Yale Preoperative Anxiety Scale (mYPAS), a validated preoperative/procedural anxiety score, to decrease preoperative anxiety via distraction in pediatric oncology patients (primary outcome).

2.2 Secondary Objectives

2.2.1 Parents or legally authorized representative (LAR) subjective report decreased anxiety with the use of VR (secondary outcome).

2.3 Endpoints

2.3.1 We expect to see statistically significant changes in the preoperative anxiety scores using the mYPAS when the VR group is compared to the non-VR group.

2.3.2 We expect parents or the legally authorized representative (LAR) to subjectively report decreased anxiety with the use of VR.

3.0 SUBJECT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Any patient of the Children's Medical Center CCBD

3.1.2 5-18 years of age

3.1.3 Patient requiring their port accessed twice or more within a year

3.1.4 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Subjects younger than 5 and older than 18

3.2.2 Patients requiring recovery in PICU or sites other than PACU

3.2.3 If parents or subject is not willing to participate

3.2.4 Subjects with severe developmental delays and subjects with developmental challenges preventing them from keeping the VR device on are also excluded

3.2.5 Patients who will not be in CCBD for port access at least twice within a year

4.0 STUDY PROCEDURES

4.1 Screening/Baseline Procedures

Potential subjects will be identified from the CCBD schedule. Subjects are not patients of the study investigator, so a member of the study staff will request permission from the treating team to approach and include subjects in the study.

The legal authorization of parents to be approached will be verified by a member of the study team before approaching them in the preoperative holding area.

The study will be explained to the subject (if old enough to participate in discussion) and the parents on a telephone call the night before the CCBD visit in order to determine interest in participation.. It will be explained that participation is completely voluntary and that whether they choose to participate or not will not affect their treatment in our facility. They will be given ample time to consider participation and ask any questions they may have with the study doctor and their treating physician. The next day, in clinic, it will be verified if they are still interested in participating, all questions will be answered by a member of the research team in the room virtually on the CHST telemedicine tablet platform. If they agree, written informed consent will be obtained and a copy of the signed consent form will be given to the subject's LAR by their nurse or child life specialist.

Children's Medical Center has a large Hispanic population; therefore, the study will be discussed using a certified on-site Spanish translator, or virtual platform Spanish translator if this language barrier exists. A Spanish version of the parent questionnaires and the consent form will be provided.

4.2 Procedures During Treatment

Once it is confirmed that the subject qualifies and the parents (LARs) are willing to participate, the parents (LARs) will be given the demographics form to fill out and the subject will be randomized in the study system. Whether the patient participates in the Virtual Reality group or the Non-Virtual Reality group first will depend on a computerized randomization process independent of the study researchers.

For the Non-virtual reality group, a member of the study team will evaluate the patient using the mYPAS prior to port access. Parents will be asked to fill out a questionnaire evaluating their child's preoperative anxiety after port access is complete (see study schema).

For the port access with virtual reality (VR) distraction, the patient will be able to play the VR game for 15 minutes prior to actual port access procedure start. During this first 5-15 minutes of being in their CCBD procedure/infusion room with the placement of the VR headset, a researcher will be doing the first mYPAS observation and scoring (Holding). The patient will then continue to play the game through the port access procedure. The point where the port access kit is opened by the nurse marks the start of the Port access portion of the mYPAS observation (Induction 1). The end of the second mYPAS observation is when the Tegaderm dressing is applied to the port access needle.

After port access is complete with VR, or control, the parents or LAR will then be asked to fill out a questionnaire assessing their child's perioperative anxiety.

NOTE: For safety of the researchers and patients, all mYPAS patient observations on day of CCBD visit, as well as any further consent questions, will be performed through a virtual telemedicine platform with approved tablets run and vetted by telemedicine at Children's Health System of Texas (CHST). The process has already been approved and vetted by CHST telemedicine so that there is little to no risk of virtual PHI breach. The observation of the patients will be done in real time with no recording of the encounter. Tablets are currently in place from CHST, and nursing and Child Life are informed of process.

4.3 Follow-up Procedures

We will examine the CCBD schedule for the second opportunity to include each subject and complete the study in the other study arm (VR-distraction or Non-VR distraction). Surveys and Assessments will be filled out twice: once without the use of VR (control group) and the second time with the use of VR (study group).

Data collected will be compared and analyzed for statistically significant difference in anxiety scores with mYPAS. Parents' questionnaires will also be scored and evaluated for subjective improvement in parental assessment of preoperative anxiety.

All the study forms and questionnaires will be identified with the unique study ID number assigned in the study system with no other identifying data. There are no additional procedures outside the standard of care participants would normally receive. There will be no additional costs to subjects for participating in this study.

4.4 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request or if deemed necessary by the study team due to distress.

5.0 SAFETY MONIITORING

5.1 Definition of an Adverse Event

Any issues experienced while being observed by the research team should be recorded as a potential adverse event for evaluation by the PI as to the seriousness, relatedness, and expectedness in relation to the study.

It is expected that a patient may experience some discomfort or motion sickness while using VR.

5.2 Data and Safety Monitoring Plan

The researchers will be monitoring should a patient encounter any issues, particularly any discomfort or motion sickness while using the VR device. If so, the VR device will be removed, and the subject will be eliminated from the study.

The study staff will record all concerns experienced by enrolled subjects, the total number of side effects experienced by all enrolled subjects, and the number of subjects eliminated from the study due to side effects.

□ **Reporting requirement**: The principal investigator will oversee the subject safety and data records and report all pertinent information to the IRB, as necessary.

6.0 TREATMENT INFORMATION

6.1 Potential Risks of VR distraction

While this study is considered low risk, patient discomfort and motion sickness are potential risks. Should a patient experience any discomfort or motion

sickness, VR device will be removed, and the subject will be excluded from study. Disposable VR covers will be used, and device will be sanitized between patients to minimize risk of infection.

There is a risk of the loss of confidentiality, but measures will be taken to minimize this risk, such as only the named study staff will be handling the study forms and all the subjects will be assigned unique study numbers. The only document that could identify a patient is the informed consent that would be linked to a study participant by a study number. These informed consents will be kept in a locked cabinet in the locked office of the principal investigator. No other identifiers will be collected as a part of the research data that links a study number to the patient PHI.

For the safety of the researchers and patients, all mYPAS patient observations on day of CCBD visit, as well as any further consent questions, will be performed through a virtual telemedicine platform with approved tablets run and vetted by telemedicine at Children's Health System of Texas (CHST). The process has already been approved and vetted by CHST telemedicine so that there is little to no risk of virtual PHI breach.

7.0 STATISTICAL CONSIDERATIONS

7.1 Design/Study Endpoints

To assess the effect of the VR on children's Modified Yale Preoperative Anxiety Scale (mYPAS), a cross over study will be performed. Subjects will be randomized (1 to 1 randomization via Proc Plan in SAS 9.4) at their initial encounter to either VR or Non-VR. During their second visit patients will be given the alternative mode of care (i.e. patients who initially received VR distraction will be given Non-VR distraction, and patients who initially received Non-VR distraction will receive VR distraction)

7.2 Sample Size and Accrual

To fully power our study, we will recruit 77 patients to detect a difference of 3.5 in the mYPAS score; assuming a standard deviation of 10, a 10% reduction in patient participation due to attrition, and a power of 0.8. If attrition exceeds 10% additional post hoc power analysis will be performed.

7.3 Data Analyses

Categorical outcomes will be presented as frequency and percentages and compared using chi-square and/or Fisher's exact test. Continuous outcomes will be summarized by median and inter-quartile range (IQR) OR mean and standard deviation (depending on the data's distribution). Depending on the data's distribution a paired t-test or Wilcoxon-sign rank test will be performed to assess the difference between VR distraction and Non-VR distraction. For this crossover design a mixed model will also be implemented, which accounts for

treatment/intervention (VR vs. non-VR), sequence, and period as fixed effects. Patients will be nested within sequence.

7.4. Interim Analysis Plan

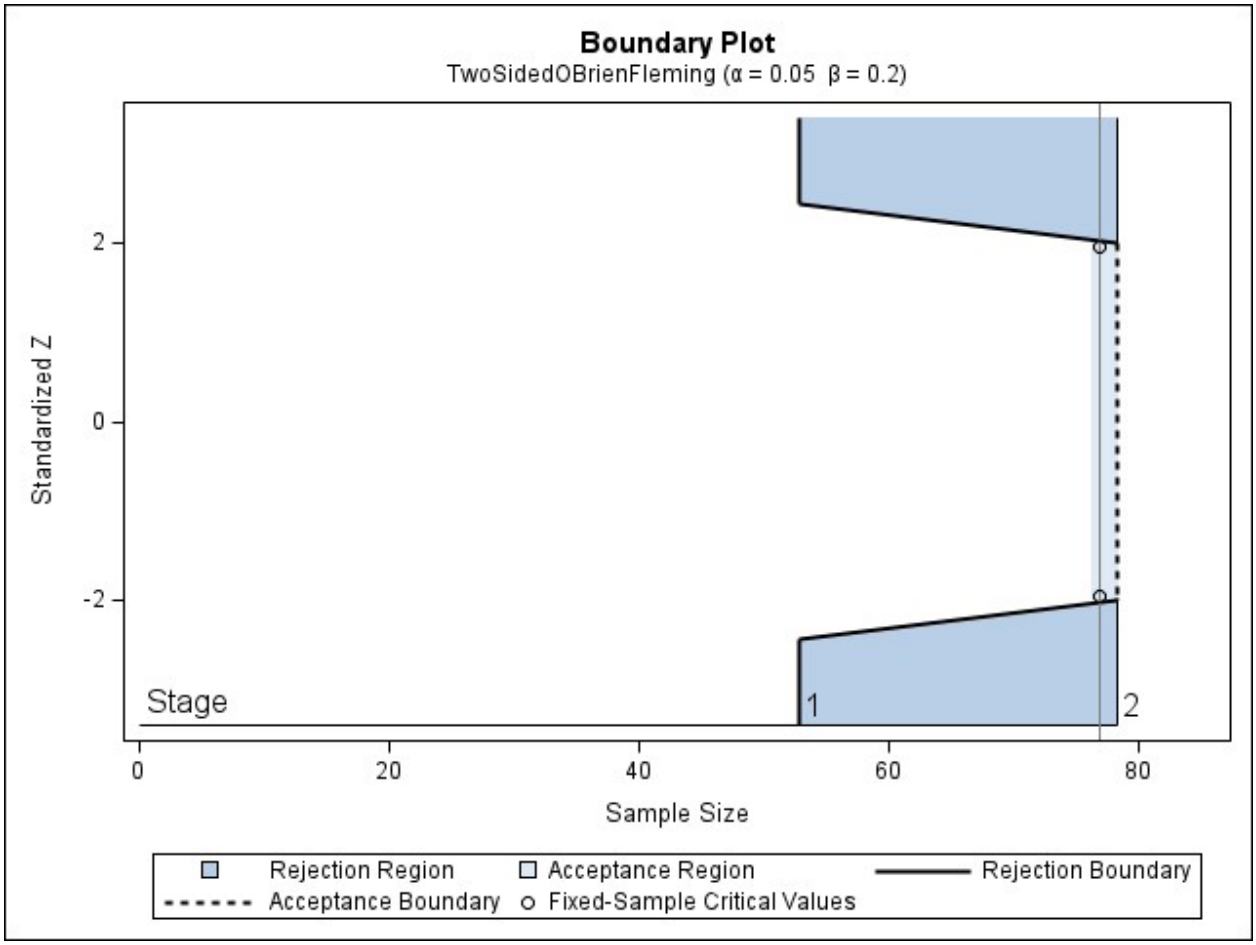
Interim Analysis for Efficacy and Safety

This two-sided symmetrical group sequential design, which is based upon the existing sample size specified in the protocol (N=77), has two planned stages: 1 interim stage at information fraction 0.67 (n=52) and a final stage (N=77). We will implement the two-sided O'Brien-Fleming methodology to monitor the clinical trial for early stopping because of efficacy or "safety" (exacerbated anxiety). The latter is not anticipated, but will be evaluated. We used the procedures of PROC SEQDESIGN in SAS to create the group sequential design by computing boundary values for the stages (based on the O'Brien-Fleming methodology). The boundary values are derived in such a way that the overall Type I (0.05) and Type II (0.20) error probability levels will be maintained in this design. With early stopping to reject the null hypothesis, the lower rejection boundary is constructed by connecting the lower critical values (on the Z scale) for the stages. Similarly, the upper rejection boundary is constructed by connecting the upper critical values (on the Z scale) for the stages. See Table 1 and Figure 1 (boundary plot).

We will then use the procedures of PROC SEQTEST in SAS to compare the obtained test statistic with these boundary values (at each stage) to evaluate the trial for stopping. For this two-sided symmetrical group sequential design, a standardized Z test statistic will be computed by standardizing the estimate of the effect in Preoperative Anxiety, and a negative Z test statistic indicates a beneficial effect. Thus, at the interim stage, if the standardized Z test statistic is less than or equal to the corresponding lower alpha boundary value, the null hypothesis is rejected for efficacy and the trial will be considered for stopping. Conversely, while not anticipated, if the standardized Z test statistic is greater than or equal to the corresponding upper alpha boundary value, the null hypothesis is rejected for a "harmful/safety" effect (exacerbated anxiety) and the trial will be considered for stopping. Otherwise, the process continues to the next stage. At the final stage (stage 2), the null hypothesis is rejected for efficacy if the Z statistic is less than or equal to the corresponding lower alpha boundary value of -2.004, and the null hypothesis is rejected for a "harmful/safety" effect if the Z statistic is greater than or equal to the corresponding upper alpha boundary value of 2.004. Otherwise, the null hypothesis is not rejected. When the trial is stopped at either the interim stage or at the final stage, the SEQTEST procedure can also be used to derive parameter estimates, confidence limits for the parameter, and p-values for hypothesis testing.

Figure 1.

Boundary Plot, which corresponds to the information in Table 1.



Note. Fixed Sample Design Critical Values (α=0.05 two-sided): ±1.96.

Note. Two planned stages: 1 interim stage at information fraction 0.67 (n=52) and a final stage (N=77).

Table 1.

Nominal Critical Values and Alpha Levels for a two-sided symmetrical group sequential design, with 2 stages, for Efficacy and Safety (O'Brien-Fleming, α=0.05 two-sided, β=0.20)

Stage	Sample Size (N)	Nominal Critical Value (Z-value scale)	Nominal Alpha Level Lower	Upper	Nominal Alpha Level (two-sided)
1	52	±2.431	0.00737	0.00737	0.01474
Final	77	±2.004	0.02280	0.02280	0.04560

Note. Fixed Sample Design Critical Values (α=0.05 two-sided): ±1.96.

Interim Analysis for Futility

Futility analyses are planned to be conducted to coincide in timing with the tentatively scheduled interim analysis for efficacy and "safety" at each stage of

information. The stochastic curtailment method is adopted based on conditional power (Lan et al, 1982). The informal criterion for determination of futility is that at the interim stage, if the conditional power (defined as the probability of rejecting the null hypothesis of no effect once some data are available at each stage) is low (e.g., <20%), then a conclusion could be reached that it would be futile to continue the trial. At this juncture, the research team will evaluate all study information to consider stopping the study for futility. The evaluation will be conducted in a blinded manner.

Evaluation of futility using conditional power allows flexibility in that it can be calculated and assessed at any time during the study without inflation of the Type I error probability and that the threshold does not necessarily have to be pre-specified. This approach to assessing futility holds appeal because it allows other information to be taken into consideration such as recruitment and safety data and conditional power at other alternative effect sizes (Freidlin B and Korn EL, 2002). We will use the procedures of PROC SEQTEST in SAS to compute conditional power at each stage of the group sequential trial.

8.0 STUDY MANAGEMENT

8.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

8.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining verbal or written informed consent and documentation, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Potential subjects will be identified from the CCBD schedule. Subjects are not patients of the study investigator, so a member of the study staff will request permission from the treating team to approach and include subjects in the study. The legal authorization of parents to be approached will be verified by a member of the study team before approaching them. The study will be explained to the subject (if old enough to participate in discussion) and the parents the night before their CCBD visit by a named member of the study team designated to perform the task of obtaining informed consent. It will be explained that participation is completely voluntary and that whether they choose to participate or not will not affect their treatment in our facility. They will be given ample time to consider participation and ask any questions they may have with the study team members and their treating physician.

Once verbal consent from the LARs and verbal assent from study participant (if old enough to participate in the discussion) is obtained over the phone the night prior to the CCBD visit (see study schema), the researcher will prepare for the following day's mYPAS observation.

On the next day's CCBD visit, when the patient is placed in their CCBD holding room prior to port access, it will be verified that they are still interested in participating. If the LAR or patient has any additional questions, the researcher will be in the room virtually on the CHST telemedicine tablet platform to answer any further questions. Then, written informed consent will be obtained and a copy of the signed consent form will be given to the subject's LAR by their nurse or the child life specialist.

Children's Medical Center has a large Hispanic population; therefore, the study will be discussed using a certified on-site Spanish translator, if a language barrier exists. Fully translated Spanish versions of the parent questionnaires and the study consent form will be provided.

The study PI will keep a list of study subjects on a firewalled Children's Medical Center (Dallas Campus) computer which links study number with the study subject. This study subject list will be kept in a password protected file accessible only to the faculty mentor and the PI for the duration of the study. To protect PHI, this list will be deleted at the end of the study.

8.3 Registration/Randomization Procedures

All subjects must be registered with the CMC Anesthesiology Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Study Coordinator.

New subjects will receive a number beginning with 1-001 upon study consent such that the first subject consented is numbered 1-001, the second subject consented receives the number 1-002, etc.

Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 1-001 will become 1-001-01 upon enrollment. If subject 1-002 screen fails, and subject 1-003 is the next subject enrolled, subject 1-003 will become 1-003-02 and so-on.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

To assess the effect of the VR on children's Modified Yale Preoperative Anxiety Scale (mYPAS), a cross over study will be performed. Subjects will be randomized (1 to 1 randomization via Proc Plan in SAS 9.4) at their initial encounter to either VR or Non-VR. During their second visit patients will be given the alternative mode of care (i.e. patients who initially received VR distraction will be given Non-VR distraction, and patients who initially received Non-VR distraction will receive VR distraction).

8.4 Data Management and Monitoring/Auditing

Only the subjects assigned unique study number will be used on study questionnaires, staff mYPAS assessments, and exclusion log. The only link to participants identity will be the electronic subject enrollment log, which will include only the name, date of port access appointments, medical record number, and unique study ID #.

A password-protected computer file will be created, and all study data will be saved on a Children's Medical Center computer, in the secure research file, kept behind the Children's Health firewalled system. The secure research file will be limited access, only members of the study team will be given password access for the purpose of data analysis.

At the conclusion of study enrollment, the data from the questionnaires and assessment forms will be transferred into the secure study REDCap database, and the paper forms will be properly discarded according to HIPPA standards at Children's Health System. In addition, the electronic enrollment and exclusion log will also be properly discarded. No paper documents or link to study participants identities will be retained.

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project. All the study data will be stored within the UTSW RedCap system, which is stored behind the secure UTSW firewall.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

8.5 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.5.1 **Exceptions** (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

□ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

8.5.2 **Emergency Deviations:** include any departure from IRB-approved research that is necessary to:

- Avoid immediate apparent harm, or
- Protect the life or physical well-being of subjects or others

□ **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

8.5.3 **Major Deviations** (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

□ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

8.5.4 **Minor Deviations:** include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

□ **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

8.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

8.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

8.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

9.0 REFERENCES

1. Eijlers R, Dierckx B, Staals LM, et al. Virtual reality exposure before elective day care surgery to reduce anxiety and pain in children: A randomised controlled trial. *Eur J Anaesthesiol.* 2019;36(10):728-737.
2. Kain ZN, Mayes LC, Cicchetti DV, Bagnall AL, Finley JD, Hofstadter MB. The Yale Preoperative Anxiety Scale: how does it compare with a "gold standard"? *Anesth Analg.* 1997;85(4):783-788.
3. Nilsson S, Finnstrom B, Kokinsky E, Enskar K. The use of Virtual Reality for needle-related procedural pain and distress in children and

adolescents in a paediatric oncology unit. *Eur J Oncol Nurs.* 2009;13(2):102-109.

4. Brown NJ, Kimble RM, Rodger S, Ware RS, Cuttle L. Play and heal: randomized controlled trial of Ditto intervention efficacy on improving re-epithelialization in pediatric burns. *Burns.* 2014;40(2):204-213.
5. Birnie KA, Kulandaivelu Y, Jibb L, et al. Usability Testing of an Interactive Virtual Reality Distraction Intervention to Reduce Procedural Pain in Children and Adolescents With Cancer [Formula: see text]. *J Pediatr Oncol Nurs.* 2018;35(6):406-416.
6. Dunn A, Patterson J, Biega CF, et al. A Novel Clinician-Orchestrated Virtual Reality Platform for Distraction During Pediatric Intravenous Procedures in Children With Hemophilia: Randomized Controlled Trial. *JMIR Serious Games.* 2019;7(1):e10902.
7. KindVR. https://www.kindvr.com/. Accessed 4/8/2020.
8. Agrawal AK, Robertson S, Litwin L, et al. Virtual reality as complementary pain therapy in hospitalized patients with sickle cell disease. *Pediatr Blood Cancer.* 2019;66(2):e27525.
9. O'Brien, P. C. and Fleming, T. R. (1979), "A Multiple Testing Procedure for Clinical Trials," Biometrics, 35, 549–556
10. Freidlin B, Korn EL. A comment on futility monitoring. Controlled Clinical Trials 2002; 23: 355-366.
11. Lan KKG, Simon R, Halperin M. Stochastically curtailed tests in longterm clinical trials. Communications in Statistics – Sequential Analysis 1982; 1: 207-219.

10.0 APPENDICES

10.1 Subject Demographics

VR_mYPAS Demographics.docx

10.2 Parent VR Group Questionnaire

VR_mYPAS Parent questionaire VR.doc

10.3 Parent Control Group Questionnaire

VR_mYPAS Parent questionnaire_Cont

10.4 Study Datasheet

VR_mYPAS datasheet.xlsx