UTSouthwestern
Harold C. Simmons
Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

STU-2021-1005

Pediatric Radiation Oncology with Movie Induced Sedation Effect (PROMISE): A Phase II Clinical Trial to Safely Reduce Anesthesia Use

Principal Investigator: Kiran A. Kumar, MD MBA
UT Southwestern Medical Center
2280 Inwood Rd, Dallas, TX, 75390
Telephone: (214) 645-8525 Fax: 214-645-8526
E-mail: Kiran.Kumar@UTSouthwestern.edu

Lead Sub-Investigator(s):

Department of Radiation Oncology
Tu Dan, MD
Malgorzata Kozak, MD

Department of Anesthesia, Pediatrics
Christopher Setiawan, MD
Edgar Kiss, MD

Department of Pediatrics, Hematology-Oncology
Matthew Campbell, MD
Avanthi Shah, MD

Department of Radiation Physics
Tsuiecheng Chiu, Ph.D.
Steve Jiang, Ph.D.

Biostatistician:

Department of Clinical Sciences
Chul Ahn, PhD
UT Southwestern Medical Center
5801 Forest Park Rd, Dallas, TX, 75390
(214)648-9418
Chul.Ahn@UTSouthwestern.edu

Study Drug/Treatment: PROMISE

Funding Source: Wipe Out Kids' Cancer

NCT Number: NCT05148078

Initial version: 1.0 (7/1/2021)

Amended: Version 2 – 8/15/2023
Version 2.1 – 8/28/2023
Version 2.2 – 12/21/2023

UT Southwestern Medical Center (UTSW)
Harold C. Simmons Comprehensive Cancer Center
Attn: Clinical Research Office
5323 Harry Hines Blvd. MC 9179
Dallas, Texas 75390-9179

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 # 2.2

STU-2021-1005

Pediatric Radiation Oncology with Movie Induced Sedation Effect (PROMISE): A Phase II Clinical Trial to Safely Reduce Anesthesia Use

Principal Investigator (PI) Name: ___Kiran A. Kumar, MD MBA__

PI Signature: _____

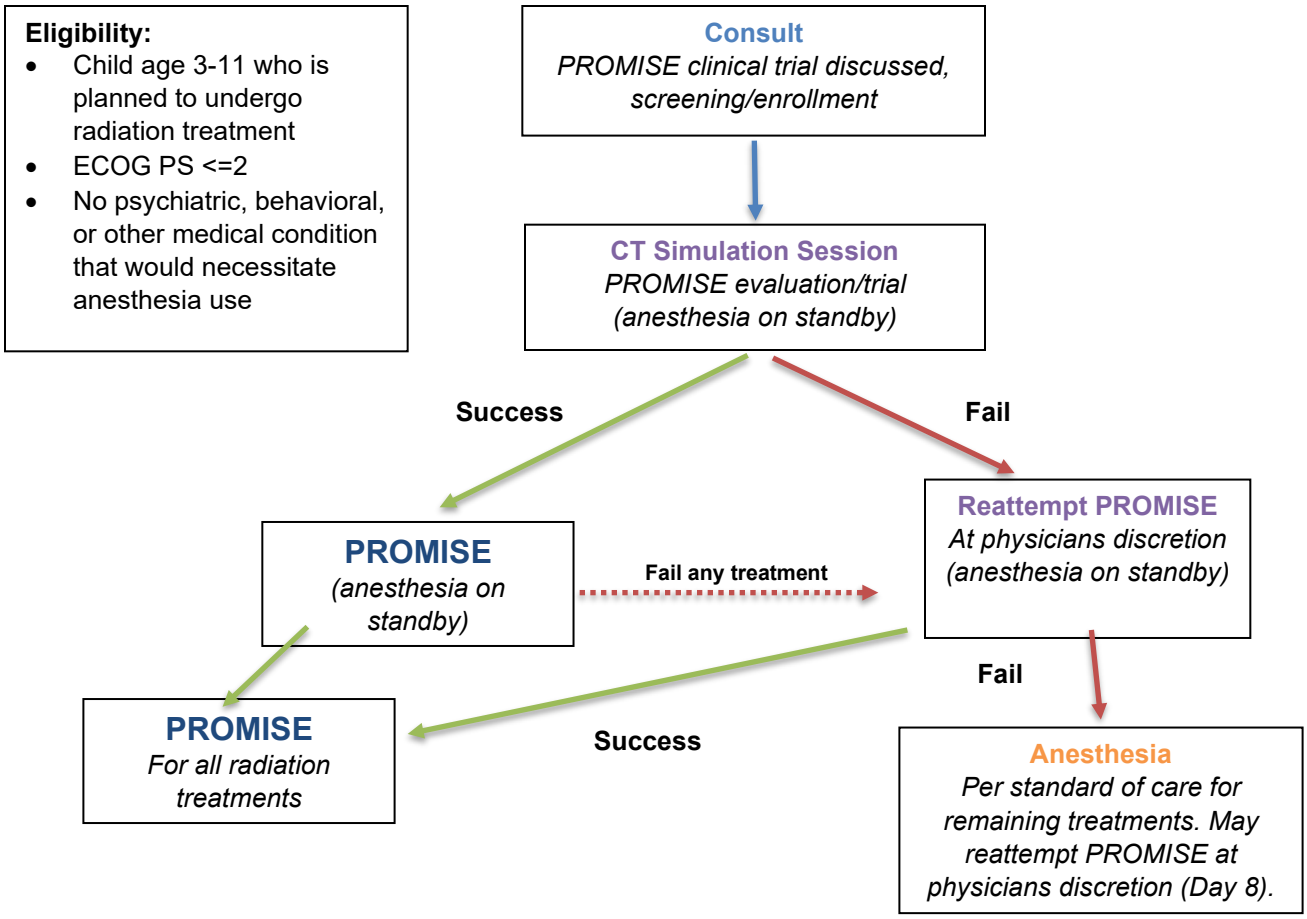
Date: _____

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
BT	Brachytherapy
CBC	Complete Blood Count
CBCT	Cone Beam Computed Tomography
CMP	Comprehensive Metabolic Panel
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HDR	High Dose Rate
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IV (or iv)	Intravenously
LDR	Low dose rate
mpMRI	Multi-parametric Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
OS	Overall Survival
pCR	Pathologic Complete Response
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PROMISE	Pediatric Radiation Oncology with Movie Induced Sedation Effect
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAbR	Stereotactic ablative body radiotherapy
SBRT	Stereotactic body radiotherapy
SCCC	Simmons Comprehensive Cancer Center
scRNAseq	Single cell RNA sequencing
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TRUS	Transrectal ultrasound
WBC	White Blood Cells

STUDY SCHEMA



Primary Endpoint & Hypothesis

- Percentage of Children Ages 3-7 Requiring General Anesthesia: We hypothesize that PROMISE will lead to a reduction in the percentage of patients **ages 3-7** who require general anesthesia during radiation treatment from **70%** (institutional historical control) to **30%.**

Secondary Endpoints

Secondary endpoints will be analyzed for those on trial treated with PROMISE vs. anesthesia.

- Patient/family-reported health quality of life (PedsQL 3.0 Cancer Module) and anxiety (mYPAS-SF).
- Workflow data: treatment time, average patient movement, and number of beam turn offs due to movement beyond threshold.
- Overall cost of treatment.

STUDY SUMMARY

Title	Pediatric Radiation Oncology with Movie Induced Sedation Effect (PROMISE): A Phase II Clinical Trial to Safely Reduce Anesthesia Use
Short Title	PROMISE Clinical Trial to Reduce Anesthesia Use
Protocol Number	STU-2021-1005
Phase	Phase II
Methodology	Single-arm, open label
Study Duration	2 years
Study Center(s)	Single-center
Objectives	Primary: To decrease the total number of pediatric patients who require general anesthesia through the use of PROMISE. Secondary: - To assess the impact that PROMISE has on patient/family anxiety and quality of life, treatment time and clinical efficiency, and overall cost. - To determine the average patient movement and beam stoppages with the use of PROMISE.
Number of Subjects	30
Diagnosis and Main Inclusion Criteria	Age 3-11 and planned to undergo radiation therapy.
Study Product(s), Dose, Route, Regimen	PROMISE: an audio/visual technology for children to focus on during each radiation treatment to prevent movement.
Duration of administration	PROMISE will be used for each fraction of radiation treatment; number of fractions will vary by patient depending on individual diagnosis and treatment plan.
Reference therapy	Institutional historical control of percentage of patients age 3-7 who required general anesthesia during radiation therapy.
Statistical Methodology	We hypothesize that PROMISE will lead to a reduction in the percentage of patients ages 3-7 who require general anesthesia use from 70% (historical control) to 30%. Using a two-sided exact binomial test with a significance level of 0.05 and power=80%, a sample size of 13 patients (ages 3-7) will be needed to detect this difference. In our past experience, ~42% of children ages 3-11 (eligibility criteria) are between 3-7 years old, so 30 children total will be needed to enroll 13 who are between 3-7 years old.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Pediatric Radiation Oncology:

Childhood cancers are the leading cause of death in children in the United States. Over 10,000 children are diagnosed annually[1,2] and, each year, the disease claims more lives than asthma, cystic fibrosis, diabetes, and pediatric AIDS combined. Very little is known about childhood cancer prevention[3], and the most common types include leukemias, lymphomas, and central nervous system tumors[1,2]. Both pediatric cancer incidence and cure rates increased from 1975 to 2004, with cure rates increasing in part because of the advancements in radiation therapy[1,4]. Some of the innovations that have improved both local tumor control and systemic spread include conformal radiotherapy, brachytherapy, proton beam therapy, and stereotactic radiosurgery[5]. For children with a diagnosis of cancer, radiotherapy is a main curative and palliative treatment modality often administered in combination with surgical resection and/or chemotherapy[6]. While radiation treatments are effective, they are also very intensive. The entire course of radiotherapy for a pediatric patient often consists of 25 to 30 fractions, lasting for 5 to 6 weeks.

General Anesthesia Use in Pediatric Radiation Oncology:

Due to the precise nature of radiation therapy, immobilization is crucial for treatment effectiveness and patient safety[3,4,7]. For this reason, according to current standard radiotherapy practice most pediatric cancer patients under 7 years of age receive general anesthesia at each fraction to ensure that the patient remains still during the treatment. Almost all children under the age of three, the majority of children under 7, and even some children up to age 12 require general anesthesia[7]. Based on a study by Ntoukas, we estimate 70% of patients age 3-7 can avoid general anesthesia with the implementation of Pediatric Radiation Oncology with Movie Induced Sedation Effect (PROMISE)[8], which is further described below.

General anesthesia reduction is important because, if a child requires general anesthesia, he or she may receive up to 30 episodes of general anesthesia in succession[6,9,10]. This also means that, for the 6-week duration of radiotherapy, a child may never fully return to his/her baseline activity. More importantly, the excessive use of sedatives introduces many risks and side effects that, combined with chemotherapy, and cancer itself, can greatly affect the overall treatment experience for the children and their families[10–12]. Multiple other factors associated with frequent anesthesia administration worsen the treatment experience, and would be immediately eliminated if general anesthesia was no longer needed. For example, fasting on a daily basis, a necessary part of the anesthesia process, is often difficult in the pediatric population and strains both the child and parents[13]. Currently, pediatric radiation visits last multiple hours because of the need for lengthy pre- and post- anesthesia care. These visits could easily be shortened to minutes if anesthesia were avoided. Lastly, the anxiety, stress, and fears both patients and families experience largely due to anesthesia administration would dissipate with its disuse[14].

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

PROMISE

Pediatric Radiation Oncology with Movie Induced Sedation Effect (PROMISE) is an interactive, incentive-based movie system that integrates with a video surveillance gating module (VisionRT) to help keep a children's attention and prevent him or her from moving during radiation treatment. This technology is being studied as an alternative sedation

solution for pediatric patients needing radiation treatment. There are no known or expected toxicities associated with PROMISE.

As part of the trial, patients will be attempted to have CT simulation scan and first radiation treatment(s) using PROMISE, with general anesthesia on standby should PROMISE be unsuccessful. The only toxicity that could be indirectly associated with PROMISE is if the child moves during radiation treatment and this results in radiation temporarily being delivered to the wrong target. However, PROMISE is integrated with the video surveillance gating module VisionRT, so that if the patient moves beyond predefined safety threshold, the beam will automatically stop, so this is not an event that would ever be expected to happen. This auto-beam off ability is a unique feature of PROMISE that is not seen in competing technologies.

If PROMISE is unsuccessful for a given patient, then standard of care general anesthesia will be used for that patient's radiation treatments.

Side Effects of General Anesthesia:
Studies have discovered a plethora of adverse effects of anesthesia that manifest in pediatric patients even after they are discharged from the hospital. These effects range from motor imbalance and restlessness to excessive sedation, which requires admittance to the emergency room[11]. In a recent study, after a single episode of general anesthesia, 31% of patients exhibited motor imbalance, 23% experienced gastrointestinal effects, and 4% required medical advice after dismissal[11]. Furthermore, 5% of the children did not return to baseline activity until the second day after the procedure[11]. All effects were experienced after the patients had already been discharged from the hospital, meaning that they were able to meet the nationally recommended discharge criteria, but still were not functioning at a baseline level. Many pediatric cancer patients receive general anesthesia before every single fraction (essentially every 24 hours); for patients with six-week treatments, this translates to a minimum of 30 episodes of anesthesia over the course of 40 days. For small children, 24 hours may not be enough time to fully recover from the effects of anesthesia; thus, for the 6-week duration of radiotherapy, a child may never fully return to his/her baseline activity given the potential duration of the effects sustained from each administration.

Short-Term and Long-Term Risks of General Anesthesia:
Upon receiving general anesthesia, some patients may experience a paradoxical reaction[15,16], rendering them irritable and violent. This outcome is unpredictable and cannot be foreseen by anesthesiologists. If a patient exhibits this response, the sedation regimen must be recalculated using alternative sedatives. Other potential risks of anesthesia include primary failure, where the prescribed dose of the drug is not enough to elicit the desired state of consciousness for the patient, and secondary failure, where the effects wear off more quickly than expected and the patient unexpectedly awakes during treatment. Primary or secondary failure result in an undesired, heighted level of patient consciousness, referred to as anesthesia awareness[17,18]. Not only have anesthesia awareness patients reported excruciating surgical pain upon premature arousal, but anxiety, PTSD, and sleep disturbances are frequently reported in the wake of such incidents[17,18]. Even when anesthesia is successfully administered, the use of intubation for airway assistance is needed, possibly leading to a laryngospasm that can be fatal within a minute for children[7,15,19]. Respiratory, cardiovascular, and gastric complications as well can be life threatening even when anesthesia is administered properly[7]. Propofol sedation, a commonly used pediatric radiation therapy anesthesia method, can produce a wide spectrum of side effects ranging from increased secretions to seizures[15]. The short-term risks associated with anesthesia grow exponentially with increased administration, possibly leading to anesthesia failure and/or a laryngospasm. Additionally, following several episodes of general anesthesia, there is a chance that the child may incur long-term permanent neurological damage[20–22]. Neurological adverse

effects are currently being investigated. Although the long-term risks of repeated general anesthesia have not been thoroughly studied, there is consensus within the clinical community that repeated general anesthesia should not be used to children if possible.

Lowered Efficacy and Added Costs with General Anesthesia:
Daily rounds of general anesthesia can easily double the amount of time patient, parents, and medical staff (including anesthesiologists) spend in the hospital for administration and recuperation, making the process less efficient and increasingly expensive. For example, anesthesia costs average $50,000 per child over a typical six week treatment, therefore a reliable alternative to general anesthesia would drastically and immediately decrease costs[23]. Logistically, involvement of anesthesia is difficult. Radiation oncology suites are often stand-alone structures not located near or in major hospitals or academic centers, where anesthesia is more easily provided[6]. Because anesthesiologists are not normally on site in a radiation oncology suite, it creates obstacles in scheduling, transportation, and compensation. This problem is likely to worsen moving forward because radiation oncology suites are more frequently being built further from, not closer to, major hospitals or academic centers[24]. Anesthesia care provided in pediatric radiation therapy oncology suite is also often less efficient and safe. Anesthesiologist may be accustomed to working in operating room suites, which compared to radiation oncology suites, are relatively more efficient and have safer facilities, equipment, and personnel[24]. One such example is an anesthesiologist is not allowed in the radiation suite during treatment, which is not the case in a typical operating room[3,6].

Current Attempts to Minimize Anesthesia in Pediatric Oncology
Multiple options are being explored to minimize the use of anesthesia in pediatric radiation oncology with varying levels of success: music therapy plays music pre-selected by the patient during treatment[3,25]; interactive intervention and psychoeducational therapy entails preparatory play therapy, interactive support, and behavioral modeling[3,26–28]; psychological preparation prepares patients emotionally and mentally for the upcoming treatments[3,29]. Electronic monitors working in concert with behavioral training display movies or cartoons to distract patients during treatment used to increase patient cooperation and avoid anesthesia[3,28]. AVATAR, a similar device to PROMISE created by Stanford, has shown promising results. Stanford's study, published online January 11, 2020 reviewed 224 pediatric patients three years before and three years after AVATAR implementation. They found that more patients avoided general anesthesia for all ages; 73.2% before AVATAR implementation versus 63.4% after implementation. AVATAR use also demonstrated a reduction in treatment time per session by 38% and 326 fewer anesthesia sessions over a three year period, a total cost savings of roughly $500,000[30].

1.3 Rationale

In pediatric neuroimaging studies, it is critical to keep children motionless during the long periods of scanning[31–34]. Programmed feedback loops between movement and continued access to audio/video systems and mock MRI scanners have been used to train children to remain still during the scanning, using operant conditioning[20,35–37]. Great success has been achieved. Patients under study were reported[35] meeting a movement criterion of 2 mm per second or less, during a 20-min simulated scan. Subsequently, these patients cooperated with actual MRI scans without sedation. One hundred percent task compliance[38] during fMRI scan was observed among pediatric patients who were trained with multiple-reward compliance tactics.

The successful results obtained in non-sedated pediatric neuroimaging techniques have inspired us to develop similar technologies to facilitate pediatric radiotherapy without repeated general anesthesia. We have developed and validated technologies to facilitate pediatric radiotherapy without general anesthesia, which we have called Pediatric Radiation Oncology with Movie Induced Sedation Effect (PROMISE). While other

audiovisual distraction techniques have previously been described, as outlined above, PROMISE is the first system that allows for real time monitoring of patient motion and automatic shutting off of the beam if the patient moves outside of defined parameters, activating a built-in safety mechanism. When video integration becomes available, the video will also shut off if the patient moves allowing for real time behavioral training that incentivizes patients not to move.

We propose implementing PROMISE for all children between ages 3-11 undergoing radiation treatment through a phase II clinical trial with the following workflow: 1) During the CT simulation scan, a training session will be conducted, where the child will learn to lie still with positive and negative feedbacks provided by our system for behavioral training. This session will also be used as a screening test to choose children suitable for PROMISE. Only children meeting the movement-requirements during the training session will be selected as candidates for the following non-sedated radiation treatment. 2) During the treatment, a child will watch an age-appropriate movie or video of his/her choice. A 3D surface imaging system will be used to monitor the motion of the child. If the motion exceeds any pre-defined positioning thresholds (e.g., conventional radiotherapy (CRT): 0.5 cm in translation movements and 2° in three rotational angles; stereotactic radiotherapy (SBRT): 0.15 cm and 0.5 degree), the treatment beam will be shut off and the movie will be paused. 3) Beyond threshold movements the child will be instructed with the effectiveness of movement control strategy. 4) If the child reverts to treatment position within a pre-defined temporal threshold (e.g. 1 minute), the treatment will be resumed with a continuing movie. 5) If the child cannot revert to the treatment position within a pre-defined time threshold/or the movement is beyond any pre-defined re-alignment threshold value (e.g., 1 cm / 5° in three rotational angles), the radiation beam and the movie will be turned off, the patient will be readjusted and the treatment will resume. 6) In any treatment fraction, PROMISE treatment will be ceased if according to the physician, excessive movement is compromising the childs safety.. If the child is consecutively noncompliant with PROMISE treatments for two fractions, he/she will receive radiotherapy treatment with general anesthesia for all subsequent fractions, unless instructed by physician to re-attempt PROMISE.

This proposed PROMISE project offers several innovation features: 1) safer cancer radiotherapy modality for pediatric patients; 2) replacing repeated general anesthesia with behavioral training and motion monitoring to enable pediatric radiotherapy without sedation; 3) using a video/audio system and movies/cartoons for behavioral training; 4) using a 3D surface imaging system to monitor the patient motion and to provide negative feedback for operant conditioning. Our work success will lead to a novel radiotherapy modality for pediatric cancer patients with reduced risks and side effects, and also lowered cost and increased efficiency. Most children who currently need general anesthesia for radiotherapy will benefit from this new technology.

2.0 STUDY OBJECTIVES

Hypothesis: We hypothesize that PROMISE will lead to a reduction in the percentage of pediatric patients ages 3-7 who require general anesthesia use for daily radiation treatment from 70% (historical control) to 30%.

2.1 Primary Objectives

2.1.1 To decrease the total number of pediatric patients who require general anesthesia through the use of PROMISE.

2.2 Secondary Objectives

2.2.1 To assess the impact that PROMISE has on patient/family anxiety and quality of life, treatment time and clinical efficiency, and overall cost.

2.2.2 To determine the average patient movement and beam stoppages with PROMISE.

2.3 Endpoints

2.3.1 Primary: The percentage of pediatric patients age 3-7 who require daily general anesthesia for all treatments, compared to historical control. (Correlates with Primary Objective 2.1.1)

2.3.2 Secondary: Secondary outcomes will be measured comparing those who successfully are treated using PROMISE for any fraction vs. those who require general anesthesia for all fractions. (Correlates with Secondary Objective 2.2.1)
- Patient/family-reported health quality of life, assessed using PedsQL 3.0 Cancer Module.
- Patient anxiety, measured by the modified Yale Preoperative Anxiety Survey Short Form (mYPAS-SF).

2.3.3 Exploratory: Exploratory outcomes will also be measured comparing those who successfully are treated using PROMISE for any fraction vs. those who require general anesthesia for all fractions. (Correlates with Secondary Objectives 2.2.1 and 2.2.2).
- Treatment time per fraction.
- Workflow data: treatment time, average patient movement (magnitude, vertical, longitudinal, lateral, yaw, roll, and pitch), the number beam turn offs due to movement beyond threshold and total time out of tolerance.
- Cost savings.

3.0 Subject ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of 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 Planned to undergo radiation treatment

3.1.2 Age 3-11 years

3.1.3 Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 at screening (See Section 12.1, Appendix A).

3.1.4 Parents or guardians with the ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Subjects with documented medical behavior conditions or other conditions necessitating anesthesia use

3.2.2 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements.

3.2.3 Subjects whose parents opt to not include them (the subject) in the clinical trial.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

Pediatric Radiation Oncology with Movie Induced Sedation Effect (PROMISE) is an interactive, incentive-based movie system that integrates with a video surveillance gating module (VisionRT) to help keep a children's attention and prevent him or her from moving during radiation treatment. This technology is being studied as an alternative sedation solution for pediatric patients needing radiation treatment.

All patients on study will receive radiation treatment per standard of care for patient's diagnosis. The dose, fractionation, and possible concurrent treatments will all vary from patient to patient. Because we plan to enroll such a wide variety of patients, treatment will be unique for every patient. PROMISE will be consistent throughout the study, though, and attempted in every patient that can tolerate it.

The following protocol will be used to implement PROMISE for each patient:

- 1) Consultation:
  - During initial consultation with eligible patients, the clinical trial will be discussed and should they agree to participate, patients/families will be consented.
- 2) CT simulation session:
  - Initial screening for PROMISE will occur in CT simulation suite.
  - Patient will be instructed to be NPO for 6 hours, and anesthesia will be available as stand-by.
  - CT scan of region of interest, per standard clinical practice, will be attempted with modified version of PROMISE for audiovisual distraction, with patient under direct observation.
  - If the patient cannot comply with instructions of laying still for a few minutes for the CT scan, the attending radiation oncologist will be asked to re-evaluate the appropriateness of evaluating the child with PROMISE.
  - If PROMISE ultimately is unsuccessful, the patient will undergo general anesthesia for the CT simulation and subsequent treatments.
- 3) Treatment sessions:
  - For the first treatment, a 60-minute slot will be scheduled. Patient will be instructed to be kept NPO for 6 hours and anesthesia will be available on stand-by. Patient will be immobilized with PROMISE, and treatment will be attempted.
  - If patient successfully completes treatment with PROMISE, future treatments will be scheduled in 30-minute slots without anesthesia available on standby
  - If patient cannot successfully complete PROMISE, second treatment will be scheduled and planned similar to the first treatment, in a 60-minute slot with patient NPO and anesthesia on standby.
  - If second treatment is also not successful, no more attempts will be made with PROMISE and remaining treatments will be done under general anesthesia.
  - If the second treatment is successful, third treatment will be performed similarly.
  - If third treatment is successful, remaining treatments will be with PROMISE only, in 30-minute slots without anesthesia on standby.

- If third treatment is not successful, no more attempts will be made with PROMISE and remaining treatments will be done under general anesthesia.
- For each treatment session, the following workflow data will be measured: 1) total treatment time, 2) average patient movement (VisionRT), 3) number of beam turn offs due to movement beyond threshold (VisionRT).

4.2 Toxicities and Dosing Delays/Dose Modifications

There are no known or expected toxicities associated with PROMISE. The only toxicity that could be indirectly associated with PROMISE is if the child moves during radiation treatment and this results in radiation temporarily being delivered to the wrong target. However, PROMISE is integrated with the video surveillance gating module VisionRT, so that if the patient moves beyond predefined safety threshold, the beam will automatically stop, so this is not an event that would ever be expected to happen. This auto-beam off ability is a unique feature of PROMISE that is not seen in competing technologies.

4.3 Concomitant Medications/Treatments

N/A. Radiation and any other concomitant medications/treatments will be done as per standard of care. If patient cannot do PROMISE, general anesthesia will be used for each radiation treatment as per standard of care.

4.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment (PROMISE) may continue for **duration of radiation treatment course** or until any of the following that may necessitate stopping radiation treatment:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject's parent or guardian decides to withdraw subject from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.5 Duration of Follow Up

Follow up will occur 30 days (+/- 14 days) after treatment termination.

4.6 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Informed Consent*

5.1.2 *Medical history*

Complete medical and surgical history

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria*

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Performance status*

Performance status evaluated prior to study entry according to Appendix A (Section 12.1)

5.1.8 *Quality of life (QOL) questionnaires*

Baseline patient/family-reported health quality of life (QOL), assessed using PedsQL 3.0 Cancer Module, and patient/family-reported anxiety, measured by the modified Yale Preoperative Anxiety Survey Short Form (mYPAS-SF), will be assessed. The PedsQL for the patient will be optional.

5.2 Procedures During Treatment

5.2.1 Prior to Initiation of Treatment

- History, physical exam, vital signs
- PROMISE Screening
    - Initial screening for PROMISE will occur in CT simulation suite.
    - Patient will be instructed to be NPO for 6 hours, and anesthesia will be available as stand-by.
    - CT scan of region of interest, per standard clinical practice, will be attempted with modified version of PROMISE for audiovisual distraction, with patient under direct observation.
    - If the patient cannot comply with instructions of laying still for a few minutes for the CT scan, the attending radiation oncologist will be asked to re-evaluate the appropriateness of evaluating the child with PROMISE.
    - If PROMISE ultimately is unsuccessful for the CT simulation, the patient will undergo general anesthesia for the CT simulation and (at treating physician's discretion) subsequent treatments.

5.2.2 Radiation Treatment

- For the first treatment, a 60-minute slot will be scheduled. Patient will be instructed to be kept NPO for 6 hours and anesthesia will be available on stand-by. Patient will be immobilized with PROMISE, and treatment will be attempted.
    - If patient successfully completes treatment with PROMISE, future treatments will be scheduled in 30-minute slots without anesthesia available on standby

If patient cannot successfully complete PROMISE, the second treatment may be scheduled and planned similar to the first treatment at treating physician's discretion, in a 60-minute slot with patient NPO and anesthesia on standby, or patient can proceed with anesthesia for subsequent treatments.The patient may continue subsequent treatments with anesthesia at the physician's discretion..

- At the treating physicians discretion, the same procedures undertaken on Day 1 may be attempted a week later (+/- 7 days) if PROMISE was previously unsuccessful. By this time, many patients will potentially be calmer and more accustomed to treatment, a new environment, etc. and more likely to tolerate PROMISE.

5.2.3 At Each Treatment

- For each radiation treatment session, the following workflow data (as applicable) will be measured for all patients: 1) total treatment time, 2) average patient movement (VisionRT), and 3) number of beam turn offs due to movement beyond threshold (VisionRT).

5.2.4 Weekly (starting Day 1 +/- 5 days)

- Patient/family-reported health quality of life (QOL), assessed using PedsQL 3.0 Cancer Module, and patient/family-reported anxiety, measured by the modified Yale Preoperative Anxiety Survey Short Form (mYPAS-SF), will be assessed once a week during standard of care weekly on treat visit. The PedsQL for the patient will be optional.

5.3 Follow-up Procedures

Subject will be followed up **30 days (+/- 14 days) after treatment termination** for:

- History & physical exam, vital signs
- Patient/family-reported health quality of life (QOL), assessed using PedsQL 3.0 Cancer Module, and patient/family-reported anxiety, measured by the modified Yale Preoperative Anxiety Survey Short Form (mYPAS-SF). The PedsQL for the patient will be optional.

5.4 Time and Events Table

PROMISE	**Pre-study**	**Daily For Each Radiation Treatment Session**	**Weekly During Radiation Treatment[3]**	**Follow-up** (30 days +/- 14 days)
Procedures				
Informed Consent	X			
History and PE	X			X
Performance Status	X			X
QOL Questionnaires[1]	X		X	X
Workflow data[2]		X		

1: Patient/family-reported health quality of life (QOL), assessed using PedsQL 3.0 Cancer Module, and patient/family-reported anxiety, measured by the modified Yale Preoperative Anxiety Survey Short Form (mYPAS-SF). The PedsQL for the patient will be optional.

2: Workflow data to be measured: 1) treatment time, 2) average patient movement (magnitude, vertical, longitudinal, lateral, yaw, roll, and pitch), and 3) the number beam turn offs due to movement beyond threshold and total time out of tolerance.

3: During standard of care weekly on treat visits QOL questionnaires were be administered. This will not result in additional visits for the patient or family.

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject's parent or guardian voluntarily withdraws subject from treatment (follow-up permitted);

5.5.2 Subject's parent or guardian withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator);

5.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the subject's best interest;

5.5.7 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.8 Lost to follow-up: If a research subject cannot be located to document survival after a period of 30 days, the subject may be considered "lost to follow-up." All attempts to contact the subject during the 30 days must be documented.

6.0 MEASUREMENT OF EFFECT

Because PROMISE is not a treatment, it will have no direct impact on cancer progression or remission, but its effects on other aspects of treatment and patient quality of life will be measured as discussed in section 2.3.

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

No experimental therapy (standard of care radiation treatment is used)

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

7.2.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through the end of radiation treatment will be considered acute adverse events. These events will not be captured.

Late Adverse Events

Adverse events occurring up to 30 days (+/- 14 days) after the acute adverse event period will be considered late adverse events. These events will not be captured.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A “Serious adverse event” is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase “unanticipated problems involving risks to subjects or others” is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.3 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur during the acute adverse event period, as defined in section 7.2.1, and is attributed (possibly, probably, or definitely) to the use of PROMISE. Any event that occurs during the late adverse event period and is attributed (possibly, probably, or definitely) to the use of PROMISE must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

7.3.1 Reporting SAES and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See*

Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: Sarah Neufeld, Clinical Research Manager (214) 648-1836
Written reports to: Department of Radiation Oncology Clinical Research Office The University of Texas Southwestern Medical Center Attention: Sarah Neufeld, Clinical Research Manager 2280 Inwood Rd. Dallas, Texas 75390-9303 Fax: (214) 645-8913 Email: Sarah.Neufeld@utsouthwestern.edu UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: (214) 648-5949 UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device

effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

8.0 DRUG/TREATMENT INFORMATION

N/A (This trial does not use any non-standard or unapproved drug therapy).

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

9.1.1 To decrease the total number of pediatric patients who require general anesthesia compared to historical controls through the use of PROMISE (Primary Outcome).

9.1.2 To assess the impact that PROMISE has on patient anxiety and quality of life, treatment time and clinical efficiency, and overall cost.

9.1.3 To determine the average patient movement and beam stoppages with PROMISE.

9.2 Sample Size and Accrual

In order to detect a reduction in the rate of general anesthesia use in pediatric patients age 3-7 from the historical control of 70% to the hypothesized 30%, the total number of patients needed to achieve 84% power is 13, using a two-sided exact binomial test with a significance level of 0.05. Over the last two years (2018-2019) at the University of Texas Southwestern we treated 52 pediatric patients aged 3-11 who would be eligible for this study, so on average 26 patients/year. We estimate the ability to enroll the large majority (>80%) of patients who are eligible for this trial, and so we estimate enrolling 20 patients per year. Of these patients, ~42% are ages 3-7, so we estimate that 8-9 patients in our 3-7 age target range per year will be enrolled. Thus, we expect to enroll a total of 30 patients, of whom 13 will be ages 3-7, in ~1.5 years, with the total trial completed in ~2 years.

9.3 Data Analyses

Interim Reports: Interim reports will be prepared annually until the results of the study is closed to enrollment. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, as well as other preliminary data as available including PROMISE success rate (i.e. percentage of children enrolled who do not need general anesthesia).

10.0 STUDY MANAGEMENT

10.1 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.

10.2 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 and documenting informed consent, 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.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

10.3 Registration Procedures

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

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

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

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

Subjects that previously enrolled and are receiving subsequent treatments will be eligible at any time, while study is open to enrollment, to continue the study under the same subject number.

10.4 Data Management and Monitoring/Auditing

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

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.

Trial monitoring will be conducted according to the study specific monitoring plan. For guidance on creating a monitoring plan, refer to the UTSW SCCC IIT Management Manual.

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.

10.5 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.

10.5.1 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. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

10.5.2 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.

10.5.3 Serious Noncompliance (formerly called **major deviations** or **violations**): include any departure from IRB-approved research that:

- Increase risk of harm to subjects; and/or
- Adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or
- Adversely affects the integrity of the data and research (i.e., substantially compromises the integrity, reliability, or validity of the research)

➢ **Reporting requirement***: Serious Noncompliance must be promptly reported tothe IRB within 5 working days of discovery.

10.5.4 Continuing Noncompliance: includes a pattern of repeated noncompliance (in or more protocols simultaneously, or over a period of time) which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventive action within a reasonable time frame.

➢ **Reporting requirement***: Continuing Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

10.5.5 Noncompliance (that is neither serious nor continuing; formerly called minor deviations) any departure from IRB-approved research that:

- Does not meet the definition of serious noncompliance or continuing noncompliance

➢ **Reporting requirement***: Noncompliance that is neither serious nor continuing should be tracked and summarized the next IRB continuing review, or the notice of study closure- whichever comes first..

*Reporting Requirements reflect UTSW HRPP/IRB guidelines; participating sites should follow the reporting guidelines for their IRB of record

10.6 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.

10.7 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.

10.8 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.

11.0 REFERENCES

1. Jairam, V., Roberts, K. B. & Yu, J. B. Historical Trends in the Use of Radiation Therapy for Pediatric Cancers: 1973-2008. *Int. J. Radiat. Oncol.* **85**, e151–e155 (2013).
2. Herzog, C. E., Andrassy, R. J. & Eftekhari, F. Childhood cancers: hepatoblastoma. *The Oncologist* **5**, 445–453 (2000).
3. *Pediatric Radiation Oncology*. (Lippincott, Williams & Wilkins, 2016).
4. Khurmi, N., Patel, P., Koushik, S., Daniels, T. & Kraus, M. Anesthesia Practice in Pediatric Radiation Oncology: Mayo Clinic Arizona's Experience 2014-2016. *Paediatr. Drugs* **20**, 89–95 (2018).
5. Habrand, J.-L., Abdulkarim, B. & Roberti, H. Radiotherapeutical innovations in pediatric solid tumors. *Pediatr. Blood Cancer* **43**, 622–628 (2004).
6. McFadyen, J. G., Pelly, N. & Orr, R. J. Sedation and anesthesia for the pediatric patient undergoing radiation therapy. *Curr. Opin. Anaesthesiol.* **24**, 433–438 (2011).
7. Verma, V. *et al.* Anesthesia complications of pediatric radiation therapy. *Pract. Radiat. Oncol.* **6**, 143–154 (2016).
8. Ntoukas, S. M. *et al.* Minimizing General Anesthetic Use in Pediatric Radiation Therapy. *Pract. Radiat. Oncol.* **10**, e159–e165 (2020).
9. Harris, E. A. Sedation and anesthesia options for pediatric patients in the radiation oncology suite. *Int. J. Pediatr.* **2010**, 870921 (2010).
10. Frush, D. P., Bisset, G. S. & Hall, S. C. Pediatric sedation in radiology: the practice of safe sleep. *AJR Am. J. Roentgenol.* **167**, 1381–1387 (1996).
11. Malviya, S., Voepel-Lewis, T., Prochaska, G. & Tait, A. R. Prolonged recovery and delayed side effects of sedation for diagnostic imaging studies in children. *Pediatrics* **105**, E42 (2000).
12. Karian, V. E. *et al.* The development of a pediatric radiology sedation program. *Pediatr. Radiol.* **32**, 348–353 (2002).
13. Cook-Sather, S. D. & Litman, R. S. Modern fasting guidelines in children. *Best Pract. Res. Clin. Anaesthesiol.* **20**, 471–481 (2006).

14. Mavridou, P., Dimitriou, V., Manataki, A., Arnaoutoglou, E. & Papadopoulos, G. Patient's anxiety and fear of anesthesia: effect of gender, age, education, and previous experience of anesthesia. A survey of 400 patients. *J. Anesth.* **27**, 104–108 (2013).
15. Golparvar, M., Saghaei, M., Sajedi, P. & Razavi, S. S. Paradoxical reaction following intravenous midazolam premedication in pediatric patients - a randomized placebo controlled trial of ketamine for rapid tranquilization. *Paediatr. Anaesth.* **14**, 924–930 (2004).
16. Fillmore, M. T., Rush, C. R., Kelly, T. H. & Hays, L. Triazolam impairs inhibitory control of behavior in humans. *Exp. Clin. Psychopharmacol.* **9**, 363–371 (2001).
17. Ghoneim, M. M. Awareness during anesthesia. *Anesthesiology* **92**, 597–602 (2000).
18. Spitellie, P. H., Holmes, M. A. & Domino, K. B. Awareness during anesthesia. *Anesthesiol. Clin. N. Am.* **20**, 555–570 (2002).
19. Cravero, J. P. *et al.* The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: a report from the Pediatric Sedation Research Consortium. *Anesth. Analg.* **108**, 795–804 (2009).
20. Bakri, M. H. *et al.* Behavioral and emotional effects of repeated general anesthesia in young children. *Saudi J. Anaesth.* **9**, 161–166 (2015).
21. Ing, C. *et al.* Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* **130**, e476-485 (2012).
22. Flick, R. P. *et al.* Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. *Pediatrics* **128**, e1053-1061 (2011).
23. Scott, M. T. *et al.* Reducing Anesthesia and Health Care Cost Through Utilization of Child Life Specialists in Pediatric Radiation Oncology. *Int. J. Radiat. Oncol. Biol. Phys.* **96**, 401–405 (2016).
24. Buchsbaum, J. C. *et al.* Repetitive pediatric anesthesia in a non-hospital setting. *Int. J. Radiat. Oncol. Biol. Phys.* **85**, 1296–1300 (2013).
25. Barry, P., O'Callaghan, C., Wheeler, G. & Grocke, D. Music therapy CD creation for initial pediatric radiation therapy: a mixed methods analysis. *J. Music Ther.* **47**, 233–263 (2010).
26. Klosky, J. L. *et al.* Brief report: Evaluation of an interactive intervention designed to reduce pediatric distress during radiation therapy procedures. *J. Pediatr. Psychol.* **29**, 621–626 (2004).

27. Haeberli, S. *et al.* A psychoeducational intervention reduces the need for anesthesia during radiotherapy for young childhood cancer patients. *Radiat. Oncol. Lond. Engl.* **3**, 17 (2008).
28. Slifer, K. J. A video system to help children cooperate with motion control for radiation treatment without sedation. *J. Pediatr. Oncol. Nurs. Off. J. Assoc. Pediatr. Oncol. Nurses* **13**, 91–97 (1996).
29. Engvall, G. *et al.* Children's experiences and responses towards an intervention for psychological preparation for radiotherapy. *Radiat. Oncol. Lond. Engl.* **13**, 9 (2018).
30. Balazy, K. E. *et al.* Impact of Audiovisual-Assisted Therapeutic Ambience in Radiation Therapy (AVATAR) on Anesthesia Use, Payer Charges, and Treatment Time in Pediatric Patients. *Pract. Radiat. Oncol.* (2020) doi:10.1016/j.prro.2019.12.009.
31. Byars, A. W. *et al.* Practical aspects of conducting large-scale functional magnetic resonance imaging studies in children. *J. Child Neurol.* **17**, 885–890 (2002).
32. Akshoomoff, N. *et al.* Outcome classification of preschool children with autism spectrum disorders using MRI brain measures. *J. Am. Acad. Child Adolesc. Psychiatry* **43**, 349–357 (2004).
33. Raschle, N. M. *et al.* Making MR imaging child's play - pediatric neuroimaging protocol, guidelines and procedure. *J. Vis. Exp. JoVE* (2009) doi:10.3791/1309.
34. Schumann, C. M. *et al.* Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *J. Neurosci. Off. J. Soc. Neurosci.* **30**, 4419–4427 (2010).
35. Slifer, K. J., Cataldo, M. F., Cataldo, M. D., Llorente, A. M. & Gerson, A. C. Behavior analysis of motion control for pediatric neuroimaging. *J. Appl. Behav. Anal.* **26**, 469–470 (1993).
36. Slifer, K. J., Koontz, K. L. & Cataldo, M. F. Operant-contingency-based preparation of children for functional magnetic resonance imaging. *J. Appl. Behav. Anal.* **35**, 191–194 (2002).
37. Epstein, J. N. *et al.* Assessment and prevention of head motion during imaging of patients with attention deficit hyperactivity disorder. *Psychiatry Res.* **155**, 75–82 (2007).
38. Schlund, M. W. *et al.* Pediatric functional magnetic resonance neuroimaging: tactics for encouraging task compliance. *Behav. Brain Funct. BBF* **7**, 10 (2011).

12.0 APPENDICES

12.1 Appendix A: ECOG Performance Status

ECOG/ZUBROD PERFORMANCE STATUS

0 Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).

1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4 Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).

5 Death (Karnofsky 0).

12.2 Appendix B: PedsQL Cancer Module 3.0

ID# _____

Date:_____

PedsQL™

Cancer Module
Acute Version

Version 3.0

CHILD REPORT (ages **8-12**)

DIRECTIONS

Children with cancer sometimes have special problems. Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **7 days,** how much of a **problem** has this been for you …*

PedsQL 2

PAIN AND HURT *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I ache or hurt in my joints and/or muscles	0	1	2	3	4
2. I hurt a lot	0	1	2	3	4

NAUSEA *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I become sick to my stomach when I have medical treatments	0	1	2	3	4
2. Food does not taste very good to me	0	1	2	3	4
3. I become sick to my stomach when I think about medical treatments	0	1	2	3	4
4. I feel too sick to my stomach to eat	0	1	2	3	4
5. Some foods and smells make me sick to my stomach	0	1	2	3	4

PROCEDURAL ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Needle sticks (i.e. injections, blood tests, IV's) hurt	0	1	2	3	4
2. I get scared when I have to have blood tests	0	1	2	3	4
3. I get scared about having needle sticks (i.e. injections, blood tests, IV's)	0	1	2	3	4

TREATMENT ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I get scared when I am waiting to see the doctor	0	1	2	3	4
2. I get scared when I have to go to the doctor	0	1	2	3	4
3. I get scared when I have to go to the hospital	0	1	2	3	4

WORRY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I worry about side effects from medical treatments	0	1	2	3	4
2. I worry about whether or not my medical treatments are working	0	1	2	3	4
3. I worry that my cancer will come back or relapse	0	1	2	3	4

COGNITIVE PROBLEMS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to figure out what to do when something bothers me	0	1	2	3	4
2. I have trouble solving math problems	0	1	2	3	4
3. I have trouble writing school papers or reports	0	1	2	3	4
4. It is hard for me to pay attention to things	0	1	2	3	4
5. It is hard for me to remember what I read	0	1	2	3	4

*In the past **7 days,** how much of a **problem** has this been for you …*

ID# _____

Date:_____

PedsQL 3

PERCEIVED PHYSICAL APPEARANCE ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I feel I am not good looking	0	1	2	3	4
2. I don't like other people to see my scars	0	1	2	3	4
3. I am embarrassed when others see my body	0	1	2	3	4

COMMUNICATION ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to tell the doctors and nurses how I feel	0	1	2	3	4
2. It is hard for me to ask the doctors and nurses questions	0	1	2	3	4
3. It is hard for me to explain my illness to other people	0	1	2	3	4

ID# _____

Date:_____

ID#_____

Date:_____

PedsQL™

Cancer Module
Acute Version

Version 3.0

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

Children with cancer sometimes have special problems. On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **7 days,** how much of a **problem** has your child had with …*

PAIN AND HURT *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Aches in joints and/or muscles	0	1	2	3	4
2. Having a lot of pain	0	1	2	3	4

NAUSEA *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Becoming nauseated during medical treatments	0	1	2	3	4
2. Food not tasting very good to him/her	0	1	2	3	4
3. Becoming nauseated while thinking about medical treatments	0	1	2	3	4
4. Feeling too nauseous to eat	0	1	2	3	4
5. Some foods and smells making him/her nauseous	0	1	2	3	4

PROCEDURAL ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Needle sticks (i.e. injections, blood tests, IV's) causing him/her pain	0	1	2	3	4
2. Getting anxious about having blood drawn	0	1	2	3	4
3. Getting anxious about having needle sticks (i.e. injections, blood tests, IV's)	0	1	2	3	4

TREATMENT ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting anxious when waiting to see the doctor	0	1	2	3	4
2. Getting anxious about going to the doctor	0	1	2	3	4
3. Getting anxious about going to the hospital	0	1	2	3	4

WORRY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Worrying about side effects from medical treatments	0	1	2	3	4
2. Worrying about whether or not his/her medical treatments are working	0	1	2	3	4
3. Worrying that the cancer will reoccur or relapse	0	1	2	3	4

COGNITIVE PROBLEMS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty figuring out what to do when something bothers him/her	0	1	2	3	4
2. Trouble solving math problems	0	1	2	3	4
3. Trouble writing school papers or reports	0	1	2	3	4
4. Difficulty paying attention to things	0	1	2	3	4
5. Difficulty remembering what he/she reads	0	1	2	3	4

*In the past **7days,** how much of a **problem** has your child had with …*

ID# _____

Date: _____

PedsQL 3

PERCEIVED PHYSICAL APPEARANCE ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling that he/she is not good looking	0	1	2	3	4
2. Not liking other people to see his/her scars	0	1	2	3	4
3. Being embarrassed about others seeing his/her body	0	1	2	3	4

COMMUNICATION ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Difficulty telling the doctors and nurses how he/she feels	0	1	2	3	4
2. Difficulty asking the doctors or nurses questions	0	1	2	3	4
3. Difficulty explaining his/her illness to other people	0	1	2	3	4

ID# _____

Date: _____

ID# _____

Date:_____

PedsQL™

Cancer Module
Acute Version

Version 3.0

YOUNG CHILD REPORT (ages **5-7**)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

PedsQL 2

Think about how you have been doing for the past 7 days. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PAIN AND HURT *(problems with…)*	Not at all	Some-times	A lot
1. Do you ache or hurt in your bones and/or muscles	0	2	4
2. Do you hurt a lot	0	2	4

NAUSEA *(problems with…)*	Not at all	Some-times	A lot
1. Does your medicine make you sick to your stomach	0	2	4
2. Does food taste bad to you	0	2	4
3. Do you get sick to your stomach when you think about your medicine	0	2	4
4. Do you feel too sick to your stomach to eat	0	2	4
5. Do some foods and smells make you sick to your stomach	0	2	4

PROCEDURAL ANXIETY *(problems with…)*	Not at all	Some-times	A lot
1. Do needle sticks (i.e. shots, blood tests, IV's) hurt you	0	2	4
2. Do you get scared when you have to have blood tests	0	2	4
3. Do you get scared about having needle sticks (i.e. shots, blood tests, IV's)	0	2	4

TREATMENT ANXIETY *(problems with…)*	Not at all	Some-times	A lot
1. Do you get scared when you are waiting to see the doctor	0	2	4
2. Do you get scared when you have to go to the doctor	0	2	4
3. Do you get scared when you have to go to the hospital	0	2	4

WORRY *(problems with…)*	Not at all	Some-times	A lot
1. Do you worry about how medicines make you feel	0	2	4
2. Do you worry about whether or not your medicine is working	0	2	4
3. Do you worry that your cancer illness will come back	0	2	4

COGNITIVE PROBLEMS *(problems with…)*	Not At all	Some-times	A lot
1. Is it hard to know what to do when something bothers you	0	2	4
2. Is it hard for you to work with numbers or do math	0	2	4
3. Is it hard for you to pay attention to things	0	2	4
4. Is it hard for you to remember what is read to you	0	2	4

ID# _____

Date: _____

PedsQL 3

*Think about how you have been doing for the past **7 days**. Please listen carefully to each sentence and tell me how much of a problem this is for you.*

PERCEIVED PHYSICAL APPEARANCE ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Do you feel you are not good looking	0	2	4
2. Does it bother you when other people see your scars	0	2	4
3. Are you embarrassed when other people see your body	0	2	4

COMMUNICATION ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Is it hard for you to tell the doctors and nurses how you feel	0	2	4
2. Is it hard for you to ask the doctors and nurses questions	0	2	4
3. Is it hard for you to tell other people that you are sick	0	2	4

ID# _____

Date:_____

PedsQL 3.0 (5-7) Cancer Acute
03/00

Not to be reproduced without permission

ID# _____

Date:_____

How much of a problem is this for you?

PedsQL 4

ID#_____

Date:_____

PedsQL™

Cancer Module
Acute Version

Version 3.0

PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

Children with cancer sometimes have special problems. On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **7 days,** how much of a **problem** has your child had with …*

PAIN AND HURT *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Aches in joints and/or muscles	0	1	2	3	4
2. Having a lot of pain	0	1	2	3	4

NAUSEA *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Becoming nauseated during medical treatments	0	1	2	3	4
2. Food not tasting very good to him/her	0	1	2	3	4
3. Becoming nauseated while thinking about medical treatments	0	1	2	3	4
4. Feeling too nauseous to eat	0	1	2	3	4
5. Some foods and smells making him/her nauseous	0	1	2	3	4

PROCEDURAL ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Needle sticks (i.e. injections, blood tests, IV's) causing him/her pain	0	1	2	3	4
2. Getting anxious about having blood drawn	0	1	2	3	4
3. Getting anxious about having needle sticks (i.e. injections, blood tests, IV's)	0	1	2	3	4

TREATMENT ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting anxious when waiting to see the doctor	0	1	2	3	4
2. Getting anxious about going to the doctor	0	1	2	3	4
3. Getting anxious about going to the hospital	0	1	2	3	4

WORRY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Worrying about side effects from medical treatments	0	1	2	3	4
2. Worrying about whether or not his/her medical treatments are working	0	1	2	3	4
3. Worrying that the cancer will reoccur or relapse	0	1	2	3	4

COGNITIVE PROBLEMS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty figuring out what to do when something bothers him/her	0	1	2	3	4
2. Difficulty working with numbers or doing math	0	1	2	3	4
3. Difficulty paying attention to things	0	1	2	3	4
4. Difficulty remembering what is read to him/her	0	1	2	3	4

*In the past **7 days,** how much of a **problem** has your child had with …*

ID# _____

Date:_____

PedsQL 3

PERCEIVED PHYSICAL APPEARANCE *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling that he/she is not good looking	0	1	2	3	4
2. Not liking other people to see his/her scars	0	1	2	3	4
3. Being embarrassed about others seeing his/her body	0	1	2	3	4

COMMUNICATION *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Difficulty telling the doctors and nurses how he/she feels	0	1	2	3	4
2. Difficulty asking the doctors or nurses questions	0	1	2	3	4
3. Difficulty explaining his/her illness to other people	0	1	2	3	4

ID# _____

Date:_____

ID#_____

Date:_____

PedsQL™

Cancer Module
Acute Version

Version 3.0

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

Children with cancer sometimes have special problems. On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **7 days,** how much of a **problem** has your child had with …*

PAIN AND HURT *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Aches in joints and/or muscles	0	1	2	3	4
2. Having a lot of pain	0	1	2	3	4

NAUSEA *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Becoming nauseated during medical treatments	0	1	2	3	4
2. Food not tasting very good to him/her	0	1	2	3	4
3. Becoming nauseated while thinking about medical treatments	0	1	2	3	4
4. Feeling too nauseous to eat	0	1	2	3	4
5. Some foods and smells making him/her nauseous	0	1	2	3	4

PROCEDURAL ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Needle sticks (i.e. injections, blood tests, IV's) causing him/her pain	0	1	2	3	4
2. Getting anxious about having blood drawn	0	1	2	3	4
3. Getting anxious about having needle sticks (i.e. injections, blood tests, IV's)	0	1	2	3	4

TREATMENT ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting anxious when waiting to see the doctor	0	1	2	3	4
2. Getting anxious about going to the doctor	0	1	2	3	4
3. Getting anxious about going to the hospital	0	1	2	3	4

WORRY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Worrying about side effects from medical treatments	0	1	2	3	4
2. Worrying about whether or not his/her medical treatments are working	0	1	2	3	4
3. Worrying that the cancer will reoccur or relapse	0	1	2	3	4

COGNITIVE PROBLEMS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty figuring out what to do when something bothers him/her	0	1	2	3	4
2. Difficulty paying attention to things	0	1	2	3	4
3. Difficulty remembering what is read to him/her	0	1	2	3	4

ID# _____

Date: _____

PedsQL 3

*In the past **7 days,** how much of a **problem** has your child had with …*

PERCEIVED PHYSICAL APPEARANCE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling that he/she is not good looking	0	1	2	3	4
2. Not liking other people to see his/her scars	0	1	2	3	4
3. Being embarrassed about others seeing his/her body	0	1	2	3	4

COMMUNICATION *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty telling the doctors and nurses how he/she feels	0	1	2	3	4
2. Difficulty asking the doctors or nurses questions	0	1	2	3	4
3. Difficulty explaining his/her illness to other people	0	1	2	3	4

ID# _____

Date:_____

12.3 Appendix C: Modified Yale Preoperative Anxiety Survey Short Form (mYPAS-SF)

- A. Activity
  - 1 = Looking around, curious, playing with toys, reading (or other age-appropriate behavior); moves around holding area/treatment room to get toys or go to parent; may move toward OR equipment
  - 2 = Not exploring or playing, may look down, may fidget with hands or suck thumb (blanket); may sit close to parent while waiting, or play has a definite manic quality
  - 3 = Moving from toy to parent in unfocused manner, nonactivity-derived movements; frenetic/frenzied movement or play; squirming, moving on table, may push mask away or clinging to parent
  - 4 = Actively trying to get away, pushes with feet and arms, may move whole body; in waiting room, running around unfocused, not looking at toys or will not separate from parent, desperate clinging
- B. Vocalizations
  - 1 = Reading (nonvocalizing appropriate to activity), asking questions, making comments, babbling, laughing, readily answers questions but may be generally quiet; child too young to talk in social situations or too engrossed in play to respond
  - 2 = Responding to adults but whispers, “baby talk,” only head nodding
  - 3 = Quiet, no sounds or responses to adults
  - 4 = Whimpering, moaning, groaning, silently crying
  - 5 = Crying or may be screaming “no”
  - 6 = Crying, screaming loudly, sustained (audible through mask)
- C. Emotional expressivity
  - 1 = Manifestly happy, smiling, or concentrating on play
  - 2 = Neutral, no visible expression on face
  - 3 = Worried (sad) to frightened, sad, worried, or tearful eyes
  - 4 = Distressed, crying, extreme upset, may have wide eyes
- D. State of apparent arousal
  - 1 = Alert, looks around occasionally, notices/watches what anesthesiologist does with him/her (could be relaxed)
  - 2 = Withdrawn, child sitting still and quiet, may be sucking on thumb or face turned into adult
  - 3 = Vigilant, looking quickly all around, may startle to sounds, eyes wide, body tense
  - 4 = Panicked whimpering, may be crying or pushing others away, turns away

Scoring: Divide each item rating by the highest possible rating (i.e., 6 for the “vocalizations” item and 4 for all other items), add all of the produced values, divide by 4, and multiply by 100.

ID# _____

Date:_____