**Abbreviated Title:** *PhII VR Brain Tumors*

**NIH Protocol Number:** 20C0065

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**Title:** A Phase II Feasibility Trial Using Immersive Virtual Reality (VR) at the Time of Clinical Evaluation to Improve Psychological Distress and Anxiety in Primary Brain Tumor (PBT) Patients

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**Device:**

| | |
|---|---|
| Device Name: | Pico G2 4K Headset with Applied VR software |
| IDE Number: | none |
| Sponsor: | none |
| Manufacturer: | Pico, Applied VR |
| Supplier: | Applied VR |

## PRÉCIS

### Background

- Psychological distress is a common concern for patient across the cancer trajectory, which has been associated with worse clinical outcomes in terms of quality of life, adherence to treatment regimens, satisfaction with care, and poorer survival in past research.
- Virtual reality (VR) has the potential to alleviate some of the negative aspects of illness by allowing individuals to "escape" from their lives and experience more positive thoughts and emotions, which can be accomplished using cardiac coherence breathing techniques and distraction (both of which can improve psychological symptoms).
- Past VR research has shown promising improvements in anxiety, pain, distress and distraction through use of immersive VR interventions, though there is scant evidence in PBT populations, particularly in the time period surrounding their neuroimaging and clinical appointments when distress and anxiety can be highest.
- Recent evidence has demonstrated that the COVID-19 pandemic and associated mitigation procedures introduce additional stress for cancer patients, with higher levels of anxiety, depression, loneliness, and financial toxicity being reported during this time.
- The purpose of this phase II clinical trial is to determine the feasibility of implementing an immersive VR relaxation intervention in a PBT population and to assess the efficacy of the intervention to improve psychological distress and anxiety at the time of clinical evaluation. VR is an innovative delivery approach to teach our patients validated breathing and mindfulness techniques that can improve their psychological symptoms and their ability to self-manage these symptoms.

### Objective:

- To describe the feasibility of implementing a VR intervention in a PBT population, including eligibility, accrual, compliance, adverse device effects, study completion, and participant satisfaction with the intervention

### Eligibility

- PBT patients enrolled on the Natural History Study (NHS) trial in the Neuro-Oncology Branch (NOB) (all tumor types and grades eligible)
- Patients can be newly diagnosed, receiving active treatment, or on surveillance
- Adults (≥ 18 years of age) who are English-speaking and able to self-report symptoms
- Active corticosteroid therapy is permissible
- Exclude patients without tissue diagnosis, recent cranial surgery (≤ 2 weeks), scalp wound healing issues, epilepsy, or seizures within the last 6 weeks
- Participants have reported ≥ 1 on distress item from MDASI-BT prior to past clinic appointment
- Exclude patients who have a hypersensitivity to motion, severe nausea, or visual field deficits that might interfere with VR experience
- Exclude patients with a current diagnosis of generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), claustrophobia, or panic disorder

- Those with visual deficits that might interfere with the VR experience, including hemianopsia, diplopia, and agnosia, based on their most recent clinical assessment

**Design**

- This is a phase II feasibility clinical trial with a single arm experimental design. The VR intervention and all patient-reported outcome measures (PROs) will be done remotely using telehealth.
- Study will include collection of self-reported PROs for distress, anxiety, mood disturbance, symptom burden/interference, quality of life, cognitive function, loneliness, and financial toxicity, as well as optional salivary stress biomarkers. These measures will be collected at baseline and immediately after a brief VR relaxation intervention to determine *acute* effects on distress, anxiety, and biological stress measures. Repeat post-intervention assessments will be done approximately 1 week and 1 month following the initial intervention to determine *sub-acute* effects on distress and anxiety, as well as impact on other symptoms. A semi-structured qualitative interview will also be conducted 1 month after the initial intervention to assess participant satisfaction with the intervention and how the pandemic has affected their psychological symptoms.
- Descriptive statistics, *T*-tests, Wilcoxon rank sum tests, and multiple logistic regression models will be used to evaluate the feasibility of the VR intervention. Linear mixed models and effect size calculations will be used to evaluate the acute and sub-acute effects of the VR intervention on self-reported PROs. Pearson or Spearman correlations will be used to evaluate the relationship between the biological stress measures and self-reported PROs.
- A total of 120 PBT patients will participate in this study.

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## STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

# 1 INTRODUCTION

## 1.1 STUDY OBJECTIVES

### 1.1.1 Primary Objective

To describe the feasibility of implementing a VR intervention in a PBT population, including eligibility, accrual, compliance, adverse device effects, study completion, and participant satisfaction with the intervention

### 1.1.2 Secondary Objectives

1.1.2.1. To assess the effects of a VR intervention on self-reported *acute* and *subacute* distress (as measured by the NCCN Distress Thermometer [DT]) and anxiety (as measured by the State Anxiety Inventory [STAI-6]) in PBT patients

1.1.2.2. To determine if the effects VR has on distress and anxiety are more pronounced in those with high distress (based on DT cut-off score of ≥ 5) compared to those with low distress (based on DT scores of 0-4)

1.1.2.3. To determine if the effects VR has on distress and anxiety are more pronounced in those individuals not on systemic corticosteroids (CS) compared to those who are on active CS therapy.

### 1.1.3 Exploratory Objectives

1.1.3.1 To explore the correlations between biological stress measures (as measured by salivary cortisol, salivary dehydroepiandrosterone-sulfate [DHEA-S], salivary α-amylase [sAA], and heart rate [HR]) and self-reported outcome measures

1.1.3.2 To explore the effects of a VR intervention on self-reported patient outcome measures collected on the Natural History Study (NHS), including mood disturbance (as measured by PROMIS®-Anxiety & PROMIS®-Depression Short Forms), symptom burden and interference (as measured by the MD Anderson Symptom Inventory Brain Tumor [MDASI-BT]), health-related quality of life (HRQOL) (as measured by the EQ-5D) and cognitive function as measured by the Neuro-QoL™

1.1.3.3 To explore the impact of loneliness (as measured by the UCLA Loneliness Scale) and financial toxicity (as measured by the Comprehensive Score for Financial Toxicity) on distress (as measured by the DT) and anxiety (as measured by the STAI-6) during the COVID-19 pandemic

1.1.3.4 To determine the proportion of patients with adjustment disorder (AjD) (as measured by the ADNM-20) in a PBT population to assess potential utility of VR for improving AjD-related symptoms

## 1.2 BACKGROUND AND RATIONALE

### 1.2.1 Distress and Anxiety in the PBT Population

Psychological distress in cancer patients has been defined by the National Comprehensive Cancer Network (NCCN) as a multifactorial unpleasant emotional experience of a psychological, social, and/or spiritual nature that can interfere with the ability to effectively cope with the cancer diagnosis, its physical symptoms, treatment-related toxicities, and diagnostic imaging (1-3). Distress is a common concern for patients across the cancer trajectory, beginning at the time of diagnosis and extending into the post-treatment and survivorship phase. Past cross-sectional studies have reported approximately 30–45% of cancer patients in North America experience significant levels of distress (4, 5), and in the advanced cancer population the prevalence may be as high as 60% (6, 7). Significant levels of distress have been associated with worse clinical outcomes for oncology patients, in terms of worse quality of life, poor adherence to treatment regimens, lower satisfaction with care, and poorer survival (3). In recent years, distress has been designated the "6$^{th}$ vital sign" by various accrediting bodies, both in the United States and worldwide, in order to increase the frequency of distress screenings for cancer patients across the disease trajectory (minimally at the time of initial diagnosis, before, during and after treatment, and at the transition to end-of-life care) (1, 8). In doing so, the goal is to identify individuals with significant distress who would most benefit from interventions or referrals to manage their symptoms or concerns.

Distress, anxiety, and other psychological disorders may be more prevalent in PBT patients, compared to both the general population and those with non-CNS tumors (9, 10). Once diagnosed, the overall prognosis for PBT patients remains poor, and they often have a difficult clinical course that is complicated and unpredictable due to significant morbidity from both tumor-related and psychological symptoms (11-13). In addition to the distress and anxiety patients experience related to cancer progression, symptom burden, and therapeutic toxicities, the experience of these symptoms can also be related to diagnostic imaging and clinical evaluation. The term "scanxiety" describes the distress related to often-debilitating anxiety cancer patients can experience in the period surrounding their diagnostic imaging studies and leading up to their clinic appointments (14). While there are some PBT patients who are claustrophobic and experience severe anxiety during MRI imaging, we hypothesize that the distress reported by approximately 20–30% of our patients is more often related to the uncertainty of their disease and what the diagnostic scans will reveal. Past research has shown that PBT patients experience significant uncertainty surrounding their illness and that alterations in mood (e.g. anxiety and depression) may be modifiers of the relationship between uncertainty and overall symptom burden (15). Therefore, we propose that by mitigating clinically significant distress in PBT patients, improvements in their psychological and physical health are likely to follow.

### 1.2.2 Psychosocial Impact of the COVID-19 Pandemic

It is well-established that oncology patients are at increased risk for experiencing higher psychological distress compared to the general population (16, 17), as cancer is a life-threatening disease that can adversely impact all aspects of their life. The COVID-19 pandemic and associated mitigation procedures, including social distancing, lockdowns, travel bans, and changes to work practices, have imposed additional stress on these individuals, as well as the general population (18, 19). There is emerging evidence across the globe that fear of contracting

COVID-19, the negative impact of social distancing and other mitigation procedures, and economic uncertainty are associated with higher levels of distress, anxiety, and depression within the general population (20-24), though less is known about the psychosocial impact of the pandemic for cancer patients.

Recent work that has focused on psychological symptoms in adult oncology patients during the pandemic (18, 25) have reported that over 30% of patients are experiencing high levels of stress, anxiety, and depression, as well as higher levels of loneliness and financial toxicity in those with severe psychological symptoms. While this data is primarily from breast and hematologic cancer populations, we hypothesize that a similar impact on psychological symptoms exists for PBT patients during the pandemic. We are interested in exploring loneliness and financial toxicity with distress and anxiety symptoms in our patients so that we may better understand how the pandemic has adversely impacted their psychological well-being.

### 1.2.3 Adjustment Disorder as Relevant Clinical Diagnosis

Adjustment disorder (AjD) is one of the most common mental disorders in clinical practice, accounting for up to 30% of all cases in psychiatric samples (26, 27), though its prevalence in oncology populations is unclear. AjD can be defined as a maladaptive reaction to an identifiable psychosocial stressor (or multiple stressors) with 2 explicitly defined core symptom groups, namely 1) a preoccupation (including excessive worry, recurrent and distressing thoughts about the stressor, or constant rumination about its implications), and 2) a failure to adapt that significantly interferes with everyday functioning (e.g. difficulty concentrating or sleep disturbances) (28). The emotional and behavioral symptoms in AjD include the otherwise normative reactions that manifest more intensely than usually expected when individuals are confronted with a specific stressor and are associated with significant social, occupational, and/or academic performance-related impairments (29). These symptoms are suggested to emerge within 1 month of the onset of the stressor(s) and tend to resolve within 6 months, unless the stressor persists for a longer duration. Given that AjD is associated with serious illness as a predisposing stressor, it seems prudent to investigate this diagnostic concept in oncology populations. For the purposes of this study, we will use a validated screening instrument to assess the prevalence those at high-risk for AjD in PBT patients. By doing so, we aim to assess the potential need for interventions that could improve AjD-related psychological symptoms, such as distress and anxiety, which could not only improve their quality of life and tolerance of therapies, but also potentially increase survival.

### 1.2.4 Use of Virtual Reality in Oncology Populations

Virtual reality (VR) is defined as a computer-generated simulation, such as a set of images and sounds that represent a real place or situation, that allows users to explore and interact with a virtual environment in a way that makes them feel actually present in that world (30-32). As such, VR has the potential to alleviate some of the negative aspects of illness by providing multisensory information and allowing individuals to “escape” to pleasant locations and more positive thoughts and emotions (33). VR systems can be classified into 2 types: immersive and non-immersive. Immersive VR can be characterized by full immersion in a virtual environment through use of a head-mounted display, which is able to provide distraction by presenting the user with a view of a computer-generated world, thus allowing them to lose awareness of time and the real world (34). In contrast, the non-immersive type of VR is often experienced with a

computer screen or other non-wearable media platform where the user can still remain connected to the external world while being able to explore the virtual one.

Past empiric research has found VR technology to be efficacious in improving a variety of patient symptoms across both adult and pediatric populations, including distraction during stressful medical procedures (35), improved pain control during burn dressing changes (36, 37), and improved anxiety and depressive symptoms (38-40). However, there are few studies that have examined the effects of a VR intervention on adverse symptoms in oncology populations, which is somewhat surprising given the high prevalence of cancer and its associated symptom burden. A systematic review of the literature focused on use of VR in adult and pediatric oncology populations revealed some promising effects of VR on distress (41-45), pain (33, 46, 47), anxiety (33, 42-44, 46, 48), depression (43, 49), and distraction (41, 44, 48, 50), though sample sizes were small and included very few PBT patients in the study populations. There also was significant heterogeneity in the instruments used to operationalize the outcome measures in these studies, so comparing findings across different cancer populations was difficult. Additionally, the study designs relied solely on self-reported outcome measures to assess the efficacy of the VR intervention to improve symptoms, with no inclusion of biomarkers or any correlative biology to better elucidate mechanisms of effects. Ultimately, further investigation is needed to determine the feasibility and efficacy of using VR technology to improve adverse physical and psychological symptoms in PBT patients, which have to date been largely understudied in this context.

### 1.2.5 Stress Physiological Pathways and Biomarkers of Interest

Little is known about the biological pathways involved with symptomatic improvement from VR use, but it is hypothesized that VR can improve distress and other psychological symptoms through a combination of distraction and promotion of relaxation states. Both of these approaches could help blunt or decrease the severity of the physiological stress response, which involves the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) system (51) **(Figure 1)**. Activation of these neuroendocrine systems is essentially an adaptive mechanism that enables the human body to maintain physiological stability in response to stress (52-55). While measurement of biomarkers has historically be performed with serum samples in clinical research, many stress hormones and enzymes that once required blood samples now have validated salivary assays available (53). Utilizing salivary biomarkers provides a sound, cost-effective, and relatively simple approach to measuring neuroendocrine analytes, and is currently the “gold standard” in biomedical stress research.

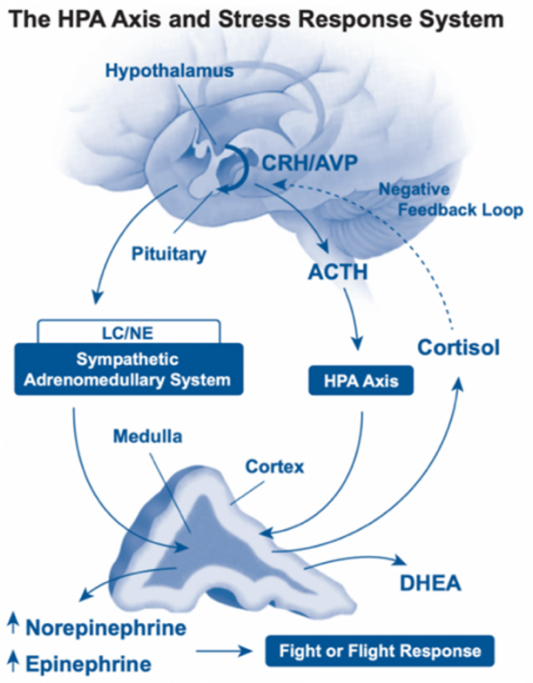


**Figure 1** The HPA Axis and Stress Response System

For this study, we will focus on salivary cortisol, DHEA, sAA, and HR, which together represent activity of the neuroendocrine stress regulatory systems. In response to stress, cortisol and DHEA are released from the adrenal glands in response to upstream hormonal signaling from the hypothalamus and pituitary gland (51). Release of cortisol, a glucocorticoid, shunts metabolic activity away from regulatory processes towards those that function primarily in immediate survival and homeostasis (51). In contrast, DHEA, a glucocorticoid antagonist, can counter the effects of systemic glucocorticoid exposure and is thought to serve as an anxiolytic and protective factor against stress (56). Salivary α-amylase, an enzyme secreted by the parotid gland, and HR have been shown to increase in response to both physical and psychological stressors as a part of the SAM system response (53, 54). By measuring these stress biomarkers and correlating their activity with self-report psychological measures, we hope to gain a more holistic picture about the efficacy of stress reducing interventions for PBT patients and what biological mechanisms are involved.

# 2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

## 2.1 ELIGIBILITY CRITERIA

### 2.1.1. Inclusion Criteria

2.1.1.1 Primary brain tumor (PBT) patients enrolled on the Natural History Study (NHS) trial (16C0151) in the Neuro-Oncology Branch (NOB) who have an upcoming scan and clinical appointment

2.1.1.2 Participants can be newly diagnosed, receiving active treatment, or on surveillance

2.1.1.3 Concurrent enrollment in other NOB trials is permissible

2.1.1.4 Adults (≥ 18 years of age) who are English-speaking

2.1.1.5 Participants must be able to reliably self-report symptoms, based on clinician assessment

2.1.1.6 Participants have reported ≥ 1 on distress item from MDASI-BT prior to a previous clinic appointment

2.1.1.7 Active corticosteroid therapy is permissible

2.1.1.8 Ability of subject to understand and the willingness to sign a written informed consent document

### 2.1.2 Exclusion Criteria

2.1.2.1 Participants who do not have a tissue diagnosis (no past surgery or biopsy to confirm diagnosis)

2.1.2.2 Cranial surgery ≤ 2 weeks prior to initiation of study intervention

2.1.2.3 Scalp wound healing issues that might interfere with comfortable VR headset use

2.1.2.4 Those who have epilepsy or have had a seizure in the last 6 weeks

2.1.2.5 Participants with a current diagnosis of generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), claustrophobia, or panic disorder

2.1.2.6 Participants who have a hypersensitivity to motion or severe nausea, which could make the VR experience uncomfortable

2.1.2.7 Those with visual deficits that might interfere with the VR experience, including hemianopsia, diplopia, and agnosia, based on their most recent clinical assessment

### 2.1.3 Recruitment Strategies

Participants will be recruited from the Natural History Study as outlined in Section **2.2.1**

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms.

## 2.2 SCREENING EVALUATION

### 2.2.1 Screening Activities Performed Prior to Obtaining Informed Consent

Research staff from the Neuro-Oncology Branch (NOB) will screen participants for study inclusion by targeting those who have reported distress scores ≥1 on the MDASI-BT questionnaire within the previous 12 months. Those with past distress will be contacted by phone or email to assess eligibility, introduce the VR trial, and determine their interest in participating in the trial. Patients who meet eligibility criteria and are interested in participating will be consented to the study and the date of their upcoming neuro-oncology scan appointment (either with NOB or outside neuro-oncology providers) will be documented. The VR intervention will be aligned with this upcoming scan appointment.

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects that are enrolled in the NIH16C0151 Natural History Protocol.
- Review of existing medical records to include H&P, laboratory studies, MDASI-BT, etc.
- Phone call or email to introduce the VR study and determine their interest in participating

### 2.2.2 Screening Activities Performed After a Consent for Screening Has Been Signed

No additional screening activities are required.

## 2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

### 2.3.1 Intervention Assignment

**Cohorts**

| Number | Name | Description |
|---|---|---|
| 1 | Group 1 | Primary brain tumor patients |

**Arm**

| Number | Name | Description |
|---|---|---|
| 1 | Experimental intervention | Experimental VR intervention, completion of questionnaires, and (optional) biological sample submission |

### Arm Assignment

Participants will be assigned to Cohort 1 and directly assigned to Arm 1.

### 2.4 BASELINE EVALUATION

All baseline evaluation procedures should be done prior to the VR intervention. All baseline PROs measures will be administered using the Scribe electronic interface.

- NCCN Distress Thermometer (DT)
- State-Trait Anxiety Inventory (STAI-6)
- UCLA Loneliness Scale
- Comprehensive Score for Financial Toxicity (COST)
- Adjustment Disorder Instrument (ADNM-20)
- Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)
- Correlative stress biomarkers (salivary hormones) – Kits will be sent to participants with instructions in section **15.2** included.

## 3 STUDY IMPLEMENTATION

### 3.1 STUDY DESIGN

This protocol is a single arm experimental design and will target PBT patients currently enrolled on the Natural History Study. The VR intervention and all assessments will be done remotely using telehealth. Following consent, the timing of the VR intervention will be aligned with the participant's upcoming neuro-oncology scan appointment (either with NOB or outside neuro-oncology providers). Once consented, the participant will be asked if they would like to participate in the correlative biomarkers portion of the protocol, and if interested they will be provided with saliva sampling materials. Prior to their appointment, NOB research staff will provide participants with a VR headset and saliva sampling materials (optional) and send baseline questionnaires for participants to complete prior to the VR intervention. The intervention will include a 5-minute relaxation scenario delivered via an immersive, head-mounted VR device. Repeat assessments of PROs and salivary biomarkers will be done immediately following the intervention, as well as repeat PROs 1 week and 1 month later in order to assess acute and subacute effects on symptoms and stress hormones. Additionally, a semi-structured qualitative phone interview will be done 1 month following the VR intervention.

### 3.2 DEVICE ADMINISTRATION

The VR headset to be utilized in this study, called the Pico G2 4K was designed by Pico. The AppliedVR™ company designed the AppliedVR™ software for therapeutic use in clinical populations.

#### 3.2.1 VR Intervention

Research staff will introduce participants to the VR headsets demonstrating how to put it on and adjust the fit, how to navigate the main virtual interface and select different scenarios, and proper

use of the handheld remote. Additionally, NOB research staff will go over any questions participants have about use of the headset in a virtual meeting prior to administering the intervention. Once all baseline questionnaires have been completed and participants feel comfortable with use of the VR headset, they will complete the VR intervention under the supervision of research staff.

The VR intervention will take place in a telehealth meeting on an NIH approved platform with NOB research staff with the participant sitting in a comfortable chair. Participants will select a VR scenario from the pre-loaded options on the VR headset (each around 5 minutes in duration), which fall into one of the following categories:

3.2.1.1 Dynamic breathing

Experiences that teach breath awareness and slow, diaphragmatic breathing in order to induce relaxation and increase HR variability to manage stress

3.2.1.2 Guided relaxation

Experiences that provide meditative environments to practice mindfulness, relaxation, and attention to streams of thought

3.2.1.3 Instant escape

Experiences that are specifically designed to provide immersive, multi-sensory distraction from unpleasant symptoms

3.2.1.4 Interactive games

Fun distraction activities designed to redirect attention away from unpleasant symptoms or thoughts

*** These games will be available for participants to enjoy on the VR headsets while using them at home, but not for the initial VR intervention.

For the purposes of standardizing duration of the initial VR experience in clinic across individuals, participants will not be allowed to change scenarios once they have begun, which will keep the duration to approximately 5 minutes. Research staff will remain in the virtual meeting with the participants during the VR intervention in order to monitor for any issues or adverse device effects related to the intervention and also to address any questions that arise.

Immediately following completion of the intervention, participants will repeat the DT, STAI-6, and PRO-CTCAE questionnaires using the Scribe interface.

### 3.2.2 Post-Intervention VR Use and Measurements

Following completion of the initial VR intervention, participants will continue use of the VR headsets at their discretion. Participants will have the opportunity to share their thoughts about the VR headset and study experience during a semi-structured qualitative phone interview 1 month following the remote VR intervention. Participants will also be asked the Was It Worth It (WIWI) questions immediately post-intervention as well as at the 1 month post-VR timepoint to ascertain their satisfaction with initial VR use as well as their experience throughout the participation period. All post-intervention PROs measurements will be done electronically through Scribe. If for technical or physical reasons the participant is unable to complete their questionnaires electronically, the questionnaires may be read to them by research staff and their

responses documented within Scribe. Research staff will follow-up with participants weekly to help assist with any issues or questions about the VR headsets and will ask about any adverse effects participants experience while using the headset.

Following completion of the study, participants will be allowed to keep the VR headsets indefinitely. Other members of the household are allowed to use the VR headsets and we will encourage participants to let us know if that occurs.

## 3.3 QUESTIONNAIRES

### 3.3.1 National Comprehensive Cancer Network (NCCN) Distress Thermometer (DT)

The NCCN Distress Thermometer (DT) will be used to operationalize distress in this study. This instrument was first developed in 1997 based on release of the NCCN distress management guidelines, which consisted of a global distress screener (the Distress Thermometer), an accompanying 40-item problem list, and treatment recommendations for psychosocial issues (57-59). The DT is a one-item, 11-point Likert scale that is represented on a visual graphic of a thermometer that ranges from 0 (no distress) to 10 (extreme distress), with patients reporting their level of distress over the preceding week (including the day of assessment). Individuals who report high levels of distress can be given the accompanying problem list that identifies commonly reported problems related to the cancer experience. The DT has been validated using receiver operating characteristic (ROC) curve analyses in numerous oncology populations and has demonstrated validity and reliability against other validated legacy instruments (57, 60-62), including the Hospital Anxiety and Depression Scale (HADS), the Brief Symptom Inventory (BSI), and the Behavioral Health Status (BHS) Scale.

There has been a lack of uniformity in reporting clinically significant cut-off scores for moderate-severe distress on the DT, with cut-off scores ranging from 3 to 6. When the DT was initially validated, a cut-off score of 5 was used to identify patients experiencing significant distress, as this as the midpoint of the 11-point Likert Scale (59). In much of the DT research that utilizes mixed oncology patient samples, cut-off scores indicating distress varied by culture, setting, demographics, and cancer type, but most studies support a DT cut-off score of either 4 or 5 (58, 60, 63). For the purposes of this study, we will implement a cut-off score for moderate-severe (and clinically significant) distress of ≥ 5, mirroring that of the MDASI-BT instrument (63-65).

### 3.3.2 State-Trait Anxiety Inventory, 6-Item Short-Form (STAI-6)

The State-Trait Anxiety Inventory 6-item Short-Form (STAI-6) will be used to operationalize anxiety . The Spielberger State-Trait Anxiety Inventory (STAI), initially developed in 1970 (Form X) and revised in 1983 (Form Y), is one of the most commonly used measurement tools for anxiety in applied psychology research, with demonstrated reliability and validity across numerous sample populations (66-69). Despite its popularity and sound psychometrics in past research, the legacy instrument is rather lengthy, consisting of 40 items total with 2 subscales: state anxiety, known as the S-scale (how anxious one feels in that moment) and trait anxiety, known as the T-scale (how anxious one generally feels). For the purposes of this study, we are more interested in state anxiety and how a VR intervention might be effective at reducing this kind of transient anxiety. A shortened 6-item version of the original S-scale of the STAI was initially validated by Marteau and Bekker (66) in 1992 in a sample of pregnant women, student

nurses and medical students, finding that the 6-item version (known as STAI-6) produced acceptable reliability ($\alpha = 0.82$) compared to that of the full 20-item version ($\alpha = 0.91$) with similar sensitivity to detect change in anxiety levels. Since then, other 6-item short-forms of the S-scale for STAI have been developed and validated (67-69), all of which demonstrate highly correlated scores with the 20-item STAI and similar internal consistency reliabilities. For this study, we will be utilizing the STAI-6 S-scale developed by Marteau and Bekker, given it was validated in outpatient participants and tends to perform best from a psychometric standpoint compared to other short versions of the instrument.

### 3.3.3 UCLA Loneliness Scale

The UCLA Loneliness Scale will be used to operationalize loneliness and social isolation. This instrument is the widely used in the literature and has well-established psychometrics in a variety of clinical populations (70, 71) (including oncology) (72), with internal consistency reported at 0.95 (73). It utilizes a 20-item scale that is designed to measure one's subjective feelings of loneliness (10 items) as well as feelings of social isolation (10 items), with participants rating each item on a Likert scale from 1 (Never) to 4 (Often). Scoring for this instrument is fairly straightforward and involves summing the responses for the 20 items (including reverse scoring of a few questions), with higher scores indicating higher levels of loneliness and social isolation (71). While short-forms of this instrument have been developed, they do not perform as well from a reliability standpoint, therefore we will be utilizing the full 20-item version of the UCLA Loneliness Scale for the purposes of this trial.

### 3.3.4 Comprehensive Score for Financial Toxicity (COST)

The Comprehensive Score for Financial Toxicity (COST) instrument will be used to operationalize financial toxicity. Financial toxicity has been defined as "the distress patients can experience related to the high costs of cancer treatment and subsequent economic challenges (such as loss of income)" (74). This is a recently developed instrument that was initially validated in 155 patients with advanced cancer using item analysis and exploratory factor analysis, which demonstrated good content and face validity as well as internal consistency (Cronbach's alpha of 0.9) (75). The COST is an 11-item instrument using a 5-point Likert scale ranging from 0 (Not at All) to 4 (Very Much) asking patients about the financial impact that their disease and treatment has had on their lives. Scores for individual items are summed (with a few questions reverse scored) and higher scores on the COST indicate higher levels of distress related to financial toxicity (75).

### 3.3.5 Adjustment Disorder New Module 20-Item

The Adjustment Disorder New Module 20-item instrument (ADNM-20) will be used to screen for AjD in this study population. The ADNM-20 questionnaire is a theory-driven instrument that measures AjD as a stress response disorder, according to the new diagnostic concept of the International Classification of Diseases, 11$^{th}$ edition (ICD-11) (28). The first iteration of the ADNM, developed by Einsle, Kollner (76), was a 29-item self-report measure that was validated in adult cardiac and psychosomatic outpatients. In this study, the most frequently reported stressor reported by individuals was their own physical illness, followed by financial difficulties, illness of a significant other, and work difficulties or unemployment. Due to newer diagnostic criteria for AjD according to the ICD-11, the ADNM instrument was revised to 20-items using

confirmatory factor analysis (77), and it has demonstrated validity and sound psychometrics in past studies (28, 78, 79).

The contemporary ADNM-20 consists of 2 parts: a stressor list and an item list (80). The stressor list captures a broad range of acute (e.g. divorce, moving) and chronic (e.g. serious illness, family or work conflicts) stressors that have occurred over the last two years (76, 77, 80). The item list measures the symptoms in response to the most distressing event identified by the participant. Individuals indicate on a 4-point Likert scale, ranging from 1 (never) to 4 (often), how often they have experienced different symptoms of an adjustment disorder in the past 2 weeks. The ADNM-20 has 6 subscales: preoccupation (4 items), failure to adapt (4 items), avoidance (4 items), depressive mood (3 items), anxiety (2 items), and impulse disturbance (3 items) (80). Preoccupation and failure to adapt are considered the core symptoms and the remaining subscales are considered accessory symptoms. Based on cluster analysis and ROC-analysis, a cut-off total score of 47.5 on the ADNM-20 is clinically predictive of the presence of AjD (test sensitivity 87%, specificity 74%, positive predictive value 57%, negative predictive value 93%) (80).

Identifying individuals who are at high risk for AjD can be based on the presence/severity of core AjD symptoms, as well as their total ADNM-20 score, with the following criteria:

- 1 item rated ≥ 3 and at least 2 items rated ≥ 2 in both core symptom clusters (preoccupation and failure to adapt) AND a rating of ≥ 3 on the impairment question
  - (Item 20: “All in all, the situation causes serious impairment in my social life or occupational life, my leisure activities, or other important areas of functioning.”)
- A total score ≥ 48 on the ADNM-20 questionnaire

### 3.3.6 Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE)

PRO-CTCAE is a patient-reported outcome measurement system that was developed by the NIH in order to capture the symptomatic adverse events in patients on oncology clinical trials. This instrument allows us to select, but not be limited to, the symptoms that are anticipated with use of the VR headset based on past clinical research and experience with the technology, including nausea, vomiting, dizziness, and headache, with the option to report other unanticipated symptoms as well.

### 3.3.7 Virtual Reality Qualitative Interview Guide

A brief, 7-item semi-structured questionnaire developed by a trained qualitative NOB researcher will be used during a phone interview with participants approximately 1 month following the remote VR intervention. The purpose of the interview is to allow the participants to share their experiences with VR and to provide feedback about their likes and dislikes of the experience, as well as about the headset itself. Additionally, information regarding any side effects or adverse symptoms from using the VR headset will be discussed. The interviewer may ask additional probe questions to obtain complete information regarding the participants’ VR experience. There is also a question related to their experience with having a brain tumor during the COVID-19 pandemic and any psychological symptoms they are having during this time. The phone

interview will be recorded, and the content transcribed in preparation for qualitative thematic analysis.

### 3.3.8 Was It Worth It (WIWI) Questionnaire

The WIWI is a brief questionnaire that is designed to measure a participant's opinion of their participation in a phase 2 or 3 clinical trial. Knowledge of whether participants thought the clinical trial experience was beneficial to them may provide insights for barriers to accrual, improvements in the intervention, and can inform future trial design. WIWI questions are typically dichotomous (yes/no) and are tailored to be specific to the intervention involved in that particular clinical trial. For the purposes of this study, there will be 4 yes/no questions that ascertain the participants' satisfaction with the initial VR intervention as well their experience over the 1 month participation period, which will be collected electronically via Scribe.

### 3.3.9 Completion Time for Questionnaires

The DT and STAI-6 instruments will be administered at 4 timepoints (baseline, immediately post-intervention, 1 week later, and 1 month later) and are estimated to take approximately 5 to 10 minutes to complete, in addition to the questionnaires currently administered as part of the main Natural History Study (MDASI-BT, PROMIS®-Anxiety and PROMIS®-Depression Short-Forms, Neuro-QoL™, and EQ-5D). The PRO-CTCAE questionnaire will be administered at 3 timepoints (baseline, immediately post-intervention & 1 month later) and is estimated to take less than 5 minutes to complete. The UCLA Loneliness Scale, COST, and ADNM-20 will be administered once at baseline and is estimated to take 10 to 15 minutes to complete. The WIWI Questionnaire will be collected at 2 timepoints (immediately post-intervention and 1 month later) electronically via Scribe and will take approximately 5 minutes to complete. The qualitative VR questionnaire administered during the phone interview is estimated to take 15 minutes to complete.

## 3.4 STUDY CALENDAR

| **Evaluation** | **Screening Measures** | **Study Entry & Baseline Measures** | **Post-VR Measures** ($T_1$ = within 1 hour) | **Post-VR Measures** ($T_2$ = 1 week later, +/- 3 days) | **Post-VR Measures** ($T_3$ = 1 month later, +/- 7 days) |
|---|---|---|---|---|---|
| Informed consent | | **X** | | | |
| **Patient-Reported Outcomes** | | | | | |
| NCCN Distress Thermometer (DT), section **3.3.1** | | **X** | **X** | **X** | **X** |
| State-Trait Anxiety Inventory (STAI-6), section **3.3.2** | | **X** | **X** | **X** | **X** |
| UCLA Loneliness Scale, section **3.3.3** | | **X** | | | |
| Comprehensive Score for Financial Toxicity (COST), section **3.3.4** | | **X** | | | |

| **Evaluation** | **Screening Measures** | **Study Entry & Baseline Measures** | **Post-VR Measures** ($T_1$ = within 1 hour) | **Post-VR Measures** ($T_2$ = 1 week later, +/- 3 days) | **Post-VR Measures** ($T_3$ = 1 month later, +/- 7 days) |
|---|---|---|---|---|---|
| Adjustment Disorder Instrument (ADNM-20), section **3.3.5** | | **X** | | | |
| PRO-CTCAE Section **3.3.6** | | **X** | **X** | | **X** |
| Was It Worth It (WIWI) questionnaire Section **3.3.8** | | | **X**[1] | | **X**[1] |
| Review PROs and forms collected on Natural History Study[2] | **X** | **X** | | **X** | **X** |
| **Qualitative Assessment** | | | | | |
| Semi-structured phone interview, section **3.3.7** | | | | | **X** |
| **Correlative Biomarkers and Device** | | | | | |
| Salivary hormones<br>▪ Cortisol<br>▪ DHEA-S<br>▪ sAA | | X[3] | X[3] | | |
| VR Instrument[4] | | → | → | → | → |

[1] WIWI questionnaires will be administered electronically via Scribe.
[2] PROs (MDASI-BT, PROMIS®-Anxiety and PROMIS®-Depression Short-Forms, Neuro-QoL™ and EQ-5D) and clinical/demographic information will be collected as part of the Natural History Study.
[3] Salivary hormone collection kits will provided to participants for pre/post-intervention assessments. This is an optional collection at the discretion of the participant and investigator. If participants agree to the saliva sample collection, they will be asked standard screening questions for COVID symptoms by research staff within 72 hours of collecting their saliva. See Section **5.1.1** for instructions if the COVID screen is positive.
[4] Instrument use will be as defined in Section **3.2.**

## 3.5 Cost and Compensation

### 3.5.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

### 3.5.2 Compensation/Incentives

The cost estimate of the Pico G2 4K headsets sold unlocked with full content is approximately $400, however, the devices used in this study are locked and have a limited amount of pre-loaded software. As a result, the value of the headsets utilized in this trial is likely considerably less, given the limited content and inability to upload additional software. Therefore, the concern for attempted resale of the Pico G2 4K devices by participants is considerably mitigated.

AppliedVR™ has agreed to provide the headsets and uploaded relaxation software free of charge for the purposes of this trial, per Collaboration Agreement 45562-19, and participants will be allowed to keep the device (if they choose) after they have completed study participation.

### 3.5.3 Reimbursement

This study does not offer reimbursement for, or payment of, travel, lodging or meals.

## 3.6 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to removal from study, effort must be made to have all subjects complete a safety phone call approximately 30 days after the initial VR intervention.

### 3.6.1 Criteria for removal from protocol therapy

- Completion of protocol intervention
- Participant requests to be withdrawn from study
- Investigator discretion

### 3.6.2 Off-Study Criteria

- Completed study follow-up period
- Participant requests to be withdrawn from study
- Participant lost to follow-up
- Permanent loss of capacity to consent
- Adverse device effect warranting participant to be taken off study (i.e., seizure)
- Death

### 3.6.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to participate in the 1 week and 1 month post-intervention data collection timepoints and is unable to be contacted by the study site staff.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

# 4 CONCOMITANT MEDICATIONS/MEASURES

Non-Applicable.

# 5 CORRELATIVE STUDIES FOR RESEARCH

## 5.1 BIOSPECIMEN COLLECTION

### 5.1.1 Saliva Samples (optional, at discretion of investigator and participant)

If participants choose to participate in the saliva sample collection, they will be asked standard screening questions by research staff for any COVID symptoms that may have been experienced within the 72 hours prior to collecting their saliva. If the screening is positive (e.g., reveals that a participant may have COVID, COVID symptoms or exposure), the sample will not be collected.

Passive drool saliva samples will be collected in a Cryovial 2mL passive drool collection tube (please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator) from participants at 2 different time points, according to the study calendar: at baseline and immediately following the initial VR intervention. To avoid fluctuations attributed to circadian rhythms in some of the stress biomarkers (specifically salivary cortisol and sAA), the collection times for the salivary samples will be standardized across timepoints for each participant. Additionally, levels of two of the analytes are flow-rate dependent (DHEA-S and sAA), meaning that concentrations of these molecules decrease as saliva flow increases. Given the variability of saliva flow from person to person (or even for the same person at different times) the total time necessary to collect the desired volume of saliva will be recorded by participants when collecting at home. With this information, assay results can later be multiplied by the flow rate (mL/min) to calculate a secretion rate that can be covaried in analyses **(**81**)**.

Adherence to a salivary hormone collection protocol will be important to ensure validity of specimens collected. See Appendix **15.2** for the Salivary Biospecimen Collection Information Sheet that will be reviewed with participants and provided to them as a reference during the trial. Freezing samples as soon as possible at or below -20°C (temperature of a household freezer) is ideal to minimize sample degradation and to prevent bacterial growth. If immediate freezing is not possible, participants can briefly refrigerate samples at +4°C (for up to 1 day) prior to freezing them. Contact information for the lead study investigator is provided on the saliva collection form to address any participant questions that arise related to salivary biospecimen collection.

Once collected, salivary samples will be sent to the Clinical Laboratory Services Core (CLSC) for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which will be responsible for aliquoting, storing, and processing the samples (Mary Walter, Director, Clinical Laboratory Services Core, https://www.niddk.nih.gov/research-funding/at-niddk/cores-support-services/clinical-laboratory-core, Contact: mary.walter@nih.gov). Salimetrics enzyme-linked immunosorbent assay (ELISA) kits specific for each hormone/enzyme will be used by the CLSC to process saliva samples and provide final biological data to the research team.

| Salivary hormone/enzyme | Optimal collection volume | Type of collection tube [3] | Considerations | Specimen storage and processing |
|---|---|---|---|---|
| Cortisol | 75 µL | Cryovial – 2 mL (passive drool) | Diurnal variation | NIDDK lab core |
| DHEA-S | 225 µL | Cryovial – 2 mL (passive drool) | Flow-rate dependent | NIDDK lab core |
| sAA | 25 µL | Cryovial – 2 mL (passive drool) | Diurnal variation, flow-rate dependent | NIDDK lab core |
| **Minimum total saliva volume** | **325 µL**[1] | | | |
| **Recommended total saliva volume** | **625 µL**[2] | | | |

[1] Reflects minimum saliva volume for each of the 2 collection timepoints

[2] Salimetrics recommends adding an extra 300 µL of collection volume when measuring multiple analytes from saliva samples in order to account for any sample handling losses and potential repeat analyses

[3] Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.

## 5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

- Samples will be ordered in CRIS. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required. All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.
- All salivary biospecimens processed and stored by the CLSC are tracked by a web-based system called Biological Specimen Inventory (BSI), which maintains a full audit trail. Detailed records are maintained on the status, location, and nature of the sample. These data are backed up every night on a server, which is at a different location.
- The CLSC has been compliant with government regulations and NIH policy since June 2009. The CLSC maintains a detailed Standard Operating Procedure manual so that the samples can be maintained in the biorepository indefinitely, irrespective of the tenure of the technician.
- All freezers are locked and maintained in locked rooms in the CLSC. Freezer temperatures are continuously monitored electronically by Rees Scientific and a detailed phone tree has been established if there are any temperature deviations. Additionally, multiple lab personnel are emailed and with any temperature deviations. There are 2 empty freezers at all times set at -80$^{o}$C to serve as backup freezers if there is a main freezer failure. Freezers are also connected to emergency power in the event of a power failure, and the freezer rooms are located in multiple sites.
- All salivary biospecimens will be labelled using Thermal transfer, high-definition self-laminating polyester labels that are abrasion and smudge resistant, and also stable in a 100$^{o}$C water bath to liquid nitrogen. These labels have a unique identifier and contain a 2-dimensional barcode with electronic record documentation. There is no personal

identifying information on the label, however the unique identifier is linked to the database which contains the clinical or research data about the participant.
- If the participant withdraws consent, the participants data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.
- The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

# 6 DATA COLLECTION AND EVALUATION

## 6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system Labmatrix and ensuring data accuracy, consistency and timeliness. Research staff in the CLSC will use the Biological Specimen Inventory (BSI) system for tracking and processing salivary biospecimens. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse device effects, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document adverse device effects from the first study intervention, Study Day 1, through 30.

**End of study procedures:** Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

**Loss or destruction of data:** Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

## 6.2 DATA SHARING PLANS

### 6.2.1 Human Data Sharing Plan

**What data will be shared?**

I will share human data generated in this research for future research as follows

_x__ Coded, linked data in an NIH-funded or approved public repository.

_x__ Coded, linked data in another public repository.

_x__ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

_x__ Identified or coded, linked data with approved outside collaborators under appropriate agreements.

**How and where will the data be shared?**

Data will be shared through

_x__ An NIH-funded or approved public repository. Insert name or names:___clinicaltrials.gov_____.

___ Another public repository. Insert name or names: _____.

_x__ BTRIS (automatic for activities in the Clinical Center)

_x__ Approved outside collaborators under appropriate individual agreements.

_x__ Publication and/or public presentations.

**When will the data be shared?**

_x__ Before publication.

_x__ At the time of publication or shortly thereafter.

### 6.2.2 Genomic Data Sharing Plan

Non-Applicable.

### 6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

## 7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

### 7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

### 7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

### 7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

### 7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

## 7.3 NCI Clinical Director Reporting

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death NCICCRQA@mail.nih.gov within one business day of learning of the death.

## 7.4 Institutional Biosafety Committee (IBC) Reporting Criteria

Non-Applicable.

## 7.5 NIH Required Data and Safety Monitoring Plan

### 7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis weekly to discuss participants enrolled on the trial.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse device effect and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

# 8 MANUFACTURER SAFETY REPORTING

## 8.1 Safety Reporting Criteria to the Device Collaborator

Reporting will be per the collaborative agreement.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 STATISTICAL HYPOTHESIS

### 9.1.1 Primary Endpoint:

To describe the feasibility of implementing a VR intervention in a PBT population, including eligibility, accrual, compliance, adverse events, study completion, and participant satisfaction with the intervention

### 9.1.2 Secondary Endpoints:

9.1.2.1. To assess the effects of a VR intervention on self-reported acute and subacute distress (as measured by the NCCN Distress Thermometer [DT]) and anxiety (as measured by the State Anxiety Inventory [STAI-6]) in PBT patients

9.1.2.2. To determine if the effects VR has on distress and anxiety are more pronounced in high distress (based on DT cut-off score of ≥ 5) compared to low distress (based on DT scores of 0–4) individuals

9.1.2.3. To determine if the effects VR has on distress and anxiety are more pronounced in those individuals not on systemic corticosteroids (CS) compared to those who are on active CS therapy.

## 9.2 SAMPLE SIZE DETERMINATION

The primary objective of this study is to determine the feasibility of implementing a VR intervention that aims to reduce psychological distress and anxiety in primary brain tumor patients. This study will be considered successful if the following feasibility conditions are met: 80% of approached eligible patients agreed to participate, 70% compliance with the VR headset use, no grade 3 or higher intervention-related adverse device effects during the remote VR intervention, and 70% of required data points are completed. Assuming that about 80% of patients approached for the study are eligible, with a target of 100 patients in the final study sample, we would be reasonably certain (95% confident) that our estimate of the proportion of eligible patients would lie within 7.8% of the true proportion of eligible patients. In other words, a two-sided 95% confidence interval around an expected proportion of 80% of eligible patients will have a width of +/- 7.8%. To account for 10% attrition of participants during the trial, we will plan to recruit a total of 120 patients for this study.

In order to ensure adequate representation of low/high distress individuals and those on/off CS therapy to address the secondary objectives of this study, we will utilize the following enrollment strategies:

- For distress levels, we will aim to enroll approximately 20% of the sample with high distress (*N*=24) and approximately 80% with low distress (*N*=96).
- For corticosteroid use, we will aim to enroll approximately 20% of the sample on active CS therapy (*N*=24) and approximately 80% who are not on CS therapy (*N*=96).

## 9.3 POPULATIONS FOR ANALYSES

### 9.3.1 Analysis of the Primary Endpoints

To evaluate the feasibility of the VR intervention, we will use descriptive statistics to summarize information, including rates of recruitment and retention. We will calculate total scores, subscale scores, and/or t-scores (if applicable) for the DT, STAI-6, PROMIS®-Depression and Anxiety Short Forms, Neuro-QoL™, MDASI-BT, EQ-5D, and PRO-CTCAEs questionnaires, completed at varying timepoints (baseline, immediately post-intervention, 1-week post-intervention, and 1-month post-intervention). The quantity of missing data, variability of the data over time, and trends over time will be especially important to report to assess the feasibility of this intervention. This data will be summarized by time point quantitatively and graphically. Patients who drop out will also be compared to those who continue, based on their demographic characteristics (such as gender, age) and on other baseline assessments using t-tests or Wilcoxon rank sum tests. A multiple logistic regression model will be constructed to identify variables independently associated with dropping out. This information will help determine the characteristics of patients who are recruited into the study and those who are retained in the study. This will help guide future recruitment efforts and identify types of patients who may require special attention to minimize attrition.

We will also use descriptive statistics to report how patients rate their responses on various measures. For the NCCN Distress thermometer, we will report the proportion of patients who scored ≥ 5 on DT that indicate moderate-severe distress. We will report subscale scores for the MDASI-BT and the proportion of patients with 5 or greater (moderate to severe) and 7 or greater (severe) ratings on the 0-10 numeric rating scale of each symptom items. T-scores from the PROMIS®-Anxiety and Depression Short-Forms and Neuro-QoL™ instrument will also be reported.

Additionally, we will report participant satisfaction with the VR experience using descriptive statistics for responses from the WIWI questionnaire, as well as through qualitative thematic analysis from participant responses from the semi-structured phone interview.

### 9.3.2 Analysis of Secondary Endpoints

To determine the effect of a VR intervention on self-reported acute and subacute distress, we will fit a linear mixed model with patients as random effect and time as fixed effect using scores from the DT as the dependent variable. To quantify the acute VR effect, we will calculate effect size difference between baseline scores and immediate post-use of VR scores. To quantify the subacute VR effect at home, we will calculate effect size differences in distress scores between baseline and week 1. Likewise, we will calculate effect size differences in distress ratings between baseline and week 4. A similar approach will be taken to analyze effects of the intervention on acute and subacute anxiety, using the STAI-6 as the dependent variable in a linear mixed model. Similar effect size calculations will be made comparing anxiety scores between the baseline and immediate post-intervention, week 1, and week 4 timepoints.

To determine if the effect VR has on distress and anxiety is more pronounced in high distress (based on DT cut-off score of ≥ 5) compared to low distress (based on DT scores of 0–4) individuals, we will calculate difference scores in distress between baseline and immediate post use of VR. We will then perform an independent t-test on the distress difference scores using

two groups based on their baseline DT scores (≥ 5 vs. < 5). We hypothesize that the changes in distress scores will be greater in the high baseline distress group, compared to the low baseline distress group. We will repeat the analyses using the same groups, but with changes in anxiety as the dependent variable.

To determine if the effect VR has on distress and anxiety is more pronounced in those who are not on systemic corticosteroids (CS) (compared to those on active CS therapy), we will calculate difference scores in distress and anxiety between baseline and immediate post use of VR. We will then perform an independent t-test on the distress difference scores using two groups based on whether or not they are on steroids. We hypothesize that changes in distress and anxiety will be greater in those who are not on active CS therapy, compared to those who are currently taking CS, due to alterations in adrenal function, behavior, and mood associated with CS use.

### 9.3.3 Analysis of Exploratory Endpoints

To evaluate the relationship between the biological stress measures (salivary cortisol, DHEA-S, sAA, and HR) and self-reported distress, anxiety, mood disturbance, symptom burden, cognitive function, and quality of life, we will calculate either Pearson or Spearman correlations (whichever is appropriate) at each available timepoint (baseline, immediate post-VR intervention). For these exploratory analyses, we will take note of the magnitude of the relationships between the biological stress measures and self-report measures.

We will perform linear mixed models and effect size calculations to explore the effects of VR on symptom burden and interference, mood disturbance, HRQOL, and cognitive function using raw and subscale scores from the MDASI-BT and EQ-5D, and using t-scores from the PROMIS®-Anxiety and Depression Short-Forms and Neuro-QoL™ instrument. We will also evaluate the relationships between loneliness and financial toxicity on distress and anxiety by calculating either Pearson or Spearman correlations.

To evaluate the proportion of patients with AjD, we will use descriptive statistics to report participant scores on the ADNM-20 questionnaire. Individuals that meet at least one of the following criteria will be reported as at high risk for AjD:

- 1 item rated ≥ 3 and at least 2 items rated ≥ 2 in preoccupation and failure to adapt core symptom clusters AND a rating of ≥ 3 on the impairment question
- A total sum score ≥ 48 for all items on the ADNM-20

### 9.3.4 Planned Interim Analyses

Non-Applicable.

## 10 COLLABORATIVE AGREEMENTS

### 10.1 AGREEMENT TYPE

Pico G2 4K headsets have been provided by Applied VR™ under a Collaboration Agreement 45562-19.

# 11 HUMAN SUBJECTS PROTECTIONS

## 11.1 RATIONALE FOR SUBJECT SELECTION

Adult patients will be invited to enroll onto this trial if they are already enrolled on the Natural History Protocol (NIH 16C0151) and meet the eligibility criteria outlined in Section **2.1**. No gender, racial or ethnic groups will be excluded from participation in this trial. Only English-speaking individuals will be invited to enroll in this trial, given that the PROs questionnaires utilized in this study have not been validated in other languages.

## 11.2 PARTICIPATION OF CHILDREN

This protocol will not include those less than 18 years old since the patients will be only recruited from the Natural History Protocol (NIH 16C0151), and the patient population for that study is ≥ 18.

## 11.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. In such cases, subjects would be removed from the study.

## 11.4 RISK/BENEFIT ASSESSMENT

### 11.4.1 Known Potential Risks

Though infrequent, side effects of VR headset use reported by the manufacturers include motion sickness, dizziness, eyestrain, headaches, or other visual abnormalities, as well as a small number of individuals (up to 0.025%) reporting seizures. For seizure risk mitigation, individuals with epilepsy or seizures within the last 6 weeks will be excluded from the trial. In addition, the relaxation scenarios on the VR headsets will not include any flashing lights that might trigger seizure activity in participants. Any participant that experiences a seizure while using the VR headset will be instructed to discontinue use immediately and notify NOB research staff, at which point the adverse event will be reported and they will come off study.

While there is scant past research using similar VR headset devices for symptomatic improvement in PBT patients, literature in solid tumor patients was reviewed and revealed very few side effects reported by participants in experimental studies using VR **(**33**,** 41**,** 47**,** 82**)**, none of which were serious or life-threatening. Should participants experience any unpleasant or serious side effects while using the Pico G2 4K device used in this study, they will be instructed to discontinue use and notify NOB research staff immediately. Additionally, we will be collecting PRO-CTCAEs information related to any adverse effects related to use of the headset for each participant at 3 of the 4 timepoints in this study, which will be helpful for monitoring for and reducing risks associated with the VR headset.

An additional potential risk relates to the physical safety of the participant while using the VR device, which the device manufacturer provides recommendations for. All study participants will be instructed to use the Pico G2 4K headset while in a seated position in a safe environment in order to mitigate risk for injury, given that individuals will lose awareness of the real world and their body position in it while immersed in the virtual relaxation environments. These

instructions will be reviewed with participants at study entry and reinforced throughout the duration of the study by research staff.

### 11.4.2 Known Potential Benefits

While VR has been used in clinical populations for the last 2 decades, there is little data in oncology populations, thus its potential benefits for symptomatic improvement in PBT patients is relatively unknown. However, a systematic review of literature of VR interventions in primarily solid tumor patients revealed promising improvements in patient anxiety (42, 48, 83), pain or physical discomfort (43, 45, 83, 84), and distress (44, 45, 84), with near universal reporting that it was an effective distraction tool that promoted relaxation. For the purposes of this study, immediate potential benefits for PBT participants include improvements in psychological symptoms they experience at the time of clinical evaluation (i.e. distress and anxiety), as described in the protocol background sections. Longer-term potential benefits include improvements in overall symptom burden and quality of life, greater ability to tolerate oncologic therapies, increased ability to self-manage their psychological symptoms, and improved overall survival.

### 11.4.3 Assessment of Potential Risks and Benefits

The potential benefits to subjects that participate in this study include improvements in their psychological health (particularly psychological distress and anxiety), which may or may not have a favorable impact on symptoms and/or survival. The potential risks for patients participating in this study are related to use of the VR Pico G2 4K headset, both in terms side effects experienced and physical safety while using the device.

## 11.5 Consent Process and Documentation

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. A templated PowerPoint, covering all aspects of the consent form, may be utilized by consenting investigators during remote consents for ease of viewing and to aid participant understanding.

Note: When required, witness signature will be obtained similarly as described for the investigator and participant as described below.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

> Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

# 12 REGULATORY AND OPERATIONAL CONSIDERATIONS

## 12.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants and investigators. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable Food and Drug Administration (FDA).

## 12.2 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

## 12.3 CONFLICT OF INTEREST POLICY

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

## 12.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the appropriate parties.

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

The study monitor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

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

Study participant research data, which is for purposes of statistical and scientific reporting, will be transmitted to and stored at NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH Clinical Center.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

# 13 DEVICE INFORMATION

There will be no IDE obtained for the use the PICO G2 4K headset with Applied VR software used in this study based on FDA's guidance, Policy for Device Software Functions and Mobile Medical Applications. The FDA has indicated in the guidance that they will apply regulatory oversight only to those software functions that are medical devices and whose functionality could pose a risk to a participant's safety if the device were to not function as intended. This device is similar to the non-exhaustive list of devices provided in Appendix B of the guidance. It is designed to manage psychiatric symptoms and its malfunction will not cause the participant additional harm.

The Applied VR software was designed by Applied VR company for therapeutic use in clinical populations, which aims to improve adverse symptomatology and promote relaxation in participants.

## 13.1 PICO G2 4K VR HEADSET WITH APPLIED VR SOFTWARE

Pico G2 4K is a lightweight stand-alone VR headset that comes with an orientation-tracked controller and does not require a smartphone or a PC to run. The headset provides the user with a premium viewing experience that features a 4K LCD 3840 X 2160 5.5-inch display with blue ray reduction, a refresh rate of 75 hertz, and 615 pixels per inch (PPI). The headset features a Qualcomm Snapdragon 835 central processing unit (CPU) with 4G high-speed LPDDR4-1866 RAM to run virtual content and a battery that allows 3 hours of continuous use.

The following use instructions and health and safety information is provided by the manufacturer and will be reviewed with participants prior to use. A trained study staff member will be present in the telehealth meeting during initial use of the headset to ensure participant safety and monitor for any adverse symptoms or events.

Participants using the VR headset may experience side effects common to users of VR and those who view 3D video, including motion sickness, dizziness, eye strain, headaches, and other visual

abnormalities. If an individual experiences any of these symptoms, they will be asked to stop using the device and to notify NOB research staff immediately.

A small number of participants (up to 0.025%) may experience seizures or severe symptoms (e.g. disorientation, nausea, or drowsiness) upon viewing the VR scenarios. Seizures from flashing lights are more common in children and epileptic individuals (who are excluded from use in this trial). Importantly, flashing lights are not present in the VR experiences built into the Pico G2 4K headset. If any seizure activity occurs while a participant is using the headset, the intervention will be discontinued, clinical staff will be notified, the adverse event will be reported, and the participant will come off study.

Some individuals may find the VR headset uncomfortable to wear or may feel it to be confining. Research staff will assist participants with adjusting the fit of the headset during the initial use.. Comfort and fit information related to the VR headset will be collected from participants by NOB research staff during a qualitative interview.

To date, individuals with claustrophobia have not reported discomfort using this VR headset, as this type of therapy is often utilized for treatment of that condition. Nevertheless, those previously diagnosed with claustrophobia will be excluded for the purposes of this clinical trial.

The VR headset does not support focus adjustment, so participants should continue use of glasses/contacts if they have poor eyesight.

Refer to Pico G2 4K User Manual for additional information.

### 13.1.1 Source/Acquisition and Accountability

Applied VR Company will supply Pico G2 4K headsets with Applied VR Software under Tech Transfer Agreement Collaboration Agreement 45562-19.

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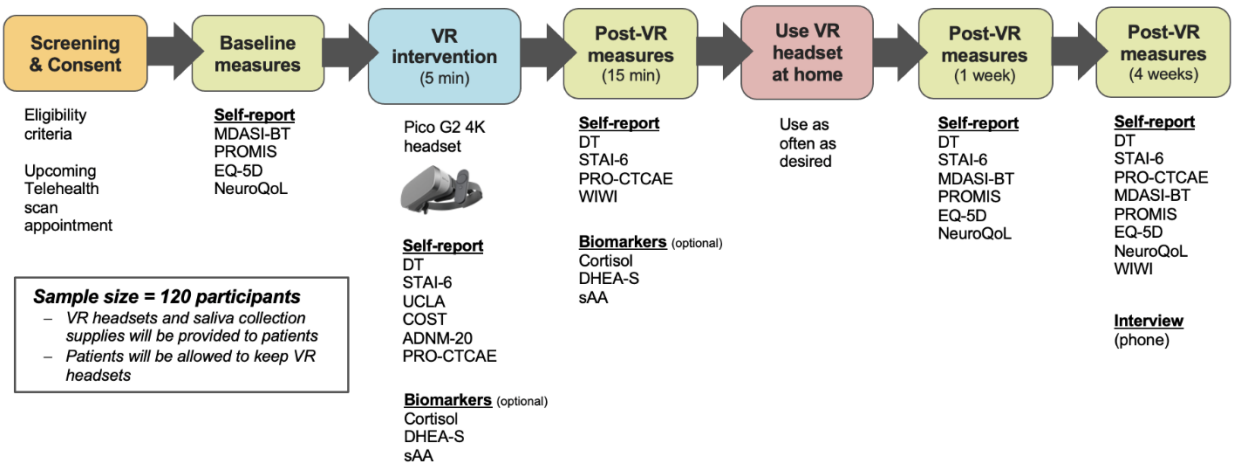
# 15 APPENDICES

## 15.1 STUDY PROTOCOL FLOW DIAGRAM



## 15.2 SALIVARY BIOSPECIMEN COLLECTION INFORMATION SHEET

Optional

NOB NEURO-ONCOLOGY BRANCH

### Saliva Sample Collection Instructions

**Researcher:** Amanda King, PhD **Phone:** (240) 535-7958 **Email:** amanda.king2@nih.gov

#### 1 When to Collect Saliva

Please collect saliva samples at these times:

1. **Baseline** (before VR use)
2. **Post-VR** (after 1st VR use)

****Samples need to be collected at a similar time of day** (study team will help you plan this)

#### 2 Preparing for Collection

**The night before collection**

1. **Freeze the ice pack.** Keep in freezer until you are ready to ship your sample.
2. **Set an alarm or reminder for your collection time.** So you don't forget!

**The day of collection, DO NOT:**

- Consume food or drinks that contain caffeine
- Eat or drink (except water) within 1 hour of saliva collection
- Perform any vigorous exercise within 1 hour of saliva collection
- Brush or floss teeth within 45 minutes of saliva collection (to avoid blood contamination)

#### 3 Collecting Saliva

***Step 1***

Wash hands with soap and water. **Rinse your mouth with water and wait 10 minutes** before starting collection.


***Step 2***

Open foil pouch and **attach saliva collection aid to the collection tube.** Write down the time you begin collection.

***Step 3***

**Allow saliva to pool in your mouth.** Then with your head tilted forward, **gently guide saliva into the collection tube.**

**Tip: Smelling food, yawning, or pressing the tip of your tongue against your teeth can help with saliva flow.*

***Step 4***

**Fill tube with saliva** (ideally at least ½ full). Bubbles or foam are okay. **Dispose of saliva collection aid when done.** Write down the time you finish collection.

***Step 5***

**Close lid securely** and put collection tube in small Ziploc bag. **Place in freezer as soon as possible.**

NOB NEURO-ONCOLOGY BRANCH

### Saliva Sample Collection Instructions

**Researcher:** Amanda King, PhD **Phone:** (240) 535-7958 **Email:** amanda.king2@nih.gov

#### 4 Preparing Samples for Shipment

1. **Freeze samples for at least 4 to 6 hours prior to shipment.** Samples must remain cold during transit.
2. **Be sure to write the date and times of saliva collection** (start and finish time) on provided labels and place in bag.
3. **Remember to freeze ice pack** in preparation for shipment.
4. **Try to send samples back to NIH within 7 days** of collection (next day whenever possible is ideal).

#### 5 Shipping Your Sample

**When you are ready to ship your sample:**

- Remove bag with tube and ice pack from freezer
- Ensure all labels are filled out and placed in bag
- Wrap ice pack around bag with samples and insert into padded shipping envelope
- Be sure pre-paid FedEx label is attached to envelope and seal it firmly
- Drop off envelope at FedEx location to send samples back to NIH

#### Questions?

**If you have any questions about the saliva sample collection or shipment, please contact the NOB researcher for this study** (information provided above).
Phone calls and emails will be returned by the next business day.

*Thank you for your participation!*

## 15.3 STUDY INSTRUMENTS

The following study instruments, forms and questionnaires are maintained and provided separately from the protocol document include the following:

- National Comprehensive Cancer Network (NCCN) Distress Thermometer (DT)
- State-Trait Anxiety Inventory, 6-Item Short-Form (STAI-6)
- UCLA Loneliness Scale
- Comprehensive Score for Financial Toxicity (COST)
- Adjustment Disorder New Module 20-Item
- Virtual Reality Qualitative Interview Guide, including Was It Worth It (WIWI)
- SootheVR QuickStart Guide
- SootheVR Care and Cleaning Information

The following study instruments are provided in the protocol and are cross-referenced:

- Study Protocol Flow Diagram Section **15.1**
- Salivary Biospecimen Collection Information Sheet **15.2**