Safety and Effectiveness of Virtual Reality utilizing RelieVRx for Total Knee Arthroplasty (TKA) for the Reduction of Acute Postoperative Pain and Opioid Use

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1 ABBREVIATIONS USED IN THE PROTOCOL

Abbreviation	Term
ACC	Anterior Cingulate Cortex
AE	Adverse event
AUC	Area under Curve
BMI	Body Mass Index
CDC	Center for Disease Control
CMS	Centers for Medicare & Medicaid Services
DVT	Deep Vein Thrombosis
EHR	Electronic Health Record
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GIRB	Geisinger IRB
IRB	Institutional Review Board
LOS	Length of Stay
KOOS	Knee Injury and Osteoarthritis Outcome Score
MME	Morphine Milligram Equivalents
MRI	Magnetic resonance Imaging
MRN	Medical Record Number
MRSA	Methicillin-Resistant Staphylococcus Aureus
NPRS	Numerical Pain Rating Scale
OUD	Opioid Use Disorder
PACU	Post Anesthesia Care Unit
PDMP	Prescription Drug Monitoring Program
PE	Pulmonary Embolism
PI	Principal Investigator

Abbreviation	Term
PT	Physical Therapy
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
SAE	Serious adverse event
SOC	Standard of Care
TKA	Total Knee Arthroplasty
VR	Virtual Reality
VR-12	Veterans Rand 12 Item Health Survey

2 ABSTRACT

In 2016, the American Pain Society published guidelines on the management of postoperative pain based on a systematic review of the various interventions and management strategies. A key recommendation was that "clinicians offer multimodal analgesia, or the use of a variety of analgesic medications and techniques combined with non-pharmacological interventions, for the treatment of postoperative pain in children and adults (strong recommendations, high-quality evidence). [1]

According to the August 21, 2013 Journal of Bone and Joint Surgery, one half of patients now receiving knee replacements are under 65 and demand for Total Knee Arthroplasty (TKA) is expected to exceed 3.5 million procedures per year by 2030. [2]

Multimodal treatment plans provide an advantage for acute postoperative pain. Multi-modal pain treatment can also be improved by discharge to home and performing activities of daily living, physical therapy treatment within 24 hours of discharge and weight bearing as tolerated. The use of virtual reality (VR) has been shown to be a safe and effective adjunctive therapy for pain and low risk opioid sparing treatment. [3]

We propose to study the effects of a VR-based pain management program, RelieVRx, in acute postoperative pain after orthopedic TKA surgery in 100 patients (50 patients in the standard of care plus RelieVRx test group and 50 patients in the standard of care control group). RelieVRx is a virtual reality therapy intended as adjunctive treatment for acute surgical pain. RelieVRx is intended to be a prescription therapy for the reduction and/or elimination of opiate use in patients suffering from acute surgical pain. Patients will be randomized to one of the two groups after study enrollment, and patients in the test arm will be educated about the device preoperatively to facilitate its use in the acute postoperative period. The goals of VR will be presented in the context of an alternate to opioids for pain control. Subjects will be assured they will receive SOC analgesic management in addition to the VR headsets.

3 BACKGROUND AND SIGNIFICANCE

Pain following orthopedic injuries and operations, including over 6.6 million orthopedic surgeries anticipated in 2020 [1], is significant and sustained during the entire period of recovery. This recovery period can be quite long depending on the specific orthopedic operation and underlying disease or comorbidities. Treatment and management of this pain is traditionally based primarily around utilizing pharmacological management.

Opiates are commonly prescribed as part of post-operative pain management which can lead to Opioid Use Disorder (OUD). These agents can yield both inconsistent and sub-optimal results [4] and greatly increase the risk of the patient developing an opioid addiction or OUD. Data from the U.S. Center for Disease Control (CDC) revealed that even a single day of opioid therapy can predict up to a 6% increase in the risk of the patient developing a dependency within a year [5].

Two retrospective cohort studies found opioid therapy prescribed for acute pain was associated with greater likelihood of long-term use. One study evaluated opioid-naïve patients who had undergone low-risk surgery, such as cataract surgery and varicose vein stripping [5]. Use of opioids within 7 days of surgery was associated with increased risk for use at 1 year. The second study found that among patients with a workers' compensation claim for acute low back pain, compared to patients who did not receive opioids early after injury (defined as use within 15 days following onset of pain), patients who did receive early opioids had an increased likelihood of receiving five or more opioid prescriptions 30–730 days following onset that increased with greater early exposure [6]. While new opioid guidelines, such as the 2016 CDC opioid guidelines [7] or 2018 Centers for Medicare and Medicaid Services (CMS) rules [8], are limiting the number of opioids available to opioid "naïve" patients to an initial 7-day supply, regardless of dose, a lack of alternative pain management solutions exist.

Unlike VR, opioids have a significant adverse event profile that includes hypotension, respiratory depression or arrest, aspiration, or vomiting. Although both risks and costs are often considered manageable, it is imperative to devise alternatives to address pain after surgery that are cost-effective and improve the risk benefit profile well above standard of care.

It is hypothesized that the anterior cingulate cortex (ACC) plays a significant role in both the detection and response to pain. Indeed, functional MRI (fMRI) studies with VR have shown diminished pain-related brain activity in five regions associated with pain sensation. Regarding emotion, it has been demonstrated that emotions can modulate pain by activation/deactivation of the amygdala. Negative emotions, such as anxiety and depression, can facilitate pain while positive emotions can inhibit the pain-control pathway.

To reduce addiction, low risk, non-opioid pain analgesics are in great need and virtual reality (VR) shows great promise as a solution. Therapeutic VR has emerged as an effective, non-pharmacological treatment modality for pain [4]. Users of VR wear a pair of goggles with a close-proximity screen that creates a sensation of being transported into immersive, three-dimensional worlds. A hypothesis for the mechanism of action for VR suggests that by stimulating the visual cortex while simultaneously engaging other senses, VR is able to limit the user's processing of pain signals [4].

4 SPECIFIC AIMS

4.1 SPECIFIC AIM 1

Among standard of care (SOC) plus RelieVRx (SOC+RelieVRx) group, compare pain scores before and after use of RelieVRx. *Hypothesis: Acute postoperative pain scores will decrease by at least 20% or 2 points on a 0-10 Numerical Pain Rating Scale (NPRS) after each use of RelieVRx.*

4.2 SPECIFIC AIM 2

Compare pain scores between the SOC group and SOC+RelieVRx group. *Hypothesis: Cumulative pain scores will be comparable among the SOC+RelieVRx group and SOC group.*

4.3 SPECIFIC AIM 3

Compare opioid use between the SOC group and SOC+RelieVRx group. *Hypothesis: Opioid consumption will be reduced by at least 20% over a 90-day postoperative period in the SOC+RelieVRx group compared to the SOC group.*

5 STUDY DESIGN

5.1 DESCRIPTION

This is a prospective, randomized, controlled study of the appliedVR RelieVRx pain management solution in subjects undergoing Total Knee Arthroplasty (TKA).

Patients at each study site will be randomized by computer 1:1 to either the SOC (control) group or the SOC+RelieVRx (test) group. The SOC+RelieVRx group will receive education and hands-on experience with the VR headset and RelieVRx pain management solution at a routine preoperative patient education class or during the history and physical encounter visit through a predetermined script to make the patient feel comfortable using the device on their own. The goals of VR will be presented in the context of an alternate method of pain control to opioids. Subjects will be assured they will receive SOC analgesic management in addition to the headsets. The participating surgeons and anesthesiologists at Geisinger Medical Center will

adhere to a standardized medication regimen for anesthesia and pain relief prescriptions in order to minimize confounding between the groups due to differences in pain medication treatment plans.

5.2 STUDY POPULATION

5.2.1 Approximate Number of Subjects

Approximately 100 Geisinger subjects who have TKA surgery at Geisinger will participate in this study (50 will be in the SOC group and 50 will be in the SOC+RelieVRx group).

5.2.2 Inclusion Criteria

For inclusion, the study subjects should fulfill the following criteria:

1. ≥ 18 years old
2. Willing and able to read, comprehend, and sign the study informed consent form in English prior to study specific procedure
3. Scheduled for Total Knee Arthroplasty (TKA) surgery
4. Score of 1-3 based on the American Society of Anesthesiologists Physical Status Classification System
5. Attended the pre-op Total Joint Arthroplasty Patient Education class (Proven Recovery Program©)
6. Agrees to be enrolled in Force Therapeutics, a web-based, digital rehabilitation and education program
7. Has family member, friend, or community support during post-surgical recovery period

5.2.3 Exclusion Criteria

For exclusion criteria, subjects should not enter the study if any of the following exclusion criteria are filled:

1. Diagnosed with chronic pain syndrome
2. Body Mass Index (BMI) ≥ 40
3. Current tobacco user at time of surgery
4. Uncontrolled sleep apnea
5. Bilateral TKA
6. Current or recent history (in past year) of substance abuse disorder

7. Uncontrolled diabetes (HbA1c ≥ 7.0) 7.8 at time of surgery
8. History of Pulmonary Embolism (PE) or Deep Vein Thrombosis (DVT)
9. Currently being treated with blood thinners at time of surgery
10. Diagnosis of Rheumatoid Arthritis (RA)
11. Has Methicillin-resistant Staphylococcus aureus (MRSA)
12. Currently pregnant/breastfeeding or planning to in the next 3 months
13. Comorbidities including neurological, psychosocial, sensory, or other disorders that may impact pain perception
14. Diagnosis of epilepsy, dementia, migraines, or other neurological disorders that may prevent VR usage, and/or other medical conditions predisposed to nausea and dizziness
15. Hypersensitivity to flashing lights or motion
16. Claustrophobia
17. Lack of stereoscopic vision
18. Severe hearing impairment
19. Injury to eyes, face, or neck that prevents comfortable VR usage

5.3 RECRUITMENT

The primary and collaborating investigator(s) will identify potential subjects in their respective clinics that have elected to undergo primary TKA. These patients will also be pre-screened via manual chart review of their electronic health record (EHR) by the research team. Patients meeting the inclusion/exclusion criteria will be approached by an IRB approved study team member (e.g. primary and collaborating physicians, research project manager and/or project coordinator) during their orthopaedic clinic visit, orthopaedic health and physical, and/or Total Joint Class. Before asking for patient consent, the study will be explained in its entirety and the patient will have ample opportunity to ask any questions or express any reservations.

5.4 STUDY DURATION

5.4.1 Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 4 months.

5.4.2 Approximate Duration of Study

This study will be completed in approximately two years. The end of the study is the last visit of the last subject or end of collection of data from the patient's electronic medical record (EMR).

5.5 PROCEDURES

Standard of Care: Both the SOC+RelieVRx group and the SOC group will be enrolled in the Geisinger ProvenRecovery Program©, which includes a "My Rapid Recovery Kit" containing care instructions for mobility and nutrition, an antiseptic body wash to lessen the chances of infection, a spirometer to measure lung capacity, and immunonutrition drinks to avoid malnutrition and dehydration. Surgery through ProvenRecovery© is opioid avoiding and in many cases opioid free. During surgery, a patient's pain is controlled by targeting only the surgical area. Known as multi-modality pain management, this technique allows for effective pain control of just one area and eliminates additional pain sources. A combination of non-opioid medications is used, depending on the surgery, such as a local anesthesia, ibuprofen, acetaminophen, gabapentin, ketamine, and lidocaine.

Intervention: For all participants who are randomly assigned to the SOC+RelieVRx group, the RelieVRx headset will be provided by a study team member during the preoperative period, along with instructional materials. While in the hospital, use of the VR headset will be offered either in addition or as an alternative to SOC pain medication. The headset will be provided pre-operatively, but patients will not be instructed to use the device until after their surgery. Patients will be instructed to use the device on the day of surgery after they are discharged from the Post Anesthesia Care Unit (PACU) to the inpatient unit, or at least 4 hours post-surgery. The device will then go with the patient upon discharge for use through the entire treatment period (i.e. 14 days). Participants will use the RelieVRx headset for 14 days postoperatively a maximum of 3 times per 24-hour period (morning, noon, and evening) for not more than 30 minutes consecutively. The patients will be instructed not to use the device while ambulating.

Assessments: In inpatient postoperative periods, pain will be assessed as per routine with a Numerical Pain Rating Scale (NPRS) of 0-10, where zero equals the lowest pain level and 10 equals the highest. This will be administered every 4 hours during the patient's hospital stay, and each time the patient requests pain medication, either intravenous or oral. After patients are discharged from the hospital, they will be asked to complete a paper or online REDCap diary to track their pain levels, opioid/non-opioid pharmacotherapy, and device use from home. The daily log will capture the NPRS at the same time each evening (± 2 hours). Participants will be asked to record their NPRS at least 2 hours after taking any pain medication. In the SOC+RelieVRx group, NPRS also will be recorded before (within 15 minutes prior to use) and immediately after each use of the RelieVRx device. Analgesic medication use will be recorded in terms of medication type, dose, and time of administration.

All participants will be enrolled in Force Therapeutics, a web-based, digital rehabilitation and education program. The patient is automatically enrolled when surgery is scheduled, and patient

participation is reinforced in the patient education class. This will allow for the easy collection of patient-reported outcome measures, such as VR-12 and KOOS Jr., after discharge. Outcomes data also may be collected via OBERD, a software system for patient-reported outcomes already in use at the study clinics. To assess opioid use, the investigators will query Pennsylvania's Prescription Drug Monitoring Program (PDMP) database. To maintain compliance with ABC-MAP Act 191 of 2014, study investigators will query the PDMP only for their existing patients.

The RelieVRx devices will collect information related to device usage (i.e. frequency and duration of use, experiences selected, etc.). Patients who are not using their RelieVRx device as prescribed and/or not completing the prescribed questionnaires in Force may be contacted via phone or email by the study team to further encourage participation. Participants will be asked to return their device to the study team at a routine postoperative clinic visit.

Outcome measures include:

- Pain will be assessed via the standard Geisinger Numerical Pain Rating Scale (NPRS) ranging 0-10 (0 = least amount of pain, 10 = worst amount of pain).
    - Every 4 hours during patient's hospital stay
    - Daily for the remainder of the first 14 postoperative days
    - Before (within 15 minutes prior to use) and immediately after each use of their device
- Physical function will be assessed by the KOOS Jr. (Knee Osteoarthritis Outcome)
- Analgesic medication use will be assessed in three ways:
    - Reviewing inpatient use as recorded in EMR
    - Extrapolating total milligrams of morphine equivalent doses filled from PDMP database through 90-days postoperative
    - Patient self-reported consumption
- Quality of life will be assessed using the Veterans RAND 12 Health Survey (VR-12) – physical component score
- PACU length of stay (LOS)
- Hospital LOS
- Time to initial ambulation
- Clinic and emergency department visits within 90-days postoperative
- Inpatient readmissions for uncontrolled pain within 90-days postoperative
- Surgical complications, such as infection or delayed healing, within 90-days postoperative

5.5.1 Study Time and Events Table

Study Procedures	Pre-surgery	Day of Surgery	Inpatient stay (multiple times per day)	Daily for 14 days postoperative (multiple times per day)*	14, 30, 60, 90 days postoperative*
Review inclusion/exclusion	X				
Demographics, medical history	X				
Informed consent	X				
Randomization	X				
Device set-up and orientation[1]	X				
Surgery[2]		X			
NPRS pain score	X	X	X	X	X
KOOS Jr. and VR-12	X				X
Analgesic medication use	X	X	X	X	
Opioid use	X	X	X	X	X
LOS, time to initial ambulation, ED visits, readmissions					X
Device utilization statistics[3]	X	X		X	
AE / Complication Reporting	X	X	X	X	X

1 RelieVRx group only

2 Corresponds to pre-surgery, day of surgery, and inpatient stay timepoints on the billing determination

** Data collected from patient at home via phone or online; not an in-person visit*

5.6 STUDY ENDPOINTS AND STATISTICAL PLAN

This study will evaluate two primary endpoints – effectiveness of a single use of RelieVRx in the reduction of acute postoperative pain by 20%; and overall effectiveness of RelieVRx as an opioid-sparing intervention, where opioid and non-opioid consumption is reduced by at least 20% over a 90-day postoperative period in the SOC+VR group compared to the SOC group.

Acute effectiveness will be evaluated using NPRS data collected before and after each use of RelieVRx (up to 3 times per day) over the 14-day postoperative period. NPRS is measured on a scale of 0-10, with 0 being the least amount of pain and 10 being the most. Because pain levels will vary by time of day administered and are expected to peak in the first 24-72 hours postoperatively and drop afterward, acute effectiveness will be evaluated at all stages of recovery. The expected 20% reduction after single use will be scaled relative to the pre-use pain score [e.g. users reporting a pre-VR pain level of 8 would need to report post-VR pain levels of 6.4 (8 * 80%) on average; users reporting pre-VR pain of 5 would need to report pain levels of 4 post-VR, etc.]. Each SOC+VR patient will use VR up to 44 times over the 14-day recovery period, requiring linear mixed model analysis to assess acute changes in pain scores while accounting for stage of recovery and other covariates, such as age, preoperative health status and opioid use, and postoperative complications. For interim and final endpoint analyses, pain %-change scores will be calculated for each use and averaged for each patient across the 72-hour acute postoperative period, the following week, after 10 days, and overall. These averages will be evaluated using one-sample unpaired *t*-tests (or the nonparametric one-sample Wilcoxon signed-rank test, as needed for non-normal data).

Overall effectiveness will be evaluated by tracking daily opioid usage 90 days postoperatively in both SOC and SOC+VR groups. Average MMEs (Morphine Milligram Equivalents) per day will be compared using unpaired Student's *t*-test (or the nonparametric Wilcoxon rank-sum test) in interim and final endpoint analyses. In addition, changes in usage over time will be evaluated using linear mixed models (or nonlinear models, given data shape), accounting for variations in recovery time across patients and other covariates, such as other analgesic medications used postoperatively, preoperative opioid use, and dosage changes. A sub-analysis will compare usage in the 14-day acute postoperative recovery period.

The secondary endpoint of this study is a comparison of the cumulative experience of pain over the 14-day acute postoperative period between SOC and SOC+VR groups. In order to quantify pain that fluctuates over time, NPRS pain scores will be plotted for each patient over the acute postoperative period, using straight-line interpolation between measurements. This approach will allow for incorporation of all data collected (even if some patients participate more than others), and will avoid overemphasis on a single outcome measure (e.g. pain on day 14). Percent-area-under-the-curve (VAS-%AUC) measurement will be calculated for each patient by adding the

areas of consecutive trapezoids defined by time on the x-axis and pain level measurements on the y-axis (e.g. 100% would indicate pain scores of 10 across the entire time period; 50% would indicate a linear reduction from 10 to 0 over the same time period). In interim and final endpoint analyses, NPRS-%AUC accumulated to date will be compared between groups using an unpaired Student's *t*-test (or nonparametric equivalent). In addition, linear mixed models will be used to compare cumulative pain between SOC and SOC+VR groups over time, as well as pain experienced in the inpatient postsurgical period and following days.

Additional outcome data will be compared between groups in preliminary analyses using chi-squared tests (for categorical variables), unpaired Student's t-tests (for single-measure normal continuous data), or nonparametric equivalent (for non-normal data), as appropriate. For measures collected at multiple time points, %AUC values will be calculated per patient and compared using aforementioned tests. In final analyses, outcomes will be compared using linear mixed models, allowing for data missing at random and evaluation of covariates.

When approximately 25% of the total required sample has been collected, patient data will be summarized to verify adequate study power, and interim analyses will be conducted. In order to preserve a Type I error rate of 5% (i.e., $\alpha = 0.05$) for final analyses, interim analyses will be conducted with *p*-value threshold of 0.001, as suggested using the Hybittle-Peto method, meaning that only effects where $d > 2.0$ will be significant. Additional patients may be recruited as needed to ensure sufficient study power, and fewer patients may be recruited if interim analyses demonstrate highly significant effects. All statistical analyses will be performed with SAS (SAS 9.4, SAS Institute, Cary, NC), Stata (SE 14.2, StataCorp, LLC, College Station, TX), or R (R 3.5.2, The R Foundation, Vienna, Austria) statistical software, with p-values of <0.05 considered statistically significant.

5.6.1 Sample Size Considerations

This study has been designed with consideration for power requirements of both primary and secondary endpoint evaluations, as well as requirements for a noninferiority trial evaluating the overall effectiveness of RelieVRx as an opioid-sparing product.

Primary Endpoints

Preliminary data collected at Geisinger Medical Center (Danville, PA) between March 2017 and December 2018 from 1,052 patients who underwent total joint arthroplasty showed an average postoperative pain score of 8.50 following the procedure, and 6.16 on day 2 (SD = 2.0; change $d = 1.2$, or a 28% pain reduction) under SOC.

To assess the acute effectiveness endpoint of 20% average reduction in pain scores, each one-sample *t*-test only requires data from 13 patients to demonstrate a significant difference from zero, assuming 20% attrition, a Type I error rate of 5% and a Type II error rate of 20% (i.e., 80%

power). In order to observe significance of a lower threshold (e.g., a 10% reduction in pain level on average), data from **43 patients using VR** will be required, assuming 20% attrition, a Type I error of rate 5% and 80% power.

To assess the overall effectiveness for reducing opioid usage by at least 20%, this study assumes an average MME per day of 12.5mg (SD = 3) across all users, although continuous opioid users may report averages higher than 50mg/day. Observing a 20% relative reduction in opioid usage in the SOC+VR group compared to SOC (2.5mg) will require **64 patients total (32 per group)**, assuming 25% attrition, a Type I error rate of 5% and 80% power. If interim data analysis reveals unexpectedly high variability in opioid consumption, a revised power calculation based on new data may increase data collection requirements to address this question.

Secondary Endpoint

Using aforementioned preliminary data, two patients groups were created with simulated VAS-%AUC data (with day 14 VAS means of 6.16 and 4.93, SD = 2.0; or, a 20% greater reduction at day 14) corresponding to a 7% difference in VAS-%AUC (0.86 versus 0.79; SD = 0.1; difference d = 0.7). Assuming 25% attrition, the study will require **92 patients total** (**46 per group**). Data from at least 68 patients is needed to observe a statistically significant VAS-%AUC difference between SOC and SOC+VR of 7% in an unpaired t-test, with a Type I error rate of 5% and 80% power.

5.7 DATA MANAGEMENT

5.7.1 Data Collection and Storage

The following data points will be recorded via direct data collection, retrospective EMR review, and/or the Pennsylvania Prescription Drug Monitoring Program (PDMP) database:

- Medical Record Numbers (MRN) (Will not be included in final data set)
- Name (Will not be included in final data set)
- Patient contact information (e.g. phone, email) (Will not be included in final data set)
- Date of birth
- Patient demographics such as gender, race/ethnicity, and BMI
- Medical history relevant to inclusion/exclusion
- Date(s) of clinic visits
- Outcome measures (see section 5.5. for complete list)

The study coordinator(s) will randomly assign study ID numbers in place of MRNs. All study data will be stored on a secure Geisinger Health System server, and hard copy data will be double locked and accessible only to the study investigators. Only group-level information without personal identifiers will be included when presenting results or submitting manuscripts for publication. An IRB approved study team member will share the dataset with appliedVR via a secured e-mail.

The RelieVRx devices will collect information related to device usage (i.e. frequency and duration of use, features utilized, completion rates). When connected to WiFi, the devices will automatically and securely transmit de-identified logs of headset usage. This data contains no PHI, is encrypted in transit, transmitted as frequently as every 5 minutes, and stored in appliedVR's secure and compliant cloud environment. Data will be aggregated and sent in a compatible format to Geisinger to be analyzed and cross referenced with patient study ID numbers.

5.7.2 Records Retention

Records of the data generated within the course of this study will be kept indefinitely and may be used for future research studies that have been reviewed and approved by the IRB.

6 SAFETY MONITORING

6.1 ADVERSE EVENT REPORTING

Clinical adverse events (AEs) will be monitored throughout the study. All AEs will be reported to the institutional review board (IRB) regardless of whether they are considered study related. The date and time of onset and outcome, course, intensity, action taken, and causality to study treatment will be assessed by the study PI. In the event of a serious AE (SAE), this will be reported to the Geisinger IRB (GIRB) according to the GIRB guidelines. All other AEs will be summarized and submitted to GIRB during continuing review.

6.2 DEFINITIONS

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or in a clinical study. The event does not need to be causally related to the test article or clinical study.

A **serious adverse event** (SAE) is an AE that:

- Results in death.
- Is life-threatening (see below).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see below).

- Results in a persistent or significant disability or incapacity (see below).
- Results in cancer.
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the participating investigator. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.

In addition, a hospitalization for a preexisting condition that has not worsened does not constitute an SAE.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the test article but is considered by the investigator or the medical monitor (or designee) to be

related to the research conditions, i.e., related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Other Reportable Information. Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- Pregnancy exposure to a test article, except for exposure to prenatal vitamins. If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposure are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.
- Lactation exposure to a test article with or without an AE.
- Overdose of a test article as specified in this protocol with or without an AE. Baby formula overdoses without any AEs are excluded.
- Inadvertent or accidental exposure to a test article with or without an AE.

6.3 RECORDING AND REPORTING

A subject's AEs and SAEs will be recorded and reported from the signing of the informed consent form through 1 year post-operative.

6.4 SERIOUS ADVERSE EVENT REPORTING

Michael Suk, MD, JD, MPH, MBA, FACS, Chief Physician Officer, Geisinger System Services Chair, Musculoskeletal Institute & Department of Orthopaedic Surgery Geisinger Health System, will notify GIRB of all study SAEs in accordance with policy guidelines. If an SAE has not resolved at the time of the initial report, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to GIRB. An SAE will be followed until either resolved or stabilized.

7 PROTECTION OF HUMAN SUBJECTS

7.1 INFORMED CONSENT

The investigator will provide for the protection of the subjects by following all applicable regulations. The informed consent form will be submitted to the IRB for review and approval. Before any procedures specified in this protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.

- Be given time to ask questions and time to consider the decision to participate.
- Be allowed to visually and manually inspect the device.
- Voluntarily agree to participate in the study.
- Sign and date an IRB-approved informed consent form.

7.2 PROTECTION OF HUMAN SUBJECTS AGAINST RISKS

The investigator will provide for the protection of the subjects by following all applicable regulations. Anticipated risks in this study are minimal. The major risk to human subjects is the accidental disclosure of PHI. In this regard, the assignment of a study ID number to each individual participant and the protocol of providing only the necessary associated clinical information to the remainder of the research team will mitigate this risk. All data will be coded and encrypted while being transferred.

8 PUBLICATION PLAN

After clinical trials are completed, we intend to submit, together with our collaborators, results of the evaluations of RelieVRx for publication in order to promptly disseminate information on its efficacy. appliedVR will also prepare all study data for *de novo* submission to the FDA to obtain Class II review and clearance.

9 REFERENCES

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10. KOOS Jr., Hospital for Special Surgery, developer Stephen Lyman PhD (HSS validation cohort and FORCE-TJR registry) – Non-proprietary and free to use.