DETAILED STUDY PROTOCOL

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Summary of Revisions Made:

- Added the following assessments:
  - PROMIS SF v1.0 – ED – Anxiety 8a (8 items)
  - PROMIS SF v1.0 – ED – Depression 8a (8 items)
  - PROMIS SF v1.0 – ED – Positive Affect 15a (15 items)
  - PROMIS – Meaning and Purpose Scale (adult version)
  - Life Fulfillment Scale
- Added references for new assessments
- Replaced “narcotics” with “opioids”
- Added Seizures and Motion Sickness to exclusion criteria
- Added racial and ethnic categories to Planned Inclusion Enrollment
- Added Numeric Pain Rating to every visit
- Added treatment tracking to pain medication tracking form
- Added tracking for all medications
- Removed Numeric Pain Rating Scale from visits when Pain, Medication, and Health Form are administered (NPRS is included in the PMH form)
- Significant revisions to Study Interventions – Virtual Environment (Section 5.1) to reflect developments in virtual reality game programming and participant experience
- Added Timeline Between Visits Section 6.1.1
- Added an allowance of 30 additional days to the total intervention
- Added Seizures to the list of exclusion criteria
- Changed Quebec Task Force Inclusion Criteria to <4
- Added risks: nausea, motion sickness, fall risk
- Added “Working proficiency in English” to the inclusion criteria
- Revised and rearranged the descriptions of evaluations
- Removed the video link from the description of the Informed Consent process
- Removed muscle relaxant from the list of exclusion criteria

- Added process and/or criteria to be used by the study team to determine if a participant is able to continue participation after an incident to Reasons for Early Termination (section 6.2.6)
- Removed agrees with statement “It is not really safe for a person with my back problem to be physically active,” and added Tampa Scale of Kinesiophobia score greater than 36 to inclusion criteria.

TABLE OF CONTENTS

Page

Tool Revision History 2

TABLE OF CONTENTS 43

STUDY TEAM ROSTER 76

PARTICIPATING STUDY SITES 76

PRÉCIS 76

1. STUDY OBJECTIVES 99

1.1 Primary Objective 99

1.2 Secondary Objectives 109

2. BACKGROUND AND RATIONALE 109

2.1 Background on Condition, Disease, or Other Primary Study Focus 109

2.2 Study Rationale 1110

2.2.1 Epidemiology of Low Back Pain 1110

2.2.2 Fear-Avoidance Model of Low Back Pain 1110

2.2.3 Virtual Reality Games for Health Promotion and Rehabilitation 1111

2.2.4 Mechanisms Underlying Proposed Game Intervention 1211

3. STUDY DESIGN 1312

4. SELECTION AND ENROLLMENT OF PARTICIPANTS 1312

Planned Inclusion Enrollment 1312

4.1 Inclusion Criteria 1413

4.2 Exclusion Criteria 1514

4.3 Study Enrollment Procedures 1514

5. STUDY INTERVENTIONS 1615

5.1 Interventions, Administration, and Duration 1615

5.2 Handling of Study Interventions 1919

5.3 Concomitant Interventions 1919

5.3.1 Allowed Interventions 1919

5.3.2 Prohibited Interventions 1919

5.4 Adherence Assessment 1919

6. STUDY PROCEDURES 2121

6.1 Schedule of Evaluations 2121

6.1.1 Time between visits 2121

6.1.2 Time between treatment weeks 22
6.2 Description of Evaluations 23
6.2.1 Screening Evaluation 27
6.2.2 Enrollment, Baseline, and/or Randomization (Visit 1) 28
6.2.3 Blinding 28
6.2.4 Follow-up Visits 29
6.2.5 Completion/Final Evaluation 30
6.2.6 Reasons for Early Termination 30

7. SAFETY ASSESSMENTS 31

7.1 Specification of Safety Parameters 32
7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters 33
7.3 Adverse Events and Serious Adverse Events 33
7.4 Reporting Procedures 34
7.5 Follow-up for Adverse Events 35
7.6 Safety Monitoring 35

8. INTERVENTION DISCONTINUATION 35

9. STATISTICAL CONSIDERATIONS 36

9.2 Sample Size and Randomization 36
Treatment Assignment Procedures 37
9.3 Definition of Populations 37
9.4 Interim Analyses and Stopping Rules 38
9.5 Outcomes 38
9.5.1 Primary Outcome 38
9.5.2 Secondary Outcomes 38
9.6 Data Analyses 38

10. DATA COLLECTION AND QUALITY ASSURANCE 39

10.1 Data Collection Forms 39
10.2 Data Management 40
10.3 Quality Assurance 40
10.3.1 Training 40
10.3.2 Quality Control Committee 40
10.3.3 Metrics 40
10.3.4 Protocol Deviations 40
10.3.5 Monitoring 41

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY 41

11.1 Institutional Review Board (IRB) Review 4140
11.2 Informed Consent Forms 4140
11.3 Participant Confidentiality 4141
11.4 Study Discontinuation 4241

12. COMMITTEES 4241

13. PUBLICATION OF RESEARCH FINDINGS 4242

14. REFERENCES 4242

I. Procedures Schedule

II. Informed Consent Form Template

III. Other (add as many appendices as necessary)

STUDY TEAM ROSTER

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PARTICIPATING STUDY SITES

This is a single site study conducted at Virginia Commonwealth University.

PRÉCIS

A fundamental clinical problem in individuals with chronic low back pain is the significant alteration in movement patterns that restrict lumbar spine motion. This restriction of lumbar motion is particularly evident in patients with kinesiophobia; that is, a fear of movement due to possible injury or reinjury. For chronic back pain patients with kinesiophobia it is critical to develop an effective intervention to increase spine motion while minimizing concerns of pain and harm. Accordingly, we have developed an innovative suite of virtual reality games that track whole-body motion and are designed to encourage spinal flexion while reducing concerns of pain and harm among individuals with low back pain. Our games have two distinct advantages. First, within this game environment we can manipulate the target locations to encourage progressively larger amounts of lumbar spine flexion during game play. Second, virtual reality games are potent distractors that can reduce attention to pain.

We have recently established safety and feasibility when played for 3 consecutive days. In the proposed study participants will complete 18 intervention visits over 9 weeks with the number of sessions tapered across weeks (i.e., 3 sessions/week in weeks 1-3, 2 sessions/week in weeks 4-6, and 1 session/week in weeks 7-9).

Our co-primary outcome variables will be change in pain and change in disability from baseline to 1-week post-treatment (Aim 1). We will also examine changes in expectations of pain/harm and lumbar flexion as potential mechanisms of change in pain and disability (Aim 2). Aim 3 will examine maintenance of treatment gains at 1-, 6-, 12-, 24-, and 48-weeks post-treatment, additional measures of emotional functioning, pain vulnerability, and pain resilience, and real-world activity monitoring

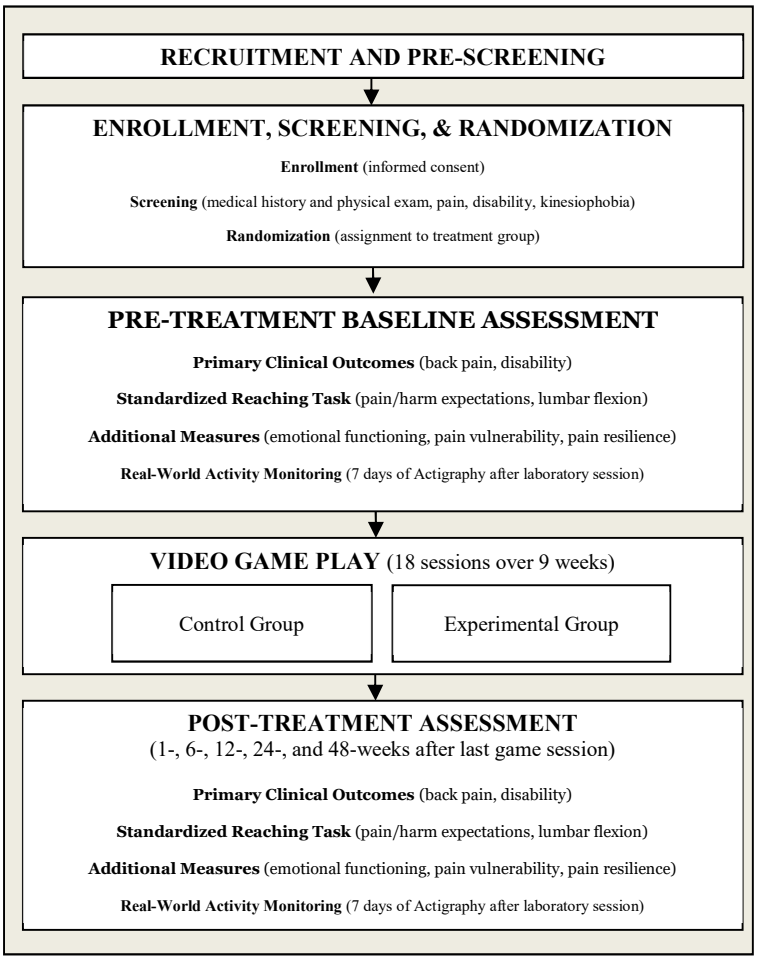
(See Recruitment and Pre-Screening – Figure1).

Figure 1

Study Title

VIGOR - Virtual Immersive Gaming to Optimize Recovery in Low Back Pain

Objectives



The co-primary clinical outcomes are changes in pain and disability. Secondary objectives are to examine potential mechanisms of pre- to post-treatment changes in clinical outcomes and maintenance of treatment gains.

Design and Outcomes

VIGOR is a Phase II, double-blind, randomized, placebo-controlled trial to test the efficacy and safety of a novel, immersive, virtual reality intervention on outcomes of pain, disability, pain/harm expectancy, and lumbar flexion in individuals aged 18-60 years of age with chronic low back pain.

Individuals with chronic low back pain will be randomly assigned to play one of two versions of the virtual reality game suite for 9-weeks. In the experimental group, gameplay will promote progressive increases in lumbar flexion. The control group will play the same immersive video games, but the parameters will be modified such that

only small excursions of lumbar flexion are needed to successfully complete gameplay. The co-primary clinical outcomes of changes in pain and disability will be assessed at 1-, 6-, 12-, 24-, and 48-weeks post-treatment. Additionally, individual differences in expected pain, expected harm, and lumbar flexion will be measured at pre-treatment baseline and at each of the follow-up intervals in the laboratory. Finally, participant activity in their natural environment will be monitored for 7 days following each follow-up laboratory visit using accelerometry.

Interventions and Duration

Participants will complete 18 intervention visits over 9 weeks with the number of sessions tapered across weeks (i.e., 3 sessions/week in weeks 1-3, 2 sessions/week in weeks 4-6, and 1 session/week in weeks 7-9).

Sample Size and Population

We will recruit 230 participants with chronic low back pain (CLBP) and fear of movement. We will include participants with CLBP between the ages of 18-60 and who report no health condition(s) that may restrict movement or preclude safe participation. Participants will be recruited from the general population and specific organizations such as Virginia Commonwealth University's Medical Associates.

Aim 1: Power analyses were conducted to determine the sample size needed to achieve clinically important differences in our co-primary clinical outcome measures of pain and disability. Based on the extant literature, we based our analyses on a $\geq$ 30% decrease in pain ratings[1] (on the 0-10 NRS scale) and a 30% decrease in disability ratings on the RMDQ[2] in the experimental group. Further, we predict a 10% decrease in pain and disability in the control group to account for potential placebo effects. The population standard deviations were set at 75% of the population mean values. The pre-post correlation was estimated as r=0.7. These population parameters translate into an effect size of f=0.30. Using these parameters, we drew 10,000 samples from a normal population distribution. Based on these parameters, to achieve power of 80% and α=0.05 will require a total N=78.

Aim 2 & 3: Power analyses were conducted to determine the sample size needed to address hypotheses 2.1, 2.2, and 3. Using the method described by Morris (2008),[3] we calculated effect size estimates from randomized clinical trials on the effects of graded activity or graded exposure interventions on changes in disability among individuals with CLBP.[4-7] For our power analyses, we adopted the median estimated effect size: $\delta = .45$, which corresponds to what would commonly be described as a medium effect size. Following Raudenbush and Liu's (2000) recommendation,[8] we set the residual error variance to 1 and estimated the between-subject slope variance to be 0.30. For power equal to .80 and α=0.05, a sample size of 209 participants was indicated.

Based on the sample size calculations, using a sex-stratified random allocation table, we need a minimum sample of 209 participants to address Aims 1-3. To allow for 10% attrition from baseline to 48-week follow-up, we will recruit 230 participants.

1. STUDY OBJECTIVES

1.1 Primary Objective

The co-primary clinical outcomes are changes in pain and disability. We will examine immediate clinical outcomes as a function of treatment. Relative to the control group, participants in the experimental group will show greater reductions in pain and

disability at post-treatment relative to pre-treatment baseline (Hypothesis 1). To test Hypothesis 1, we will examine the Treatment by Time (baseline-post treatment) interaction in a LME model: a greater reduction in pain and disability in the experimental group than in the control group. The co-primary clinical outcomes of changes in pain and disability will be assessed at 1-, 6-, 12-, 24-, and 48-weeks post-treatment.

1.2 Secondary Objectives

Secondary objectives are to examine potential mechanisms of pre- to post-treatment changes in clinical outcomes and maintenance of treatment gains. Participants in the experimental group will exhibit greater pre- to post-treatment decreases in pain/harm expectancy and increases in lumbar flexion as compared to the control group (Hypothesis 2.1). Decreases in pain/harm expectancy and increases in lumbar flexion will be positively related to pre- to post-treatment reductions in pain and disability (Hypothesis 2.2). Examination of maintenance of treatment gains will occur at 1-, 6-, 12-, 24-, and 48-weeks post-treatment. Relative to the control group, participants in the experimental group will continue to show lower levels of pain and disability at each time point as well as increased activity in their natural environment (Hypothesis 3).

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Low back pain is the second most common reason for a visit to a physician, with direct medical costs exceeding $90 billion per year in the United States alone.[9, 10] These costs are driven primarily by 7-10% of patients who develop chronic low back pain (CLBP) that can last for many years.[9-11] Fear of movement (i.e., kinesiophobia) due to expectations of pain and harm is an important risk indicator for the development of persistent pain and disability, with studies consistently showing that high fear is one of the strongest predictors of the transition from sub-acute to CLBP.[12-15] Specifically, fear encourages the adoption of maladaptive movement patterns wherein tasks of daily living are performed with reduced lumbar spine flexion and compensatory increases of knee, hip, and shoulder flexion. Using our standardized reaching tasks, we have repeatedly demonstrated reduced lumbar spine flexion in fearful acute, sub-acute, and CLBP sufferers.[16-20] While avoidance of lumbar flexion may benefit these CLBP sufferers in the short-term by reducing their fear of injury, in the long-term, limited lumbar flexion becomes an entrenched pattern that can lead to shortening of spinal peri-articular connective tissues, changes in surrounding muscles,[21-23] and increased risk for chronicity.

The current standard of care for individuals with high fear and CLBP is graded exposure therapy, which promotes gradual confrontation of avoided movements in order to reduce expectations of pain/harm.[24] Although recent RCTs with CLBP patients indicate that this approach significantly reduces fear of movement, it has not led to greater reductions in disability when compared to standard therapy.[4, 6] We posit that prior studies have not seen the full benefit of this approach because they have failed to make restoration of lumbar flexion an explicit focus of therapy. Without this goal, patients are able to complete the graded movement tasks using maladaptive movement patterns that can impede full recovery. Therefore, we hypothesize that explicit efforts to increase lumbar flexion are required to benefit those with CLBP who are typically viewed as having intractable pain and disability.[25]

With the support of an NIH R21, we completed a Phase I trial of an immersive virtual reality dodgeball game designed specifically to increase lumbar flexion among individuals with CLBP and high fear of movement. The results of this proof-of-concept study demonstrated that 3 daily sessions of virtual dodgeball was safe, did not exacerbate existing back pain, was highly rated by participants, and increased lumbar spine flexion during gameplay. The current Phase II RCT will determine the efficacy of a 9–week course of treatment of virtual dodgeball to reduce pain and disability among individuals with CLBP and high fear of movement.

2.2 Study Rationale

2.2.1 Epidemiology of Low Back Pain

Low back pain (LBP) is one of the most common reasons for seeking medical care and accounts for over 3.7 million physician visits per year in the United States alone.[9] It is the leading cause of pain in the U.S., affecting 28.1% of adults each year[11] and 90% of adults in their lifetime.[9, 26-31] Back pain is associated with $200 billion in lost wages and productivity annually, and is the second leading contributor to annual disability costs of $300 billion.[9-11] These costs are driven largely by 7-10% of patients who develop chronic low back pain (CLBP)that typically lasts for many years.[26] According to Foster (2011), “Despite decades of research and improved quality of clinical trials, the reality is that the treatments we have to offer patients tend to produce small effects, often only in the short term and none appear to change effectively the longer-term prognostic paths or trajectories for patients.”[27]

2.2.2 Fear-Avoidance Model of Low Back Pain

The fear-avoidance model of low back pain explains why some people with acute musculoskeletal pain go on to develop chronic pain and disability.[32, 33] Central to this model, individuals who have high kinesiophobia are prone to catastrophic thoughts (e.g., “The pain will get worse!”), are more likely to experience greater fear of movement and re-injury, and hence will engage in behavioral adaptations to avoid or escape pain. In contrast, individuals with low kinesiophobia have little fear of movement and re-injury, and therefore are more likely to confront potential or actual pain-provoking situations that are needed to progress towards recovery (e.g., return to daily activities, work, rehabilitation). While the fear-avoidance model posits a generic avoidance of all forms of movement that are perceived as threatening, we have repeatedly shown that individuals with high fear and LBP display very similar patterns of motor behavior – they specifically avoid flexion of the lumbar spine.[16, 34, 35] Over time, avoidance of lumbar spine motion increases the risk for re-injury due to shortening of peri-articular connective tissues and changes in the surrounding muscles.[21-23] These changes increase the risk of injury when the individual is exposed to common, unexpected environmental challenges (e.g., slipping on ice). Thus, interventions for individuals with CLBP and high fear must explicitly address avoidance of lumbar flexion.

2.2.3 Virtual Reality Games for Health Promotion and Rehabilitation

Virtual reality (VR) games have been used to promote health education, disease management, distraction from discomfort, increased physical activity, and rehabilitation involving motor performance, such as following a stroke.[36-38] Further, strong evidence has accumulated regarding the utility of VR gaming for short-term pain relief.[39, 40] One of the clear positive benefits of games is that they motivate

players to compete and score points. Games also provide a level of distraction from the actual behavior being performed, and individuals are willing to engage in behaviors that might cause pain due to the competitive nature of the game.[41] Consistent with this notion, VR gaming has been shown to significantly reduce pain during burn debridement, wound dressings, painful activity, and uncomfortable medical procedures.[39, 40] However, to date, VR gaming interventions have not been adapted to address CLBP,[39, 40] and have not taken advantage of VR interface features (e.g., full-body control of avatars, real time feedback/reinforcement).

2.2.4 Mechanisms Underlying Proposed Game Intervention

Both Graded Activity (GA) and Graded Exposure (GE) are common approaches to the treatment of CLBP. Graded activity focuses on restoring function regardless of pain. The intervention begins with provision of a treatment rationale emphasizing the negative effects of inactivity and the positive effects of physical activity on well-being, and then uses a combination of activity quotas and positive reinforcement to promote increased activity over time. In contrast, GE focuses on reducing fear of pain and expectations of harm upon movement. Treatment begins with provision of a treatment rationale emphasizing the role of fear as an impediment to functional restoration, and then proceeds with development of an individualized hierarchy of feared movements to guide subsequent sessions of graded exposure. Systematic exposure to feared movement provides repeated opportunities to confront and correct patient misperceptions of the expected relationship between movement and risk of harm. RCTs have shown that both GA and GE produce significant reductions in pain and disability, and that these intervention effects do not differ significantly at post-treatment and 1-, 6-, and 15-month follow-up intervals.[4, 6, 42] However, a systematic literature review concluded that GA is no more effective than other forms of exercise and that GE is no better than wait-list or usual care controls.[43] We hypothesize that GA and GE approaches to CLBP fail to outperform other forms of exercise or usual-care controls because patients can complete the prescribed tasks with restricted lumbar spine motion simply by increasing motion at the ankles, knees, and hips. Indeed, continued restriction of lumbar spine motion may be a key impediment to optimal restoration of function as we have consistently demonstrated that pain-related fear is associated with restricted lumbar flexion among: 1) individuals with subacute LBP,[16, 35] 2) individuals with CLBP,[18] 3) asymptomatic individuals who have recently recovered from LBP,[34] and 4) healthy individuals with experimentally-induced back pain.[19] To address the ubiquitous and persistent problem of restriction of lumbar spine flexion among those with pain-related fear, we specifically designed a suite of virtual reality games (i.e. VR Dodgeball) that necessitate progressively larger excursions of the lumbar spine to successfully complete the games. Similar to GA, we believe that our intervention does not require an explicit focus on psychological factors related to avoidance behavior, but rather operates through a combination of acute distraction from pain, repeated reinforcement of movement goals with feedback of progress, and graded increases in expectations of spinal lumbar flexion across sessions. In a Phase I trial, we demonstrated that individuals with CLBP and pain-related fear who played virtual dodgeball had significant increases spinal motion across sessions. They also rated the game as highly enjoyable and had no adverse outcomes. With sufficient exposure to this intervention, we posit that individuals with CLBP and pain-related fear will develop an implicit understanding that lumbar spine motion is not dangerous and will generalize the unrestricted lumbar spine motion that is promoted by the

game to their daily lives. In so doing, we expect that they will restore the normal patterns of spinal motion that are necessary to promote a lasting recovery.

3. STUDY DESIGN

The proposed project is a Phase II RCT in which CLBP participants will be randomly assigned to one of two intervention arms. Those assigned to the experimental group will play our immersive video games that encourage participants to produce progressively larger lumbar flexion excursions at each game level and across treatment sessions. Those in the control group will play the same immersive games but the parameters will be modified such that only small excursions of lumbar flexion are needed to successfully complete gameplay. Treatment frequency and duration is based on existing evidence that graded activity and graded exposure interventions, typically lasting 6-12 weeks with 8-18 treatments sessions, result in significant reductions in disability.[44],[43] Accordingly, participants in the proposed study will complete 18 intervention visits over 9 weeks with the number of sessions tapered across weeks (i.e., 3 sessions/week in weeks 1-3, 2 sessions/week in weeks 4-6, and 1 session/week in weeks 7-9). Our co-primary outcome variables will be change in pain and change in disability from baseline to 1-week post-treatment (Aim 1). We will also examine changes in expectations of pain/harm and lumbar flexion as potential mechanisms of change in pain and disability (Aim 2). Aim 3 will examine maintenance of treatment gains at 1-, 6-, 12-, 24-, and 48-weeks post-treatment.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

According to the most recent statistics from the U.S. National Health Interview Survey (NHIS), when collapsing across gender, approximately 29.2% of Whites, 27.2.0% of Blacks/African Americans, and 27.4% of Hispanics reported low back pain in the previous three months. These data, shown in the table below are adapted from the Summary Health Statistics for U.S. Adults: National Health Interview Survey published in 2012. Although these national statistics indicate that low back pain is slightly more common amongst Whites as compared to African Americans and Hispanics, we will recruit our sample to ensure that it meets or exceeds the proportion of ethnic and racial minorities in the population according to 2010 U.S. Census figures. Specifically, we plan to enroll 16% Hispanic and 84% Non-Hispanic participants as well as 73% White, 17% African American, 7% Asian American, 2% American Indian/Alaskan Native, and 1% Native Hawaiian or Other Pacific Islander.

Planned Inclusion Enrollment

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	1	1	0	0	2
Asian	8	8	0	0	16
Native	1	1	0	0	2

Hawaiian or Other Pacific Islander					
Black or African American	16	16	4	3	39
White	71	70	15	15	171
More than One Race	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0
Total	97	96	19	18	230

Using recruitment procedures that we have successfully employed in prior CLBP trials (R01 AT00697, R21AR064430, R21AR063909) as well as prior cohort studies,[18, 35, 45-48] we will recruit 230 participants with CLBP and fear of movement. We will include participants with CLBP between the ages of 18-60 and who report no health condition(s) that may restrict movement or preclude safe participation. Participants will be recruited through advertisements and flyers posted in the local community, and via a combination of electronic, radio, print, and possibly television announcements in the local and surrounding communities. We may also recruit from local clinics. Finally, ResearchMatch.org will be used as a recruitment tool for this protocol. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository (see IRB #090207).

4.1 Inclusion Criteria

Participants must meet all of the following inclusion criteria:

- 18-60 years of age
- Low back pain that has been ongoing for at least half the days in the last 6 months
- Average pain intensity of 3 or higher over the past week on a 0-10 Numerical Rating Scale
- Disability >4 on Roland and Morris Disability Questionnaire
- Tampa Scale for Kinesiophobia score >36
- Has sought care or consultation from a health care provider for back pain
- Meets category < 4 on the Classification System of the Quebec Task Force on Spinal Disorders,[49] which reflects low back pain without neurological signs
- Working proficiency in English

4.2 Exclusion Criteria

Candidates meeting any of the following exclusion criteria at baseline will be excluded from study participation:

- Has a personal history of the following neurological disorders: Alzheimer's, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Parkinson's, Neuropathy, Stroke, Seizures
- Has a personal history of the following cardiorespiratory disorders: Congestive heart failure, heart attack in past 2 years
- Has a personal history of the following musculoskeletal disorders: Rheumatoid Arthritis, muscular dystrophy, pathologic fractures of the spine, avascular necrosis or osteonecrosis, severe osteoarthritis
- History of spine surgery or a hip arthroplasty
- Has active cancer
- Has a chronic disease that may restrict movement or preclude safe participation
- Has used opioids within 30 days prior to study enrollment
- Reports being pregnant, lactating, or that they anticipate becoming pregnant within 2-months
- Reports pending litigation related to CLBP
- Has current drug or alcohol use or dependence that, in the opinion of the PIs, would interfere with adherence to study requirements
- Has significant visual impairment that would prevent virtual reality headset use
- Has significant motion sickness that would prevent virtual reality headset use

4.3 Study Enrollment Procedures

When an individual expresses interest in the study, he or she will be directed to complete an online or phone Prescreen Assessment Questionnaire (CRFs VIGOR Pre-Screen) after providing assent to the prescreen. If a potential participant passes the initial eligibility screening, the study coordinator will contact the potential participants by e-mail and/or by phone to schedule a full screening assessment (Visit 0). At this time the study coordinator will verbally describe the study to the potential participant and answer any questions. The consent process will be conducted in a quiet, private room. During the consent process, potential participants will be informed about the study purpose and procedures and be given the opportunity to ask questions. They will be shown a video of the game to help them with the process. If they wish to continue, they will be asked to read and sign an informed consent document. Next, a member of the research team will review the signed consent form and will ask the participant to explain the procedures in their own words to ensure that they comprehend the study procedures before proceeding to the initial assessment.

Participants will then complete the screening visit surveys. Based on the responses to the questions, interested individuals who meet the inclusion/exclusion criteria will be identified and then undergo a physical exam by a licensed physical therapist or

physician. Participants who remain eligible following the physical exam will then be formally enrolled into the study. The study coordinator will then randomly assign them to their respective intervention group using a sex-stratified random allocation table.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Participants will complete 18 intervention visits over 9 weeks with the number of sessions tapered across weeks (i.e., 3 sessions/week in weeks 1-3, 2 sessions/week in weeks 4-6, and 1 session/week in weeks 7-9).

Provision of Treatment Rationale: After completing all pre-treatment assessments, participants will be given a rationale for the intervention. This includes an educational component that will be used to correct biomedical misconceptions, explain how pain persists without underlying pathology, and describe the interaction among biological, psychological, and social factors in maintaining pain and disability. Further, as virtual dodgeball provides a unique platform to distract an individual from focusing on pain, the treatment rationale will be followed by 1) an initial exposure to the virtual dodgeball environment, 2) specific details on how the intervention is designed to promote increased spinal motion and decreased disability, and 3) an opportunity to play a practice level to review basic game constructs (e.g., scoring metrics, moving the avatar, sound and visual cues).

Virtual Environment: A head mounted display (e.g., HTC Vive) will be used to provide a virtual environment for both the weekly standardized reaching tasks and for gameplay. The head mounted display is used to present the virtual world with a screen refresh rate of 90 Hz. The environmental parameters are controlled by custom software developed in the Unity game engine to manipulate and control all presented graphics and audio. During the initial testing session and at each post treatment follow-up (1,6,12, 24, & 48 weeks), the 6-DOF kinematic data from the clusters of light reflective markers placed on the participant is streamed to the game environment at 100 Hz using Vicon Tracker software allows for near real time presentation of the participant's avatar. Motion Monitor software sets up bi-directional communication with the Unity game engine and records all kinematic data (e.g., joint excursions, joint moments) during the initial gaming session. This integration allows us to individualize the game experience to each participant. During the intervention visits, presentation of the participant's avatar is controlled through the 6-DOF position data from the head mounted display, hand controllers, and Vive trackers attached to the thorax and pelvis of the participant.

Fig. 2. A participant with the head-mounted display and instrumented with the marker clusters (left). Matchality environments are illustrated in the second column: day one on earth (top), day two in orbit (middle), and day 3 on alien planet (bottom). Fishality environment is illustrated in the third column. Dodgeball variants are illustrated in fourth column: Cannon (top), standard (middle), alien planet (bottom).

As shown in **Fig. 2**, the participant will have a variety of immersive experiences across the 9 week intervention. The purpose of a suite of VR games is twofold. First, the games increase from difficulty across the intervention. That is the VR Dodgeball then has multiple opposing players launching virtual balls at higher velocities. Thus the suite is designed to provide a graded exposure in this cohort. Secondly, the use of multiple virtual environments within and across the suite of VR games is designed to encourage engagement with the protocol and to prevent boredom. In week one, they will engage inCannon Dodgeball, all balls are launched from the same position. In week two they will engage inDay Dodgeball increasing difficulty with the number of positions the ball can come from. Weeks 3-4 they will engage in night Dodgeball which gives less surrounding information making it more difficult to gage the speed of the ball. Wekks 4-9 Dodgeball will be played on an alien planet, with atomosheric conditions like the moon, causing balls to be launched more straight at you. In all cases, the movement of the avatar will be controlled by the participant's actual body movements.

Participants will play variants of Virtual Dodgeball. All versions of VR Dodgeball consist of launched virtual balls that are directed at the participant's avatar. The goal is to either block the launched virtual ball with the dodgeball held by the participant or to duck the launched virtual ball if it changes color to black and is accompanied by a quacking sound. In all variants of VR Dodgeball, there are 15 launched virtual balls per set, 2 sets per level, and 3 levels per game. Additionally, 3D sound is incorporated into the game in a number of ways, including crowd cheering, buzzers and referee whistles, and a duck quacking sound that occurs when a black ball is launched. Performance is updated in real-time and displayed on a virtual scoreboard in the basketball arena, and the participant will be awarded progressively more cash rewards for each successful block or dodge at each level of play (Level 1= 1¢, Level 2=2¢, Level 3=5¢, Level 4=10¢). Successful contact of each highlighted ball presented between each set will result in a bonus 25¢ reward. Conversely, the participant loses cash rewards for each failure to block or duck the launched ball (N.B. a player starts the game with a cash balance on the scoreboard such that if

they failed on every launched or presented ball, their cash balance would be zero).

The four versions of VR of dodgeball are described below.

Dodgeball Cannon - This consists of a single cannon that is located on the opposite free throw line of the virtual gym in which VR Dodgeball is played. In this game, the participant only has to worry about a single opponent and the launch trajectory of virtual launched balls has been adjusted to increase the height of the parabolic flight pattern to make interception of the launched virtual ball less challenging. Thus, the Dodgeball Cannon is less difficult than the subsequent dodgeball versions.

Dodgeball Day - In this classic version of VR Dodgeball the participant plays dodgeball against four virtual opponents. The participant is virtually located on one free-throw line and the four virtual opponents are located opposite the free throw line and have the ability to move 1 m fore-aft and 1 m left-right during gameplay. Virtual balls are launched in a randomized order from each of the four virtual opponents. If the launched ball is red, then the participant must attempt to block the ball with the ball held in their hands (corresponds to the virtual ball held in the virtual world). If the launched ball is black, the participant must attempt to duck to avoid the ball. There is a large scoreboard within the virtual gym that tracks participant performance and cash rewards earned during gameplay.

Dodgeball Night - This game is identical to the game described above, only the gym lights have been removed and the opposing avatars and launched virtual balls glow in the dark. This variation of the game 1) increases the challenge by making the distance of the launched balls harder to judge and 2) increases immersion in the virtual space, and 3) enhances novelty to avoid boredom by altering the environment.

Dodgeball Space - This game takes place on an alien planet with the gravitational constraints of the moon. The opposing players now are aliens and the physics of the ball launces has been adjusted to the reduced gravity of the moon. This again requires an adjustment by the participant to successfully control their avatar and in so doing helps to maintain challenge, immersion, and novelty.

Shaping Lumbar Spine Motion

Experimental Group: The location and presentation of static and dynamic virtual targets (dodge balls) will be manipulated to maximize lumbar flexion in the experimental group. The location of the virtual objects are set to necessitate 15, 30, 45, & 60 degrees lumbar spine motion. After week 1 of gameplay, visual gain will be manipulated such that virtual objects will be farther away and at a lower height (5% adjustment) to necessitate greater lumbar flexion to successfully intercept the virtual objects. In week 2 there will be a 10% adjustment (i.e, farther away and at a lower height), in week 3, and 15% adjustment will be made for weeks 4-9.

Control Group: To ensure that lumbar flexion is minimized while playing the virtual reality games, we will manipulate the presentation of virtual targets (balls in Dodgeball) such that the participant will only need to flex the spine 15 degrees to successfully intersect the virtual objects (pilot data indicate that lumbar excursions in virtual dodgeball typically range from 15-60 degrees of lumbar flexion).

At the end of each week, we will provide each participant with a graphic printout that indicates game performance such as hits, misses, points acquired across each week.

Schedule of Interventions

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
Treatment #	0	1, 2, 3	4, 5, 6	7, 8, 9	10, 11	12, 13	14, 15	16	17	18
Visit #	1	2, 3, 4	5, 6, 7	8, 9, 10	11, 12	13, 14	15, 16	17	18	19
Intro	x									
Dodgeball Cannon		x	x	x						
Dodgeball Day					x					
Dodgeball Night						x				
Dodgeball Space							x	x	x	x
Experimental Group % Gain Decrease			-5%	-10%	-15%	-15%	-15%	-15%	-15%	-15%
Experimental Group Gain	1	1	0.95	0.90	0.85	0.85	0.85	0.85	0.85	0.85

5.2 Handling of Study Interventions

The principal investigators, the statistician, and members of the data collection team will remain blinded to intervention assignment throughout the duration of the study. They will be given the identifying codes only at the end of the study when it is necessary to interpret the results. The un-blinded study coordinator, who is responsible for scheduling testing and treatment sessions, will greet participants and escort them to the testing lab; however, the study coordinator will not participate in the assessments of clinical outcomes or testing.

5.3 Concomitant Interventions

Participants in the study will be permitted to use over the counter pain medications (e.g., Non-Steroidal Anti-Inflammatory Drugs, Acetaminophen, Aspirin), or to apply heat or ice to manage back pain symptoms. All concomitant pain management interventions will be recorded at the beginning of each visit.

5.3.1 Allowed Interventions

Although participants who report using pain interventions other than over-the-counter pain relievers or heat/ice will be allowed to remain in the study, they will be excluded from the per-protocol analyses.

5.3.2 Prohibited Interventions

None.

5.4 Adherence Assessment

Adherence: Adherence to all scheduled intervention contacts is recorded by the study coordinator in a tracking system. Reports on adherence will be reviewed during regular meetings of a Recruitment, Adherence, and Retention Committee, which is composed of the PIs and the study coordinator. If a study participant misses a scheduled treatment, every effort will be made to re-schedule that treatment in the proposed weekly time frame. For the per-protocol analyses, successful adherence will be defined as $\geq$70% attendance (i.e., 13 out of the 18 treatments). To allow for flexibility in participant scheduling due to events that may conflict with scheduled visits (e.g., acute illness), the total length of the 9 week intervention period can be

extended by up to 30 days (i.e., total intervention = 9 weeks + 30 days).

Retention: Retention is enhanced by the addition of more frequent follow-up assessments as well as use of incentive payments at each participant visit. Specifically, participants will receive remuneration for performance at each gameplay session. In addition, attendance at post-treatment follow-up sessions at 1-, 6-, 12-, 24-, and 48-weeks will be encouraged by incentive payments of $100 per session attended.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Prescreen	Screen Visit 0	Enrollment & Baseline Visit 1	Treatment Visits 2-19	Post-Treatment Assessments Visit 20	Post-Treatment Assessments Visits 21-24
Numeric Pain Rating Scales 7-day & 24-hour	x	x	x	x*	x	x
Roland-Morris Disability Questionnaire	x	x	x		x	x
Fear Question	x	x				
Medical History - Back Pain	x	x				
Medication Log		x	x	x	x	x
Informed Consent Form		x				
Inclusion/Exclusion Criteria		x				
Enrollment/Randomization		x				
Medical History		x				
Physical Exam Form		x				
Adverse Events			x	x	x	x
Numeric Pain Rating Scale - Right Now			x	x	x	x
Standardized Reaching Paradigm • Pain & Harm Expectancy • Lumbar Spine Flexion			x	x*	x	x
Tampa Scale for Kinesiophobia			x		x	x
Center for Epidemiologic Studies - Depression			x		x	x
Pain Catastrophizing Scale			x		x	x
Pain Resilience Scale			x		x	x
Pain Self Efficacy Questionnaire			x		x	x
Brief Pain Inventory - Short Form			x		x	x
PROMIS-Anxiety			x		x	x
PROMIS-Depression			x		x	x
PROMIS-Positive Affect			x		x	x
PROMIS – Meaning and Purpose Scale			x		x	x
Life Fulfillment Scale			x		x	x
Profile of Mood States			x		x	x
Real World Activity Monitoring			x		x	x
Treatment Evaluation Inventory - Short Form			x		x	
Patient Global Impression of Change					x	x

*assessed at the first visit of each week

Note: Prescreening, Visit 0 screening, Visit 1 baseline, and Visit 2 first intervention can all occur on the same day.

6.1.1 Time between visits

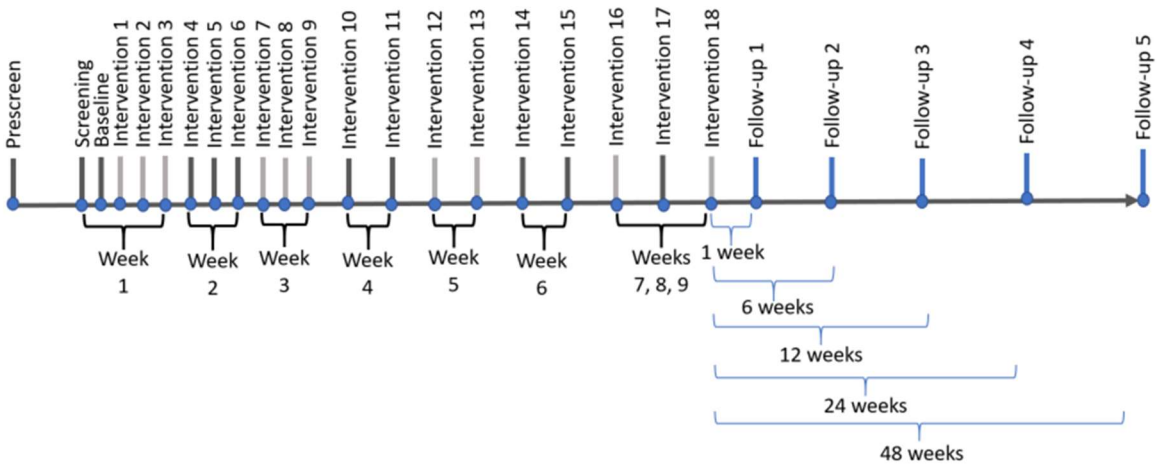
- Prescreening to Screening is ≤ 30-days

- Screening to Baseline V1 is ≤ 7-days
- Baseline V1 to Intervention V2 is ≤ 7-days
- Intervention W1 V2 (T1), V3(T2), V4(T3) are 2-3-days apart (encompassing ≤ 7-days)
- Intervention W2 V5 (T4), V6 (T5), V7 (T6) are 2-3-days apart (encompassing ≤ 7-days)
- Intervention W3 V8 (T7), V9 (T8), V10 (T9) are 2-3-days apart (encompassing ≤ 7-days)
- Intervention W4 V11 (T10), V12 (T11) are 2-6-days apart (encompassing ≤ 7-days)
- Intervention W5 V13 (T12), V14 (T13) are 2-6-days apart (encompassing ≤ 7-days)
- Intervention W6 V15 (T14), V16 (T15) are 2-6-days apart (encompassing ≤ 7-days)
- Intervention W7 V17 (T16) is 6-10-days after previous Intervention V16
- Intervention W8 V18 (T17) is 6-10-days after previous Intervention V17
- Intervention W9 V19 (T18) is 6-10-days after previous Intervention V18
- Final Intervention V19 to First Post-Intervention Assessments V20 7-days +/- 3-days
- Final Intervention V19 to Post-Intervention Assessment V21 is 6-weeks +/- 1-week
- Final Intervention V19 to Post-Intervention Assessment V22 is 12-weeks +/- 1-week
- Final Intervention V19 to Post-Intervention Assessment V23 is 24-weeks +/- 1-week
- Final Intervention V19 to Post-Intervention Assessment V24 is 48-weeks +/- 1-week

6.1.2 Time between treatment weeks

- Intervention V4 to V5, V7 to V8 are 2-3-days apart
- Intervention V10 to V11, V12 to V13, V14 to V15 are 2-6-days apart
- Intervention V16-V17 is 6-10-days apart

Note: To allow for flexibility in participant scheduling due to events that may conflict with scheduled visits (e.g., acute illness), the total length of the intervention period (i.e., V2 T1 through V19 T18) can be extended by up to 30 days.



6.2 Description of Evaluations

Numeric Pain Rating Scales - Right now, 7-day & 24-hour: To assess pain, separate ratings of back pain intensity "right now", over the preceding 24 hours, and over the preceding 7 days will be measured using an 11-point numerical rating scale (NRS) with anchors of 0 (No pain) and 10 (Pain as bad as you can imagine). This scale will quantify the study candidates rating of their low back pain symptoms.

Roland-Morris Disability Questionnaire: To assess physical functioning will be using the Roland-Morris Disability Questionnaire (RMDQ).[50,51] The RMDQ includes 24 yes/no items that are designed to assess physical disability related to CLBP. This form quantifies the self-report level of disability.

Fear Question: Candidates will be screened for participation in the pre-screening and the full screening by indicating whether or not they agree with the statement "It is not really safe for a person with my back problem to be physically active." An affirmative response will indicate a fear of movement.

Medical History – Back Pain: This form documents the candidate's history of back pain.

Medication Log: To assess pain, participants will be asked to report current frequency and dosage of medications used for back pain. Additionally, all medication use will be documented in this form.

Informed Consent Form: Subjects must provide written informed consent prior to beginning the screening process and prior to implementation of any study procedures.

Inclusion/Exclusion Criteria: This form will document whether the study candidate meets all of the inclusion and exclusion criteria.

Enrollment/Randomization: This form will note the enrollment and randomization dates.

Medical History: To monitor safety, participants will complete a brief health screening at the beginning of each game session to determine if there are any changes in back pain or radiating symptoms.

Physical Exam Form: This form documents the study candidate's physical exam

findings.

Adverse Events: A structured safety monitoring system will be established to both assure real-time participant care and unbiased monitoring of adverse events (AE). For ongoing participant safety, events will be assessed by the PIs and co-investigators to determine if they are Serious, Unexpected, and/or On-site. If so, an event evaluation form will be completed that will include a description of the event, a classification of seriousness, assessment of potential relationship to the intervention, assessment of need for change in the consent or the study activities, a summary of known prior health issues, event outcome, and a classification of the main organ system involved.

Standardized Reaching Paradigm (Pain & Harm Expectancy, Lumbar Spine Flexion):

Lumbar Spine Flexion: Movement of light-reflective marker clusters attached to the head, upper arms, forearms, hands, trunk, pelvis, thighs, shanks, and feet will be measured and recorded using a 10-camera Vicon Bonita system. This optoelectric-based kinematic system can track the three-dimensional coordinates of light reflective marker clusters attached to the participant with a spatial resolution of 0.1 mm. Kinematic data will be sampled at 100Hz. Participants point with their hand to 4 virtual targets co-located in the mid-sagittal plane. Location of the targets are adjusted to the individual as illustrated in **Fig.** 3**.** This method: 1) allows for comparison of movement patterns across individuals, 2) challenges participants with tasks that require progressively more lumbar spine flexion, and 3) is sensitive to changes in LBP patients.[16, 18, 34, 35, 45] Participants will perform five reaching trials to each virtual target location with each hand, pause at the target for 2 seconds, and then return to an upright posture. These tasks will be repeated 1-, 6-, 12-, 24-, and 48-weeks post-treatment. Instructions will emphasize that participants should reach for the targets as fast as possible in a way that is “natural and comfortable for them” so as not to bias participants with a perceived correct way to move. Moreover, performing the reaching tasks at a rapid pace challenges the participant by increasing the loading required to perform the tasks. While forward excursions of the trunk must be counterbalanced by backward movement of the lower extremities, the targets are located such that they do not require an individual to move anywhere near

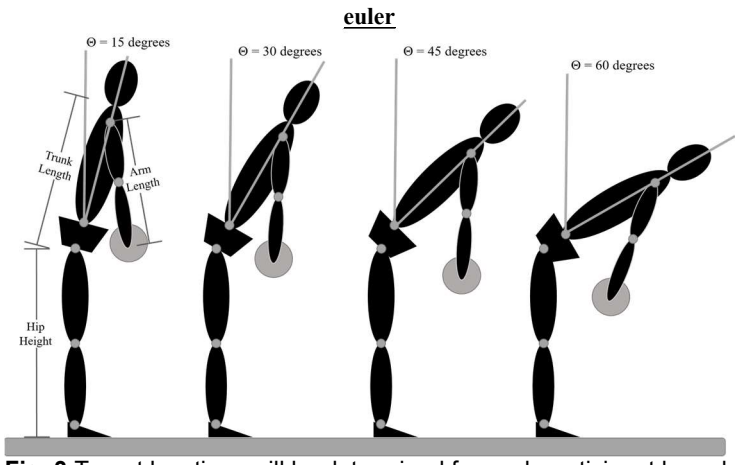


Fig. 3 Target locations will be determined for each participant based on their hip height, trunk length, and arm length. The high target is located such that the subject could, in theory, reach the target by flexing the hips 15° with the shoulder flexed 90° and the elbow extended. The middle and low targets could be reached by flexing the hips 30° and 60°, respectively. NOTE: Target locations are determined mathematically (i.e., participants are not actually placed in the positions illustrated).

the limits of available range of motion of the lumbar spine, pelvis, knee, and ankle in this paradigm. Thus, participants can reach these targets using an infinite combination of joint excursions. Even though the reaching task requires no lifting and the loads on the lumbar spine are small, we have shown that individuals with elevated levels of kinesiophobia exhibit reduced lumbar spine flexion at this combination of target height and reaching speed.[16, 18, 34, 35, 45] The time series joint angle data are calculated from the 3-D segment coordinate data using an Euler angle sequence of: 1) flexion-extension, 2) lateral bending, and 3) axial rotation[52] using Motion Monitor software. This is defined as the change in joint angle (i.e., the difference between the joint angles at the beginning of the trial before the go signal and those extracted 100 ms after target contact). The standardized reaching paradigm will be used to assess lumbar flexion and expectations of pain and harm at pre-treatment baseline and will be repeated at 1-, 6-, 12-, 24- and 48-weeks after the last treatment session.

Pain & Harm Expectancy: Consistent with our prior work,[20, 46, 47, 53] expectations of pain and harm will be measured during standardized reaches performed at pre-treatment baseline, the first visit of each week of interventions, and post-treatment. Specifically, for each target height, prior to the first reaching trial, participants will be asked to rate the level of "expected pain" and "expected harm" using a visual analog scale displayed through the head mounted display (e.g., HTC Vive). The scale will consist of a 10 cm horizontal line with no numbers, marks, or descriptive vocabulary along its length. For expected pain ratings, the scale will be anchored with the descriptors "No pain" and "Worst pain imaginable", respectively, at each end of the line. For expected harm, the scale will be anchored with "Not at all concerned" and "Extremely concerned" regarding potential harm to the back during task performance. Participants will indicate their response by moving a virtual sliding scale. Expectations of pain/harm will be used as dependent variables in Aim 2.

Tampa Scale for Kinesiophobia: This is used to assess candidate's level of fear of movement due to perceived risk for back injury or re-injury. It is one of two pain vulnerability measures assessed in the study and is included among our additional analyses.

Center for Epidemiologic Studies – Depression: We will administer the Center for Epidemiological Studies-Depression (CES-D) scale [54] to assess symptoms of depression that often accompany chronic pain. The CES-D is included among our additional analyses as a measure of emotional functioning.

Pain Catastrophizing Scale: This survey is used to identify characteristics of rumination, magnification, and helplessness in the face of ongoing or intense pain. It is one of two pain vulnerability measures assessed in the study and is included among our additional analyses.

Pain Resilience Scale: This survey is used to measure behavioral perseverance as well as cognitive and affective positivity in the face of intense or prolonged pain. It is one of two pain resilience measures assessed in the study and is included among our additional analyses.

Pain Self Efficacy Questionnaire: This survey is used to measure the respondent's confidence in their ability to carry out daily and enjoy daily activities despite pain. It is

one of two pain resilience measures assessed in the study and is included among our additional analyses.

Brief Pain Inventory – Short Form: We will use the Brief Pain Inventory[55] pain interference subscale as one of two measures to assess physical functioning. The pain interference subscale includes 7 items that assess the degree to which back pain has interfered with general activity, mood, walking, work, relations with others, sleep, and enjoyment of life.

PROMIS-Anxiety: We will administer the PROMIS[56] Anxiety scale as a measure of psychological distress that may accompany chronic pain, particularly among those with low back pain and fear of movement. The PROMIS-Anxiety scale is included among our additional analyses as a measure of emotional functioning.

PROMIS-Depression: We will administer the PROMIS Depression scale as a measure of negative affect that often accompanies chronic pain. The PROMIS Depression scale is included among our additional analyses as a measure of emotional functioning.

PROMIS-Positive Affect: We will administer the PROMIS Positive Affect scale as a measure of positive affect that may be reduced in chronic pain, and possibly enhanced by successful intervention. The PROMIS Positive Affect scale is included among our additional analyses as a measure of emotional functioning.

PROMIS-Meaning and Purpose: We will administer the PROMIS Meaning and Purpose[57] scale as a measure of positive engagement in daily living, which may be impaired in chronic pain and possibly enhanced by successful intervention. The PROMIS Meaning and Purpose is included among our additional analyses as a measure of emotional functioning.

Life Fulfillment Scale: This Life Fulfillment Scale[58] will be administered as a measure of positive cognitive and emotional adaptation, and is included among our additional analyses of emotional functioning.

Profile of Mood States: The Profile of Mood States questionnaire will be administered to assess positive and negative affective states. The Profile of Mood States is included among our additional analyses as a measure of emotional functioning.

Real World Activity Monitoring: Following pre-treatment baseline and each of the post-treatment assessments, the participant will be given an activity monitor to wear on the non-dominant wrist for 1-week and returned to the laboratory by pre-paid postage. The total number of steps/day will be the primary dependent variable to determine the effects virtual dodgeball on activity levels measured in a natural environment (Aim 3). We will also examine ancillary outcomes of physical activity intensity by examining step cadence and using standard thresholds to aggregate data into sedentary, light, moderate, and vigorous activity.[59]

Treatment Evaluation Inventory – Short Form: To assess participant acceptance of the intervention, we will administer a modified version of the Treatment Evaluation Inventory, Short Form[60] at Visit 1 and again at Visit 20 (i.e., 1-week follow-up).

Patient Global Impression of Change: This scale is used to quantify a participant's perception of their level of positive, negative, or no change as a function of participating in the intervention. It will be included among our additional analyses.

6.2.1 Screening Evaluation

Consenting Procedure

The consent process will be conducted in a quiet, private room. During the consent process, potential participants will be informed about the study purpose and procedures and be given the opportunity to ask questions. They will be shown a video of the game to help them with the process. If they wish to continue, they will be asked to read and sign a single informed consent document. Next, a member of the research team will review the signed consent form and will ask the participant to explain the procedures in their own words to ensure that they comprehend the study procedures before proceeding to the initial assessment. Informed consent must be obtained before participants are screened. A copy of the signed and dated consent form will be given to participants, and the original document will be electronically stored on a secure server.

Pre-Screening

The purpose of pre-screening is to determine if the research candidates will qualify for the research. This web-based survey will take approximately 15-minutes to complete and includes the following forms:

- Numeric Pain Rating Scales 7-day & 24-hour
- Roland-Morris Disability Questionnaire
- Fear Question
- Medical History – Back Pain

Screening (Visit 0)

The purpose of the screening visit is to 1) describe the study protocol to candidates and begin the informed consent process, and 2) determine if study candidates will qualify for the study. The screening visit will take approximately two hours. During the screening visit the study coordinator will complete, in cooperation with the study candidate, the following:

- Numeric Pain Rating Scales 7-day & 24-hour
- Roland-Morris Disability Questionnaire
- Fear Question
- Medical History – Back Pain
- Medication Log
- Quebec Task Force Classification
- Informed Consent Form
- Inclusion/Exclusion Criteria Form
- Enrollment & Randomization Form
- Medical History
- Physical Exam

Re-screening participants may be considered and reviewed by the PIs on a case-by-case basis. Screening must occur within 30-days of prescreen completion. Visits 1 and 2 (Baseline and Intervention 1) may occur on the same day as screening and must occur within 7 days of screening. If these deadlines are not met the participants will be assigned a new PID, re-screened, and re-consented.

6.2.2 Enrollment, Baseline, and/or Randomization (Visit 1)

Enrollment

A single informed consent form that describes both screening and study procedures will be used. The date of enrollment in The VIGOR Study will be defined as the date all of the screening criteria are met and the individual agrees to participate. The enrollment date will be recorded on a case report form along with the allowable window between screening and randomization.

- CRF: Randomization and Enrollment Form

Baseline Assessments

Participants enrolled in the study will complete the following baseline assessments at Visit 1:

- Numeric Pain Rating Scales 7-day & 24-hour
- Roland-Morris Disability Questionnaire
- Medication Log
- Adverse Events Log
- Numeric Pain Rating Scale – Right Now
- Standardized Reaching Paradigm (Pain & Harm Expectancy, Lumbar Spine Flexion)
- Tampa Scale for Kinesiophobia
- Center for Epidemiologic Studies – Depression
- Pain Catastrophizing Scale
- Pain Resilience Scale
- Pain Self Efficacy Questionnaire
- Brief Pain Inventory – Short Form
- PROMIS-Anxiety
- PROMIS-Depression
- PROMIS-Positive Affect
- PROMIS-Meaning and Purpose Scale
- Life Fulfillment Scale
- Profile of Mood States
- Real World Activity Monitoring
- Treatment Evaluation Inventory – Short Form

Randomization

The study coordinator will use a sex-stratified random allocation table, created by the study statistician, to assign participants to a treatment group. A maximum of 7-days will be permitted between enrollment and randomization or initiation of the study intervention.

6.2.3 Blinding

The principal investigators, the statistician, and members of the data collection team will remain blinded to intervention assignment throughout the duration of the study. They will be given the identifying codes only at the end of the study when it is necessary to interpret the results. The un-blinded study coordinator, who is responsible for scheduling testing and treatment sessions, will greet participants and

escort them to the testing lab; however, the study coordinator will not participate in the assessments of clinical outcomes or testing.

6.2.4 Follow-up Visits

Treatment visit assessments for each visit 2-19 include the following:

- Numeric Pain Rating Scales 7-day & 24-hour
- Medication Log
- Adverse Events Log
- Numeric Pain Rating Scale – Right Now
- Standardized Reaching Paradigm (Pain & Harm Expectancy, Lumbar Spine Flexion)

Assessments at first post-treatment follow-up visit, Visit 20, include:

- Numeric Pain Rating Scales 7-day & 24-hour
- Roland-Morris Disability Questionnaire
- Medication Log
- Adverse Events Log
- Numeric Pain Rating Scale – Right Now
- Standardized Reaching Paradigm (Pain & Harm Expectancy, Lumbar Spine Flexion)
- Tampa Scale for Kinesiophobia
- Center for Epidemiologic Studies – Depression
- Pain Catastrophizing Scale
- Pain Resilience Scale
- Pain Self Efficacy Questionnaire
- Brief Pain Inventory – Short Form
- PROMIS-Anxiety
- PROMIS-Depression
- PROMIS-Positive Affect
- PROMIS-Meaning and Purpose Scale
- Life Fulfillment Scale
- Profile of Mood States
- Real World Activity Monitoring
- Treatment Evaluation Inventory – Short Form
- Patient Global Impression of Change

Assessments at post-treatment follow-up visits 21-24 include:

- Numeric Pain Rating Scales 7-day & 24-hour
- Roland-Morris Disability Questionnaire
- Medication Log
- Adverse Events Log
- Numeric Pain Rating Scale – Right Now
- Standardized Reaching Paradigm (Pain & Harm Expectancy, Lumbar Spine Flexion)
- Tampa Scale for Kinesiophobia
- Center for Epidemiologic Studies – Depression
- Pain Catastrophizing Scale
- Pain Resilience Scale

- Pain Self Efficacy Questionnaire
- Brief Pain Inventory – Short Form
- PROMIS-Anxiety
- PROMIS-Depression
- PROMIS-Positive Affect
- PROMIS-Meaning and Purpose Scale
- Life Fulfillment Scale
- Profile of Mood States
- Real World Activity Monitoring
- Treatment Evaluation Inventory – Short Form

6.2.5 Completion/Final Evaluation

Assessments to be performed at the participant's final visit include:

- Numeric Pain Rating Scales 7-day & 24-hour
- Roland-Morris Disability Questionnaire
- Medication Log
- Adverse Events Log
- Numeric Pain Rating Scale – Right Now
- Standardized Reaching Paradigm (Pain & Harm Expectancy, Lumbar Spine Flexion)
- Tampa Scale for Kinesiophobia
- Center for Epidemiologic Studies – Depression
- Pain Catastrophizing Scale
- Pain Resilience Scale
- Pain Self Efficacy Questionnaire
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- PROMIS-Anxiety
- PROMIS-Depression
- PROMIS-Positive Affect
- PROMIS-Meaning and Purpose Scale
- Life Fulfillment Scale
- Profile of Mood States
- Real World Activity Monitoring
- Patient Global Impression of Change

All assessments will be performed for participants who discontinue study intervention early.

6.2.6 Reasons for Early Termination

A subject would be discontinued from the study intervention if a medical condition develops that precludes the continuation of the treatment intervention. For participants who discontinue The VIGOR Study prior to completing all scheduled treatment sessions (regardless of the reason), we will make every attempt to obtain the outcome measurements. If the study participant is unwilling or unable to undergo the laboratory-based tests (e.g., difficulty tolerating the protocol, experienced an adverse event to a lab test) we will still attempt to obtain the clinical outcome

measures. In instances where an adverse event does occur, we will follow-up with participants until the event is resolved or until the IRB deems it unnecessary to continue to follow the participant.

If the participant complains of any sudden onset of muscle or joint pain, the current session will be terminated, and the Principal Investigator will be contacted to complete an assessment. If he is unavailable, one of the other clinicians on the study team will be contacted to provide a clinical assessment of the participant. They will then consult with the PI to assess if the participant should continue to stay on protocol. If an exclusion criterion is identified from the presenting signs and symptoms, the participant will then be withdrawn from the study. If the presenting signs and symptoms do not meet the exclusion criteria, the participant will be invited to return for their next scheduled visit when the sudden onset of symptoms has abated. Upon return, the PI or a clinician on the study team will again assess the participant and make a clinical judgement about their fitness to continue with the intervention. However, if the participant has a second episode of sudden onset of joint or muscle pain, they will be immediately withdrawn from the study.

7. SAFETY ASSESSMENTS

Threats to Individual Privacy and Data Confidentiality: To minimize risk to participant privacy, all study procedures are conducted in private testing rooms by qualified study personnel and the collection of sensitive information is limited to the minimum necessary to conduct the necessary screening and testing. To minimize risk to participant confidentiality, we will use secure web-based applications (i.e., REDCap) to collect and manage participant information and all data will be stored with unique identification codes such that no personal identifying information will be available in the study files. All data collection forms are electronic Case Report Forms (eCRF). As source documents, all forms are signed or electronically verified and dated by a study staff member. In case of interruption of internet connectivity during data collection, participants will complete a paper version of the eCRF and the Study Coordinator or Research Assistant will transfer all data from the paper forms to the database. Every 2-weeks a Research Assistant will perform a quality assurance check by comparing data entered into the database from paper-based forms. All paper data collection forms will be kept in locked file cabinets located in locked testing rooms.

Voluntary Reaching Task: Bending of the trunk could possibly aggravate current low back pain symptoms; however, these reaching tasks have been chosen because they mimic everyday activities and are within the available range of motion of individuals with low back pain. The reaching tasks minimize potential risks to the participant in that they do not require any lifting; thus, spine loads are minimal. Risk is further minimized because we inform all participants that they are free to stop at any time if they find the procedure too uncomfortable. We have been conducting this reaching protocol with back pain participants for more than a decade and we have never had any incidents of injury or sustained aggravation of back pain symptoms.

Virtual Reality Game Play: Consistent with our Phase I trial, prior to testing participants will be fully informed of the game procedures, including information on the available rewards for performance. The movements required during video game play will be very similar to those required to perform the reaching tasks and will be within the available range of motion of individuals with low back pain. The game play

minimizes potential risks to the participant in that they do not require any lifting; thus, spine loads are minimal. We further minimize risk by informing the participants that they are free to stop at any time if they find the procedure too uncomfortable. Finally, each session will begin with the participant starting with the most basic movement task to encourage success and to allow for the adaption of movement patterns while reducing the risk of exacerbating back pain symptoms.

Some participants could feel nauseated from being in the virtual reality environment, but this is minimized by having precise synchronization of motion of the headset and the graphics presented to the participant. Care is also taken to avoid rapid changes in the visual scenes that can induce motion sickness. Finally, we are pre-screening our applicants to ensure they are not highly susceptible to motion sickness.

There is a risk of falling as vision of the real world is fully occluded by the virtual reality headset. Risk of falling is minimized by having the participant first stand in the testing area and then put on the headset. None of the virtual reality activities require steps to be taken; in fact, we will instruct participants to move their feet as little as possible. Further, the headset will be removed while the participant is still in the testing environment; hence, at no time will participants be ambulatory while their real world vision is obstructed. Additionally, the testing area is an open space with a level surface, minimizing the risk of injury if a participant should fall. Two research staff members will conduct every appointment which allows one to run the software and the other to monitor the study subject.

In keeping with Virginia Commonwealth University Institutional Review Board and US Department of Health and Human Services, Office for Human Research Protections requirements, all study personnel who interact with participants or have access to research data will maintain valid certification of training in the protection of human research participants.

7.1 Specification of Safety Parameters

At each visit the study staff will use the Adverse Event Log to ask the study participants if they have had any change in general health since the last visit. If fever or unexplained weight loss is reported, suggesting systemic infection / disease may be causing their low back pain, the clinician will do a basic physical exam and specifically assess for the possibility they have other systemic illness. They will be advised to seek medical care and research participation may be delayed, temporarily discontinued, or permanently suspended at the discretion of the examining clinician and in consultation with the Medical Directors if needed.

Before each treatment the study staff will use the Contraindications Form to inquire about change in back related signs indicative of increased severity of symptoms. Specifically if they have any new symptoms such as weakness, numbness, or difficulty walking. If the study participant reports yes on any of these items the clinician will do a basic physical exam and assess neurological function by checking myotomes, dermatomes, and reflexes to determine whether the study participant now presents with hard neurological signs (e.g., loss of motor function, significant changes in reflexes), or symptoms of other systemic disease. If the participant does present with hard neurological signs or serious systemic disease, they will be encouraged to seek consultation with their personal physician, and they will be excluded from further participation from the study.

All negative changes in health status other than back pain will be recorded as

Adverse Events, logged, and reported per requirements of the Virginia Commonwealth University IRB and NIH. In the case of dismissal from the protocol for the above stated reasons, the Medical Safety Committee will meet to determine whether the AE was caused by the intervention (Definite, Probable, Possible, Unknown) and an adverse event report will be filed according to the specific requirements of the Virginia Commonwealth University IRB and NIH.

Adverse events will be entered directly into RedCap™, an electronic data management system and assessed twice monthly by the unmasked study coordinator using Tables 4, 5, and 6 located in Appendix A. Adverse events will be recorded and these will be monitored at each study visit to be entered by the RAs. The study coordinator will routinely assess recruitment, participant status, upcoming visits, and outstanding assessments. All Adverse Events will be assessed, classified, and reported according to Appendix A.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

All Adverse Events will be reported to the Study Coordinator who will complete an Adverse Event Form and collaborate with study staff involved in the AE. If applicable, the Medical Director will review the AE and determine the Common Terminology Criteria for Adverse Events (CTCAE) scale. The Study Coordinator then compiles masked AE reports for the PIs to review. Twice monthly, adverse events and serious adverse events will be assessed by the unblinded study coordinator. Potential unanticipated side effects of the interventions will be monitored at each study visit and entered by a research assistant into the database. A tracking report will be developed as part of the database to allow the coordinator to assess recruitment, participant status, upcoming visits, and outstanding assessments. Annually, an AE summary report will be generated and provided to the Independent Monitors for review and forwarded to the NICHD. At each periodic review, AEs will be reported to the IRB.

All adverse events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation will be recorded. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.3 Adverse Events and Serious Adverse Events

Adverse events: A structured safety monitoring system will be established to both assure real-time participant care and unbiased monitoring of adverse events (AE). For ongoing participant safety, events will be assessed by the PIs and co-investigators to determine if they are Serious, Unexpected, and/or On-site. If so, an event evaluation form will be completed that will include a description of the event, a classification of seriousness, assessment of potential relationship to the intervention, assessment of need for change in the consent or the study activities, a summary of known prior health issues, event outcome, and a classification of the main organ system involved. (See Protection of Humans Subjects for definitions of adverse events).

Adverse Events include any reaction, side effect, or other untoward medical event, regardless of the relationship to the study intervention. For ongoing participant

safety, any adverse events will be characterized within 24 hours by the study team to determine if it was Non-series/Serious, Unexpected/Expected, and Off-site/On-site.

Non-serious adverse events will be defined as conditions that may be unpleasant and bothersome to the participant (e.g., mild nausea) that do not require discontinuing the study intervention or components of the intervention. All adverse events will be documented for review by the Independent Monitoring Committee (IMC) and reported to the IRB. Serious events includes any event that is 1) life threatening, 2) may result in prolonged, permanent, or severe disability, 3) may worsen a pre-existing condition, or 4) requires inpatient hospitalization or surgical procedure, or a treatment to prevent a serious event. All serious adverse events will require immediate notification of a Physician, 24 hour notification of the IRB, and an assessment of the implications for the continuation of the study and/or modification of the consent form.

Unexpected adverse events are defined as events that are not listed in the consent form. Monitoring for unexpected serious adverse events attributable to the intervention is the responsibility of the investigators. Specific reporting and review requirements are defined for unexpected events, so that, if an unexpected event is found to be related to the intervention, the protocol and consent can be modified.

We will utilize the NCI Common Terminology Criteria for adverse Events which are a descriptive terminology that can be utilized for Adverse Event (AE) reporting and provides a grading (severity) scale for each AE. AEs will be labeled according to severity, which is based on their impact on the patient.

Attribution: An assessment of the relationship between the AE and the intervention will be performed using the NCI guidelines which do not define an AE as necessarily “caused by a therapeutic intervention”, after naming and grading the event, the clinical investigator will assign an attribution to the AE as unrelated, unlikely, possible, probable, or definite.

Note that back pain is not considered an adverse event within this research.

7.4 Reporting Procedures

The site staff must immediately report to the coordinating center PI any serious adverse event, whether or not considered study related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study caused the event within 48 hours of PI awareness of the event.

They must also report any unanticipated problems within the same timeframe. The Site staff must also report any protocol deviations or violations to the coordinating center PI within 7 days of awareness. Participating centers must also submit all reports to their local IRB in accordance with their institutional policies.

SAEs that are unanticipated, serious (Grade 3), and possibly related to the study intervention will be reported to the Independent Monitors, IRB, and NICHD in accordance with requirements.

Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NICHD Program Officer and Independent Monitoring Committee within 2 days and to the IRB within 1 day. Other serious and unexpected AEs related to the intervention will be reported to the NICHD Program Official within 7 days.

Other anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Monitor(s), IRB, NICHD, and other oversight organizations in accordance with their requirements. In the annual AE summary, the Independent Monitor(s) Report will state that they have reviewed all AE reports.

7.5 Follow-up for Adverse Events

In instances where an adverse event does occur, we will follow-up with participants until the event is resolved or until the IRB deems it unnecessary to continue to follow the participant.

7.6 Safety Monitoring

We have developed a Data Safety and Monitoring Plan which oversees the progress of the proposed study and establishes Independent Monitoring Committee (IMC). Membership in the IMC will be determined in collaboration with the NICHD program officer and the principal investigators and will include individuals that have expertise in chronic low back pain, biomechanics, clinical trials, and biostatistics.

The goals of the Data and Safety Monitoring Plan include 1) evaluation of the progress of the study, including periodic assessments of participant recruitment, accrual, retention, and timeliness; participant risk versus benefit; and other factors that can affect study outcome, and 2) consideration of factors external to the study, such as scientific developments that may have an impact on the safety of participants or the ethics of the study. A structured safety monitoring system will be established to both assure real-time participant care and unbiased monitoring of Adverse Events (AE).

The IMC will be scheduled to meet annually to conduct safety reviews. These meetings will cover all aspects of study progress, including participant recruitment, accrual, and retention; a review of data collection forms for assurance of data quality and timeliness; consideration of participant risk versus benefit; and other factors that can affect study outcome including a review of incidents of protocol deviation and actions taken in response to such deviations. In addition, these meetings will address any factors external to the study (e.g., recent scientific developments) that may have an impact on the safety of participants or the ethics of the study.

In addition to scheduled annual meetings, the IMC will also be consulted on an as-needed basis in the case of unanticipated serious adverse events or otherwise difficult situations that may arise. In such cases IMC members will discuss and implement the appropriate course of action to remedy any critical incident that may occur during the course of the study. A journal will also be maintained during the project to record the nature of any such critical incident, personnel involved, solutions considered, and the final action implemented to resolve the incident. Reporting of such critical incidents will be made to the Virginia Commonwealth University IRB as well as the NICHD. The IMC will also have responsibility to make recommendations to NICHD, the IRB, and the PIs concerning continuation or conclusion of the study, or possible modification of the ongoing protocol.

8. INTERVENTION DISCONTINUATION

A subject would be discontinued from the study intervention if a medical condition develops that precludes the continuation of the treatment intervention. For participants who discontinue The VIGOR Study prior to completing all scheduled treatment sessions (regardless of the reason), we will make every attempt to obtain

the outcome measurements. If the study participant is unwilling or unable to undergo the laboratory-based tests (e.g., difficulty tolerating the protocol, experienced an adverse event to a lab test) we will still attempt to obtain the clinical outcome measures. In instances where an adverse event does occur, we will follow-up with participants until the event is resolved or until the IRB deems it unnecessary to continue to follow the participant.

9. STATISTICAL CONSIDERATIONS

The co-primary clinical outcomes are changes in pain and disability. We will examine immediate clinical outcomes as a function of treatment. Relative to the control group, participants in the experimental group will show greater reductions in pain and disability at post-treatment relative to pre-treatment baseline (Hypothesis 1). To test Hypothesis 1, we will examine the Treatment by Time (baseline-post treatment) interaction in a LME model: a greater reduction in pain and disability in the experimental group than in the control group. The co-primary clinical outcomes of changes in pain and disability will be assessed at 1-, 6-, 12-, 24-, and 48-weeks post-treatment.

Secondary objectives are to examine potential mechanisms of pre- to post-treatment changes in clinical outcomes and maintenance of treatment gains. Participants in the experimental group will exhibit greater pre- to post-treatment decreases in pain/harm expectancy and increases in lumbar flexion as compared to the control group (Hypothesis 2.1). Decreases in pain/harm expectancy and increases in lumbar flexion will be positively related to pre- to post-treatment reductions in pain and disability (Hypothesis 2.2). Examination of maintenance of treatment gains will occur at 1-, 6-, 12-, 24-, and 48-weeks post-treatment. Relative to the control group, participants in the experimental group will continue to show lower levels of pain and disability at each time point as well as increased activity in their natural environment (Hypothesis 3).

This project is a Phase II RCT in which CLBP participants will be randomly assigned to one of two intervention arms. Those assigned to the experimental group will play immersive games that will encourage progressively larger lumbar flexion excursions at each game level and across treatment sessions. Those in the control group will play the same immersive games, but the parameters of the game will require smaller excursions of lumbar flexion to successfully complete gameplay. Treatment frequency and duration is based on existing evidence that graded activity and graded exposure interventions, typically lasting 6-12 weeks with 8-18 treatments sessions, result in significant reductions in disability.[44],[43] Accordingly, participants in this study will complete 18 visits over 9 weeks with the number of sessions tapered across weeks (i.e., 3 sessions/week in weeks 1-3, 2 sessions/week in weeks 4-6, and 1 session/week in weeks 7-9). Our co-primary outcome variables will be change in pain and change in disability from baseline to 1-week post-treatment (Aim 1). We will also examine changes in expectations of pain/harm and lumbar flexion as potential mechanisms of change in pain and disability (Aim 2). Aim 3 will examine maintenance of treatment gains at 1-, 6-, 12-, 24-, and 48-weeks post-treatment.

9.2 Sample Size and Randomization

We will recruit 230 participants with chronic low back pain (CLBP) and fear of movement. We will include participants with CLBP between the ages of 18-60 and who report no health condition(s) that may restrict movement or preclude safe participation. Participants will be recruited from the general population and specific

organizations such as Virginia Commonwealth University's University Medical Associates.

Aim 1: Power analyses were conducted to determine the sample size needed to achieve clinically important differences in our co-primary clinical outcome measures of pain and disability. Based on the extant literature, we based our analyses on a ≥ 30% decrease in pain ratings[1] (on the 0-10 NRS scale) and a 30% decrease in disability ratings on the RMDQ[2] in the experimental group. Further, we predict a 10% decrease in pain and disability in the control group to account for potential placebo effects. The population standard deviations were set at 75% of the population mean values. The pre-post correlation was estimated as r=0.7. These population parameters translate into an effect size of f=0.30. Using these parameters, we drew 10,000 samples from a normal population distribution. Based on these parameters, to achieve power of 80% and α=0.05 will require a total N=78.

Aim 2 & 3: Power analyses were conducted to determine the sample size needed to address hypotheses 2.1, 2.2, and 3. Using the method described by Morris (2008),[3] we calculated effect size estimates from randomized clinical trials on the effects of graded activity or graded exposure interventions on changes in disability among individuals with CLBP.[4-7] For our power analyses, we adopted the median estimated effect size: $\delta = .45$, which corresponds to what would commonly be described as a medium effect size. Following Raudenbush and Liu's (2000) recommendation,[8] we set the residual error variance to 1 and estimated the between-subject slope variance to be 0.30. For power equal to .80 and α=0.05, a sample size of 209 participants was indicated.

Based on the sample size calculations, using a sex-stratified random allocation table, we need a minimum sample of 209 participants to address Aims 1-3. To allow for 10% attrition from baseline to 48-week follow-up, we will recruit 230 participants.

Treatment Assignment Procedures

Randomization & Stratification: The study statistician will use the R statistical language to block randomize treatments stratified by sex. Then the study coordinator will assign subjects to the treatment arms.

Masking or Blinding: The principal investigators, the statistician, and members of the data collection team will remain blinded to intervention assignment throughout the duration of the study. They will be given the identifying codes only at the end of the study when it is necessary to interpret the results. The un-blinded study coordinator, who is responsible for scheduling testing and treatment sessions, will serve to receive the study patients and escort them to the various testing and treatments sites to minimize the interaction between patients; however, the study coordinator will not participate in the assessments.

9.3 Definition of Populations

Intention to Treat Analysis (ITT): We will include all randomized study participants who have at least baseline endpoint assessments in our ITT analysis. The ITT analysis is our primary method for assessing outcomes, and how it is performed will be determined based on the pattern of missingness. If the missingness is deemed MCAR, the LOCF method will be used: simply the most recent valid observation will be "carried forward" to replace the subsequent missing observations. If the missingness is deemed MAR, missing observations will remain as missing, and

maximum likelihood estimation, the default estimation algorithm of LMER, will be used to estimate these observations. If the missingness is found to be MNAR, multiple-imputed data will be used to construct LMER models.

Per-Protocol Analysis (PPA): For the PPA we will exclude study participants who: 1) fail to attend 13 out of 18 treatment sessions; 2) develop an exclusionary medical condition while on study protocol, or 3) receive interventions outside of the Allowed (Section 5.3.1) during treatment. Finally, we will assess how comparable estimated parameters vary between ITT and PPA analyses.

9.4 Interim Analyses and Stopping Rules

No interim analyses are planned as they relate to either the primary or secondary outcome data. An individual subject would be discontinued from the study intervention if a medical condition develops that precludes the continuation of the treatment intervention. Additionally, the study will be stopped if the IMC, in consultation with NICHD, decides that the risks associated with the treatment interventions (i.e., excessive SAEs) outweigh the potential benefits of the knowledge gained from continuing the study.

9.5 Outcomes

9.5.1 Primary Outcome

The co-primary clinical outcomes are pain and disability, which will be assessed at pre-treatment baseline (visit 1) and at 1-, 6-, 12-, 24-, and 48-weeks post-treatment (i.e., visits 20-24).

9.5.2 Secondary Outcomes

Secondary outcomes include expected pain, expected harm, and lumbar flexion during standardized reaching, which will be measured at pre-treatment baseline (visit 1), at the beginning of each week during treatment (visits 2, 5, 8, 11, 13, 15, 17, 18, 19), and at 1-, 6-, 12-, 24-, and 48-weeks post-treatment (i.e., visits 20-24).

9.6 Data Analyses

We will analyze all outcome variables (pain, disability, pain/harm expectancy, and lumbar flexion) using linear mixed-effects (LME) models with treatment (Experimental, Control) as a between-subject fixed effect and time (pre-treatment, 1, 6, 12, 24, and 48 weeks) as a within-subject fixed effect. Given the expected findings, both linear and quadratic time effects will be tested in every model. We will also include demographic covariates (e.g., age, BMI) and potential confounders (e.g., radiating versus non radiating pain) as well as sex stratification in the LME models. Any variables that differ at baseline will be included in the statistical models as potential confounders.

Intention-to-treat analyses are commonly conducted to analyze randomized clinical trial data in the presence of missing values. While various imputation strategies have been proposed to estimate missing data, such as last observation carried forward, use of LME models to analyze longitudinal data renders these strategies largely unnecessary. We will also conduct equivalent per-protocol analyses that will include only successfully adhered participants (i.e., attending $\geq$ 70% of gaming sessions).

Aim 1. Examine immediate clinical outcomes as a function of treatment. Relative to

the control group, participants in the experimental group will show greater reductions in pain and disability at post-treatment relative to pre-treatment baseline (Hypothesis 1).

To test Hypothesis 1, we will examine the Treatment by Time (baseline-post treatment) interaction in a LME model: a greater reduction in pain and disability in the experimental group than in the control group.

Aim 2. Examine potential mechanisms of pre- to post-treatment changes in clinical outcomes. Participants in the experimental group will exhibit greater pre- to post-treatment decreases in pain/harm expectancy and increases in lumbar flexion as compared to the control group (Hypothesis 2.1). Decreases in pain/harm expectancy and increases in lumbar flexion will be positively related to pre- to post-treatment reductions in pain and disability (Hypothesis 2.2).

Aim 3. Examine maintenance of treatment gains at 1-, 6-, 12-, 24-, and 48-weeks post-treatment. Relative to the control group, participants in the experimental group will continue to show lower levels of pain and disability at each time point as well as increased activity in their natural environment (Hypothesis 3).

To address aims 2 & 3 we will build and test linear mixed-effects models for each of the outcome variables. For hypotheses 2.1 and 3, pain, disability, pain/harm expectancy, and lumbar flexion will be the outcome variables, while time (linear and quadratic), treatment group, and the interactions of time and treatment group will be the primary predictor variables. For hypothesis 2.2, pain/harm expectancy and lumbar flexion will serve as the outcome variables, while time (linear and quadratic), treatment group, the time-by-group interactions, pain, and disability will be predictor variables. For hypothesis 3, planned comparisons will be conducted to compare the control and experimental groups at each time period for pain, disability, and activity levels in the natural environment. As noted above, covariates will be added to analyses as needed. The significance level for every omnibus test will be set to 0.05, while Holms procedure will be used to control familywise type-I error rate for post-tests at .05.

Checking Assumptions: Assumptions of LME models will be checked by conducting analyses of model residuals. Violations of normality will be addressed by transforming the data, while outliers or influential cases will be handled by conducting sensitivity analyses. In contrast to the standard repeated measures analyses of variance, with their rigid assumptions about the error covariance structure, LME models permit numerous alternative error covariance structures. This allows for modeling of data that exhibit both heteroscedasticity and autocorrelation, which is likely to characterize the data collected for this study.

Additional Analyses: We will use the same analytic framework to analyze additional measures of core outcome domains, including emotional functioning (e.g., CES-D, POMS-2, PROMIS measures), pain vulnerability (TSK, PCS), pain resilience (PRS, PSEQ), and patient global impression of change (PGIC).

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

All data collection forms are paper-based or electronic (eCRF) with the exception of

the prescreen survey which is always an online form, but can be completed by study staff as a source document during a phone interview. As source documents, all forms are signed or electronically verified and dated by a study staff member. Forms are identified with Participant Identification Numbers with no personal identifying information. The Study Coordinator or Research Assistant transfers all data from the paper forms to the database. Every 2-weeks a Research Assistant performs a quality assurance check by comparing paper-based forms to data entry in the database.

All paper data collection forms will be kept in a locked file cabinet in the Study Coordinator's office or the respective offices or laboratories of the PIs. Data will also be entered into an electronic database. The data management system has been developed by the Virginia Commonwealth University Office of Research and Sponsored Programs. Specifically, we will use REDCap™, a web application for building and managing online surveys and databases. Subjects will be identified by a unique identification number and no personal identifying information will be stored in the study database or used in any of the analyses files.

10.2 Data Management

This is a single site study and as such Virginia Commonwealth University will serve as the Coordinating Center and is responsible for all data management.

10.3 Quality Assurance

10.3.1 Training

Prior to data collection, the following will take place:

1. The Steering Committee will review and approve all protocols.

2. All study personnel will be trained in all study procedures for which they are responsible.

10.3.2 Quality Control Committee

This is a single site study and the Steering Committee will be responsible for overseeing quality control.

10.3.3 Metrics

The PIs will monitor treatment administration records on a monthly basis to determine whether study participants are receiving appropriate treatments as prescribed.

10.3.4 Protocol Deviations

A list of potential protocol deviations will be created and maintained for tracking by the Steering Committee. Each protocol violation report will include a description of the violation, the type of deviation that occurred, whether the date the deviation occurred, and whether the IRB was notified. The Steering Committee will review protocol deviations on an as needed basis to determine if subjects should continue in the study, the impact on the procedures, and the next steps for subject continuation. Examples of protocol violations include enrollment of an ineligible subject, randomization of an ineligible subject, failure to collect all screening tests, serious adverse events not reported in a timely fashion, breach of confidentiality, subject lost to follow-up, and visits outside of time window.

10.3.5 Monitoring

The Steering Committee will be responsible for study monitoring. This committee will review and approve the study protocol prior to initiation of enrollment, will review SAEs and AEs at least twice annually and will be alerted to any interim concerns. Should any SAEs occur, they will be reported within 24 hours to the PIs.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the Virginia Commonwealth University IRB.

11.2 Informed Consent Forms

An initial screening will be conducted with all participants to describe the research study and determine their interest. For subjects who are interested in potentially volunteering for the study the study coordinator and/or principal investigators will meet with interested candidates. At this time individuals interested in participating can ask questions about the study. If they wish to be considered for the study they will then be asked to read and sign an informed consent document. A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record. The principal investigators will work with the Virginia Commonwealth University IRB on an as needed basis to make provisions for special populations.

11.3 Participant Confidentiality

Data from self-report instruments and physical assessments are the primary source of research material. Measures will be taken to ensure the confidentiality of participant responses. Only those persons directly involved with conducting the study will be able to link the participant names with their information. All participants will be provided with a random ID number and no personal identifiers will be kept with the raw data. All informed consent documents will be filed separately so that there is no direct connection between participant names and any of their data. All hard copy data will be kept in locked filing cabinets. Physical and questionnaire data will be stored digitally using filenames corresponding to the participants ID number only. No identifying information will be used in any publications or presentations that result from this research. The code linking the random ID number with the participants name and contact information will be maintained through the follow-up period of the last enrolled subject (i.e., ~August 2023), at which point it will be destroyed.

All health-related data will be kept confidential by the investigators involved in this study. Specifically, only the investigators in the study will have access to patient data. Published or presented data will not identify patients in any way. Patients will not be audiotaped or videotaped. Data, forms, reports, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID). All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Additionally, while every effort will be made to keep study-related information confidential, there may be circumstances where this information must be shared with: 1) Federal agencies, for example the Office of Human Research Protections, whose responsibility is to protect human

subjects in research; and 2) Representatives of Virginia Commonwealth University VCU, including the Institutional Review Board, a committee that oversees the research at VCU.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NICHD, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

Steering Committee: The VIGOR Study Steering Committee, which is charged with the overall governance of study conduct, consists of James S. Thomas, PhD, PT, and Christopher R. France, PhD. The Steering Committee approves the final protocols and manuals of operations, supervises the overall execution of the trial, generates and approves study policies, considers modifications of the protocol and study operations, and plans and drafts study-related publications. The Steering Committee appoints and charges the subcommittees described below. All major scientific decisions are determined by consensus of the Steering Committee.

Medical Safety Committee: The VIGOR Study Medical Safety Committee, which consists of James S. Thomas, PhD, PT, Christopher R. France, PhD, Tim Law, D.O. and Study Coordinator Tiffany Amos, reviews masked study data related to the overall safety of study participation, develops safety reports for the Data and Safety Monitoring Board, addresses IRB issues (related to participant safety) that may arise, reviews clinical practice-related issues and oversees the clinical safety of all study participants.

Data Safety and Monitoring Board: A Data Safety Monitoring Board (DSMB) that consists of an Independent Monitoring Committee IMC (IMC) monitors all aspects of the study, including those that require access to any blinded data.

Recruitment, Adherence, and Retention Committee: The VIGOR Study Recruitment, Adherence and Retention Committee (James S. Thomas, PhD, PT, Christopher R. France, PhD., and members of the Study Coordination and Data Collection Team) refines and optimizes protocols and strategies for recruitment, adherence and retention of study participants. The Committee oversees recruitment progress, intervenes in cases of under-recruitment, and reports recruitment progress to the Steering Committee.

13. PUBLICATION OF RESEARCH FINDINGS

This study is governed by a Steering Committee and publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee.

14. REFERENCES

1. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105-121.
2. Jordan K, Dunn KM, Lewis M, Croft P. A minimal clinically important difference was derived for the Roland-Morris Disability Questionnaire for low back pain. J Clin Epidemiol 2006;59:45-52.
3. Morris SB. Estimating effect sizes from pretest-posttest-control group designs. Organizational Research Methods 2008;11:346-386.

4. Leeuw M, Goossens ME, van Breukelen GJ, et al. Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. Pain 2008;138:192-207.
5. Linton SJ, Boersma K, Jansson M, Overmeer T, Lindblom K, Vlaeyen JW. A randomized controlled trial of exposure in vivo for patients with spinal pain reporting fear of work-related activities. Eur J Pain 2008;12:722-730.
6. Woods MP, Asmundson GJ. Evaluating the efficacy of graded in vivo exposure for the treatment of fear in patients with chronic back pain: a randomized controlled clinical trial. Pain 2008;136:271-280.
7. Smeets RJ, Vlaeyen JW, Hidding A, Kester AD, van der Heijden GJ, Knottnerus JA. Chronic low back pain: physical training, graded activity with problem solving training, or both? The one-year post-treatment results of a randomized controlled trial. Pain 2008;134:263-276.
8. Raudenbush SW, Liu X. Statistical power and optimal design for multisite randomized trials. Psychol Methods 2000;5:199-213.
9. Institute oM. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC): The National Academies Press, 2011.
10. Freburger JK, Holmes GM, Agans RP, et al. The rising prevalence of chronic low back pain. Arch Intern Med 2009;169:251-258.
11. Prevention CfDCa. Prevalence and most common causes of disabilty among adults - United States. Hyattsville, MD2010.
12. Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? Jama 2010;303:1295-1302.
13. Nicholas MK, Linton SJ, Watson PJ, Main CJ, Decade of the Flags" Working G. Early identification and management of psychological risk factors ("yellow flags") in patients with low back pain: a reappraisal. Phys Ther 2011;91:737-753.
14. George SZ, Beneciuk JM. Psychological predictors of recovery from low back pain: a prospective study. BMC Musculoskelet Disord 2015;16:49.
15. Main CJ, George SZ. Psychologically informed practice for management of low back pain: future directions in practice and research. Phys Ther 2011;91:820-824.
16. Thomas JS, France CR. Pain-related fear is associated with avoidance of spinal motion during recovery from low back pain. Spine (Phila Pa 1976) 2007;32:E460-466.
17. Thomas JS, France CR. The relationship between pain-related fear and lumbar flexion during natural recovery from low back pain. Eur Spine J 2008;17:97-103.
18. Thomas JS, France CR, Sha D, Vander Wiele N, Moenter S, Swank K. The effect of chronic low back pain on trunk muscle activations in target reaching movements with various loads. Spine (Phila Pa 1976) 2007;32:E801-808.
19. Trost Z, France CR, Sullivan MJ, Thomas JS. Pain-related fear predicts reduced spinal motion following experimental back injury. Pain 2012;153:1015-1021.
20. Trost Z, France CR, Thomas JS. Pain-related fear and avoidance of physical exertion following delayed-onset muscle soreness. Pain 2011;152:1540-1547.
21. Hides JA, Richardson CA, Jull GA. Magnetic resonance imaging and ultrasonography of the lumbar multifidus muscle. Comparison of two different modalities. Spine (Phila Pa 1976) 1995;20:54-58.
22. Hides JA, Richardson CA, Jull GA. Multifidus muscle recovery is not automatic after resolution of acute, first-episode low back pain. Spine (Phila Pa 1976) 1996;21:2763-2769.
23. Lieber RL. Skeletal muscle structure, function, and plasticity: The physiological basis for rehabilitation., 2nd ed. Baltimore: Lippincott, Williams &Wilkins, 2002.
24. Vlaeyen J, Morley SJ, Linton SJ, Boersma K, de Jong J. Pain-related fear: Exposure-based treatment of chronic pain. Seattle, WA: International Association for the Study of Pain Press, 2012.
25. Wertli MM, Rasmussen-Barr E, Held U, Weiser S, Bachmann LM, Brunner F. Fear-avoidance beliefs-a moderator of treatment efficacy in patients with low back pain: a systematic review. Spine J 2014;14:2658-2678.
26. Hoy D, Brooks P, Blyth F, Buchbinder R. The Epidemiology of low back pain. Best Pract Res Clin Rheumatol 2010;24:769-781.

27. Foster NE. Barriers and progress in the treatment of low back pain. BMC Med 2011;9:108.
28. Andersson GBJ. Epidemiological features of chronic low-back pain. Lancet 1999;354:581-585.
29. Carey TS, Garrett JM, Jackman AM. Beyond the good prognosis. Examination of an inception cohort of patients with chronic low back pain. Spine (Phila Pa 1976) 2000;25:115-120.
30. Klenerman L, Slade PD, Stanley IM, et al. The prediction of chronicity in patients with an acute attack of low back pain in a general practice setting. Spine (Phila Pa 1976) 1995;20:478-484.
31. Von Korff M. Studying the natural history of back pain. Spine (Phila Pa 1976) 1994;19:20415-20465.
32. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. J Behav Med 2007;30:77-94.
33. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 2000;85:317-332.
34. Thomas JS, France CR, Lavender SA, Johnson MR. Effects of fear of movement on spine velocity and acceleration after recovery from low back pain. Spine (Phila Pa 1976) 2008;33:564-570.
35. Thomas JS, France CR. The relationship between pain-related fear and lumbar flexion during natural recovery from low back pain. Eur Spine J 2008;17:97-103.
36. Laver K, George S, Thomas S, Deutsch JE, Crotty M. Cochrane review: virtual reality for stroke rehabilitation. Eur J Phys Rehabil Med 2012;48:523-530.
37. Primack BA, Carroll MV, McNamara M, et al. Role of video games in improving health-related outcomes: a systematic review. Am J Prev Med 2012;42:630-638.
38. Warburton DER. The health benefits of active gaming: Separating the myths from the virtual reality. Current Cardiovascular Risk Reports 2013;7:5.
39. Garrett B, Taverner T, Masinde W, Gromala D, Shaw C, Negraeff M. A rapid evidence assessment of immersive virtual reality as an adjunct therapy in acute pain management in clinical practice. Clin J Pain 2014;30:1089-1098.
40. Keefe FJ, Huling DA, Coggins MJ, et al. Virtual reality for persistent pain: a new direction for behavioral pain management. Pain 2012;153:2163-2166.
41. Van Damme S, Van Ryckeghem DM, Wyffels F, Van Hulle L, Crombez G. No pain no gain? Pursuing a competing goal inhibits avoidance behavior. Pain 2012;153:800-804.
42. Goossens ME, de Kinderen RJ, Leeuw M, et al. Is exposure in vivo cost-effective for chronic low back pain? A trial-based economic evaluation. BMC Health Serv Res 2015;15:549.
43. Macedo LG, Smeets RJ, Maher CG, Latimer J, McAuley JH. Graded activity and graded exposure for persistent nonspecific low back pain: a systematic review. Phys Ther 2010;90:860-879.
44. Lopez-de-Uralde-Villanueva I, Munoz-Garcia D, Gil-Martinez A, et al. A Systematic Review and Meta-Analysis on the Effectiveness of Graded Activity and Graded Exposure for Chronic Nonspecific Low Back Pain. Pain Med 2016;17:172-188.
45. Thomas JS, France CR, Sha D, Wiele NV. The influence of pain-related fear on peak muscle activity and force generation during maximal isometric trunk exertions. Spine (Phila Pa 1976) 2008;33:E342-348.
46. Trost Z, France CR, Thomas JS. Exposure to movement in chronic back pain: evidence of successful generalization across a reaching task. Pain 2008;137:26-33.
47. Trost Z, France CR, Thomas JS. Examination of the photograph series of daily activities (PHODA) scale in chronic low back pain patients with high and low kinesiophobia. Pain 2009;141:276-282.
48. Clark BC, Walkowski S, Conatser RR, Eland DC, Howell JN. Muscle functional magnetic resonance imaging and acute low back pain: a pilot study to characterize lumbar muscle activity asymmetries and examine the effects of osteopathic manipulative treatment. Osteopath Med Prim Care 2009;3:7.

49. Spitzer W, LeBlanc F, Dupris M. Scientifice approach to the assessment and management of activity related spinal diorders. A monograph for clinicians. Report of the Quebec Task Force on Spinal Disorders. Spine (Phila Pa 1976) 1987;12:S1-S59.
50. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. Spine (Phila Pa 1976) 1983;8:141-144.
51. Stratford PW, Binkley J, Solomon P, Finch E, Gill C, Moreland J. Defining the minimum level of detectable change for the Roland-Morris questionnaire. Phys Ther 1996;76:359-365; discussion 366-358.
52. McGill SM, Cholewicki J, Peach JP. Methodological considerations for using inductive sensors (3SPACE ISOTRAK) to monitor 3-D orthopaedic joint motion. Clin Biomech (Bristol, Avon) 1997;12:190-194.
53. Trost Z, France CR, Sullivan MJ, Thomas JS. Pain-related fear predicts reduced spinal motion following experimental back injury. Pain 2012.
54. Radloff LS. The CES-D Scale: A Self-report depression scale for research in the general population. Applied Psychol Measurement 1977;1:385-401.
55. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129-138.
56. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol 2010;63:1179-1194.
57. Salsman JM, Lai JS, Hendrie HC, et al. Assessing psychological well-being: self-report instruments for the NIH Toolbox. Qual Life Res 2014;23:205-215.
58. Trompetter HR, Ten Klooster PM, Schreurs KM, Fledderus M, Westerhof GJ, Bohlmeijer ET. Measuring values and committed action with the Engaged Living Scale (ELS): psychometric evaluation in a nonclinical sample and a chronic pain sample. Psychol Assess 2013;25:1235-1246.
59. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc 1998;30:777-781.
60. Kelley ML, Heffer RW, Gresham FM, Elliott SN. Development of a Modified Treatment Evaluation Inventory. Journal of Psychopathology and Behavioral Assessment 1989;11:235-247.