Adapting Virtual Reality Technology for the Treatment of Phantom Limb Pain

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RESEARCH PLAN
A. BACKGROUND

Few medical injuries are more devastating to physical function and quality of life than the loss of a limb. Among Veterans, the loss of limbs (amputation) may occur from a diverse set of causes ranging from acute injuries suffered by soldiers in combat situations to increasingly common chronic diseases such as diabetes that disproportionately affect the Veteran population[1]. Following amputations, the majority of patients report continuing sensations associated with the missing limb, referred to as phantom limb sensation[2]. Phantom limb pain (PLP) is a specific phantom limb sensation that is experienced by up to 85% of patients with amputations[3]. Amputees with PLP report poorer functioning, reduced quality of life, and greater psychological distress than amputees without PLP[4]. Although there is some evidence that the severity of PLP decreases over time[3], the majority of patients continue to experience symptoms chronically. One study reported patients had experienced PLP for an average of 29 years[3]. However, there is also evidence that frequency of episodes of PLP varies from over 20 days per month (34%) to 1 day per month (14%) and duration of episodes varies from seconds (38%) to continuous (12%)[2-3]. This indicates that PLP can vary on a day-to-day basis and may benefit from versatile approaches to assessment and treatment that can meet Veterans when and where PLP occurs.

Although traditional pain medication treatments are less effective for PLP[2], recent research offers promising possibilities for treating PLP[5]. Ramachandran and Rogers-Ramachandran[6] demonstrated that engaging in simple physical exercises while using a mirror to create the illusion of the missing limb altered participant's experience of their phantom sensations and in some cases even eliminated PLP. The authors argued that the mirror-fed visual input facilitates changes in neural activation that reduces the experience of PLP. Evidence from newer trials provides additional support and suggests that visual feedback from the mirror is a critical feature in pain symptom changes[7-9].

In order to provide validation for mirror therapy in a larger PLP trial, the current team of investigators obtained VA R&D support from 2008-2011 to carry out a clinical trial (clinicaltrials.gov/show/NCT00731614), comparing mirror therapy to a form of supportive psychotherapy designed to control for non-specific effects of treatment. Veterans receiving the mirror therapy treatment reported significant reduction in PLP, which was further maintained at 24 weeks post-treatment ($F[10, 80]=2.26$, $p=.024$ [unpublished data]). A limitation of the mirror therapy treatment was the reliance on self-reported changes in PLP sensations that required the participant's recall of symptoms from days or weeks prior. PLP differs from other forms of chronic pain in that it is usually intermittent in nature (In one study of amputees, 81% reported intermittent PLP in the prior month, and only 9% constant PLP in the prior month[10]) rather than a constant sensation. In this study, we propose to extend our previously mirror therapy trial using immersive virtual reality (VR) technology that will allow Veterans to engage in the treatment in their natural living environment while simultaneously measuring the effectiveness of the treatment using real time assessment technology.

VR is a novel, technology-based treatment approach that preliminary research has shown to be effective for the management of acute and chronic pain[11-12]. VR technology is usable by patients in non-clinical environments and includes assessment features that can allow for the real-time collection of data concerning device usage patterns and changes in PLP sensations during daily living circumstances. Several small studies have adapted visual feedback aspects of mirror therapy to VR treatments for PLP[13-14]. Perry[13] summarized four recent efforts in a 2014 review, with protocols using different motion sensor technology with the patient's intact limb to create an avatar in a simulated VR environment, where the patient engages in different exercises. Patients find these simulations engaging[9] and often effective for PLP[15-16]. Studies to date adapting visual feedback aspects of mirror therapy to VR, however, are small (5-14 patients), use mostly intermittent practice protocols, did not include Veterans, and employed only passive controls[13]. In the current study, we propose to test a VR for PLP with 20 Veteran amputees using a daily practice protocol, real time assessments to monitor home-based PLP benefits, and will compare to an active control in the form of standard mirror therapy.

The proposed study will take place over a two year period comprised of a 1) a technical innovation and usability phase; and 2) a feasibility trial phase each lasting approximately twelve months.

Table 1. Overview of study proposal: methodology & outcomes.

Study phase	Sample size	Methodology	Primary outcomes
Technical innovation &	N=15	Iterative testing with participants using the VR equipment in order improve usability,	Satisfaction scores, usability ratings, problem reports, side

usability (year 1)		satisfaction, and effectiveness	effects, immersiveness
Feasibility trial (year 2)	N=20	Between groups design comparing VR treatment versus standard mirror therapy to estimate effects for larger scale trial	Adherence, satisfaction, changes in PLP, mood, function, quality of life

SIGNIFICANCE

There is arguably no mission more central to the VA than improving the outcomes for combat-injured Veterans such as those with amputations. The VA system performs 10% of all amputations in the U.S., primarily in response to diabetes and vascular disease[17]. Between 1989 and 1998, 60,324 Veterans had a lower limb amputation, with 62% being secondary to diabetes[17]. Although amputation rates have decreased in the past decade, the total number of Veterans with amputations is likely to remain high with both the increased age of Veterans and the continuation of active military operations for the foreseeable future.

The proposed study will provide a novel, Veteran-tailored VR application towards PLP that we will evaluate in direct comparison to standard mirror therapy. The study represents a collaboration of senior VA pain researchers and VR development expertise. The design of the study will allow for rigorous testing among and feedback by Veterans with PLP in order to develop VR software promoting optimal patient accessibility as well as efficacy for pain symptom reduction and functional enhancement.

B. RESEARCH DESIGN AND METHODS

Overview

In the technical innovation and usability phase, we will develop VR software designed for the treatment of PLP and deploy this software with a pilot sample of Veterans with PLP for feedback concerning usability, side effects, and effectiveness. The research team includes the co-founder and chief technology officer (Mr. Garland Wong) of Virtual Reality Medical Applications Inc., a San Diego-based company applying VR products to hospital settings. Mr. Wong's prior experience with VR applications for healthcare settings will allow us to expand upon his existing VR applications and expedite the development of a VR treatment integrating mirror therapy components. This initial phase will include software development and interactive refinement of the VR software based upon feedback from a pilot sample of Veteran amputees with PLP. The feasibility trial phase will take place during year two of the proposal. In this phase, we will conduct a small scale two group clinical trial design with a pilot sample, evaluating the novel VR treatment relative to standard mirror therapy. Participants will receive either the VR or mirror therapy treatment for one month, with the treatments matched for in person visit frequency and homework frequency recommendations. The VR treatment will include real-time assessments of usage statistics and pain-related outcomes. The goal of the feasibility trial is to obtain preliminary efficacy data and obtain effect size and comparative effectiveness data for a larger trial application.

Methods

1. Participants and Enrollment. In each year of the project, we will recruit samples of Veterans with PLP from primary care and amputee clinics. Co-investigator Deborah Velez, NP, is the PACT (Primary Aligned Care Team) coordinator in the amputee clinic at the VA San Diego Healthcare System (VASDHS) and has specific recruitment experience with the PLP population from our previous R&D-supported clinical trial for PLP. **2. Inclusion criteria**. 1) Ages 21-75 Veteran receiving care at VASDHS**;** 2) Upper or lower extremity amputation with reported PLP for at least six months; 3) PLP intensity $\geq$ 4/10; 4) English-speaking, literate, with stable residence; 6) Able to operate a VR headset as evidenced by direct observation. **3. Exclusion Criteria**. 1) Major medical illness that might confound effects of pain on function (e.g., advanced cardiac or pulmonary disease); 2) current active alcohol or substance use disorder as evidenced from medical record; 3) currently active suicidality, homicidality, or unstable psychiatric status in previous three months as measured by direct observation, patient self-report, or medical record; 4) moderate or severe cognitive impairment as demonstrated by medical diagnosis or clinical observation; 5) Prior mirror therapy experience.

Patient Selection and Recruitment

Co-investigator Deborah Velez, NP, is member of the VASDHS clinical staff and will meet with Veterans with amputations in the vascular, orthopedic, and amputee clinics as part of her clinical position and inform them about the study. Ms. Velez will attempt to contact every amputee receiving VASDHS services during the study period. If a patient expresses interest and agrees to be contacted, Ms. Velez will then provide the study coordinator with the patient's contact information. The coordinator will contact the patient, explain the study, obtain informed consent, and screen for PLP using the Trinity Amputation and Prosthetic Experience Scale[16].

Women and Minorities

Approximately 37% percent of VA patients with amputations are minorities and we will attempt to sample minorities at or above this percentage in the pilot samples. Women may also be included. However,

because women comprise less than one percent of Veterans with amputations in the VA system[15] it is possible that no or few women will be eligible to participate in the study.

Recruitment Feasibility.

The VA San Diego Healthcare System (VASDHS) currently provides care for over 450 Veterans with amputations, and up to 36 new Veterans a year undergo amputations in San Diego each year. Based upon our previous PLP trial, it is projected that dropout during will be ~ 10% and loss to follow-up will be modest (<10%). Allowing for 18 months for subject recruitment (see project timeline below). During the innovation and feasibility trial periods, we project that 4-5 subjects will be recruited per month. In our R&D PLP pilot study, 62.5% of amputees had PLP and 74% were willing to participate in the mirror therapy treatment. If we conservatively estimate that half of Veterans with PLP show frequency and severity of PLP symptoms sufficient to enroll, this project to approximately 150 amputees among the current population of 450 amputees enrolled at the VASDHS. Assuming we recruit just 20% of the eligible sample that will permit sufficient recruitment.

Project Timeline
Months 0-3: IRB approval; hiring of personnel; development of forms and database, recruitment
Months 3-12: VR software Development, Usability Testing (N=15), VR refinement
Months 13-24: Recruit and conduct feasibility trial (N=20); Months 21-24 will include data analyses, preparation of manuscripts and Merit Review applications for a larger VR treatment trial

Procedures

Year 1 Technical innovation and usability phase (Research Aim 1)

The primary study goal in Year 1 is the development and refinement testing of a VR treatment for PLP. Our VR team experts Mr. Garland Wong and Dr. Huan Giap, and a half-time VR technician will oversee the development of the VR-mirror therapy using state of the art Oculus VR headsets, specialized VR software available to Mr. Wong for treatment development purposes, and motion sensor equipment that will allow the VR staff to customize the VR exercises to the Veteran's missing limb[19-20]. Among VR headset options, Oculus headsets represent a cost-effective option that incorporates the most recent VR technology advancements while maintaining costs at a level affordable by consumers (~$500.00). We believe this choice is the best available for developing a VR treatment with practical applicability to a Veteran population. Following the initial software development (months 3-4; See Appendix 3 for illustrated description of VR development phases including images of currently developed VR environment), we will evaluate an alpha version of the VR protocol with 10 Veterans with PLP (months 5-10). Their participation will consist of laboratory visits to customize the software to their amputation location and train them with use of the VR headset over two weeks. We will collect feedback concerning patient satisfaction, effects on PLP, side effects, and immersiveness (Measures shown in Table 2) and open feedback that we will code qualitatively for analysis. The VR technician will contact them 2-3 times/week over their pilot test period. There is considerable usability data to date suggesting that VR technology is tolerated well by participants, including patients with chronic pain, for short term use[12]. In the final two months of Year 1, we will test a beta version of the VR software with a second group of 5 Veterans with PLP. Their participation will be identical to the beta test group, with the goal of maximizing the immersiveness, usability, and benefits of the VR protocol as a Gold Master version for deployment in Year 2 of the study.

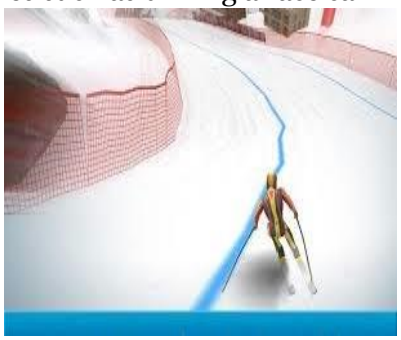
Real-Time VR Embedded Pain Assessment.

In addition to the development of the VR treatments, a second novel feature of the VR software is the incorporation of real-time PLP assessment and usability information at random intervals prior, during and after VR interaction. The VR assessments will not collect personal health information. Assessment data will be stored in the VR device during usage and connected by study identification number to the participant's database record for download during their in person visits. VR incorporates eye tracking technology that can allow a user to respond to questions about PLP, mood, immersiveness, or side effects using a visual analogue scale presented in the visual field, confirmed by participants' movements (e.g., a nod to confirm or head shake to disconfirm). Incorporation of a real-time pain assessment is merely an extension of the existing participant interaction system used to navigate VR menus, and so is straightforward to create. The ability to incorporate such ratings in the context of the VR protocol provides several compelling advantages over typical paper-and-pencil diary based methods for pain assessment, including 1) increasing validity by eliminating retrospective "backfilling", 2) assuring precise and time stamped collection of pre- and post-session pain intensity, and 3) provision of real-time feedback to participants, which may reinforce participation. Refining the real time assessment features will be part of the Year 1 goals. Dr.'s Rutledge and Depp each have substantial prior experience with the real-time assessment of psychosocial and behavioral factors [21-22].

VR Mirror Therapy Condition

Using a VR headset, motion sensors, and VR software, we will create a customized VR treatment for

each participant that engages them in movements and exercises involving their missing limb in a game-like environment. For example, participants may use the headset to engage in activities such as driving a race car around a course requiring both arms, ski down simulated slopes (see illustration), or manipulate objects. We will use a validated "presence" questionnaire to assess realism and level of immersiveness by participants. Preliminary studies of VR among patients with PLP suggest they interpret VR simulations as realistic representations of their body, including physiological responses when engaging the avatar in motion[23]. Compared to standard mirror therapy, the VR adaption to mirror therapy has unique advantages, such as the ability for the avatar to engage in a much broader range of activities and comparatively diminished fatigue compared to usual mirror therapy exercises. The latter advantage may allow VR participants to obtain longer and more frequent mirror therapy treatments that could enhance the intervention. We can also modify the VR environment specifications for participants reporting a history of motion sickness – for example, by decreasing the degree of sensitivity to head movements – to minimize side effects and improve usability.



Standard Mirror Therapy Condition

Standard mirror therapy makes use of an external mirror, wherein an amputee carries out simple exercises (e.g., clenching & relaxing their fist) with their intact limb while positioned by the mirror in a manner that gives the visual illusion of the missing limb also being engaged in the exercise (see illustration). Users commonly experience changes in PLP and other phantom sensations with mirror therapy[8]. The mirror therapy condition will consist of a 4-week treatment following the same mirror therapy training used in our previous R&D trial that demonstrated significant reductions in PLP severity. Veterans in this treatment will meet with the study coordinator on a weekly basis to receive video-based and didactic education about the theory behind mirror therapy for PLP and instruction with specific mirror therapy exercises to be used in coordination with a study-provided mirror. Participants will spend 10-30 minutes of each visit performing mirror therapy exercises (see Appendix 4 for a description) under supervision and receive instructions to carry out home exercises on a daily basis. They will further complete an at home log of their mirror therapy use during the week that poses the same questions answered by VR participants.

Year 2 feasibility trial phase (Research Aims 2-3).

In year two of the study, a second sample of PLP patients (N=20) will receive the VR or standard mirror therapy treatment in a feasibility trial. Eligible and consented participants will receive training with the study coordinator and VR development team as part of their baseline visit. The baseline visit will consist of obtaining written informed consent, questionnaires (see below), and training with the VR/mirror therapy equipment. VR participants will be requested to use the VR headset at home daily for at least 30 minutes and no more than 120 minutes, over one or more sessions. We will specifically encourage them to use the VR treatment when experiencing PLP. Mirror therapy participants will receive homework instructions matching the VR recommended practice time and setting. VR training will include how to use the real-time assessment features in the headset. The total baseline visit time is projected to be ~ two hours, and the weekly visits and post-treatment visits ~ one hour (including VR/mirror therapy visit content and questionnaire completion). Participants will receive compensation for time and travel. We will inform VR participants that the headsets can track daily usage time and time of day when used in addition to their self-report feedback, anticipating that this knowledge may encourage adherence. They will have contact information for the VR development team, who will assist with any user problems with the VR equipment during their participation. Mirror therapy participants will similarly receive contact information for the study coordinator for questions. We will request that participants maintain their usual pain medication and psychotropic regimen during the study.

Feasibility outcomes – including satisfaction, adherence, side effects, and mood and PLP changes – will be compared pre-to-post treatment separately for the VR and mirror therapy protocols and between the two treatments. Participants will utilize each treatment for one month. This treatment duration is consistent with periods allowing for pain symptom reductions in previous VR studies and for PLP changes in mirror therapy participants[5,13]. During this phase, participants will complete in person baseline and weekly visits for four weeks with either the VR technical staff (VR) or study coordinator (mirror therapy) in addition to their daily homework exercise recommendations. Following IMMPACT (Initiative on Methods, Measurement and Pain Assessment in Clinical Trials[24]) guidelines, the baseline and post-treatment visits will include measures of PLP (Phantom Limb Pain Questionnaire (PLPQ[25]), adjustment to amputation and prosthesis (Trinity Amputation

and Prosthetic Experience Scale (TAPES[18]), mood (Beck Depression Inventory[26]), and life quality (Medical Outcomes Study (SF-12[27]). The study coordinator will administer the assessment measures with both treatment groups. Team statistician, Dr. Golshan, will receive outcome data blinded to treatment assignment.

Study Measures

Table 2. Timetable of Study Measures During Feasibility Trial

Evaluation/Study Week	Baseline	Weeks 2-3	Week 4
Screening and Qualification	X		
Medical Chart History Review	X		
Dependent Variable Measures			
Phantom Limb Pain Questionnaire (PLPQ)	X	X	X
Trinity Amputation and Prosthetic Experience Scale (TAPES)	X	X	X
Pain Interference (Brief Pain Inventory, SF-12)	X	X	X
Pain Intensity (Numerical Pain Rating Scale)	X	X	X
Mood (BDI)	X	X	X
Treatment Credibility/Feasibility & side effects	X	X	X
Treatment Satisfaction		X	X
Immersiveness of mirror therapy experience		X	X

Satisfaction, Feasibility, and Validity Measures

1. Client Satisfaction Questionnaire-Revised (CSQ): measures satisfaction with health care treatment on a four-point Likert scale[28]. **2. Credibility-Expectancy:** Likert-style ratings (0-6) will monitor participant expectations, credibility, and belief in the relevance and usefulness of treatment. **3. Igroup Presence Questionnaire (IPQ):** a measure used to assess immersiveness of VR-type artificial environments that contains subscales assessing three components of presence, spatial presence, involvement, and realness[29]. **4. Side effects:** participants will complete a check list of side effects used by our VR researchers in the prior development testing (e.g., dizziness, headaches, nausea, history of motion sickness).

Pain, Mood, and Functional Measures

1. Phantom Limb Pain Weekly Questionnaire (PLPQ). The PLPQ assesses the severity of PLP, stump pain and phantom limb sensation. Severity is assessed on a standard 11-point Likert scale pain measure, as recommended by the IMMPACT review group[24]. **2. Trinity Amputation and Prosthetic Experience Scale (TAPES)**: includes 27 items measuring activity, social functioning, and pain associated with the amputation, including PLP. **3. Short Form – 12 (SF-12):** measures physical functioning, general health, vitality, social functioning, and mental health. **4. Numeric Rating Scale** (NRS): current pain intensity (0=No Pain, 10= Pain as bad as you can imagine)[30]. **5. Brief Pain Inventory (BPI):** interference subscale rates pain interference in everyday contexts (e.g., activity, sleep, relationships) on a Likert type scale[31]. **6. Beck Depression Inventory (BDI):** The BDI is a standard index of depressed mood[26].

Summary of study strengths and innovation contributions

1. Adapts mirror therapy for PLP to a patient centered VR treatment easily used by patients at home.
2. Boasts a team of experienced chronic pain researchers with successful prior experience carrying out an R&D-funded PLP trial in combination with VR development expertise.
3. Brings affordable, state of the art VR technology to the care of Veterans with PLP including features to measure real-time effects of VR treatment on PLP.
4. Includes a feasibility trial assessing the treatment in comparison to standard mirror therapy.
5. Explicitly uses the feasibility trial phase as a crucial step in collecting effect size, adherence, and satisfaction data for a larger scale comparative effectiveness trial evaluating benefits of the VR.

Long term study objectives

The long terms aims are to evaluate the efficacy of the VR treatments in a larger scale randomized controlled trial, to explore biological mechanisms explaining PLP reductions – such as changes in somatosensory cortex activity viewable pre- and post-VR treatment through fMRI – and to expand the VR treatment to be usable by double limb as well as single limb amputees.

Conflict of interest statement

The study proposal is designed to minimize potential conflicts of interests. The VA investigator team will conduct the clinical trial, maintain the study database, and perform all statistical analyses independent of the VR developers. The VA investigators have no financial relationships with the VR industry.

C. Data Management and Statistical Analyses

Data management and analysis will be conducted using SPSS and R statistical software and carried out by co-investigator and study senior statistician, Dr. Golshan. Qualitative data will be coded and categorized for analysis. The primary aims of our data analytic strategy in year 1 will be directed toward the collection of data that will inform modification of the VR treatment. In year two it will be directed toward examining the feasibility of the VR treatment. We would like to emphasize that although we will estimate effect sizes to assist in future power calculations, this is not our major focus. Recent work by Kraemer[32] highlights important limitations of this aim due to the large standard error surrounding the pilot study effect size. Our goal is to collect important data regarding the development of VR treatment and optimized recruitment strategies. Information derived from our research will leads to better-designed full-scale studies and informs decisions regarding whether it is worthwhile to commit additional resources to future VR treatment development.

For quantitative data, descriptive statistics will be used to summarize the variables as well as detect outliers and data entry errors. When applicable, normality of the distribution will be examined for outcome variables. Other preliminary analyses will include evaluation of patterns of missing data, dropout rates, distributional properties of variables, and correlations among measures. Although there are important limitations associated with the analysis of our year 2 data, we do propose to conduct limited statistical analyses. First, we will calculate an estimated effect size for our primary outcome in the context of the 95% confidence interval that surrounds it. It will also be interpreted within the context of other important information such as the clinical significance of study findings, and existing data from prior relevant studies.

During the innovation and usability phase, the VR device will record usage frequency and time as measures of adherence. Satisfaction and usability ratings will result from self-report when participants return the VR equipment as well as real-time measures concerning changes in PLP symptoms while using the VR headset, with the study goal of achieving a mean 80% satisfaction/usability rating on Likert scale items.

Regarding the feasibility trial Aims 2-3, we will assess feasibility of the study and if the use of the VR and mirror therapy treatments are associated with reductions in PLP, mood symptoms, or improvements in function. We will focus on our ability to implement recruitment strategies, conducting this innovative treatment and measurements, recruitment rate, consent rate, reasons for not participating, reasons for dropping off, the rate of missing data, pattern of missing values, adherence rate and subjects satisfaction. Data analyses will proceed in stages. At first, descriptive statistics and exploratory graphing such as frequencies, means, standard deviations, box and whisker plots, stem and leaf diagrams, and scatter plots will be used to assess the distribution and normality of the data in terms of the presence of skew and/or outliers. The continuous outcome data will be transformed if necessary by using an appropriate transformation such as the log transform for skewed long tailed data. Similarly, potential covariates will also be summarized with descriptive statistics and graphs to determine the most appropriate way to treat these variables to determine if a continuous, categorical, or an interval representation is the most appropriate approach. The comparability of the two treatment groups in baseline demographic and clinical features will be tested with analyses of variance (ANOVAs) for continuous variables and Chi-square analyses for dichotomous variables. Our randomization procedure is expected to control patient and treatment variables that might be associated with outcome. Any variables on which the groups differ initially will be explored as covariates in subsequent analyses, and we will take this into account in the interpretation of the outcome. Primary analyses will be based on a hierarchical model (HLM) using an intent-to-treat method that uses all available data. The model will include a random intercept, a random effect for assessment time, and fixed effects for comparison groups and group-by-time interaction. Denominator degrees of freedom will be calculated using the Kenward-Roger small sample correction. Data will be analyzed from all randomized subjects on whom we have a baseline assessment and at least one post-baseline evaluation. All hypothesis tests will be two-sided with alpha set at .05 and a medium to large effect size (i.e., Cohen's $d \geq 1.0$) for changes from baseline to treatment. We will control Type I error by reducing measures to one key variable or a total or composite score when possible and will use Bonferroni correction for secondary outcomes in a domain family and secondary analyses. Using statistical power software for independent sample designs, an N of 10 for each treatment group and a minimum effect size of 1.0 standard deviation units of PLP (approximately two points on the PLPQ) results in an estimated power of .72 for the within group changes from pre- to post-treatment. <u>The feasibility trial is not powered to detect between group differences.</u> Based on our previous R&D trial, it will require several years of recruitment in a larger study to enable appropriately powered between group comparisons with a PLP sample. However, we will examine group means and standard deviations for the purpose of calculating effect sizes for a future trial application.