Virtual reality for improving activity levels in people with chronic pain: A feasibility study

Catherine Pollard

1261238

A thesis submitted to Auckland University of Technology in partial fulfilment of the requirement for the degree of Masters of Health Practice (MHPrac)

2021

Health and Environmental Sciences

Clinical Sciences

Practice Project Paper

HEAL997

Abstract

Background People with chronic pain can develop a more sedentary lifestyle. Activity-based virtual reality (AVR) interventions may help increase activity and improve outcomes for people with chronic pain.

Aim This study explored the acceptability and feasibility of AVR for improving activity levels and other pain relevant outcome measures among people with chronic pain.

Participants Thirteen people with chronic musculoskeletal pain were recruited and randomised into a physiotherapy treatment as usual group (TAU) or AVR group.

Design Randomised, non-blinded, pilot study involving within subject testing pre- and post-intervention. In addition, the TAU group underwent a pre-intervention waiting time to act as a control.

Methods Each treatment arm (AVR, TAU or wait-time) lasted six weeks. Outcome measures were collected at the start and end of each six-week period and included self-report questionnaires, activity monitoring and physical function measures. Effect sizes were calculated and minimal clinical important differences in activity levels and pain relevant outcomes were documented where available. Feasibility was determined through recruitment and retention rates and acceptability through participant's evaluation of sessions, perceived benefit and adherence to data collection processes.

Results Recruitment was low and indicated the need for changes to the exclusion criteria and recruitment sourcing when conducting a future study. Retention rates, however, were reasonable and participants enjoyed the sessions and perceived to gain benefit from the AVR. Preliminary analysis of activity levels and other outcomes indicated that AVR was somewhat less effective than TAU, but effect sizes across the groups were small. Several limitations to the study protocol demand further research to quantify results.

Conclusion The study confirmed that AVR was acceptable for a chronic pain population, but the study protocol as it stands would not be feasible for a future randomised controlled trial. Revisions may improve standardisation, and changes to the recruitment process are needed to increase participant numbers. Initial findings validate that AVR is an enjoyable intervention for people with chronic pain, but pain relevant outcome measures did not demonstrate substantial differences in outcomes compared to standard physiotherapy or a waiting list control.

Contents

List of Figures

List of Tables

Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief contains no material previously published or written by another person, nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Date: 15/02/2021

Acknowledgments

I would like to thank my primary supervisor Dr Natalie Tuck, for providing prompt support and invaluable guidance throughout this project and her patient understanding during my sleep deprived rants. Thanks also to Clinton Good for delivering the active virtual reality sessions and helping with data collection.

In addition, I would like to thank Astha Singh, Murray Hames, Connor Silvester, Dina-Sara Vajsakovic and the rest of the TARPS whanau for assistance with recruitment and administration during the project and on-going support as always. Appreciation must also go to the subjects who dedicated their time to participate in this study.

Ethics Approval for this study was granted by the Health and Disability Ethics Committee on 01 July 2019 (HDEC ref19/CEN/106).

Virtual reality for improving activity levels in people with chronic pain

1.1 What is chronic pain and why does it matter?

Chronic pain, defined as pain lasting more than three months (Treede et al., 2019), was identified as the leading cause of disability in most countries in 2015 (Vos et al., 2016) and affects approximately 785,000 people in New Zealand (Ministry of Health, 2020). As opposed to acute pain, which is triggered by a specific disease or injury, chronic pain has no biological purpose and no clear end-point (Grichnik & Ferrante, 1991). Living with chronic pain has profound implications for a person's quality of life, emotional well-being, psychological state and functional abilities (Geneen et al., 2017; Miller, MacDermid, Walton, & Richardson, 2015). Due to the complex, multifactorial nature of chronic pain, management of this condition needs to encompass a biopsychosocial approach (Pergolizzi et al., 2013) delivered by a multidisciplinary team. The focus of treatment is to educate people on how to live with their pain and lead fulfilling lives despite the pain (Pergolizzi et al., 2013).

1.2 Activity and pain

Chronic pain can lead to reductions in an individual's activity (Martin, Beasley, Macfarlane, & Whibley, 2014). This may occur as a result of reduced capacity to perform activity (due to physical impairment or deconditioning) or due to negative psychological states. Negative psychological states include pain catastrophising, where an actual or anticipated painful experience produces exaggerated negative thoughts (Sullivan et al., 2001), and kinesiophobia, where a person becomes fearful of movement or activity due to concerns they may become (re)injured and therefore develop activity avoidance (Kori, Miller, & Todd, 1990).

Physical activity is essential for good health, with a wealth of literature demonstrating the positive impact of regular exercise on physical well-being (e.g. heart, blood pressure, bone strength, cholesterol) (Ambrose & Golightly, 2015), mental health (reduced stress, anxiety, depression) (Dunn & Jewell, 2010; Jayakody, Gunadasa, & Hosker, 2014; Wegner et al., 2014), cognition (improved mental focus, retention and learning) (Lees & Hopkins, 2013), physical function (increased strength, stamina, speed and flexibility) (Chou, Hwang, & Wu, 2012; Kokkinos & Myers, 2010), sleep and overall quality of life (Ambrose & Golightly, 2015). Ensuring people with chronic pain

do not fall into a downward spiral of reducing activity levels/physical deconditioning, or reversing this spiral should it occur, is critical in the rehabilitation process.

In addition to the multiple health benefits, activity can directly influence pain modulation leading to reductions in pain intensity known as exercise-induced hypoalgesia (EIH) (Hughes & Patterson, 2020). EIH has been attributed to several different mechanisms including stimulation of arterial baroreceptors (Koltyn & Umeda, 2006; Nijs, Kosek, Van Oosterwijck, & Meeus, 2012), conditioned pain modulation (Vaegter, Handberg, & Graven-Nielsen, 2014), activation of the endogenous opioid system (Ellingson, Koltyn, Kim, & Cook, 2014), activation of the endocannaboid system (Dietrich & McDaniel, 2004) and up-regulation of genes such as those within the glutamatergic system (Molteni, Ying, & Gómez-Pinilla, 2002). However, in some chronic pain disorders such as fibromyalgia, the endogenous analgesia effects usually obtained with exercise may be dysfunctional and instead of pain reducing, it may increase (Nijs et al., 2012; Rice et al., 2019). In these instances, exercise is no longer rewarding (Rice et al., 2019) so finding strategies to make activity more enjoyable is important to encourage individuals to remain active despite limited perceived gain.

1.3 What about inactivity?

Not only are the benefits of activity among people with chronic pain well documented (Geneen et al., 2017), researchers have also investigated the detrimental impact of inactivity. An overall sedentary lifestyle, for example spending the majority of the day sitting, negatively impacts physical and mental health with links to a higher risk of obesity (Sugiyama, Healy, Dunstan, Salmon, & Owen, 2008), diabetes and cardiovascular disease (Wilmot et al., 2012) and a higher risk of anxiety (Teychenne, Costigan, & Parker, 2015). Results from research into sedentary behaviour suggest that even bouts of moderate-vigorous physical activity may not undo the detrimental effects of continuous hours of sedentary time (Lee et al., 2015; Semanik et al., 2015). This indicates that rehabilitation should focus on increasing general activity/reducing sedentary behaviour throughout the day, rather than focusing on short bouts of exercise.

Additionally, there is conflicting evidence that sedentary behaviour can influence pain. Although one systematic review failed to find correlation between pain and sedentary behaviour (Chen, Liu, Cook, Bass, & Lo, 2009), the studies included were methodologically flawed as they failed to encompass all types of active or sedentary behaviours and relied solely on participant recall. There is now a growing body of work demonstrating that increased breaks from sedentary behaviour, such as

changing positions from sitting to standing more frequently and spending less time sitting, reduces musculoskeletal pain (Barone Gibbs et al., 2018; Davis & Kotowski, 2014; Pronk, Katz, Lowry, & Payfer, 2012). One study involving people with fibromyalgia found that spending less time sedentary and more time performing light physical activities was associated with improved pain ratings (Segura-Jiménez et al., 2017). Improvements in pain intensity and impact of pain on daily life were also found in people with fibromyalgia who simply increased their daily step count (Kaleth, Slaven, & Ang, 2014). Functional magnetic resonance imaging (fMRI) of cortical activity in people with fibromyalgia revealed that higher physical activity levels were positively correlated with activating brain areas involved in down regulation of pain, whereas increased sedentary time was negatively correlated with less cortical activation in these same areas (Ellingson, Shields, Stegner, & Cook, 2012).

1.4 Promoting activity

The benefits of activity and detrimental effects of sedentary behaviour highlight the importance of promoting activity in chronic pain populations. Physiotherapists play an important role in encouraging activity by supporting people to perform graded exposure to concerning tasks, gradually increasing exercise tolerance and working towards specific goals. However, there are no strict guidelines for duration, type, or intensity of physical activity for people with chronic pain. This lack of guidance allows freedom for tailoring to the individual, with slow progression and consideration of the multitude of elements that influence activity, such as psychosocial factors (e.g. personal traits, pain catastrophising, coping strategies and pain self-efficacy), physical limitations, and available resources (Ambrose & Golightly, 2015). However, for success, activity programmes need to be implemented that facilitate patient motivation, self-efficacy and adherence (Jordan, Holden, Mason, & Foster, 2010).

To improve motivation and treatment adherence, forms of exercise which are considered enjoyable and are goal orientated are recommended (Jordan et al., 2010). Performing enjoyable activities stimulates the brain’s reward systems, releasing dopamine, which strengthens and consolidates learning and neurological plasticity (the ability of the nervous system to modify its structure and function) (Harley, 2004; Wise, 2004). In chronic pain, undesirable neuroplastic changes can occur which reinforce pain pathways such as functional (e.g. cortical reorganisation), anatomical (receptor changes) and chemical changes (neurotransmitter changes) (Siddall, 2013). Any technique which

encourages neuroplasticity in a positive manner to reverse these changes is therefore beneficial (Siddall, 2013).

1.5 Virtual reality

Gaming technology has long been recognised as a useful adjunct for encouraging activity in a fun and playful form (Pasch, Bianchi-Berthouze, van Dijk, & Nijholt, 2009). As technology advances, virtual reality (VR) is being explored as a tool in managing pain in many arenas, such as during routine medical procedures (Gold et al., 2005), burn patients (Hoffman, Patterson, & Carrougher, 2000), cancer pain (Schneider & Workman, 2000), and in complex regional pain syndrome (Sato et al., 2010).

In experimentally induced pain, VR has been shown to produce analgesic effects through modulation of sensory and emotional aspects of pain processing, with reduced activity demonstrated via fMRI in areas such as the caudal anterior cingulate cortex which is involved in the emotional aspects of pain; the somatosensory areas, involved in registering location and intensity of pain; the thalamus involved in general arousal and attention; and the insula involved in pain unpleasantness, intensity coding, opioid related pain modulation, as well as anxiety, depression and aversive states (Hoffman et al., 2004). The degree of pain relief attained with VR may be influenced by the type and quality of equipment used. Immersive VR, involving head mounted gear that allows the person to become absorbed in their environment, produces greater reductions in pain intensity than other forms of VR, such as via a computer monitor (Gold et al., 2005; Hoffman et al., 2006).

At present, a large proportion of the research into VR for pain management focuses on acute or experimentally induced pain with few studies looking into its use for chronic pain. Studies that have investigated chronic pain have predominantly involved passive strategies such as meditation or relaxation (Botella et al., 2013; Garrett, Taverner, & McDade, 2017; Gromala, Tong, Choo, Karamnejad, & Shaw, 2015; Jones, Moore, Rose, & Choo, 2016; Wiederhold, Camelia Sulea, & Wiederhold, 2014). Meditation and relaxation have been shown to be beneficial for people with chronic pain both in regards to symptoms and quality of life (Cherkin et al., 2016; Kwekkeboom & Gretarsdottir, 2006; Morone, Rollman, Moore, Li, & Weiner, 2009; Schaffer & Yucha, 2004), with activation and inhibition of different brain centres to produce down regulation of pain (Zeidan & Vago, 2016). While this provides a useful tool for assisting to control pain, it does not address the issues of building activity

levels, reducing fear avoidance to activity, or promoting increased function and engagement in life, all of which are essential components of pain self-management (Harding & Williams, 1995). These factors may be better addressed with active VR strategies (AVR), involving gross body movement to perform physical activities / tasks within a virtual environment. There are suggestions that AVR strategies can produce better outcomes in regards to tolerance of pain, enjoyment within VR, and a greater sense of immersion, compared to passive forms, although this research was based on experimental acute pain (Phelan et al., 2018). Whether these findings can be replicated among people with chronic pain is not known.

AVR for chronic pain management has only been assessed in a handful of studies. Fowler et al. (2019) performed a feasibility study exploring a hierarchy programme of VR starting with meditation then progressing to active based programmes involving torso and upper extremity movements among war veterans with chronic pain. Sessions were performed for twenty minutes daily, for three weeks. In the preliminary data from a small sample (16 participants), effect sizes were large for improvement in self-perceived function, but only small for improvement in pain intensity. In a feasibility randomised controlled trial (RCT) (Thomas, France, Applegate, Leitkam, & Walkowski, 2016), 52 participants with chronic back pain played virtual dodgeball for fifteen minutes over three consecutive days. The intervention was shown to encourage increased lumbar spine movement during play, but did not change lumbar flexion range, expected harm or anticipated pain beliefs when re-tested outside of the VR.

Following a different approach, Chen et al. (2017) designed an AVR programme to examine how people with or without chronic neck pain performed in an environment which altered visual feedback to neck movements, such that visual feedback appeared less than the actual degrees of movement performed. The authors considered that this strategy may be useful in people with chronic neck pain who displayed features of fear avoidance to movement. However, the study did not investigate pre- and post-scores in respect to pain or fear avoidance. Instead it focused on the degrees of movement that could be manipulated before people with or without neck pain could notice the difference between the visual feedback and the sensed movement, therefore its value in chronic pain management is unclear. Rezaei, Razeghi, Ebrahimi, Kayedi, and Rezaeian Zadeh (2019) also investigated the management of chronic neck pain using AVR with a specially designed game

involving a head mounted pointer to move a virtual rabbit to dodge obstacles and get carrots. It was developed to retrain proprioception and improve pain, and was compared to standard proprioceptive training of eye follow, gaze stability, eye-head co-ordination as well as movement and position sense training. Interventions for both groups consisted of eight sessions lasting twenty minutes, delivered twice weekly for four weeks. The outcome measures were assessed both immediately after the intervention and at five-week follow-up. This well designed RCT demonstrated that both interventions resulted in a reduction in pain and disability and improved dynamic balance in people with neck pain which were maintained at the 5-week follow-up, but the AVR group improved by approximately 50% more than the standard physiotherapy group. When assessing minimal clinical important differences (MCID), only the virtual reality group met targets for pain reduction and neck disability both immediately after and at the follow-up period.

In summary, preliminary research into AVR for chronic pain management shows promise in regards to improvements to pain and function but further work involving larger samples and more varied types of chronic pain is now required. In addition, exploration of whether AVR may promote changes to an individual's overall activity would enhance application of this management strategy.

1.6 Monitoring activity

Information examining changes to physical activity behaviour could be obtained via monitoring of active and sedentary levels among people with chronic pain undertaking AVR. As alluded to earlier, this would be most appropriate over prolonged periods of time as even short bouts of moderate to vigorous activity may not undo the negative effects of hours of sedentary behaviour (Lee et al., 2015; Semanik et al., 2015). Historically, activity monitoring has been assessed via self-report measures such as recording screen time (watching television, computer, phone), or time spent sitting reading, travelling by bus, car or train (El-Kotob & Giangregorio, 2018). Unfortunately, this lies open to bias, such as social desirability bias, difficulties in estimating physical activity amounts and incomplete data (El-Kotob & Giangregorio, 2018) and fails to take into account all types of sedentary or active events (El-Kotob & Giangregorio, 2018). Recently, accelerometers have been used as a more accurate means for real time measurement of type, frequency, duration and intensity of physical activity, as they do not rely on memory and can represent real life activity in its entirety. Rosenberger, Buman, Haskell, McConnell and Carstensen

(2016) compared nine different activity monitoring devices across a 24-hour period. They concluded that no devise accurately measured activity data across the full 24-hours; however, the ActivPAL was considered the most effective tool for measuring sedentary behaviour. The ActivPAL has been reported to be effective in chronic pain populations for measuring global body movement and highly sophisticated for recording time spent in different postures (Verbunt, Huijnen, & Seelen, 2012).

1.7 ActivPAL

The ActivPAL is a small device which is positioned on the thigh. It contains an inclinometer to differentiate between postures based on thigh position, providing data on time spent standing, sitting and lying down. It also contains a pedometer and accelerometer and can calculate an estimate for overall daily energy expenditure (Dowd, Harrington, & Donnelly, 2012; Pfister et al., 2017).The ActivPAL has been demonstrated in laboratory studies to be valid for estimating time spent in different postures (Grant, Ryan, Tigbe, & Granat, 2006), step count (Maddocks, Petrou, Skipper, & Wilcock, 2010; Ryan, Grant, Tigbe, & Granat, 2006), sit to stand transitions (Grant et al., 2006) and static and dynamic behaviours (Godfrey, Culhane, & Lyons, 2007). In real-life monitoring, the ActivPAL was able to produce highly accurate and precise estimates of total sedentary time (Kozey-Keadle, Libertine, Lyden, Staudenmayer, & Freedson, 2011). Additionally, compared to other devices, the ActivPAL provided more descriptive features on sedentary behaviour such as the number of breaks from sedentary behaviour and total sedentary time (Lyden, Keadle, Staudenmayer, & Freedson, 2017; Pfister et al., 2017).

Although the ActivPAL's success in measuring sedentary behaviour is well reported, its ability to measure activity, in particular differentiating between intensities of activity (low, moderate, high) is less accurate (Rosenberger et al., 2016). To investigate the validity of the ActivPAL to predict time spent in various intensities of physical activity during real-life activity, Lyden et al. (2017) compared direct observation against monitored activity with the tracker among 13 participants for three 10-hour periods. The authors were able to demonstrate the ActivPAL's ability to accurately estimate time in sedentary, light, or moderate-vigorous intensity activities.

Ryan, Grant, Gray, Newton, and Granat (2008) investigated the validity of the ActivPAL among people with chronic low back pain while performing activities of daily living in a laboratory setting, and confirmed it was effective for measuring posture, physical activity, step count and cadence. This research was then expanded to

identify whether there was a difference in physical activity levels and patterns in people with low back pain compared to healthy occupational, age, and gender-matched individuals (Ryan et al., 2009). Activity was monitored via the ActivPAL for 24 hours a day over a seven-day period, with the tracker only removed for water-based activities. The researchers found that people with chronic low back pain had lower-levels of activity and took fewer steps per day than healthy individuals. While this information suggests that the ActivPAL is useful for measuring sedentary time among people with chronic pain, it does not provide insight into whether the ActivPAL is sensitive to changes in activity levels following interventions to promote increased activity in people with chronic pain.

The vast array of data obtained by the ActivPAL could add valuable information to explore behaviour change in regards to activity levels following AVR interventions among people with chronic pain. This data could be compared against standard physiotherapy treatment and a no-input control to better determine the efficacy of AVR.

1.8 Aims

There is a lack of research demonstrating efficacy and appropriateness of AVR for chronic pain management. An RCT to demonstrate the impact to relevant pain outcome measures is warranted.

In preparation for this RCT, a pilot study to determine the feasibility and acceptability of performing research utilising AVR as an intervention for people with chronic pain would be pertinent. Pilot studies have been suggested to be integral to the success of future trials by ensuring the study protocol runs smoothly, interventions are safe and efficacious, and recruitment processes allow large enough sampling (Lancaster, 2015). Such a pilot study is currently being performed through the Auckland Regional Pain Service (TARPS) in conjunction with AUT (Auckland University of Technology), utilising a mixed-method approach of qualitative and quantitative procedures. The feasibility study presented here will focus on the quantitative elements of this pilot study to address the following questions;

1. Is AVR an acceptable intervention for people with chronic pain and would a future RCT be feasible? This will be explored through;

a. Sample size, eligibility and recruitment processes.
b. Retention rates.
c. Adherence to the intervention.

d. Acceptability of the AVR intervention - fidelity of session content, enjoyment, immersion, impact on pain, satisfaction and improvement ratings.
e. Safety of the intervention.

2. Do activity levels measured by the ActivPAL activity tracker change with interventions? And is the ActivPAL a suitable tool for measuring this in a chronic pain population?
3. Can undertaking AVR lead to changes in pain-relevant outcome measures and how does this compare to standard physiotherapy management and a waitlist control?

Although feasibility studies are not adequately powered to address the effectiveness of interventions (Lancaster, 2015), questions two and three will involve descriptive analysis, calculation of effect size (ES) and consideration of MCID to confirm appropriate data collection methods have been employed and to clarify whether or not a full trial is warranted.

The future RCT will be considered feasible if:

1. Thirty participants were recruited within a six-month time frame.
2. Retention rate was greater than 80%.
3. Adherence to intervention was greater than 80%.
4. The AVR intervention was considered acceptable with scores for benefit and satisfaction indicating a positive response (greater than 4 on the Likert scale) and enjoyability was greater than 80%.
5. No serious adverse events occurred as a result of AVR. Minor adverse events were no worse than standard physiotherapy input.

Methods

2.1 Design overview

The present feasibility study investigated an AVR intervention for people with chronic pain. It involved the recruitment and randomisation of patients to either AVR or physiotherapy treatment as usual (TAU). In addition, the TAU group completed a six-week waitlist control prior to commencing TAU. The design utilised repeated measures to assess changes over time. Measures included basic demographic information, pain relevant outcome measures, patient-rating scales for satisfaction and perceived benefit of treatment and objectively assessed activity levels.

2.2 Participants and setting

Participants aged 18 to 70 were recruited from patients that had been assessed by TARPS from 1st October 2019 to 31st August 2020. Patients deemed suitable for physiotherapy input were screened for eligibility as per inclusion/exclusion criteria and during their initial assessment provided with a brief explanation about VR, a study information sheet and consent form for the study. Inclusion criteria were as follows; aged 18-70 years, diagnosed with musculoskeletal pain, residing in Auckland, could communicate in English, were able to complete the full six-week rehabilitation programme and were able to maintain stable medication usage for the duration of the trial. Exclusion criteria included; diagnosis of non-musculoskeletal pain (for example migraine, abdominal /gynaecological pain, cancer pain, headaches), experiencing a severe medical or psychiatric condition, reported experiencing motion sickness, were receiving pain management input outside of TARPS, healthcare was being managed by the Accident Compensation Corporation (ACC) or they were unavailable for the duration of the intervention and follow-up period.

Individuals who expressed interest in participating in the trial were provided with the contact information (work email and telephone) for the study coordinator and requested to contact within three days from the assessment. At this point further screening of eligibility was performed and any queries from the potential participant addressed. If consent to enrol was granted, an online questionnaire was sent via email (baseline/time 1 outcome measure) to be completed at their convenience. Individuals who did not return the questionnaire or make contact within one-month, were contacted to clarify continued interest, then prompted to return the questionnaire or removed from the trial and returned onto the usual TARPS treatment pathway.

Recruitment processes were recorded to include the number of patients attending TARPS for initial assessment, the number considered not eligible to participate with reasons for non-inclusion, and the number randomised into the final study with dropout rate and reasons for withdrawal.

Ethics was granted from the Health and Disability Ethics Committee in July 2019 (HDEC ref19/CEN/106). Patients did not receive any award/compensation for participating. Subjects provided written informed consent prior to participation, with confirmation that they could withdraw at any point with no detrimental impact to their care provided through TARPS.

2.3 Procedures

Following return of the baseline questionnaire, the participants were randomly assigned (via computer random generator number) to either six-week AVR, or TAU groups. The TAU group had a six-week waitlist time before attending standard physiotherapy to act as a no-treatment control (Figure 1).

The AVR intervention consisted of twice-weekly, 20-min AVR sessions, across six weeks (totalling 12 sessions). TAU involved patients attending once weekly sessions for 30-60 min duration for six weeks. Data were collected on the number of sessions attended during the six-week period with reasons for non-attendance and compared between groups. Furthermore, the duration of the AVR session and reasons for deviation from the time frame were noted. At the physiotherapist's discretion, AVR sessions could include non-active strategies such as relaxation or meditation to accommodate variation to individual participant's baseline activity rates, functional abilities or pain intensity reported. Time spent performing non-active strategies during the session was documented with reasons for digressions, in order to gain an accurate account of session content and acceptability of AVR as a standalone treatment. Additionally, at each AVR session participants completed self-report evaluations of the session experience including pre-and post-session pain ratings, perceived immersion and perceived enjoyment (detailed below).

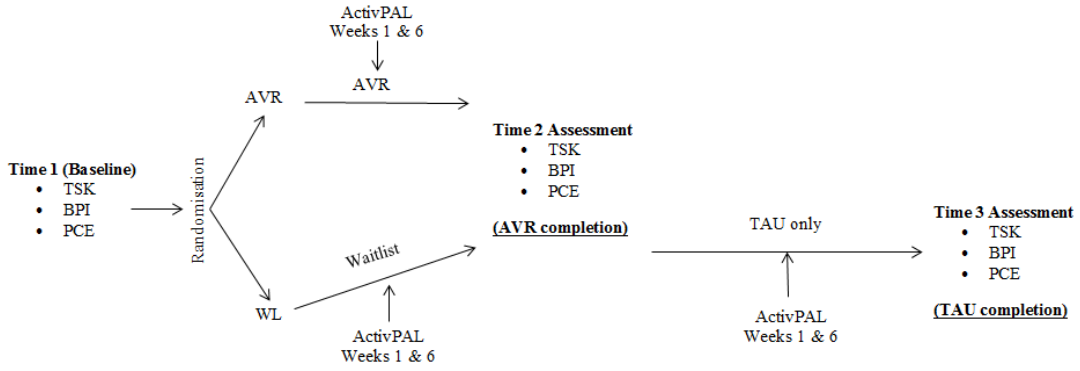
Online questionnaires and physical function measures were completed at baseline (time 1), then after six weeks of either AVR treatment, waitlist time (WL) (time 2) or standard physiotherapy (TAU group) (time 3).

To determine activity levels of participants in each intervention arm, including waitlist control, participants wore an ActivPAL activity tracker for weeks one and six of

each intervention period. The tracker was able to monitor days of wear, therefore any interruptions to this were documented, along with reasons for non-wear and any adverse events / dissatisfaction to tracker use.

Once the six-week trial period finished participants were able to continue with treatment as usual, as deemed appropriate by the treating therapist.

.



Note. TSK = Tampa Scale for Kinesiophobia, BPI = Brief Pain Inventory, PCE = Physical Capacity Evaluation (physical function measures), AVR = Active virtual reality, WL = Waiting list, TAU = Treatment as usual

Figure 1 Programme for Outcome Measure Collection and Intervention Sessions

2.4 Outcome measures

The outcome measures selected were based on the Initiative on Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) recommendations for chronic pain clinical trials (Dworkin et al., 2005) and tests routinely used for assessment and progress evaluation within TARPS.

Demographic information was documented including participant's age, gender, ethnicity, employment status, pain location and duration.

2.4.1 Physical activity

Physical activity was assessed using the ActivPAL during weeks one and six of the AVR intervention period, waitlist, and TAU to compare activity levels over time, and across conditions. The ActivPAL was attached using Tegaderm™ (a low allergy, waterproof dressing) to the midline of the anterior thigh. The monitor collects data at a sampling rate of 20 Hz. Participants were instructed to go about their normal daily activities while wearing the tracker and to keep it on continuously for the full seven days. Data were downloaded using the ActivPAL software (PAL Technologies ™).

While the software utilises algorithms to produce vast output data, for the purpose of this study, the following data were extracted; average daily number of steps, sedentary time (combined sleep, lying, sitting times), upright time (combined standing, walking cycling times) a metabolic equivalent task score (MET) and days of wear. The MET score is an estimate of energy expenditure which provides an indication of the intensity of an activity. Sedentary behaviour is defined as a MET of less than 1.5 while in a lying, reclining or sitting posture and takes into account that even standing can be considered a form of physical activity (van der Ploeg et al., 2007). Between 1.5-3 MET is considered low-intensity physical activity, 3-6 MET moderate activity and >6 vigorous activity (Ainsworth et al., 2011).

2.4.2 Pain

The Brief Pain Inventory (BPI) was administered at baseline (time 1), time 2 and time 3 as part of the online questionnaire. The BPI assesses the severity and location of pain and its impact to function. Participants indicate the location of their pain and the severity of their 'worst' 'least' 'average' and 'current' pain on scales ranging from '0' ('no pain') to '10' ('pain as bad as you can imagine'). Severity scores are averaged, and range from 0-10 with higher scores indicating greater pain severity.

The pain interference subscale assesses the impact of pain on seven life domains including mood, general activity, walking ability, normal work, sleep, relations with others and enjoyment of life. Interference scores are also averaged and range from 0-10 with higher scores indicating greater pain interference. The BPI has been shown to be valid and reliable in different pain conditions (Keller et al., 2004).

2.4.3 Fear of movement

The Tampa Scale for Kinesiophobia (TSK) was administered at times 1, 2 and 3 as part of the online questionnaires. The TSK comprises 17 statements to measure fear of movement and avoidance of activity. Respondents indicate on a four-point Likert scale to what extent the statements are a true description of their beliefs about movement and (re)injury, from *strongly disagree* to *strongly agree.* Four of these statements are inversely phrased (statements 4, 8, 12 and 16) and therefore scoring for these must be inversely calculated. Total scores range from 17 – 68 with higher scores indicating a greater fear of activity (Roelofs, Goubert, Peters, Vlaeyen, & Crombez, 2004). The TSK has been shown to be valid and reliable (Crombez, Vervaet, Lysens, Baeyens, & Eelen, 1998; Koho, Aho, Watson, & Hurri, 2001; Swinkels-Meewisse,

Roelofs, Verbeek, Oostendorp, & Vlaeyen, 2003; Vlaeyen, Kole-Snijders, Boeren, & van Eek, 1995; Vlaeyen, Kole-Snijders, Rotteveel, Ruesink, & Heuts, 1995).

2.4.4 Physical function

At baseline and completion of the AVR and TAU intervention periods participants undertook two physical function assessment measures: the 50 metre (m) speed walk test and the dynamic box lift test. The 50 m speed walk test measures the time taken to walk 25 m and back. Participants are asked to walk as quickly as they can without running; a quicker time indicates better physical performance. This test has been shown to be valid and repeatable and correlates highly with one leg standing, quadriceps muscle strength and other physical tests including timed up and go and the 30s chair stand tests (Hachiya et al., 2015). For the dynamic box lift, participants lift an empty box from a table to the floor and back, four times in 20s. Weight is then added (2.5 kg for females, 5 kg for males) and the four times in 20s lifting procedure repeated. This process is repeated until the maximum weight is lifted four times (12.5 kg for females and 20 kg for males) or if the patient exceeds the 20s to perform the four lifting procedures. Participants are instructed that they can also stop at any point. The time, maximum amount of weight and repetitions performed at that weight are recorded. This test is used routinely within TARPS. Multiple variants of the test have been described in the literature, but there is no reliability or validity testing of this exact procedure. However, a similar method (the Behavioural Avoidance Test – Back pain) involving lifting a crate containing an 8 kg weight repetitively from a table to the floor was examined in chronic back pain subjects and found to be a reliable and valid measure of pain-related avoidance behaviour (Holzapfel, Riecke, Rief, Schneider, & Glombiewski, 2016)

2.4.5 Global impression of change and satisfaction

To measure impression of change and satisfaction with the intervention received the online questionnaire completed at time 2 and time 3 included Likert scales for participants to rate the difference between their current and previous health state from 1 = ‘very much worse’ to 7 = ‘very much improved’ and satisfaction with treatment from 1 = ‘not at all satisfied’ to 7 = ‘very satisfied’. Global impression of change scores have been shown to be valid in people with fibromyalgia, but should be interpreted within the context of the complete clinical picture (Rampakakis et al., 2015).

2.4.6 AVR session experience

At each AVR session, participants completed a self-report evaluation of the session experience. This included pre-and post-session pain ratings utilising the numeric pain rating scale (0 = 'no pain' to 10 = 'pain as bad as you can imagine'), as well as numeric ratings scales to indicate levels of enjoyment (0 = 'not enjoyable' to 10 = 'very enjoyable') and level of immersion within the virtual environment (0 = 'not at all' to 10 = 'very much'). The difference in pain pre-post was computed to generate change scores. The average score for pain change, level of enjoyment and immersion was calculated across sessions for each participant.

2.5 Interventions

2.5.1 AVR Intervention

Participants attended twice weekly 20-minute AVR sessions, supervised by a physiotherapist with four years' experience utilising VR for people with chronic pain. Participants were given the standardised explanation that it was expected that AVR is an appropriate and useful treatment for chronic pain. The VR device used was an HTC Vive (HTC with technology by Valve, Taiwan) Head Mounted Display (HMD) with accompanying hand sensors. The HMD provides a viewing field of 110 degrees with a resolution of 1080 x 1200 pixels per eye. The programme is run through a wall mounted desktop display which allows the therapist to view a two-dimensional version of the frontal vision of the participant. Games are played in the first-person perspective so the participant becomes the virtual avatar. Clinical judgement was made as to the appropriate game/programme for the individual, through information gained from the TARPS initial assessment written reports. A suggested guideline for progression (Table1) was followed from 1 = 'minimal difficulty' to 6 = 'very difficult' but this was dependent on the participants pain location and varied on an individual basis. As mentioned earlier, at the therapist's discretion, AVR sessions could include non-active strategies as a means to accommodate variation in participants baseline activity levels, functional abilities or pain intensity reported. Written documentation was kept as to the type and duration of each game/programme utilised in every session.

Table 1

Guideline for Virtual Reality Gaming Progression

Grade	Game program
Grade One	***Fruit Ninja***: Hand controls become swords which are used to slice fruit which shoot up from the ground at varying speeds.
	Holodance: Hand controls become catching batons used to catch orbs within a set rhythm, includes interactions with dragons.
Grade Two	***Candy Smash***: Hand controls become candy canes, which are used to smash candy which is fired at you from different directions.
Grade Three	***Quiver***: Archery, shooting monsters with a bow and arrow to stop them invading.
	NBA: Virtual basketball game, shooting hoops.
Grade Four	***Lightblade***: Hand controls become light blades which are used to stop incoming lasers.
	Bitslap: Striking cubes in quick succession.
Grade Five	***Space Pirates***: Hand controls become guns/shields used to shoot/ defend against drones attacking in quick succession.
Grade Six	***Doritos***: Hand controls become virtual hands which are used to grab Doritos while moving through an obstacle course. Requires rapid whole-body movements, such as squatting, bending, dodging side to side, forwards and backwards.
	Fancy skiing: Hand controls become ski poles; participant needs to turn body to move through a challenging ski slope.

Following completion of the six weeks AVR and collection of all outcome measures, involvement in the trial ended. Participants were then able to continue with physiotherapy treatment as usual, with or without VR as deemed appropriate by the treating physiotherapist.

2.5.2 Treatment as usual

Standard physiotherapy for chronic pain management was conducted by either of two physiotherapists both with over 10 years' experience working with TARPS. Therapy incorporated education to better understand the complexities of chronic pain, including the impact on daily function and activity. Participants were taught about factors which negatively influence activity, such as fear avoidance and deconditioning and provided with strategies to help manage these factors more effectively. The exercise component involved provision of a home-based exercise regimen and tailored gym-based activity programme focused on graded activation and exposure therapy. Descriptive data were collected to record attendance to sessions and reasons for non-

attendance, or breaks to the six-week regime. Again, once the trial period ceased, participants were able to continue with usual treatment as needed.

2.5.3 Waitlist control

Participants attended the physiotherapy department for application and removal of the activity tracker during weeks one and six of their wait and were instructed to continue with life as usual during the six-week wait time.

2.6 Data processing and analysis

Data were collated and entered into SPSS statistical software version 26 (IBM, USA). To investigate the primary aim of feasibility and acceptability of AVR as an intervention for people with chronic pain, descriptive data were used to explore;

a. Sample size, eligibility and recruitment processes; recruitment data were examined for patient numbers assessed, screened, excluded and eligible for inclusion.
b. Retention; details of drop-out rates across the study.
c. Adherence to the intervention; number of sessions completed (TAU and AVR) and mean duration of sessions (AVR only).
d. Acceptability of the AVR intervention;
    i. Fidelity; mean duration of performing AVR within each session with details of deviations such as the inclusion of non-active strategies.
    ii. Self-report evaluation of the session experience (enjoyment, immersion, pre-post pain ratings) averaged across the sessions.
    iii. Baseline to completion differences calculated for satisfaction and improvement ratings and compared against WL control and TAU group.
e. Safety of the intervention; adverse event reporting.

To explore the second aim of the study regarding whether (a) activity levels change with interventions and (b) if the ActivPAL activity tracker was suitable for measuring this in a chronic pain population, average daily summaries were obtained for total number of steps, sedentary time, upright time and MET and days of wear was recorded. Mean, standard deviations and ES relative to the waitlist control and TAU groups were calculated and compared against the MCID, where available in the literature. ES was intended to guide suitability of these measures for future research. As this is a feasibility study further statistical analysis was not appropriate at this point.

The final aim of whether AVR produced changes in pain-relevant outcome measures with comparisons against TAU and a WL control was addressed through

descriptive analysis (absolute scores, means, standard deviations) for pain intensity, pain interference, fear of movement and physical measures. For each measure ES of AVR relative to the WL and TAU groups was calculated and compared against the MCID, where available in the literature. ES was intended to indicate the necessary sample size for an RCT, using the calculation formula described by Kadam and Bhalerao (2010).

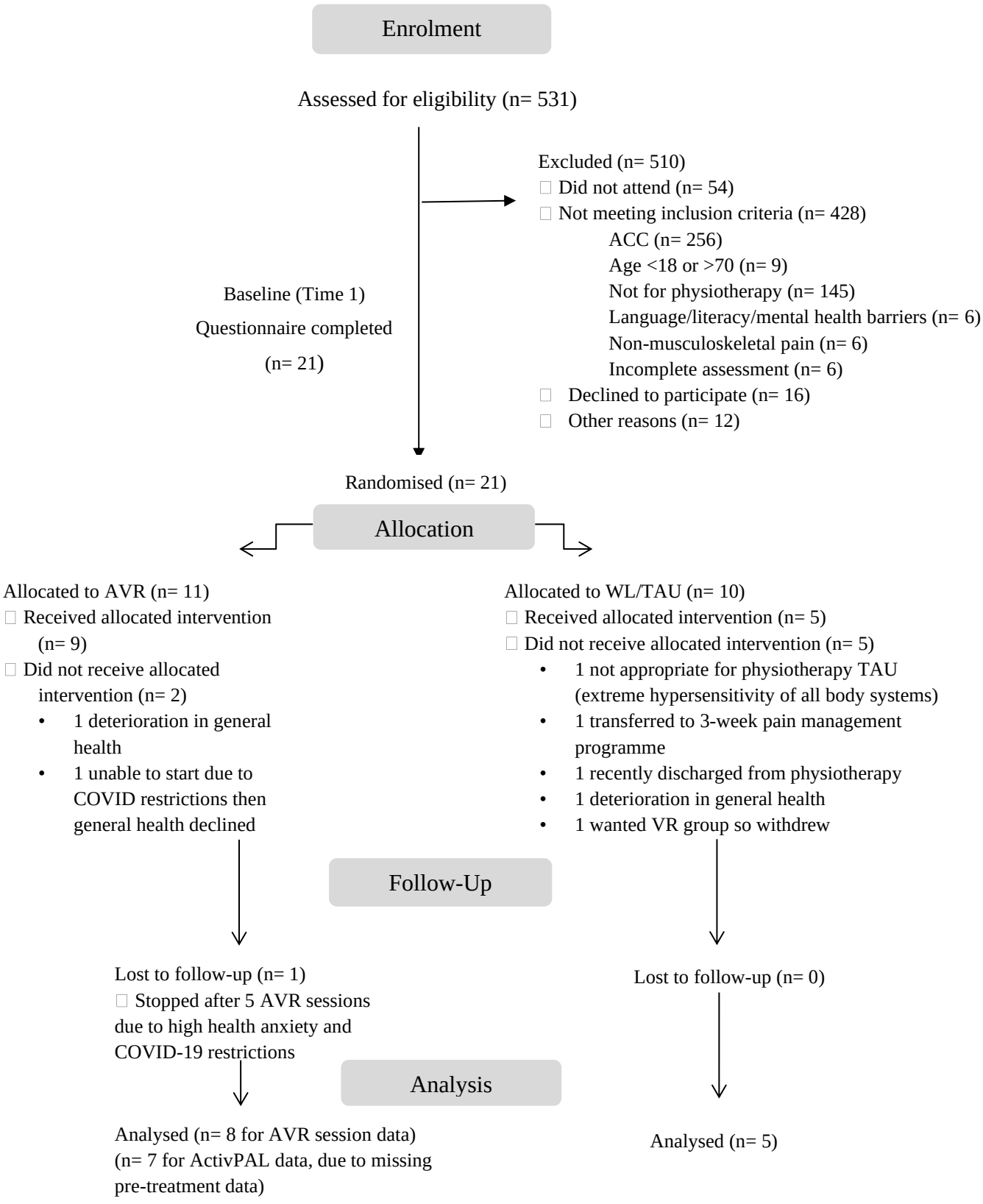
Results

3.1 Exploration of feasibility and acceptability

3.1.1 Sample Size, eligibility and recruitment

Over the period 1st October 2019 to the 11th August 2020, 531 people were referred for initial assessment through TARPS. During this time, a number of halts to the recruitment process occurred due to COVID-19 restrictions. This included a 2-month period from 24th March to 22nd June 2020 and also necessitated the recruitment period to finish two weeks earlier than planned due to a second lockdown period.

Figure 2 shows the flow of participants through the study. Of the 531 people referred during the 32-week period, only 21 potential candidates were enrolled, a recruitment rate of 4%. This would indicate a recruitment rate of approximately 2.6 recruits per month. The most common reasons for exclusion included; treatment being funded by ACC (Accident Compensation Corporation) (n= 256) and not requiring physiotherapy input (n= 145). Less common reasons included; being under 18 years or over 70 years (n= 9), non-musculoskeletal pain (n= 6), assessment was incomplete (n= 6) and language, literacy or mental health barriers (n= 6).



Note. N= number of people, ACC = Accident Compensation Corporation, AVR = Active virtual reality, WL = Waitlist, TAU = Treatment as usual.

Figure 2 Recruitment Process

As illustrated in Figure 2 initial randomisation procedures produced reasonably equal allocation between groups with 11 participants in the AVR group and 10 in the TAU group. However, further exclusion or drop-out prior to commencing the intervention led to unequal distribution between groups with eight participants in the AVR group and five in the TAU group.

Characteristics of participants who completed the full trial are provided in Table 2. As demonstrated, there were more females (n= 10) recruited than males (n= 3), with 1:7 male to female ratio for the AVR group and 2:3 ratio for the TAU group. The AVR group had been experiencing pain for a longer duration (median 7.5 years compared to 5 years) and the median age in the AVR group was slightly younger (39.5 years) than the TAU group (44 years). In addition, the AVR group reported higher ratings for pain interference (BPI interference 6.03 compared to 5.40) and intensity (BPI intensity 6.66 compared to 5.77), as well as higher fear of movement (TSK 43.3 compared to 38.8) prior to commencing treatment. However, similar characteristics were demonstrated between the groups in regards to ethnicity, employment/study rates and pain locations, with back pain being the most common problematic region.

3.1.2 Retention

As highlighted in Figure 2, of the 21 people recruited to the study only 14 people received the allocated intervention with 13 completing the full study, a completion rate of 61%.

Once randomised, five people from the TAU group and two from AVR group did not start the intervention. Reasons for drop-out/ exclusion included the chosen treatment was inappropriate, participant's health status deteriorated and one participant withdrew from the TAU arm as they only wanted the AVR treatment.

Once the intervention commenced, one person from the AVR group did not complete the full six weeks, due to health anxiety and COVID-19 restrictions.

Table 2

Demographic and Baseline Clinical Characteristics across Whole Sample

		AVR (N=8)	TAU (N=5)
		Median (IQR) / % / Frequency / Mean (SD)	
Demographics	Gender	M = 1, F = 7	M = 2, F = 3
	Age (years)	39.5 (42)	44 (31)
	Working/studying	50%	67%
	Pain duration (years)	7.5 (14)	5 (15)
	Ethnicity - NZ European	5	5
	Māori	-	1
	Indian	2	-
	Other	1	-
Main Pain Location (frequency)	Neck	0	0
	Back	2	3
	Upper limb	0	0
	Lower limb	1	1
	Stomach/abdomen	1	1
	Chest	1	0
	Hips/ pelvis/ groin	2	0
	Other	1	1
Self-report (mean, (SD))	BPI – Intensity	6.03 (2.20)	5.40 (1.33)
	BPI - Interference	6.66 (2.16)	5.77 (2.43)
	Tampa Scale for Kinesiophobia (TSK)	43.3 (5.50)	38.8 (5.85)
Physical Tests (mean, (SD))	Timed walk test (seconds)	43.63 (16.94)	35.80 (4.15)
	Dynamic lift test	8.5kg x3	8kg x3

Note. AVR = Active virtual reality, TAU = Treatment as usual, IRQ = Interquartile range, SD = Standard deviation, M = Male, F = Female.

3.1.3 Adherence to intervention

As demonstrated in Table 4, only half of the AVR participants attended all 12 sessions. Two participants missed only one session (participant number 6 slept in, participant number 21 the VR room was unavailable). One participant (number 19) missed two sessions as they were out of town and one participant (number 27) failed to attend four sessions due to high pain intensity.

In respect to breaks during the six-week treatment block, AVR participants were not always able to attend twice a week either due to personal commitments or scheduling demands of the therapist. Two participants had a break of more than one week, one participant (number 27) for three weeks due to the Christmas/ New Year holidays and one participant (number 41) for two weeks due to the COVID-19 lockdown.

Overall, the compliance rate for AVR session attendance was 92%.

For the TAU group only two out of five participants attended the full six-weeks of intervention time, two participants (numbers 18 and 40) missed one week due to being unwell and one participant (number 51) missed two sessions, one of which was due to ill health and the other due to exacerbation of back pain. Only one participant (number 18) in the TAU group had a break of two weeks between sessions due to work commitments.

The overall compliance rate for TAU session attendance was 87%.

Table 3

Attendance Rates

AVR		TAU	
Participant number	No. Sessions attended (/12)	Participant number	No. Sessions attended (/6)
2	12	23	6
6	11	10	6
4	12	18	5
27	8	40	5
19	10	51	4
16	12		
21	11		
41	12		
Mean	11	Mean	5.2

Notes. AVR = Active virtual reality, TAU = Treatment as usual.

The session duration was only monitored for the AVR group as the TAU group did not have clearly defined activity quotas within the sessions. Table 4 illustrates that the AVR session duration deviated from the planned 20 minutes, with average session duration ranging from 14 to 20 minutes. This provides an adherence rate of 85% for

intervention time. In three cases (participants 4, 27 and 16), most of the sessions fell below the 20-minute duration due to requests to stop secondary to increasing pain intensity.

Table 4

AVR Intervention Measures

Participant number	Change in pain score; mean (range)	Enjoyment; mean (range)	Immersion; mean (range)	Session duration; mean (mins)	Relaxation / meditation time; mean (mins)	Corrected AVR time; mean (mins)
2	-0.167 (-1-0)	9.75 (8-10)	9.72 (8-10)	20	0	20
6	0.250 (-1-0)	9.75 (9-10)	9.5 (8-10)	16	1	15
4	0.417 (0-1)	9.75 (9-10)	9.58 (9-10)	16	1	15
27	-1.429 (-3-1)	9.86 (9-10)	8.86 (8-9)	14	7	7
19	0.222 (-1-1)	9.78 (9-10)	9.89 (9-10)	19	0	19
16	-0.167 (-1-0)	9.75 (8-10)	9.25 (8-10)	14	3	11
21	-0.083 (-1-1)	9.27 (8-10)	9.18 (8-10)	18	0	18
41	-2.42 (-1- -4)	9.42(7-10)	9.33 (8-10)	19	1	18
Mean	-0.42	9.67	9.41	17	1.6	15

Notes. AVR = Active virtual reality

3.1.4 Acceptability of AVR intervention

3.1.4.1 Fidelity of session content

The inclusion of passive strategies involving meditation and relaxation was deemed necessary for five out of the eight AVR participants. Three of these cases (numbers 6, 4 and 41) only required a short duration, with an average of just one minute of non-active time within the AVR. However, participant's numbers 3 and 27 required longer periods with an average of 3 and 7 minutes respectively performing passive strategies per session. The main reason for this adaptation was high reported pain intensity either on commencing or during the AVR session. Most commonly passive strategies were used to ease participants into the session and/or as a technique to reduce pain following the active components. As a result of this non-active time, the adherence in performing solely AVR drops to 77%.

3.1.4.2 Enjoyment, immersion and impact on pain

Self-reported session evaluations indicated that all participants experienced high levels of enjoyment in undertaking AVR (mean scores ranging from 9.27-9.86 out of 10) (Table 4). Average immersion level was also rated highly (mean scores 8.86-9.89), indicating that participants felt immersed in the virtual environment. With respect to immediate impact on pain, there was a mean reduction in pain intensity in five cases but

an increase in three cases (Figure 3). According to Salaffi, Stancati, Alberto Silvestri, Ciapetti, and Grassi (2004) the MCID for visual analogue scale (VAS) pain ratings is a 15% reduction, only one participant (41) achieved a reduction of this magnitude.

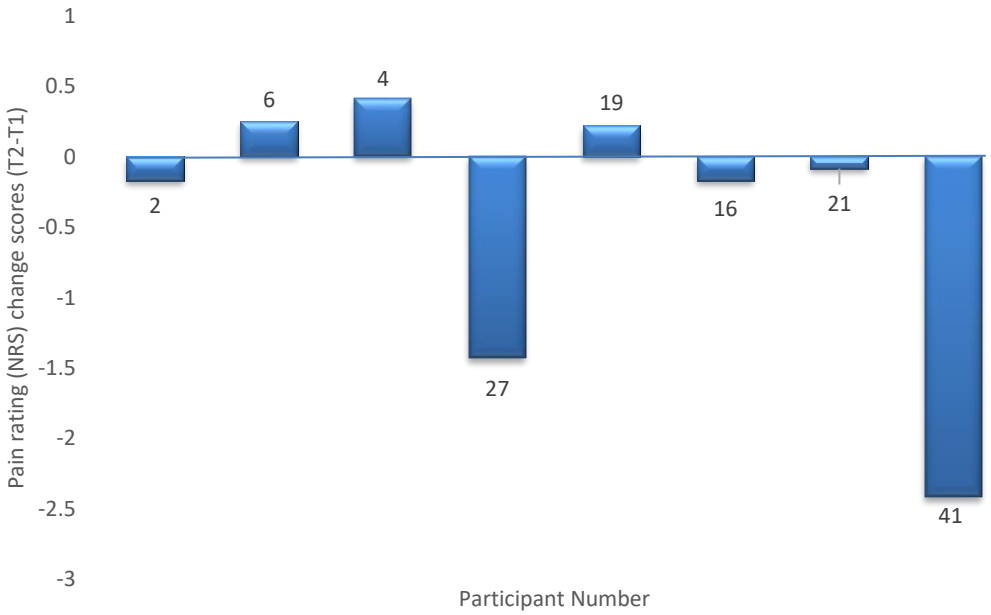


Figure 3 Mean Pain Rating Change Scores (T2-T1) for AVR Participants

3.1.4.3 Satisfaction and improvement

Questions regarding impression of change following input were asked of all participants within the outcome measures questionnaire, including the WL period.

As shown in Table 5, AVR participants rated their overall satisfaction with treatment as 6 out of 7 on the Likert scale. This is slightly higher than the TAU group who rated satisfaction as 5.6. Interestingly, the WL group also rated satisfaction with treatment as somewhat satisfied (5.2) despite not receiving any intervention.

In regard to overall improvement, both intervention groups noted a small improvement on the Likert scale (AVR 4.7 and TAU 4.8) as opposed to the WL group which showed a slight deterioration in symptoms (rated as 3.5) (Table 5)

Table 5

Mean Satisfaction and Improvement Scores across Treatment Arms

	Participant N^{o}	Mean Improvement (/7)	Mean Treatment Satisfaction (/7)
AVR	2	4	7
	6	5	7
	4	5	6
	27	6	4
	19	-	-
	16	5	6
	21	4	6
	41	4	6
	Mean	**4.7**	**6**
WL	23	3	5
	10	5	5
	18	4	4
	40	4	6
	51	5	6
	Mean	**3.5**	**5.2**
TAU	23	4	6
	10	6	7
	18	5	6
	40	3	4
	51	6	5
	Mean	**4.8**	**5.6**

Note. AVR = Active virtual reality, WL = Waitlist, TAU = Treatment as usual.

3.1.5 Safety of intervention

There were no severe adverse events noted as a result of either intervention (such as falls, or significant pain exacerbation following input). However, one participant from the AVR group reported a mild adverse effect of dizziness when progressed to Grade 6 skiing activity. This activity was therefore not utilised again for other participants.

In respect to safety of data collection procedures, one person, who withdrew from the trial due to extreme whole-body sensitivity, reported a severe adverse reaction to wearing the ActivPAL activity tracker producing skin break down requiring

antihistamines and antibiotics. Two other participants reported a mild skin rash which was managed by changing the monitor between legs on a regular basis.

No other issues were reported by either the AVR of TAU groups.

3.2 Activity monitoring with the ActivPAL

To investigate whether activity levels changed with each intervention, average daily summaries (categorised as total number of steps, sedentary time, upright time and MET) were compared pre- and post- intervention and control periods. These are demonstrated in Table 6 and described separately below with preliminary analysis of ES of AVR calculated against the WL control and the TAU group.

The ActivPAL was worn for the requested time by all participants obtaining a total of six full days of data. However, due to technical issues one participant (number 16) from the AVR group had missing baseline data. This participant was therefore excluded from the ActivPAL data analysis.

3.2.1 Daily steps

Daily steps increased in all groups with the greatest increment seen in the WL group (mean change = 696 steps, SD 2549), followed by the AVR group (Mean change = 434 steps, SD 2901) and the TAU group (mean change = 269 steps, SD 2043) (Figure 4). One participant (number 18, WL group) was a significant outlier, with a large reduction in step count secondary to being unwell during the week six monitoring period.

The ES of the AVR intervention in relation to the WL control on step count was -0.09 (CI -1.24-1.06) indicating that AVR had a negative effect compared to the control. The ES calculated for AVR in relation to the TAU group was 0.06 (CI -1.09-1.21), which according to Cohen's criteria (Cohen, 1988) would indicate an extremely small ES favouring AVR over TAU.

A MCID of between 600-1100 steps per day has been suggested for people undertaking pulmonary rehabilitation (Demeyer et al., 2016) but has not been explored in people with chronic pain. Applying this MCID however, would indicate that three out of seven participants (42%) in the AVR group and three out of five participants (60%) in the WL and TAU groups achieved this.

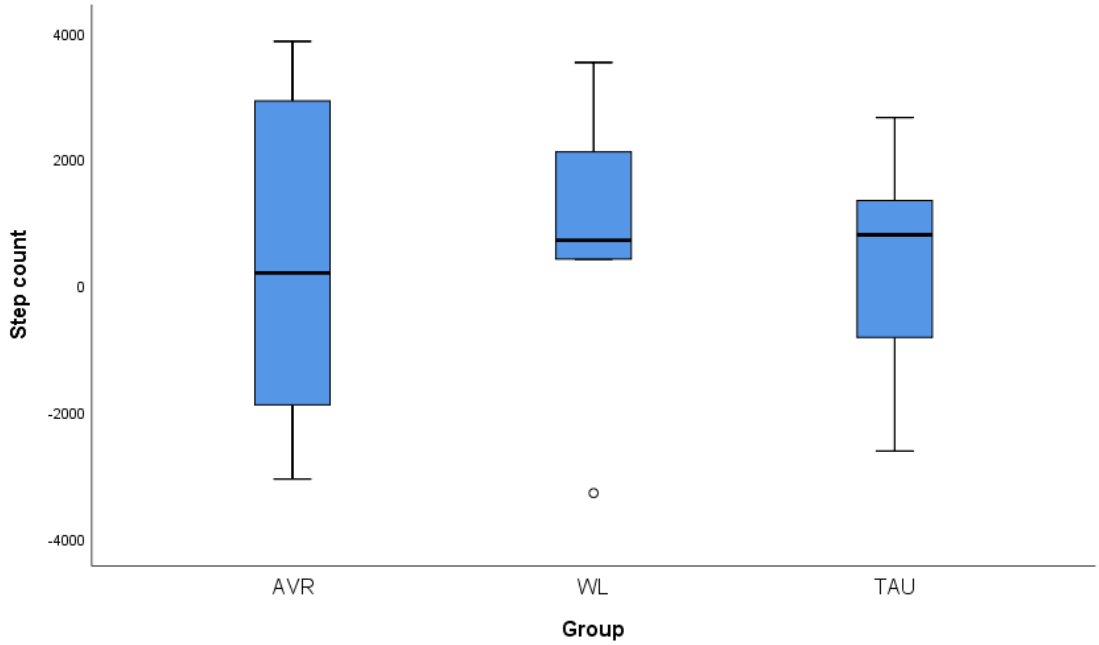


Figure 4 Boxplot Demonstrating Average Daily Step Count Differences from Baseline to Completion

3.2.2 Sedentary time

Average daily sedentary time reduced in the AVR group by -11.23 minutes (SD 67.37) and in the WL by -5.53 minutes (S.D. 104.82) but increased by 17.41 minutes (SD 160.69) in the TAU group (Figure 5). Three subjects were considered outliers. Participant number 6 from the AVR group had a larger increase in sedentary time at completion secondary to a flare-up of pain. Participant numbers 19 (AVR) and 10 (TAU) had large decreases in sedentary time which they verbally attributed to feeling more confident with movement. However, these results are far below the suggested MCID for sedentary behaviour of a reduction of 2.03 hours (Dontje et al., 2018).

The ES of the AVR intervention in relation to the WL control for change in sedentary time was -0.07 (CI -1.21-1.08) and the ES of AVR in relation to the TAU group was -0.24 (CI -1.38-0.93). These negative scores indicate very small ES's (Cohen, 1988) favouring the AVR intervention over the WL and TAU groups for reducing sedentary behaviour.

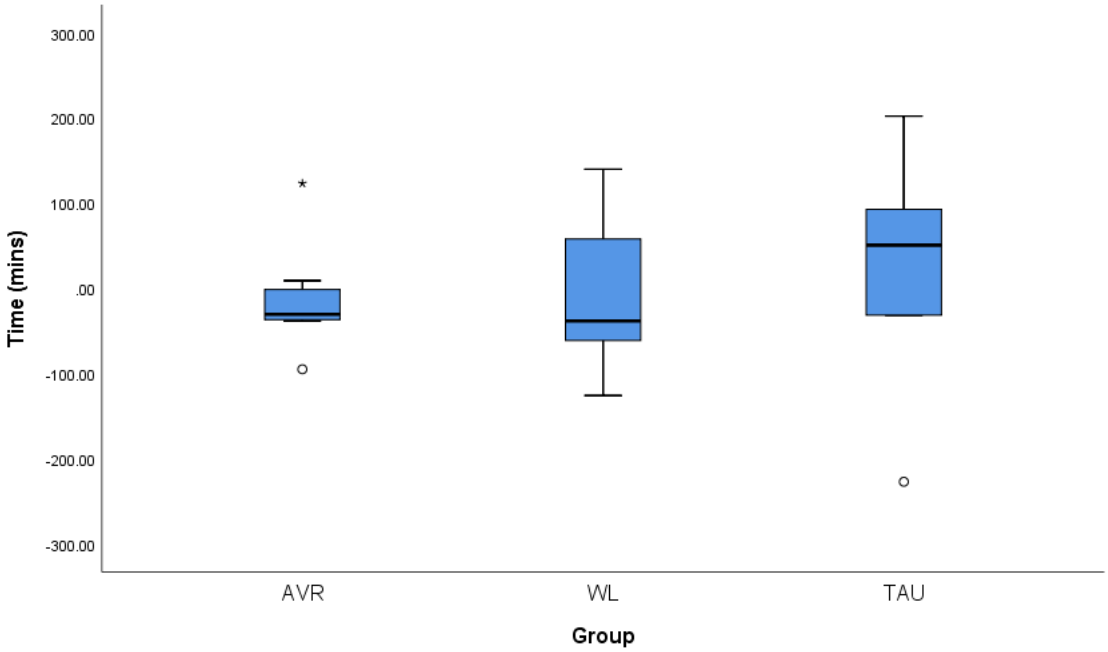


Figure 5 Boxplot Demonstrating Change in Average Daily Sedentary Time from Baseline to Completion

3.2.3 Upright (active) time

Daily upright time increased in the AVR group by 13.60 minutes (SD 67.33) and the WL group by 2.06 minutes (S.D. 71.76), but decreased in the TAU group by -51.84 minutes (SD 57.92) (Figure 6). Three outliers again were noted. Large reductions in active time were noted in participant 6 (AVR) due to the pain flare-up mentioned above and in participant number 18 (WL) due to being unwell at follow-up. A larger increase in activity was noted again in participant number 10 even during the WL time period, indicating factors aside from the intervention may have been responsible for these changes.

The ES of the AVR intervention in relation to the control group on upright time was 0.02 (CI -1.13-1.17) and the ES of AVR in relation to the TAU group was 0.13 (CI -1.03-1.27). According to Cohen's criteria (Cohen, 1988) these indicate very small positive effects of AVR compared to WL and TAU groups.

There is currently no research to define a MCID for time spent being active. Dworkin et al. (2005) suggest that an ES of 0.50 is a reasonable criterion to start with when exploring important changes and in this instance none of the groups achieved this level.

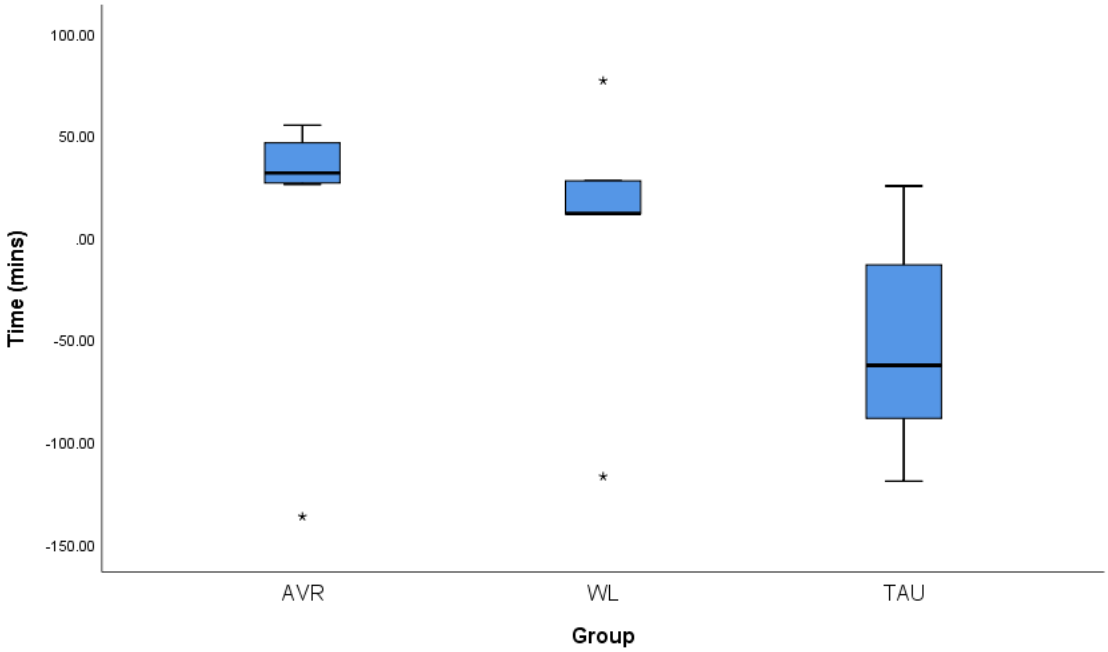


Figure 6 Boxplot Demonstrating Change in Average Daily Upright Time from Baseline to Completion

3.2.4 Energy expenditure

MET scores increased in the AVR group by 0.18 MET (SD 1.15) and by 0.26 MET (S.D. 1.08) for the WL group but decreased by -0.19 (SD 0.64) for TAU (Figure 7). Again participant 18 (WL) was an outlier with a reduction in energy expenditure secondary to being unwell during the week six data collection.

The ES of the AVR intervention relative to the WL group for MET scores was -0.07 (CI -1.21-1.08) indicating that AVR had a negative effect compared to the WL control. The ES of AVR relative to TAU was 0.38 (CI -0.81-1.51), indicating a small ES (Cohen, 1988) favouring AVR over TAU.

There is no research to determine a MCID for change in MET scores but applying the criteria relating to ES above, none of the groups achieved a MCID (Dworkin et al., 2005).

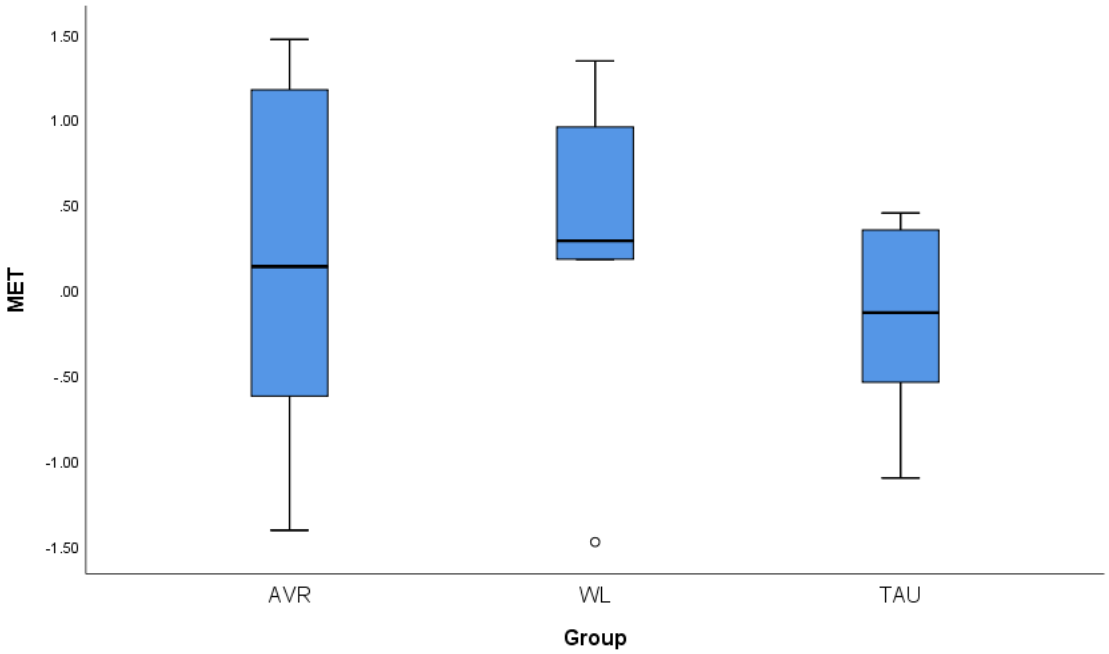


Figure 7 Boxplot Demonstrating Change in Average Daily MET Scores from Baseline to Completion

Table 6

Mean Daily Summaries

		Baseline (Time 1)				Completion (Time 2 (VR) /3 (TAU))				Change Scores			
Group	Participant	Steps	MET	ST (mins)	UT (mins)	Steps	MET	ST (mins)	UT (mins)	Steps	MET	ST (mins)	UT (mins)
AVR	2	5932	33.05	1141	362	8160	33.99	1130	417	2228	0.94	-12	55
	6	10028	34.87	1003	498	7067	33.46	1126	361	-2961	-1.41	123	-137
	4	9811	34.30	1181	331	13673	35.77	1151	385	3862	1.47	-31	54
	27	2672	31.26	1394	117	2868	31.39	1403	144	192	0.13	9	27
	19	9237	34.04	1272	288	8413	33.84	1177	320	-824	-0.2	-95	31
	21	7128	33.37	1223	319	10739	34.77	1188	358	3611	1.4	-35	39
	41	8507	34.05	1095	390	5438	33.00	1057	416	-3069	-1.05	-38	26
	Mean	**7616 (SD 2632)**	**33.56 (SD 1.18)**	**1187 (SD 126)**	**329 (SD 115)**	**8051 (SD 3503)**	**33.75 (SD 1.38)**	**1176 (SD 109)**	**343 (SD 94)**	**435 (SD 2901)**	**0.18 (SD 1.15)**	**-11. (SD 67)**	**14 (SD 673)**
WL	23	7161	33.19	1262	243	7577	33.37	1320	255	416	0.18	58	11
	10	5266	32.37	1397	188	7379	33.33	1359	265	2113	0.95	-38	77
	18	11246	35.28	1022	489	7956	33.80	1162	372	-3290	-1.48	140	-117
	40	8626	33.92	1318	322	12153	35.26	1192	350	3527	1.34	-126	28
	51	7863	33.68	1199	336	8577	33.97	1138	348	714	0.29	-61	12
	Mean	**8032 (SD 2186)**	**33.70 (SD 1.07)**	**1240 (SD 142)**	**316 (SD 114)**	**8728 (SD 1968)**	**33.95 (SD 0.79)**	**1234 (SD 99)**	**318 (SD 54)**	**696 (SD 2549)**	**0.26 (SD 1.08)**	**-5 (SD 105)**	**2 (SD 72)**
TAU	23	9534	34.15	1222	283	6910	33.05	1273	220	-2624	-1.10	51	-63

10	5988	32.65	1538	194	6786	33.00	1311	219	798	0.35	-227	25
18	9523	34.73	995	525	8698	34.19	1088	436	-825	-0.54	93	-89
40	7871	33.59	1285	299	9212	34.04	1253	285	1341	0.45	-32	-14
51	3237	33.00	1057	416	5892	32.87	1259	297	2655	-0.13	202	-119
Mean	**7230 (SD 2668)**	**33.63 (SD 0.84)**	**1219 (SD 214)**	**343 (SD 129)**	**7500 (SD 1397)**	**33.43 (SD 0.63)**	**1237 (SD 86)**	**291 (SD 88)**	**269 (SD 2043)**	**-0.19 (SD 0.64)**	**17 (SD 161)**	**-52 (SD 58)**

Note. MET = Metabolic equivalent task, ST = Sedentary time, UT = Upright time, SD = Standard deviation, AVR = Active virtual reality, WL Waitlist, TAU = Treatment as usual.

3.3 Outcome measures

Baseline questionnaire data were obtained for all participants. Only one participant (number 19 AVR group) did not complete the follow-up questionnaire. This was due to prolonged postponement of the final two sessions due to the COVID-19 lockdown. When it was clear that these sessions could not be completed it was deemed that too long a duration had passed to gain an accurate recollection of the intervention outcomes.

3.3.1. Pain intensity and interference

There was an overall increase in pre-post pain intensity scores for the AVR group from 6.03 to 6.25 (Table 7). The WL group also noted a slight increase in pre-post pain intensity from 5.30 to 5.40, while the TAU group displayed a reduction from 5.40 to 4.15.

The ES calculated for AVR in relation to the WL control in regards to pain intensity was 0.32 (CI -0.82-1.42), a small ES (Cohen, 1988) indicating that those in the AVR group had a small increase in pain relative to the control group. When comparing AVR against TAU, the ES was large (1.37, CI 0.06-2.5) suggesting a much larger increase in pain for the AVR group relative to the TAU group.

In respect to pain interference, there was a reduction in BPI interference scores for all groups. This was from 6.66 to 6.26 in the AVR group, from 6.77 to 5.77 in the WL control and from 5.77 to 4.80 for the TAU group.

The ES calculated for AVR in relation to the WL control for pain interference was -0.13 (CI -1.23-1.00), indicating that to a small extent AVR was less effective than the WL control at reducing pain interference (Cohen, 1988). When comparing AVR against TAU the ES was -0.62 (CI -1.72-0.56) indicating that those in the AVR group had a moderately smaller reduction in pain interference than those in the TAU group (Cohen, 1988).

Mean scores demonstrated that none of the groups achieved the MCID of ≥30% reduction in total BPI score considered to be a clinically meaningful improvement (Dworkin et al., 2005). However, participant number 51 from the TAU group did achieve over 30% reduction in pain intensity and participant number 10 from the WL control displayed greater than 30% reduction in pain interference.

3.3.2. Fear of movement

There was a reduction in fear of movement across all three groups (Table 7). This was smallest in the AVR group with a reduction from 43.3 to 41.83, followed by the WL group

with a reduction from 42.40 to 38.80 and most pronounced in the TAU group with a reduction from 38.80 to 33.80.

The ES calculated for AVR in relation to the WL control in regards to kinesiophobia was 0.44 (CI -0.72-1.54). As the TSK aims to display improvements to fear of movement with a reduction in score this positive number indicates that to a small to moderate extent (Cohen, 1988) AVR was less effective at reducing fear of movement than the WL control. When comparing AVR against the TAU the ES was 0.71 (CI -0.49-1.80) a moderate to large ES (Cohen, 1988) indicating that AVR was less effective than TAU at reducing fear of movement.

Mean scores indicate that none of the groups achieved the suggested MCID of 18% reduction in the TSK (Monticone, Ambrosini, Rocca, Foti, & Ferrante, 2016). However, closer inspection of individual results revealed this was achieved by participant number 18 of the TAU group with a 24% reduction in TSK score.

3.3.3. Objective physical assessment measures

Physical assessment outcome data were missing for a number of the AVR participants due to lost data sheets. Therefore, results were based on small sample sizes (TAU = 5, AVR = 4). On the whole, the AVR group showed a mean increase in walking speed by 10s (SD 15.47), this is a walking velocity difference of 0.4m/s. The TAU group were faster by 4.2s (SD 3.03), a walking velocity difference of 0.08m/s. The MCID for walking speed has been reported to range from 0.10-0.17m/s (Bohannon & Glenney, 2014). Although preliminary inspection of the mean changes would suggest that only the AVR group achieved this range, inspection of individual data showed that four out of the five TAU subjects achieved MCID range, with improvements to speed of -0.18, -0.19, -0.48 and -0.15m/s. Three out of the four AVR participants included in this analysis achieved improvements of -0.57, -0.49 and -0.12m/s.

Both groups displayed improved functioning in the dynamic lift test with a 1kg increase and an additional lift in the AVR group and 2.5kg increase with two additional lifts in the TAU group.

Table 7

Physical and Outcomes Measures

	Participant Nº	Baseline (Time 1)					Completion (Time 2/3)					Change Sores				
		Physical Measures		Self-Report			Physical Measures		Self-Report			Physical Measures		Self-Report		
		Box Lift (Kg/ reps)	Walk (secs)	BPI- Intensity	BPI - Interference	TSK	Box Lift (Kg/ reps)	Walk (secs)	BPI- Intensity	BPI - Interference	TSK	Box Lift (Kg/ reps)	Walk (secs)	BPI- Intensity	BPI - Interference	TSK
AVR	2	15kgx4	30	5	4	38			3	3	37			-2	-1	-1
	6	10kgx4	33	4	6.43	44	10kg x4	24	4.25	5.43	38	0	-9	0.25	-1	-6
	4	10kgx4	48	7.75	8.71	37			7.25	6.29	42			0.5	-2.42	+5
	27	2.5kgx1	60	9.5	9.43	52			9	9.43	52			-0.5	0	0
	19	7.5kgx4	42	4.25	3.29	39	COVID-19 Lockdown, data incomplete									
	16	0kg x2	76	8.25	7.86	46	2.5kg x3	44	8.75	7.14	39	2.5kg 5lifts	-32	0.5	-0.72	-7
	21	10kg x4	30	5.75	7.43	43	12.5 x4	33	5.25	6.29	43	2.5kg 4lifts	+3	-0.5	-1.14	0
	41	12.5kgx4	30	3.75	6.14	40	12.5 x4	28	3.5	4	40	0	-2	-1.25	-2.14	0
	Mean	**8.5kg x3**	**43.63 (SD 16.94)**	**6.03 (SD 2.20)**	**6.66 (SD 2.16)**	**43.3 (SD 5.50)**	**9.5kg x4**	**32.25 (SD 8.66)**	**6.25 (SD 2.46)**	**6.26 (SD 2.10)**	**41.83 (SD 5.49)**	**1kg x1**	**-10 (SD 15.47)**	**0.43 (SD 0.94)**	**-1.20 (SD 0.83)**	**-1.29 (SD 4.07)**
WL	23	7.5kgx4	35	5	8.14	39	-	-	5.25	8.71	37	-	-	+0.25	0.57	-2
	10	0kg x2	43	6.5	8.00	54	-	-	5	4	43	-	-	-1.5	-4	-11
	18	5kg x1	33	3.5	4.29	39	-	-	3.5	2.86	46	-	-	0	-1.43	+7
	40	15kgx4	35	7	5.43	45	-	-	7	7.57	37	-	-	0	2.14	-8
	51	12.5kgx4	33	4.5	8.00	35	-	-	6.25	5.71	31	-	-	+1.75	-2.29	-4
	Mean	**8kg x3**	**35.80 (SD 4.15)**	**5.30 (SD 1.44)**	**6.77 (SD 1.79)**	**42.40 (SD 7.40)**	**-**	**-**	**5.40 (SD 1.33)**	**5.77 (SD 2.43)**	**38.80 (SD 5.85)**	**-**	**-**	**0.1 (SD 1.15)**	**-1.00 (SD 2.41)**	**-3.60 (SD 6.88)**
TAU	23	7.5kgx4	35	5.25	8.71	37	10kg x3	31	4.25	7.00	35	2.5kg 3lifts	-4	-1	-1.71	-2
	10	0kg x2	43	5	4	43	5kg x2	37	5	5.71	42	5kg 4lifts	-6	0	1.71	-1

18	5kg x1	33	3.5	2.86	46	10kgx1	25	4	1.57	30	5kg 4lifts	-8	0.5	-1.5	-16
40	15kgx4	35	7	7.57	37	15kg x4	35	4.5	5.57	38	0	0	-2.5	-2	+1
51	12.5kg x4	33	6.25	5.71	31	12.5kg x4	30	3	4.14	24	0	-3	-3.25	1.57	-7
Mean	**8kg x3**	**35.80 (SD 4.15)**	**5.40 (SD 1.33)**	**5.77 (SD 2.43)**	**38.80 (SD 5.85)**	**10.5kg x3**	**31.6 (SD 4.67)**	**4.15 (SD 0.74)**	**4.80(SD 2.07)**	**33.80 (SD 7.01)**	**2.5kg x2 lifts**	**-4.2 (SD 3.03)**	**-1.25 (SD 1.60)**	**-0.39 (SD 1.86)**	**-5.00 (SD 6.82)**

Note. Kg= kilograms, Reps = Repetitions, Secs = seconds, BPI = Brief Pain Inventory, TSK = Tampa Scale for Kinesiophobia, SD = Standard deviation, AVR = Active virtual reality, WL Waitlist, TAU = Treatment as usual.

Discussion

The present study was part of a mixed-method pilot study designed to assess the feasibility and acceptability of performing an RCT to explore AVR as an intervention for people with chronic pain. This feasibility study focused on three main questions. The first question addressed acceptability of AVR as an intervention for people with chronic pain and the feasibility in undertaking the future RCT. Taking into account sample size, recruitment processes and retention rates it would appear that an RCT following the protocol utilised here would not be feasible. In particular, changes to the recruitment process to increase the number of participants enrolled would be necessary. However, AVR as an intervention was deemed acceptable by people with chronic pain. Participants reported positive outcomes for satisfaction with treatment, enjoyment, global impression for change and immersion when using the VR. Compliance and adherence rates were high even in instances when pain increased during sessions.

The second question aimed to determine whether activity levels measured by the ActivPAL activity tracker changed with interventions, comparing AVR against a WL control and TAU. Preliminary analysis of the ActivPAL data demonstrated either small positive ES's or small negative ES's (worse outcomes) of the AVR relative to TAU or WL, with large variability (SD's) to mean outcomes. These results may indicate that the tracker is not suitable for measuring meaningful change within a chronic pain population.

Finally, this feasibility study aimed to identify whether undertaking AVR led to changes in pain-relevant outcome measures, with comparisons made against TAU and a WL control. On the whole AVR was not substantially different to the TAU and WL groups with small ES differences favouring TAU and WL groups over the AVR. However, these results are based on small sample sizes and therefore caution is warranted with their interpretation. Each of these key findings is discussed in detail and reviewed in the context of the relevant literature below.

4.1 Exploration of feasibility and acceptability

4.1.1 Sample Size, eligibility and recruitment

Recruitment for the study was low with only 4% of people seen through TARPS recruited to the study and just 2.6% receiving the allocated treatment. The initial criterion to explore feasibility of the future RCT specified thirty participants were to be recruited within a

six-month time frame. This did not occur, with only 21 participants recruited over eight months.

The full mixed-method pilot study used G-power software (3.0.10) based on a power of 90% and alpha of .05 to calculate an estimated sample size for the proposed RCT. This power analysis suggested a sample of 104 participants would be needed to demonstrate a small to medium ES using repeated-measures analysis of variance (ANOVA). Based on the final completion rate of 2.4%, it would take 43 months to obtain the recommended sample size. Additionally, considering the small ES results demonstrated within this study it could be argued that the original power analysis produced a sample size estimate that was too small for some of the outcome measures used. Recalculating sample size based on the current findings (as discussed below) reveals in some instances larger sample sizes would be required. This would take many years to attain if adhering to the pilot study recruitment strategies.

A large proportion (almost 50%) of potential candidates were excluded because of being managed by ACC (n= 256). ACC provides support for people with chronic pain resulting from injury with a large number experiencing musculoskeletal complaints requiring physiotherapy input. ACC funds standard packages of care, therefore to perform AVR as a stand-alone treatment would require specific authority from ACC and this was not obtained for the pilot study. To increase recruitment numbers and improve study quality, future research should consider inclusion of ACC cases. Additionally, the COVID-19 situation led to unforeseen disruptions to recruitment and retention, with breaks to the recruitment process, delays for some participants starting the trial or recruits leaving the trial due to increased health anxiety. Furthermore, TARPS is a tertiary service receiving referrals for highly complex cases. Opening recruitment to a wider spectrum of people with chronic pain from other service providers and the community may improve access, allowing greater representation of chronic pain populations and potentially fewer barriers to physical activity input (such as significant health anxiety or mental health issues).

The characteristics of the sample population were somewhat representative of the NZ chronic pain population. The NZ Health Survey 2019/2020 (Ministry of Health, 2020) reported that chronic pain more commonly affects females, which may explain the higher number of females recruited to the study. However, the survey indicated that chronic pain is more prevalent in adults aged over 55 years (Ministry of Health, 2020), whereas median ages in this study were 39 and 44 years. A possible reason for this could be gaming technology is more appealing to younger people with older adults being less inclined to engage with

activities deemed more complex (Blocker, Wright, & Boot, 2014). This may indicate a need for better explanation on the use of VR technology to recruit a wider spectrum of ages.

According to the NZ Health Survey 2019/2020 (Ministry of Health, 2020) Maori people have a high prevalence of chronic pain, yet Maori were poorly represented in this study, with ethnicity mainly composed of NZ European participants. This may highlight the impact of culture differences on healthcare utilisation or other possible barriers to AVR such as the use of HMD equipment where the head (which is deemed Tapu) is involved. However, to fully understand the reasons for reduced uptake within this culture closer inspection of the recruitment logs to identify the number of Maori patients assessed through TARPS and the reasons for non-inclusion, as well as qualitative interviews to gain insight into Maori views on chronic pain management and the use of AVR would be necessary.

The most common pain location reported in participants was low back pain which is deemed one of the foremost causes of pain-related disability globally (Vos et al., 2016). Neck pain has also been ranked as a major cause of disability (Vos et al., 2016) but interestingly none of the participants recruited experienced pain in this area. It could be speculated that wearing the HMD may have deterred people with neck pain, with previous research reporting neck and shoulder discomfort to be common when wearing the head mounted gear (Tong, Gromala, Gupta, & Squire, 2016). However, further research, such as interviewing patients with neck pain who were deemed eligible to participate but did not enrol, may clarify reasons behind low uptake in this cohort.

4.1.2 Retention

Of those recruited and randomised to the study only 67% received the intervention. Three subjects were withdrawn as they were not suitable for the planned intervention. This may indicate the recruitment team needed clearer guidance on the inclusion/exclusion criteria. One subject withdrew because he was randomised to the TAU group but only wanted AVR. Improved education on the aim of the study, or blinding participants to the nature of the study may have negated this. Three further subjects had unavoidable deteriorations in general health. These results show the feasibility criterion dictating retention should be greater than 80% was not achieved. However, if the suggested changes to reduce the drop-out rate prior to commencing the intervention are made there is a high probability this will improve considering retention rate was high (93%) once the study commenced.

4.1.3 Adherence to intervention

The study adherence requirements for AVR were to attend 20 minutes of AVR, for 12 sessions over six weeks. Attendance was high at 92% attendance compared to the TAU group which was 87%. Adherence to the sessions was only monitored for the AVR group and demonstrated an adherence rate of 85% thus achieving the feasibility criterion which stipulated greater than 80% adherence to the intervention. This is positive considering active components to increase function in people with chronic pain have shown poor adherence and high dropout rates (Friedrich, Gittler, Halberstadt, Cermak, & Heiller, 1998; Vlaeyen, Morley, Linton, Boersma, & de Jong, 2012). Increased pain during or after activities has been suggested to be a primary contributing factor in poor attendance and adherence (Palazzo et al., 2016; Vlaeyen et al., 2012). In our study, only one participant cancelled several sessions due to high pain intensity but for the majority, participants were agreeable to continue and reported to enjoy the sessions even if pain increased. AVR offers a new and exciting activity to people with chronic pain focusing on game play and task specific activities to encourage movement rather than standard input promoting activity through exercise. It could be speculated that the enjoyability factor influenced attendance rates. The qualitative component of the full mixed-method pilot study involving participant interviews may clarify this.

The intervention 'dose' used was similar to the study by Garrett et al. (2017) who explored VR for chronic pain patients as an adjunct to home therapy. Within their study twelve sessions of 30 minutes were considered a reasonable time frame to explore clinical effectiveness. However, studies which have delivered VR in fewer sessions and/or over shorter timeframes have also demonstrated positive outcomes in terms of pain and disability (Fowler et al., 2019; Rezaei et al., 2019). Although attendance rates were high this may pose the question as to whether the full 12 sessions over the six weeks are necessary to explore outcomes related to efficacy. At present there is no research to identify an optimal dosage of AVR treatment.

4.1.4 Acceptability of intervention

The feasibility criterion which specified that AVR as an intervention was considered acceptable was explored through several means.

4.1.4.1 Fidelity of session content

Inspection of session content revealed that passive strategies involving relaxation or meditation were often incorporated into the sessions. When considering the impact this had to

adherence to session content the adherence rate drops to 77% and no longer meets the criterion for feasibility which required an adherence rate of 80%.

Relaxation using VR has been studied in detail for chronic pain with positive responses (Botella et al., 2013; Garrett et al., 2017; Gromala et al., 2015; Jones et al., 2016; Wiederhold et al., 2014). The inclusion of these non-active strategies may influence outcomes and the interpretation of effectiveness of AVR as a standalone treatment. To clarify this, the effectiveness of either intervention needs to be explored. Currently, there is no research to compare outcomes from passive versus AVR strategies in chronic pain populations. Garrett et al. (2017) compared passive strategies (experiences in VR environment and meditation) against exploratory and active problem-solving skills (based on active thinking not physical activity), with no significant difference in pain reported from the different strategies. Fowler et al. (2019) utilised passive and active strategies as a hierarchy of progression over a three-week programme, starting with low intensity meditation and visualisation prior to progressing to medium intensity (such as virtual walking / swimming, controlling vehicles) then high intensity apps involving larger body movements (for example 3D painting, music or rhythm-based activities). However, the focus of their study was to explore the hierarchy as a means for reducing fear avoidance and not to compare the outcomes from the different type of VR experience. Research to compare outcomes from passive and active strategies or combinations of the two would be beneficial in the future to guide the most appropriate approach to this type of intervention.

4.1.4.2 Enjoyment, immersion and impact on pain

Overall, our study reported high levels of enjoyment (96%) and perceived immersion (94%) with the AVR. This supported acceptability for AVR in our study population and is similar to previous studies exploring VR (Fowler et al., 2019; Garrett et al., 2017; Rutledge et al., 2019). Even when pain was reported to increase following the AVR experience it did not detract from participants enjoyment or perceived level of immersion within the virtual world. Again this concurs with previous research demonstrating that despite negative side effects such as motion sickness or increased pain, participants were still able to positively enjoy the experience (Tong et al., 2016).

Immediately following the AVR sessions modest improvements to pain were reported in five out of eight cases. Despite an increase in pain in three participants, satisfaction with

treatment and global impression of change were still rated highly. The study confirmed that pain did not dramatically increase with input or influence dropout rates.

4.1.4.3 Satisfaction and improvement

Self-report scores for satisfaction with treatment between the groups revealed higher ratings in the AVR group than the WL and TAU groups. The average score for satisfaction was 6 out of 7 on the Likert scale and again supported acceptability of AVR as an intervention. However, as the WL group also reported being 'somewhat satisfied' with treatment despite not receiving any intervention, it is likely this question is flawed either in phrasing or with biasing such as social desirability bias. Alternatively, it is possible the WL subjects considered the education provided during initial assessment or contact with the research team as therapeutic input and were satisfied with these interactions. Future trials may need to review this question, and account for elements of the assessment process that may also have therapeutic value.

The AVR and TAU groups reported similar levels for overall improvement following treatment (4.7 and 4.8 out of 7 respectively in the Likert scale), supporting the acceptability for AVR. This was despite distinct differences between the groups in the focus and content of sessions. The AVR sessions aimed solely at increasing activity levels utilising fun and interesting strategies. Whereas the TAU sessions delivered specialised knowledge involving evidence-based education on the concepts of chronic pain and strategies to improve overall function such as graded activation and graded exposure. There is a vast amount of research to support the positive impact of these standard approaches on chronic pain such as reducing pain and catastrophising, and improving function and movement (Louw, Diener, Butler, & Puentedura, 2011; Tegner, Frederiksen, Esbensen, & Juhl, 2018; Woods & Asmundson, 2008) but limited evidence to support the use of AVR. If similar positive improvements can be perceived in individuals with chronic pain with less specialised input, this may improve patient access to care, reduce resource constraints and be advantageous to chronic pain management. Research exploring this is still in its infancy but there is already encouraging evidence to suggest positive improvements to chronic pain outcomes with VR interventions used in the patient's own home (Garrett et al., 2017). Performing VR independent from the clinic would allow individuals to increase treatment sessions (duration and frequency) as they feel appropriate without time and economic costs associated with hospital visits (Garrett et al., 2017; Rutledge et al., 2019).

4.1.5 Safety of intervention

In regard to adverse events, only one case of mild dizziness was reported when using AVR which occurred when a participant was progressed to a fast-paced game. This fulfils the final criterion for feasibility but conflicts with previous research which suggest that negative side effects such as motion sickness and discomfort from wearing the head mounted gear can be common (Tong et al., 2016). It is possible that as technology and image resolution have improved the occurrence of motion sickness has reduced. Also, none of the participants recruited had neck or upper limb pain which may predispose them to discomfort from the head gear.

4.1.6 Summary

The study protocol would not be feasible for a future RCT. To proceed, changes to the recruitment process and sourcing, as well as improved guidance to the recruitment team on inclusion/exclusion criteria are required. Positively, AVR was deemed acceptable as an intervention by people with chronic pain with high levels of enjoyment and satisfaction even when pain was reported to increase following the session. Adherence rates suggest that these positive outcomes cannot be attributed to active strategies alone and it should be recognised that the inclusion of passive strategies may have influenced these results.

4.2 Activity monitoring with the ActivPAL

The data displayed in the activity trackers revealed measurable accounts of activity, which could be compared between groups. In general, the AVR group demonstrated increased active (upright) time, a corresponding reduction in sedentary time and an increase to energy expenditure, with the opposite effect occurring in the TAU group. However, ES's were very small to small, signifying a weak relationship between AVR and the activity levels. In addition, the large SD's highlight a wide variation across the sample and indicate that an RCT would need a very large sample size to demonstrate effectiveness. Taking the results from the step count data for example, using the sample size calculator on clincalc.com (Kane, 2019) applying a power of 90% and alpha of .05, the minimum sample size required for sufficient statistical power to determine a treatment effect of AVR against the WL group would be 1298 participants.

Furthermore, considering the WL group also displayed improvements in activity levels, it is probable that other factors independent of intervention influenced these results, such as life events, seasonal / weather variations, or COVID-19 restrictions. As mentioned by

El-Kotob and Giangregorio (2018) monitoring snapshots in time is open to bias. This certainly was the case for a number of participants with life events contributing to significant discrepancies in the tracker results, such as participant number 6 moving house while wearing the ActivPAL at baseline and therefore performing significantly more activity than normal or participant number 19 being unwell during Time 2 monitoring and spending long periods in bed. In both cases, physical activity appeared to decline when re-tested after the AVR interventions. These results may skew the outcomes significantly. In order to minimise this Edwardson et al. (2017) recommends a longer monitoring time of up to 14 days where viable, however this would need a longer commitment from participants, the acceptability for which would require further exploration.

In regards to the data provided by the ActivPAL, it did not offer information on whether the intensity of the activity performed was low, medium or high. This could be important when aiming to achieve exercise induced neurobiological changes such as to mood or pain intensity, with research demonstrating that moderate to high intensity exercise is more effective at signalling these changes than low intensity (Raichlen, Foster, Seillier, Giuffrida, & Gerdeman, 2013). Previous research using the ActivPAL monitors has demonstrated that with additional software and data calculations, obtaining activity intensity is possible (Lyden et al., 2017). Inclusion of activity intensity data may prove insightful in a future trial, particularly to clarify which types of AVR games/ programmes may influence change in activity levels and pain relevant outcome measures more effectively than others. There is also evidence indicating that how an individual breaks up sedentary time is just as relevant as total time spent sedentary (Chastin, Egerton, Leask, & Stamatakis, 2015; Dempsey et al., 2016; Duvivier et al., 2017; Hamilton, Hamilton, & Zderic, 2007). In a study comparing sedentary behaviour in people with chronic health conditions against healthy individuals, there was no difference in total sedentary time between the groups, but significant differences revealing the healthy individuals had more breaks from sedentary behaviour (Chastin & Granat, 2010). Determining breaks in sedentary activity can be attained with the ActivPAL monitor as the tracker is capable of recording the number of sit to stand transitions and displaying this as an average daily summary.

Including data on activity intensity and breaks to sedentary behaviour may identify positive changes to active and sedentary behaviours that were not detectable with the current measurement categories assessed within this study.

Several drawbacks from using the ActivPAL tracker were noted such as skin irritation in three subjects. One subject (who was not included in the final trial) developed a severe skin reaction requiring medical intervention to manage. Previous research has attempted to reduce negative effects such as skin break down in vulnerable people (such as elderly, frail skin) through removal of the tracker at night (Chan, Slaughter, Jones, & Wagg, 2016). This could be considered in future studies but may miss valuable data into sleeping patterns or bouts of activity over night (such as one individual who would regularly get up in the middle of the night to let his dogs out). Additionally, when a person has irregular sleep habits ensuring constant tracker wear reduces the issue of identifying precisely when one day starts and another day finishes. During our study skin irritation was managed as best as possible through provision of extra adhesive dressings and suggesting participants switch the tracker between thighs on a regular basis; a technique that has been supported in other research (Edwardson et al., 2017).

Other downsides to using the ActivPAL were the inconvenience and personal expense (parking and travel) of attending the clinic for application and removal of the tracker. Although no participant complained about this, future studies may wish to consider monetary compensation to participants for their time and resources for undertaking the study. Finally, technical issues did occur in one case and have been reported in other research (Chastin & Granat, 2010). Should these technical issues occur more frequently the completeness of the data may be adversely impacted.

4.2.1 Summary

Considering the very small to small ES's, the large variance to outcomes (SD's) and that the WL control produced similar (or even better at times) outcomes for activity, it is likely the ActivPAL activity tracker is not appropriate as an outcome measure for the study sample. It would be the recommendation from this trial to forego the inclusion of activity monitoring in a future RCT. Should the ActivPAL activity data still be deemed valuable for inclusion, additional data such as the intensity of the activity performed and breaks to sedentary behaviour may detect between group differences not recognised here.

4.3. Outcome measures

4.3.1 Pain intensity

On average, reported pain intensity increased in the AVR group but reduced in the TAU group. When considering the high self-report levels for satisfaction, enjoyment and

improvement, this increase in pain intensity did not seem to deter participants. No subject from the AVR group, and only one from the TAU group achieved the recommended MCID of greater than 30% reduction in pain intensity (Dworkin et al., 2005). This is in contrast to prior work looking at AVR for people with neck pain which found improvements in pain scores both immediately and at five-week follow-up (Rezaei et al., 2019). Significant pre-post session reductions in pain intensity and phantom sensations were also demonstrated in a study using AVR for chronic phantom limb pain; however, this was based on the collated data of just four subjects (Rutledge et al., 2019). Both these studies utilised AVR specifically targeted to problematic painful areas whereas our study did not. Future research to explore potential differences to outcomes with targeted activity as opposed to generalised body movement would provide further insight into the appropriate application of AVR.

To assist in planning a future RCT the mean results for pain intensity of AVR against the WL control were entered into the sample size calculator clincalc.com (Kane, 2019). Applying a power of 90% and alpha of .05 the minimum sample size required to have sufficient statistical power to demonstrate a treatment effect would be 85 participants. Unlike the data from the ActivPAL, this indicates a sample size less than originally calculated would be sufficient to demonstrate effectiveness for the proposed RCT.

4.3.2 Pain interference

Pain interference reduced in all groups but this reduction was smaller in the AVR group than the WL and TAU groups and only one participant (from the WL control) displayed greater than 30% reduction in pain interference to be considered a MCID. Again, this indicates that the changes noted were unlikely to be the result of the intervention received and indeed other factors may have influenced this, such as attending a specialised pain service for assessment, improved knowledge about pain through the education provided during initial assessment or the development of other factors deemed to hold greater importance to the participant at the time of the trial such as COVID-19.

Applying the mean pain interference results of AVR against the WL group in the sample size calculator clincalc.com (Kane, 2019), applying a power of 90% and alpha of .05, the minimum sample size required to have sufficient statistical power to demonstrate a treatment effect would be 181 participants.

4.3.3 Fear of movement

Fear of movement reduced in all groups, but those in the TAU group had a greater reduction in kinesiophobia than those in the AVR group with a moderate to large ES. Kinesiophobia was directly addressed within the TAU group through education to explain pain-related fear of activity and by challenging participants to confront activities that they considered concerning. This was not directly targeted within the AVR group with activities selected based on what participants would consider fun and engaging. Games were not tailored to the participants needs or designed to build confidence with specific concerning tasks and a generic guideline was used for progression of activities. It was originally considered that encouraging people to perform global body movements while being distracted or entertained may produce a cross-over effect to increase confidence with movement in other activities. While this may be the case to a small degree, the inclusion of standardised methods for addressing fear of movement as per usual care may have demonstrated stronger outcomes. Alternatively, recording the participant undertaking the AVR session, then playing this back to them could demonstrate to the individual the extent to which they were able to move their body while performing AVR. Real-time visual feedback has been demonstrated to have an impact on lowering pain intensity in people with chronic low back pain (Diers, Löffler, Zieglgänsberger, & Trojan, 2016) and feedback in other forms (such as biofeedback) has been shown to have positive impacts to numerous pain-related outcomes both in the short and long term (Sielski, Rief, & Glombiewski, 2017). Future research may wish to explore whether inclusion of video feedback changes pain relevant outcome measures with AVR use.

Entering the mean TSK score results for AVR against the WL group into the sample size calculator clincalc.com (Kane, 2019) with a power of 90% and alpha of .05, the minimum number of subjects needed to have sufficient statistical power to demonstrate a treatment effect would be 33 participants. This would be an achievable sample size for a future RCT to obtain.

4.3.4 Objective physical assessment measures

Both groups displayed improvements in physical assessment measures. Walking speed improved to a greater extent in the AVR group but dynamic lift test was better in the TAU group. However, these tests were based on a small sample sizes with only four participants data included from the AVR group and five in the TAU. Additionally, these tests

were not completed at the end of the WL period, so it would not be possible to accurately evaluate if these differences were due to intervention or chance.

4.3.5 Summary

Overall, small changes were noted in the pain relevant outcome measures used. No group was substantially different in effectiveness as suggested by ES calculations, though TAU and WL were marginally more favourable than AVR for pain intensity, pain interference and fear of movement. Considering the WL control results were more auspicious than AVR, it is probable that changes to the outcome measures were secondary to factors unrelated to the efficacy of AVR. The inclusion of additional measures such as those designed to detect changes to functional based activity (for example the Patient Specific Functional Score) may help to more specifically identify changes over time related to the treatment. Positively, the sample size calculations suggest more feasible sample size populations than the ActivPAL data with results indicating samples ranging from 33 to 181 participants would be required to demonstrate treatment effect in the pain relevant outcome measures used here.

4.4 Limitations

A number of limitations must be considered when reviewing the study findings. Primarily the small sample size adds significant bias to results and influences the accuracy of data analysis. Future work using a larger sample would allow greater representation of NZ chronic pain populations, reduce the degree of variability in the data, allow more precise ES calculations and permit more detailed analysis such as calculations of significance.

Secondly, there were differences between the focus and content of the treatment interventions received. One of the main directives of chronic pain management is to work towards the individual's goals and improve quality of life despite pain (Pergolizzi et al., 2013). The TAU group addressed this by identifying and working towards individualised goals. Progressive goal attainment regimes have demonstrated greater improvements to outcomes such as pain catastrophising, fear avoidance and pain related disability in people with chronic pain compared to standard physiotherapy input alone (Sullivan, Adams, Rhodenizer, & Stanish, 2006). The AVR group had no structured goal planning but involved game play to increase activity levels. This could unfairly bias some of the outcome measures used such as the TSK to favour the TAU intervention and could suggest the AVR intervention may have less transferability into activities of daily life. Another variation was

the provision of education. The TAU group received a large amount of education to understand their pain. Systematic reviews have shown that education in neurophysiology of pain can be beneficial for people experiencing chronic pain (Tegner et al., 2018). In addition, the TAU group was provided with a home-based exercise programme designed to encourage activity on a daily basis. Although the current study did not indicate that this changed outcomes (rather a deterioration in activity levels occurred) this may influence results in a future study. To accurately evaluate the efficacy of AVR within chronic pain management it would be pertinent to ensure other components of chronic pain management such as pain education, goal setting, and home-based activity plans are standardised.

Thirdly, the TAU group attended once weekly sessions while the AVR group attended twice weekly. For true between group comparisons of acceptance and outcome effectiveness more standardisation in this regard would be recommended. As mentioned previously, there are no clear guidelines for AVR dosage, neither for optimal planning of exercise regimes when it comes to chronic pain management. Therefore, once weekly sessions using the AVR to mirror the TAU protocol, or twice weekly sessions of TAU are both feasible options. Twice weekly physiotherapy sessions should be manageable considering the high attendance for the twice weekly sessions by the AVR group.

Finally, there was no blinding of the therapist to the treatment and no blinding of the patient to the treatment arm. As the questionnaire data was obtained electronically and data was recorded via participant number only, the person performing analysis of the data could have been blinded to the treatment group. Blinding of participants could have been done by altering the information about the nature of the treatment and aims of the study, such as describing the AVR as a ‘novel physical intervention’, rather than an ‘appropriate treatment for chronic pain’. Another consideration to reduce potential biasing could be to utilise a cross-over study design, randomising subjects to either six weeks of AVR or TAU and then crossing-over to the other treatment arm. This would allow the same subjects to be compared between groups and reduce between group differences in baseline measures.

Conclusion

This feasibility study confirmed that AVR is an acceptable treatment modality for people with chronic musculoskeletal pain, with participants rating high levels of satisfaction and enjoyment. However, a future RCT utilising the study protocol adhered to within the pilot study would not be feasible. Current recruitment strategies greatly restricted the sample size obtained and would need to be modified with wider recruitment sourcing and amendments to the exclusion criteria. Greater standardisation across the intervention groups with equal number and frequency of sessions and similar directives for session content such as the provision of pain education and activities directed towards individualised goals would allow more accurate comparisons between groups.

The ActivPAL activity tracker demonstrated small between group differences favouring AVR over TAU for increasing activity levels. However, there were large variances with this data, ES calculations were very small to small and WL outcomes were only marginally smaller than the AVR results, indicating that factors aside from the intervention may have influenced these results. Consequent to these findings, as well as the drawbacks to use, such as skin irritation and participant inconvenience, the ActivPAL may not be suitable for monitoring activity levels in a chronic pain population.

Pain relevant outcome measures representing pain intensity, pain interference and fear of movement all indicated to a small extent TAU and WL control were more effective than AVR. Large differences between the content and goals of the intervention arms may in part explain these results, but again, external influences are potential contributing factors. Despite these outcomes, global impression of change scores indicated similar self-perceived improvements for AVR compared with standard physiotherapy.

Although outcomes from this study were not substantially different between groups, small sample sizes impose caution when interpreting these findings. Applying the suggested changes to strengthen the study protocol and modify outcome measures may alter the conclusions drawn. Additionally, undertaking this feasibility study has identified a number of proposed questions which may assist to direct future trials to better explore the efficacy and application of AVR as an intervention for people with chronic pain.

References

Ainsworth, B. E., Haskell, W. L., Herrmann, S. D., Meckes, N., Bassett, D. R. J., Tudor-Locke, C., . . . Leon, A. S. (2011). 2011 Compendium of physical activities: A second update of codes and MET values. *Medicine & Science in Sports & Exercise, 43*(8), 1575-1581. doi:10.1249/MSS.0b013e31821ece12

Ambrose, K. R., & Golightly, Y. M. (2015). Physical exercise as non-pharmacological treatment of chronic pain: Why and when. *Best Practice & Research Clinical Rheumatology, 29*(1), 120-130. doi:https://doi.org/10.1016/j.berh.2015.04.022

Barone Gibbs, B., Hergenroeder, A. L., Perdomo, S. J., Kowalsky, R. J., Delitto, A., & Jakicic, J. M. (2018). Reducing sedentary behaviour to decrease chronic low back pain: The stand back randomised trial. *Occupational and Environmental Medicine, 75*(5), 321-327. doi:10.1136/oemed-2017-104732

Blocker, K. A., Wright, T. J., & Boot, W. R. (2014). Gaming preferences of aging generations. *Gerontechnology, 12*(3), 174-184. doi:10.4017/gt.2014.12.3.008.00

Bohannon, R. W., & Glenney, S. S. (2014). Minimal clinically important difference for change in comfortable gait speed of adults with pathology: A systematic review. *Journal of Evaluation in Clinical Practice, 20*(4), 295-300. doi:https://doi.org/10.1111/jep.12158

Botella, C., Garcia-Palacios, A., Vizcaíno, Y., Herrero, R., Baños, R. M., & Belmonte, M. A. (2013). Virtual reality in the treatment of fibromyalgia: A pilot study. *Cyberpsychology, Behavior, and Social Networking, 16*(3), 215-223. doi:10.1089/cyber.2012.1572

Chan, C. S., Slaughter, S. E., Jones, C. A., & Wagg, A. S. (2016). Measuring activity performance of continuing care residents using the activPAL: An exploratory study. *Journal of Frailty Aging, 5* (3), 158-161.

Chastin, S. F. M., Egerton, T., Leask, C., & Stamatakis, E. (2015). Meta-analysis of the relationship between breaks in sedentary behavior and cardiometabolic health. *Obesity, 23*(9), 1800-1810. doi:10.1002/oby.21180

Chastin, S. F. M., & Granat, M. H. (2010). Methods for objective measure, quantification and analysis of sedentary behaviour and inactivity. *Gait and Posture, 31*(1), 82-86. doi:10.1016/j.gaitpost.2009.09.002

Chen, Liu, M. F., Cook, J., Bass, S., & Lo, S. K. (2009). Sedentary lifestyle as a risk factor for low back pain: A systematic review. *International Archives of Occupational and Environmental Health, 82*(7), 797-806. doi:10.1007/s00420-009-0410-0

Chen, K. B., Sesto, M. E., Ponto, K., Leonard, J., Mason, A., Vanderheiden, G., . . . Radwin, R. G. (2017). Use of virtual reality feedback for patients with chronic neck pain and kinesiophobia. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 25*(8), 1240-1248. doi:10.1109/TNSRE.2016.2621886

Cherkin, D. C., Sherman, K. J., Balderson, B. H., Cook, A. J., Anderson, M. L., Hawkes, R. J., . . . Turner, J. A. (2016). Effect of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain and functional limitations in adults with chronic low back pain: A randomized clinical trial. *JAMA, 315*(12), 1240-1249. doi:10.1001/jama.2016.2323

Chou, C.-H., Hwang, C.-L., & Wu, Y.-T. (2012). Effect of exercise on physical function, daily living activities, and quality of life in the frail older adults: A meta-analysis. *Archives of Physical Medicine & Rehabilitation, 93*(2), 237-244. Retrieved from https://ezproxy.aut.ac.nz/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=s3h&AN=71370462&site=eds-live

Cohen, J. (1988). *Statistical power analysis for the behavioural sciences* (2nd ed.). Hillsdale New Jersey Lawrence Erlbaum Associates.

Crombez, G., Vervaet, L., Lysens, R., Baeyens, F., & Eelen, P. (1998). Avoidance and confrontation of painful, back-straining movements in chronic back pain patients. *Behavior Modification, 22*(1), 62-77. doi:10.1177/01454455980221004

Davis, K. G., & Kotowski, S. E. (2014). Postural variability: An effective way to reduce musculoskeletal discomfort in office work. *Human Factors, 56*(7), 1249-1261. doi:10.1177/0018720814528003

Demeyer, H., Burtin, C., Hornikx, M., Camillo, C. A., Van Remoortel, H., Langer, D., . . . Troosters, T. (2016). The minimal important difference in physical activity in patients with COPD. *PloS one, 11*(4), e0154587. doi:10.1371/journal.pone.0154587

Dempsey, P. C., Larsen, R. N., Sethi, P., Sacre, J. W., Straznicky, N. E., Cohen, N. D., . . . Dunstan, D. W. (2016). Benefits for type 2 diabetes of interrupting prolonged sitting with brief bouts of light walking or simple resistance activities. *Diabetes Care, 39*(6), 964-972. doi:10.2337/dc15-2336

Diers, M., Löffler, A., Zieglgänsberger, W., & Trojan, J. (2016). Watching your pain site reduces pain intensity in chronic back pain patients. *European Journal of Pain, 20*(4), 581-585. doi:https://doi.org/10.1002/ejp.765

Dietrich, A., & McDaniel, W. F. (2004). Endocannabinoids and exercise. *BRITISH JOURNAL OF SPORTS MEDICINE, 38*(5), 536-541. doi:10.1136/bjsm.2004.011718

Dontje, M. L., Dall, P. M., Skelton, D. A., Gill, J. M. R., Chastin, S. F. M., & on behalf of the Seniors, U. S. P. T. (2018). Reliability, minimal detectable change and responsiveness to change: Indicators to select the best method to measure sedentary behaviour in older adults in different study designs. *PloS one, 13*(4), e0195424. doi:10.1371/journal.pone.0195424

Dowd, K. P., Harrington, D. M., & Donnelly, A. E. (2012). Criterion and concurrent validity of the activPAL™ professional physical activity monitor in adolescent females. *PloS one, 7*(10), e47633-e47633. doi:10.1371/journal.pone.0047633

Dunn, A. L., & Jewell, J. S. (2010). The effect of exercise on mental health. *Current Sports Medicine Reports, 9*(4), 202-207. doi:10.1249/JSR.0b013e3181e7d9af

Duvivier, B. M. F. M., Schaper, N. C., Hesselink, M. K. C., van Kan, L., Stienen, N., Winkens, B., . . . Savelberg, H. H. C. M. (2017). Breaking sitting with light activities vs structured exercise: A randomised crossover study demonstrating benefits for glycaemic control and insulin sensitivity in type 2 diabetes. *Diabetologia, 60*(3), 490-498. doi:10.1007/s00125-016-4161-7

Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., . . . Witter, J. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain, 113*(1), 9-19. doi:10.1016/j.pain.2004.09.012

Edwardson, C. L., Winkler, E. A. H., Bodicoat, D. H., Yates, T., Davies, M. J., Dunstan, D. W., & Healy, G. N. (2017). Considerations when using the activPAL monitor in field-based research with adult populations. *Journal of Sport and Health Science, 6*(2), 162-178. doi:https://doi.org/10.1016/j.jshs.2016.02.002

El-Kotob, R., & Giangregorio, L. M. (2018). Pilot and feasibility studies in exercise, physical activity, or rehabilitation research. *Pilot and Feasibility Studies, 4*(1), 137. doi:10.1186/s40814-018-0326-0

Ellingson, L. D., Koltyn, K. F., Kim, J.-S., & Cook, D. B. (2014). Does exercise induce hypoalgesia through conditioned pain modulation? *Psychophysiology, 51*(3), 267-276. doi:10.1111/psyp.12168

Ellingson, L. D., Shields, M. R., Stegner, A. J., & Cook, D. B. (2012). Physical activity, sustained sedentary behavior, and pain modulation in women with fibromyalgia. *The Journal of Pain, 13*(2), 195-206. doi:https://doi.org/10.1016/j.jpain.2011.11.001

Fowler, C. A., Ballistrea, L. M., Mazzone, K. E., Martin, A. M., Kaplan, H., Kip, K. E., . . . Winkler, S. L. (2019). Virtual reality as a therapy adjunct for fear of movement in veterans with chronic pain: Single-arm feasibility study. *JMIR Form Res, 3*(4), e11266. doi:10.2196/11266

Friedrich, M., Gittler, G., Halberstadt, Y., Cermak, T., & Heiller, I. (1998). Combined exercise and motivation program: Effect on the compliance and level of disability of patients with chronic low back pain: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation, 79*(5), 475-487. doi:https://doi.org/10.1016/S0003-9993(98)90059-4

Garrett, B., Taverner, T., & McDade, P. (2017). Virtual reality as an adjunct home therapy in chronic pain management: An exploratory study. *JMIR Med Inform, 5*(2), e11. doi:10.2196/medinform.7271

Geneen, L. J., Moore, R. A., Clarke, C., Martin, D., Colvin, L. A., & Smith, B. H. (2017). Physical activity and exercise for chronic pain in adults: An overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews*(4). doi:10.1002/14651858.CD011279.pub3

Godfrey, A., Culhane, K. M., & Lyons, G. M. (2007). Comparison of the performance of the activPAL™ Professional physical activity logger to a discrete accelerometer-based activity monitor. *Medical Engineering and Physics, 29*(8), 930-934. doi:10.1016/j.medengphy.2006.10.001

Gold, J., Reger, G., Rizzo, A., Buckwalter, G., Kim, S., & Joseph, M. (2005). Virtual reality in outpatient phlebotomy: Evaluating pediatric pain distraction during blood draw. *The Journal of Pain, 6*(3), S57. doi:10.1016/j.jpain.2005.01.224

Grant, P. M., Ryan, C. G., Tigbe, W. W., & Granat, M. H. (2006). The validation of a novel activity monitor in the measurement of posture and motion during everyday activities. *BRITISH JOURNAL OF SPORTS MEDICINE, 40*(12), 992-997. doi:10.1136/bjsm.2006.030262

Grichnik, K. P., & Ferrante, F. M. (1991). The difference between acute and chronic pain. *The Mount Sinai journal of medicine, New York, 58*(3), 217-220. Retrieved from http://europepmc.org/abstract/MED/1875958

Gromala, D., Tong, X., Choo, A., Karamnejad, M., & Shaw, C. D. (2015). *The virtual meditative walk: Virtual reality therapy for chronic pain management*. Paper presented at the Proceedings of the 33rd Annual ACM Conference on Human Factors in Computing Systems, Seoul, Republic of Korea. https://doi.org/10.1145/2702123.2702344

Hachiya, M., Murata, S., Otao, H., Kamijou, K., Mizota, K., & Asami, T. (2015). Reproducibility and validity of the 50-meter walking test in community-dwelling elderly. *Journal of physical therapy science, 27*(5), 1511-1514. doi:10.1589/jpts.27.1511

Hamilton, M. T., Hamilton, D. G., & Zderic, T. W. (2007). Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. *Diabetes, 56*(11), 2655-2667. doi:10.2337/db07-0882

Harding, V., & Williams, A. d. C. (1995). Extending physiotherapy skills using a psychological approach: Cognitive-behavioural management of chronic pain. *Physiotherapy, 81*(11), 681-688.

Harley, C. W. (2004). Norepinephrine and dopamine as learning signals. *Neural Plasticity, 11*, 360813. doi:10.1155/NP.2004.191

Hoffman, H. G., Patterson, D. R., & Carrougher, G. J. (2000). Use of virtual reality for adjunctive treatment of adult burn pain during physical therapy: A controlled study. *The Clinical Journal of Pain, 16*(3), 244-250. Retrieved from https://journals.lww.com/clinicalpain/Fulltext/2000/09000/Use_of_Virtual_Reality_for_Adjunctive_Treatment_of.10.aspx

Hoffman, H. G., Richards, T. L., Coda, B., Bills, A. R., Blough, D., Richards, A. L., & Sharar, S. R. (2004). Modulation of thermal pain-related brain activity with virtual reality: Evidence from fMRI. *NeuroReport, 15*(8), 1245-1248. doi:10.1097/01.wnr.0000127826.73576.91

Hoffman, H. G., Seibel, E. J., Richards, T. L., Furness, T. A., Patterson, D. R., & Sharar, S. R. (2006). Virtual reality helmet display quality influences the magnitude of virtual reality analgesia. *The Journal of Pain, 7*(11), 843-850. doi:https://doi.org/10.1016/j.jpain.2006.04.006

Holzapfel, S., Riecke, J., Rief, W., Schneider, J., & Glombiewski, J. A. (2016). Development and validation of the Behavioral Avoidance Test - Back pain (BAT-Back) for patients with chronic low back pain. *The Clinical Journal of Pain, 32*(11), 940-947. doi:10.1097/AJP.0000000000000349

Hughes, L., & Patterson, S. D. (2020). The effect of blood flow restriction exercise on exercise-induced hypoalgesia and endogenous opioid and endocannabinoid mechanisms of pain modulation. *Journal of Applied Physiology, 128*(4), 914-924. doi:10.1152/japplphysiol.00768.2019

Jayakody, K., Gunadasa, S., & Hosker, C. (2014). Exercise for anxiety disorders: Systematic review. *BRITISH JOURNAL OF SPORTS MEDICINE, 48*(3), 187-196. doi:10.1136/bjsports-2012-091287

Jones, T., Moore, T., Rose, H., & Choo, J. (2016). The impact of virtual reality on chronic pain. *The Journal of Pain, 17*(4), S102-S103. doi:10.1016/j.jpain.2016.01.319

Jordan, J. L., Holden, M. A., Mason, E. E. J., & Foster, N. E. (2010). Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews, 1*(1), 65. doi:10.1002/14651858.CD005956.pub2

Kadam, P., & Bhalerao, S. (2010). Sample size calculation. *International journal of Ayurveda research, 1*(1), 55-57. doi:10.4103/0974-7788.59946

Kaleth, A. S., Slaven, J. E., & Ang, D. C. (2014). Does increasing steps per day predict improvement in physical function and pain interference in adults with fibromyalgia? *Arthritis Care & Research, 66*(12), 1887-1894. doi:10.1002/acr.22398

Kane, S. (2019). Sample size calculator. Retrieved from https://clincalc.com/stats/samplesize.aspx

Keller, S., Bann, C. M., Dodd, S. L., Schein, J., Mendoza, T. R., & Cleeland, C. S. (2004). Validity of the Brief Pain Inventory for use in documenting the outcomes of patients with noncancer pain. *The Clinical Journal of Pain, 20*(5), 309-318. Retrieved from https://journals.lww.com/clinicalpain/Fulltext/2004/09000/Validity_of_the_Brief_Pain_Inventory_for_Use_in.5.aspx

Koho, P., Aho, S., Watson, P., & Hurri, H. (2001). Assessment of chronic pain behaviour: Reliability of the method and its relationship with perceived disability, physical impairment and function. *Journal of Rehabilitation Medicine, 33*(3), 128-132. Retrieved from https://ezproxy.aut.ac.nz/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=s3h&AN=5446473&site=eds-live

Kokkinos, P., & Myers, J. (2010). Exercise and physical activity: Clinical outcomes and applications. *Circulation, 122*(16), 1637-1648. doi:doi:10.1161/CIRCULATIONAHA.110.948349

Koltyn, K. F., & Umeda, M. (2006). Exercise, hypoalgesia and blood pressure. *Sports Medicine, 36*(3), 207-214. doi:10.2165/00007256-200636030-00003

Kori, S. H., Miller, R. P., & Todd, D. D. (1990). Kinesiophobia: A new view of chronic pain behavior. *Pain management, 3* 35-43.

Kozey-Keadle, S., Libertine, A., Lyden, K., Staudenmayer, J., & Freedson, P. S. (2011). Validation of wearable monitors for assessing sedentary behavior. *Medicine & Science in Sports & Exercise, 43*(8), 1561-1567. doi:10.1249/MSS.0b013e31820ce174

Kwekkeboom, K. L., & Gretarsdottir, E. (2006). Systematic review of relaxation interventions for pain. *Journal of Nursing Scholarship, 38*(3), 269-277. doi:10.1111/j.1547-5069.2006.00113.x

Lancaster, G. A. (2015). Pilot and feasibility studies come of age! *Pilot and Feasibility Studies, 1*(1), 1. doi:10.1186/2055-5784-1-1

Lee, J., Chang, R. W., Ehrlich-Jones, L., Kwoh, C. K., Nevitt, M., Semanik, P. A., . . . Dunlop, D. D. (2015). Sedentary behavior and physical function: Objective evidence from the osteoarthritis initiative. *Arthritis Care & Research, 67*(3), 366-373. doi:10.1002/acr.22432

Lees, C., & Hopkins, J. (2013). Effect of aerobic exercise on cognition, academic achievement, and psychosocial function in children: A systematic review of randomized control trials. *Preventing Chronic Disease, 10*. doi:10.5888/pcd10.130010

Louw, A., Diener, I., Butler, D. S., & Puentedura, E. J. (2011). The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Archives of Physical Medicine and Rehabilitation, 92*(12), 2041-2056. doi:https://doi.org/10.1016/j.apmr.2011.07.198

Lyden, K., Keadle, S. K., Staudenmayer, J., & Freedson, P. S. (2017). The activPAL accurately classifies activity intensity categories in healthy adults. *Medicine and science in sports and exercise, 49*(5), 1022-1028. doi:10.1249/MSS.0000000000001177

Maddocks, M., Petrou, A., Skipper, L., & Wilcock, A. (2010). Validity of three accelerometers during treadmill walking and motor vehicle travel. *BRITISH JOURNAL OF SPORTS MEDICINE, 44*(8), 606. doi:10.1136/bjsm.2008.051128

Martin, K. R., Beasley, M., Macfarlane, G. J., & Whibley, D. (2014). Chronic pain predicts reduced physical activity in a large population cohort study. *Arthritis & Rheumatology, 66*, S434-S434. Retrieved from https://ezproxy.aut.ac.nz/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000344384902081&site=eds-live

Miller, J., MacDermid, J. C., Walton, D. M., & Richardson, J. (2015). Chronic pain self-management support with pain science education and exercise (COMMENCE): Study protocol for a randomized controlled trial. *Trials, 16*(1), 462. doi:10.1186/s13063-015-0994-5

Ministry of Health. (2020). *Annual Data Explorer 2019/20* Retrieved from: https://minhealthnz.shinyapps.io/nz-health-survey-2019-20-annual-data-explorer/

Molteni, R., Ying, Z., & Gómez-Pinilla, F. (2002). Differential effects of acute and chronic exercise on plasticity-related genes in the rat hippocampus revealed by microarray. *European Journal of Neuroscience, 16*(6), 1107-1116. doi:10.1046/j.1460-9568.2002.02158.x

Monticone, M., Ambrosini, E., Rocca, B., Foti, C., & Ferrante, S. (2016). Responsiveness of the Tampa Scale of Kinesiophobia in Italian subjects with chronic low back pain undergoing motor and cognitive rehabilitation. *European Spine Journal, 25*(9), 2882-2888. doi:10.1007/s00586-016-4682-2

Morone, N. E., Rollman, B. L., Moore, C. G., Li, Q., & Weiner, D. K. (2009). A mind–body program for older adults with chronic low back pain: Results of a pilot study. *Pain Medicine, 10*(8), 1395-1407. doi:10.1111/j.1526-4637.2009.00746.x

Nijs, J., Kosek, E., Van Oosterwijck, J., & Meeus, M. (2012). Dysfunctional endogenous analgesia during exercise in patients with chronic pain : To exercise or not to exercise? . *Pain Physician, 15*(3S), ES205–ES213.

Palazzo, C., Klinger, E., Dorner, V., Kadri, A., Thierry, O., Boumenir, Y., . . . Ville, I. (2016). Barriers to home-based exercise program adherence with chronic low back pain: Patient expectations regarding new technologies. *Annals of Physical and Rehabilitation Medicine, 59*(2), 107-113. doi:https://doi.org/10.1016/j.rehab.2016.01.009

Pasch, M., Bianchi-Berthouze, N., van Dijk, B., & Nijholt, A. (2009). Movement-based sports video games: Investigating motivation and gaming experience. *Entertainment Computing, 1*(2), 49-61. doi:https://doi.org/10.1016/j.entcom.2009.09.004

Pergolizzi, J., Ahlbeck, K., Aldington, D., Alon, E., Coluzzi, F., Dahan, A., . . . Varrassi, G. (2013). The development of chronic pain: physiological CHANGE necessitates a multidisciplinary approach to treatment. *Current Medical Research and Opinion, 29*(9), 1127-1135. doi:10.1185/03007995.2013.810615

Pfister, T., Matthews, C. E., Wang, Q., Kopciuk, K. A., Friedenreich, C., & Courneya, K. (2017). Comparison of two accelerometers for measuring physical activity and sedentary behaviour. *BMJ Open Sport and Exercise Medicine, 3*(1), 1-8. doi:10.1136/bmjsem-2017-000227

Phelan, I., Furness, P. J., Fehily, O., Thompson, A. R., Babiker, N. T., Lamb, M. A., & Lindley, S. A. (2018). A mixed-methods investigation into the acceptability, usability, and perceived effectiveness of active and passive virtual reality scenarios in managing pain under experimental conditions. *Journal of Burn Care & Research, 40*(1), 85-90. doi:10.1093/jbcr/iry052

Pronk, N. P., Katz, A. S., Lowry, M., & Payfer, J. R. (2012). Reducing occupational sitting time and improving worker health: The take-a-stand project, 2011. *Preventing Chronic Disease, 9*(10). doi:10.5888.pcd9.110323

Raichlen, D. A., Foster, A. D., Seillier, A., Giuffrida, A., & Gerdeman, G. L. (2013). Exercise-induced endocannabinoid signaling is modulated by intensity. *European Journal of Applied Physiology, 113*(4), 869-875. doi:10.1007/s00421-012-2495-5

Rampakakis, E., Ste-Marie, P. A., Sampalis, J. S., Karellis, A., Shir, Y., & Fitzcharles, M.-A. (2015). Real-life assessment of the validity of patient global impression of change in fibromyalgia. *RMD Open, 1*(1), e000146. doi:10.1136/rmdopen-2015-000146

Rezaei, I., Razeghi, M., Ebrahimi, S., Kayedi, S., & Rezaeian Zadeh, A. (2019). A novel virtual reality technique (Cervigame®) compared to conventional proprioceptive training to treat neck pain: A randomized controlled trial. *Journal of biomedical physics & engineering, 9*(3), 355-366. doi:10.31661/jbpe.v0i0.556

Rice, D., Nijs, J., Kosek, E., Wideman, T., Hasenbring, M. I., Koltyn, K., . . . Polli, A. (2019). Exercise-induced hypoalgesia in pain-free and chronic pain populations: State of the art and future directions. *The Journal of Pain, 20*(11), 1249-1266. doi:https://doi.org/10.1016/j.jpain.2019.03.005

Roelofs, J., Goubert, L., Peters, M. L., Vlaeyen, J. W. S., & Crombez, G. (2004). The Tampa Scale for Kinesiophobia: Further examination of psychometric properties in patients with chronic low back pain and fibromyalgia. *European Journal of Pain, 8*(5), 495-502. doi:https://doi.org/10.1016/j.ejpain.2003.11.016

Rosenberger, M. E., Buman, M. P., Haskell, W. L., McConnell, M. V., & Carstensen, L. L. (2016). Twenty-four hours of sleep, sedentary behavior, and physical activity with nine wearable devices. *Medicine and science in sports and exercise, 48*(3), 457-465. doi:10.1249/MSS.0000000000000778

Rutledge, T., Velez, D., Depp, C., McQuaid, J. R., Wong, G., Jones, R. C. W., III, . . . Giap, H. (2019). A virtual reality intervention for the treatment of phantom limb pain: Development and feasibility results. *Pain Medicine, 20*(10), 2051-2059. doi:10.1093/pm/pnz121

Ryan, C. G., Grant, M. P., Dall, P. M., Gray, H., Newton, M., & Granat, M. H. (2009). Individuals with chronic low back pain have a lower level, and an altered pattern, of physical activity compared with matched controls: An observational study. *Australian Journal of Physiotherapy, 55*(1), 53-58. doi:https://doi.org/10.1016/S0004-9514(09)70061-3

Ryan, C. G., Grant, P. M., Gray, H., Newton, M., & Granat, M. H. (2008). Measuring postural physical activity in people with chronic low back pain. *Journal of Back and Musculoskeletal Rehabilitation, 21*, 43-50. doi:10.3233/BMR-2008-21106

Ryan, C. G., Grant, P. M., Tigbe, W. W., & Granat, M. H. (2006). The validity and reliability of a novel activity monitor as a measure of walking. *BRITISH JOURNAL OF SPORTS MEDICINE, 40*(9), 779-784. Retrieved from https://ezproxy.aut.ac.nz/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=edsovi&AN=edsovi.00002412.200609000.00010&site=eds-live

Salaffi, F., Stancati, A., Alberto Silvestri, C., Ciapetti, A., & Grassi, W. (2004). Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *European Journal of Pain, 8*(4), 283-291. doi:https://doi.org/10.1016/j.ejpain.2003.09.004

Sato, K., Fukumori, S., Matsusaki, T., Maruo, T., Ishikawa, S., Nishie, H., . . . Morita, K. (2010). Nonimmersive virtual reality mirror visual feedback therapy and its application for the treatment of complex regional pain syndrome: An open-label pilot study. *Pain Medicine, 11*(4), 622-629. doi:10.1111/j.1526-4637.2010.00819.x

Schaffer, S. D., & Yucha, C. B. (2004). Relaxation & pain management: The relaxation response can play a role in managing chronic and acute pain. *AJN The American Journal of Nursing, 104*(8), 75-82. Retrieved from https://journals.lww.com/ajnonline/Fulltext/2004/08000/Relaxation___Pain_Management__The_relaxation.44.aspx

Schneider, S. M., & Workman, M. L. (2000). Virtual reality as a distraction intervention for older children receiving chemotherapy. *Pediatric Nursing, 26*(6), 593-597.

Segura-Jiménez, V., Borges-Cosic, M., Soriano-Maldonado, A., Estévez-López, F., Álvarez-Gallardo, I. C., Herrador-Colmenero, M., . . . Ruiz, J. R. (2017). Association of sedentary time and physical activity with pain, fatigue, and impact of fibromyalgia: The al-Ándalus study. *Scandinavian Journal of Medicine & Science in Sports, 27*(1), 83-92. doi:10.1111/sms.12630

Semanik, P. A., Lee, J., Song, J., Chang, R. W., Sohn, M.-W., Ehrlich-Jones, L. S., . . . Dunlop, D. D. (2015). Accelerometer-monitored sedentary behavior and observed physical function loss. *American journal of public health, 105*(3), 560-566. doi:10.2105/AJPH.2014.302270

Siddall, P. J. (2013). Neuroplasticity and pain: What does it all mean? *Medical Journal of Australia, 198* (4), 177-178. doi:10.5694/mja13.10100

Sielski, R., Rief, W., & Glombiewski, J. A. (2017). Efficacy of biofeedback in chronic back pain: A meta-analysis. *International Journal of Behavioral Medicine, 24*

25–41. doi:10.1007/s12529-016-9572-9

Sugiyama, T., Healy, G. N., Dunstan, D. W., Salmon, J., & Owen, N. (2008). Joint associations of multiple leisure-time sedentary behaviours and physical activity with obesity in Australian adults. *International Journal of Behavioral Nutrition and Physical Activity, 5*(1), 35. doi:10.1186/1479-5868-5-35

Sullivan, M. J. L., Adams, H., Rhodenizer, T., & Stanish, W. D. (2006). A psychosocial risk factor–targeted intervention for the prevention of chronic pain and disability following whiplash injury. *Physical Therapy, 86*(1), 8-18. doi:10.1093/ptj/86.1.8

Sullivan, M. J. L., Thorn, B., Haythornthwaite, J. A., Keefe, F., Martin, M., Bradley, L. A., & Lefebvre, J. C. (2001). Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain, 17*(1), 52-64. Retrieved from https://journals.lww.com/clinicalpain/Fulltext/2001/03000/Theoretical_Perspectives_on_the_Relation_Between.8.aspx

Swinkels-Meewisse, I. E. J., Roelofs, J., Verbeek, A. L. M., Oostendorp, R. A. B., & Vlaeyen, J. W. S. (2003). Fear of movement/(re)injury, disability and participation in acute low back pain. *Pain (03043959), 105*(1/2), 371-379. doi:10.1016/S0304-3959(03)00255-0

Tegner, H., Frederiksen, P., Esbensen, B. A., & Juhl, C. (2018). Neurophysiological pain education for patients with chronic low back pain. *The Clinical Journal of Pain, 34*(8), 778-786. doi:10.1097/AJP.0000000000000594

Teychenne, M., Costigan, S. A., & Parker, K. (2015). The association between sedentary behaviour and risk of anxiety: A systematic review. *BMC Public Health, 15*(1), 513. doi:10.1186/s12889-015-1843-x

Thomas, J. S., France, C. R., Applegate, M. E., Leitkam, S. T., & Walkowski, S. (2016). Feasibility and safety of a virtual reality dodgeball intervention for chronic low back pain: A randomized clinical trial. *The Journal of Pain, 17*(12), 1302-1317. doi:https://doi.org/10.1016/j.jpain.2016.08.011

Tong, X., Gromala, D., Gupta, D., & Squire, P. (2016). Usability Comparisons of Head-Mounted vs. Stereoscopic Desktop Displays in a Virtual Reality Environment with Pain Patients.

. In J. D. Westwood, S. W. Westwood, & F.-T. L. (Eds.), *Medicine Meets Virtual Reality 22* (Vol. 22). Los Angeles: IOS Press.

Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., . . . Wang, S.-J. (2019). Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain, 160*(1), 19-27. doi:10.1097/j.pain.0000000000001384

Vaegter, H. B., Handberg, G., & Graven-Nielsen, T. (2014). Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. *Pain, 155*(1), 158-167. doi:https://doi.org/10.1016/j.pain.2013.09.023

van der Ploeg, H. P., Streppel, K. R. M., van der Beek, A. J., van der Woude, L. H. V., Vollenbroek-Hutten, M., & van Mechelen, W. (2007). The physical activity scale for individuals with physical disabilities: Test-retest reliability and comparison with an accelerometer. *Journal of Physical Activity and Health, 4*(1), 96-100. doi:10.1123/jpah.4.1.96

Verbunt, J. A., Huijnen, I. P. J., & Seelen, H. A. M. (2012). Assessment of physical activity by movement registration systems in chronic pain: Methodological considerations. *The Clinical Journal of Pain, 28*(6), 496-504. doi:10.1097/AJP.0b013e31823ae44e

Vlaeyen, J. W., Kole-Snijders, A. M., Boeren, R. G., & van Eek, H. (1995). Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain, 62*(3), 363-372. doi:10.1016/0304-3959(94)00279-N

Vlaeyen, J. W., Kole-Snijders, A. M. J., Rotteveel, A. M., Ruesink, R., & Heuts, P. H. T. (1995). The role of fear of movement/(re)injury in pain disability. *Journal of Occupational Rehabilitation, 5*(4), 235-252. doi:10.1007/bf02109988

Vlaeyen, J. W., Morley, S., Linton, S. J., Boersma, K., & de Jong, J. (2012). *Pain-related fear: Exposure-based treatment of chronic pain*. Seattle, WA, US: IASP Press.

Vos, T., Allen, C., Arora, M., Barber, R. M., Bhutta, Z. A., Brown, A., . . . Murray, C. J. L. (2016). Global, regional, and national incidence, prevalence, and years lived with

disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *The Lancet, 388*(10053), 1545-1602. doi:https://doi.org/10.1016/S0140-6736(16)31678-6

Wegner, M., Helmich, I., Machado, S., E. Nardi, A., Arias-Carrion, O., & Budde, H. (2014). Effects of exercise on anxiety and depression disorders: Review of meta- analyses and neurobiological mechanisms. *CNS & Neurological Disorders - Drug Targets, 13*(6), 1002-1014. Retrieved from https://www.ingentaconnect.com/content/ben/cnsnddt/2014/00000013/00000006/art00012

Wiederhold, B. K., Camelia Sulea, K. G., & Wiederhold, M. D. (2014). Virtual reality as a distraction technique in chronic pain patients. *Cyberpsychology, Behavior, and Social Networking, 17*(6), 346-352. doi:10.1089/cyber.2014.0207

Wilmot, E. G., Edwardson, C. L., Achana, F. A., Davies, M. J., Gorely, T., Gray, L. J., . . . Biddle, S. J. H. (2012). Sedentary time in adults and the association with diabetes, cardiovascular disease and death: Systematic review and meta-analysis. *Diabetologia, 55*(11), 2895-2905. doi:10.1007/s00125-012-2677-z

Wise, R. A. (2004). Dopamine, learning and motivation. *Nature Reviews Neuroscience, 5*(6), 483-494. doi:10.1038/nrn1406

Woods, M. P., & Asmundson, G. J. G. (2008). 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, 136*(3), 271-280. doi:https://doi.org/10.1016/j.pain.2007.06.037

Zeidan, F., & Vago, D. R. (2016). Mindfulness meditation-based pain relief: A mechanistic account. *Annals of the New York Academy of Sciences, 1373*(1), 114-127. doi:10.1111/nyas.13153