Virtual reality for the treatment of people with cancer-related pain

# Administrative information

## Trial registration – ANZCTR 377329

## Protocol version 1.1

## Funding - Sydney Vital seed funding grant - $50,000

# Roles and Responsibilities

* **Philip Austin**: Postdoctoral Fellow at HammondCare, Greenwich Hospital.
  + Responsible for the day to day running of this VR project. Phil will recruit subjects, administer questionnaires, organise clinic visits, perform virtual reality and electrophysiological testing, collect and analyse data and draft presentations and reports.
  + Responsible for drafting applications to obtain further funding
* **Melanie Lovell**: Associate Professor of Palliative Care and Director of Clinical Trials at HammondCare, Greenwich Hospital
  + Responsible to ensure that procedures used are consistent with sound research design and do not unnecessarily expose subjects to risk/harm.
  + Responsible for the supervision and suitability of potential participants
* **Philip Siddall**: Director of the Department of Pain Management and Senior Staff Specialist - Pain Medicine at HammondCare, Greenwich Hospital
  + Responsible to ensure that procedures used are consistent with sound research design and do not unnecessarily expose subjects to risk/harm.
  + Assures that the study design is appropriate for the proposed research question

# Introduction

## Background and rationale

### Literature review

Despite the availability of cancer pain guidelines, the management of pain in people with cancer remains inadequate (1). As such, there is a need to develop innovative alternative therapeutic options, particularly those with no adverse effects. One potential option that is gathering interest is the use of virtual reality (VR) devices. Developments in VR technology offer an alternative approach that been used with good effect in the treatment of several medical and psychological conditions (2, 3). This technology shows promise in reducing pain and psychological symptoms in both the short and long-term.

VR is a simulated creation of a 3D environment using computer technology (4). While early VR systems used computer screen technology which were non-immersive, current VR systems include immersive head-mounted devices with 3D-enabled glasses with other sensory input devices such as headphones for noise-cancelling, sound and music, head and/or body-tracking sensors and other input hardware such as joysticks and data gloves (5). Together, this system forms a realistic multisensory experience. Over the previous decade, VR technology has been taken from the entertainment business sector to clinical medicine. Here, researchers and clinicians have explored the use of VR technologies for physical rehabilitation, pain management, psychiatric treatment as well as surgical training and anatomical education (5).

The mechanisms underlying the effect of VR on pain have been divided generally into two types or processes: distraction and neuroplasticity. These processes that are thought to contribute to the analgesic effect of VR have quite different mechanisms of action (6). Distraction refers to the short-term diversion of attention away from pain towards an alternative stimulus. Here, VR may act directly and indirectly by ‘hijacking’ attention, emotion and memory away from pain using auditory and touch senses (7). Neuroplasticity refers to long-term structural changes in neuronal populations. This may occur harmfully due to a stroke, or positively following long-term practice of a skill such as playing a musical instrument. In the case of VR, repeated immersion into interactive real-time simulations of scenes or activities appears to be associated with positive neuroplastic alterations in sensory and motor brain regions (8). Although cancer-related pain has strong contributions from a number of peripheral, spinal and supraspinal nervous system mechanisms, pharmacological treatments using antidepressants and antiepileptics carry a significant adverse effect burden affecting quality of life as well as the potential for interactions with anti-cancer drugs (9, 10). Additionally, other non-pharmacological such as pain education, coaching and online support groups are shown to be insignificant in their effect on cancer pain (11). VR may present an effective and relatively harmless alternative option for the management of pain in people with cancer.

### Clinical applications of VR

There has been rapid progress in the therapeutic use of VR for many clinical conditions including acute and chronic pain management; for example, fibromyalgia (12), spinal cord injury pain (13), phantom limb pain (14) and chronic migraine (15), in addition to anxiety disorders (16), neurorehabilitation (17) and posttraumatic stress disorder (18). Additionally, VR technologies have also been used for pain and stress control during medical procedures especially concerning burn and wound debridement and chemotherapy (19, 20).

### Clinical applications of VR in cancer

Currently, several VR studies show positive results for the reduction of pain and anxiety during cancer procedures, especially during chemotherapy (19). Psychological factors such as emotional distress and dysfunctional coping are shown to increase the risk of painful chemotherapy induced nausea, vomiting (21) and peripheral neuropathy (22). Although distraction interventions such as relaxation and guided imagery show success in reducing these symptoms, they often require practice and full concentration that are not always achieved. Promisingly, VR does not require any previous practice where it is attention-grabbing while also having the ability to detach patients from the anxiety of their clinical surroundings. Currently, only two studies have investigated the short-term effects of immersive head-mounted device (HMD) VR on cancer pain.

First, in a randomised control trial, Mohammed and Ahmed investigated the effectiveness of a single VR intervention as a distraction for reducing pain and anxiety in 80 female patients with breast cancer(23). For the intervention group (n-40), immersive VR HMDs with headphones showing either a 15- minute deep sea diving or sitting on a beach application were started at the peak time effect for either oral or intravenous morphine. The comparison group was given morphine alone. Pain and anxiety assessment were done just prior to giving morphine and just after finishing the VR session (which started exactly at the peak time effect for 15 minutes), which means that the reassessment was done 15 minutes from the peak morphine effect. There were significant post-intervention differences between mean pain intensity scores of the two groups (P < 0.001) and between pre and post VR mean pain intensity scores for intervention and control groups (P < 0.001). Additionally, similar significant differences in reductions in state anxiety were found between the intervention and comparison groups and between intra-group pre and post VR anxiety scores (both P < 0.001).

Second, and most recent, Niki and colleagues in a prospective multicentre single arm study, investigated the use of simulated travel using immersive HMD VR for improving symptoms in 20 terminal cancer patient (24). Using Google Earth VR® participants experienced one VR session of up to 30 minutes and could travel to either “a memorable place” or “return home”. The primary endpoints was measured using the Edmonton Symptom Assessment Scale immediately prior to and after the VR session. Their results show that VR was most effective in reducing anxiety (p<.001), well-being (p<.001), depression (p=.001), tiredness (p=.004) and pain (p=.005). Encouragingly, like the work of Mohammed and Ahmed, these findings show that VR may be beneficial for both physical and mental health with no side effects and thus improving symptom burden.

### Applications of VR in other chronic pain settings

Analgaesic effects of VR have been investigated in various chronic pain settings such as fibromyalgia (25), post-stroke (3), spinal cord injury (26) and phantom limb pain (27). Although the positive short-term analgaesic effects on pain is well established in many chronic pain conditions, long-term effects of VR on pain intensity shows potential but requires further investigation (26). A recent meta-analysis investigating the effect of virtual reality on pain perception shows that although frequency and time of exposure appear to be important aspects of VR interventions when managing chronic pain, current evidence is inconsistent (28). Encouragingly however, studies examining long-term VR effects on pain in people with spinal cord injury do show that repeated exposure over a longer period, does show greater reductions in pain intensity. In these studies, VR has been used alone, or in combination with other forms of treatment approach such as transcranial direct current stimulation and exoskeleton muscle training (29-31). Here, VR (3D and 2D) exposure over multiple sessions show greatest reductions in pain severity where in some cases, analgaesic effects continued several weeks after treatment (29, 30), suggesting long-term neuroplastic changes to central pain pathways. Although no data exists on the duration of analgaesic effect after single-use VR or the long-term effects of VR use in cancer pain (32), these findings are encouraging in that HMD VR may be a feasible option for pain relief, alone or an adjunct to ongoing treatment.

### Adverse effects of VR

Although VR environments are effective in many fields of application, there is potential for adverse effects, the most predominant of which s motion sickness. This is experienced commonly with VR use and is known as “VR simulator sickness”. However technical innovations with software – something as simple as adding a visible nose to the graphic head mounted display have reduced the incidence of some of these side effects. In this study, we have chosen a VR application that has minimal pitch and roll, no teleportation and no zero-gravity type motions, all if which are shown to increase VR simulator sickness (33).

### Significance

Evidence now shows that distraction type VR is useful for people with persistent pain who have difficulty diverting their attention away from ongoing pain by enhancing the level of immersion within a distracting environment. A meta-analysis has shown no difference in effect between specifically developed VR computer software and commercially available packages and thus they appear to be equally effective. VR is therefore becoming increasingly affordable and available for use in both clinical and experimental settings. Despite growing evidence of benefit and increased accessibility and affordability, only two studies have examined the effectiveness of distraction type VR in people with cancer pain, one in combination with the administration of morphine. Reductions in the intensity of cancer pain using affordable VR software would be a huge advance for people who currently face major challenges in obtaining satisfactory relief of their cancer pain, especially breakthrough pain.

### Study feasibility

This project is highly feasible given the demand for readily accessible non-pharmacological pain management tools for people with cancer pain. Given encouraging experimental findings and meta-analysis of studies using visual imagery and virtual reality techniques for acute pain, chronic pain and spinal cord injury pain we are confident we can expand on and increase the rigour of preliminary investigations of the effects of VR on cancer pain (32, 34). Thus, we not only aim to show that an easily accessible and cost-effective intervention can be deployed in both inpatient and outpatient settings, but additionally expand on previous work by examining the hypothesis that increased levels of VR immersion result in greater levels of pain relief. Given the use of numerical and visual analogue pain scales in previous VR cancer pain studies, we also aim to capture more comprehensive pre and post intervention pain data by using the Brief Pain Inventory (BPI-SF). Similarly, we will use the Depression, Anxiety and Stress Scale (DASS-21) to gain more comprehensive pre and post VR mood data compared to previous studies.

### Future studies

This feasibility study is investigating short-term pain relief due to distraction using detailed outcome measures. Thus, given recent findings in studies investigating both short and long-term VR use in a range of chronic pain populations and the increased accessibility to wireless portable HMDs that require no computer, we hope that by gaining more comprehensive data concerning the effects of VR on cancer pain, we can continue more specifically with further studies investigating longer-term benefits of HMD VR applications at home.

## Study objectives

**Primary objective**

* To determine whether there is a significant reduction in cancer-related pain, both statistically (p-values, strength of correlation) and clinically (effect size and numbers needed to treat), immediately after and up to 20-minute after each VR session.

**Secondary objective**

* To determine whether there is a significant reduction in cancer-related mood both statistically (p-values, strength of correlation) and clinically (effect size and numbers needed to treat), immediately and up to 20-minutes post VR session.

# We hypothesise that using a HMD VR application will have significant short-term effects in reducing the intensity and negative perceptions of pain in people with cancer-related pain.

## Trial Design

We will use a randomised, crossover design, where after completion of baseline questionnaires, all participants will undergo immersive and non-immersive VR interventions in randomised order. Each intervention will be 15 minutes duration with a two-day- washout period between interventions.

# Methods: participants, interventions and outcomes

## Study setting

All data will be collected from the Greenwich Hospital cancer pain clinic in Northern Sydney, NSW.

## Eligibility criteria

All participants will be sampled from consecutive cancer pain patients referred to the Greenwich Hospital Pain Clinic. Potential participants will be screened for this feasibility study using a background questionnaire that includes sections relating to medical history, pain information and current medication. Participants must also give written informed consent and are willing to comply with the study. Potential participants will be excluded if they are unable to participate in two VR sessions, two days apart, condition such as to interfere with the patient’s ability to understand the requirements of this study. Participants are required to attend two study sessions.

### Inclusion criteria

* 18 years of age and over
* Diagnosed with all types of cancer
* All types of constant or intermittent cancer-related pain for 4-weeks or more with an intensity of 4/10 on a numerical pain rating scale
* Life expectancy of one month and over
* Hospitalised and home-based patients

### Exclusion criteria

* Cancer-related pain under 4/10 on an NPRS for four weeks prior to the study
* Significant unrelated non-cancer pain
* Psychiatric comorbidities (not including anxiety, stress and depression)
* Ability to Understand English (written and spoken)
* Legally blind
* History of motion sickness

## Interventions

The two interventions will be:

1. **Test intervention -** Immersive 3D VR application using a head mounted display. Using Oculus Rift® headsets with noise cancelling headphones and facilities for the use of eye glasses, we will use a commercially available VR application called Nature Treks®. All participants will have a single option of alpine meadow scene. The application will be a 3D filmed experience that enables the participant to engage in an immersive environment.  The experience will be non-interactive. This is for several reasons. Firstly, the sessions are only 15 minutes length and we do not want to create unnecessary frustration by participants trying to master a very interactive or difficult application in this short time. Secondly, some people with cancer pain will have limited energy and an interactive application requiring manipulation of a controller will be challenging. This will also create varying experiences for people with different levels of injury and differing hand motor ability. Thirdly, a non-interactive experience will be the same for each participant and will standardise the intervention across the group. Finally, the chances of motion (or cyber) sickness are minimised where the participants control all movements in all directions. Additionally, there are no pitch and roll motions in the VR program, a major contributor to motion sickness.
2. **Control intervention -** The control intervention will be the same VR application viewed on a 50-cm TV display (“flat”/non-3D) with noise cancelling headphones

## Outcomes

### Primary outcomes

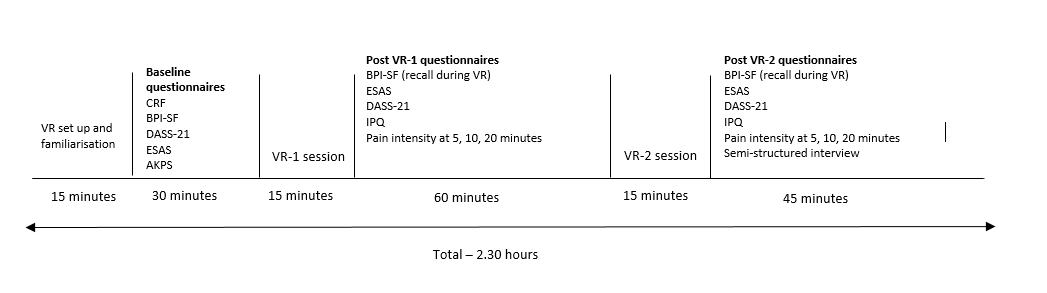
* **Modified Brief Pain Inventory (Short Form) (BPI-SF)**: For our study at baseline, we will use items 3-6 (pain intensity in the past 24 hours) from the BPI-SF and have been modified to determine levels of pain intensity for four weeks prior to study participation. We also included items 2 (body diagram) and 7 (current pain treatments). Additional items include cancer pain duration, consistency, duration of flare-ups (breakthrough pain), and time of day when pain is worse. We will also administer the BPI-SF after each VR intervention. Here, we have modified items 3-6 to assess pain intensity directly after VR as well as the average, least and worst pain during each VR intervention. The latter three recordings are to gain information concerning the time of peak VR effect. We chose the BPI-SF as it is a reliable and valid self-report measure that rapidly assesses the severity of pain and its impact on functioning in people with cancer (35, 36). Additionally, we will use item six of BPI at 5, 10 and 20 minutes after each VR intervention in order to assess the duration of any VR- related alterations in pain intensity.

### Secondary Outcomes

* **The Depression, Anxiety and Stress Scale (DASS-21)**: The DASS-21, recently validated in cancer populations is set of three seven-item self-report scales designed to assess emotional states of depression, anxiety and stress (30, 31). Participants rate their levels of emotional states on a four point Likert scale ranging from 0 (Did not apply to me at all) to 3 (Applied to me very much or most of the time) (37). In order to determine the effect of VR on more specific factors relating to depression, anxiety and stress, the DASS-21 will be administered at baseline and then immediately after each VR session. Due to the DASS-21 capturing data relating to stress, anxiety and depression it presents a reduced response burden while preserving the psychometric strengths of other individual mood-based self-report measures. The DASS-21 is also predictor of poorer treatment outcomes in chronic pain populations (38).
* **iGroup Presence Questionnaire (IPQ)**: The IPQ is a scale for measuring the presence experienced in a virtual environment and contains three factors including spatial presence (the sense of being physically present), involvement (the attention devoted to the VR experience) and experienced realism (the subjective experience of realism) (39). The IPQ will be administered at baseline and then immediately after each VR session.
* **The Edmonton Symptom Assessment System (ESAS)**: The ESAS is a well-validated self-reporting tool used in cancer populations that consists of nine visual analogue scales measuring pain, activity, nausea, depression, anxiety, drowsiness, lack of appetite, well-being and shortness of breath in cancer and palliative care settings (40). The ESAS will be administered at baseline and then immediately after each VR session.
* **The Australian-modified Karnofsy Performance Status (AKPS):** For overall performance status at baseline we will use the AKPS, a well-validated measure of a patient’s overall performance status or ability to perform daily activities (41). The AKPS is a sensitive predictor of poor prognosis and may be useful in predicting primary outcomes in this study. The AKPS will be administered at baseline only.
* **Case-report form:** Demographic, cancer and cancer pain historydata such as pain duration and frequencygained in the case report form will be used to determine potential predictors for study outcomes
* **Semi-structured interview** at the end of the study by the researcher to capture the participants perceptions of their overall impressions of the VR experience, adverse effects and the value of VR in the management of their pain.

### Participant timeline

To account for circadian influences on wakefulness, all study interventions will take place between 11.00am and 1.30pm. Forty-five minutes will be required to collect baseline demographic and pain history information (Case report form), administer questionnaires (BPI-SF, DASS-21, ESAS, AKPS) and familiarise the participant with the VR set-up (figure 1). The participant will then undergo two interventions in randomised order. Each intervention will be 15 minutes duration with a two-day- washout period between interventions. Assessments using the BPI-SF, DASS-21 and ESAS will be further administered immediately after each intervention (30 minutes).



**Figure 1** *A schematic diagram of the VR protocols that includes a) VR and baseline questionnaire completion, b) first VR session, c) between-VR application wash-out period, d) second VR session, e) post VR session questionnaire completion.*

### Sample size

The sample size for recruitment is 22 and was calculated using effect size, standard deviations and differences in population means from previous studies and also from a recent meta-analysis on studies investigating the use of VR distraction on clinical and experimental pain, especially those relating to VR programs versus games (42, 43). Based on these data, we estimate an effect size of .75 and a standard deviation of pre-post change test intervention scores of 1.25

### Missing data

In order to avoid missing data, our study protocols are relatively simple.

* We will collect data that is absolutely necessary to fulfil our objectives.
* Our sample size is small
* All participants will complete self-report measures in the presence of a researcher, where any confusion concerning the understanding of questionnaire items can be explained.
* We are only collecting data directly after each VR session, thus, no follow-up data collections are required, thus reducing chances of missing data.

### Recruitment

Participants will be recruited consecutively from patients attending the cancer pain clinic at Greenwich Hospital between January and October 2020.

## Allocation

In order to determine which VR intervention is experienced first, we will use computer-generated random allocation software (Tripod®).

## Data collection methods

* **Baseline Assessment:**
  + Demographic data using a case report form including gender, race, clinical cancer and pain characteristics (modified BPI), levels of function (AKPS), mood (DASS-21) and cancer symptoms (ESAS) will be administered after consent has been given to take part in the study.
* **Post intervention assessment** 
  + **Pain Intensity:** The BPI will be administered first at baseline and then immediately post VR. In order to determine peak VR effect, participants will answer items relating to worst, least and average pain intensities during VR. Additionally, pain ratings will be taken at five, 10 and 20 minutes after each VR intervention in order to determine the duration of analgaesic effect (change from baseline).
* **ESAS:** In order to determine the effect of VR on other cancer-related symptoms, the ESAS will be administered immediately after each VR session.
  + **DASS-21:** In order to determine the effect of VR on cancer-related mood, the DASS-21 will be administered immediately after each VR session
* **Participant interviews:** 
  + Qualitative data will be retrieved after NPRS, ESAS, IPQ and DASS measurements at the end of the study. Here we will request participant information on VR expectations, experiences and levels of immersion, distraction and enjoyment. Additionally, based on participants experiences in this study we will inquire about their willingness to participate in long-term HMD VR studies.

## Data Management

* Data will be stored in both paper and computer files at the Department of Pain Management Greenwich Hospital, Sydney. Data will be secured in lockable cabinets and computers with password protection.
* All data from this study will be stored for a period of 15 years, after which paper will be shredded and destroyed and computer files securely deleted.
* All incidental/secondary findings will be reported and with permission from the participants sent to both the attending relevant clinical departments and general practitioner.

## Feasibility of outcomes

The primary outcome of this feasibility study is adherence to and acceptability of an easily accessible VR intervention. Additionally, given the scarcity of data in relation to the effects of VR on cancer pain, we aim to establish and increase knowledge gained from existing studies with:

* Data relating to the length of time pain relief occurs after VR has stopped
* Data relating to the effects of VR on more specific areas of anxiety, depression and stress
* Practical areas such as time, commitment and acceptability of cancer patients to VR exposure
* Gaining insight into expanding HMD VR treatment to more long-term use in this population

Therefore, an adherence rate of at least 80% of participants completing both the immersive and control VR intervention will be considered.

Concerning acceptability, we chose 15 minute VR sessions as previous studies suggest a minimum duration of 10 minutes and a general maximum of 30 minutes. Given the potential for user fatigue and motion sickness in this participant cohort, we have chosen:

* A VR application that allows full user control, minimal chance of motion sickness, no gaming or challenge-based functions and is designed for relaxation
* 15 minutes of VR: a suitable duration to a) maximise both affect and adherence and b) considered as minimum evidence that the intervention is feasible.

Concerning acceptability data for test and control VR sessions, we will use the iGroup Presence Questionnaire (IPQ) that measures the sense of presence in a virtual environment to retrieve quantitative data. To gain more qualitative data, we will use participant interviews about their thoughts on the useability of hardware (handset, headset etc.) and the effect of the VR scenes on their pain, anxiety and other symptoms recorded at baseline.

Although this study is examining the short-term benefits of HMD 3D VR, the accessibility, relative low cost of currently available VR units and current evidence on the benefits of more long-term use, should warrant continued research investigating possible long-term pain relief using of HMD 3D VR.

## Statistical methods

Data analyses will be performed using SPSS Statistics 24 and R software. Here, we will first calculate descriptive statistics from demographic and clinical characteristics of the sample including age, years since cancer diagnosis, type of cancer, type of treatment(s) disease reoccurrence and remission status and worst, least and average pain intensity over the previous four weeks.

Secondly, we will use a paired T-Test to determine any mean differences from baseline in pain intensity, stress, anxiety, depression, nausea, drowsiness, lack of appetite, well-being and shortness of breath and levels of immersion between HMD 3D and 2D VR interventions. However, because this study features a repeated measures design, we also used linear mixed models analysis with post 3D and 2D VR pain and immersion scores as dependent variables. These regressions included a factor for the condition (HMD 3D and 2D VR), the sequence (randomised sequence of conditions between subjects) and time (randomised sequence of conditions within subjects). We further conducted mediation analysis to understand relationships between levels of VR immersion, the type of VR (3 and 2D) and post VR pain scores.

We will also use Pearson’s correlation coefficient (r) to measure strength of association between baseline questionnaire data and post-test and control VR pain ratings and other cancer related variables.

Given evidence from recent studies investigating the effects of VR in both cancer and other chronic disease samples, we expect to observe decreases in mood, well-being and drowsiness variables. Concerning pain intensity, we also expect to observe decreases during VR use followed by a gradually return to pre-VR pain levels over a period of 15 minutes post VR session. We are unsure how VR will effect nausea and shortness of breath.

# Ethics and Dissemination

## Protocol amendments

An ethics application will be completed after approval of our protocol modifications based upon review feedback from the Cancer Symptom Trials review panel.

## Consent or assent

Study information sheets will be given or mailed to all potential participants for them to read in their own time. On arrival for the study, participants will be asked if they understand all the information given in the sheet, where they will then be asked to sign the consent form. If a participant is not able to understand the requirements of the study or do not wish to participate, they will be excluded.

## Confidentiality and access to data

Only named investigators will have access to participant details. Any identifiable information collected about participants in this study are confidential and will be disclosed only with participant permission, except as required by law. All participant details will be stored securely in lockable cabinets at the Pain Management Services Department and password protected computers on Greenwich Hospital servers.

Participant health records and information may be disclosed to other agencies such as the Northern Sydney Local Health District HREC and other government agencies. This will only occur when necessary and the provisions of Australian privacy law will be complied with. All research information will be stored for a period of 15 years, after which paper will be shredded and destroyed and computer files securely deleted.

## Declaration of interests

We have no competing of financial interests for the overall trial at Greenwich Hospital

## Ancillary and post-trial care

Motion sickness is the only known risk related to immersive VR, thus minor complications may arise as a result of this study. In such cases participants should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment.

## Dissemination policy

We plan to publish the overall results in peer review journals, presentations at conferences or in other professional forums but in a form where participant information will not be personally identified.

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