RSVR study protocol

Title of Project: A **R**andomised pilot **S**tudy to evaluate the use of **V**irtual **R**eality Mindfulness and Wellbeing session during pre- and post-surgical admission to reduce anxiety and stress undergoing first time elective cardiac surgery – RSVR study.

Dated 03/10/2023.

Version V0.1

IRAS Number

Sponsor Reference: 14098 (Funder ID: **NUFA86)**

Chief Investigator: Prof. Bhuvaneswari Krishnamoorthy, PhD.

University of Salford Manchester, UK.

This project will be conducted in accordance with the study protocol and the ethical principles outlined by Good Clinical Practice (GCP) and the Declaration of Helsinki in its most current version.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:
.....
......./...../.....

Name (please print):

.....

Position:
.....

Chief Investigator:

Signature: Date:
..../...../.....

Name: (please print):

.....

Table of contents

KEY STUDY CONTACTS

Chief Investigator and Principal Investigator	Prof. Bhuvaneswari Krishnamoorthy Professor of Nursing/Surgical Practice University of Salford b.bibleraaj@salford.ac.uk bhuvaneswari.bibleraaj@mft.nhs.uk
Study Coordinator	Miss. Hayley Grey-Shepherd The University of Salford Research Contract officer H.Gray-Shepherd1@salford.ac.uk
Sponsor	The University of Salford.
Funder(s)	University of Salford Prime Fund 2023 - £10,000 until July 2024.
Key Protocol Contributors	Prof. Heather Iles-Smith Professor of Nursing University of Salford H.M.Iles-Smith@salford.ac.uk Mrs. Azita Rajai Medical Statistician Manchester Foundation Trust and University of Manchester Azita.rajai@mft.nhs.uk Mr. Moslem Abdelghafar Cardiothoracic surgery- Senior clinical fellow Manchester Foundation Trust Moslem.Abdelghafar@mft.nhs.uk Mr. Rick Air Cardiothoracic surgery – Surgical Care Practitioner Manchester Foundation Trust Rick.air@mft.nhs.uk Mr. Giulio Citarella Cardiothoracic surgery- Senior clinical fellow Manchester Foundation Trust Giulio.citarella@mft.nhs.uk Mr. Rajamiyer Venkateswaran Cardiothoracic surgery- Consultant Manchester Foundation Trust rajamiyer.venkateswaran@mft.nhs.uk

ROLE OF STUDY SPONSOR AND FUNDER

The University of Salford will act as the sponsor for this study, accepting the financial and legal responsibility for the study. Delegated responsibilities will be assigned to the Chief Investigator, Principal Investigator and the research team (Dr. Moslem Abdelghafar (Associate Principal investigator), Mr. Giulio Citarella and Mr. Rick Air (Co-Investigators)) to manage the study on behalf of the sponsor.

Funder: The University of Salford, Prime Fund. Funded October 2023 to July 2024.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Data Monitoring Committee

This project is a pilot study Virtual Reality mindfulness and wellbeing study, the medical statistician will be an independent person, Prof. Venkateswaran and Prof. Heather Iles-Smith. The DMC will meet by Skype or teleconference as much as possible for sustainability. However, if there are number of any adverse events or serious adverse events reported such as severe dizziness, severe skin rashes, severe confusion related to the VR application, the data will be looked into at any time of the study period. Procedure will be conducted in accordance with MHRA Good Clinical Practice Guide. The committee will have full access to the anonymous data after approximately 10% to 25% of participants have been recruited. The aim of the DMC is to identify any safety issues that may give cause for concern and to inform the study Steering Committee (including early study termination, if required). The DMC will meet before the Steering Committee (SC) meeting and the minutes from the DMC will be forwarded to the SC for their consideration. The role of the committee will be to monitor and advise the study safety.

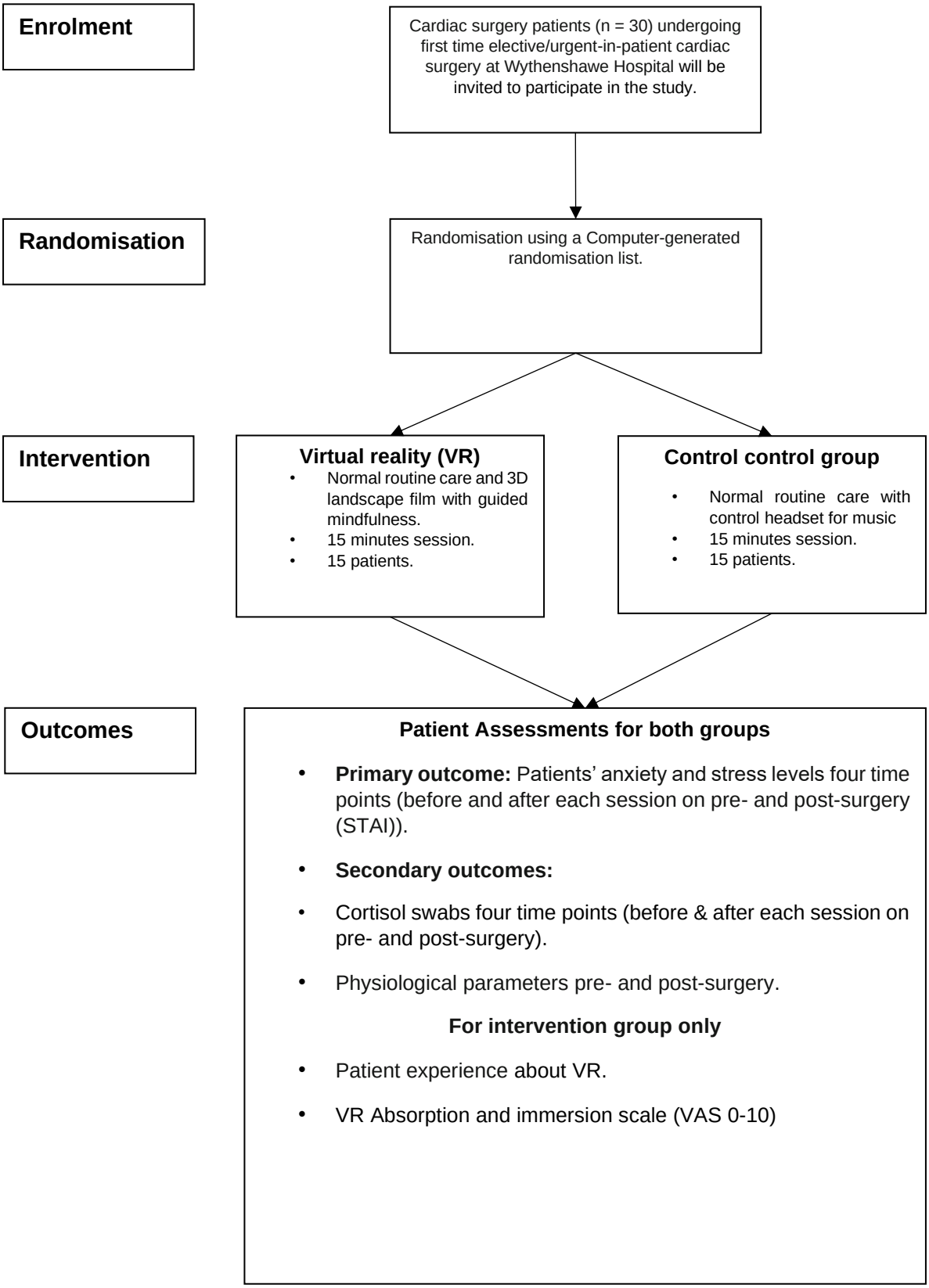
Steering Committee

The Steering committee will be independent to the DMC. The plan for steering committee to meet at least once to make sure that there are no reports of an unexpected events such as severe confusion, severe dizziness unable to recover which requires emergency admission due to VR application during the study period. The committee will be chaired by the Clinical surgical experts, Prof. Venkateswaran, and a lay person, all of whom will be completely independent of the study. The lay person who is our previous heart patient who sits on a Ticker club (heart charity club) at Wythenshawe hospital will be given full training about this study.

ABBREVIATIONS

3D	3 Dimensions
GP	General Practitioner
STAI	State Trait Anxiety Inventory
VAS	Visual Analogue Scale
VR	Virtual Reality

STUDY FLOW CHART



STUDY PROTOCOL

1 Abstract

Background (Lay):

Non-drug methods like hypnosis and Virtual Reality (VR) are used alongside other treatments to help patients with anxiety and different types of pain. But when it comes to using VR to help people who are having heart surgery, there haven't been many studies. One reason for this might be that using VR for this purpose is relatively new, VR technology is changing quickly, and it can be expensive to get started with VR.

Scientific

The use of mindfulness and relaxation techniques such as immersion in nature and natural landscapes is steadily rising in the clinical care [1]. Different non-pharmacological techniques, including hypnosis and immersive virtual reality (VR) are currently used as complementary tools in the treatment of acute and chronic pain. Anxiety, stress are other common problems for patients undergoing cardiac surgery. [1,2,3] Many practices have sought to develop nonpharmacologic strategies to ameliorate preoperative stress, anxiety and pain. Hendricks et al. showed that in post-cardiac surgery patients immersive VR significantly reduced multiple measures of state anxiety compared with baseline, including feeling tense, strained, and upset.[4]. However, the control group in their study had an intervention of tabletop games and standard care was not measured within either group.

Aims and objectives:

This pilot study will assess immersive head mounted VR simulations in adult patients undergoing first time elective cardiac surgery to understand the impact on patient anxiety and stress. The primary objective is to assess anxiety and stress levels between two groups.

Methods:

Cardiac surgery patients (n = 30) undergoing first time elective/urgent-in-patient cardiac surgery at Wythenshawe Hospital site will be randomly assigned equally to two arms (control with control or VR) using a computer-generated randomisation list. The control group will receive standard care admission process which includes a surgical information booklet, online Microsoft Teams experiential talk about the surgery pathway by a heart charity and two sessions of 15 minutes music session with WorWoder Wireless blue tooth headset as a control pre- and post-surgery as same timings as intervention group. The VR intervention group will receive the same as the control group with the addition of two VR sessions: session one 15 minutes VR session will be one hour before surgery and sessions two on day 3 evening (around 6pm) postoperatively. Patients who are ventilated on day 3 will be removed from the study and additional patients will be recruited on both groups. Questionnaires will be handed to the patients pre- and post-surgery in both groups to rate their levels of anxiety and stress level (STAI), physiological assessments, VR experience and VR-absorption (VAS) in intervention group will be recorded.

In addition, we will explore if there is association between salivary cortisol levels as a potential biomarker for stress and self-completed questionnaires anxiety level (STAI). We will obtain four samples of before and after control/VR intervention pre- and post-surgery to see the co-relation.

Expected outcomes:

This study will identify whether the use of VR technology has the potential impact to reduce pre and post operative anxiety and stress.

2. Research Question

1. Can immersive head mounted Virtual Reality headset intervention reduce pre-and postoperative anxiety and stress in adult patients undergoing elective cardiac surgery?
2. Is the use of VR technology being feasible immediate post-surgery on cardiac surgery patients?

3 Objectives and Outcomes assessments

2.1 Primary Objectives:

- Assessment of anxiety, stress levels between two groups

2.2 Secondary Objectives:

- Feasibility of VR technology.
- Correlation between cortisol level and STAI
- VR experience
- VR absorption

2.3 Outcome Measures:

- **Primary outcome:** patients' anxiety and stress levels four time points (before and after each session on pre- and post-surgery (STAI)
- **Secondary outcomes:**
- Cortisol swabs four time points (before & after each session on pre- and post-surgery).
- Physiological parameters pre- and post-surgery.

For intervention group only:

- Patient experience about VR (Rescape™ company questionnaire))
- VR Absorption and immersion scale (VAS 0-10)
- Proportion of patients consenting to VR.
- Proportion of patients completing the VR sessions.
- Adverse events due to VR.

4 STUDY SETTING

- The single-centre study will be conducted at the Manchester Foundation Trust, Wythenshawe Hospital site. Patients will be identified from our annual waiting list register at the cardiac waiting list office.

5 SAMPLE AND RECRUITMENT

This pilot study will have a randomised design and will be a single-centre trial with 2 arms, including one experimental immersive head mounted VR group and one control control group.

They will be randomly allocated:

1. Control group: Normal routine care with 15 minutes music session with WorWoder Wireless blue tooth headset.
2. Virtual reality (VR): Normal routine care and 3D landscape images with guided mindfulness for 15 minutes session with VR headset.
3. Please note that we will be recruiting patients who are undergoing surgery in the morning and afternoon. This may alter the cortisol levels of the patient, but this will be taken into consideration while comparison analysis.

Control group: Normal routine care

Control group patients will receive normal preoperative surgical admission processes which includes admission to the hospital by the administration/nursing team, meeting with surgical core trainees to complete preoperative details and informed consent. Patients may also receive an experiential talk about the surgery pathway given by Ticker Club (heart charity) volunteers; this is an ad hock service. Full surgical pre, intra and postoperative booklet will be provided to the patient by the preoperative outpatient nurses. As a control, we will be asking the control group patients to listen to music of their choice for 15 minutes music session with WorWoder Wireless blue tooth headset.

Session one pre surgery: They will be asked to listen to the music for 15 minutes within one hour time period of their surgery.

Session two: They will be asked to listen to the music post-surgery on day 3 (around 6pm).

Intervention arm: VR

Intervention group patients will receive the same pre-operative preparation as the control group with the addition of three Virtual Reality (VR) sessions using a head-mounted 3D display. This 15 minute long immersive VR experience from Rescape Innovations (https://www.rescape.health/) features the visualisation of 10 beautiful environments and landscapes (Figure 1). It provides the viewer two guided mindfulness sessions which teach breathing and relaxation techniques and is accompanied by the sounds of nature and soothing guidance. In between the two mindfulness sessions lies a montage of natural environments to enjoy whilst calmly relaxing and escaping to these peaceful surroundings. Participants are not required to interact with this experience; they simply relax during the session.

Patients will be instructed to discontinue use if they experienced any discomfort or side effects (dizziness, motion sickness, etc); this will be recorded as a side effect and limitation of the therapy. Participants will be instructed to refrain from engaging in other video game activities, watching television, or using their phones during the time of intervention to standardise the impact of their assigned intervention.

Session one: Patient will receive the VR session pre surgery within one hour time period of their surgery.
Session two: They will receive the VR session on day 3 post surgery (around 6pm).

Hygiene measures:

Two VR headsets (£6000) and two WorWoder Wireless blue tooth headset (£100) will be provided by the company free of cost for this study and it will be used within the hospital premises. Infection control measures will be used as per manufacturer recommendation. Adequate hand hygiene is required upon

handling the device or the controllers. Adequate disinfection of the device between each patient use, includes dismantling of all separable parts and thorough disinfection with non-alcoholic cleaners as per manufacturer's recommendation.

Patients who might not adequately understand verbal explanation or written information given in English will be provided with hospital interpreters. All the patients whose first language is not English will have an interpreter booked by the hospital.

Eligibility criteria are as follows:

All adult cardiac surgery patients will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation except where the study inclusion and exclusion criteria EXPLICITLY state otherwise.

Inclusion criteria:

- Adults undergoing first time elective cardiac surgery (coronary artery bypass surgery and aortic/mitral valve surgeries), age more than 18 years, who will give informed consent for their participation to this study.
- Urgent in patient who are well enough to read and understand the study and patient information leaflet.

Exclusion criteria:

- Psychiatric antecedents, claustrophobia or acrophobia, diagnosis or self-reported anxiety disorder, hearing or visual impairment, Infectious cases (example: conjunctivitis), redo surgery, critical preoperative state, impaired cognitive function, current diagnosis of epilepsy, dementia, or other neurologic disease, receipt of anxiolytic drugs or sedatives within the preceding 24 hours, or injury to the face, or non-infectious, infectious skin conditions that would prevent comfortable use of the VR hardware.
- Patient who are having complex cardiac surgeries.
- Patient who are admitted for an emergency cardiac surgery.
- Patients who do not want to listen to music on their bedside Bluetooth enabled headphones.
- Patient who does not want to wear VR headsets.

5.1 Patient Recruitment

All adult cardiac surgery eligible patients will be fully informed of what the study entails and will be provided with written patient information sheet on the study. Urgent in patient will be approached in the cardiology ward 1 to 2 weeks after the surgical referral and they will be given more than 48 hours to consider whether they wish to take part. Elective patients will be approached at the outpatient clinic which is 4 to 6 weeks prior to the surgery.

5.2 Patient Consent

Elective patients will be approached by the cardiac surgeon during their outpatient clinic appointments. Urgent in patient will be approached by the cardiac surgeon in the cardiology ward. Potential participants are required to read the Participant Information Sheet. Fully informed written and verbal consent will be gained on admission to cardiac surgery ward 24 hours before the surgery is undertaken. A copy of the completed consent form will be given to the participant.

All participants will be informed that they may withdraw from the study at any point without giving a reason.

6 DATA COLLECTION AND DATA ANALYIS

6.1 Data Collection

Patient data: Generic

- All preoperative clinical data of patient demographics will be obtained from the patients' clinical notes, clinical database, laboratory reports.
- The STAI and cortisol outcomes will be measured for this study at 4 time points pre- and post-surgery.

Clinical patient data:

All clinical data will be collected by research team members.

All the clinical data will be collected prospectively into a relational database. General demographics including age, sex, race, body mass index, hospital admission.

Data collection: Please note that the questionnaires, STAI, (Table 1) will be applicable to both study arms.

Demographic factors

All basic pre and post operative variables will be collected such as on age and gender, duration of the surgery, medications, consumption of alcohol, tobacco and type of cardiac surgery. Alcohol and tobacco consumption will be recorded as withdrawal symptoms could also influence the participant's behaviour postoperatively.

Time points of collecting anxiety STAI scores and cortisol assay:

Control/VR intervention group:

The first and second set of STAI questionnaire and cortisol assay swab will be collected before and after the control/VR session within 30 minutes after the control/intervention. The third and fourth set of STAI questionnaire and cortisol swab will be collected on day 3 post-surgery around 6 pm before and after the control/VR session within 30 minutes.

Physiological variable

We will record heart rate, blood pressure and respiratory rate at baseline (pre-surgery), before and after the VR intervention, post-surgery to assess the changes and compare between the two groups. We will record same physiological assessment for the control group before and post-surgery. The time period of the assessment will be matched as similar as possible to reduce any bias.

Psychological variable

State-Trait Anxiety Inventory (STAI) will be used to measure patients' self-evaluation stress and anxiety. It is a set of 20 statements with scores 1 to 4 which people have used to describe how they feel "at this moment."

It will be collected pre- and post-surgery and at the same time points for both groups to assess any difference in anxiety between groups.

In addition,

- VR experience for pre- and post-surgery.

- Absorption is the “tendency to become fully involved in a perceptual, imaginative, or ideational experience”. We will ask the intervention subjects to answer this question: “Could you estimate on a 0- (not at all) to 10- (fully) scale how deeply you felt absorbed and felt your attention as focalised and focused by the experience you have just lived?”. Immersion and presence will be assessed using a Visual Analogue Scale. The questions will be of the form “from 0 to 10, how much did you feel present in the environment?”

Cortisol assay:

- Both group patients will have 4 samples, before and after control/VR intervention pre- and post-surgery which will give a total of 4 x 30 = 120 samples.

Sample collection:

- Salivary cortisol is considered a reliable and valid measure of unbound or free cortisol levels in plasma. Oral swabs (30 x 10mm cylinder) and salivette storage tubes will be used to collect samples from the participants. During collection, participants will be instructed to place the swab under their tongue on the floor of the mouth for 1-2 minutes. Swabs will be placed in salivettes and within an hour after collection, stored in a lab freezer below -20°C. The storage, transport and testing procedures or the samples will be subject to standard practice and all usual risk assessment procedures as per MFT hospital.

Analysis:

- The Cortisol free in Salvia ELISA kit will be used to determine the concentration of cortisol in the samples. Upon the receipt of the samples, they will be immediately stored at -20°C until analysis. The frozen samples will be thawed and centrifuged for 5 to 10 minutes at 2000-3000 x g. Of the standard and reagent, the control reagent, and the saliva sample,50 µL will be dispensed in microtiter wells, as well as 50 µL of a cortisol-horseradish peroxidase conjugate for binding to the coated antibody. The wells will be incubated for 60 minutes at room temperature. Afterwards, they will be rinsed 3 times with 300 µL diluted wash solution and 200 µL of substrate solution will be added. Again, the wells will incubate for 30 minutes at room temperature and 50 µL of stop solution will be added to each well. The absorbance of each well will be determined with the use of a microtiter plate calibrated reader at 450 ± 10 nm within 15 minutes.

6.2 Sample size and power calculation

Sample size has been determined on pragmatic grounds and rule of thumb for pilot studies. 15 patients are required in each group giving a total of 30 patients. We decided to enrol 10% more to compensate for dropouts after the surgery making the total 34 patients.

6.3 Planned Statistical analyses: Clinical

Analyses will be mainly descriptive. Any test will be for exploratory and for hypothesis generating purposes. Proportion of consent and dropouts and their 95% CI will be reported. Demographics, baseline, physiological and medical characteristics will be summarised for the whole cohort and for each arm separately. Summary statistics of anxiety and stress score and cortisol levels will be provided at each time point (baseline and day 3 post operatively) for each arm.

Number of patients approached and proportion consenting to participate will be reported.

Number and percentage of patients removed due to ventilation will be reported.

Number and percentages of patients not completing VR session for any reason will be reported.

Pre and post operation anxiety scores will be compared between the two groups using t-test or equivalent non-parametric test. Pre and post operation cortisol levels will be compared between the two groups using t-test or equivalent non-parametric test. Changes in stress scores and cortisol levels will be assessed. Pre and post operation cortisol levels and anxiety scores will be correlated for all and for each arm separately.

Result from VR experience and VR absorption for the intervention group will be summarise.

6.4 Data analyses and Study Stopping Criteria

Data will be analysed at the end of the study. Any serious Major Adverse events such as severe dizziness, severe skin rashes, severe confusion related to the VR application which requires emergency hospital admission/treatment will trigger study stopping criteria and will be discussed immediately at an emergency steering and data monitoring committee. The final clinical data will be analysed at the study end point.

6.5 Data Confidentiality and security

All data will be kept strictly confidential according to Good Clinical Practice (GCP) Guidelines. All data will be anonymised using unique study reference numbers for each patient.

Excel spreadsheets used for the study, including the recruitment log in excel, will be saved under a study folder that will be permissions based as to who can amend and view the data within the study team. These will be stored on Trust encrypted password protected devices within MFT recruitment site.

All personal identifiable participant information will be destroyed securely and immediately at the end of the research according to the local hospital research protocol. All study data will be stored by the Manchester University NHS Foundation Trust in a secure fashion for 10 years in accordance with the ICH GCP. The trial data and documentation will be archived as per the University of Salford archiving SOP.

Further details can be found in the Data Management Plan held by the University of Salford as study sponsor.

7 SAFETY REPORTING

We are not expecting any major adverse events for this study. However, if there are any adverse events, including serious adverse events (SAE), that the chief investigator suspects could have been related to procedures in the study protocol will be reported to the study Sponsor.

All adverse event assessments and reporting will be carried out in line with MFT trust and the University of Salford SOP's. The serious adverse events are defined as an adverse event which results in one of the following:

a. Severe confusion which requires immediate hospital admission and treatment.
b. Severe dizziness or headache which requires immediate hospital admission and treatment.

c. Severe skin or allergic rashes which requires immediate hospital admission and treatment.

Serious adverse events and adverse events will be collected and recorded on the electronic case report form according to the local hospital research protocol.

The main role of the Principal investigator (PI) will report any adverse and serious adverse events:

a. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated.
b. Ensuring that all SAE/SARs are recorded by completing the SAE form as soon as possible after becoming aware of the event and send a scanned copy to the University of Salford sponsor office using the email address ethics@salford.ac.uk
c. SAE/SARs must be reported to the sponsor office within 24 hours of the research team becoming aware of the event.
d. Reviewing and reporting the accuracy and completeness of all SAE/AE.
e. Closely monitoring patients for any new events.
f. Ensuring a log of all events is kept within the Site File and which may be reviewed by oversight committees such as the Steering Committee.

The Chief Investigator (CI) is responsible for:

a. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
b. Using medical judgement in assigning the SAEs/SARs seriousness, causality and whether the event was anticipated where it has not been possible to obtain local medical assessment.
c. Using medical judgement in assigning whether an event/reaction was anticipated or expected.
d. Immediate review of all Serious Unexpected Serious Adverse Reactions (SUSARs).
e. Review of specific SAEs/SUSARs in accordance with the protocol and trust SOPs on Safety Reporting for Studies other than Clinical Trials of Investigational Medicinal Products (CTIMPs).
f. The Investigator is expected to maintain a log or spreadsheet of all adverse events and effects (including those reported as serious), which may be reviewed by oversight committees such as the Steering Committee. Any trends must be reported by the Investigator to oversight committees in a timely manner.

7.1: Expected safety reporting.

Cross contamination and patient reported side effects from VR headset use will be reported such as severe nausea, severe dizziness, severe disorientation, severe balance problems, severe headache, severe eye strain, severe fatigue and severe cross infection which requires immediate medical treatment.

8 STUDY MANAGEMENT

8.1 Protocol compliance

- If the patient refuses to participate any more follow-up postoperatively on day 3, they will be terminated and withdrawn from the study, but we will use the pre-operative collected data.
- We will try to minimise, and every effort will be taken to obtain any missing data. If it occurs which will be recorded and reported appropriately.

8.2 End of the study

The end of the final data capture will be of the last patient data collecting point which is day 3 at 6 pm, from the day of patient surgery. There will be no data will be obtained from any research participants after this date.

8.3 Public and Patient Involvement

The patients have been involved in this project on various timepoints.

Both patients and the general public were involved through the Ticker Club, a charitable organisation for cardiothoracic patients at Wythenshawe hospital. It was founded in 1987 at Wythenshawe Hospital by a group of patients who had undergone pioneering heart surgery. Currently, there are 462 club members who offer support and practical advice to heart patients and their families, as well as raising money for new equipment and research.

They have played a major role in the CI various research projects, advising on patient recruitment, ethics application, developing a patient information leaflet and facilitating dissemination of the findings at their annual membership meeting every year. Their involvement has been found to be essential in enabling and supporting/development of applications, projects that are important to patients and for providing an opportunity to discuss and identify potential problems at an early stage.

Representatives of the Ticker Club will also be members of the study steering group, advising on study progress, ensuring patient safety and supporting dissemination of findings to patients and carers. Most importantly, they will advise on local patient recruitment and facilitate collaboration with charitable organisations in other UK cardiac hospitals regarding patient recruitment.

The Patient Public Involvement (PPI) group will be involved in writing the research protocol, consent form and questionnaires. Patients and the public will contribute to study management through their role on the steering group, writing the study report and disseminating research findings, including the lay and plain language summaries. They will also be formally consulted during refinement of the training tool after the qualitative phase of the study.

The Ticker Club meets several times a year. During the study the project will be added as a formal agenda item to three of these meetings per year to enable PPI consultation as the study progresses. There will be no additional out of pocket costs for group members. However, in recognition of the group's support, the project will cover meeting expenses, including room hire and refreshments at these three meetings.

Wider public engagement will be enabled through presentations, e.g., the Public Lecture series at Salford University and the annual Manchester Foundation NHS Trust Open Day.

8.4 Monitoring

The study will be subject to audit and monitoring by the site MFT and the sponsor University of Salford SOPs and policies. There will be an agreement between oversite MFT and the sponsor using site initiation form and OID.

The Steering Committee will be an independent committee overseeing the study, they will meet to provide independent oversight to the trial. Additional data monitoring is described in the Data Management Plan.

8.5 Regulatory Review and Compliance

Before the start of the study, a favourable opinion will be sought from an NHS Research Ethics Committee (REC) for the study and all the supporting documents including the protocol, information sheets, informed consent forms and other relevant documents. The study team will be responsible for the maintenance of a study site file, in which all current and superseded study documents will be retained. Also contained in the site file will be the approval documentation including correspondence with relevant authorities such as the HRA and REC.

The study team are responsible for producing progress reports throughout the study, including annual reporting (APR) to REC as required. The Chief Investigator will notify the REC of the end of the study, and will submit a final report with the results, including any publications/abstracts, to the REC within 12 months of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

During the life of the study, there may be amendments to the study protocol and/or documentation. Substantial amendments will not be implemented until NHS REC review is in place and local approvals have been obtained.

No participants will be enrolled into this research study prior to the study being reviewed by the relevant regulatory authorities and receiving HRA and REC approvals, as well as approval from the R&D office at Manchester University NHS Foundation Trust with OID contract.

8.6 Indemnity

The University of Salford indemnity scheme will apply to this study to ensure it meets the potential legal liability of the sponsor, equipment, employer and investigators/collaborators for harm to participants arising from the management, design and conduct of the research. No arrangements will be made for the payment of compensation in the unlikely event of harm.

9 DISSEMINIATION POLICY

The researcher is submitting this study to the ClinicalTrials.gov database (https://clinicaltrials.gov/) or ISCTRN which is UK clinical trial database. This registration will provide easy access to information about the study for patients, family members, researchers, clinicians and healthcare professionals. The study data will be presented at national and international conferences and published in a peer reviewed journal.

REFERENCES

1. Pourmand A, Davis S, Lee D, Barber S, Sikka N (2017): Emerging utility of virtual reality as a multidisciplinary tool in clinical medicine. Games Health J; 6:263–70. https://doi.org/10.1089/g4h.2017.0046.
2. Scheffler M, Koranyi S, Meissner W, Strauß B, Rosendahl J (2018): Efficacy of nonpharmacological interventions for procedural pain relief in adults undergoing burn wound care: a systematic review and meta-analysis of randomized controlled trials. Burns ;44:1709–20. https://doi.org/10. 1016/j.burns.2017.11.019.
3. Jensen MP, Jamieson GA, Lutz A, Mazzoni G, McGeown WJ, Santarcangelo EL, Demertzi A, De Pascalis V, Bányai EL, Rominger C, Vuilleumier P, Faymonville ME, Terhune DB (2017): New directions in hypnosis research: strategies for advancing the cognitive and clinical neuroscience of hypnosis. Neurosci Conscious;3:2057-107. https://doi.org/10.1093/nc/nix004.
4. Tina M. Hendricks, MS Claudia N. Gutierrez, MS John M. Stulak, MD Joseph A. Dearani, MD Jordan D. Miller, PhD (2020): The Use of Virtual Reality to Reduce Preoperative Anxiety in First-Time Sternotomy Patients: A Randomized Controlled Pilot. DOI:https://doi.org/10.1016/j.mayocp.2020.02.032
5. Spielberger. Manual for the State-Trait Anxiety Inventory. rev. ed. 1983.
6. Maurice-Szamburski A, Auquier P, Viarre-Oreal V, et al. (2015): Effect of sedative premedication on patient experience after general anesthesia: a randomized clinical trial. JAMA. ;313(9):916-925.
7. Kassie GM, Nguyen TA, Kalisch Ellett LM, Pratt NL, Roughead EE (2017): Preoperative medication use and postoperative delirium: a systematic review. BMC Geriatratrics;17(1):298.
8. Li A, Montano Z, Chen VJ, Gold JI (2011): Virtual reality and pain management: current trends and future directions. Pain Manag;1(2):147–57.
9. Whitehead AL, Julious SA (2018): Guidance for using pilot studies to inform the design of intervention trials with continuous outcomes. Clinial Epidemiology; 10:153-157.
10. Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study, M Dawn Tear, et al. Trials volume 15, Article number: 264 (2014)

APPENDICES

Figure 1: The images below depict the various environments featured in this film.

Table 1. STAI questionnaire

State-Trait Anxiety Inventory (S.T.A.I.)

Read each statement and select the appropriate response to indicate how you feel right now, that is, at this very moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Statement	Not at all 1	A little 2	Somewhat 3	Very Much So 4
1	I feel calm				
2	I feel secure				
3	I feel tense				
4	I feel strained				
5	I feel at ease				
6	I feel upset				
7	I am presently worrying over possible misfortunes				
8	I feel satisfied				
9	I feel frightened				
10	I feel uncomfortable				
11	I feel self-confident				
12	I feel nervous				
13	I feel jittery				
14	I feel indecisive				
15	I am relaxed				
16	I am worried				
17	I feel content				
18	I feel confused				
19	I feel steady				
20	I feel pleasant				
	Total score:				