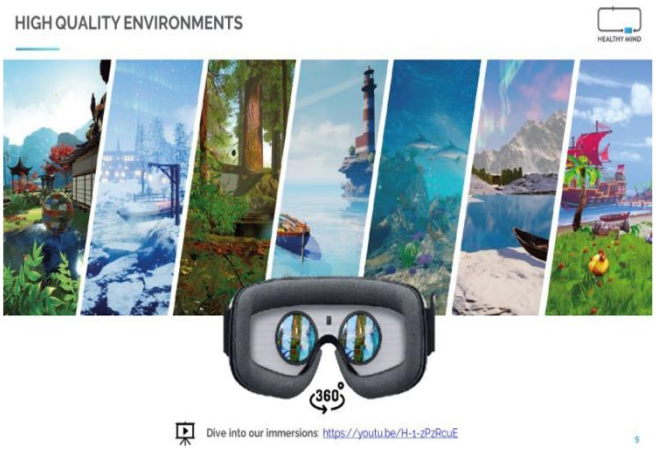
Title

Pilot randomised controlled trial of Virtual Reality immersive therapy (VRIT) in addition to usual care compared to usual care in patients undergoing joint arthroplasty – VROOM Trial

Chief Investigator: Dr Dev Srivastava. MBBS,MSc, MD, FRCA, FFPMRCA. Consultant Anaesthesia and Pain Medicine, Raigmore Hospital and Hon Sr Lecturer, Univ of Dundee. Email: dev.srivastava@nhs.scot





Co Investigators : Prof Ben Shelley (Uni of Glasgow); Prof Lesley Colvin (Uni of Dundee); Dr Line Caes (Uni of Stirling); Raigmore Hospital; Prof David Finn, Uni of Galway; Ms Charlotte Barr (NHSH RD&I);Ms Petra Rauchhaus (Uni of Dundee); Dr Siddharth Bassetti (NHSH RD&I); Dr Caroline Thomas (Leeds Teaching Hospitals NHS Trust); Jill Jones, Study Coordinator (NHSH RD&I); Mr Raj Thangaraj (Raigmore Hospital).

Confidential

Intentionally left blank

STUDY SUMMARY	
Study Title	Pilot randomised controlled trial of Virtual Reality immersive therapy in addition to usual care compared to usual care in patients undergoing joint arthroplasty – VROOM Trial
Internal ref. no. (or short title)	H1955 IRAS 339185
Clinical Phase	Phase III
Study Design	Randomised controlled trial (RCT)
Study Participants	NHS Highland patients on the waiting list for total hip or knee replacement at National Treatment Centre (NTC), Inverness.
Planned Sample Size NHSH	40 Control arm N=20 Interventional arm N=20
Methodology	Participants will be randomised on 1:1 ratio of control arm (CaU) or interventional arm (CaU with VRIT). Control arm will be asked to complete questionnaires at baseline (from 10 to 7 days prior to surgery), day of surgery, 24hrs post surgery, 7 days, 14 days, 21 days, 30 days and 90 days post surgery. Five control arm participants will provide blood samples at baseline (from 10 to 7 days prior to surgery), day of surgery, 24hrs post surgery and 30 days post surgery. Interventional arm will participate in VRIT training, and undertake 20 minute VRIT sessions from -7D surgery until +30D surgery. They will complete questionnaires at baseline (from 10 to 7 days prior to surgery), day of surgery, 24hrs post surgery, 7 days, 14 days, 21 days, 30 days and 90 days post surgery. Five interventional arm participants will provide blood samples at baseline (from 10 to 7 days prior to surgery), day of surgery, 24hrs post surgery and 30 days post surgery. Data from VRIT sessions will be obtained automatically via server and transferred to EDC system.
Intervention duration	From 37 to 40 days
Follow up duration	60 days
Planned Study Period (total)	12 Months

List of Abbreviations

Intervention	Objectives	Outcome measures
Primary	The primary objective will be to assess the feasibility of the study (CSO Scotland guidance). 1. Percentage of patients from whom blood is collected 2. Staff time required per patient. 3. NTC and research staff feedback 4. Patient feedback	This will include the following measures: 1. Number of patients approached for study 2. Number of participants recruited overall 3. Percentage of patients excluded overall. 4. Percentage of patients who refused to participate. (Should not be greater than 70%) 5. Participant compliance rate with use of VR over 37 days [number of days VR used for 20 minutes/37 days] 6. Percentage preoperative VR compliance [number of days/7] 7. Percentage postoperative VR compliance [number of days/30] 8. Percentage of participants with complete questionnaires. (Should be greater than 80%) 9. Percentage of participants who withdraw during the trial 10. VR related technical complications noted 11. Standard deviation of the outcome measures to calculate sample size for the main trial.

Summary Study Process

This pilot research study is designed to test feasibility and acceptability of VRIT in this patient population to compare clinical and cost effectiveness of adding VRIT therapy to Care as Usual in joint arthroplasty patients compared to usual care without VRIT. There is an expectation that VRIT intervention participants will gain benefit from the programme, with outcome measurements relating to pain scores, anxiety reduction, quality of life, and other measures. Data will be collected at baseline (from 10 to 7 days prior to surgery); day of surgery; 24hrs post surgery; 7, 14, 21, 30 and 90 days post surgery. Data will be processed and analysed by NHSH Research study team and collaborators at University of Dundee.

ASA	American Society of Anaesthesiologists
CaU	Care as Usual
CSO	Chief Scientist Office
GIRFT	Getting It Right First Time
NHSH	NHS Highland
NTC	National Treatment Centre
PI	Principal Investigator
PROM	Patient Reported Outcome Measures
RST	Research Study Team
VR	Virtual Reality
VRIT	Virtual Reality Immersive Therapy

Abstract

Psychological factors, (anxiety in particular) link into the biological human stress response systems and can thus have an important bearing on perioperative outcomes. Current pharmacological and non- pharmacological interventions to manage anxiety are not as effective as desired due to a multitude of reasons (side effects, staffing requirements such as psychologists, expense or lack efficacy).

Addressing psychological factors like perioperative anxiety with a relatively easy to use, non-invasive technique such as Virtual Reality (VR) is likely to improve PROM (Patient Reported Outcome Measures). Recently, Virtual Reality (VR) has emerged as a non-pharmacological method to manage preoperative anxiety. VR is theorised to decrease perioperative pain and anxiety by diverting attention away from nociception stimulus, extinction of negative expectancy and fear towards pain and modulating pain related neuroendocrine stress responses. VR thus is able to improve PROM (Patient Reported Outcome Measures) and also improve post-operative pain /opioid use, length of stay in hospital and joint arthroplasty complication rates.

We aim to perform a pilot feasibility study in preparation for the multi-centre randomised control trial that will follow. The primary objective of the pilot feasibility trial will be to test the acceptability, level of adherence to the trial protocol by patients, the ease with which the intervention can be implemented and estimates of the effect size/variability that should be used in the statistical design of the main study.

Key words: psychology, surgery, anxiety, perioperative, virtual reality, randomised controlled trial, joint arthroplasty.

Introduction:

Background

Patients who undergo surgery evoke a stress response by the body that aims to heal but can cause harm if it follows an abnormal trajectory. There is growing recognition of the role of psychological factors in influencing surgical mortality and morbidity in the short and long term by influencing the stress response after surgery (Levett et al,2019).

In a large study of 15,040 patients in the United Kingdom (Moonesinghe et al,2016),33.3% (4653) patients cited anxiety as the worst thing about their operation. Anxiety is a psychological, physiological, and behavioural state induced in animals and humans by a threat to well-being or survival, either actual or potential. Anxiety is an unpleasant emotional arousal in anticipation of threatening situations, demands, or dangers where the fear/distress is disproportionate to the threat posed (Craske et al,2017). The function of these changes is to facilitate coping with an adverse or unexpected situation (Steimer,2002). Anxiety can be an adaptive response driving coping behaviours to face possible dangers, but if excessive and unmotivated, can become dysfunctional, paving the way for developing post-operative morbidity (Kassahun et al, 2015).

Anxiety is one of the most commonly identified factors that impacts surgical outcomes. Anxiety can link into the biological human stress response systems and can thus have an important bearing on perioperative outcomes (Daviu et al, 2019 and Fonseca et al, 2021). Inadequately managed anxiety around surgery can cause high rates of cardiac mortality, adverse effects during anaesthetic induction and patient recovery such as high post-operative pain, increased analgesic and anaesthetic consumption, prolonged hospital stay, poor quality of life, and decreased satisfaction with perioperative care (Abate et al,2020). Perioperative anxiety has thus emerged as a very important contributor to surgical morbidity and mortality and increased hospital stay (Schaal et al,2020).

Perioperative anxiety (anxiety prior to and after surgery) is a widespread issue affecting adults undergoing elective surgery, highly prevalent globally and across different types of surgery (Bedaso et al, 2022). In a meta-analysis, Abate et al,2020 reported that the global pooled prevalence of preoperative anxiety among surgical patients was 48% (95% confidence interval (CI): 39 to 47%.)

With respect to surgery, it is important to understand two constructs of perioperative anxiety i.e. trait and state anxiety. Trait anxiety is a characteristic trait of an individual's personality, and it can be associated with different psychopathological conditions and constant high arousal. State anxiety is a more transient intense emotional state, associated with a temporarily increased sympathetic nervous system activity (Spielberger, 1972). It is not yet clear whether state and trait anxiety are unidimensional or multidimensional constructs, i.e. do these states exist separately or are they part of a continuum? (Saviola et al,2020). Most studies of preoperative anxiety measure both state

and trait anxiety utilising questionnaires such as STAI (State Trait Anxiety Inventory) with a minority measuring anxiety as a unidimensional construct with HADS A (Hospital Anxiety and Depression Scale) and APAI (Amsterdam Preoperative Anxiety and Information Scale). However, the role of state anxiety has been found to be important for perioperative outcomes (Ni et al,2023).

The factors associated with state anxiety prior to surgery include the presence of psychiatric disorders, uncertainties of what the surgeon might find (Montgomery et al2003), perioperative factors such as pain, loss of independence, the surgery itself, anesthesia, and death (Mitchell et al,2003), unfamiliarity and uncertainty regarding the surgical and anaesthesia process (Cheng et al, 2021 and Mitchell et al,2003).

With respect to timing, anxiety can occur prior to and after surgery. Although preoperative anxiety has been extensively studied, there is growing awareness of the importance of post-operative anxiety and its adverse effect on surgical outcomes (Jellish ,2012). In a study of 1771 patients undergoing elective surgery, Nguyen et al ,2022 reported that anxiety as defined by PROMIS T score of 55 or above was observed in 30% of patients prior to surgery,15.2% at 1 month,15% at 3 months and 14.2% at 6 months post-surgery. Gandotra et al,2023 performed an observational study on 1546 patients undergoing elective non cardiac surgery measuring psychological distress (Anxiety /Depression) utilising the EQ5D 3L questionnaire. They reported that moderate to severe psychological distress was reported by 32.6% of participants before surgery; 27.3% at 30 days after surgery; and 26.2% at 1 year after surgery suggesting that interventions to manage perioperative anxiety should target both preoperative and postoperative anxiety to improve surgical outcomes.

To summarise, surgical patients very commonly have state anxiety. If there is an underlying trait anxiety or anxiety disorder, the magnitude of state anxiety around surgery (perioperative anxiety) is exaggerated and can be a significant factor in surgical outcomes.

Current interventions for Perioperative Anxiety and their efficacy

A number of interventions have shown promise in reducing perioperative anxiety. A Cochrane review (Powell,2016) studying the efficacy of psychological preparation for surgery found that psychological preparation may be beneficial for the outcomes of postoperative pain, behavioural recovery, negative affect and length of stay, and is unlikely to be harmful. However, preoperative psychological preparation is limited by time constraints, uncertainty of surgery dates, cost of employing psychologists and hence there are very few NHS Trusts that provide psychological preparation services as part of their pre-assessment process.

A large amount of research has investigated music-based interventions in the perioperative setting; however, results are mixed for their effect on anxiety (Pittman & Kridli, 2011; Tola et al, 2021). Evidence also exists for the use of acupressure and

acupuncture interventions, although the quality of this evidence base is deemed to be low (Tong et al, 2021).

Preoperative education can also significantly reduce preoperative anxiety (Alanazi, 2014). However, a recent Cochrane review (MacDonald, 2014) has found that there is low-quality evidence suggesting that preoperative education may not improve pain, function, health-related quality of life and postoperative anxiety any more than usual care in joint replacement surgery patients.

The most common clinical interventions used to manage perioperative anxiety is the use of medications (anxiolytics, sedatives like Benzodiazepines). In a survey of 3661 Anaesthesiologists in the United States of America (Musa et al,2020),91.6% used preoperative medications to manage anxiety . A multi-centre French randomised control trial study (Szamburski et al,2015) of 1062 patients who were pre-medicated with Lorazepam found that time to extubation was 17 minutes (95% CI, 14-20 minutes) in the Lorazepam group, 12 minutes (95% CI, 11-13 minutes) for the no premedication group, and 13 minutes (95% CI, 12-14 minutes) for the placebo group ($P < .001$) and the rate of early cognitive recovery was 51% (95% CI, 45%-56%), 71% (95% CI, 66%-76%), and 64% (95% CI, 59%-69%), respectively ($P < .001$).This study highlighted the detrimental effects of premedication on time to extubation and cognitive recovery.

Premedication has been shown to increase the rate of nausea and vomiting in children (Sinha et al,2012). Taken along with the fact that patients arrive in hospitals on a staggered schedule for surgery, use of anxiolytic drugs can be limited by a long onset of effect and duration of action, and so it is often difficult to determine the optimal time to administer these drugs in a busy surgical setting. Thus, this limitation with premedication becomes important as we move towards a model of heightened efficiency to clear NHS waiting list patients (BMA,2024).

In summary, current interventions to manage perioperative anxiety are not as effective as desired due to a multitude of reasons that include cost, staffing issues and time to engage with surgical patients (Levett & Grimmett, 2019).

Newer interventions -Virtual Reality (VR)

Novel technologies are now being used to create innovative solutions for managing perioperative anxiety. Multimedia audiovisual solutions such as videos and interactive games are now accessible and have been tested in clinical settings, with promising results, particularly in paediatric populations (Dai & Livesley, 2018; Chow et al, 2016). Therefore, it may be that new technologies can enhance, or be used in conjunction with, formerly tested interventions, to have a greater and more definite impact on perioperative anxiety.

One such technological solution is virtual reality, which can be described as “an all-inclusive, sensory illusion of being present in another environment” (Biocca & Levy, 1995).

Virtual reality (VR) is the computer-generated simulation of a real environment which enables the user to interact with certain elements in the simulated setting via a man-machine interface (Diz et al,2015). Virtual reality creates a simulated world that users find comparable to the real world. Multi-sensory stimuli (visual, auditory, olfactory, motion and tactile) presented via a headset draws the user's attention away from the real world (see Figure 1). Users engage with the virtual environment using real time computer graphics and inputs such as position trackers, mouse and data glove and outputs such as head mounted displays. The extent to which the person in the virtual environment perceives that they are in the virtual environment is termed as 'immersion' (Korkut et al, 2023). VR vary in terms of equipment used, content and nature of the virtual world and levels of engagement with users.

Virtual reality can be:

1. Fully-immersive: users typically wear a headset with a screen and headphones and interact with the virtual environment as if they were really in it. Immersion is the amount of sensory input the VR headset creates. Presence is a subjective value of the illusion one experiences when using the system. An increase in immersion often leads to an increase in presence felt by the user.
2. Semi-immersive: users interact with a partially virtual environment (for example, a flight simulator where the controls are real, but the windows display virtual images).
3. Non-immersive: the user is connected to the virtual world by a separate monitor (for example, a computer) but can still experience the real world.The person using VR becomes an active participant within a 3D world.

Active interaction, navigation and immersion are the key characteristics of VR immersion. Virtual Reality Immersion Therapy (VRIT) provides an immersive, interactive experience that can be conducted privately and inexpensively (Freeman et al, 2017; Oing and Prescott, 2018). The versatility of VR allows various environments and scenarios to be generated while giving therapists control over variables that would otherwise be impossible in a natural setting.

VR (Virtual Reality) appears to decrease anxiety and post operative pain by diverting attention away from nociception stimulus and by increasing the increased cognitive load of the brain via the VR immersive experience (individual performs tasks that compete for limited cognitive resources of the human brain). This appears to divert attention away from anxiety and pain (Chuan et al, 2021). Attentional distraction due to VR immersion appears to engage descending pain pathways and appear to be mediated by endogenous opioids (Valeria et al,2022). Additionally, nociception triggers the release of dopamine in the limbic system that increases top down pain relief and the sense of reward from pain relief (Navratilova and Porreca,2014).VR has been postulated to provide an external form of reward (game based rewards, serene environment etc) to engage reward signalling (Medina et al,2024).

There is evidence to suggest that virtual reality interventions can effectively reduce perioperative anxiety in paediatric populations, as well as lowering reported pain intensity (Chen et al, 2023; Eijlers et al, 2019; Simonetti et al, 2022) especially for painful procedures. Virtual Reality has emerged as a non-pharmacological method to manage

preoperative anxiety (Oing and Prescott, 2018) and postoperative pain (Pandrangi et al,2022).

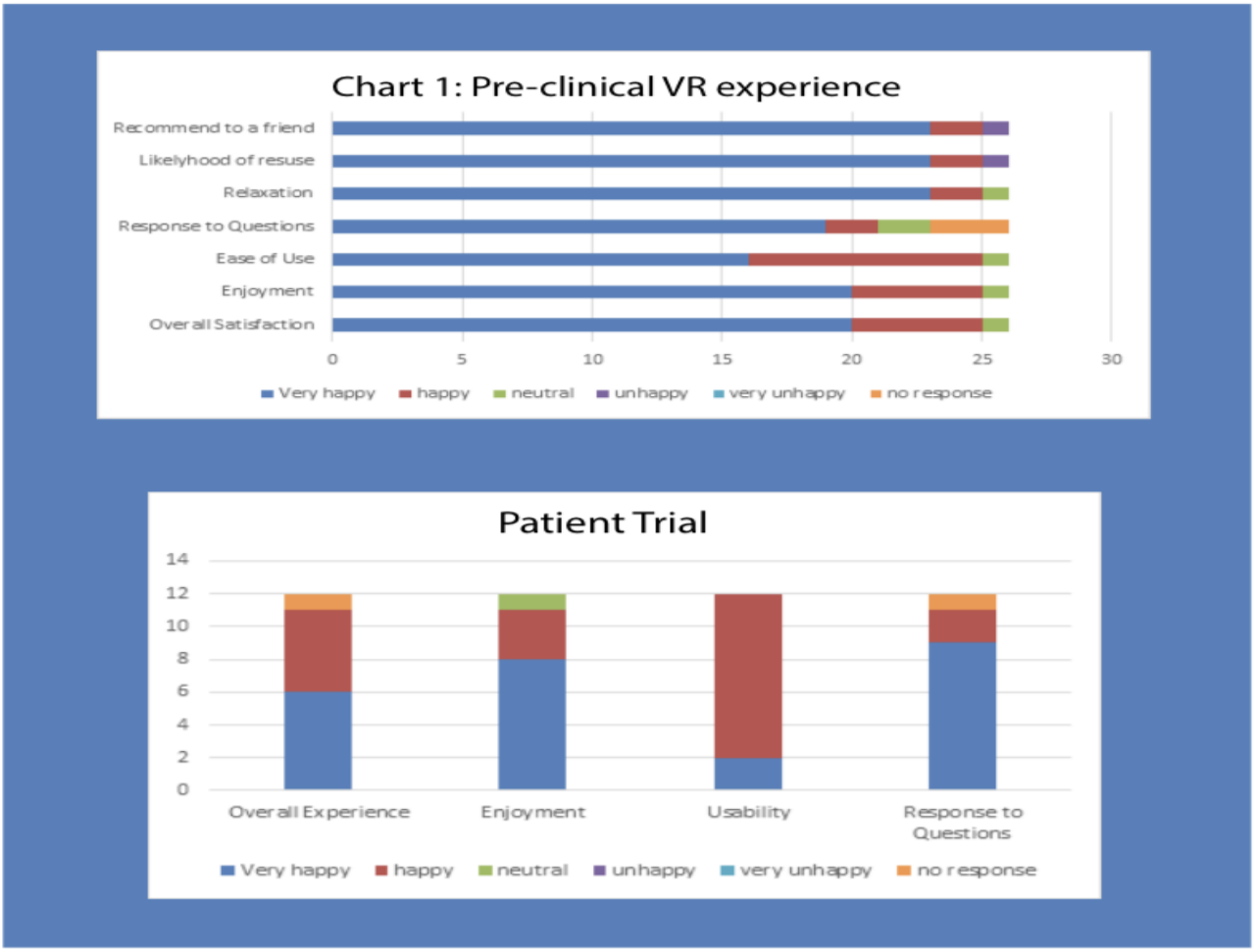
The majority of VR immersion research in paediatrics pertains to use of VR for anxiety or pain or both for painful procedures. However, there is significantly less research exploring the effect of virtual reality as a method of reducing perioperative anxiety in adult populations and for major surgery, although evidence suggests that this type of technological intervention may reap similar effects in adults (Aguinis, 2001). A review (Yu et al,2023) highlighted three studies in adults that utilised operating room visual tours to reduce anxiety in adult surgical patients while another review (Mbewe et al,2023) reported that five studies utilising VR in adult surgical patients reported decrease in anxiety. However, only one of these five studies reported frequency of VR exposure.

Our group (Kayleigh Maxwell et al, 2023; unpublished) performed a systematic review to evaluate the efficacy of virtual reality (VR) therapy on preoperative anxiety in adults. A total of 14 studies were included. We found that overall, nine studies reported between-group effects of the intervention on anxiety outcomes. Three of these studies found perioperative anxiety to be significantly less for participants using VR than controls, five studies found no significant difference, and one study reported mixed results. Of the six studies reporting within-group effects of the VR intervention, five found that the VR intervention significantly reduced perioperative anxiety, and the remaining study reported mixed results. In summary, our hypothesis that VR would significantly reduce perioperative anxiety was mostly confirmed.

A recent metanalysis (Gao et al,2023) reported that VR did decrease anxiety between groups. Our systematic review along with the results from Gao et al, 2023 thus demonstrates that VR may be used as an effective technological intervention to decrease perioperative anxiety in adult patients undergoing elective surgery.







.
Figure 1- The test bed results on the use of VR .

We initially performed a test bed study at our local hospital in conjunction with our local Research Development and Innovation Division (RD&I) to test the acceptability and safety of the VR headsets in a clinical environment (patients undergoing surgery) in the United Kingdom. This test bed study provided an opportunity to test a technical VR device in a clinical environment to assess what preparation is required to implement the VR device safely. The VR device and experience was acceptable to both staff and patients (see Figure 2). There were no serious safety incidents. Feedback from patients using the VR set prior to surgery was very positive.

Rationale for this VROOM trial pilot study.

After performing a systematic review and a test bed exercise, we summarise that there is at paucity of high-quality VR studies in adult populations to improve anxiety /pain, and surgical outcomes. The significant heterogenity in the type of VR therapy used (education /Operating room tours, immersive VR) ,duration of VR use (usually 5-55 minutes minutes) , timing of VR use (mostly preoperative),risk of bias (most had concerns) and mostly measured procedural pain and anxiety. None of the studies mentioned above have measured patient reported outcomes after major surgery nor measured biomarkers of surgical stress with the use of VR immersive therapy in surgical patients.

To the best of our knowledge, to date, there has been no study that has evaluated the efficacy of VR immersive therapy (that has been provided both before and after surgery) to improve patient reported outcomes after joint replacement surgery such as quality of recovery, early ,intermediate and late surgery outcomes (Boney et al,2016). The proposed study would be the first to evaluate the effects of VR immersive therapy on stress biomarkers in the blood.

Anxiety can occur from prior to surgery up to 6 months after surgery (Flowers et al,2023) . This would also be the first study to utilise VR prior to surgery and also post operatively (from 7 days before, till 30 days after surgery) to assess its effectiveness in decreasing surgical complications. This duration of VR immersive therapy from 7 days prior to 30 days after surgery should ensure that ‘adequate dose’ of VR immersive therapy is provided to avoid losing any outcome signals.

This pilot study will assess the feasibility of a larger trial that will be able to integrate psychological factors like anxiety into hard surgical outcome prediction modelling, and will foster a more holistic mind body approach for joint replacement surgery. A future successful multicentre RCT trial to follow this pilot could allow adoption of VR therapy across a wide range of elective surgical procedures as an essential component of psychological preparation for surgery.

Hypothesis:

Our hypothesis is that VR immersive therapy intervention to manage perioperative anxiety would be effective in reducing anxiety and stress and improve post operative pain, opioid use and surgical outcomes (early, intermediate and late) for joint replacement patients.

Aims and objectives

Aim

This pilot study aims to assess the feasibility of a future large trial to compare clinical and cost effectiveness of adding VRIT therapy to usual care in joint arthroplasty patients compared to usual care without VRIT.

Objectives -
The primary objective will be to assess the feasibility of the study (CSO Scotland guidance). This will include the following measures:

1. Number of patients approached for study
2. Number of participants recruited overall
3. Percentage of patients excluded overall
4. Participant compliance rate with use of VR over 37 days (number of days VR used for 20 minutes /37days)
5. Percentage preoperative VR compliance
6. Percentage postoperative VR compliance
7. Percentage of participants with complete questionnaires
8. Percentage of participants who withdraw during the trial
9. VR related technical complications noted
10. Standard deviation of the outcome measures to calculate sample size for the main trial

11. Percentage of participants from whom blood is collected
12. Staff time required per participant
13. NTC and research staff feedback
14. Participant feedback

The secondary objectives will be collection of clinical research data.

Outcomes
This pilot trial will provide a useful test of outcome data collection methods, including key clinical outcomes, and provide information on the likely changes in these outcomes in the control and intervention arms. This will not be statistically tested and presented due to the small sample size. However, we will run through the performance of statistical tests as a preparation for the main trial. The following secondary outcomes will be statistically tested to determine feasibility and anticipated effect sizes for the main trial (See Figure-detailed trial flow pathway):

1. PROMs- immediate ,intermediate and late recovery
2. Change of anxiety, stress and biomarkers from baseline at D0,D30,D90

Study Design

Method:

The VROOM trial will be a single centre pilot study for a future multicentre randomised controlled trial comparing the clinical efficacy and cost effectiveness of VRIT versus usual enhanced recovery care in joint arthroplasty patients.

This pilot study will use a two arm, single centre, parallel, randomised controlled trial design with an allocation ratio of 1:1.

This trial will be piloted at the National Treatment Centre (NTC), Inverness and Clinical Research Facility (CRF), NHS Highland, Inverness. Potentially eligible participants will be identified from those who have been listed for elective joint arthroplasty surgery (hip or knee) at the NTC and will be recruited via invitation letters, and pre-operative assessment clinics. Information will also be advertised via social media and GP surgeries [posters], for potential participants to self-identify and approach the research team directly.

We aim to recruit 40 participants into the study (20 participants in each arm). This pilot study aims to assess the feasibility/acceptability of methods and procedures to be used in the larger study. This study aims to field test the logistic aspects of the larger study and to incorporate these into the larger study design. We do not aim to statistically evaluate the data changes in usual care versus VR intervention arm as the pilot sample will not be of sufficient size.

Literature review (Stat Methods Med Res. 2016 Jun; 25(3): 1057–1073.) suggests a sample size between 24-70 for pilot trials. We have chosen a sample size of 40 which fits into the research budget.

Participants will be randomised to Care as Usual (CaU) or CaU with VRIT (CaU plus VRIT). Participants' active involvement in the study will be approximately 100 days. Participants in the intervention arm will be required to complete a minimum of 20 minutes VRIT daily from 7 days (7 days prior to surgery) to +30 days (30 days post surgery) and all participants will be required to complete data collection questionnaires from -10 to-7 days (from 10 to 7 days prior to surgery) until +90 days (90 days post surgery).

The control arm will receive standard perioperative care (enhanced recovery for joint arthroplasty) whilst the intervention arm will receive standard care plus Virtual Reality Immersive Therapy (VRIT). The enhanced recovery pathway for joint arthroplasty is a standardised pathway at the National Treatment Centre that has been adopted from guidances suggested by national bodies such as GIRFT. This includes patient education by a joint arthroplasty nurse a week prior to the surgery.

The intervention arm will be requested to use the VRIT daily, from 7 days pre-operative to 30 days post-operative, for 20 minutes per session. Our systematic review (Kayleigh Maxwell et al,2023) revealed a median VR exposure time of 20 minutes at each sitting of

the VR in the randomised controlled trials included in the study . This was further tested by means of a test bed exercise at our Institution (Mason et al, 2023) that confirmed patient acceptability and safety of the use of VR headsets for 20 minutes.

The VRIT used will be a VR headset from Healthy Mind Inc that has been CE approved in the UK and has been tested during our test bed exercise at our Institution. The VR headset offers an immersive experience with 8 therapeutic environments in 3D along with hypnotic speeches designed for each environment to distract attention. Breathing exercises are available throughout the immersive experience along with a soothing sound atmosphere and music composed specifically for each environment that offers a multi-sensory experience.

Each participant will be provided with training on how to use the device and then requested to use the device at home for 7 days prior to surgery. The participants will be asked to bring these devices to the hospital on the day of surgery and continue using them during the hospital stay and for 30 days post operatively. Upon completion of 30 days after surgery, the participants will return the VR headsets to the research team.

Both arms will provide data (via questionnaires or medical notes) at baseline, day of surgery, 24 hours post operatively, 7, 14, 21, 30 and 90 days post-operatively.

Five participants from the Care as Usual (CaU) arm and five participants from the CaU with VRIT arm will be randomly selected to provide blood samples at baseline, 24 hours post op, 30 days and 90 days post-operative time points.

Study Population:

Patients who live in the NHS Highland area, who have been listed for elective joint arthroplasty surgery (hip or knee) at the NTC, Inverness and who meet the inclusion/exclusion criteria will be approached to participate in the study.

Researchers aim to recruit 40 participants total; 20 participants to the control arm (CaU) and 20 participants to the intervention arm (CaU with VRIT).

Patients listed for surgery at NHSH NTC from other Health Boards will be excluded from participating.

Eligibility criteria

Inclusion criteria :

NHS Highland patients
Able to provide written informed consent (remotely)
ASA Grade 1 and 2
Listed for elective surgery at NHSH NTC
Adults>18 years undergoing joint arthroplasty surgery (hip and knee) will be included
Fluent in English
Able to receive and write emails

Willing to comply with study protocols/training
Access to Wi-Fi to undertake VRIT and complete questionnaires online

Exclusion criteria:

Not able to provide written informed consent
Considered unsuitable by Clinician (with reason)
Vision /hearing difficulties which preclude interaction with immersive environment
Unable or unwilling to comply with study procedures and activities
Participation in another interventional trial which undermines the scientific basis of the study
Have a history of alcohol or substance abuse or Parkinson's disease or Multiple Sclerosis or Labyrinthitis (Ménière's disease), history of seizures, motion sickness or dementia .
Non NHS Highland patients.
Photosensitive epilepsy
Patients with surgery scheduled for a Friday

Participant identification and screening

To identify potential participants, research study team (RST) members will liaise with clinical staff to identify possible trial participants who may be eligible for inclusion. This will include liaising with surgeons, pre-assessment team, anaesthetists and screening NTC allocation lists. A member of the RST with appropriate knowledge and training will make an initial assessment of eligibility for the potential trial participant and participant eligibility will then be formally confirmed by the Principal Investigator (PI), or a medically qualified nominee, prior to participant being approached. Participants not deemed eligible will be recorded on the screen fail log.

Participants eligible to participate will either 1) receive an information sheet and consent to contact form when they attend their scheduled pre-assessment visit. A member of the RST will be available to discuss the study with eligible participants. A member of the research team will collect signed consent to contact forms following the clinics, and will follow-up with the individual within the coming weeks.
or 2) receive an invitation letter and information sheet in the post or by email The initial contact will be followed up by a phone call from an RST member, to enquire if the individual is interested in participating. If they are interested, the RST member will discuss the study further, establish they are still eligible and gain consent to contact and will follow up with the individual within the coming weeks.

Informed consent

Following receipt of the signed consent to contact form or verbal consent to contact on the phone, a member of the RST will contact the potential participant to discuss interest in participating and will seek consent. The initial approach may be via email, phone or online (depending on potential participant's preference), and will provide an opportunity to discuss the study in more detail, answer any questions they may have, establish they meet all eligibility criteria and confirm if they wish to participate.

This process will include the provision of a participant information sheet and related consent form, and an explanation of the aims, methods, anticipated benefits and potential burdens of the trial. The RST member will explain to all potential participants that they can decline to participate in the trial and may withdraw at any time during the trial, for any reason, without their standard care being affected.

Participants willing to take part will be asked to complete the remote consent process, along with the member of RST.

If new safety information results in significant changes in the risk/benefit assessment, the participant information sheet and consent form will be reviewed and updated if necessary, and provided to the participants. The PI or designee will assess the potential participant's capacity to give informed consent, and those who lack capacity to give or withhold informed consent will not be recruited. If a participant loses capacity during their participation in the trial, the original consent by the participant will be respected. If this situation occurs, clinical outcome data will continue to be collected, but participant questionnaires will not need to be completed.

Details of patients who are potentially eligible for the trial, but are subsequently not recruited, should be recorded (including reason not recruited) on the electronic anonymised patient-screening log.

Enrolment and Randomisation

Enrolment

Once consented, the participant will be enrolled into the trial [see figure 3 below- Trial Recruitment Pathway]. and allocated a study specific ID number. The participant will be asked to contact the RST member when they receive a date for their surgery. Once a surgery date has been received, the participant will be randomised. Baseline data will be collected after randomisation when the participant attends an appointment with the research team from 10 to 7 days prior to surgery.

After randomisation, we expect to have four groups viz Group 1 [VR+Blood+Questionnaires], Group 2 [VR+Questionnaires], Group 3 [Usual standard care+Bloods+Questionnaires] and Group 4 [Usual standard care+Questionnaires]. Groups 1, 2 and 3 will attend a face to face visit and meet with the research team from 10 tp 7 days prior to surgery while Group 4 participants will be contacted by phone from 10 to 7 days prior to surgery to answer questionnaires.

Randomisation

Randomisation to the control or intervention arm will be performed on a 1:1 ratio using computer generated random number sequence using blocks of four.

Due to the nature of the intervention, blinding of participants and all RST members is not possible; however, allocation will remain concealed from the participant until baseline data has been collected, and RST members will be blinded, except those supporting VR headset training and data collection.

Post-randomisation withdrawals, exclusions

Participants will be withdrawn immediately from the study if they express a wish to withdraw or their clinician or PI decides that it is in their best interests to do so. Withdrawal criteria will be discussed with participants during the consenting process, so they are fully aware that participants may withdraw from the trial at any time without prejudice to their standard of care. Data will be collected as per the trial protocol unless the participant has explicitly withdrawn their consent for this.

If the participant's surgery date is postponed following their baseline visit, all study activities will be stopped and started again with a repeat baseline visit, once their rescheduled date has been received. Any blood samples previously taken will be marked for destruction and new blood samples will be taken at the repeat baseline visit.

Participant training

Participants randomised to the intervention arm, will be provided with training on the VR headset by an appropriate member of the RST

Participants will be required to attend the NTC for the training session, between 10 and 7 days prior to their surgery. The training session is anticipated to last three hours. Sessions will be on an individual basis, between the participant and one or two members of the RST.

The RST members providing the participant training will have completed specific training from the VR headset company (Healthy Mind) and undertaken 'test' training sessions with members of the wider research team who have had no previous VRIT use.

During the training session, participants will be assisted to set up a daily reminder (e,g, in their phone or electronic diary) to complete their 20 minute VRIT session at a regular time which suits their schedule.

Research staff training

The CI and Trial Manager/Coordinator will provide trial-specific training to all sites prior to site initiation and subsequently as required to ensure consistency of practice across all sites. Research team will be provided with access to the secure web-based randomisation

system once training is complete. Research delivery staff will be listed on the Site Delegation log, detailing the trial activities they are permitted to undertake.

Criteria for discontinuing the trial in an individual.

TheRST will monitor for side effects in participants. If a side effect occurs or postoperatively the participant is no longer cognitively engaged, the individual's VR session will cease immediately and a referral will be made to the medical team. If at any stage of the study, the participant wishes to withdraw, that wish will be respected.

Concomitant care and interventions

No treatment is prohibited during the trial period. If participants regularly use anti-anxiety medications, this will be documented prior to surgery. All new therapies or medications will be self-reported at the FU visits.

Minimising detection bias and contamination

The RST assessing participant outcomes may not be blinded as the intervention (VR) would be quite obvious. Similarly, the VR participants would know their allocation arm. The majority of the outcomes are patient reported outcomes and hence there is a likelihood of a placebo effect due to treatment arm allocation.

The RST reviewing and analysing the data will be blinded to all data.

End of trial

This pilot feasibility study will end when 40 participants in total have been randomised and the last participant has provided the PROMS, the data cleaning is complete and the database is locked.

The trial will be stopped prematurely if:

- Mandated by Research Ethics Committee
- Following recommendations from the Data Monitoring Committee and Trial Steering Committee or Sponsor
- Funding for the trial ceases

The Research Ethics Committee that provided a favourable opinion will be notified within 90 days of the trial conclusion or within 15 days if terminated early.

Study Assessments (See schedule of data collection below)

Baseline data collection and Follow-up (FU) Data Collection

Baseline and FU data (at 7, 14, 21, 30 and 90 days post-operative) will be collected from participants via questionnaires, which participants will receive via an email from the RST.

Participants will be encouraged to complete the questionnaires independently but an RST member can provide support, over the telephone or via Teams call, if required.

Data at 24 hours post-operative will be collected by an RST member from the participant's medical notes, pharmacy records and patients.

Virtual reality intervention (VRIT)

Following completion of VRIT training, participants in the intervention arm will be asked to wear the VR headset for a minimum of 20 minutes each day for 7 days prior to surgery , on the day of surgery and post operatively for 30 days. Upon completion of 30 days after surgery, the participants will be asked to return the VR headsets to the research site, in person.

To support participants, an FAQ sheet will be provided on VR headset use and contact details provided, should they require to discuss a technical issue of VR use with a member of the RST.

The data collected from the VR headset will be downloaded by the research team at the end of the participant's VR use. The data will be sent by secure email to the VR headset company (Healthy Mind).

.

A 'grace period' of 7 days post-surgery will be provided to participants who may forget to undertake VRIT daily for 20 minutes, and their data will still be included in data analysis.

Blood Collection and Analysis

Blood samples will be analysed on stress biomarkers in a sample of participants.

Blood samples will be collected from five participants from the Care as Usual (CaU) arm and five participants from the CaU with VRIT arm (N=10 total), at baseline (D-10/-7), day of surgery (D0), 24 hours post surgery (D+1), 30 days post surgery (D30+) and 90 days post surgery (D90+). Venepuncture will be carried out by suitably qualified member of the RST at the NTC clinic setting. Samples will be collected as per NHSH SOP. Collected samples will be processed on site immediately and stored at the NHS Highland Clinical Research Facility at -80c for the duration of the study. Once all blood samples have been collected, the samples will be packaged and shipped to the Galway and Cambridge laboratories as per their shipping instructions. Any baseline blood samples taken from participants whose surgery was then postponed will be destroyed at site.

Results of blood sample analysis will be emailed to the CI and relevant members of the RST. Data will be transcribed to the EDC.

Minimising detection bias and contamination

The RST assessing participant outcomes may not be blinded as the intervention (VR) would be quite obvious. Similarly, the VR participants would know their allocation arm. The majority of the outcomes are patient reported outcomes and hence there is a likelihood of a placebo effect due to treatment arm allocation.

The RST analysing data will be blinded.

Schedule of data collection:

Visit	1	2	3	4	5	6	7	8
Visit window	**Pre-screen**	**Consent**	**Baseline Questionnaires /VR headset training /Bloods (Pre-op)- From 10 to 7 days prior to surgery**	**Day of surgery**	**24 hrs after surgery**	**7, 14, & 21 days**	**30 days after surgery**	**90 days after surgery**
Consent to Contact or Invitation letter received	X							
Screening using Inc/exclusion criteria		X						
Informed consent		X						
Enrolment		X						
Randomisation		X						
VR Training			X					
Baseline data-demographics			X					
Bloods (Stress biomark			X (N=10)	X	X		X	~~X~~

ers) IL1,IL6,IL10,TNFa,CRP Neuropeptide Y, CRH ,Cortisol, DHEA AEA,OEA,PEA,2AG *N=20 total)								
Anxiety - STAI Q Form Y			X	X		X	X	X
Anxiety - APAIS			X	X				
QOL-EQ5D 5L			X	X		X	X	X
Stress-Cohen Q [AM(H1] [DS2]			X	X		X	X	X
Quality of Recovery Q [AM(H3] [DS4]					X			
Time to gastro-intestinal recovery					X			
Time to mobilise out of bed [AM(H5] [DS6]					X			
Morphine use (OME) 24 hrs [AM(H7] [DS8]					X			
PROM2-Persistent Opioid use								X
PROM3 - Persiste								X

nt pain at site of surgery								
PROM4-Oxford knee score								X
PROM5-Oxford hip score								X
Total number of days spent in the hospital for the surgery [AM(H9] [DS10]								X

Unplanned hospital admissions within 30 days of surgery						X	
Return to work Y/N/NA							X
Survival Status (Alive/Dead at 90 days)							X

Statistical analysis

We will recruit 40 participants into the study (20 participants in each arm). This would conform with the minimum (median) number of participants (25) that are standard in UK feasibility studies [Billingham et al, 2013].

The pilot trial will evaluate the feasibility of conducting the main RCT utilising the following outcome metrics:

1. Number of patients approached for study
2. Number of participantss recruited overall
3. Percentage of patients excluded overall.
4. Percentage participant compliance rate (average in the intervention arm) with use of VR over 37 days (number of days VR used for 20 minutes /37)
5. Percentage pre operative compliance with use of VR
6. Percentage post operative compliance with use of VR
7. Percentage of participants with complete questionnaires
8. Percentage of participants who withdraw during the trial
9. VR related technical complications noted /feedback by participants or staff.
10. Standard deviation of the outcome measures to calculate sample size for the main trial.
11. Percentage of participants from whom blood is collected out of the total sample
12. Staff time required per participant
13. NTC and research staff feedback
14. Participant feedback

This pilot trial will provide a useful test of outcome data collection methods, including key clinical outcomes, and provide information on the need for change in these outcomes in the control and intervention arms. This will not be statistically tested formally and presented due to the small sample size. However, we will run through the performance of statistical tests as a preparation for the main trial. This is highlighted in the next few paragraphs.

This trial will follow a pre-specified analysis plan based on comparing both arms as randomised (intention to treat). Baseline characteristics will be compared using descriptive statistics (mean, SD, 95% CIs). Differences in outcomes (e.g. Psychological test scores, surgical outcomes, mortality etc.) between the intervention and control arms will be examined using student tests (Wilcoxon rank-sum tests are used if the assumptions of normality and homogeneity of variance are not met) and chi-squared tests. Any significant difference between these arms would be noted for future predictive modelling work in the next stages of this trial.

To address our primary aim, we will compare changes in stress biomarkers and questionnaire scores between the arms, a two-way analysis of variance (ANOVA) [group × time (baseline, day of surgery, and 30 days after surgery)] with repeated measures on the time factor will be performed (Friedman two-way ANOVA by ranks will be used if the assumptions of normality and homogeneity of variance are not met). The day of surgery

will be of primary interest. Similar analyses with the secondary outcome measures will be performed for the day of surgery to 30 days post data to address aim 2.

This is a superiority trial, as a pilot study we feel it is important to understand the effect size of the variables measured and will calculate the Hedges g statistic for this purpose. This in addition to the ANOVA analyses will allow the selection of appropriate covariates, providing a suitable springboard for a larger scale trial and allowing the development of a mathematical model to potentially predict surgical outcomes based on the patients' anxiety and stress parameters.

Study Management

The Sponsor is responsible for ensuring, before a study begins, that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

The Chief Investigator takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than one site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site. The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards. The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the REC of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

The NHS Highland RDI QA team will be responsible for monitoring the study, to ensure compliance with Good Clinical Practice and scientific integrity.

Study Management Group

The study will be coordinated by a Study Management Group, consisting of the Sponsor representative, CI, Study Coordinator, RDI Snr Data Manager, RDI Lead Nurse, and RDI Statistician.

Assessment & Management of Risk

The VROOM trial will compare Care as Usual (CAU) vs CAU with VR immersive therapy in joint arthroplasty patients. No treatment will be administered, withheld, delayed, or

modified as a result of participation, and standard care will continue to be provided by the treating clinical team.

VRIT has been evaluated by means of a test bed exercise at our site and found to be safe, with no adverse events or issues raised amongst the group of participants. However, we recognise that VRIT can cause mild motion sickness for some participants. If this occurs, participants will be encouraged to take a break for VRIT and return to it a later time that day. If the side effect continues, and the participant seeks to stop VRIT use, this will be recorded as an outcome and the participant will be asked to remain in the study for data collection only, if agreeable.

Venepuncture confers a small risk to participants (N=10 total), of localised bruising and/or infection. Trained and experienced staff will undertake blood collection, as per NHSH SOP.

Though the risks to participants are considered low, we do recognise that the time burden is slightly higher than CaU, due to additional visits and/or additional data collection. The time burden on participants is clearly described in participant information sheets and during discussions, to ensure participants are fully aware of study activities and assessments and the time commitment that is required prior to consenting.

Risk Assessment / Deviation from the Protocol – Clinical Investigation Plan

The project is considered to be low risk, however, there is an expectation of a basic reporting process relating to SAEs and device deficiencies for the Sponsor, REC and the MHRA (as appropriate), consisting of reporting events once notified within 24 hours.

Post consent advice will be given to all participants with regards to contacting primary care provider or NHS 24 immediately upon any concerns regards health issues, as per standard of care. Participants will be asked to report to the study team during the next available office hours. SAE recording will cover the intervention period only and will be picked up via the Questionnaires and/or review of patient records. Patient NHSH records will always be checked prior to sending out study material to ensure the participant is not incapacitated or deceased which would trigger SAE reporting. The CI will follow up all SAEs for causality and report as per NHSH SOP CLIN006b.

RECORDING AND REPORTING OF EVENTS AND INCIDENTS

<u>Definitions of Adverse Events</u>

Adverse Event (AE) - Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved. Only Adverse events that fulfil the Seriousness criteria below will be recorded.

Serious Adverse Event (SAE) - Any adverse event that: results in death, is life-threatening*, requires hospitalisation or prolongation of existing hospitalisation**, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect.

**A life-threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.*

Assessments of Adverse Events

Each adverse event will be assessed for severity, causality and seriousness.

Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form NHSH Form035 and recorded on an SAE log on Form013. It is of particular importance in this study to capture events related to the intervention.

The assessment of relationship of an adverse event to this/these additional safety issue(s) will also be carried out as part of the study.

The following categories will be used to define the causality of the adverse event:

Category Definition

Definitely: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Probably: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Possibly: There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).

Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).

Not related: There is no evidence of any causal relationship.

Not Assessable: Unable to assess on information available.

Recording adverse events

Only Adverse Events that satisfy the seriousness criteria will be explored with the participants if they answer "yes" to the appropriate follow up question or an admission to hospital or death is noted in the medical review.

Procedures for recording and reporting Serious Adverse Events

Following consent and up to and including Day+90, all Serious Adverse Events will be recorded in the CRF. Any SAEs thought to be causally related will be reviewed by the Sponsor and escalated as appropriate in line with NHSH RD&I SOP CLIN006b. All SAEs (except those specified as not requiring reporting to the Sponsor) must be recorded on a Serious Adverse Event (SAE) form. The Chief Investigator will respond to any SAE queries raised by the Sponsor as soon as possible. Completed forms for SAEs thought to be causally related must be sent within 24 hours of becoming aware of the event to the Sponsor Email forms to: randd.nhsh@nhs.scot

All SAEs will be recorded.

Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures, as per RD&I SOP CLIN008.

Protocol deviations and notifications of protocol deviation.

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the Sponsor. The CI will monitor protocol deviations. A protocol violation is a breach which is likely to effect to a significant degree – (a) the safety or physical or mental integrity of the participants in the study; or (b) the scientific value of the study. The CI and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

Monitoring and auditing

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality. The Chief Investigator will inform the Sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

Audits and Inspections

The study may be subject to inspection and audit by NHS Highland RD&I Division or by an independent auditor employed by NHS Highland under their remit as Sponsor and any other regulatory bodies to ensure adherence to GCP. The Principal Investigator will ensure the capability for inspection of applicable study - related facilities and materials.

See Appendix 1 for further details about the Monitoring Plan.

Regulatory and Peer Review

Ethics Approval, MHRA and R&D Management Approval

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable EU and international regulatory requirements.

The study will be conducted in accordance with the principles of ICH Good Clinical Practice (GCP) Rev 3. As this has been deemed as Research, it will be submitted for approval to NHS Research Ethics Committee and NHS R&D Management Approval.

It will also comply with all applicable UK legislation, Framework and the Standard Operating Procedures (SOPs) of NHS Highland RD&I, as Sponsor. All data will be stored securely and held in accordance with the UK GDPR.

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from the appropriate Research Ethics Committee (REC) and appropriate NHS Research and Development (R&D) approval will be obtained from NHS Highland Health Board, prior to commencement of the study.

Peer Review

The study has been peer reviewed by various experts including Prof Lesley Colvin (University of Dundee), Prof Ben Shelly (NRS Glasgow), Prof David Finn (University of Galway), Dr Line Caes (University of Stirling) and Dr Caroline Thomas (University of Leeds),

The proposal has received comment from National Institute of Academic Anaesthesia, through grant submission review.

NHSH Colleagues and PPIE volunteers have provided oversight and input into the study design, with all feedback incorporated.

The RDI Division of NHS Highland will process the study through the Information Governance process to ensure all IG issues are addressed.

The Chief Investigator will act as custodian for the study data. The following guidelines will be strictly adhered to:

- Participant data will be pseudo-anonymised and all pseudo-anonymised data will be stored on a secure server.
- All consent will be logged on the Study Consent Log.
- All study data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act 2018, and the General Data Protection Regulation 2016/679/EU.

Data Management Indemnity

NHSH will provide NHS indemnity cover for negligent harm via CNORIS, as appropriate. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Board will only extend NHS indemnity cover for negligent harm to its employees; substantive and honorary, conducting research studies that have been approved by the R&D Department. The Board cannot accept liability for any activity that has not been properly registered and Board approved. Potential claims should be reported immediately to the NHSH RD&I Governance Lead.

Publication policy

Publication policy is regulated by NHS Highland. We plan to publish this study in a peer reviewed journal.

Financial aspects

Participant Stipend or Compensation

Participants will be provided with a £25 gift voucher to thank them for their participation in the study and travel expenses of £15 per research visit.

Clinical Study Agreement

The study activity and attributable costs are described in the SoeCAT. There is no requirement for study agreement or Organisational Information Document, as this is a single centre study.

Conflict of Interest

Any Investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Sponsor prior to participation in this study.

Study Funding

This study is being funded by NHS Highland RD&I Endowment.

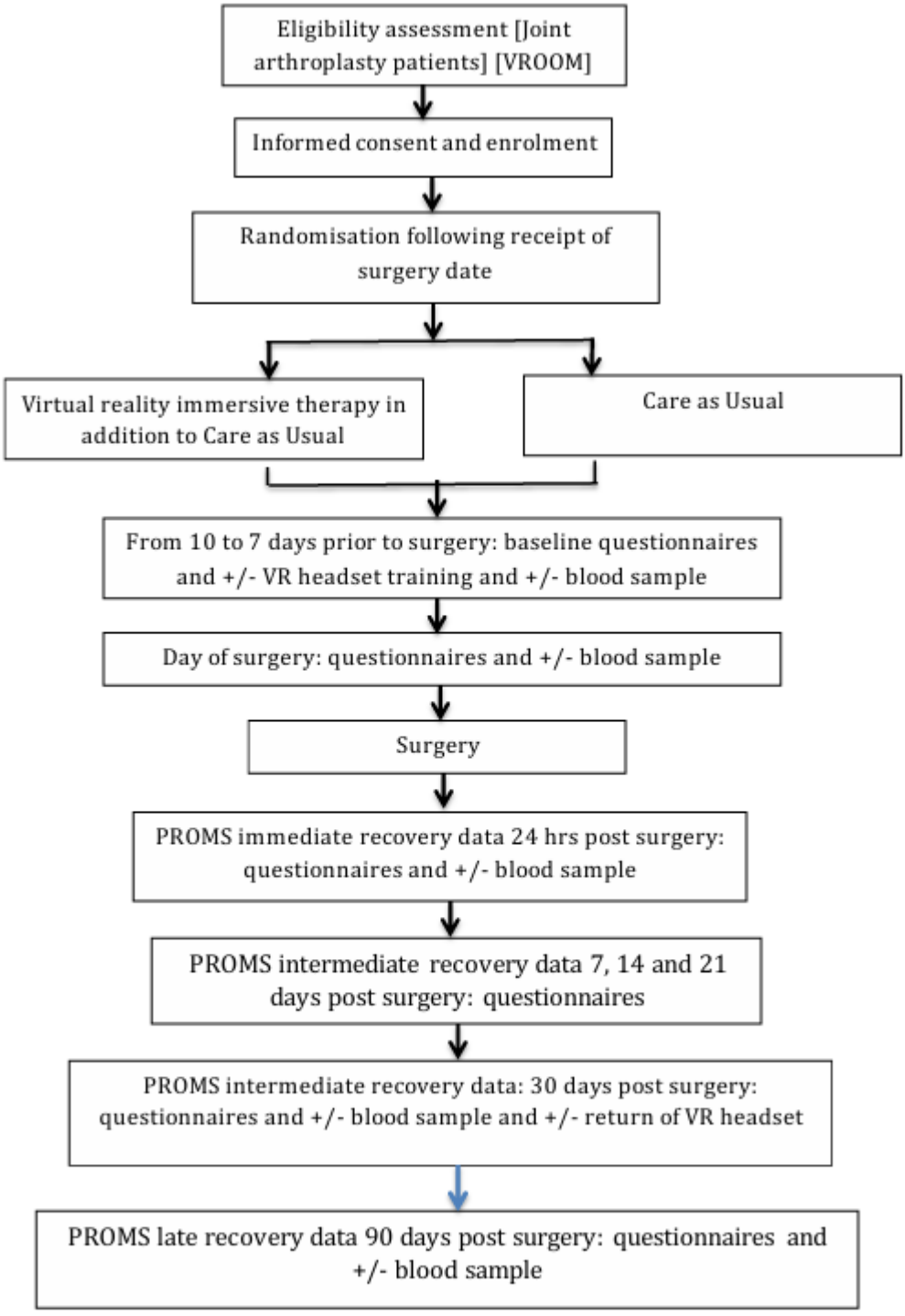


Fig 1 – Overview of the trial (v3)

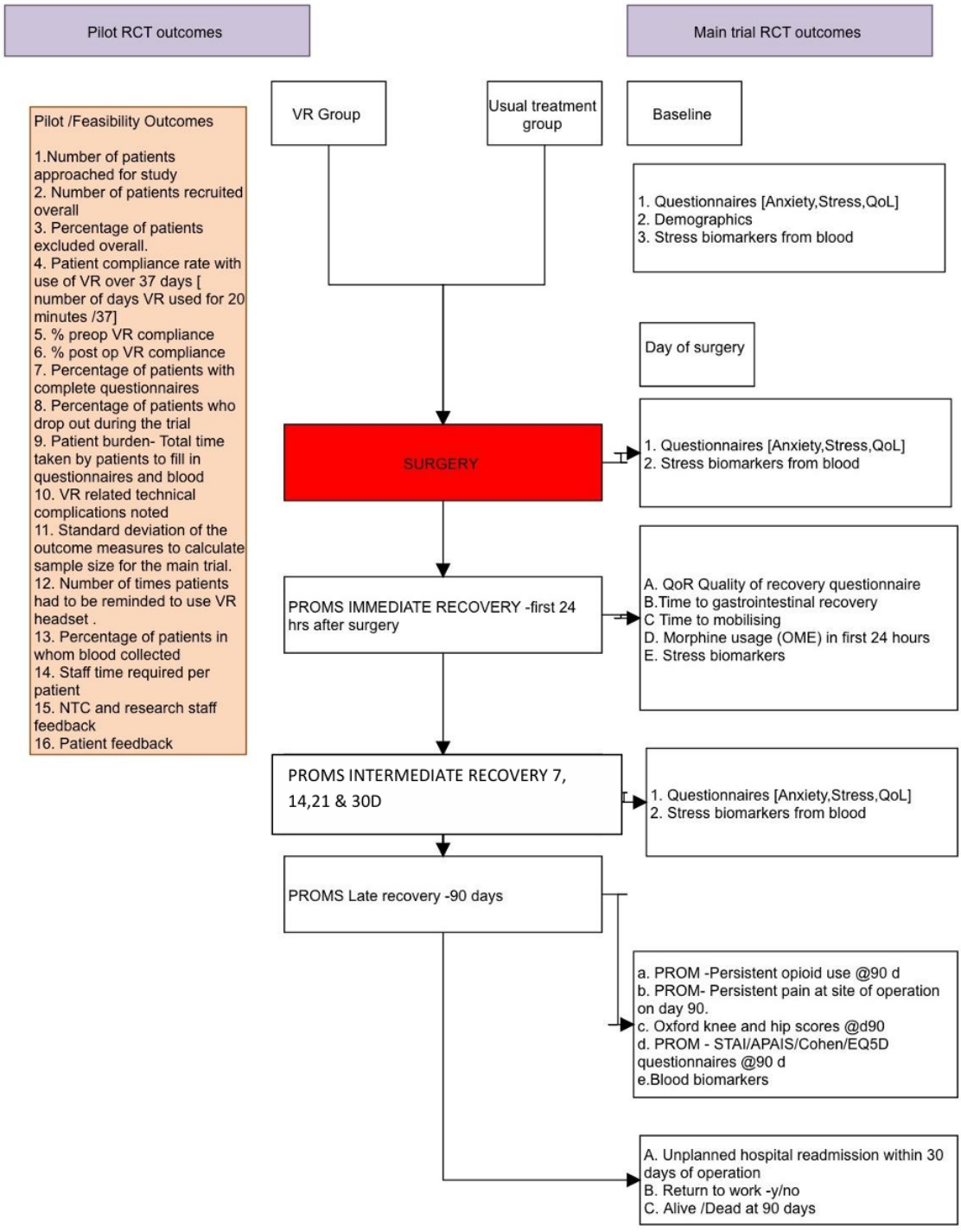


Figure 2: The detailed trial pathway (V2)

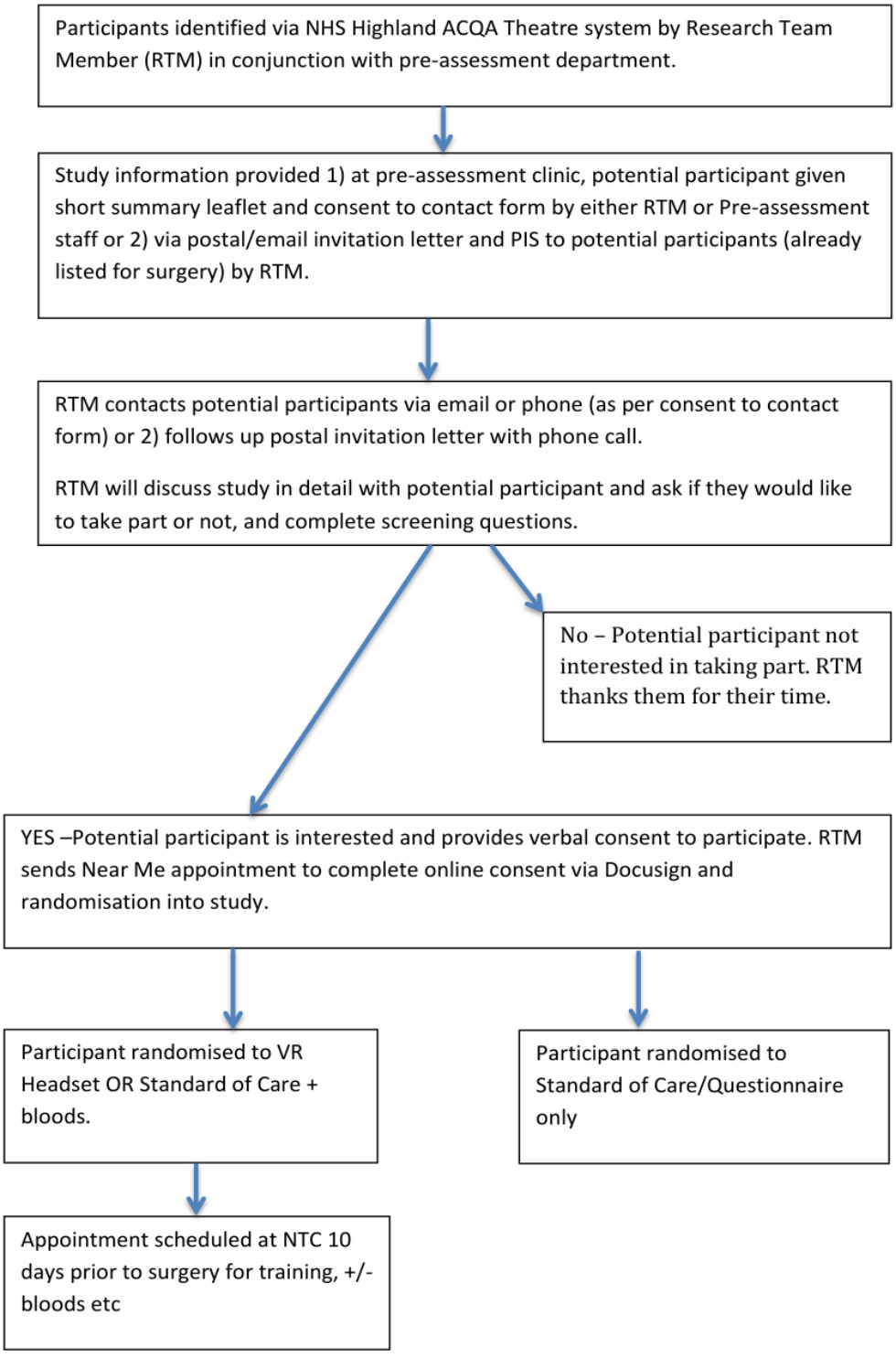


Figure 3: Trial recruitment pathway (V2)

Appendix 1 – Monitoring Plan

Reason for Monitoring

The primary objective for conducting monitoring visits is to ensure that the rights, safety and well-being of the trial participants are being observed as the most important considerations and that they prevail over the interests of science and society. Therefore, the monitoring visits will ensure that the trial documentation and activities are complete and in accordance with the principles of GCP and applicable regulations.

Monitoring methods and frequency of visits for this study

The frequency and method of monitoring visits for this study have been determined on the basis of a risk assessment carried out by the RD&I Governance Team. The study will be monitored in accordance with the NHS Highland Standard Operating Procedures for monitoring Health Board sponsored studies.

For this study, the monitoring methods and frequency are outlined below.

Method of Monitoring	**Frequency / Timing**
Initiation Visit (On site visit)	Delivered by CI / Monitor / Trial Coordinator. Training provided to key personnel. Discussion of study activities. Review of ISF and TMF set up.
Interim Monitoring (On site visit)	Review after first participant randomised, for data completeness, eligibility, procedure review and consent documentation. Stop moment. If no problems are identified, recommence recruitment. Review after first twenty participants are randomised, carried out by Monitor to NHSH SOPs Review after study recruitment is complete, carried out by Monitor to NHSH SOPs
Heightened monitoring / reduced monitoring (Changes to frequency and / or methods of monitoring / further investigation into a suspected serious breach / further investigation and CAPA / 'For cause'	The above scheduled Monitoring Visits may require adjusting due to protocol amendments & changes to risk assessment / participant recruitment rate / quality concerns / GCP and / or Protocol compliance issues / staff changes. Escalation procedures should be followed to trigger heightened monitoring on NHSH RD&I advice.

monitoring. Terminate the investigator site and notify competent authority and / or REC).	
Close-out monitoring visit (On site visit)	Close–out using NHSH SOPs and checklists.

Initiation Visit

The following activities will be carried out by the CI / Monitor / Trial Coordinator during the initiation visit:

Training provided to key personnel

Review Investigator Site File – The Monitor / Trial Coordinator to check all essential documents in ISF

Discuss:

- Monitoring Plan with investigator team
- Overview of the Protocol / applicable SOPs and discuss consenting, discontinuation and withdrawal process
- Primary and secondary endpoints
- Definitions of Source Data
- CRF completion procedures, data collection, file notes
- Data management
- Safety reporting requirements and responsibilities
- Documenting and reporting breaches/deviations
- Receiving and implementing amendments

The Monitor / Trial Co-ordinator should also undertake a review of the Trial Master File and ensure it is complete.

Interim Monitoring

The following activities will be carried out by the CI / Monitor / Trial Coordinator during each interim monitoring visit:

Discussion with research team (to include study progress and recruitment, staff changes, amendments submitted, any other identified issues)

Review:

- Source Data Verification
- Data checking: missing data / CRF data verified against source data

- Participant Eligibility – Monitor to SDV Eligibility for all participants recruited.
- Consent forms – Monitor to check validity of consent forms for all participants.
- Review of ISF and TMF
- Study documentation up to date
- Delegation logs
- Screening logs
- Recruitment logs
- Safety reports/reconciliation of investigators AE / SAE Log with Sponsor's records
- Amendments and completed amendments log
- Review of recorded/identified Protocol / GCP breaches
- Check if any findings from previous monitoring visits have been addressed.

NOTE: After each monitoring visit the Monitor will:

Discuss any significant issues immediately with the CI / RD&I Governance Team (sponsor representative). Significant issues or potential risk issues will be escalated to the RD&I Safety Event Review Group and / or immediately within the organisation.

Report to the Sponsor, within 24 hours of becoming aware of them, any individual events, or series of events that they consider may be a Serious Breach of the Protocol, GCP or other urgent issues the Sponsor should review carefully.

Heightened or reduced monitoring and/or changes to monitoring methods

(This section is to be completed when changes to the above interim Monitoring Plan have been considered as appropriate).

Changes / actions to be taken:

- Changes to frequency and / or methods of monitoring (specify)
- Further investigation into a suspected serious breach
- Further investigation and CAPA / 'For cause' monitoring
- Terminate the investigator site and notify competent authority and/or REC

Close out visit

On–site close out monitoring visit will be conducted within 30 days of the last participant last visit.

The following activities will be carried out by the Monitor during the on-site close out visit:

- Close out of site via study specific checklist
- Full scrutiny of the study ISF and TMF
- Discussion of archiving arrangements

References:

Abate, S.M., Chekol, Y.A. & Basu, B. 2020, Global prevalence and determinants of preoperative anxiety among surgical patients: A systematic review and meta-analysis.
Agüero-Millan, B., Abajas-Bustillo, R. & Ortego-Maté, C. 2023, Efficacy of nonpharmacologic interventions in preoperative anxiety: A systematic review of systematic reviews.
Ali, A., Lindstrand, A., Sundberg, M. & Flivik, G. 2017, "Preoperative Anxiety and Depression Correlate With Dissatisfaction After Total Knee Arthroplasty: A Prospective Longitudinal Cohort Study of 186 Patients, With 4-Year Follow-Up", Journal of Arthroplasty, vol. 32, no. 3.
Bay, S., Kuster, L., McLean, N., Byrnes, M. & Kuster, M.S. 2018, A systematic review of psychological interventions in total hip and knee arthroplasty.
Beattie, W.S., Lalu, M., Bocock, M., Feng, S., Wijeysundera, D.N., Nagele, P., Fleisher, L.A., Kurz, A., Biccard, B., Leslie, K., Howell, S., Landoni, G., Grocott, H., Lamy, A., Richards, T., Myles, P., Gan, T.J., Peyton, P., Sessler, D., Tramèr, M., Cyna, A., De Oliveira, G.S., Wu, C., Jensen, M., Kehlet, H., Botti, M., Boney, O., Haller, G., Grocott, M., Cook, T., Fleisher, L., Neuman, M., Story, D., Gruen, R., Bampoe, S., Evered, L., Scott, D., Silbert, B., van Dijk, D., Kalkman, C., Chan, M., Eckenhoff, R., Rasmussen, L., Eriksson, L., Bartlett, R.J., McMonnies, R., Gerstl, J., Jay, M., Kishlyansky, D., Machina, M., Bobcock, M., Pearse, R., Mythen, M., Canet, J., Moller, A., Gin, T., Schultz, M., Pelosi, P., Gabreu, M., Futier, E., Creagh-Brown, B., Abbott, T., Klein, A., Corcoran, T., Cooper, D.J., Dieleman, S., Diouf, E., McIlroy, D., Bellomo, R., Shaw, A., Prowle, J., Karkouti, K., Billings, J., Mazer, D., Jayarajah, M., Murphy, M., Bartoszko, J., Sneyd, R., Morris, S., George, R., Moonesinghe, R., Shulman, M., Lane-Fall, M., Nilsson, U., Stevenson, N., Cooper, J.(., van Klei, W., Cabrini, L., Miller, T., Pace, N., Jackson, S., Buggy, D., Short, T., Riedel, B., Gottumukkala, V., Alkhaffaf, B. & Johnson, M. 2021, Systematic review and consensus definitions for the Standardized Endpoints in Perioperative Medicine (StEP) initiative: cardiovascular outcomes.
Billingham, S.A., Whitehead, A.L. & Julious, S.A. 2013, "An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database", BMC Medical Research Methodology, vol. 13, no. 1.
BMA Online- https://www.bma.org.uk/advice-and-support/nhs-delivery-and-workforce/pressures/nhs-backlog-data-analysis#:~:text=The%20latest%20figures%20for%20December,individual%20patients%20waiting%20for%20treatment
Brummett, C.M., Waljee, J.F., Goesling, J., Moser, S., Lin, P., Englesbe, M.J., Bohnert, A.S.B., Kheterpal, S. & Nallamothu, B.K. 2017, "New persistent opioid use after minor and major surgical procedures in us adults", JAMA Surgery, vol. 152, no. 6.
Caumo, W., Schmidt, A.P., Schneider, C.N., Bergmann, J., Iwamoto, C.W., Bandeira, D. & Ferreira, M.B.C. 2001, "Risk factors for preoperative anxiety in adults", Acta Anaesthesiologica Scandinavica, vol. 45, no. 3.
Charney, D.S. & Drevets, W.C. 2002, "Neurobiological basis of anxiety disorders", Neuropsychopharmacology: The fifth generation of progress,

Cheng JY, Wong BW, Chin YH, Ong ZH, Ng CH, Tham HY, et al. Preoperative concerns of patients undergoing general surgery. Patient Educ Couns. Jun 2021;104(6):1467-1473. [doi: 10.1016/j.pec.2020.11.010] [Medline: 33303283]
Chuan, A., Zhou, J.J., Hou, R.M., Stevens, C.J. & Bogdanovych, A. 2021, Virtual reality for acute and chronic pain management in adult patients: a narrative review.
Cortés-Martínez, L.A., Cardoso-García, L.E., Galván-Talamantes, Y., Morales-Maza, J., Rosas-Sánchez, M.A., Vargas-Aguilar, D.M., Bañuelos-Ortiz, E. & Álvarez-Reséndiz, G.E. 2020, "Pregabalin as a premedication for anxiety in patients undergoing plastic surgery: Randomized double-blind, placebo-controlled study", Cirugia y Cirujanos (English Edition), vol. 88, no. 5.
Daviu, N., Bruchas, M.R., Moghaddam, B., Sandi, C. & Beyeler, A. 2019, Neurobiological links between stress and anxiety.
Dobson, G.P. 2015, Addressing the Global Burden of Trauma in Major Surgery.
Edwards, P.K., Mears, S.C. & Lowry Barnes, C. 2017, Preoperative Education for Hip and Knee Replacement: Never Stop Learning.
Euteneuer F, Kampmann S, Rienmüller S, Salzmann S, Rüsch D. Patients' desires for anxiolytic premedication - an observational study in adults undergoing elective surgery. BMC Psychiatry. 2022 Mar 17;22(1):193. doi: 10.1186/s12888-022-03845-y. PMID: 35300643; PMCID: PMC8932104.
Maurice-Szamburski A, Auquier P, Viarre-Oreal V, Cuvillon P, Carles M, Ripart J, Honore S, Triglia T, Loundou A, Leone M, Bruder N; PremedX Study Investigators. Effect of sedative premedication on patient experience after general anesthesia: a randomized clinical trial. JAMA. 2015 Mar 3;313(9):916-25. doi: 10.1001/jama.2015.1108. PMID: 25734733.
Flanigan, D.C., Everhart, J.S. & Glassman, A.H. 2015, Psychological Factors Affecting Rehabilitation and Outcomes Following Elective Orthopaedic Surgery.
Freeman, D., Reeve, S., Robinson, A., Ehlers, A., Clark, D., Spanlang, B. & Slater, M. 2017, Virtual reality in the assessment, understanding, and treatment of mental health disorders.
Garcia, L.M., Darnall, B.D., Krishnamurthy, P., Mackey, I.G., Sackman, J., Louis, R.G., Maddox, T. & Birckhead, B.J. 2021, Erratum: Self-administered behavioral skills-based at-home virtual reality therapy for chronic low back pain: Protocol for a randomized controlled trial (JMIR Res Protoc (2021) 10:1 (e25291) DOI: 10.2196/25291).
Gouin, J.P. & Kiecolt-Glaser, J.K. 2011, The Impact of Psychological Stress on Wound Healing: Methods and Mechanisms.
Gürler, H., Yılmaz, M. & Türk, K.E. 2022, "Preoperative Anxiety Levels in Surgical Patients: A Comparison of Three Different Scale Scores", Journal of Perianesthesia Nursing, vol. 37, no. 1.
Juster, R.P., McEwen, B.S. & Lupien, S.J. 2010, Allostatic load biomarkers of chronic stress and impact on health and cognition.
Kayleigh Maxwell, L.C., Devjit Srivastava. 2023, Do virtual reality interventions reduce preoperative anxiety and improve perioperative outcomes in adult patients undergoing elective surgery? .
Kleshchova, O. & Weierich, M.R. 2022, "The Neurobiology of Stress" in Biopsychosocial Factors of Stress, and Mindfulness for Stress Reduction.
Knapp, P., Layson, J.T., Mohammad, W., Pizzimenti, N. & Markel, D.C. 2021, "The Effects of Depression and Anxiety on 90-day Readmission Rates After Total Hip and Knee Arthroplasty", Arthroplasty Today, vol. 10.

Korkut, E.H. & Surer, E. 2023, "Visualization in virtual reality: a systematic review", Virtual Reality, vol. 27, no. 2.
Kyranou, M; Puntillo, K; Dunn, Laura et.al 2014, "Predictors of Initial Levels and Trajectories of Anxiety in Women Prior to and For Six Months Following Breast Cancer Surgery", Cancer nursing, vol. 37, no. 6.
Loomis, J.M., Blascovich, J.J. & Beall, A.C. 1999, "Immersive virtual environment technology as a basic research tool in psychology", Behavior Research Methods, Instruments, and Computers, vol. 31, no. 4.
Mavros, M.N., Athanasiou, S., Gkegkes, I.D., Polyzos, K.A., Peppas, G. & Falagas, M.E. 2011, "Do psychological variables affect early surgical recovery?", PLoS ONE, vol. 6, no. 5.
McDonald, S., Page, M.J., Beringer, K., Wasiak, J. & Sprowson, A. 2014, Preoperative education for hip or knee replacement.
McEwen, B.S. 2000, "The neurobiology of stress: From serendipity to clinical relevance", Brain Research, vol. 886, no. 1-2.
Medina S, Clarke S, Hughes S. Virtual reality-based analgesia: towards a novel framework for the biopsychosocial management of chronic pain. Br J Anaesth. 2024 Sep;133(3):486-490. doi: 10.1016/j.bja.2024.06.005. Epub 2024 Jul 12. PMID: 38997839.
Mitchell M. Patient anxiety and modern elective surgery: a literature review. J Clin Nurs. Nov 13, 2003;12(6):806-815. [doi: 10.1046/j.1365-2702.2003.00812.x] [Medline: 14632973
Montgomery GH, David D, Goldfarb AB, Silverstein JH, Weltz CR, Birk JS, et al. Sources of anticipatory distress among breast surgery patients. J Behav Med. Apr 2003;26(2):153-164. [doi: 10.1023/a:1023034706298] [Medline: 12776384]
Moonesinghe SR ,Walker EMK, Bell M, Cook TM, Grocott MPW, ; Central SNAP-1 Organisation; National Study Groups. Patient reported outcome of adult perioperative anaesthesia in the United Kingdom: a cross-sectional observational study. Br J Anaesth. 2016 Jun 12;117(6):758-766. doi: 10.1093/bja/aew381. Erratum in: Br J Anaesth. 2017 Sep 1;119(3):552. doi: 10.1093/bja/aew471. PMID: 27956674.
Navratilova E, Porreca F. Reward and motivation in pain and pain relief. Nat Neurosci. 2014 Oct;17(10):1304-12. doi: 10.1038/nn.3811. Epub 2014 Sep 25. PMID: 25254980; PMCID: PMC4301417.
NCT05178615 2022, "Investigation of the Effect of Preoperative Education on Postoperative Outcomes in Total Knee Arthroplasty Patients", https://clinicaltrials.gov/show/NCT05178615,
Nguyen, S.N., Hassett, A.L., Hu, H.M., Brummett, C.M., Bicket, M.C., Carlozzi, N.E. & Waljee, J.F. 2022, "Prospective cohort study on the trajectory and association of perioperative anxiety and postoperative opioid-related outcomes", Regional Anesthesia and Pain Medicine, vol. 47, no. 10.
Ni, K., Zhu, J. & Ma, Z. Preoperative anxiety and postoperative adverse events: a narrative overview. *APS* **1**, 23 (2023). https://doi.org/10.1007/s44254-023-00019-1
No authors listed 2021, The National Joint Registry 18th Annual Report 2021.
Oing, T. & Prescott, J. 2018, "Implementations of Virtual Reality for Anxiety-Related Disorders: Systematic Review", JMIR Serious Games, vol. 20, no. 11.
Pagé, M.G., Watt-Watson, J. & Choinière, M. 2017, "Do depression and anxiety profiles over time predict persistent post-surgical pain? A study in cardiac surgery patients", European Journal of Pain (United Kingdom), vol. 21, no. 6.
PROMs Analytical Team 2020, "Finalised Patient Reported Outcome Measures (PROMs) in England for Hip & Knee Replacements, April 2018 – March 2019 - NHS Digital", NHS Digital , , no. April 2018.

Radianti, J., Majchrzak, T.A., Fromm, J. & Wohlgenannt, I. 2020, "A systematic review of immersive virtual reality applications for higher education: Design elements, lessons learned, and research agenda", Computers and Education, vol. 147.
Rasouli, M.R., Menendez, M.E., Sayadipour, A., Purtill, J.J. & Parvizi, J. 2016, "Direct Cost and Complications Associated With Total Joint Arthroplasty in Patients With Preoperative Anxiety and Depression", Journal of Arthroplasty, vol. 31, no. 2.
Saviola, F., Pappaianni, E., Monti, A., Grecucci, A., Jovicich, J. & De Pisapia, N. 2020, "Trait and state anxiety are mapped differently in the human brain", Scientific Reports, vol. 10, no. 1.
Schwartz, F.H. & Lange, J. 2017, Factors That Affect Outcome Following Total Joint Arthroplasty: a Review of the Recent Literature.
Sheen, M.J., Chang, F.L. & Ho, S.T. 2014, Anesthetic premedication: New horizons of an old practice.
Sim, J. & Lewis, M. 2012, "The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency", Journal of Clinical Epidemiology, vol. 65, no. 3.
Sinha, C., Kaur, M., Kumar, A., Kulkarni, A., Ambareesha, M., & Upadya, M. (2012). Comparative evaluation of midazolam and butorphanol as oral premedication in pediatric patients. Journal of Anaesthesiology, Clinical Pharmacology, 28, 32–35. doi:10.4103/0970-9185.92431
Soffin, E.M. & Yadeau, J.T. 2016, Enhanced recovery after surgery for primary hip and knee arthroplasty: A review of the evidence.
Spielberger, C.D. 1972, "CONCEPTUAL AND METHODOLOGICAL ISSUES IN ANXIETY RESEARCH" in Anxiety.
Srivastava, D. 2017, "Chronic post-amputation pain: peri-operative management – Review", British Journal of Pain, vol. 11, no. 4.
Stark, P.A., Myles, P.S. & Burke, J.A. 2013, "Development and psychometric evaluation of a postoperative quality of recovery score: The QoR-15", Anesthesiology, vol. 118, no. 6.
Steckl, A.J. & Ray, P. 2018, "Stress Biomarkers in Biological Fluids and Their Point-of-Use Detection", ACS Sensors, vol. 3, no. 10.
Steimer T. The biology of fear- and anxiety-related behaviors. Dialogues Clin Neurosci. 2002 Sep;4(3):231-49. doi: 10.31887/DCNS.2002.4.3/tsteimer. PMID: 22033741; PMCID: PMC3181681.
Yu Y, Zhou X, Zeng G, Hou Y. Impact of virtual operating room tours on relieving perioperative anxiety in adult patients: a systematic review. J Perianesth Nurs. Aug 2023;38(4):657-63.e7. [FREE Full text] [doi: 10.1016/j.jopan.2022.11.013] [Medline: 36697345]
Wang, R., Huang, X., Wang, Y. & Akbari, M. 2022, Non-pharmacologic Approaches in Preoperative Anxiety, a Comprehensive Review.
Weiser, T.G., Regenbogen, S.E., Thompson, K.D., Haynes, A.B., Lipsitz, S.R., Berry, W.R. & Gawande, A.A. 2008, "An estimation of the global volume of surgery: a modelling strategy based on available data", The Lancet, vol. 372, no. 9633.
Wolf, T.G., Schläppi, S., Benz, C.I. & Campus, G. 2022, Efficacy of Hypnosis on Dental Anxiety and Phobia: A Systematic Review and Meta-Analysis.
Xu, J., Twiggs, J., Parker, D. & Negus, J. 2020, "The Association Between Anxiety, Depression, and Locus of Control With Patient Outcomes Following Total Knee Arthroplasty", Journal of Arthroplasty, vol. 35, no. 3.