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CEDAR
Centre for Healthcare Evaluation, Device Assessment and Research

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board

SPIN-VR

SENSOR-BASED PHYSIOTHERAPY INTERVENTION WITH VIRTUAL REALITY

A randomised feasibility study to evaluate home-based personalised virtual reality physiotherapy rehabilitation compared to usual care in the treatment of pain for people with knee osteoarthritis.

STUDY PROTOCOL

Version 4.0 (25/11/2024)

Sponsor SPON1947-23
IRAS 328066
REC 23/WA/0311

Signature Page

The undersigned confirm that the following study 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 GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other relevant regulatory requirements.

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 study without the prior written consent of the Sponsor.

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

For, and on behalf of the Trial Sponsor:

Signature: Date:

…… ……/……./…….

Name: (print):

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Position:

……

Chief Investigator:

Signature: Date:

…… ……/……./…….

Name: (print):

……

For, and on behalf of the trial coordination centre (CEDAR):

Signature: Date:

…… ……/……./…….

Name: (print):

……

Key Contacts

Sponsor: Cardiff University

Trial coordination centre: CEDAR, Cardiff & Vale University Health Board, Cardiff Medicentre, Heath Park, Cardiff, CF14 4UJ

Funder: Versus Arthritis (Grant reference: 22967)

Chief investigator:
Dr Mohammad Al-Amri, Senior Research Fellow
Room 13.04, 13th Floor, Eastgate House, 35-43 Newport Road, Cardiff, CF24 0AB
Telephone: 02920 687 115
Email: al-amrim@cardiff.ac.uk

Investigators:
Dr Judith White
CEDAR, Cardiff & Vale UHB, Cardiff Medicentre, Heath Park, CF14 4UJ
Telephone: 02921 841 599
Email: Judith.White3@wales.nhs.uk

Samuel Bird
CEDAR, Cardiff & Vale UHB, Cardiff Medicentre, Heath Park, CF14 4UJ
Telephone: 02921 848 692
Email: Samuel.Bird2@wales.nhs.uk

Dr Rhys Morris
CEDAR, Cardiff & Vale UHB, Cardiff Medicentre, Heath Park, CF14 4UJ
Telephone: 02921 844 772
Email: Rhys.Morris@wales.nhs.uk

Dr Kate Button
Room 13.17, 13th Floor, Eastgate House, 35-43 Newport Road, Cardiff, CF24 0AB
Telephone: 02920 687 734
Email: ButtonK@cardiff.ac.uk

Professor David Walsh
Sherwood Forest Hospitals NHS Foundation Trust, Kings Mill Hospital, Mansfield Road, Sutton in Ashfield, NG17 4JL
Telephone: 01623 622515
Email: David.Walsh@nottingham.ac.uk

Dr Martin Warner
School of Health Sciences, University of Southampton, Southampton, SO17 1BJ
Telephone: 02380 598 990
Email: m.warner@soton.ac.uk

Table of contents

1 Synopsis

Study Title	A randomised feasibility study to evaluate home-based personalised virtual reality physiotherapy rehabilitation compared to usual care in the treatment of pain for people with knee osteoarthritis
Internal ref. no. / short title	SPIN-VR
Study Design	Feasibility randomised controlled trial (RCT)
Planned Sample Size	50 (25 in each arm)
Planned Study Duration	23 months
Objectives	**Outcomes measures**
Main outcome measures relating to feasibility (no primary)	
Feasibility of recruitment	Ability to achieve a recruitment and randomisation of 4 patients per month, 50 patients within 13 months (number screened, consented, and randomised will be logged; reasons for non-consent or withdrawal will be recorded).
Completeness of outcome measures	Number (%) of each questionnaire and mechanistic outcome completed at 12-weeks and 24-weeks post randomisation.
Fidelity of healthcare professionals delivering intervention	Treatment logs for face-to-face contact, observation of two assessments and training sessions for setting up patients with knee osteoarthritis with the intervention.
Acceptability of intervention and trial procedures	Interviews with patients and staff about expectations and experience of the intervention, and barriers and facilitators to trial participation.
Adverse events	Treatment logs and patient interviews will be used to find issues related to knee symptoms or muscle soreness and falls, and motion sickness, plus any unexpected adverse events.
Adherence	Number of times and date/time of when patients logged in to the VR games and number of physiotherapy follow-up consultations.
Secondary outcomes	
Evaluate the processes for exercise mechanism of action at improving pain outcomes	A variety of measurements relating to muscle strength and endurance, aerobic capacity, exercise technique, central pain processing, and self-reported pain outcomes and moderators.
Assess intervention to treat knee osteoarthritis	The OMERACT-OARSI core domain set. A variety of patient-reported outcome measures. Pain sensitisation by algometer. Dynamic balance using a step test.
Intervention	VR-based home physiotherapy
Statistical Methodology and Analysis	Descriptive statistics for numerical outcomes will be reported, including an evaluation of patient eligibility, recruitment, acceptability of and adherence to the intervention. Qualitative data will be analysed using thematic analysis.

1.1 Funding and Support in kind

Funder(s)	Financial and non-financial support given
Versus Arthritis	£299,998.56 'Accelerating New Treatments' grant, as part of the Musculoskeletal Translational Research Collaboration. (Grant code: 22967)

1.2 Role of Study Sponsor and Funder

The study will be sponsored by Cardiff University (CU). They will retain all sponsorship responsibilities, but many of these responsibilities will be delegated as per study agreements and delegation logs.

Dr Mohammad Al-Amri (MA) will act as Chief Investigator (CI) who will take overall responsibility for the study including data analysis, report writing, and financial management.

Himself alongside research assistants (RA) will be responsible for managing the day-to-day research including patient recruitment, medical history taking and study eligibility assessment, patient consent, data recording, adverse event management and recording.

Dr Kate Button (KB) will act as the clinical lead for the study. She will link with the physiotherapist team that will be identifying and screening patients for eligibility and performing any necessary clinical assessments of patients throughout the study.

Samuel Bird (SB) and Dr Judith White (JW) from CEDAR in Cardiff & Vale University Health Board (CVUHB) will act as a study coordinator and will be responsible for the management of the study on a day-to-day basis including governance, documentation, and monitoring, data analysis, and report writing.

Dr Rhys Morris (RM) (CEDAR, Cardiff & Vale UHB) will have overall responsibility for CEDAR's component of this study.

Professor David Walsh (DW) (Sherwood Forest Hospitals NHS Foundation Trust), Dr Martin Warner (MW) (University of Southampton), and Dione Shorten (DS) are co-applicants on the research grant, have contributed to the development of the protocol, and are part of the trial management group (TMG).

If any of the study team leave, they will be replaced with a new study team member of suitable grade and experience.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study.

Versus Arthritis have provided a grant to fund the feasibility study.

1.3 Protocol Contributors

The study has been designed by MA, KB and JW.

The main contributors to the protocol have been MA and KB from Cardiff University, and SB and JW from CEDAR.

DW, MW, and DS have contributed to the protocol as part of the TMG.

2 Abbreviations

ACR	American College of Radiology
AE	Adverse event
BMI	Body mass index
CEDAR	Centre for Healthcare Evaluation, Device Assessment, and Research
CI	Chief investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CU	Cardiff University
CVUHB	Cardiff & Vale University Health Board
DT	Neuromuscular challenging dual-tasks
GP	General practitioner
ICF	Informed consent form
JRO	Joint Research Office
KOOS	The Knee Injury and Osteoarthritis Outcome Score
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OA	Osteoarthritis
PIS	Participant information sheet
PROM	Patient reported outcome measure
RA	Research assistant
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event
SPIN	Sensor Physiotherapy Intervention
UHW	University Hospital of Wales
VA	Versus Arthritis
VR	Virtual reality
VRHP	Virtual reality home physiotherapy

3 Background

3.1 The Clinical Problem

Osteoarthritis (OA) is a costly major worldwide challenge impairing function and quality of life. It is one of the leading causes of musculoskeletal pain and disability worldwide[1], mainly affecting the knees and hips. The global prevalence of knee and hip OA in 2017 was approximately 303 million, and with an aging population the projected years lived with disability rate is estimated to be 111.8 per 100,000[2]. Pain is the dominant symptom. Persistent pain can be associated with widespread sensitisation, which may impair neuromuscular control[3]. OA pain fluctuates, often with intermittent and severe flares from which both symptomatic and functional recovery might be incomplete. Ultimately, pain impairs the differential control of muscles around the painful area leading to a loss of functional independence and a profound reduction in physical activity, quality-of-life, and mental wellbeing[4, 5].

3.2 Physiotherapy-based exercise

Guidelines advocate physiotherapy-based exercise for the management of OA. Physiotherapy-based exercise is a core element of non-pharmacological interventions for OA pain management[6, 7]. It may be a safer and a lower cost option than surgery or long-term pharmacological interventions[8-10]. Exercise has shown to be beneficial for reducing pain and widespread pain sensitisation in people with OA[11, 12]. Exercise may reduce pain in OA through multiple mechanisms. Acute exercise can activate endogenous descending pain inhibitory pathways involving spinal dorsal horn neurones (exercise-induced hypoalgesia)[13-15]. Changes in muscle perfusion following exercises are associated with less pain in patients with knee OA[16, 17]. Other influences include reducing the impact of pain on function and improving muscle strength and control to improve the loading of the joint during everyday tasks.

3.3 Exercise adherence

The physiological changes that accompany exercise may be expected to reverse if exercise is not continued. A key reason that efficacy of exercise in randomised control trials (RCTs) has not yet translated into optimal clinical benefit is that treatment adherence is challenging for the patient. Prolonged treatment may maintain benefits, to reduce pain and promote optimal functional outcome[18]. An important aspect of ongoing management is therefore that of equipping individuals with the skills and motivation to continue performing prescribed exercises once face-to-face support from a clinician has stopped. Delayed effective intervention can permanently compromise the benefit from eventual treatments such as arthroplasty[19].

3.4 Home-based physiotherapy

There is an urgent need for home-based physiotherapy approaches that cater to the specific needs, time constraints, and preferences of patients. This personalised support is crucial in helping patients effectively manage their condition at home and potentially improve long-term outcomes. When home-based physiotherapy is tailored to utilize the appropriate techniques, it can play a vital role in addressing OA. Various studies[20-23] have reported that home-based physiotherapy can be as effective as a clinic-based physiotherapy, but self-efficacy and adherence are poor[24, 25]. Home-based physiotherapy interventions require high levels of individual capability and motivation[26]. A Cochrane review[18] revealed that people reported difficulties sustaining regular exercise but that they could exercise regularly if they perceived exercise to be related, important, fun, and enjoyable. Prescribing an exercise programme that is tailored to individual abilities, targets, and preferences and motivates them to adhere to exercise is needed for effective physiotherapy exercise interventions[18, 27, 28].

3.5 VR-based home physiotherapy (VRHP)

Virtual Reality (VR) include technologies such as movement sensors which are worn on a person's body that move an animated character on a computer screen so that the character follows the person's body movements. It has been a

feasible approach across a range of other clinical conditions including Stroke and Parkinson's disease [29-31]. Wearable and VR technologies can revolutionise home-based physiotherapy for people with OA. Combining the use of wearable sensors with VR games in a physiotherapy exercise intervention has substantial potential to improve pain outcomes in people with knee OA. This may be achieved by motivating them to adhere to their exercise program, increasing capability by giving feedback to ensure they do the exercises with the correct technique, perform the exercises within a context through which pain relief can be harnessed, to enable them to learn and be immediately rewarded for optimal exercise technique.

A novel real-time VR-feedback game during a squatting exercise was found to allow people with OA to alter their squatting strategy in response to real-time targeted feedback[32, 33]. This exercise can improve lower body strength and balance to reduce fall risk in individuals with knee pain[34-36]. Additionally, a VR physiotherapy dynamic balance exercise game has been developed whereby people have to control their balance whilst standing and performing an additional task[37, 38]. This has been tested in healthy subjects in a laboratory environment and demonstrated potential in improving postural sway. These VR games have been adapted for the clinic and home settings so that the patients can control the games with body-worn sensors on the pelvis or trunk whilst still tracking their movement in real-time. Given the impacts of pain on ability and motivation to exercise and the central role of exercises to reduce pain and thereby improve function among patients with OA, it is important to ensure these games are acceptable and effective in home and clinical settings.

3.6 Sensor-based physiotherapy intervention with VR

A sensor-based VR physiotherapy exercise intervention for people with OA has been developed in-house by the Sensor Physiotherapy Intervention (SPIN) Research Group at Cardiff University. This has followed the guidance set out by the Medical Research Council for developing and evaluating complex interventions[39]. A sensor-based clinical movement analysis toolkit[40] has been developed through collaboration with Biomechanics & Bioengineering Research Centre Versus Arthritis at Cardiff University, Cardiff and Vale University Health Board (CVUHB), and an industry partner (Xsens Technologies B.V.). The reliability and validity of measuring joint angles using sensors during everyday tasks in comparison to the 'gold standard' lab-based equipment has been demonstrated[41]. These findings are addressing pain management challenges identified by NICE guideline on OA[42] and NIHR's Themed review[43].

The VR-based physiotherapy system is an integration of basic physiotherapy approaches, movement science, intelligent algorithms, affordable motion capture technology (i.e., body-worn sensors and depth cameras like Azure Kinect DK), and bespoke software. It provides detailed movement feedback to users instantly[44, 45]. The system can estimate relevant movement outcomes like squat depth, maximum joint angles and range, symmetry, and postural sway. Movement correction based on research[46-48] and clinical experience can be practiced in a real-time within a gaming context.

The system key components include:

(i) monitoring performance;

(ii) exercise goal setting;

(iii) exercise progressions.

To personalise the VR-based physiotherapy games, the system consists of an algorithm to optimise VR games based on progression and exercise quality. A variety of scenarios are employed to enable the algorithm to select the game and adjust the parameters of the game based on the patient's real-time progression as appropriate. The progression is based on a composite total score of feedback about pain severity and how the patient moves. Once the participants score is above the threshold, the system will be triggered to progress from simple tasks to more advanced neuromuscular challenging dual-tasks (DT). Each VR-based physiotherapy game scenario comes with several game levels (e.g. frequency and size of virtual objects) to motivate and engage participants to progress.

4 Rationale

This study will assess the feasibility of conducting a large RCT of the VR-based physiotherapy exercise intervention. This will involve an evaluation of recruitment rates and participant willingness to be randomised and participate in the trial, and the acceptability and safety of the VR-based physiotherapy exercise intervention use in participant's homes.

4.1 Clinical development

It has been reported that home-based physiotherapy can be as effective as clinic-based physiotherapy by various studies[20-23], but adherence is poor[24, 25]. Therefore, prescribing an exercise programme that is tailored to individual abilities, targets, and preferences and motivates them to adhere to exercise is needed for effective physiotherapy exercise interventions[27, 28, 49]. This is where the VR-based physiotherapy exercise intervention comes in. VR has been a feasible approach across a range of other clinical conditions including Stroke and Parkinson's disease[29-31], but it has not been fully explored in OA. The reliability and validity of measuring joint angles using sensors during everyday tasks in comparison to the 'gold standard' lab-based equipment has been demonstrated[41], as well as the physiotherapist acceptability of feedback combining a personalised movement report and video avatars to treat people with knee injury[50-52]. The VR-based physiotherapy exercise intervention has been demonstrated to allow people with OA to alter their squatting strategy in response to real-time targeted feedback[53, 54]. This exercise can improve lower body strength and balance to reduce fall risk in individuals with knee pain[34-36]

4.2 Benefits and risks of the intervention and study

4.2.1 Potential benefits

This feasibility study hopes to show that providing patients with high quality information that links exercise to a purposeful and enjoyable VR game will provide a means to counter fears about exercise, remove barriers to moving and exercising safely, and therefore improve function and reduce pain. People with knee OA often develop pain elsewhere, and reduced pain sensitisation should reduce the risk of these incident secondary pain problems. Feedback on movement will increase engagement and persistence with good exercise technique, increasing its effectiveness.

It is hoped that patients with OA will be that they will gain confidence from a greater understanding of how to accurately move allowing them to exercise wisely. Feedback within the VR game will help motivate participants to adhere to continuing exercise. Allowing patients to continue to exercise more effectively will reduce risks from comorbidities and reduce their healthcare needs. It is anticipated that this will empower patients to more effectively manage their condition, reducing dependence on and avoiding risks, side-effects, inconvenience and personal or financial cost from medical and surgical treatments.

In addition to the benefits from the study interventions, and to thank patients for the time they contributed to the study, patients will also receive a £20 voucher as a gift for each assessment they complete, and for completing the intervention. The voucher will be given to the patient at the end of each assessment, and when they have completed the intervention. Patients will receive £80 in vouchers if they complete all parts of the study. Additionally, patients will receive a £25 voucher if they take part in the post-intervention interview.

4.2.2 Potential risks

There are no safety risks anticipated with the use of this intervention. Participants that are involved will be screened to ensure that they can perform the exercises independently in their own homes without the risk of injury. When starting new exercises there is a risk of some increased pain or muscle soreness. The exercises will have been prescribed by a physiotherapist to minimise this. As part of normal practice physiotherapists warn patients that there might be some increased soreness whilst exercising but should stop after exercising or within 24 hours.

Patients may face challenges in using the necessary equipment for the home intervention. To address this potential issue, a comprehensive demonstration will be offered to patients prior to them taking the equipment home. They will also receive clear instructions on how to use the equipment and a contact number will be provided for additional support, if needed.

5 Study Design

5.1 General

This will be a single-centre, open-label, randomised controlled feasibility trial of a 12-week VRHP program with a 24-weeks post randomisation follow-up. Fifty people with knee OA who fulfil the NICE and ACR criteria for a knee osteoarthritis diagnosis[6, 55] will be randomised in equal numbers to either a VRHP programme or to receive usual care physiotherapy.

5.2 Trial setting

This is a single centre study in Cardiff & Vale University Health Board (CVUHB) and Cardiff University (CU). Participants will be approached at a clinic within the CVUHB physiotherapy department. They will complete baseline and follow up assessments at a CU clinic with a CU researcher. They will complete the VRHP program in their own homes.

5.3 Objectives and hypothesis

5.3.1 Hypothesis

As this is a feasibility RCT, the hypothesis is whether the trial is feasible and ready for a full-scale RCT.

5.3.2 Aims

This study aims to assess the feasibility of conducting an RCT to compare the VR-based home physiotherapy intervention with usual physiotherapy care. The study will investigate several feasibility measures.

5.3.3 Main objectives

- Feasibility of recruitment
- Patient willingness to be randomised
- Completeness of outcome measures
- Fidelity of healthcare professionals delivering intervention
- Acceptability of intervention and trial procedures to patients and other stakeholders (e.g. clinicians etc)
- Adverse events experienced by participants from the intervention and trial procedures
- Adherence to the physiotherapy programme prescribed

5.3.4 Secondary objectives

- Understanding how the exercises work to improve pain outcomes through muscle strength and endurance, aerobic capacity, exercise technique, central pain processing, and self-reported pain
- Assess use of intervention to treat knee osteoarthritis
- Determine the effect size of the intervention to help inform on a sample size calculation of a larger RCT

5.4 Table of outcomes measures/endpoints

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Main outcome measures relating to feasibility (no primary)		
Feasibility of recruitment	Ability to achieve a recruitment and randomisation of 4 patients per month, 50 patients within 13 months (number screened, consented, and randomised will be logged).	Continuously over duration of study
Patient willingness to be randomised	Reasons for non-consent and withdrawal will be recorded	Continuously over duration of study
Completeness of outcome measures	Number of questionnaires and mechanistic outcomes completed at 12-weeks and 24-weeks post randomisation.	End of the feasibility trial
Fidelity of healthcare professionals delivering intervention	Treatment logs for face-to-face contact, observation of two assessments for setting up knee osteoarthritis patients with the intervention.	Continuously over duration of study
Acceptability of intervention and trial procedures to participants	Interviews with patients and staff about expectations and experience of the intervention, and barriers and facilitators to trial participation.	End of the feasibility trial
Adverse events experienced by participants from the intervention and trial procedures	Treatment logs and patient interviews with be used to find issues related to knee symptoms or muscle soreness and falls, and motion sickness.	Continuously over duration of study
Adherence to the physiotherapy programme prescribed	Number of times and when patients logged in to the VR games and if follow up consultants were used.	Continuously over duration of study
Secondary outcomes		
Understanding how the exercises work to improve pain outcomes	A variety of measurements relating to muscle strength and endurance, aerobic capacity, exercise technique, central pain processing, and self-reported pain mechanisms and moderators.	End of the feasibility trial
Assess use of intervention to treat knee osteoarthritis	The OMERACT-OARSI core domain set. A variety of patient-reported outcome measures. Pain sensitisation by algometer. Dynamic balance using a step test.	End of the feasibility trial

5.5 Intervention and comparator

5.5.1 Intervention

The intervention is the VR-based home physiotherapy. The VRHP lasts 12-weeks and targets strength; neuromuscular control; and aerobic fitness, with progressive levels of difficulty for each task. The combination of exercises, level of difficulty and the exercise intensity will be set by the physiotherapist following the initial clinical assessment. Participants will be asked to do the exercise programme 3 times a week for 12 weeks at home. To personalise the VRHP games and set the optimal level of difficulty of each game for the participant, the option for setting the level of difficulty includes the number of obstacles, speed, repetition, range of motion and dual tasking. The games will be progressed during the 12 weeks if participants scored above a threshold on a composite total score so they can progress to more advanced tasks. On a weekly basis, the participant and physiotherapist will have access to a report on performance and number of times and for how long the participant has interacted with the system. The individual will continue to do the VRHP programme and will have the option of scheduling up to two appointments during the 12 weeks with their physiotherapist.

The VRHP system consists of a biomechanically validated body-worn sensors worn on the arms and legs. These control the associated VR games. The games will be played on a laptop computer that can be connected to a TV to enable a larger view of the gaming environment. Connecting it to a TV is optional. Each participant will be provided with a unique login onto the VR software, which will allow the research team to track the regularity of use and progress of all study participants. This will allow the research team to determine adherence with the VRHP program such as how often and for how long participants are using the system for each exercise. Like usual care, individuals will be given a leaflet of standard home exercises to accompany the VR exercises and advice on their condition by their treating physiotherapist as required.

5.5.2 Comparator

The comparator is standard physiotherapy care that will consist of an initial assessment and follow-on face-to-face or remote follow-up sessions with the physiotherapist as is normally delivered within the physiotherapy service. Usual care treatment will be physiotherapy advice and exercise[56] as decided by the treating physiotherapist. Individuals will be given a leaflet of standard home exercises. The content of the usual care treatment will be documented in treatment logs kept by the treating physiotherapist.

6 Trial Participants

The target population is adults with knee osteoarthritis who fulfil the NICE and ACR criteria for knee osteoarthritis diagnosis[43, 57] and who have been referred to a physiotherapy clinic.

6.1 Inclusion criteria

- Adults aged 45 or older years
- Clinical diagnosis of knee osteoarthritis
- Referred for physiotherapy for clinically diagnosed knee osteoarthritis pain
- Activity related joint pain
- Self-reported knee pain on most days for the past 3 months
- Average pain severity in the past week of 4 or greater on a 10-point numeric rating scale
- Able to understand written and spoken English
- Able to provide written informed consent

6.2 Exclusion criteria

- Where knee is not identified by the participant as the main source of pain (e.g. comorbid painful conditions, widespread pain).

- Contraindication to exercise
- Pain caused by malignancy, fractures, or inflammatory arthritis
- Has received surgery for their knee pain in the last 12 months, or had previous knee arthroplasty on the affected knee
- Has commenced another new treatment for knee pain, other than the trial interventions, during the preceding 12 weeks
- Unable to walk without a walking aid
- Unable or unwilling to engage in either active or control intervention

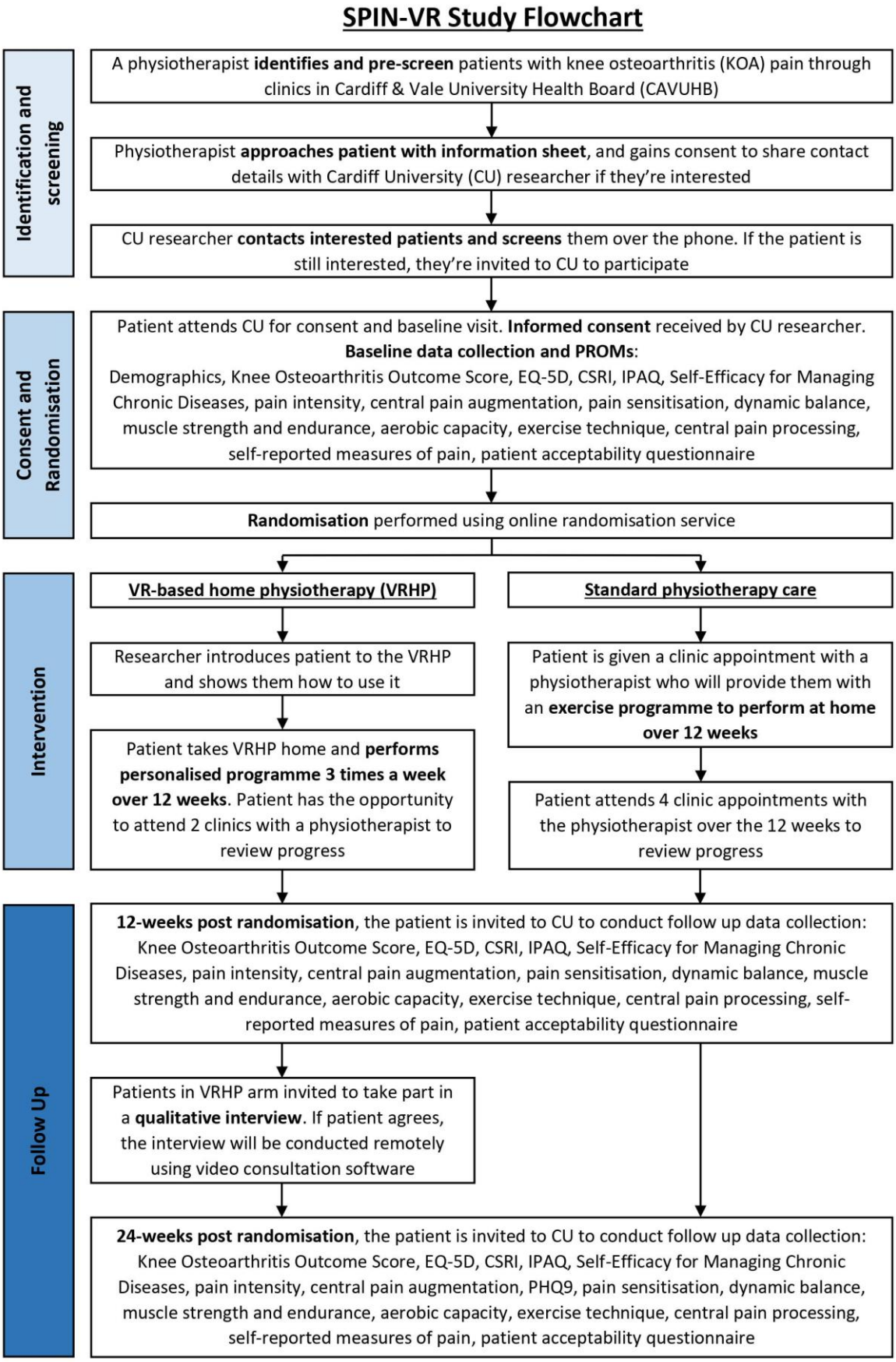
7 Trial procedures

7.1 Schedule of trial procedures

The following table below describes the study procedures and assessments.

Procedure	**Visits**				
	Screening	**Baseline**	**Treatment period** **12-weeks VRHP or SOC**	**Assessment 1** **12-weeks post randomisation**	**Assessment 2** **24-weeks post randomisation**
Eligibility Check	X	X			
Informed Consent		X			
Randomisation		X			
Demographic data recorded		X			
Patient-directed treatment at home			X (3 times a week for 12 weeks)		
Patient reported outcome measures (PROMs)		X		X	X
Pain sensitisation		X		X	X
Dynamic Balance		X		X	X
Exercise mechanisms of action		X		X	X
Adverse events			X	X	X
Qualitative interview (optional)				X	

The following flowchart outlines the trial procedures.



7.2 Identification and screening

Participants will be identified by a member of the clinical physiotherapy team at Cardiff and Vale University Health Board in outpatient clinics. Patients from the waiting list for physiotherapy care, and those already attending

musculoskeletal clinics, will be screened. They will be screened for eligibility against the eligibility criteria, and if they are interested, they will be offered a participant information sheet. Contact details will be obtained, and passed on to the research team, who will then approach participants to arrange a baseline assessment and informed consent visit. Consent to share patient contact details with the research team will be obtained beforehand.

Additionally, the study will be listed on the NIHR's Be Part of Research registry. This advertises the study to eligible patients who can then enquire with the study team and their physiotherapist about participating.

7.3 Informed consent

The participant must personally sign and date the latest approved version of the informed consent form (ICF) before any study specific procedures are performed. Written and verbal versions of the PIS and ICF will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their General Practitioner (GP) or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and received the Informed Consent. The person who received the consent will be suitably qualified and experienced and have been authorised to do so by the CI. A copy of the signed ICF will be given to the participant to keep along with a copy of the PIS. The original signed form will be retained at the study site and a further copy will be kept in the patients' medical notes.

The informed consent procedure can be conducted in 1 of 2 ways:

Face-to-face consent:
Participants are provided with an informed consent form (ICF) during their in-person baseline study visit. They sign the form, which is then countersigned by a delegated researcher. A signed copy is given to the participant for their records.

Electronic consent:
The PIS is sent to the participant. A researcher contacts them within two weeks to confirm eligibility. If the participant agrees to participate, they are sent an electronic version of the ICF to sign and return electronically, and the participant receives a copy of the completed electronic ICF.

7.4 Randomisation

Randomisation will be provided via a computer-generated list. A researcher in CEDAR will set up the randomisation module so it is independent of the research team performing assessments. The research team will access the randomisation module and enter the required data for randomisation, including; date, patient date of birth, confirmation of patient eligibility, and confirmation of informed consent, and then press the randomise button. The researcher will be presented with the randomisation allocation. The researcher can then inform the participant of their allocation.

7.5 Trial assessments

The baseline assessment will be carried out at the baseline and consent visit with a researcher. During the baseline visit, the research team will collect demographic data.

The patient will also be given paper copies of PROMs to complete. These are:

- **Knee Osteoarthritis Outcome Score:** A multi domain tool that has sub-scales to

assess pain severity, function, sport, symptoms, and quality of life[58]. The pain and function sub-scales would be co-primary outcomes in a future definitive RCT.

- **EQ-5D-5L questionnaire**
- **Client Service Receipt Inventory**
- **International Physical Activity Questionnaire**
- **Self-Efficacy for Managing Chronic Diseases:** Focuses on common domains across chronic diseases, symptom control, role function, emotional functioning and communicating with physicians.
- **Pain intensity before and after exercise:** This will quantify the pain response to exercise by asking participants to rate their pain before and after each exercise task using a 0 (no pain) to 100 (most pain imaginable) numeric rating scale. Pain intensity after exercise was chosen, since it can serve as an indirect measure of how the pain affects function.
- **Central pain augmentation:** This will be assessed using Central Mechanisms trait that is represented by items addressing 8 individual phenotypic traits, predicts pain persistence and persistent pain severity in people with knee osteoarthritis.
- **Patient acceptability questionnaire**

Additionally, the following assessments will be conducted with the patient by a researcher:

- **Pain sensitisation:** This will be assessed by using an electronic data collection unit featuring a handheld algometer (Medoc AlgoMed – Computerised Pressure Algometer) with 1cm^2 probe and pressure ramp of 50kPa/sec to determine the pressure pain detection threshold at tibialis anterior (a site distal to the affected joint affected by central sensitisation) and at the knee (affected by both peripheral and central sensitisation).
- **Dynamic Balance:** This will be assessed by using the validated step test by asking participants to maintain balance on the study leg whilst stepping the contralateral leg on and off a 15 cm step as many times as possible in 15 seconds without any weight transfer to the stepping leg.
- **Evaluation of exercise mechanisms of action:**
  - Muscle strength and endurance: 30 second time sit to stand test
  - Aerobic capacity: timed 6 metre walk test
  - Exercise technique: throughout by evaluating key biomechanical parameters for each exercise and compared to lab-based data collected on healthy subjects e.g., centre of mass motion
  - Central pain processing: quantitative sensory testing modality of Pressure Pain Detection Thresholds local and distant from the index knee
  - Self-report measures of pain mechanisms and moderators: activity, medication use, psychological wellbeing, Central Pain Mechanisms Trait

7.5.1 Follow up assessments

Patients will have two in-person, follow up assessments with the CU research team, at 12-weeks post randomisation which will occur at the end of their VRHP program, and another at 24-weeks post randomisation.

The PROMs and assessments conducted at the follow up visits are the same as those conducted at the baseline visit, minus the collection of demographic data.

7.5.2 Patient interviews

Following recruitment, patient interviews will be conducted with a sample of 15 participants after the 12 week intervention. The purpose of these interviews is to gather valuable insights and perspectives regarding the study and the intervention. Topics covered will include the participants' acceptance of the technology, factors influencing their participation in the trial, any unexpected benefits or adverse effects experienced, as well as their experiences with

pain and any impact on their overall function and exercise. It is important to note that these interviews are voluntary and not mandatory. As part of the informed consent process, participants will be asked for their consent to be contacted for these interviews. Patients will have the option to opt-in to participate in these interviews. The interviews will be conducted by a member of the research team online using video consultation software. Only audio will be recorded. Interviews will last between 30-45 minutes. The audio files will be transcribed verbatim by a professional transcription company. The data will be analysed using thematic analysis and NVIvo software will be used to manage the data analysis.

7.6 Trial assessments table

For this feasibility study, a wide range of secondary outcomes are included in line with OMERACT-OARSI core domain set. The following table describes the measures that will be taken during the study, when and how.

Measure	Timepoint	Method
Patient Reported Outcome Measures	Baseline, 12-week, 24-weeks post randomisation	• Knee Osteoarthritis Outcome Score • EQ-5D-5L questionnaire • Client Service Receipt Inventory • International Physical Activity Questionnaire • Self-Efficacy for Managing Chronic Diseases • Pain intensity before and after exercise • Central pain augmentation • Patient acceptability questionnaire
Pain sensitisation	Baseline, 12-week, 24-weeks post randomisation	Electronic data collection unit featuring a handheld algometer (Medoc AlgoMed – Computerised Pressure Algometer) with 1 cm^2 probe and pressure ramp of 50k Pa/sec to determine the pressure pain detection threshold at tibialis anterior.
Dynamic Balance	Baseline, 12-week, 24-weeks post randomisation	A validated step test that asks participants to maintain balance on the study leg whilst stepping the contralateral leg on and off a 15 cm step as many times as possible in 15 seconds without any weight transfer to the stepping leg.
Exercise mechanisms of action	Baseline, 12-week, 24-weeks post randomisation	• Muscle strength and endurance: 30 second time sit to stand test • Aerobic capacity: timed 6 metre walk test • Exercise technique: throughout by • evaluating key biomechanical parameters for each exercise and compared to lab-based data collected on healthy subjects e.g., centre of mass motion • Central pain processing: quantitative sensory testing modality of pressure pain detection thresholds local and distant from the index knee • Self-report measures of pain mechanisms and moderators; activity, medication use, psychological wellbeing, Central Pain Mechanisms Trait
Patient acceptability of intervention	Post-participation in the study	Patient interviews

7.7 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to be withdrawn from the trial at any time. In addition, the CI may discontinue a participant from the trial at any time if they consider it necessary for any reason, including:

- Pregnancy
- Ineligibility (either arising during the trial, or if a previously unknown issue becomes known which would make the participant ineligible)
- Significant protocol deviation as decided by the CI
- Significant non-adherence with the VRHP programme
- Withdrawal of consent
- Loss to follow up

Participants that are withdrawn from the trial prior to month 13 of recruitment will be replaced. If a participant does not continue with the trial, their data to the point of withdrawal will be included in the analysis, unless consent for this is withdrawn by the participant. Once a patient's data has been combined with the rest of the study data and analysed, it cannot be withdrawn.

7.8 Study duration

The target recruitment for the trial is 50. The target recruitment rate is 4 a month, and therefore the recruitment period of the trial will run for 13 months. There will be an additional 24 weeks, due to follow up, after the last participant is recruited until the trial ends.

7.9 End of trial

The end of the trial will be when the last recruited participant has had their 24-week follow up.

8 Safety reporting

This study is a study of a non-CE marked medical device. It was developed in-house at Cardiff University, and there is no intention to commercialise it. Therefore, a MHRA notice of no objection is not required. The medical device is software, and the physical component does not differ to what a patient would be expected to do in standard care physiotherapy. Therefore, it poses a minimal risk.

8.1 Definitions of adverse events, serious adverse events, and relatedness

Adverse events (AE)

Any untoward medical occurrence in a clinical trial participant to whom a study intervention has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom or disease.

Serious Adverse Event (SAE)

Adverse events are classified as serious or non– serious. A serious adverse event (SAE) is an adverse event which results in any of the following:

- Results in death
- Is life-threatening, in the sense that the patient was at risk of death at the time of the event (but not if the event could have caused death if more severe)
- Requires hospitalisation (or prolongation of existing hospitalisation) defined as an unplanned admission of any length, even if the precautionary for continued observation; however pre-planned hospitalisation (e.g.,

for an elective procedure or a pre-existing condition which has not worsened does not constitute an adverse event)

- Results in the persistent or significant disability or incapacity
- Consists of a congenital anomaly of birth defect
- Is otherwise considered medically significant by the investigator

Relatedness

Whether the reporting investigator considers the adverse event to be related to any of the study procedures can be classed as either definite, probable, possible, unlikely, or not related.

8.2 Identifying AEs

AEs will be identified by the research team and the clinical teams caring for the trial participants during their care.

8.3 Expected AEs

There are no expected AEs with the medical device.

8.4 Recording and Reporting SAEs

SAEs that are RELATED and UNEXPECTED (see definitions above) occurring from the time of randomisation until the participant's 24-week follow up must be recorded on the trial SAE form and sent to the sponsor (via the CEDAR) within 24 hours of research staff becoming aware of the event.

For each SAE, the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e., relatedness to the trial drug/investigation), in the opinion of the investigator
- Whether the event would be considered expected

Any change of condition or other follow up information should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

An SAE which has been classified by the CI as RELATED and UNEXPECTED (see definitions above) must be reported to both the Research Ethics Committee (REC) that gave a favourable opinion of the study, and the sponsor. Reports of related and unexpected SAEs should be submitted within 15 working days of the CI becoming aware of the event, using the HRA report of SAE form.

SAEs which are unrelated or expected will be recorded through standard data collection processes in the CRF.

All AEs which are related to the study device will also be reported according to section below "reporting adverse incidents involving medical devices".

8.5 Contact details for reporting SAEs

The study manager contact details for reporting SAEs:

Samuel Bird (or other delegated member of the trial coordination team)
Senior Researcher
CEDAR, Cardiff and Vale University Health Board, Cardiff Medicentre, Heath Park, Cardiff, CF14 4UJ
Tel: 029 218 44771
Email: Samuel.bird2@wales.nhs.uk

(Monday to Friday 08:00 – 17:00)

The SAE form should then be stored in the investigator site file, and a copy sent to CEDAR.

8.6 Urgent safety measures

The CI and PI may take immediate safety measures to protect research participants against any hazard to their health or safety without prior authorisation from the REC or sponsor. However, they must alert the Sponsor as soon as possible of any such urgent measures by contacting the CU JRO and CI. The CI will notify the REC of the presenting issue within 3 days of the urgent measure setting out the reasons for the urgent measure and the plan for further action.

8.7 Responsibilities

Principal/Chief Investigator

Checking for when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and whether the event was anticipated.
2. Ensuring that all SAEs which are RELATED and UNEXPECTED (see definitions above) are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs which are RELATED and UNEXPECTED (see definitions above) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that SAEs and AEs are recorded and reported in line with the requirements of the protocol.
4. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
5. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

9 Statistics and data analysis

9.1 Sample size calculation

This study is a feasibility study to assess recruitment targets and the acceptability of study procedures. As such, a sample size calculation has not been used. Instead, the sample size has been selected to assess the feasibility of recruiting 4 patients per month over 13 months. A conservative sample size of 50 patients has been selected. The information from this study will be used to inform further studies for a future pilot/RCT study.

9.2 Planned recruitment rate

A conservative recruitment rate of 4 patients per month for the duration of the study has been chosen based on a review of local data. We have estimated that 60% of eligible patients would be recruited into the study.

9.3 Statistical analysis plan

The main outcome of recruitment feasibility will be reported as frequency of patients recruited during the study period. Reasons for screening or randomisation failure will be collated and presented as frequencies. Descriptive data will include an evaluation of eligibility, recruitment, acceptability of and adherence to the intervention, with 95% confidence intervals. Secondary outcome measures including PROMs will be assessed before and after the intervention to establish any possible trend in the intervention effects over time understand the variability in data. The completion of outcome measures will be reported and changes in outcome assessments relative to baseline assessments will be analysed using appropriate parametric or non-parametric statistics based on the characteristics of the data. All tests will be two-sided with an alpha level of 0.05. Estimates of population variances of outcomes for future power calculations will use the upper 80th percentile of confidence intervals around the estimates will be carried out. In addition, individual performance and movement quality in the VR intervention will be monitored and measured during the 12-week programme, every time the patient completes a training session, to determine any improvement in comparison to baseline measurements.

9.4 Qualitative interview analysis

The qualitative interviews will be used to obtain views on participants' acceptance of the technology, factors influencing their participation in the trial, any unexpected benefits or adverse effects experienced, as well as their experiences with pain and any impact on their overall function and exercise. Data will be managed using Nvivo software. Data will be analysed using Braun and Clarkes thematic analysis

10 Data management

10.1 Data handling and record keeping

The CI/PI and research team will collect all clinical data. The data will be collected in a timely manner and be extracted from and consistent with relevant source data. Each participant will be allocated a unique Participant Study Number at trial entry, and this will be used to identify them on the CRF for the duration of the trial. Data will be collected from the time of trial entry until the participant's 24-week follow up. Trial data will be collected from the source data using both paper case report forms (CRF) and electronic case report forms (eCRF) and then entered onto a secure electronic database. The electronic database will be secured by appropriate access control and password protection.

All paper documents will be stored securely in a locked filing cabinet at Cardiff University. All electronic data will be stored on Cardiff University and CVUHB servers (electronic) and only be accessible by trial staff. No patient identifiable data (PID) will be transferred outside of Cardiff & Vale UHB or Cardiff University. Paper CRFs will be kept at the study site during the study period and when completed the CRFs will be signed-off by the study PI/CI or designee. Completed and signed-off CRFs will be transferred to CEDAR as each patient completes the study period. Appropriate checks will be made to enable cross validation against the original source data and ensure accurate data entry. The database will be stored on CAVUHB's secure servers which are backed-up every 24 hours. Data queries will be raised by CEDAR. Where clarification from site staff is required for data validations or missing data, site staff will respond to data queries ensuring that amendments are made as required.

Data reporting will comply with CONSORT guidelines for feasibility RCTs (http://www.consort-statement.org/extensions/overview/pilotandfeasibility). Descriptive data is planned to include an evaluation of eligibility, recruitment, acceptability of and adherence to the intervention, with 95% confidence intervals. Adherence will be classed as the participant carrying out at least 80% of their prescribed programme. Secondary outcome measures including PROMs will be assessed before and after the intervention to establish any possible trend in the intervention effects over time to understand the variability in data. The completion of outcome measures will be reported and changes in outcome assessments relative to baseline assessments will be analysed using appropriate

parametric or non-parametric statistics based on the characteristics of the data. All tests will be two-sided with an alpha level of 0.05. Estimates of population variances of outcomes for future power calculations will use the upper 80th percentile of confidence intervals around the estimates will be carried out.

Source data verification will be undertaken for CRFs. This will require a member of the research team to have access to patient medical records. Study participants will provide explicit consent to the use of identifiable data for the purposes of the study.

10.2 Access to data

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles.

Direct access will be granted to authorised representatives from the Sponsor for monitoring and/or audit of the study to ensure compliance with regulations.

CEDAR will perform the analyses of all study data. Procedures will be in place to enable transfer of study data as follows:

- From Cardiff University to CEDAR (anonymous data) for the purposes of analysis of outcome data and archiving.
- From Cardiff University to CEDAR to verify CRF data against the patient medical records, requiring access to personal identifiable data.

All access to personal identifiable data by the investigators will be with documented consent by the participant.

The device manufacturer will not have access to any patient identifiable data. Fully anonymised data may be made publicly available following publication of the study results.

10.3 Archiving

The TMF and Investigator Site File (ISF) containing essential documents will be kept for a minimum of 15 years after completion of study. Documents (paper and electronic) will be retained in a secure location during the study. CEDAR will archive study documentation at the end of the study in accordance with the sponsor's archiving procedures. A label stating the required retention time should be placed on the inside front cover of the medical records for study participants.

Essential documents pertaining to the study shall not be destroyed without permission from the sponsor.

10.4 Monitoring, audit & inspection

CEDAR will be responsible for trial monitoring. On-site or remote monitoring visits will be conducted in accordance with the trial monitoring plan. On-site or remote monitoring will be an on-going activity from the time of initiation until trial close-out and will comply with the principles of Good Clinical Practice (GCP). The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor. Before the trial starts at a participating site, an initiation meeting will take place to ensure that site staff are fully aware of the trial protocol and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place. Monitoring visits during the trial will check the accuracy of data entered into the CRF against the source documents, adherence to the protocol, procedures and GCP, and the progress of patient recruitment and follow up. The PI or designee should ensure that access to all trial related documents including source documents is available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan. The close out procedure at each site will commence once the final patient enrolled has completed all site follow-up required by the protocol.

11 Ethical and regulatory compliance

This study will comply with the Declaration of Helsinki (2013) and Good Clinical Practice (GCP). It will be run in accordance with all applicable regulatory guidance. In the UK this includes, but is not limited to, the UK Policy Framework for Health and Social Care (2017).

The rights, safety, and well-being of human subjects are the most important considerations and prevail over interests of science and society. The study will respect the rights of participating patients and ensure confidentiality of patient information.

On behalf of the Sponsor and the CI, CEDAR will submit this PROTOCOL, informed consent form, and participant information sheets (PIS) to an appropriate Research Ethics Committee (REC) for approval.

No site will commence study procedures (including screening) until all national and local regulatory approvals have been achieved and the Sponsor's representative has completed and signed off the Site Initiation Visit.

11.1 Research ethics and regulatory review and reporting

The study will not commence until approvals have been obtained from Health Research Authority (HRA) and Health and Care Research Wales (HCRW), an appropriate Research Ethics Committee (REC). Any additional requirements imposed by the REC shall be followed, if appropriate.

All correspondence with the REC will be retained in the Trial Master File and Investigator Site Files.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The Chief Investigator is responsible for this but can delegate the task to CEDAR.

The CI is responsible for notifying the REC at the end of the trial but can delegate the task to CEDAR. If the trial is ended prematurely, the CI or CEDAR will notify the REC, including the reasons for the premature termination. Within one year of the trial end, the CI/CEDAR will submit a final report with the results, including any publications/abstracts, to the REC.

11.2 Peer review

The protocol has been developed with input from several academics in relevant fields, trial specialists, and the Sponsor. The study will be assessed for governance and legal compliance by HCRW. Once all checks are satisfied, HCRW will issue HRA/HCRW approval. The study should not commence until local confirmation of capacity and capability is also received via email by the CI/ PI.

11.3 Patient and public involvement (PPI)

All patient-facing documents have been reviewed for content and readability by a PPI representative. There is a PPI co-applicant for the grant who will attend monthly meetings. A PPI advisory group will be established and chaired by the PPI co-applicant. Two patient representatives will be part of the Trial Steering Committee (TSC).

11.4 Breaches of GCP or Protocol

Protocol deviations are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol must not be used, except to protect the rights, safety, and well-being of human subjects under emergency circumstances. Accidental protocol deviations can happen at any time. Recurring deviations from the protocol are not acceptable, will require immediate action, and could potentially be classified as a serious breach. Deviations must be documented on the relevant study form by the PI or their representative and reported to the CI and CEDAR immediately. Deviations may also be identified during trial monitoring visits.

A “serious breach” is a breach of GCP or the protocol which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial

CEDAR will notify the Sponsor immediately of any potentially serious breach. The incident will be investigated by the Sponsor who will determine whether the breach constitutes a serious breach. CEDAR (on behalf of the Sponsor) will report serious breaches to the local NHS research governance department and will inform the REC in writing within 7 days. Any corrective action required will be undertaken by the CI/CEDAR, and REC and informed. If necessary, a protocol amendment will be submitted for review.

11.5 Data protection and patient confidentiality

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Act’s core principles.

The data custodian in this study is Dr Mohammad Al-Amri on behalf of the sponsor and the data will be held on CU’s secure server.

Study CRFs will be kept in secure locations (locked cupboard) at the study site and at CEDAR. The study database will be accessible only by delegated study personnel involved in the study.

11.6 Financial and other competing interests for the investigators

No financial or other competing interests are held by the CI, PI, or any member of the research team.

11.7 Indemnity

The Sponsor has a specialist insurance policy in place, which would operate in the event of any participant suffering harm because of their involvement in the research. The Sponsor has insurance policies in place to cover Professional Indemnity, Clinical Trials Insurance and Public Liability Insurance, which together provide cover for much of the Sponsor’s research portfolio.

11.8 Amendments

It is the Sponsor and CI’s responsibility to classify amendments as being non-substantial or substantial. On behalf of the Sponsor and CI, CEDAR will obtain approval from the REC and HCRW/HRA for all substantial amendments to the original approved documents.

Amendments will not be implemented until all relevant regulatory organisations have granted a favourable opinion (or no objection), and local site R&D office approval has been received.

11.9 Dissemination policy

The data will be analysed and tabulated and a Final Trial Report will be prepared on completion of the trial by the CI. Full trial report can be accessed at the Sponsor’s internal network. There are no any time limits or review requirements on the publications arising from the trial. The Funder will be acknowledged in the publications arising from this trial. Participants of the trial will have a right to obtain publications arising from the trial, upon formal request. Participants of the trial will have a right to obtain their individual results, upon formal request and after the results had been published. Full trial report, anonymised participant level dataset, and statistical code for generating the results will be made publicly available.

11.9.1 Authorship eligibility guidelines and any intended use of professional writers

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. Professional medical writers will not be hired.

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