1 Title Page

CLINICAL INVESTIGATION PLAN

Title: Efficacy of electronic textile based transcutaneous nerve stimulation (TENS) in patients with knee pain due to osteoarthritis: a pilot randomised controlled trial

Reference No: OA-Tex-CIP**: Protocol Version 1.8** December 2024

Short Title: OA-Tex TENS Stimulator

IRAS number: 335669

ISRCTN Number: 94599670

SPONSOR / Number: University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, SO16 6YD / RHM RHE0001

FUNDER / Number: Medical Research Council: MR/W029421/1

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Investigation Site: University of Southampton, Southampton General Hospital, Tremona Road, Southampton SO16 6YD

External Organisation = CRO: PHARMExcel | Albany Chambers, 26 Bridge Road East, Welwyn Garden City, Herts, AL7 1HL Tel: 0203 642 6654 www.pharmexcel-cro.com

Co-Investigators:

Statistician: Professor Isabel Reading, , BSc, MSc, PhD; Director, NIHR Research Design Service (RDS) South Central, Professorial Fellow in Medical Statistics within the Faculty of Medicine, University of Southampton

Statistician / Health Economist: Professor David Scott, MA, MSc, Diploma in Health Economics, Certificate in International Business Management; Principal Research Fellow of Health Economics and Medical Statistician within Southampton Health Technology Assessments Centre, University of Southampton

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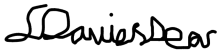
The Chief Investigator has accepted the agreed protocol and commits to conducting the trial in accordance with the approved guidelines. These guidelines include adherence to the Clinical investigation of medical devices for human subjects — Good clinical practice (BS EN ISO 14155:2020), as well as any subsequent amendments, Good Clinical Practice (GCP) guidelines, and relevant Standard Operating Procedures (SOPs) provided by the Sponsor and other regulatory requirements.

Furthermore, the Chief Investigator acknowledges that the confidential information within this document will only be used for the purpose of evaluating or conducting the clinical investigation, with prior written consent from the Sponsor. Additionally, any deviations or significant breaches of GCP outlined in the protocol will be appropriately addressed.

For and on behalf of the Trial Sponsor:		
Signature: 		Date: 07……/..10..../.2024.....
Name: Sharon Davies-Dear, University Hospital Southampton NHS Foundation Trust		
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Name: Professor Elaine Dennison, Professor of Musculoskeletal Epidemiology and Honorary Consultant in Rheumatology within Medicine at the University of Southampton		
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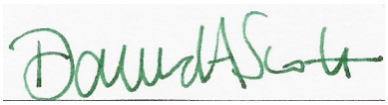
Signature: 		Date: .23..../.09..../2024.....
Name: Dr David Scott, Principal Research Fellow of Health Economics and Medical Statistician within Southampton Health Technology Assessments Centre, University of Southampton		

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List of Abbreviations

AE	Adverse Event
CI:	Chief Investigator
LCD:	Liquid Crystal Display
LED:	Light Emitting Diode
ModRUM:	Modular Resource Use Measure
OA:	Osteoarthritis
OKS:	Oxford Knee Score
OLED:	Organic Light Emitting
RCT:	Randomised Controlled Trial
TENS:	Transcutaneous Electrical Nerve Stimulation
VAS:	Visual Analog Scale
WOMAC:	The Western Ontario and McMaster Universities Arthritis Index

Summary Information:

Full title	**Efficacy of electronic textile based transcutaneous nerve stimulation (TENS) in patients with knee pain due to osteoarthritis: a pilot randomised controlled trial**
Short title	**E-Textile TENS**
Sponsor	University Hospital Southampton NHS Foundation Trust (UHSFT)
Sponsor Ref No	RHM RHE0001
Chief Investigator	Professor Elaine Dennison
Funder	Medical Research Council
Funder Ref No	MR/W029421/1
REC No	24/SC/358 IRAS ID:335669
Project Type	Clinical Validation Study (Observational Cohort)
Primary Objective	To assess the efficacy of the new wearable TENS device to reduce OA knee pain and further confirm the usability of the device at home.
Secondary Objectives	Changes in functional outcomes observed in the intervention group (TENS arm) and control group (Sham arm), Effect of using the knee wearable sleeve on knee function, health care utilisation, usability of the prototype at home over a 12 week period
Rationale	Osteoarthritis (OA) is the most common musculoskeletal condition, with painful knee OA being highly prevalent. While people with knee OA who exercise regularly experience less pain and improved physical function, pain typically reduces physical activity, which is linked to a range of adverse health events. Knee pain is traditionally managed using medication (NSAIDs/opioids), which costs the UK £195.3 million p.a.; however these medications can cause side effects. TENS is a non-pharmacological treatment that may be beneficial for pain relief, reduction of stiffness, and improvement of knee joint function. Previous research studies have highlighted a possible role for TENS in the management of painful knee OA. However, methodological concerns remain about how to use this technology optimally. Our research team has developed a wearable garment with two pairs of integrated TENS electrodes around the knee together with a TENS electronic control unit. Following laboratory and home usability studies we now wish to perform a pilot RCT to inform the design of a future trial by estimating the variability of pain reduction and functional outcomes of TENS use.
Project Design/ Classification	Observational study / Superiority Trial
Study Population	Patients with diagnosed Knee Osteoarthritis
Total No. of Sites	1 (UHSFT)
Study Duration	9 months

Data collection	Data on socio-demographic and clinical characteristics, pain, function, skin reaction, medication taken, use of assistive devices, and any adverse reaction will be collected as shown in Table 1. Medication use will be recorded at each time point, with indication. Adverse events will be recorded at each time point. Safety reporting will follow GCP guidance with suspected unexpected serious adverse reactions reported to the MHRA.
Number of Participants	80 = 2 cohorts of 40 (intervention and sham)
Primary endpoint	To evaluate efficacy of TENs on knee pain relief we will collect data on: the Visual Analog Scale, and WOMAC-pain sub-scale.
Secondary endpoints	Secondary outcomes of the study include the Oxford Knee Score, Western Ontario and McMaster Universities Arthritis Index, EuroQol-5 Dimensions-5 Levels, Modular Resource Use Measure and a list of adverse reactions.
Statistical Methods	Summary statistics, mixed-effects linear regression models.

3 Background

Osteoarthritis (OA) is the most common musculoskeletal condition, with painful knee OA being highly prevalent. While people with knee OA who exercise regularly experience less pain and improved physical function, pain typically reduces physical activity, which is linked to a range of adverse health events. Knee pain is traditionally managed using medication (NSAIDs/opioids), which costs the UK £195.3 million p.a. [1]; however, these medications can cause side effects.

TENS is a non-pharmacological treatment that may be beneficial for pain relief, reduction of stiffness, and improvement of knee joint function. Previous research studies have highlighted a possible role for TENS in the management of painful knee OA [2-6]. However, methodological concerns remain about how to use this technology optimally [7-8].

Our research team has developed a wearable garment with two pairs of integrated TENS electrodes around the knee together with a TENS electronic control unit.

Following laboratory and home usability studies we now wish to perform a pilot RCT to inform the design of a future trial by estimating the variability of pain reduction and functional outcomes of TENS use.

A description of the device = garment, electrodes, stimulator, cables etc can be found in the Investigator Brochure – document 3, with comprehensive details in Device Details – document 7.

4 Identification and description of the investigation and clinical device

4.1 Summary description of the investigational device.

TENS is a non-invasive peripheral stimulation technique that applies a safe electrical current through electrodes which are in contact with the skin. This treatment aims to reduce knee pain and therefore improve function and quality of life in patients who have knee osteoarthritis. Existing TENS machines normally use hydrogel electrodes which have a limited lifetime of 1-4 weeks thus requiring a regular change of electrodes. The medical device to be tested in this trial uses a knee sleeve garment with integrated dry electrodes that is suitable for long term use. The garment with integrated electrodes is easy to use and more cost effective for long term use. In addition, compared to the traditional TENS units which have many stimulation programmes, the TENS unit developed in this study has one programme alternating between high and low frequencies to reduce the heterogeneity and improve pain relief while simplifying the set up required and improving ease of use.

The device consists of a single leg sleeve which wraps-around the leg and zips up with a length that covers from the hip to the mid-calf to avoid the garment riding up. This garment is constructed from single-knit, 2-way stretch jersey fabric with an elasticised cuff on the lower leg opening to stabilise the garment. The elasticated

fabric provides a tight yet comfortable fit, ensuring a good contact between the skin and electrodes. A circular printed pattern around the knee on the garment helps users to correctly align the garment to the centre of the kneecap, to facilitate correct electrode placement. The garment has been graded into a range of 7 sizes, from XS to 3XL to fit a wide range of knee sizes.

The outer part of the garment fastens with a double-ended zip which begins at the mid-calf inseam, crosses over the upper thigh and finishes at the hip, supported by an adjustable, elasticised waistband. The garment has a pocket on the side to hold the TENS electronic unit; the pocket has a small hole at the bottom to allow a wire through to connect the electronic unit to the electrodes on the garment. The electrode connector has two pairs of conductive snaps with different colours (one pair is in black and the other pair is in white); the colour coding ensures that users correctly pair the electrodes on the garment.

Comprehensive details and illustrations of the complete device are included in Device Details – document 7.

4.2 The manufacturer of the investigational device

The University of Southampton (UoS) is the legal manufacturer of the investigational device and will take on responsibility for the device itself. The project team has developed a comprehensive Quality Management System (QMS) with dedicated support from IMed, a specialist regulatory consultancy company. The device will be manufactured at UoS following the QMS to ensure device safety, function, usability, and regulatory compliance. UoS will receive parts/components from approved suppliers (e.g. Conductive Transfers Ltd for printing the conductive lamination film used in electrode manufacturing, PCBway Ltd for PCB manufacturing and population for the TENS electronic control unit) who have a demonstrated capability in manufacturing the required parts of the investigational device. For example, Conductive Transfers Ltd has supplied conductive lamination film for a medical device company (e.g. Atlantic Therapeutics) who sell an electrotherapy device for strengthening pelvic floor muscles. The electrode garment will be manufactured in the lab at UoS and the TENS electronic control unit will be assembled at UoS. Device testing will be conducted at UoS to ensure quality and the safety and functional requirements, and the requirement set in the standards (e.g. IEC 60601-1).

4.3 Model Name/number including software version and accessories, permitting full identification

Each garment will have a unique serial number. Similarly, the electronic control unit will have a unique serial number (Issue1-Electronics-001 incremented for each electronic circuit. The research team will keep a record of the electronic units and garments assigned to each participant to maintain traceability of the medical device during and after the clinical investigation. Software version is Issue 1 for the RCT and is identical for all participants.

Device constituent parts:
Garment = Issue 1; Stimulator Electronics = Issue 1; Software = Issue 1.0.0
Detachable components:
Interconnecting cable model reference: Lot1-CG-Cable
Accessories:

- USB Charging cable Model: MinTENS-RCT1-USB
- Instructions for use Model: MinTENS-RCT1-IFU
- Conductive electrode gel: MinTENS-RCT1-Gel
- Plastic Bag Model: MinTENS-RCT1-Bag

4.4 How traceability shall be achieved during and after the clinical investigation, for example, by assignment of lot numbers, batch numbers, or serial numbers.

As above. All garments and units will be labelled and details recorded on a database indicating to which participants they have been allocated. Supplier batch numbers on components will also be recorded to enable fault identification / recall as appropriate.

4.5 Intended purpose of the investigational device.

The intended purpose of this device is to reduce knee pain among individuals with knee OA. The pilot study will compare pain levels between the intervention group and the sham group. Additionally, it will further confirm the usability of the device at home.

4.6 The populations and indications for which the investigational device is intended.

The intended users are people with knee pain potentially associated with knee OA.

4.7 Description of the investigational device, including materials in contact with tissues or body fluids.

The investigational device is described earlier under 'Description of the Device. It is a garment plus an associated electronic unit coupled together using an interconnecting cable between them.

Materials in contact with the skin: The inner part of the garment will be in contact with the skin, this includes the fabric, elasticated bands, electrodes and the encapsulation layer on top of the conductive tracks. Participants will be asked to ensure the skin around their knees is clean before donning the device, and a conductive electrode gel will be applied to the electrodes.

A table detailing the composition of the materials that come in contact with skin is included in the Investigator Brochure – document 3.

4.8 Summary of the necessary training and experience needed to use the investigational device based on risk assessment.

All garments and associated electronic units will have instructions that describe how to put the garment on with illustrations and how to set up the TENS treatment (i.e., intensity of TENS and duration of the session). All instructions include safety precautions and troubleshooting.

See Instructions for Use – document 10.

4.9 Description of the specific medical or surgical procedures involved in the use of the investigational device.

There are no medical or surgical procedures involved in the use of this device.

4.10 References to the IB and IFU.

As specified in this document, further details and information as appropriate are included in the Investigator Brochure – document 3 and Instruction for Use – document 10.

5 Justification for the design of the clinical investigation

5.1 An evaluation of the results of the relevant pre-clinical testing/assessment and prior clinical investigations, carried out to justify the use of the investigational device in human subjects.

Based on results from the initial lab tests and subsequent home usability testing carried out prior to this RCT there was an average reduction in pain of 54.2%. Thus this pilot trial with further participants is justified.

5.2 An evaluation of clinical data that are relevant to the proposed clinical investigation

Literature shows TENS is effective in reducing pain as described in document 3.

5.3 A description of the clinical development stage.

This investigation is at the pre-market stage of clinical development (pilot study).

6 Risks and benefits of the investigational device and clinical investigation

6.1 Anticipated clinical benefits

Reduction in pain, stiffness, medication; improvement of knee functions and quality of life.

6.2 Anticipated adverse device effects associated with device

There are no anticipated adverse effects but there is a potential for low level side effects as described in section 7.5.

6.3 Risks associated with participation in the clinical investigation

All risks have been assessed in the risk and hazard analysis (DHF-032 and DHF-031). All other risks identified are low other than the medium risk below:

6.4 Residual risks associated with study procedures

Skin irritation may take time to disappear. This depends on the individual as to whether, or when, it occurs, and typically disappears within a few days.

6.5 Possible interactions with concomitant medical treatments

There is a theoretical risk of interference with a cardiac pacemaker - patients with implanted devices are excluded from the trial.

6.6 Steps that will be taken to control or mitigate the risks.

Participants are advised to discontinue treatment if any skin irritation occurs and consult the team.

Detailed user instructions have been developed with input from the end users. Home usability feedback has been integrated to improve the device usability. The study will be conducted following the procedure set out in the MHRA/HRA documentations.

6.7 Risk-to-benefit rationale

This is a low risk device and potential benefits outweigh risks by reducing pain and improving quality of life.

7 Objectives and hypotheses of the clinical investigation

7.1 The purpose of the clinical investigation, claims for clinical performance, effectiveness or safety of the investigational device that are to be verified.

Pain relief, reduction in stiffness, further highlight efficacy of the device for pain relief. No safety aspects will be verified.

7.2 Objectives, primary and secondary – superiority.

a) Primary objective

The main objective of the study is to assess the efficacy of the new wearable TENS device to reduce OA knee pain and further confirm the usability of the device at home over a longer period.

b) Secondary objectives

As secondary objectives the trial will evaluate:

- Changes in functional outcomes observed in the intervention group (TENS arm) and control group (Sham arm),
- Effect of using the knee wearable sleeve on health care utilization, and
- Usability of the prototype over a longer (12 week) period.

7.3 Scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, where applicable.

Not applicable.

7.4 Primary and secondary hypotheses, if applicable.

- The e-textile wearable TENS is able to reduce pain for people with knee OA.
- The device is suitable for home use in terms of user comfort, ease of use, and safety (e.g. no adverse events).
- The device may improve the functions measured via the Oxford Knee Score, Western Ontario and McMaster Universities Arthritis Index (WOMAC), EuroQol-5 Dimensions-5 Levels (ED-5Q – 5L), and Modular Resource Use Measure (ModRUM).

7.5 Risks and anticipated adverse device effects that are to be assessed.

Risk: Minor skin irritation. No adverse device effects anticipated.

8 Design of the trial investigation

8.1 Description of the design type of clinical investigation to be performed (e.g. randomised, blinded or open-label, parallel groups or crossover, multicentre, international) the control group, (e.g. comparative claim and reversible treatment of a chronic state) and the comparator with rationale and justification for the choice. Absence of control(s) shall be justified.

This is a double-blind 2-arm parallel group randomised controlled trial of 80 people comparing the efficacy on knee pain relief in patients with medically-diagnosed knee osteoarthritis. 80 people will be randomly allocated in a 1:1 ratio to the intervention arm (an active TENS group) or to the sham (control) group who will have TENS programmed to switch off automatically after an initial 4 minutes of stimulation.

8.2 Description of the measures to be taken to minimize or avoid bias, such as randomisation, concealment of allocation, blinding/masking, and management of potential confounding factors.

Participants will be randomly allocated to treatment or control (sham treatment) in a 1:1 ratio according to a randomisation schedule held by the statistician. The schedule will be based on a block randomisation with varying block sizes to avoid imbalance in treatment allocation with respect to known and unknown confounders, and to avoid any potential for anticipation of future participants' treatment allocation.

8.3 Primary and secondary endpoints, with rationale for their selection and measurement. If applicable, composite endpoints, with rationale for their selection and measurement.

To evaluate efficacy of TENs on knee pain relief we will collect data on: knee pain recorded on a Visual Analog Scale, and WOMAC-pain sub-scale.

Secondary outcomes of the study include the Oxford Knee Score, Western Ontario and McMaster Universities Arthritis Index, EuroQol-5 Dimensions-5 Levels, Modular Resource Use Measure and a list of adverse reactions.

A detailed list of the outcome measures is included in the Investigator Brochure – document 3.

8.4 Methods and timing for assessing, recording, and analysing variables.

Clinical outcomes will be reported on paper questionnaires. We will collect baseline information prior to supply for the intervention/sham device. Follow up data will be collected at 1, 4, 8 and 12-weeks after supply of the wearable device. Phone calls to supplement data collection at weeks 1, 4 and 8 will be employed as appropriate.

Data from paper questionnaires will be doubled entered onto a database at the MRC LEC and then transferred to the statistician for analysis.

8.5 Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration.

Not applicable.

8.6 Any procedures for the replacement of subjects.

Not applicable

8.7 Investigation sites: number, location, and, if appropriate, differences in investigation site environment.

The study will be conducted at Southampton General Hospital, a large tertiary referral hospital in the United Kingdom, the E-Textile Innovation Laboratory at University of Southampton, Winchester School of Art and within the participants home setting.

8.8 Definition of completion of the clinical investigation (see 8.1).

The completion of the clinical investigation is defined by the conclusion of home use for 12 weeks and the return of the garment/device to the investigation site at the end of that period.

9 Trial Participants

9.1 Inclusion criteria for subject selection.

People will be able to take part in the study if they comply with the following:

- Adults between 45 and 75 years of age,
- Diagnosed with knee OA according to American College of Rheumatology criteria,
- Pain score ranging from 3 to 7 on the Visual Analog Scale (VAS)
- Participants will not have prior experience of TENS or other electrotherapy (e.g. interferential therapy)
- Able to stand up unaided, and
- Willing and able to give informed consent.

9.2 Exclusion criteria for subject selection.

- Prior major knee surgery (i.e., partial or total knee arthroplasty),
- Anticipated surgery during the study (no anticipated surgery during the 12 weeks of the study),
- Skin sensitivities and sensation problems,
- Uncontrolled epilepsy,
- Those who are pregnant; planning to become pregnant or are breastfeeding,
- An active device implant (e.g. pacemaker user),
- A stent in the lower limb.
- Inability to understand English
- Intra-articular injection to the knee

Oral medication for knee pain (paracetamol, NSAIDS, opiate based medication) will be allowed but it will be recorded.

9.3 Criteria and procedures for subject withdrawal or lost to follow-up

9.3.1 When and how to withdraw a subject from the clinical investigation or stop the use of the investigational device

We anticipate participants will be enrolled in the study until the end of the study period (12 weeks home use of the garment with wired TENS).

Participants may withdraw from the study at any time of their own volition. For participants who wish to withdraw, we will record the reason (e.g. no improvement in their pain relief, increasing pain when using TENS, no reason provided, adverse events)

Participants can withdraw from the study, but data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal.

9.3.2 Documentation of efforts to be made to trace subjects that are lost to follow-up and possible reasons

Not applicable

9.3.3 Whether and how subjects are to be replaced.

We will not replace subjects.

9.4 Point of enrolment.

There are several recruitment pathways to this study. Patients who attend a knee orthopaedic clinic will be given a patient information sheet about the study by NHS staff, or the research nurse who may be in attendance to answer any questions. NHS staff may also screen current waiting lists for knee replacement surgery and forward information about the study to potentially eligible patients. Those individuals who have

read the PIS and are interested in the trial will be invited to contact the research team by phone or e-mail. GP practices may also identify patients who appear eligible with an invitation letter to take part in the trial, and a leaflet with basic information on the study and contact details. Those who contact us will be e-mailed the patient information sheet and consent form.

People interested in the study who contact the research team will be asked some questions to determine if they are likely to comply with the eligibility criteria.

Participants will then be invited to attend a formal screen clinic where an informed consent form will be completed and participants will be enrolled in the study.

9.5 Point of randomisation

In person visit when the device is allocated.

9.6 Total expected duration of the clinical investigation.

12 weeks. Rolling recruitment over 5 month period, garment fabrication and fitting, 12 weeks home use, return of device. Total for study as a whole 9 months.

10 Study Procedures

10.1 Description of all the clinical investigation-related procedures that subjects undergo during the clinical investigation including any deviation from normal clinical practice.

A screening clinic visit will take place after an initial phone eligibility check to ensure that all participants have been diagnosed with knee OA according to the American College of Rheumatology criteria [13]**.**

People who screen positive and consent to be part of the trial will be asked to attend three visits in person, complete follow-up questionnaires, and will receive a maximum of 4 phone calls over a period of approximately 3 months. The visits in person will take place in facilities within the University of Southampton, either at Winchester School of Art or Southampton General Hospital, on a mutually convenient date (daytime or exceptionally in the evenings).

In the first in person visit, a research nurse will take body measurements and will ask participants to try the standard size of TENS garment, which is closest to their measured size. After that, when the garment is ready, participants will visit the lab at Winchester School of Art to collect a garment with instructions and will receive guidance on what they need to do at home. They will be instructed to use the garment at least 5 out of the 7 days for 12 consecutive weeks. People will choose whether they prefer to undergo daily TENS in one session of 30 to 60 minutes or two separate sessions with a duration of 30 minutes each.. Participants will be given either an intervention or sham device – only the member of the research team distributing the garment at this point will be aware of which has been assigned.

We will collect information at baseline (on supply of wearable sleeve) and at 1, 4, 8 and 12-weeks follow-up of supply of the wearable device. Data collection will be using hard copies of questionnaires supplemented by phone calls at weeks 1, 4 and 8 as needed. Hard copies of all questionnaires will be provided at baseline together with a diary to record daily use. After 12 weeks we will schedule a final session in the lab in which participants will return the garment to the lab and provide their feedback.

10.2 Activities performed by sponsor representatives (excluding monitoring).

Not applicable.

10.3 Any known or foreseeable factors that can compromise the outcome of the clinical investigation or the interpretation of results.

None

10.4 The methods for addressing these factors in the clinical investigation, for example, by subject selection, clinical investigation design, such as stratified randomisation, or by statistical analysis shall be described.

Not applicable

10.5 The follow-up period during the clinical investigation shall permit the demonstration of clinical performance, effectiveness or safety over a period of time sufficient to represent a realistic test of the investigational device and allow any risks associated with adverse device effects to be identified and assessed.

The 12 week follow-up period during the clinical investigation shall permit the demonstration of clinical performance, effectiveness or safety over a period of time sufficient to represent a realistic test of the investigational device and allow any risks associated with adverse device effects to be identified and assessed.

Data on socio-demographic and clinical characteristics, pain, function, skin reaction, medication taken, use of assistive devices, and any adverse reaction will be collected as shown in Table 1. Medication use will be recorded at each time point, with indication. Adverse events will be recorded at each time point. Safety reporting will follow GCP guidance with suspected unexpected serious adverse events reported to the MHRA. An independent data monitoring committee will be established to provide overall governance of the trial. Monitoring of the trial will be undertaken by an independent commercial organisation to enable sponsorship by the University Hospital Southampton NHS Foundation Trust.

Table 1. Timeline for data collection process

	Baseline	**1-week Follow Up (FU)**	**4-week FU**	**8-week FU**	**12-week FU**
Socio-demographic characteristics	x				
Clinical characteristics	x				
Analgesia to manage knee pain	x	x	x	x	x
Visual Analog Scale	x	x	x	x	x
Adverse effects		x	x	x	x
Western Ontario and McMaster Universities Arthritis Index	x				x
Oxford Knee Score	x		x	x	x
EuroQol-5 Dimensions-5 Levels	x		x	x	x
Modular Resource-Use Measure	x		x	x	x
Questions related to usability of the garment					x

10.6 What specific medical care is appropriate to be provided for the subjects after the clinical investigation has been completed

Not applicable

10.7 Recommended follow-up for the subjects after the clinical investigation has been completed

Not applicable

10.8 Final disposition or potential future use of samples obtained from subjects, if applicable.

Not applicable

11 Monitoring plan

This study will be monitored by PHARMExcel and may be subject to monitoring and audit by University Hospital Southampton NHS Foundation Trust, under their remit as sponsor and other regulatory bodies to ensure adherence to ICH GCP, UK Policy Framework for Health and Social Care Research, applicable contracts/agreements and national regulations. All study related documents will be made available on request for monitoring and audit by UHS, the relevant REC or other licensing bodies. A CRO, PHARMExcel will monitor the clinical study.

12 Statistical Design and analysis

12.1 Analysis population (e.g. intention-to-treat, per-protocol, as-treated) and procedures that take into account all the data.

Analysis will be on the intention-to-treat population. Levels of missing data will be monitored and we will consider whether data are missing not at random. Multiple imputation methods will be considered if <10% of the primary outcome data are missing (at random).

12.2 Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints.

Descriptive statistics of baseline clinical data will be presented by treatment arm (ITT).

Clinical data analysis: Pain score, motor function, safety and quality of life data will be summarised and will be reported according to CONSORT: extension to pilot and feasibility trials guidelines.

Changes in clinical outcomes from baseline will be summarised within treatment (ITT)

Process and feasibility outcomes such as recruitment and retention rate will be presented with 95% confidence intervals; adverse events (safety data) will be presented by treatment arm.

12.3 Analytical procedures including measures of precision such as confidence intervals, if applicable.

Changes in clinical scores from baseline will be summarized within treatment arm with 95% confidence intervals.

The primary analysis will compare the primary outcome measures (knee pain) in mixed-effects linear regression models to account for repeated measures from baseline to 12-weeks follow-up, with treatment arm as a fixed effect along with other potential important baseline factors such as socio-demographic and clinical characteristics. Recruitment and retention rates will be summarized overall and presented with 95% confidence intervals.

12.4 The significance level and the power of primary endpoint(s) and the overall statistical testing strategy, if applicable.

A significance level of 5% and power of 80% will be used.

12.5 Sample size calculation and justification taking into account:

12.5.1 All relevant clinical data on outcome variable and effect size, if applicable

These will be explored in this study.

12.5.2 Assumptions of expected outcomes across treatment groups, if applicable.

Not applicable.

12.5.3 Adjustments due to any pre-planned interim analyses, if applicable

Not applicable. There will be no interim analyses.

12.5.4 Detectable effect size and non-inferiority margin, which shall be smaller than the detectable effect size and justified with reference to the effect of the comparator, if applicable;

Non-inferiority margin is not applicable. Detectable effect size is a standardized effect size of 0.69.

12.5.5 Randomisation allocation ratio

Ratio = 1:1

12.5.6 Expected drop-out rate, such as withdrawal, lost to follow-up, death (unless death is an endpoint).

80 participants will be recruited into the study, 40 to each treatment arm. We will recruit 80 participants (40 per trial arm) to achieve a sample size of N=70, 35 in each treatment arm, allowing a 12.5% drop-out rate. We anticipate that our drop -out rate will be lower than our original, conservative, estimate of 25%. However,

if we do not achieve a sample of N=70 (35 in each treatment arm) complete data by recruiting 80 participants, we will continue to recruit until we have achieved our planned N=70 participants with complete data.

12.5.7 All the statistical parameters and methods used to calculate sample size or the non-inferiority margin shall be clearly provided.

We will assess the efficacy of the new TENS wearable device to reduce OA knee pain. A sample size of complete data of N=70 (35 in each treatment arm) will allow us to detect a standardized effect size of 0.69, with 5% significance level and 80% power.

Additionally, our sample size calculation has been calculated assuming this is a pilot randomised controlled trial that will gather data to inform a future definitive trial. Teare et al [15] conducted an extensive simulation study considering the precision gained per additional 5 patients in the estimation of the variability of a continuous normally distributed outcome. Their work demonstrated that a total sample size of 70 is required to estimate the variability of a continuous outcome to have adequate data to inform the sample size for a fully powered definitive RCT, with a sample size above 70 yielding little additional precision. Thus, this sample size will allow us to estimate the variability of the primary outcome to inform a future definitive RCT.

12.6 Rationale for the number of procedures to be performed by a single user as part of the learning curve and how these data are to be analysed, if applicable.

Not applicable.

12.7 Pass/fail criteria to be applied to the results of the clinical investigation.

Not applicable

12.8 The provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds, where applicable.

Not applicable

12.9 Management of bias and, when randomisation, matching, or blinding are applied, plan for assessment of success thereof.

We will compare baseline characteristics as an assessment of the success of the randomisation. No formal statistical tests will be used to compare baseline characteristics between the randomised treatment groups.

12.10 Management of potential confounding factors (e.g. adjustment, stratification, or stratified randomisation).

Potential confounding factors such as baseline clinical characteristics will be adjusted for as fixed effects in mixed-effects linear regression models.

12.11 Description of procedures for multiplicity control and adjustment of error probabilities, if applicable.

Not applicable.

12.12 Specification of subgroups for analysis, if applicable, or if response to treatment is expected to be different in these groups.

Not applicable.

12.13 Management, justification, and documentation of missing, unused or spurious data, including drop-outs.

All efforts will be made to collect complete data. An assessment on the amount of missing data, especially in the primary outcome, will be made. We will consider whether data are missing not at random. Multiple imputation methods will be considered if <10% of the primary outcome data are missing (at random).

12.14 Exploratory analysis and sensitivity analysis (e.g. to explore robustness of results of primary and secondary analysis with respect to different methods used for handling missing data), if applicable.

Not applicable

12.15 Procedures for reporting any deviation(s) from the original statistical analysis plan.

These will be reported according to CONSORT guidelines.

12.16 For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites.

Not applicable

12.17 A strategy for pooling data, if applicable.

Not applicable.

13 Data Management

13.1 Methods (e.g. CRF) for data entry and collection.

The questionnaires will be completed in paper format. They will then be double data entered by Data Processing Assistants at the MRC LEC. Monitoring by PHARMExcel will occur throughout the study to ensure that issues and data queries are dealt with promptly, details will be contained in a study specific monitoring plan.

13.2 Procedures used for CRF tracking, data review, database cleaning, and issuing and resolving data queries. Specifically, timely, and reliable processes for recording data and rectifying errors and omissions, medical coding uniformity, and reconciliation, if applicable, are necessary to ensure delivery of a quality database and the achievement of the clinical investigation objectives through the implementation of the planned analysis.

As above.

13.3 Procedures for verification, validation, and securing of electronic clinical data systems, if applicable.

Not applicable.

13.4 Procedures to maintain and protect subject privacy.

All investigators and study staff will comply with the Data Protection Act 2018 requirements for the collection, storage, processing and disclosure of personal information and will uphold the Act's principles. Study documents (paper and electronic) will be collected and retained in accordance with the Data Protection Act 2018 in a secure location during and after the study has finished.

13.5 Methods for database locking at the start of the analysis and storage upon completion of the clinical investigation.

All data collected will be stored on a University computer protected by a password. Only researchers involved in data collection and the statistician in charge of analysing the data will be able to access this information.

Personal details (i.e., name, surname, e-mail address and phone number) will be kept under a protected password document on a secure server and separately from the rest of the data collected during the trial. Each participant will have a unique identification number that will ensure that the information is anonymous.

13.6 Procedures for data retention.

Data retention will be in line with University Hospital Southampton NHS Foundation Trust and the University of Southampton procedures.

13.7 Specified retention period.

All study documents will be archived securely for a minimum of 15 years in line with the Sponsor's policy.

13.8 Other aspects of clinical quality assurance, as appropriate

Not applicable.

14 Amendments to the CIP

Any amendments to the CIP shall be approved by the Chief Investigator and the Sponsor and authorised bodies as appropriate. Amendment number / updated version number etc, will be recorded on all documentation.

15 Deviations from clinical investigation plan

15.1 Statement specifying that the investigator is not allowed to deviate from the CIP, except as specified in 5.6.4 c).

Deviations from the protocol, which are found to frequently recur, are not acceptable and will require immediate action by the sponsor. Frequent non-compliances could potentially be classified as a serious breach.

15.2 Procedures for recording, reporting, and analysing CIP deviations.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

15.3 Notification requirements and time frames.

As above

15.4 Corrective and preventive actions and principal investigator disqualification criteria.

See compliance.

16 Device accountability

16.1 Description of the procedures for the accountability of investigational devices as specified in 7.9;

The authorised Research Team Member will keep records documenting the following:

- name of person who received, used, and returned the device;
- the date of receipt, identification, and quantity of each investigational device (batch number/serial number or unique code);
- the date or dates of use; subject identification; date on which the investigational device was returned from subject,
- the date of return of unused or malfunctioning investigational devices, if applicable;

16.2 Procedures and particular materials and instructions for the safe return of investigational devices, including those that are potentially hazardous.

The device will be returned to the Research Team during an in person session at the end of the 12 week trial period.

17 Statements of compliance

17.1 Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki

The study will be conducted in accordance with the principles of the good clinical practice GCP. A favourable ethical opinion will be obtained from the appropriate Research Ethics Committee and local NHS R&D (Research & Development) prior to commencement of the study.

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body, Health Research Authority (HRA), main research ethics committee (REC) and that local permission has been obtained prior to any subject recruitment.

All substantial amendments and non-substantial amendments (as determined by the sponsor) will not be implemented until HRA/REC have provided the relevant authorisations. The NHS R&D departments will also be informed of any substantial amendments and non-substantial amendments. Relevant approvals must be obtained before any substantial amendment and non-substantial amendments may be implemented at sites.

All correspondence with the HRA and the REC will be retained in the Trial Master File and the Investigator Site File (maintained by the site).

Within 90 days after the end of the research project, the CI/Sponsor will ensure that the HRA and the main REC are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the main REC within 1 year after the end of the trial.

The project will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives; and the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the UK Policy Framework for Health & Social Care Research.

17.2 Statement specifying compliance with this document and any regional or national regulations, as appropriate.

This document has been compiled in accordance with ISO 14155:2020

17.3 Statement specifying that the clinical investigation shall not begin until the required approval/favourable opinion from the EC and regulatory authority have been obtained, if appropriate.

The clinical investigation will not begin until approval from MHRA has been obtained.

17.4 Statement specifying that any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

Any additional requirements imposed by the MHRA will be followed as appropriate.

17.5 Statement specifying the type of insurance that shall be provided for subjects, if appropriate.

The sponsor of the trial is University Hospital Southampton NHS Foundation Trust. For NHS sponsored research HSG (96) 48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

17.6 Statement addressing the financing of the clinical investigation including a description of the agreement between the sponsor and investigation site(s), and where applicable with the investigator(s) if not addressed in a separate agreement.

This research project is being funded by the Medical Research Council (MRC) Funder Number**:** MR/W029421/1. A High Level Agreement exists between the University of Southampton and University Hospital Southampton NHS Foundation Trust.

18 Informed consent process

18.1 Description of the general process for obtaining informed consent, including the process for providing subjects with new information and process for incentives for subjects, as needed.

No data will be collected from patients before consent has been obtained. The patient will be provided with a Participant Information Sheet in person or by email. A member of the research team will explain the study to the patient either in person or by telephone or video call, providing all the relevant information and allowing the patient to ask questions. After allowing the patient enough time for them to feel that they have been able to read the form and consider the study appropriately, with time to discuss with any next of kin if they wish, the researcher will answer any additional questions and obtain written consent.

18.2 Description of the informed consent process in circumstances where the subject is unable to give it; in the case of emergency treatment, the items specified in 5.8.3.4 shall be included.

Subjects who are unable to give informed consent will not be included in the study.

19 Adverse events, adverse device effects, and device deficiencies

19.1 Definitions of adverse events and adverse device effects.

See table below

19.2 Definition of device deficiencies.

See table below

19.3 Definitions of serious adverse events including serious health threat and serious adverse device effects and, where appropriate, unanticipated serious adverse device effects.

The terms and definitions presented below are covered by the ISO standard 14155:2020 “Clinical investigation for medical devices for human subjects: good clinical practice”

Investigational medical device	Medical device being assessed for safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device. This definition includes events related to: • the investigational device or the comparator. • the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.
Serious Adverse Event (SAE)	Adverse event that: a) led to a death, injury or permanent impairment to a body structure or a body function. b) led to a serious deterioration in health of the subject, that either resulted in: - a life-threatening illness or injury, or - a permanent impairment of a body structure or a body function, or - in-patient hospitalization or prolongation of existing hospitalization, or - in medical or surgical intervention to prevent life threatening illness c) led to foetal distress, foetal death or a congenital abnormality or birth defect. Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Device deficiency	Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

19.4 List of non-reportable adverse events, if applicable, including rationale.

Not applicable

19.5 Time period in which the principal investigator shall report all adverse events and device deficiencies to the sponsor and, where appropriate, to ECs and the regulatory authority.

Upon being made aware of a SADE/USADE, the CI will notify the Sponsor (researchsafety@uhs.nhs.uk) and the CRO (www.pharmexcel-cro.com) within 24 hours, with subsequent notification of the MHRA and REC within 15 days of completion of the SADE report.

19.6 Details of the process for reporting adverse events.

Any adverse event reported by participants or observed by the investigators involved in the study will be screened by the Research Team in the first instance. If the report is deemed an adverse event (e.g. user error), it will be recorded using an adverse events form which will be sent to the Monitor (PHARMExcel) who will adjudicate and USADEs will be reported to the MHRA and the sponsor. All staff will be GCP trained. A data monitoring committee will provide overall oversight.

When an unacceptable risk to participants' health and safety is identified the medical device will be recalled following the below procedure:

1. Participant communication: If a device fault poses an unacceptable risk, participants will receive communication explaining the recall reason. They will also be provided with a contact person (usually the project PI or clinical lead) to address any concerns or discuss the matter.
2. Return process: Participants will receive a postal address to return the faulty device and postage costs will be reimbursed.
3. Analysis and Documentation: The returned devices will undergo analysis, and the findings will be thoroughly documented.
4. Stakeholder engagement: Depending on the reason to recall the device, relevant stakeholders (such as material suppliers or PCB manufacturers) will be informed of the findings. A mitigation plan will be devised and implemented.
5. Further investigation will occur to identify the root cause of the issue, and corrective actions will be taken to prevent similar problems in the future.

The CI or Sponsor may take urgent safety measures to ensure the safety and protection of trial participants from any immediate hazard to their health and safety. The measures may be taken without prior authorisation from the MHRA or REC. However, the CI will ensure all relevant parties (Sponsor, REC and MHRA) are notified of the changes within 3 days in writing detailing the reasons for the urgent safety measures and the plan for further action.

19.7 Details of the process for reporting device deficiencies.

Any device deficiencies observed by participants should be reported immediately to a member of the Research Team – contact details are included in IFU and on device labels.

19.8 List of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation, or treatment.

Some skin irritation is a foreseeable adverse event. Use of the device should be stopped for 24 hours in the first instance to allow for recovery. If a serious irritation arises, use of the device should be discontinued. No treatment is prescribed, but a topical lotion can be applied as appropriate. There are no other anticipated adverse device effects.

19.9 Emergency contact details for reporting serious adverse events and serious adverse device effects.

Emergency contact details are included in IFU.

19.10 Information regarding the DMC, if established.

A Data Monitoring Committee will be convened.

20 Suspension or premature termination of the clinical investigation

20.1 Criteria and arrangements for suspension or premature termination of the whole clinical investigation or of the clinical investigation in one or more investigation sites.

The only criteria for suspension or premature termination of the whole clinical investigation would be a major fault arising in all the devices allocated to participants. This is not anticipated, but should such a thing occur all devices would be recalled from participants and the trial would be suspended in the first instance to enable assessment / remedy of any such fault.

20.2 Criteria for access to and breaking the blinding/masking code in the case of suspension or premature termination of the clinical investigation, if the clinical investigation involves a blinding/masking technique.

The study statistician will create the randomisation schedule and a member of the Research Team will hold a copy in case of a need to break the blinding.

20.3 Requirements for subject follow-up and continued care.

After the completion of the 12 weeks study there will be no further subject follow-up or continued care.

21 Publication policy

21.1 Statement that the clinical investigation will be registered in a publicly accessible database (see 5.4).

In accordance with the Declaration of Helsinki, a description of the clinical investigation shall be registered in a publicly accessible database before the start of recruitment activities and the content shall be updated throughout the conduct of the clinical investigation and the results, available publicly, entered at completion of the clinical investigation.

21.2 Statement indicating that the results of the clinical investigation will be made publicly available.

As above, and participants will have the option to request a summary of the results on publication.

21.3 Statement indicating the conditions and timeframes under which the results of the clinical investigation will be offered for publication including the role of the sponsor and criteria for authorship.

After full analysis of the results of the clinical investigation the data will be published in peer reviewed manuscripts authored by the Principal, co-investigators and research staff in appropriate scientific journals. The role of the sponsor, funder and affiliated institutions shall be acknowledged in all such publications.

Amendment Number	CIP version number	Date issued	Author(s) of changes	Details of changes made
	1.8	December 2024	KY/JT/LR	All previous versions checked and incorporated.

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