

Study Protocol

FULL TITLE: Feasibility of developing personalised treatment pathways for relief of plantar heel pain using a sequential multiple assignment randomised trial (SMART) study design

SHORT TITLE: HeEL Pain Pathways (HELPP)

Version 3.0 (13/03/2025)

Canolfan ar gyfer Gwerthuso, Asesu Dyfeisiau ac Ymchwil Gofal Iechyd
CEDAR
Centre for Healthcare Evaluation, Device Assessment and Research

This protocol has regard for the HRA guidance and order of content

Administrative information

Full title of the study	Feasibility of developing personalised treatment pathways for relief of plantar heel pain using a sequential multiple assignment randomised trial (SMART) study design.
Short study title / acronym	HeEL Pain Pathways (HELPP)
Protocol version number and date	Version 3.0 (13/03/2025)
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Study Coordination Centre	Centre for Healthcare Evaluation, Device Assessment and Research (CEDAR) Tel. 02921 844771
CEDAR project reference	CED306
CEDAR project web page	https://cedar.nhs.wales/our-work/clinical-research/helpp/

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Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in Good Clinical Practice guidelines, the Sponsor's (and any other relevant) standard operating procedures, and other regulatory requirements as amended.

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 clinical investigation without the prior written consent of the Sponsor.

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

For and on behalf of the Study Sponsor:



Date:
8/07/2024

Signature:

.....

Name (please print):

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Position: Research Governance Manager

Chief Investigator:

Signature:



Date:
13/3/2025

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List of abbreviations

AE	Adverse Event
BMI	Body Mass Index
CAVUHB	Cardiff and Vale University Health Board
CEDAR	Centre for Healthcare Evaluation Device Assessment and Research
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRI	Cardiff Royal Infirmary
EQ-5D-5L	[An instrument to describe and value health]
ESWT	Extracorporeal ShockWave Therapy
FFI-R	Foot Function Index - Revised
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HCRW	Health and Care Research Wales
HELPP	HeEL Pain Pathways
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
JRO	Joint Research Office (Cardiff University & CAVUHB)
MHRA	Medicines and Healthcare products Regulatory Agency
MSK	Musculoskeletal
NHS	National Health Service
PAP	Project Advisory Panel
PARIS	PAtient Record Information System
PID	Personal/Patient Identifiable Data
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PROM	Patient Reported Outcome Measure
RDCS	Research Design and Conduct Service
REC	Research Ethics Committee
RfPPB	Research for Public and Patient Benefit
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SMART	Sequential Multiple Assignment Randomised Trial
SMG	Study Management Group
TMF	Trial Master File
VAS	Visual Analogue Scale

Study summary

<table>
<tr><td>Study title</td><td>Feasibility of developing personalised treatment pathways for relief of plantar heel pain using a sequential multiple assignment randomised trial (SMART) study design</td></tr>
<tr><td>Short title</td><td>HeEL Pain Pathways (HELPP)</td></tr>
<tr><td>Clinical phase</td><td>Feasibility study</td></tr>
<tr><td>Study design</td><td>Single centre feasibility SMART (sequential multiple assignment randomised trial)</td></tr>
<tr><td>Study participants</td><td>The study population is adults (aged 18 years or more) who are referred to the podiatry department because of persistent heel pain. These include those patients with suspected plantar fasciitis.</td></tr>
<tr><td>Planned sample size</td><td>50 participants</td></tr>
<tr><td>Adaptive interventions and component treatments</td><td>
<table>
<tr><th></th><th>1st line treatment</th><th>Status at end of 1st line treatment</th><th>2nd line treatment</th><th>Outcome subgroups*</th></tr>
<tr><td rowspan="2">1</td><td rowspan="2">Virtual consultation</td><td>Responder</td><td>No further treatment</td><td rowspan="2">A+B</td></tr>
<tr><td>Non-responder</td><td>Orthotics</td></tr>
<tr><td rowspan="2">2</td><td rowspan="2">Virtual consultation</td><td>Responder</td><td>No further treatment</td><td rowspan="2">A+C</td></tr>
<tr><td>Non-responder</td><td>Shockwave therapy</td></tr>
<tr><td rowspan="2">3</td><td rowspan="2">Self-help video</td><td>Responder</td><td>No further treatment</td><td rowspan="2">D+E</td></tr>
<tr><td>Non-responder</td><td>Orthotics</td></tr>
<tr><td rowspan="2">4</td><td rowspan="2">Self-help video</td><td>Responder</td><td>No further treatment</td><td rowspan="2">D+F</td></tr>
<tr><td>Non-responder</td><td>Shockwave therapy</td></tr>
</table>
*see study flow chart
</td></tr>
<tr><td>Follow up duration</td><td>To 6 months post-recruitment</td></tr>
<tr><td>Planned study periods</td><td>Study set up: 5 months
Recruitment: 8 months
Completion of participant follow-up: 6 months
Analysis and reporting: 5 months</td></tr>
<tr><td>Methods of analysis</td><td>This feasibility study will determine whether a personalised treatment pathway (adaptive intervention) for people with heel pain can be delivered by the podiatry department, including whether enough people can be recruited within the remit of the study. Qualitative interviews and focus groups will be carried out with participants and staff, and thematic analysis will be used to summarise findings. Quantitative data will be collected clinically in a Case Report Form (CRF), and from Patient Reported Outcome Measures (PROMs). Outcome measurement data will be used only to estimate the parameters required to design a definitive trial, and will not be used to determine comparative effectiveness. Progression criteria will inform the decision whether or not to proceed to a full-scale trial.</td></tr>
<tr><td>Objectives</td><td>The primary objectives of this feasibility study are to assess the:
Feasibility of recruitment
Fidelity of clinical delivery of the correct treatment at the correct stage
Appropriateness of tailoring criteria and its threshold
Acceptability of adaptive intervention pathways amongst patients
Acceptability of adaptive intervention pathways amongst staff
Feasibility of retention</td></tr>
</table>

	The secondary objectives of this feasibility study are to assess the: • Estimated effect size and variance • Acceptability of outcome measures and data collection tools • Feasibility of collecting health service resource use data • Feasibility of long-term follow-up • Feasibility of scaling-up.

Funding and Support in kind

Funder	Financial and non-financial support given
Health and Care Research Wales	£195,131

Role of study sponsor and funder

The sponsor of this study is Cardiff and Vale University Health Board (CAVUHB). It is the role of the sponsor to confirm that there are proper arrangements to initiate, manage, monitor, and finance a study. The sponsor will also host the study within the single site at Cardiff Royal Infirmary (CRI), fulfilling this role according to the principles of Good Clinical Practice (GCP). CAVUHB will retain all Sponsor responsibilities, but many of these responsibilities will be delegated as per study agreements and delegation logs.

The sponsor will not play a role in the study design, conduct, data analysis and interpretation, manuscript writing, or the dissemination of results; this will be the responsibility of the Chief Investigator (CI).

The sponsor has responsibility for overall oversight of the study. The role of the Sponsor is to ensure the study is run safely and effectively by requiring the following:

- Proportionate peer review
- Provision of all appropriate, valid supporting documentation at the point of application
- Clear definition of roles and responsibilities of organisations and individuals, signed off prior to the study commencing
- Appropriate level of monitoring and audit
- A risk assessment process to identify any potential risks to the organisation or the health, safety, and well-being of researchers and research participants
- Involvement of patients and/or the public in study design, where appropriate
- The CI's suitability to fulfil their role, through relevant experience and appropriate training
- Dissemination of study findings in an appropriate manner.

The Sponsor, through their Research and Development department, has a veto on overall approval for the study.

Dr Nia Jones (NJ) is an employee of the sponsor organisation and is the CI of this study. She will be responsible for managing the day-to-day clinical work including patient recruitment, medical history taking and study eligibility assessment, patient consent, data recording, adverse event (AE) management and recording.

Caroline Privett (CP; Trial Manager, CAVUHB) and Ruth Louise Poole (RLP; Study Co-ordinator, CEDAR, CAVUHB) will be responsible for management of the study on a day-to-day basis including governance, documentation, data collection and monitoring, data analysis, report writing, and financial management. Dr Rhys Morris (RM; CEDAR Director, CAVUHB) will have overall responsibility for CEDAR's component of the study.

If any of the core Podiatry research team leave, they will be replaced with a new study team member of suitable grade and experience. Members of study oversight groups and Patient and Public Involvement (PPI) partners will be involved in reviewing drafts of the manuscripts, abstracts, and other publications arising from the study.

The funder's role is to finance the study and to receive a study report. The study will be run independently of any commercial companies or device manufacturers.

Study oversight

The nature of this feasibility study and the low risk associated with the use of established National Health Service (NHS) treatments means that neither a Trial Steering Committee or Data Monitoring Committee will be appointed. A Study Management Group (SMG) meets quarterly to discuss operational issues. The SMG reviews the likelihood of achieving the project's goals, and takes remedial action if amendments are necessary. The core project team (CI, Study Co-ordinator & Trial Manager) meets fortnightly to review progress and escalates any important concerns to the SMG. One of our PPI partners is a co-applicant and member of the SMG.

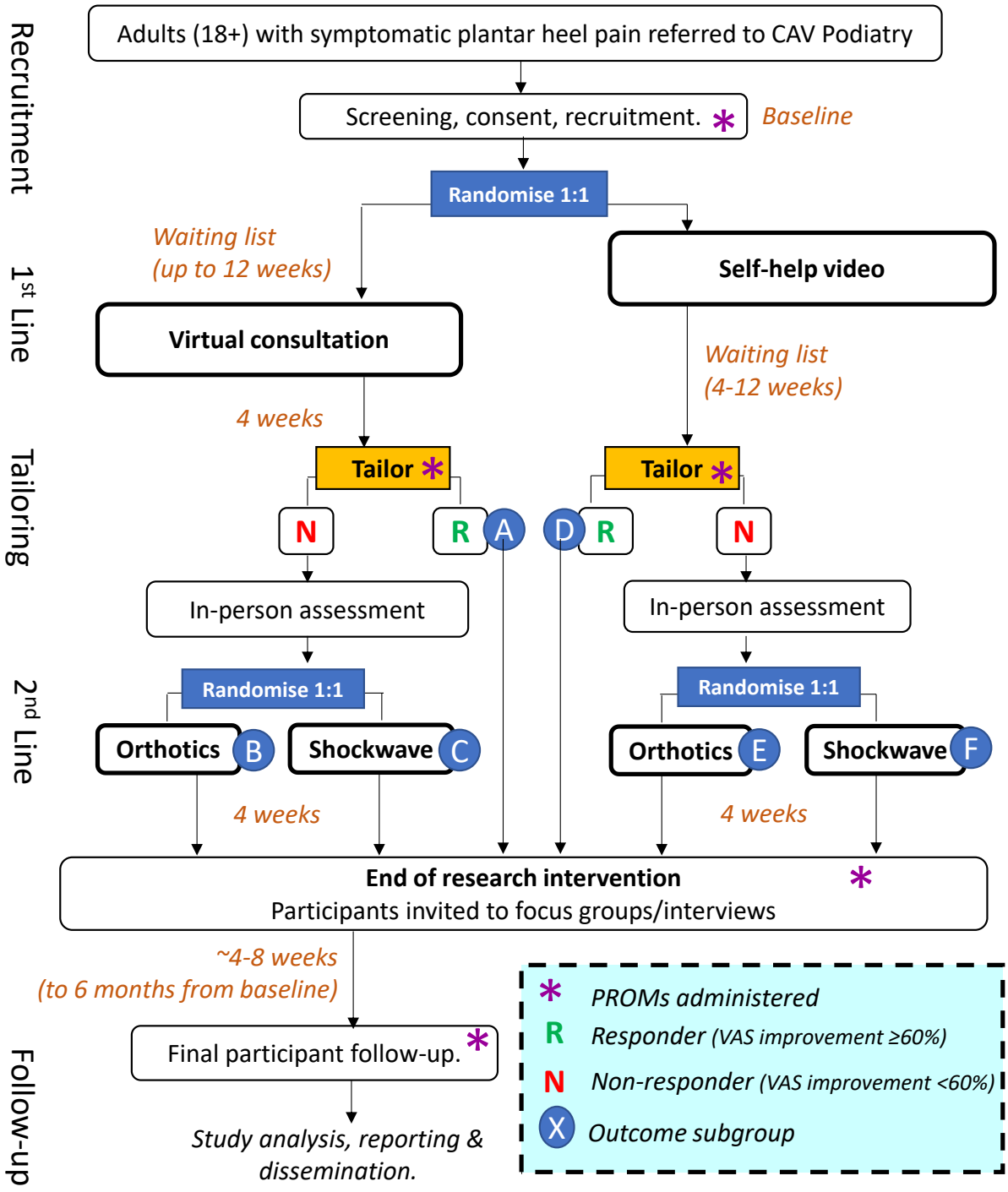
A Project Advisory Panel (PAP) has also been established to provide high-level guidance. Members of the Panel have expertise in clinical service delivery; research methods of relevance to our study; and/or lived experience of heel pain. Meetings are scheduled to coincide with key decision points. The PAP includes two PPI partners, one of whom is responsible for co-ordinating communications and contributions from our wider PPI group.

Protocol contributors

The study has been designed by NJ and RLP, with input from members of the SMG and CEDAR team. Key protocol contributors are listed in the study contacts on pages 7 and 8.

The initial idea for the study design was suggested by the South Wales Research Design and Conduct Service (RDCS). The wider public highlighted the importance of the research topic through the James Lind Alliance Priority Setting Partnership and in academic literature. PPI partners have been involved in selecting and revising outcome measurement tools, preparing a plain language summary, and reviewing project documents such as the Participant Information Sheet (PIS) and Informed Consent Form (ICF). They will continue to have key roles in the study oversight groups (SMG and PAP) throughout the project.

Study flow chart



Adaptive Intervention	First line treatment options	Status at end of first line treatment	Second line treatment options	Outcome subgroups
1	Virtual consultation	Responder	No further treatment	A+B
		Non-responder	Orthotics	
2	Virtual consultation	Responder	No further treatment	A+C
		Non-responder	Shockwave therapy	
3	Self-help video	Responder	No further treatment	D+E
		Non-responder	Orthotics	
4	Self-help video	Responder	No further treatment	D+F
		Non-responder	Shockwave therapy	

Figure 1. Study flow chart. Indicates the paths participants may follow depending on tailoring and randomised allocation to treatment.

1. Background and rationale

1.1. Heel pain

Almost one in every ten middle-aged and older adults (over 50 years old) in the UK has experienced heel pain in the last month, most of whom described it as "disabling" (Thomas et al. 2019). The pain can be severe enough that it interferes with activities of daily living, leading to reduced quality of life, and may be associated with significant psychological distress (Allam and Chang, 2022; Cotchett et al. 2020). CAVUHB Podiatry department receives in the region of 1,200 referrals for management of heel pain each year.

1.2. Inconsistency of treatment pathways

Heel pain treatment typically relies on a trial-and-error approach due to insufficient evidence of treatment effectiveness. A recent systematic review (Morrissey et al. 2021) determined that there was a lack of consensus on how clinicians should optimally treat pain and improve function in individuals with heel pain. Cotchett et al. (2020) described the development of evidence-based clinical practice guidelines for heel pain – with input from patients and other experts – as "essential".

Reflecting the findings from academic literature, there is currently geographic variation in the care provided for people with heel pain in Wales. Some health boards deliver unstructured exercise advice and orthotic therapy as standard care for patients with heel pain and then refer onwards to Orthopaedic specialists in secondary care settings for further intervention. Other regions perform Shockwave therapy and administer corticosteroid injections as third- and fourth-line treatments in community Podiatry outpatient settings.

Identifying an optimal treatment pathway is challenging. The root cause of the problem can vary between patients, and people differ in their treatment responses – there is no single intervention that works well for everyone (Peplinski and Irwin, 2010). Also, by the time patients present at the podiatry department the condition is often chronic. Patient-centred care and responsiveness to individual needs have been highlighted as important areas in which improvements could be made for people experiencing heel pain. In the qualitative study by Cotchett et al. (2020), participants were interested in high-quality online educational resources (such as clearly presented videos), as well as information about what treatments are effective at different stages of the treatment pathway.

Treatment aims to relieve pain and prevent future recurrence. Clinicians face sequential treatment decisions, based on individual patient characteristics and their prior treatment responses. Patient age, weight, and duration of symptoms are recognised modifiers of response to conservative management of heel pain (McClinton et al., 2015). Adaptive interventions have been proposed as a way to inform sequential treatment decisions with opportunities for developing evidence-based, tailored pathways (Oetting and Levy, 2011). A Sequential Multiple Assignment Randomised Trial (SMART) uses a specific study design that is intended to inform the development of adaptive interventions (Almirall et al. 2012).

1.3. Position of the feasibility study in the research programme

Our feasibility study is the next step in developing an All-Wales value-based (patient-centred and cost-effective) approach in the management of heel pain. It is step 3 in the following sequence (as shown in Figure 2): 1) Develop self-help video; 2) Review literature; 3) Single-site feasibility study; 4) Full-scale multicentre SMART to test effectiveness; 5) Spread and scale implementation across Wales; 6) Share methods with other departments.

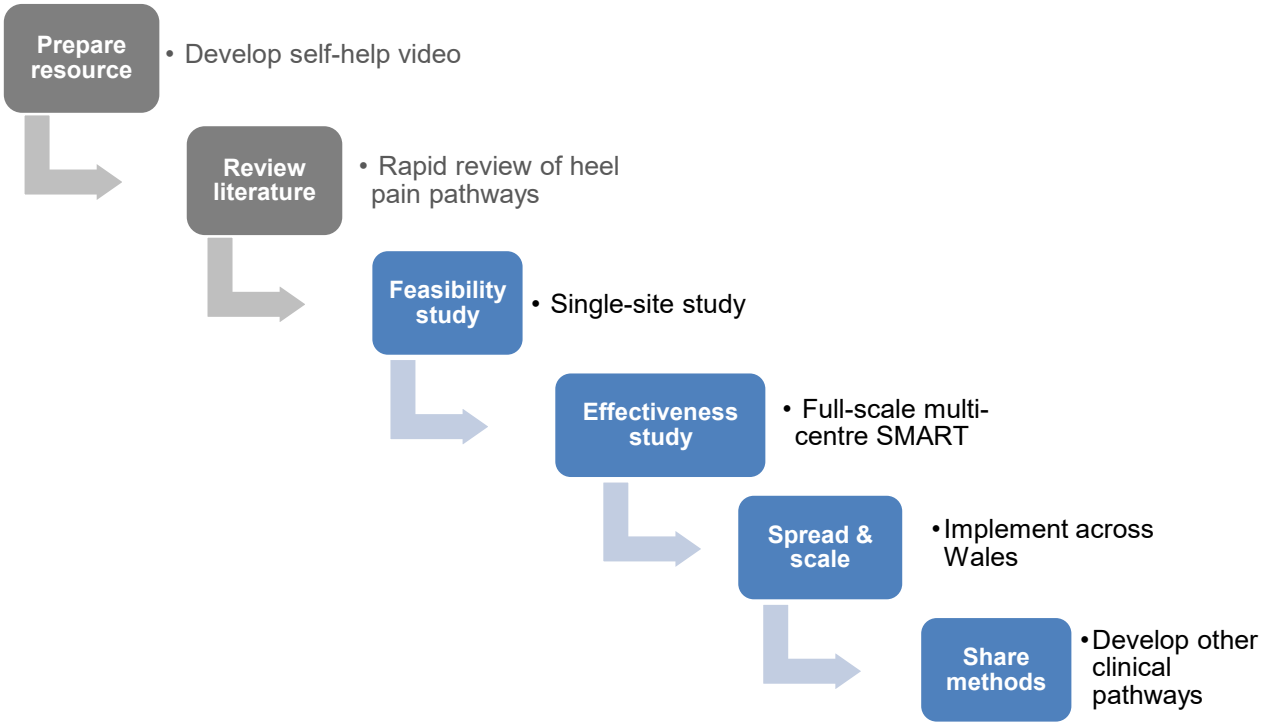


Figure 2. Research pathway. This feasibility study is the third step in a wider programme of research.

We will gather quantitative data to inform the sample size calculation, recruitment rates, and outcome measures. We will use process evaluation methods to collect qualitative data from participants and NHS clinicians to explore the acceptability of the design.

Pre-specified progression criteria will determine whether it is feasible to progress to a full-scale SMART study. Subject to securing further funding, the subsequent trial will involve other Welsh health boards and provide evidence about the effectiveness of the adaptive interventions and their associated costs. This research model could be applied to other clinical conditions where treatments are offered in sequence. Our plans align well with Welsh Government objectives set out in "A Healthier Wales", as people will be empowered to manage their own conditions at home, and high-quality, sustainable services will preserve valuable clinical time for complex cases.

2. Objectives and outcome measures/endpoints

2.1. Hypothesis

This is a feasibility study and as such will not be testing a hypothesis.

2.2. Aims

This feasibility study will determine whether a personalised treatment pathway (adaptive intervention) for people with heel pain can be delivered by the podiatry department, including whether enough people can be recruited within the remit of the study.

Key questions are:

1) Is a SMART research design feasible?

2) Are the proposed adaptive intervention pathways acceptable to patients and NHS staff?

The study will investigate several feasibility measures including recruitment, delivery of the adaptive interventions, acceptability of the study design for both patients and clinicians, and the appropriateness of tailoring criteria and outcome measures. These data will inform the decision to progress to a full-scale trial, and aspects relating to its design.

2.3. Main objectives

1. Feasibility of recruitment
2. Fidelity of clinical delivery of the correct treatment at the correct stage
3. Appropriateness of tailoring criteria and its threshold
4. Acceptability of adaptive intervention pathways amongst patients
5. Acceptability of adaptive intervention pathways amongst staff
6. Feasibility of retention

2.4. Secondary objectives

1. Estimated effect size and variance
2. Acceptability of outcome measures and data collection tools
3. Feasibility of collecting health service resource use data
4. Feasibility of long-term follow-up
5. Feasibility of scaling-up.

2.5. Outcomes

The outcomes to be measured to meet study objectives are summarised in Table 1.

Table 1. Summary of objectives, outcome measures and timings for assessment.

Objective	Outcome measures	Assessment timings
Main outcome measures relating to feasibility (no primary)		
Feasibility of recruitment	Ability to achieve recruitment rate of 6-7 patients per month. Details: - Number of patients screened - Number of patients recruited - Reasons for ineligibility or non-consent (including willingness to be randomised) - Number of participants randomised to first-line treatments	Regularly over duration of study recruitment and reviewed at final PAP meeting as a progression criterion.

Objective	Outcome measures	Assessment timings
	- Numbers of participants randomised to second-line treatments.	
Fidelity of clinical delivery of the correct treatment at the correct stage	The proportion of participants who receive the treatments they are allocated to (after each randomisation) will be calculated. Issues with delivering adaptive interventions and reasons for deviating from the protocol will be recorded.	Regularly over duration of study delivery and reviewed at final PAP meeting as a progression criterion.
Appropriateness of tailoring criteria and its threshold	Numbers of responders and non-responders to first-line treatment. This proportion will be reviewed regularly to monitor the number of participants allocated to each of the SMART outcome subgroups (A-F). Issues with applying tailoring criteria will be recorded. Numbers of 'responders' who subsequently require treatment within the study period will also be monitored.	Regularly over duration of study delivery and reviewed at final PAP meeting as a progression criterion.
Acceptability of adaptive intervention pathways amongst patients	Qualitative interviews and/or focus groups will be carried out with participants to determine the acceptability of adaptive interventions and the study design, including barriers and facilitators to following self-management advice. Issues relating to equality and diversity will be considered.	Qualitative data collection will be carried out during participant follow-up. Self-reported compliance with self-management advice will be monitored whilst treatment is in progress.
Acceptability of adaptive intervention pathways amongst staff	Qualitative interviews will be carried out with study staff to determine acceptability of adaptive interventions, including barriers and facilitators to delivering the SMART study.	Staff will be interviewed once treatment delivery is complete. Informal observations and feedback will be recorded throughout the study.
Feasibility of retention	Rate of retention. Loss to follow-up will be monitored, with reasons for withdrawal to be documented where possible.	Regularly over duration of study delivery and follow-up, and reviewed at final PAP meeting as a progression criterion.
Secondary outcomes		
Estimated effect size and variance	Data from validated PROM – FFI-R (short)	After all quantitative data collection is complete.
Acceptability of outcome measures and data collection tools	Number and completeness of questionnaires received at each key stage. Completeness of participant diaries/records. Qualitative information from staff and participant interviews/focus groups. Issues relating to equality and diversity will be considered.	Quantitative data will be reviewed regularly and summarised on completion of data collection. Qualitative data collection will be carried out during participant follow-up.

Objective	Outcome measures	Assessment timings
Feasibility of collecting health service resource use data	Staff time and equipment use will be recorded by delivery team. Participants will be invited to indicate their use of healthcare services (e.g. GP appointments). Any issues relating to data collection will also be recorded. Quality of life data will be collected from participants using the EQ-5D-5L questionnaire.	Review on completion of follow-up.
Feasibility of long-term follow-up	Number of participants who consent to their information being used to support future research. Data linkage options for long term follow-up of outcomes relevant to this study	Consent to future research will be sought as part of the initial consent process for participants. An exploration of options for data linkage will be included in the final study report.
Feasibility of scaling-up	Feedback from communications and discussions with relevant staff from other Welsh Health Boards.	Relevant emails and meeting notes to be recorded throughout the study, with summary to be reviewed at final PAP meeting.

3. Study design (overview)

This single-centre study will test the feasibility of using a SMART design (Almirall et al. 2012) to provide tailored treatment pathways for people with heel pain. The study will assess various aspects relating to the feasibility of a full-scale SMART study. This subsequent full SMART study will compare adaptive intervention pathways which combine existing treatments in sequence, rather than comparing the effectiveness of a single experimental treatment against standard care. See figure 2 (Research pathway) for the position of the feasibility study within the wider research programme.

This initial feasibility study will investigate areas of uncertainty about the future trial. Key objectives are to assess whether the research design is feasible (including whether enough people can be recruited), and to determine whether the proposed adaptive intervention pathways are acceptable to patients and NHS staff.

The study flow chart (page 13) illustrates the routes that participants will follow within the feasibility study. 50 people with heel pain will be recruited from referrals to CAVUHB. They will be randomly assigned to two groups initially – half will have a virtual consultation with a clinical therapist; the other half will receive a self-help video. Neither group will receive treatment any later than they would have under a standard NHS care pathway.

After following the advice at home for at least 4 weeks, anyone (in either group) whose Visual Analogue Scale (VAS) pain score has not improved by 60% or more will be offered an assessment in an outpatient clinic. They will then be randomised equally again to receive either an orthotic device (shoe insole) or 'Shockwave therapy' (using a non-invasive device to deliver ultrasound to the injured area).

As well as collecting Patient Reported Outcome Measures (PROMs) for a total duration of 6 months for each participant, we will use process evaluation methods (interviews and focus groups) to talk to patients. They will be asked about their experiences of adaptive intervention pathways and of participating in the feasibility study. We will also interview staff involved in trial design and delivery (clinical members of the study delivery team) about similar topics from a different perspective.

We are co-producing our research with PPI partners, who make sure we focus on outcomes that matter most to patients.

3.1. Study setting

This is a single-centre study hosted within the Podiatry Department of CAVUHB, currently located within CRI. The Centre for Healthcare Evaluation, Device Assessment and Research (CEDAR) is another department of CAVUHB and will be responsible for some of the non-clinical study management activities.

The study population is adults (aged 18 years or more) who are either referred or self-refer to the podiatry department because of persistent heel pain. These include patients with suspected plantar fasciitis.

4. Participant eligibility criteria

4.1. Inclusion criteria

- Adults aged 18 years or over
- Have symptomatic heel pain (in one or both feet)
- Able to speak, read and understand written and spoken English or Welsh
- Able to provide remote informed consent
- Access to internet and email, or DVD player, with technical support from family, friends or carers if necessary.

4.2. Exclusion criteria

- Taken part in a prescribed exercise intervention or used prescribed insoles (past 3 months)
- History of major trauma or fracture of the lower leg or below ankle surgery
- Heel pain secondary to a systemic condition/syndrome/malignancy
- Requires ankle-foot orthoses or lower limb device (splint)
- Diabetes or peripheral neuropathy
- History of inflammatory joint disease or autoimmune condition
- Chronic pain syndrome
- Pregnancy
- Pacemaker or other electrical implant
- Blood clotting disorder (haemophilia), blood clot (thrombosis), or current use of anticoagulant medication

- Cortisone injection therapy within the last two weeks[1]
- Unable to complete exercises in self-help resources.

People currently or recently involved in other research as participants will be considered for co-enrolment on a case-by-case basis, taking into account:

- Safeguarding of research participants on experimental drug trials which may cause contraindication for Shockwave therapy.
- The burden of participation in more than one study and the psychological impact.
- Any possible impact on the results of each study.
- The consequences for the design and scientific validity of our study.
- Recovery periods.

The decision should be the patient's provided that there are no overriding safety or design considerations.

5. Study procedures

5.1. Recruitment

5.1.1. Sample size

To address the feasibility objectives of this project, we aim to recruit 50 people with heel pain. The rationale behind the sample size calculation is described in Section 8 (Statistics and data analysis).

During follow-up a sample of these patients (approximately 12-20) will be invited to participate in either focus groups or semi-structured interviews. A sampling framework will be used to select participants from each of the outcome subgroups (labelled A-F on the study flow chart).

Clinical staff involved in delivery of the study will also be invited to participate in qualitative interviews. These NHS staff are members of the Podiatry research team who have responsibilities relating to trial design and conduct.

5.1.2. Participant identification

Potential study participants will be identified from Welsh Admin Portal (WAP) referrals to the CAVUHB Podiatry department. Referrals for adults at least 18 years of age with heel pain will be triaged by a suitably qualified Podiatrist and assigned to the "MSK Heel" waiting list on the Patient Record Information System (PARIS).

Adults with heel pain will also be able to refer themselves to the study directly. Study materials (posters and leaflets) will invite potential participants to contact the HELPP Study team by email, telephone, or online form. Their contact details will be added to the "MSK Heel" waiting list on PARIS.

[1] Shockwave treatment is contraindicated in people who have received "cortisone therapy up to six weeks before first treatment". Participants in HELPP will not receive Shockwave therapy until they have already been in the study for at least four weeks (whilst they complete 1st line treatment).

5.1.3. Pre-screening check

A member of the Podiatry research team will contact patients on the "MSK Heel" waiting list by telephone to offer them the opportunity to receive information about this feasibility study. Those showing interest in the study will then undergo an initial (pre-screening) eligibility check by telephone.

People considered likely to be eligible for the study will be sent an information pack including an invitation letter, a PIS, and an ICF. The patient's preferred communication methods and language (Welsh or English) will be noted for ongoing correspondence. The information pack will either be sent to participants electronically (by email with attachments and links) or by post. See section 9.1 for further information about data handling.

Those patients who decline the invitation to receive information, or who do not meet the eligibility criteria, will be provided with verbal self-help advice and will remain on the waiting list for routine NHS care. Reasons for ineligibility such as language or communication barriers will be recorded (without identifiers). These will inform the design of a subsequent full-scale trial.

5.1.4. Formal screening and consent

Within a fortnight of sending the information pack, patients will be contacted by a member of the Podiatry research team by telephone to discuss any questions they have about the study, and to talk through the consent form to make sure they are fully informed. During the same telephone call, formal screening will be undertaken to confirm eligibility using the predefined study inclusion and exclusion criteria. Patients will then be invited to return their completed (signed) ICF either electronically (by completing a personalised online form) or by post in the pre-paid envelope provided. Those using the electronic ICF will be offered the opportunity to download a PDF copy of their signed form as soon as it has been submitted.

Those patients who do not consent to participate in the study, or who do not meet the eligibility criteria, will be provided with verbal self-help advice and will remain on the waiting list for routine NHS care.

Once it has been checked by the research team, a copy of the completed ICF will be returned to each participant. It will be sent by post with a covering letter, or by secure email, accompanied by written instructions for completing baseline questionnaires and a weekly patient diary. The original copy of the ICF will be retained in the site file at CAVUHB, and another printed copy will be filed in the patient's medical notes. The participant's GP will be informed by letter, and provided with a copy of the PIS.

Patients will have the option to consent to the use of their data for future research, including linkage to other databases for the purpose of long-term follow-up. This is not an essential requirement; it will be possible for people to decline consent for this specific item and still be accepted as a study participant.

For non-responders to 1st line treatment, ongoing verbal consent will be documented at the in-person assessment. Participants will be given another opportunity to ask questions before proceeding to a 2nd line treatment.

Training specific to this study will be provided at the Site Initiation Visit (SIV) to anyone who is delegated the task of screening and confirming eligibility. Training and SIV records will be kept in the Investigator Site File (ISF). A study-specific Standard Operating Procedure (SOP) is available for reference.

No biological specimens will be acquired, transferred or stored during the study.

5.1.1. Payment

No payments will be offered to study participants.

5.2. Randomisation

Participants will be randomised sequentially at key decision points in order to balance the numbers in the final groups (Almirall et al., 2012). Recruited participants will be initially allocated in a ratio of 1:1 to 1st line treatments. Baseline data will be collected prior to initial randomisation, after which, allocation will not be concealed from patients nor clinicians delivering treatment. At the second randomisation (after tailoring), non-responders will be allocated to a 2nd line treatment, again with a 50% chance of being in either group.

Randomisation procedures will be detailed in a study-specific SOP. The first randomisation will be carried out by a CEDAR researcher once the signed ICF and completed baseline questionnaires have been received. The second randomisation will be carried out by the Podiatry research team at the in-person clinical appointment, and will only apply to non-responders (see next section). The computer-based randomisation method will be stratification, based on duration of symptoms. Duration of symptoms prior to recruitment has been found to be a significant predictor of response to intervention for PHP, with better outcomes in those who had experienced symptoms for less than 7.2 months (McClinton et al., 2015).

5.3. Tailoring

At the end of 1st line treatment, a tailoring variable will differentiate between "responders" and "non-responders". This will be based on information provided by participants through comparing bespoke diary 'snapshots' collected at baseline and end of 1st line treatment. Those "responders" who had an adequate response to 1st line treatment will then receive no further treatment within the research study, although provisions for routine care will be made in case of recurrence; they will remain in the study for data collection purposes until the end of the follow-up period. "Non-responders" will undergo a second round of randomisation to determine which of two 2nd line treatments will be provided.

The proposed tailoring variable is an improvement in pain score (worst pain experienced in the previous week in the target heel) greater than or equal to 60%, according to a VAS when compared with baseline. This threshold is based on criteria previously used in the literature to define heel pain treatment response (Gerdesmeyer et al. 2008; Ibrahim et al. 2016), and satisfies the recommended features of a tailoring variable (Almirall et al. 2012).

5.4. Blinding

Due to the nature of the treatments it is not possible to blind the care providers to the treatment groups. As this is a feasibility study and not designed to test effectiveness, it is not necessary to blind outcome assessors/data analysts.

5.5. Study assessments

Table 3. Summary of study assessments.

	Event									
Data to be collected/recorded	Pre-Screening	Screening	Baseline (remote)	Remote communication	Weekly throughout study	End of 1st line treatment	In-person assessment	End of research intervention	During follow-up	End of follow-up
Eligibility check	X	X								
Consent (verbal)		(X)	X				(X)			
Medical history		X								
Demographics		X								
Randomisation				X			X			
FFI-R (short)			X			X		X		X
EQ-5D-5L			X			X		X		X
VAS pain score			X		X	X		X		X
Adherence to advice (diary)					X	X				
Tailoring outcome						X				
Physical examination							X			
Qualitative data									X	
Adverse events					*	X	*	X	*	X
Resource use	X	X			X	X	X	X		X
Feasibility of long-term follow-up		X							X	X

*if spontaneously reported

5.6. Data collection from participants

5.6.1. Baseline data

The CRF will be completed with baseline data from patient's medical records and with relevant information provided by the patient during screening, to include:

- Patient characteristics - age, gender, ethnicity, height and weight
- Duration of heel pain symptoms (estimated date of onset)
- Are symptoms bilateral? Which heel is (most) painful? (Note – this will subsequently be referred to as the 'target' heel in our study)
- Prior management strategies or treatments.

Further baseline data will be provided directly by the patient when completing PROM questionnaires comprising:

- FFI-R (short) – this is a validated PROM, the Foot Function Index – Revised (short version) (Budiman-Mak et al. 2013)
- EQ-5D-5L – this is a validated PROM for quality of life
- Bespoke diary 'snapshot' with VAS heel pain score (target heel).

5.6.2. Data collection during 1st and 2nd-line treatment

Throughout the study, participants will be asked to complete a bespoke weekly 'diary' to record a limited set of data:

- VAS heel pain score (target heel)
- Compliance with self-help advice (stretching)
- Use of painkillers
- Use of healthcare services (e.g. access to GP).

At the end of 1st-line treatment, participants will be invited to complete another set of PROMs (FFI-R (short); EQ-5D-5L) and a bespoke diary 'snapshot' (VAS heel pain score). 'Non-responders' will be asked to repeat PROMs (FFI-R (short); EQ-5D-5L) at the end of 2nd-line treatment; 'Responders' will be asked to complete the same PROMs at an equivalent time (around 4 weeks after tailoring). This marks the end of the research intervention; participants will not be required to attend any further in-person appointments.

5.6.3. Data collection during follow-up (including interviews/focus groups)

After the end of the research intervention there will be a follow-up period, which will conclude six months after the patient entered the study. There will be no active input from clinicians at this stage, but participants will be instructed to continue following the advice they've received. A final set of PROMs (FFI-R (short); EQ-5D-5L) will be collected at the end of follow-up, and the participant's involvement in the study will be complete.

During the follow-up period, CEDAR researchers will invite some participants to provide qualitative data. A sample of approximately 12-20 patients will be invited to participate in either focus groups or semi-structured interviews. These will be carried out remotely using Microsoft Teams. Participants will be able to join by telephone or video call and can choose to be interviewed in

Welsh. Each meeting will be recorded and transcribed in full by an external agency approved by CAVUHB. Interview transcripts will be pseudonymised and any personal identifiable data will be redacted.

The main purpose will be to discuss acceptability of the adaptive intervention pathways and the study design, including the tailoring variable, data collection tools, outcome measures, as well as the acceptability of options for long-term follow-up such as data linkage. We will also enquire about barriers and facilitators to following self-management advice and explore issues related to equality, diversity and inclusion. Clinical therapists delivering the research interventions who are also members of the study team will be invited to interviews to discuss similar topics from a clinician's perspective. We do not intend nor expect to cover any highly sensitive topics.

5.7. Withdrawal criteria

Each participant has the right to withdraw from the study at any time. In addition, the CI may withdraw a participant from the study at any time if the CI considers it necessary for any reason including:

- Ineligibility (either arising during the study or if, during the study, previously unknown issues come to light which would make the participant ineligible)
- Significant protocol deviation as decided by the CI
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of consent by the patient (patients' study data up to the point of withdrawal will be kept).

If any new information becomes available during the course of the research that may be relevant to people's ongoing participation, we will forward it to them following consultation with members of the SMG and PAP. If there is any urgency (as determined by the CI) we will contact participants by telephone, otherwise they will be informed in writing.

5.8. End of study

The end of the study is defined as the end of follow-up, approximately six months after recruitment, of the final (50th) participant. A 'thank you' letter or email will be sent to the final participant on this date.

6. Adaptive intervention pathways and clinical treatments

Where any treatments involve the use of medical devices, these will be certified medical devices (CE marked) being used within their original intended purposes and within the intended population as defined by the manufacturer's instructions for use. None of the procedures are invasive. All study treatments are standard care options in routine clinical practice; there is no universally-agreed gold standard at present.

6.1. Adaptive intervention pathways

In this feasibility study there are four adaptive intervention pathways (1-4), and six potential outcome subgroups (A-F). These are detailed in Table 3 and illustrated on the study flow chart

(page 13). All participants will receive a 1st line treatment. Only non-responders will be assigned to a 2nd line treatment.

6.1. 1st-line treatment

6.1.1. Self-help video

The educational self-help video describes some causes of heel pain, and includes advice on choosing suitable footwear, as well as instructions for stretching, massage, and taping. If necessary, participants will be able nominate a carer, friend, or family member to receive instructions to help them access the video.

Table 3. Adaptive intervention pathways.

	1st line treatment	Status at end of 1st line treatment	2nd line treatment	Outcome subgroups
1	Virtual consultation	Responder	No further treatment	A+B
		Non-responder	Orthotics	
2	Virtual consultation	Responder	No further treatment	A+C
		Non-responder	Shockwave therapy	
3	Self-help video	Responder	No further treatment	D+E
		Non-responder	Orthotics	
4	Self-help video	Responder	No further treatment	D+F
		Non-responder	Shockwave therapy	

6.1.2. Virtual consultation

A virtual consultation will take place with a clinical therapist by telephone or a video call, supplemented by advice leaflets where appropriate. The nature of the therapist's advice will be similar to that provided in the self-help video.

6.2. 2nd-line treatment

6.2.1. Orthotics

Podiatrists prescribe, produce, and fit orthotic devices to be worn inside footwear. The devices used in this feasibility study will be selected according to individual patient needs. All will have regulatory certification (CE mark) and will be used in accordance with the manufacturer's Instructions For Use.

6.2.2. Shockwave therapy

Extracorporeal shockwave therapy (ESWT) uses a non-invasive device to deliver ultrasound 'shockwaves' through the skin towards the injured area of the heel. The device is certified (CE marked) and will be used in accordance with the manufacturer's Instructions For Use. The procedure will be carried out by a Podiatrist in an outpatient clinic (CRI) and repeated approximately once per week for three weeks, depending on patient need.

7. Safety reporting

No investigational medicinal products or investigational devices will be used. As such this study presents a low risk.

7.1. Definitions of adverse events, serious adverse events, and relatedness

Adverse Events (AEs): 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 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 persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect; or
- 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 follows:

- Definite
- Probable
- Possible
- Unlikely
- Not related.

7.1.1. Identifying AEs

AEs will be identified by clinical therapists interacting with study participants whilst they are in clinic or during telephone consultations. AEs may also be spontaneously reported by patients at any stage of their six-month participation in the study. The PIS explains that participants can contact the study team if they have any new concerns about their heel pain or if they experience problems with any of the treatments. All unexpected AEs identified by therapists or reported by participants should be recorded by the study team on the CRF. The therapist should also record the event and relevant comments in the participant's medical notes.

Once each participant has completed their six-month follow-up assessments (indicated by the date we send them a letter or email of thanks), we will no longer identify or record AEs on the CRF for that participant. After they complete their treatments, any patient that reports ongoing concerns

about their heel pain will be referred back to the Podiatry team for routine care. This will be recorded on the CRF only if it occurs before that participant's study completion date.

7.1.2. Expected AEs

Expected AEs are excluded from the adverse event reporting process. These will be defined as any device-related AEs as listed in the manufacturer's Instructions for Use, or known side effects of treatment:

- Swelling, reddening, haematomas (blood blisters in the skin)
- Petechiae, bruising (small red or purple spots caused by bleeding into the skin)
- Pain or temporary discomfort on walking
- Tissue damage if you had recent cortisone injections in the heel
- Skin irritation in response to taping adhesives

These side effects generally abate after 5 to 10 days.

See section 7.3 for further details about reporting adverse incidents involving medical devices.

7.2. Recording and Reporting SAEs

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 trial investigation), in the opinion of the investigator
- whether the event would be considered expected.

A SAE which has been classified by the CI or their delegated representative as RELATED and UNEXPECTED (see definitions above) must be reported to the Research Ethics Committee (REC) that gave a favourable opinion of the study. Reports of related and unexpected SAEs should be submitted within 15 working days of the CI becoming aware of the event, using the Health Research Authority (HRA) "non-CTIMP safety report to REC" form.

There is no requirement to report SAEs to the R&D Office. However, the CI or delegated representative is required to inform R&D of any concerns regarding the safe conduct of the trial and/or risks to the study participant or organisation (CAVUHB). Any incidents should also be reported via the usual CAVUHB incident reporting mechanism.

SAE information, including evidence of recording and reporting SAEs in accordance with this protocol, should be recorded in the ISF and in the CRF/source documentation (medical notes) and made available for inspection during audit.

7.2.1. Contact details for reporting SAEs and safety concerns

Contact details for reporting SAEs and safety concerns:

HELPP Study Team
CEDAR, Cardiff and Vale University Health Board, Cardiff Medicentre, Heath Park, Cardiff, CF14 4UJ
Tel: 029 218 44771
E-mail: HELPP.Study.Cav@wales.nhs.uk (cc Nia.Jones16@wales.nhs.uk)

(Monday to Friday 09:00-16:00)

A member of the HELPP study team will collect the SAE form from the clinical team at the CRI, and will ensure that it is reviewed promptly by either the CI (Dr Nia Jones) or their delegated representative for safety.

7.3. Reporting adverse incidents involving medical devices

An adverse incident is an event that causes, or has the potential to cause, unexpected or unwanted effects involving the safety of device users (including patients) or other persons. As this study is not classed as a clinical investigation of a medical device, there is no statutory requirement to report SAEs to the Medicines and Healthcare products Regulatory Agency (MHRA). Related and unexpected adverse incidents involving a CE marked medical device used in the study can be notified as usual to the MHRA via the Yellow Card Scheme (https://yellowcard.mhra.gov.uk/).

7.4. Urgent Safety Measures

The CI or their delegated representative 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 CAVUHB JRO. The CI or their delegated representative 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.

7.5. Responsibilities

The CI and their delegated representative for safety will have the following responsibilities relating to safety:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of risk/benefit.
2. Using medical judgement in assigning seriousness, causality and whether the event was anticipated.
3. Ensuring that all SAEs which are RELATED and UNEXPECTED (see definitions above: section 7.1) are recorded and reported to the REC within 15 working days.
4. Promptly informing R&D of any concerns regarding the safe conduct of the trial and/or risks to the study participant or organisation (CAVUHB).

5. Ensuring that SAEs and AEs are recorded and reported in line with the requirements of the protocol.
6. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
7. Alerting the CAVUHB JRO as soon as possible if any urgent safety measures have been implemented.

8. Statistics and data analysis

8.1. Sample size rationale

The sample size reflects the feasibility aim of the study (not powered to detect statistically significant effects) and was calculated according to the formula reported by Almirall et al., 2012. We aim to recruit n=50 participants (rounded up from 48.4 to allow initial treatment allocation at a ratio of 1:1). This assumes a minimum of n=5 will be allocated to each final subgroup. The response rate for the 1st line treatment will be one of the outcomes for the feasibility study; it has initially been estimated at 35% - local clinicians think that the actual response rate at this stage will be less than 10%. We have set the proportion higher than expected in order to ensure we capture enough people who progress to the second randomisation. If it is lower than estimated, then we will have more information on those who receive two randomisations. Therefore, this is a conservative approach to sample size estimation.

Overall attrition is estimated to be approximately 10%; none of the heel pain trials in the systematic review by Morrissey et al. (2021) reported an attrition rate greater than 10%, with study lengths up to 24 months. Quantitative data will be collected from all participating individuals until the conclusion of the study or their voluntary withdrawal, whichever occurs first.

Braun & Clarke (2019) explain that saturation is not the goal in reflexive thematic analysis and suggest that initial qualitative sample size estimates are pragmatic and provisional. We intend to invite a sample of 12-20 participating patients to join interviews or focus groups (depending on availability or preference) to provide qualitative feedback about their experience. A sampling framework will be used to improve the likelihood of including representatives from each of the six outcome subgroups (A-F). The risk of response bias will be monitored by comparing baseline demographic characteristics. Staff involved in delivery of study treatments will all be invited to interviews; we anticipate capturing data from a minimum of 4 members of the Podiatry research team.

8.2. Planned recruitment rate

A conservative recruitment rate of 6-7 patients per month for 8 months was chosen based on a review of local data. We have estimated that 50% of eligible patients will be recruited into the study.

8.3. Data analysis plan

Recruitment feasibility will be reported as frequency of patients recruited per month over the study recruitment period. Reasons for screening or randomisation failure will be collated and presented as frequencies. Dichotomous variables such as numbers of responders and fidelity of delivery will be presented as frequencies (with reasons where appropriate). Continuous outcomes (such as FFI-R (short) score) will be presented as mean (with standard deviation) or median (with interquartile range), as appropriate following tests for normality. No between-groups comparisons will be undertaken.

Proportions of patients with missing data and loss-to-follow-up will be reported in full, with reasons where available. Numbers of patients in each of the outcome subgroups (A-F) will be reported.

Inductive thematic analysis of data from interviews and focus groups will explore the acceptability of adaptive interventions and the SMART study design, and will contribute to the iterative development of a logic model. Issues described by staff in relation to any study processes will be described in a narrative fashion to feed into the design of a future full-scale trial of effectiveness. Qualitative data will be coded and managed using NVivo software.

We will report the proportion of participants who consented to long-term follow-up, and discuss the acceptability of a data linkage approach with interview and focus group participants. We will explore options for linkage of heel pain data with relevant organisations. There is potential for this work to lead to one or more related future studies.

8.4. Progression criteria

	STOP if:	CHANGE if:	GO if:
Feasibility of recruitment (average number of participants per month)	<2	2-6	>6
Feasibility of delivery (proportion of participants who receive the treatments they are allocated to after each randomisation)	<50%	50-80%	>80%
Minimum number of participants in any of the SMART outcome subgroups (A-F)	<1	1-4	>4
Loss to follow up (including withdrawals):	>50%	20-50%	<20%

As recommended by Mellor et al. (2023) these progression criteria will be viewed as guidelines rather than strict rules, and will be further informed by the qualitative findings of our feasibility study.

9. Data management

9.1. Data handling and record keeping

The CI and Podiatry research team will collect clinical data during telephone calls and face-to-face assessments. Pseudonymisation means that each participant will be allocated a unique Participant Study Number at study entry, and this will be used to identify them on the CRF for the duration of the study. Data will be collected from the date of enrolment until around 6-months post-recruitment. Some of the study data will be collected from the source data and entered onto a secure electronic database. Other data will be submitted directly by participants, either electronically or by post. When possible, those who prefer electronic communications will be emailed a unique link to complete the questionnaires and participant diary entries online. Patients who prefer hard copies will be asked to return pseudonymised paper-based questionnaires and patient diaries by post to CEDAR using pre-paid envelopes.

Some participants will be invited to participate in confidential online interviews or focus groups using Microsoft Teams. CEDAR researchers will also undertake an interview with staff involved in the study to collect data on the acceptability of study procedures and interventions. Interview and focus group recordings will be sent for transcription by an external agency. Whilst we aim to pseudonymise data before sharing it with the external transcription company, there is a possibility that some personal identifiable information will be retained. The transcription company has been approved by the Sponsor's information governance team and is contractually obliged to maintain confidentiality. Explicit consent will be sought from participants before their data is shared with the transcription company.

No patient/personal identifiable data (PID) will be accessed by someone other than members of the Podiatry research team without prior consent. All paper and electronic documents will be stored securely at CRI and CEDAR (paper) or on CAVUHB servers (electronic). These documents will only be accessible by the research team and authorised personnel; the electronic database will be secured by appropriate access control and password protection. Whilst the study is in progress, paper CRFs will be kept at CRI in a locked cupboard with access restricted only to members of the Podiatry research team. When completed, the CRFs will be signed-off by the study CI or designee. Completed and signed-off CRFs will be transferred to CEDAR (in person) once each patient completes the study. Completed CRFs and questionnaires will be stored in a locked cupboard in CEDAR, in an office only accessible with an authorised swipe card. The database will be stored on CEDAR's secure server (part of CAVUHB server), which is backed-up every 24 hours.

9.2. 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.

Access will be granted to authorised representatives of the Sponsor for monitoring and/or audit of the study to ensure compliance with regulations; these activities will be facilitated and supervised by the direct care team. 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. Study participants will provide explicit consent to the use of PID for the purposes of the study.

CEDAR researchers will perform the analyses of all study data. Procedures will be in place to enable transfer of pseudonymised study data from the Podiatry Department to CEDAR for the purposes of analysing outcome data and archiving.

Full transcripts from interview and focus group discussions will not be published. Short anonymised quotes may be included in published materials.

9.3. Archiving

Personal data will be retained for no more than 6-12 months after the end of the study for those participants who declined consent to long-term follow-up. Where we have consent from participants for use of their data for further research, personal data will be retained for 5 years after the end of this study. We will use contact details to invite participants to a stakeholder dissemination event. The Trial Master File (TMF) and Investigator Site File (ISF) containing essential documents will be kept for a minimum of 5 years after completion of study. CEDAR will archive study documentation at the end of the study in accordance with the sponsor's archiving procedures. Essential documents pertaining to the study shall not be destroyed without permission from the sponsor.

9.4. Monitoring, audit & inspection

CEDAR researchers will undertake monitoring that is proportionate to the low risk of the study; details will be set out in a monitoring plan which will comply with GCP principles and be agreed by the trial Sponsor. The plan will describe the frequency and type of monitoring, and the extent of source data verification. The purpose will be to 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 CI or designee should ensure that all study related documents including source documents are available for monitoring, audit, or inspection. Medical notes, electronic patient information databases, notes taken during remote communications and meetings, patient questionnaires, patient diaries, and recordings from focus group meetings and interviews will act as source data for the purposes of the study.

Before the study starts at the participating site, an initiation meeting will take place to ensure that site staff are fully aware of the study protocol and procedures. Checks will take place to ensure all relevant essential documents and study supplies are in place. The close out procedure at site will commence once the final patient enrolled has completed all site follow-up required by the protocol.

10. Ethical and regulatory considerations

This study complies with the World Medical Association Declaration of Helsinki (2013) and GCP. The study will respect the rights of participating patients and ensure confidentiality of patient information. Should participants have additional questions about the study, advice will be available

from both within the research team and outside the research team in the form of websites such as the NHS website page: http://www.nhs.uk/Conditions/Clinical-trials/Pages/Takingpart.aspx .

10.1. Research Ethics Committee (REC) review & reports

Before the start of the study, approval will be sought from Health and Care Research Wales (HCRW) and REC for the protocol and other important documents including the PIS and ICF.

Amendments that require review by HCRW and REC will not be implemented until approval is granted. The CI (or delegate) should submit any amendments to the Sponsor, in the first instance, and their National Coordinating Unit, HCRW). The HCRW Permissions Service will assess the amendment and decide whether to approve it.

All correspondence with the REC will be retained in the TMF/ISF.

There is no requirement for an annual Progress Report for Proportionate Review studies or where the study is two years or less in duration.

The CI will notify the REC of the end of the study. The end of the study is defined as the end of follow-up, approximately six months after recruitment of the final (50th) participant.

If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

10.2. Peer review

The protocol has undergone scientific review by CAVUHB JRO; the HCRW Research for Patient and Public Benefit (RfPPB) funding panel; and by two independent reviewers acting on behalf of HCRW.

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.

10.3. Patient and public involvement

Patient-facing documents have been reviewed for content and readability by a group of PPI representatives. PPI representatives have also been involved in study design. They will continue to have important role in overseeing the conduct of the study and the dissemination of findings, as detailed in the PPI partnership plan. Both the SMG and the PAP groups include PPI representation.

10.4. Regulatory compliance

Before any patients can be enrolled into the study, the CI or designee will ensure that appropriate approvals are in place and that they comply with the relevant guidance.

For any amendment to the study, the CI or designee, in agreement with the sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The CI

or designee will work with the site (the JRO as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment and confirm their support for the study as amended.

10.5. Protocol compliance

Protocol non-compliances are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the study protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and promptly reported to the CI and Sponsor. Deviations from the protocol which are found to frequently recur are not acceptable; they will require urgent action and could potentially be classified as a serious breach.

10.6. Notification of serious breaches to GCP and/or the protocol

In the event that a serious breach of GCP or the Protocol is suspected, this will be reported to the Sponsor immediately in accordance with CAVUHB *SOP 235 Managing Breaches of Good Clinical Practice or the Study Protocol*. The incident in question will be investigated by the Sponsor who will determine whether the breach constitutes a serious breach and report it to CAVUHB's research governance department. Any corrective action required will be undertaken by the CI and the REC informed if required. If necessary a protocol amendment will be submitted for review.

10.7. Data protection and patient confidentiality

All investigators and study site staff must comply with the requirements of GDPR and the 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 CI and research team is responsible for the data entry, quality of the data and data analysis. The CI will act as the data custodian and data controller for this study.

Study CRFs and completed questionnaires will be kept in secure locations (locked cupboard) at the study site and at CEDAR. The study database at CEDAR (part of CAVUHB) will be accessible only by CEDAR personnel directly involved in the study (password protected files on CEDAR secure NHS servers).

10.8. Financial and other competing interests for the investigators

No financial or other competing interests are currently held by the CI or any member of the research team. SMG and PAP members are required to identify and disclose competing interests that might influence study design, conduct, or reporting. This information will be collected at the first meeting of each group, and confirmed at subsequent routine meetings.

10.9. Indemnity

This is an NHS-sponsored research study, and the NHS indemnity scheme therefore applies. If there is negligent harm during the study 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 study. The NHS indemnity scheme does not cover non-negligent harm.

10.10. Amendments

It is the sponsor's responsibility to classify amendments as being non-substantial or substantial. The CI or their delegated representative will seek advice from CAVUHB JRO prior to submission of amendments to the relevant bodies. The CI will follow HRA processes for amendments to the protocol or other study documents. The NHS JRO will need to confirm capacity and capability prior to implementation. Amendments to the protocol or other study documents will not be implemented prior to appropriate approvals being granted.

11. Dissemination policy

The feasibility study will be registered on a publicly accessible trials register (such as clinicaltrials.gov) and submitted to the HCRW Research Register and Clinical Research Portfolio. Portfolio adopted research is automatically registered on the public UKCRN database. Details will also be reported on Researchfish.com.

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a study report will be prepared. The study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) extension to randomised pilot and feasibility trials (Eldridge et al. 2016).

The study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion). Study results will be submitted for publication in a peer-reviewed scientific journal on an 'Open Access' basis, so that they are freely available to anybody with internet access. Any formal publication would be in a journal that is peer reviewed and included in major evidence databases such as MEDLINE. The study report will follow the journal's authorship criteria and will acknowledge those who have contributed to the study. Funding will also be appropriately acknowledged; the most appropriate wording may vary depending on the subject matter, nature of the communication and current guidance from funding body or journal.

After the end of the study, CEDAR will invite stakeholders (including participants and staff) to a dissemination event, where the study findings will be presented and discussed. A lay language summary of study findings will be made publicly available on the CEDAR website. Study participants may request a copy of the final report by contacting CEDAR.

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