WARWICK
CLINICAL TRIALS UNIT

PROTOCOL

Big Toe OstEoarthritis (BigTOE) Trial: Inserts

ISRCTN:	81014195
Sponsor:	University of Warwick (SOC.01/24-25)
Contracting Organisation:	University Hospitals Coventry & Warwickshire NHS Trust
Funding Body:	NIHR Health Technology Assessment Programme Project Number: 157097
Ethics Approval date:	Yorkshire & The Humber – Sheffield Research Ethics Committee, approved 18 Dec 2024
Version Number:	3.0
Date:	04 Apr 2025

This protocol has regard for current HRA guidance and content.

This project (NIHR157097) is funded by the NIHR Health Technology Assessment (HTA) Programme. The views expressed are those by the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Protocol Version Log

Amendment No	Date of Amendment	Date of Approval
NSA04	04 Apr 2025	

Contact Details

Role	Name, address, telephone
Trial Contact	Email: BigToeTrial@Warwick.ac.uk Tel: +44 (0) 2476 575 111
Sponsor	Mrs Carole Harris University of Warwick Research & Impact Services University House Kirby Corner Road Coventry, CV4 8UW Tel: 024 765 75733 Email: sponsorship@warwick.ac.uk
Chief Investigator	Dr Michael Backhouse, Associate Professor of Clinical Trials Warwick Clinical Trials Unit Email: Michael.backhouse@warwick.ac.uk
Co-Chief Investigator	Professor Julie Bruce, Professor of Clinical Trials Warwick Clinical Trials Unit Email: Julie.bruce@warwick.ac.uk
Senior Project Manager	Dr Helen Bradley, Warwick Clinical Trials Unit Email: BigToeTrial@warwick.ac.uk
Trial Manager	Mrs Lauren Betteley, Warwick Clinical Trials Unit Tel: 02476 575111 Email: BigToeTrial@warwick.ac.uk
Trial Coordinator	Mr David Lomax, Warwick Clinical Trials Unit Email: BigToeTrial@warwick.ac.uk
Research Fellow	Ms. Fateme Mirzaee, Warwick Clinical Trials Unit Email: BigToeTrial@warwick.ac.uk
Co-investigators	Professor Edward Roddy, Professor of Rheumatology Keele University, Keele, UK Email: e.roddy@keele.ac.uk
	Professor Catherine Bowen, Professor of Podiatry/ NIHR ARC Wessex ACD lead, University of Southampton Email: c.j.bowen@soton.ac.uk
	Dr Martin Thomas, Senior Research Fellow in Clinical Epidemiology and Honorary Specialist Rheumatology and Musculoskeletal Physiotherapist, Keele University Email: m.thomas@keele.ac.uk
	Dr Jill Halstead-Rastrick, Clinical Lead for Podiatry & Clinical Lead for Research, Leeds Community Healthcare NHS Trust Email: jill.halstead-rastrick@nhs.net
	Dr Susanne Arnold, Assistant Professor, Warwick Clinical Trials Unit

	Email: Susanne.Arnold@warwick.ac.uk
	Professor Hylton Menz, Professor of Podiatry, La Trobe University, Melbourne, Australia Email: h.menz@latrobe.edu.au
	Professor Shannon Munteanu, Professor of Podiatry La Trobe University, Melbourne, Australia Email: s.munteanu@latrobe.edu.au
Patient representatives	Mrs Beverly Henderson, England Mrs Kathy Fell, England
Statisticians	Dr Helen Parsons (Co-investigator), Associate Professor of Medical Statistics, Warwick Clinical Trials Unit Email: H.Parsons@warwick.ac.uk
	Mr Aminul Haque, Research Associate (Statistician), Warwick Clinical Trials Unit aminul.haque.1@warwick.ac.uk
Health Economists	Dr Hema Mistry (Co-investigator), Associate Professor of Health Economics, Warwick Clinical Trials Unit Email: Hema.Mistry@warwick.ac.uk
	Dr Seyran Naghdi, Research Fellow (Health Economics), Warwick Clinical Trials Unit Seyran.Naghdi@warwick.ac.uk
For general queries and supply of trial materials please contact the coordinating centre: Warwick Clinical Trials Unit (WCTU) The University of Warwick Gibbet Hill Road Coventry CV4 7AL Email: BigToeTrial@warwick.ac.uk Tel: 024 76575111 Website: https://warwick.ac.uk/fac/sci/med/research/ctu/trials/bigtoe	
Randomisation:	Online randomisation portal: https://ctu.warwick.ac.uk/studycapture

Table Of Contents

PAGE

List of Tables

PAGE

List of Figures

PAGE

Trial Summary

Trial Title	Big Toe OstEoarthritis (BigTOE) Trial: Inserts	
Short title	BigTOE	
Phase	Phase III	
Trial duration	1st June 2024 – 30th November 2027, 42 months	
Trial design	Multicentre, parallel group, participant-blinded sham controlled randomised controlled trial (RCT) with internal pilot, embedded process and cost-effectiveness evaluation	
Participants	Adults with painful 1st Metatarsophalangeal Joint (MTPJ) Osteoarthritis (OA) seeking treatment through the NHS.	
Sample size	438 participants (219 per arm) from ~25 hospital and community sites	
Intervention	Shoe-stiffening carbon fibre inserts	
Comparison	Sham shoe inserts	
Treatment duration	Shoe inserts worn for up to 12 months	
Pilot phase	Internal pilot with target recruitment 111 participants from up to nine sites over nine months from first randomisation.	
Pilot objectives	• To test and refine trial procedures • To establish screening and recruitment processes in secondary and community care • To review data, adapt procedures to optimise performance prior to main trial	
Main trial Objective	Run a definitive multicentre parallel group, participant-blinded RCT to test the clinical and cost-effectiveness of carbon fibre shoe stiffening inserts in 438 participants with symptomatic 1st MTPJ OA	
Data collection	Baseline, one, **three (primary),** six and 12 months using electronic and postal data collection.	
Outcomes	**Construct**	**Outcome Measures**
Primary	Foot function	Manchester Oxford Foot Questionnaire (MOxFQ) standing/walking subscale at **three months**
Secondary	Foot-related QoL	MOxFQ: all subdomains and summary score
	Pain	Average pain intensity in the index 1st MTPJ & index foot recalled over the last week (NRS)
	HRQoL	EQ-5D-5L
	Insert adherence	Participant-reported adherence
	Analgesic use	Participant-reported analgesic use
	Healthcare resource use	Participant-reported healthcare resource use
	Global Rating of Change	Global Rating of Change (GROC) NRS
	Adverse events (AEs)	AEs and serious adverse events (SAEs)
	Normal shoe insert outcomes	Participant reported problems with shoe inserts
Sub-studies	**Objectives**	**Description**
Process Evaluation	Embedded process evaluation to inform recruitment, insole adherence, reasons for non-adherence;	Internal pilot: Semi-structured interviews with a purposive sample of (n=6) participants approximately 12-weeks after randomisation.

<table>
<tr><td></td><td>explore participant and healthcare practitioners' experiences of recruitment processes, intervention delivery, and intervention acceptability.</td><td>Healthcare practitioner interviews (n=10) after site opened to recruitment with potential for second interview at end of internal pilot.

<u>Main trial:</u> Participant (n=24) and healthcare practitioner (n=15) interviews to gain understanding of experiences of trial participation.</td></tr>
<tr><td>Study within a trial (SWAT)</td><td colspan="2">With University of York to investigate use of vouchers in trials:
- Does a voucher influence provision of patient reported outcome data at the primary endpoint?
- Does a second voucher influence provision of patient reported data at a final follow up?

Full details of the SWAT will be covered by a separate protocol and ethical application led by the University of York. Participants will be randomised to one of two voucher pathways separately to the main trial randomisation system:

<table>
<tr><th>Time Point</th><th>Pathway 1</th><th>Pathway 2</th></tr>
<tr><td>1 month</td><td>None</td><td>None</td></tr>
<tr><td>3 months</td><td>£10 voucher</td><td>None</td></tr>
<tr><td>6 months</td><td>None</td><td>None</td></tr>
<tr><td>12 months</td><td>£10 voucher</td><td>£10 voucher</td></tr>
<tr><td>Post FU period</td><td>None</td><td>£10 voucher</td></tr>
<tr><td>Total value per participant</td><td>£20</td><td>£20</td></tr>
</table>

Funding for the SWAT is being provided via the Implement SWATs programme. Implement SWATs is Sponsored by the University of York (UK) and funded by the NIHR (Advanced Fellowship, reference: NIHR302256).</td></tr>
</table>

List Of Abbreviations/Glossary

Abbreviation	Explanation
AE	Adverse Event
CEAC	Cost-effectiveness acceptability curves
CHEERS	Consolidated Health Economics Evaluation Reporting Standards
CI	Chief Investigator / Confidence Interval
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
HEAP	Health Economics Analysis Plan
HRQoL	Health-Related Quality of Life
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
MD	Mean difference
MOxFQ	Manchester-Oxford Foot Questionnaire
MTPJ	Metatarsophalangeal joint
NMB	Net monetary benefit
NNT	Number Needed to Treat
NRS	Numerical Rating Scale
OA	Osteoarthritis
PI	Principal Investigator
PPI	Patient & Public Involvement
PSS	Personal social services
QALY	Quality-adjusted life year
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
RR	Risk Ratio
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

WCTU	Warwick Clinical Trials Unit

2. Background

2.3 Epidemiology and burden of the condition

Painful first metatarsophalangeal joint osteoarthritis (1st MTPJ OA) has a substantial impact on the quality of life (QOL) of many older people. It is more common than painful hip OA, affecting 8% of those aged over 50 years.[1] Prevalence increases with age and is higher in women.[1-5] It is a progressive lifelong condition that is traditionally characterised by osteophytes (bone spurs) and joint space narrowing which can be seen on x-ray. These contribute to disabling pain experienced whilst walking and subsequent functional impairment, impacting on Health-Related Quality of Life (HRQoL). Research investment has not yet matched the societal impact of 1st MTPJ OA. Only four small randomised controlled trials (RCTs) have tested shoe inserts/orthoses for 1st MTPJ OA (total n=304 participants) and none of these studies were undertaken in the UK.[6-9]

There are no specific treatment recommendations for 1st MTPJ OA management from the National Institute for Health and Care Excellence (NICE) or other international bodies. Treatment of 1st MTPJ OA is primarily driven by evidence from other joints which informs management guidelines. NICE guidance is generic and does not offer joint-specific advice, but emphasises the key role of non-pharmacological, non-surgical therapies in OA management.[10] Information and support, therapeutic exercise, and weight management are considered core conservative treatments for OA management.[10]

Clinical management of 1st MTPJ OA is highly variable.[11] A 2020 survey of podiatrists and physiotherapists in the UK and Australia found that conservative care consists of a broad spectrum of interventions including acupuncture, footwear modifications, taping, injections, padding, contoured orthoses and shoe-stiffening inserts.[11] Where conservative care fails, arthrodesis (surgical fusion) of the 1st MTPJ is the gold standard procedure, however, this is an end-stage surgical procedure and comes at a high cost. Surgical waiting times are increasing in the UK NHS.[12, 13]

There are two main types of foot orthoses used in the management of 1st MTPJ OA with differing modes of action: i) traditional contoured orthoses that support the foot arch and aim to reduce load through the 1st MTPJ; and ii) thin, flat, semi-rigid carbon fibre inserts, which reduce the range and rate of movement at the 1st MTPJ. Despite lack of evidence, these devices are increasingly prescribed on the NHS for people with mild-to-moderate 1st MTPJ OA.[11, 14]

2.4 Existing Knowledge

An updated Cochrane systematic review of interventions for 1st MTPJ OA is pending.[15] Only one observational study and four clinical trials (n=304) have tested contoured orthoses or shoe-stiffening inserts for 1st MTPJ OA. One trial has measured patient-reported outcomes beyond three months.[6-9]

In 2016, Menz et al [6] compared prefabricated contoured orthoses to rocker-sole shoes (n=104, single-blind, single centre, Australia). There were no differences in foot pain intensity or function at three months. In an Australian private practice randomised trial, Paterson et al [7] compared prefabricated contoured orthoses to sham insoles (n=88), on a primary outcome of 1st MTPJ pain on walking over three months. Prefabricated contoured insoles offered no benefit over sham.[7, 16]

A small trial from the US (n=13)[8] compared carbon fibre shoe-stiffening inserts against a contoured orthoses with a rigid extension in people with 1st MTPJ OA. Those wearing carbon fibre shoe inserts had lower pain intensity and pain interference scores at six and 12 weeks. Adherence and comfort levels were higher in those wearing carbon fibre shoe-stiffening inserts.

An Australian observational case series (n=31)[17] found improvements in foot pain and disability at one and three months after wearing semi-rigid carbon fibre inserts. These shoe stiffening inserts were then compared to sham inserts in the Australian SIMPLE randomised trial (n=100).[9] The primary outcome, foot pain at three months, was measured using the Foot Health Status Questionnaire pain subscale (FHSQ; 0-100).[9] Shoe-stiffening inserts, compared to sham inserts, reduced joint pain at three months (FHSQ mean difference (MD) 6.66; 95% confidence interval (CI) 0.65 to 12.67; p<0.03) and six months (MD 9.59; 95% CI 2.00, 17.18). At one year, a clinically relevant difference in pain and function was found, favouring shoe stiffening inserts. Participant perception of global improvement was higher in those wearing shoe-stiffening inserts (61% vs 34%, Risk Ratio (RR) 1.73, 95% CI 1.05 to 2.88, number needed to treat (NNT) 4).

There were no differences in rate of adverse events over the first three months in the SIMPLE trial (sham 62% vs stiff inserts 63%), with most events being other bodily/musculoskeletal pains. Although there was a difference in the proportion of people reporting foot discomfort and foot blisters in those wearing stiffening inserts in the short term, over the first three months, rate of adverse events (AEs) were higher in the sham insert group over the one year follow-up (sham 54% vs inserts 39%).

The SIMPLE trial found that the incremental cost-effectiveness ratio was AU$12,980 per quality adjusted life year (QALY) gained, with a 55% probability of the carbon fibre inserts being cost-effective at willingness-to-pay thresholds greater than $6,500 per QALY gained. A nested biomechanical study confirmed that carbon fibre shoe inserts decreased the magnitude and rate of 1st MTPJ dorsiflexion whilst walking.[18]

In summary, small trials testing carbon fibre shoe inserts suggest evidence of short-term benefit on pain outcomes. These devices reduce joint range of motion and may improve function and quality of life in people with painful big toe OA. Survey data suggest these insert devices are used in clinical practice, but current evidence is insufficient to justify their widespread use in the NHS.

2.5 Need for a trial

The burden of painful 1st MTPJ OA is considerable and there have been repeated calls to investigate conservative, medical devices for this condition.[19] The lack of evidence for treatments has been highlighted in each NICE OA guideline since 2008. Research priorities included in the 2020 NICE guideline[19] highlighted the need to evaluate treatments for people living with painful foot OA, in particular, to investigate biomechanical interventions such as footwear, insoles, braces, and splints.

A consensus exercise led by Osteoarthritis Research Society International's (OARSI) International Foot and Ankle OA Consortium identified a lack of trials and urgent need to evaluate orthoses.[20] The UK James Lind Alliance Priority Setting Partnership for Foot Health also included recommendations to evaluate foot orthoses for foot pain problems[21].

Our previous research found that people with painful foot OA had difficulty maintaining their daily roles and responsibilities, with disabling foot pain impacting on their mobility, work and family life.[22] People described an unwelcome emphasis on drugs, supporting the need to test other conservative interventions and this was further emphasised during engagement with our Patient and Public Involvement (PPI) group.[22]

Shoe-stiffening inserts have a demonstrable mechanism of action as biomechanical studies show a reduction in rate and magnitude of 1st MTPJ dorsiflexion.[18] Data from Australian studies suggest that carbon fibre inserts could be clinically effective, but to date trials have been small with short follow-up durations and limited health economic evaluation.[15]

There is a need for a high-quality multicentre pragmatic trial to test the clinical and cost-effectiveness of carbon fibre inserts compared with sham inserts for people with painful 1st MTPJ OA. There are no registered trials of interventions for 1st MTPJ OA in either the ISRCTN, ANZCTR, or the EU/UK/USA Clinical Trials Register (searches completed 24/04/2023).

This will be the first UK RCT to compare alternative conservative interventions for people with painful 1st MTPJ OA.

2.6 Hypothesis

For people living with painful 1st MTPJ OA, carbon fibre shoe stiffening inserts compared to sham inserts improve foot function, foot pain, HRQoL, and other health-related outcomes over three months and are cost-effective over one year.

2.7 Aim and Objectives

2.7.1 Aim

The overall aim is to investigate the clinical and cost-effectiveness of carbon fibre shoe-stiffening inserts compared with sham inserts on outcomes of foot function, foot pain, health-related quality of life and other health-related outcomes at three months and twelve months post-randomisation, in people with painful 1st MTPJ OA.

2.7.2 Objectives

i) To undertake an internal pilot to test and refine trial procedures, and establish screening recruitment processes in secondary and community care;
ii) Review internal pilot data and recruitment optimisation findings, adapt procedures accordingly prior to rollout to main trial;
iii) Run a definitive multicentre parallel group, blinded RCT recruiting 438 participants from up to 25 UK centres;
iv) To conduct a mixed-methods, embedded process evaluation to inform trial recruitment and insole device adherence, reasons for non-adherence;

v) To evaluate the cost-effectiveness of shoe stiffening inserts compared to sham inserts over 12 months follow-up.

3. Trial Design

A multicentre, parallel group, participant-blinded, sham-controlled RCT with internal pilot and embedded process evaluation and economic evaluation.

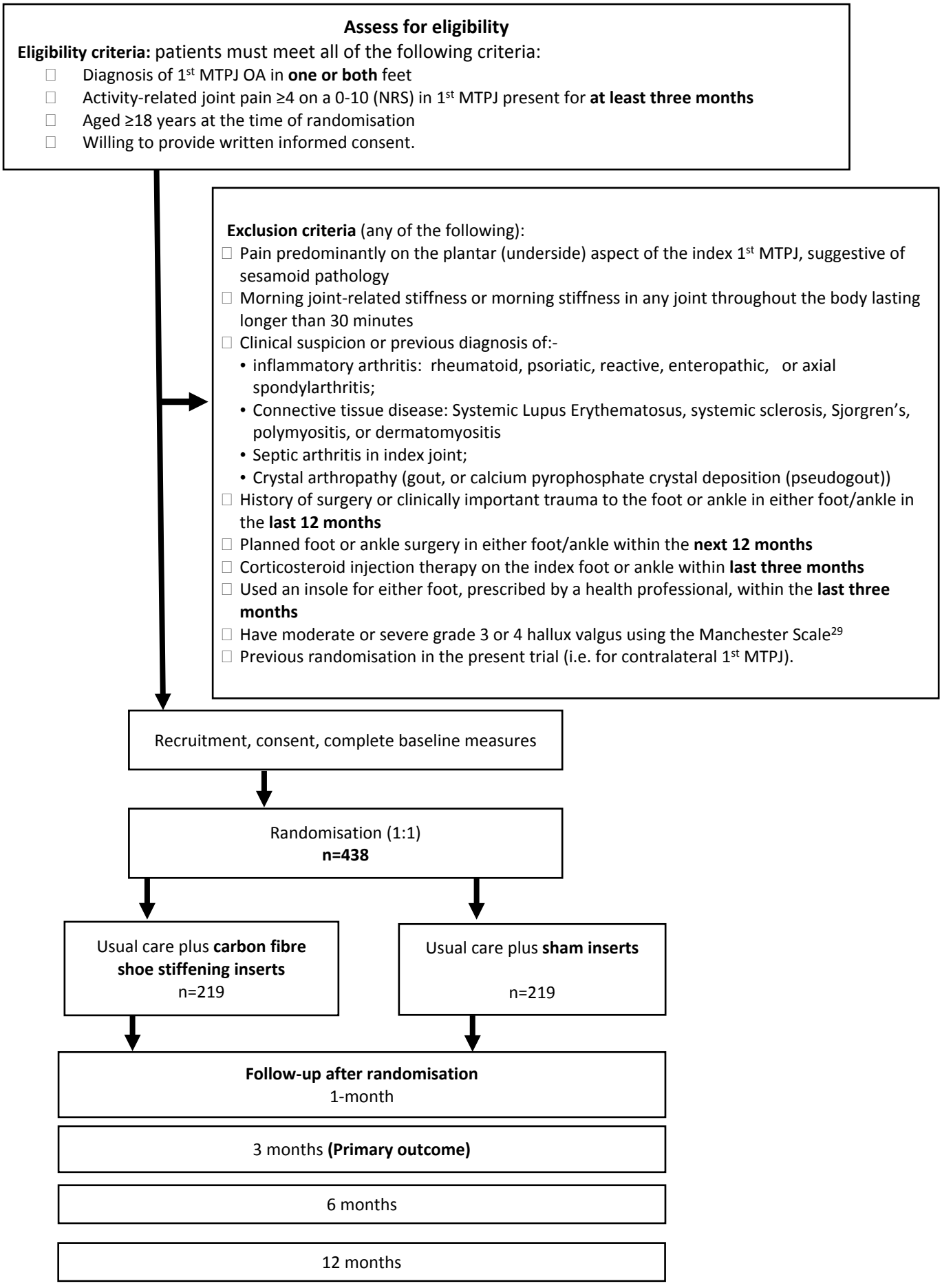
3.3 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement [23].

3.4 Trial flow diagram

See Figure 1.

Figure 1: Trial Flow Diagram



3.5 Outcome Measures

In the absence of an agreed core outcome set for assessment of function and pain in people with 1st MTPJ OA [24], outcome measures were agreed with patient and clinical partners to ensure that foot function, toe/foot pain whilst walking, and HRQoL were captured, whilst minimising participant burden.

Baseline data collection will include age, sex, height, weight, current analgesic medication, and whether they have had medical imaging performed on their foot within the last 12 months (e.g. x-ray or CT scan).

3.5.1 Primary outcome

Foot function measured using the participant-reported Manchester Oxford Foot Questionnaire (MOxFQ) Walking/Standing subscale at **three months** post randomisation.

3.5.2 Justification for primary outcome

The primary outcome is **foot function,** as measured using the seven-item standing and walking subscale of the Manchester Oxford Foot Questionnaire (MOxFQ). The 16-item full questionnaire consists of three domains/subscales: standing and walking (seven items), pain (five items) and social functioning (four items). Each subscale ranges from 0 to 100 where 100 equals the most severe symptoms/impairment. A summary score which combines all 16 items can also be calculated to produce an overall measure of the impact of foot and problems on HRQoL. This produces a score 0-100 (where 100 equals the most severe impairment).

The MOxFQ is widely used in foot/ankle research and clinical practice, and it has shown good validity and reliability.[25, 26] This scale was well received by our patient co-applicants and was thought to be culturally inclusive. Foot function rather than foot pain was selected as the primary outcome.

3.5.3 Secondary outcomes

People with foot OA report varying levels of painful symptoms and disability and it is important to capture how these impact on HRQoL and daily activities. Health and social care resource use data will be collected for health economic analyses.

Secondary outcomes will be measured at baseline, one, three, six and 12 months after randomisation.

- Foot related QoL: MOxFQ: all subdomains and summary score
- 1st MTPJ pain: average pain intensity (NRS) in the index 1st MTPJ recalled over the last week whilst at rest /walking
- Foot pain: average pain intensity (NRS) in index foot, recalled over the last week whilst at rest/walking
- HRQoL: EQ-5D-5L (VAS & Index)
- Participant reported Global Rating of change (GROC)
- Participant reported insole adherence/ reasons for non-adherence
- Analgesic medication
- Health care resource use
- AEs and SAEs
- Participant reported problems with shoe inserts

3.5.4 Timing and format of outcome assessments

All measures will be collected at baseline (pre-randomisation), one, **three,** six- and 12-months post-randomisation. Baseline questionnaires can be completed electronically, or on paper in clinic, with help from clinic staff if required, and returned to WCTU. Follow-up questionnaires will be completed remotely online, by telephone, or by post at each time point, and coordinated by WCTU. An email and/or text message will be sent to participants with an electronic link that will take them to the online questionnaire portal. Where participants need support, questionnaires can be completed via the telephone with a member of the WCTU study team for whom treatment allocation is concealed. Reminders will be sent to non-responders after two weeks following WCTU processes. The minimum core data set will include the MOxFQ and EQ-5D-5L at baseline and three months.

3.6 Participant Eligibility Criteria

For the purposes of inclusion in the trial, osteoarthritis will be diagnosed clinically using NICE NG226 [27] criteria which are as follows:

- Diagnose OA clinically **without** imaging in people who:
  - Are aged 45 years or over **and**
  - Have activity-related joint pain **and**
  - Have either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes
- **Do not** routinely use imaging to diagnose OA unless there are atypical features or features that suggest and alternative or additional diagnosis.

These NICE criteria have been incorporated into the inclusion criteria below with one adaptation – the age range has been lowered so that the BigTOE trial will accept people aged 18 years or over. This reflects that people under the age of 45 can develop OA. The trial also requires that people with bothersome pain in the big toe joint pain are included.

For clarification, no one will require an x-ray to be eligible for the trial thus OA can be diagnosed clinically in people under the age of 45 years.

People with bilateral 1st MTPJ OA will be eligible for inclusion in the trial but only one 1st MTPJ, **the most painful toe,** will be randomised and considered the index joint.

In addition to diagnosis of 1st MTPJ OA, we will also capture information at baseline to enable classification with including published assessment (Zammit) criteria for identifying radiographic OA[28]. See Appendix 1 for full details. This clinical scoring system correctly predicted the presence or absence of radiographic 1st MTPJ OA with 86% accuracy in one small Australian study. These criteria are:

- Pain duration greater than 25 months (NB *for purpose of BigTOE trial this will be interpreted as toe pain for longer than two years)*
- Presence of a dorsal exostosis (bony lump) on the dorsal surface of joint
- Hard end-feel to dorsiflexion

- Crepitus during dorsiflexion
- Less than 64 degrees of 1st MTPJ dorsiflexion

People with Grade 3 or 4 hallux valgus are excluded as this is a separate pathology affecting the 1st MTPJ which can cause pain.

3.6.1 Inclusion criteria

To be eligible to be included in the BigTOE Trial, patients must meet all of the following criteria:

- Diagnosis of 1st MTPJ OA in **one or both** feet
- Activity-related joint pain ≥4 on a 0-10 (NRS) in 1st MTPJ present for **at least three months**
- Aged ≥18 years at the time of randomisation
- Willing to provide written informed consent.

3.6.2 Exclusion criteria

Any of the following:-

- Pain primarily on the plantar (underside) aspect of the index 1st MTPJ, suggestive of sesamoid pathology.
- Morning joint-related stiffness or morning stiffness in any joint throughout the body that lasts longer than 30 minutes.
- Clinical suspicion or previous diagnosis of:
  - Inflammatory arthritis: rheumatoid, psoriatic, reactive, enteropathic, or axial spondyloarthritis,
  - Connective tissue disease: Systemic Lupus Erythematosus, systemic sclerosis, Sjorgren's, polymyositis, or dermatomyositis
  - Septic arthritis in index joint
  - Crystal arthropathy (gout, or calcium pyrophosphate crystal deposition (pseudogout))
- History of surgery or clinically important trauma to the foot or ankle in either foot/ankle in the last 12 months
- Planned foot or ankle surgery in either foot/ankle within the **next 12 months**.
- Corticosteroid injection therapy in the index foot or ankle within **last three months.**
- Used an insole for either foot, prescribed by a health professional, within the **last three months.**
- Have moderate or severe grade 3 or 4 hallux valgus in the index foot using the Manchester Scale.[29] (Appendix 2)
- Previous randomisation in the present trial (i.e. for contralateral 1st MTPJ).

3.7 Increasing participation amongst underserved communities

This trial will seek to maximise inclusivity so that the trial population, and therefore results, are reflective of the total population affected by 1st MTPJ OA. We will use the NIHR definition of an

underserved community: *"A community that is less well represented in research than would be desirable from the population prevalence and healthcare burden"[30]*

This may include, but is not limited to, minority ethnic groups, those who do not read or write English, different genders, people with low literacy levels, coastal, remote and rural communities, socioeconomically deprived people, people with limited access to digital infrastructure, and people living with learning difficulties. However, common characteristics are likely to include people or groups with:

- Lower inclusion in research than we would expect from population estimates;
- High healthcare burden that is not matched by the volume of research designed for the group;
- Differences in how a group responds to, or engages with, healthcare interventions, with research failing to address these factors.

Specific steps to increase recruitment from underserved communities are included throughout the protocol (e.g. alternative language options, paper and digital options for all trial material, and online animation videos to help those with lower levels of literacy) but we also recognise that barriers to inclusion will vary between communities and research sites. We will target inclusion strategies to help meet local needs and will specifically ask the following questions from the INCLUDE framework as part of the site set up process:

- Who are the under-served groups within our delivery area? (e.g. geographical or disease area that the delivering healthcare/clinical team operate in)
- What are the barriers to including these groups in research in our area?
- What actions can we take to overcome those local barriers?
- What tools, training and resources do we need to implement these actions successfully?[31]

3.8 Recruitment Procedures

3.8.1 Identification of sites

The trial will run in UK NHS outpatient clinics in community and secondary care that treat people with 1st MTPJ OA. Within each geographical area, we anticipate multiple services will diagnose and treat people with 1st MTPJ OA. The aim is to run the trial with different services and any clinician (e.g. podiatrists, orthotists, physiotherapists, orthopaedic foot and ankle surgeons, podiatric surgeons) responsible for the diagnosis and treatment of people with 1st MTPJ OA can recruit participants. Recruitment and training materials will be adapted for different services and pathways. These will be revised as required when opening sites.

Potential sites will be identified through the Clinical Research Network, clinical networks, and via professional engagement activities. Potentially interested sites will be asked to complete an expression of interest/feasibility form, with suitable sites progressing through the set-up process. A Principal Investigator (PI) will be identified for each site and the PI can identify suitably qualified health professionals to be trained in trial delivery.

3.8.2 Participant identification and screening

Participants will be identified and recruited via two main routes:

1) Clinical pathway
2) Self-referral

Clinical pathway: Potential participants will be identified through routine referrals at participating sites. Where a patient referral is suggestive of 1st MTPJ OA, sites will contact the patient to provide them with the trial information pack with their clinical appointment. This will allow people to consider the trial ahead of attending their clinic appointment.

The trial invitation pack will be available in electronic and paper formats to suit local systems and individual patient need. Where clinic appointments are paperless, an email will include links or attachments to the patient information pack, covering invitation letter and link to the BigTOE trial participant information website. The website will provide trial information and explainer animation videos in different languages to meet multiple needs.

Where local practice is to send clinic appointments by post, potentially eligible participants will be sent the same information, with a covering invitation letter and patient information sheet(PIS). These will also be available in easy read format and available in some languages other than English. Languages will be decided during the pilot phase in order to ensure they meet local needs. Paper-based information will also contain a link (e.g. QR code) to the participant information website.

Clinical sites will be asked to record number of invitation packs sent out. We seek to avoid patients receiving duplicate invitations by asking clinical sites to ensure patient notes or electronic records log when invitations are sent.

At clinic appointments, site clinicians trained in the trial will then discuss the study in more detail with interpreters and aids where required, answering any questions. After screening and confirmation of eligibility, written consent will be sought. All identifiable information will be held solely in the NHS until written consent has been obtained from participants.

Self-referral: Building upon approaches used in many other trials [30][32], BigTOE will also offer a self-referral route. Communities close to participating sites will be provided with information about the trial through an information raising campaign via local and national media, social media, and community groups. Working closely with local NHS Trusts, we will promote the study in trusted spaces, which will help raise awareness of the trial and may boost recruitment of underserved populations.

Whilst exact pathways will vary between locations, depending on local self-referral pathways, we anticipate that people with 1st MTPJ OA will be signposted towards the trial website and given information on how to refer themselves to the appropriate local service.

People with 1st MTPJ OA who contact WCTU directly expressing interest in participating will be signposted to their local trial site wherever possible. Where no local site is available, we will encourage these participants to seek treatment through their GP or appropriate local provider.

We will also work with local providers of musculoskeletal care such as First Contact Practitioners based within primary care, who can provide targeted information to signpost people to refer themselves into local services participating in the trial.

Assessment of Participant Eligibility (Screening):

A screening log will be completed at all sites and data will be entered directly onto the BigTOE trial database held by WCTU. This will include details of numbers of those presenting to clinical teams with 1st MTPJ OA in one or both feet, those meeting eligibility criteria, and details of those who consent to the study. These data will be used to populate the CONSORT statement.

Screening logs will include details on ethnicity, age and sex at birth. Any specific barriers to recruitment will be explored in the pilot phase. Screening data will be reviewed regularly to enable comparisons of screened participants against national and regional census data on ethnicity and deprivation, where possible. The treating clinician at the site will assess eligibility for the trial using the eligibility criteria described above. These patients will be logged on an electronic screening form. If a patient is deemed ineligible for the study, the treating clinician will thank them for their interest but inform them verbally that they are not eligible to take part. These patients can continue with their usual care.

3.8.3 Informed consent

Format: The participant consent form will be available in both electronic and paper formats, in different languages (as defined during the pilot phase), to meet service and participant needs.

Responsibilities: The local PI will retain overall responsibility for informed consent at their site and will ensure that any person listed on the site delegation log with the delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent. Only trained delegates can provide information about the trial.

Withdrawal: It will be explained that entry into the trial is entirely voluntary and the right of any person to refuse participation without giving reasons will be respected and recorded on the screening log. The participant will remain free to withdraw from the study at any time without giving reasons and without prejudice to any further treatment.

Any new information that arises during the trial that may affect the participant's willingness to continue in the trial will be discussed with the participant and, if applicable, renewed consent will be obtained using an amended consent form.

Lack/loss of capacity: If the study team are notified that any recruited participant has lost capacity or support to adhere to trial processes (for example, due to dementia), and are not expected to regain capacity, they will be withdrawn from the trial. Data collected up to this point will be retained.

Informing GPs: Participants' GPs will be informed that they are taking part in the trial although will not be informed of treatment allocation. This will be conducted by recruiting sites, typically informed by letter or email. Participants may decline for their GP being informed of their participation in the trial involvement by indicating their wishes on the consent form.

Copies of consent: The site PI or the delegated nominee must sign and date the consent form. Where paper copies are signed, a copy will be given by the clinical team to the participant and a copy stored in the patient's clinical record. Electronic copies can be printed and given or posted to participants.

Consent for participant interviews: During consent to the main trial, all participants will be given written and verbal information about the interview sub study. Willingness to be contacted by a member of the study team to arrange an interview will be recorded on the consent form; this is optional and does not affect clinical care. For those participants who give consent, they may be contacted by a researcher to arrange an interview to discuss their experience of taking part in the trial.

Consent for practitioner interviews: Healthcare practitioners involved in the trial during the internal pilot phase will be invited to take part in one or more semi-structured interviews with a researcher. Interviews will be done with a sample of different healthcare practitioners and stakeholders, e.g. podiatrists, orthotists, physiotherapists, and research staff. Staff will be given an information sheet to explain the purpose of the interview study and if they are willing to participate, asked to provide written or verbal consent (which will be recorded).

Consent for non-participant interviews: Eligible patients who decline to take part in the trial will also be offered the option to take part in a short telephone interview to understand their decision not to participate. They will be provided with an information sheet, and it will be explained that this is entirely voluntary, will not affect their clinical care, and that there will be no pressure to change their decision. Patients who indicate that they are willing to be interviewed will be asked for written consent for their contact details to be passed onto the process evaluation researcher to contact them.

3.9 Site Staff Training and Associate PI scheme

All sites will receive a remote, online Site Initiation Visit (SIV) where they will be trained on trial processes. Arrangements will be made for provision of sham and carbon fibre shoe inserts. Support by the trial team will be offered virtually and/or by telephone, and all staff on the delegation log will be given access to SIV reference slides and a trial manual. Training will include how to fit carbon fibre and sham shoe inserts. Refresher training can be provided by the trial team. The BigTOE trial website, hosted by WCTU, will be updated regularly for site staff and participants. Participants will be informed of the trial website in the PIL.

The trial will be registered with the NIHR Associate PI scheme to encourage and support healthcare practitioners interested in research.

3.10 Randomisation

Randomisation will take place using a secure on-line system accessed remotely to allow recruitment from multiple sites across the UK. Randomisation will be conducted by minimisation with a random factor in a 1:1 ratio, generated using a computerised system by WCTU, and stratified by recruitment site, whether one or both feet have OA disease (unilateral/bilateral). Allocations will be done centrally by WCTU, independent of the trial team, to ensure allocation concealment. The randomisation service will allocate a unique trial identification number to each participant in accordance with the computer-generated study randomisation schedule. To maintain confidentiality, all case report forms, study reports and all communication regarding the study will identify participants using unique identification numbers.

If for any reason the electronic randomisation portal is unavailable, please contact the WCTU study team who will be able to provide guidance.

3.10.1 Post-randomisation treatment discontinuation, withdrawals, and exclusions

Participants may discontinue trial treatment (shoe inserts) and/or withdraw from the trial at any time without prejudice. Unless a participant explicitly withdraws their consent to participate in follow up, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial. **Discontinuation of the wearing of shoe inserts is not a reason for withdrawal from the trial.** These participants remain on follow-up.

Levels of discontinuation and withdrawal include: i) discontinuation of intervention (shoe inserts) only; ii) withdrawal from future follow-up and iii) participant may also specifically request to withdraw and for all data collected to be deleted. Unless a participant specifically requests for their data to be deleted, all data will be retained and analysed using the intention to treat principle.

Participants may also be withdrawn from the trial at the discretion of the Chief Investigator, Trial Steering Committee (TSC) or Data Monitoring Committee (DMC) due to safety concerns. A clinician can also inform the trial team if they believe a participant should be withdrawn, which will then be investigated.

We do not anticipate exclusions from the trial.

3.11 Trial treatments / interventions

The carbon fibre inserts and sham devices are based on those used in the SIMPLE trial[9] and will be manufactured by Medfac Uk Ltd. under the Kinetec brand. The carbon fibre shoe stiffening insert is sandwiched within a combination of materials as this allows blinding of participants.

Intervention: Full-length carbon fibre shoe-stiffening inserts, covered with foam (such as PPT®). A full-length 1mm soft textile covering (e.g. Cambrelle®, Camtex Fabrics Ltd, UK) will make the carbon fibre insert similar in appearance to the sham.

Sham: Sham inserts are designed to appear identical to the intervention but without the carbon fibre which adds the rigidity.

Table 1: Composition of interventions

Layer	Sandwich analogy	Sham	Carbon fibre insert
Top cover	Bread	Standard top cover material e.g. Cambrelle	Standard top cover material e.g. Cambrelle
Upper mid layer	Lettuce	3.2mm foam	3.2mm foam
Lower mid layer	Ham	none	1.5mm thick carbon fibre
Bottom cover	Bread	Standard top cover material e.g. Cambrelle	Standard top cover material e.g. Cambrelle

3.11.1 Number of shoe inserts to provide per participant

Where participants have unilateral symptoms, we will provide one shoe insert for the **symptomatic foot** only. Where participants have bilateral symptoms, they will be provided with a pair of inserts.

Recognising that swapping shoe inserts from one pair of footwear to another is particularly difficult due to the rigidity of carbon fibre, we will provide participants with **two inserts** per affected foot i.e. either two inserts for those with unilateral symptoms, or four inserts (two pairs) for those with bilateral symptoms.

3.11.2 Fitting of shoe inserts

Trial inserts should only be fitted into suitable footwear and are unsuitable for wearing in slippers, sandals, ballet pumps, high heels, and flip-flops. Whilst exact footwear requirements should be determined between clinician and participant, generally the following guidance applies:-

- The footwear should be able to accommodate the allocated insert. A broad, stable heel between 1 and 3cm is preferrable.
- Removable insoles and an adjustable fastening (e.g. laces, straps, or buckles) are preferrable.
- The trial inserts are designed to be fitted **under** the shoe's removable insole and may require trimming to fit.

To trim inserts, the clinician should remove the shoes' original insole and use it as a template for trimming the trial insert. Trial inserts should be trimmed with strong sharp scissors, or a grinder and appropriate safety measures put in place.

The trial insert should then be placed into the participants footwear to ensure it fits appropriately. If further trimming is required, the insert can be removed and the process repeated as required. Once the insert has been fitted to the footwear, the original insole should be reinserted over the trial insert and the participant should try on their footwear and confirm their fit.

3.11.3 Justification for selection of shoe stiffening inserts

The SIMPLE trial found that shoe-stiffening inserts, compared to sham inserts, were effective at reducing joint pain at 12 weeks. There was a statistically significant between-group difference in the primary outcome at 12 weeks favouring shoe stiffening inserts (FHSQ pain domain MD 6.66; 95% CI 0.65, 12.67; $p<0.03$) and this benefit was maintained at 24 weeks (MD 9.59; 95% CI 2.00, 17.18). This lost statistical significance by one year, but the magnitude of difference was similar that observed at 12 weeks (FHSQ pain MD 6.97; 95% CI -0.60, 14.53). This is a clinically relevant difference in pain at one year. Authors also reported a statistically significant difference favouring the stiffening inserts in foot function (FHSQ) at 24 weeks. Additionally, participant perception of global improvement was higher in the shoe-stiffening insert group (61% vs 34%, RR 1.73, 95% CI 1.05 to 2.88, NNT 4). The incremental cost-effectiveness ratio was AU$12,980 per quality adjusted life year (QALY) gained, with a 55% probability of the carbon fibre inserts being cost-effective at willingness-to-pay thresholds greater than $6,500 per QALY gained. A nested biomechanical study confirmed that carbon fibre shoe inserts decreased the magnitude and rate of 1st MTPJ dorsiflexion whilst walking.[18]

Sham inserts for the trial have been designed in line with recommendations to make them as biomechanically inert as possible and have the same foam and textile top and bottom cover as the intervention, thus looking identical.[33, 34] Mechanical testing has shown that sham inserts have a minimal effect on joint kinematics and shoe-stiffening.[18, 34] The Australian SIMPLE trial sub-study confirmed that sham inserts were as biomechanically inert as possible and were acceptable and credible for trial participants.[9, 18]

3.12 Adherence to interventions

Carbon fibre shoe stiffening inserts work by reducing the velocity and magnitude of dorsiflexion of the 1st MTPJ. Therefore, the inserts will only work during **weight bearing activity.** Given this mechanism of action, clinicians should give advice to participants to wear the shoe inserts in the footwear they wear o**n a day to day basis for walking**. Inserts are not suitable for wearing in slippers. Therefore, the amount the person should wear the inserts will vary from person to person, depending on how active they are and whether they are on their feet whilst working or conducting usual activity.

We will define adherence as the proportion of the person's self-reported footwear use, thus 'insert use' as a proportion of the time when they could have used their inserts. A similar approach has been used to calculate adherence to offloading boots in people with diabetic foot ulcers. [35]

Adherence and reasons for non-adherence to inserts will be captured through self-reported participant questionnaires within the participant questionnaires. This was the most common approach in our recent systematic review of the measurement and interpretation of intervention adherence in NIHR funded trials. [36] This will be explored in more detail through qualitative interviews as described in section 4.2.

3.13 Blinding

3.13.1 Methods for ensuring blinding

Participants will be blinded to their allocated treatment. Allocation will be facilitated online. All baseline data will be collected after consent, prior to randomisation. Blinding will be maintained by providing specially constructed inserts. Participant-facing materials refer to different types of shoe inserts without mentioning the shoe-stiffening component. The comparator (sham) insert has been designed so that it is similar in appearance to the active carbon fibre insert. This approach has been used in a previous trial and participants thought that both treatments were credible [9, 37]. There were no differences in treatment credibility or expectancy of benefit between treatment groups[9]. Trial staff involved with collecting follow-up data will be blinded to treatment allocation where possible.

3.13.2 Methods for unblinding the trial

Given the low-risk nature of the interventions and clinician awareness of treatment allocation, a formal emergency unblinding procedure will not be required.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

3.14 Concomitant illness and medication

Details of any relevant comorbidities will be recorded at trial entry.

Details of any analgesic medication that is taken during the trial, should be collected at baseline by clinical or research staff at site, and subsequently should be self-reported on participant questionnaires. Any changes in analgesic medication should be recorded at each follow-up time-point.

3.15 Co-enrolment into other trials

We will consider co-enrolment on case-by-case basis. Co-enrolment of BigTOE participants into other interventional studies will be considered where there is no conflict with the trial objectives. The CIs

will review the protocols for other studies and will consider co-enrolment in conjunction with the Trial Management Group where appropriate. Co-enrolment does not equate to data sharing which requires separate agreement and approvals.

3.16 End Of Trial

The trial will end when the last follow-up has been received and no further follow-up activities with participants are planned. However, a period of data cleaning, statistical analysis and site closure will follow as per the Gantt chart.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the DMCTSC
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

3.17 Methods And Assessments

3.17.1 Schedule of delivery of intervention and data collection

Table 2: Schedule of events

Timepoint	**Pre-randomisation**		**Post-randomisation**			
	Screen	Baseline	Month 1	Month 3	Month 6	Month 12
Check eligibility	ü					
Informed consent	ü					
Clinical data collection by site						
Manchester Hallux Valgus Scale	ü					
Zammit assessment criteria		ü				
Participant data collection [$]						
Demographic details: sex, DOB, ethnicity, height, and weight		ü				
MOxFQ Walking-Standing		ü	ü	ü *	ü	ü
MOxFQ 16-item		ü	ü	ü	ü	ü
EQ-5D-5L		ü	ü	ü	ü	ü
Pain intensity (NRS) index foot and MTPJ, average recalled over last week at rest/walking		ü	ü	ü	ü	ü
Participant reported Global Rating of Change (GROC)			ü	ü	ü	ü
Analgesia medication use		ü	ü	ü	ü	ü
Randomise, prescribe intervention		**R***				
Health and Social Care resource use			ü	ü	ü	ü

Timepoint	Pre-randomisation		Post-randomisation			
	Screen	Baseline	Month 1	Month 3	Month 6	Month 12
Adverse events / SAEs			ü	ü	ü	ü
Participant reported problems with shoe inserts			ü	ü	ü	ü
Adherence to intervention			ü	ü	ü	ü

ü* = primary outcome; R* = randomisation after consent and baseline data collection; $ baseline data collection completed at site, post randomisation timepoints coordinated by WCTU with participants.

4. Process Evaluation

4.1 Internal pilot study

A formative process evaluation will be undertaken during the internal pilot phase of the trial. The aim of the process evaluation is to identify any areas for improvement to optimise recruitment into the main trial and minimise any potential variation in intervention delivery.

Specific objectives are to:

1. Explore participants experiences of recruitment, intervention delivery, and acceptability of the interventions.
2. Explore healthcare practitioners' experiences of recruitment processes including screening, and registration as well as intervention delivery.

Adherence and reasons for non-adherence to inserts will be captured through self-reported participant questionnaires. This will be explored in more detail through qualitative interviews.

4.1.1 Methods

4.1.1.1 Participant interviews

We will interview six participants from six different sites to explore their reasons for, and expectations of taking part in the trial; experience of recruitment into the trial; and experiences of wearing their prescribed inserts and strategies for increasing usage/promoting adherence.

Interviews will be conducted approximately 12-weeks after randomisation. Participants may also be invited to a second interview later in the pilot phase to explore ongoing adherence. Semi-structured interviews will be conducted by telephone or Microsoft Teams. Informed consent will be confirmed verbally prior to each interview. Interviews will be audio digitally recorded on an encrypted recorder or via Teams, anonymised, and transcribed verbatim.

4.1.1.2 Sampling for participant interviews

At point of consent to the main trial, participants will indicate their interest in taking part in the interview study. Their details will be passed to the process evaluation researcher who will use demographic information (age, sex, ethnicity), to generate a sampling matrix to create a pool of participants that will be used to select a sample. The aim is to select a sample which is inclusive of people from different backgrounds to represent and learn about a range of experiences. The researcher will contact them to reconsent for interview. If we receive a large response to our invitation, not everyone will be invited for interview; this will be explained to participants.

4.1.1.3 Healthcare practitioner interviews

We will interview approximately 10 healthcare practitioners to explore and understand their experiences of recruitment; understand more about the care pathways at different sites; and explore perceived facilitators and barriers to delivering the interventions as per protocol. Interviews will be arranged shortly after a site has opened to recruitment and carried out in the same way as described above. A second interview may be required for some healthcare practitioners, after a higher proportion of participants have been randomised, to further explore how inserts are being prescribed and identify any additional training or support needs.

4.1.1.4 Non-participant interviews

Semi-structured interviews will be conducted by telephone or Microsoft Teams of people who were eligible to participate in the trial but declined to do so. These interviews will seek to understand their decision not to participate. Informed consent will be confirmed verbally prior to each interview. Interviews will be audio digitally recorded on an encrypted recorder or via Teams, anonymised, and transcribed verbatim.

Quantitative and qualitative data from the internal pilot process evaluation will be analysed continuously and reported to the Trial Management Group regularly so appropriate actions can be discussed. Adaptations to recruitment and intervention delivery processes will be implemented ahead of the main trial.

4.2 Main trial interviews

A larger sample of participant (n=24) and healthcare practitioner (n=15) interviews will be conducted to gain a greater understanding of the experiences of those taking part in the main trial.

4.2.1 Participant interviews

To ensure maximum variation, purposive sampling will be used to identify and invite 24 randomised participants from across different sites to take part in an interview based on age, sex, socioeconomic and working status. Interviews will take place after three months of intervention use. We will then seek to repeat these interviews after six months to explore acceptability, adherence, and intervention fidelity.

All interviews will be arranged and conducted in the same way as the internal pilot interviews (see section 4.3.1)

4.2.2 Healthcare practitioner interviews

A sampling matrix will be used to select a purposive sample of up to 15 healthcare practitioners based on their different backgrounds and places of work e.g., community or secondary care. Staff will be invited to a one-on-one online interview or to join an online focus group. The aim will be to understand as much as possible about intervention delivery and fidelity but also to assess the impact of any adapted processes or procedures introduced because of pilot study findings.

4.3 Analysis and reporting

All qualitative data from both the pilot and main phase of the trial will be analysed using the framework method proposed by Ritchie and Spencer.[38] The framework analysis will compare and interpret the data from participants at different stages over the trial and separate frameworks will be constructed for participant and healthcare practitioner responses to enable comparison. These data will be used to aid interpretation and explanation of the main trial findings.

The software package NVivo will be used to manage the data and facilitate this process. Researcher bias will be minimised through regular crosschecking of the data and findings by the members of the research team. Quotes will be used as exemplars of key themes.

Coded interviews, observations and a full record of issues raised will be discussed in detail at the TMG and summarised for the oversight committees. Good practice at sites will be shared with other recruiting sites.

5. Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with Data Protection Act 2018 & UK GDPR.

All required ethical approvals for the trial will be sought using the Integrated Research Application System (IRAS). We do not foresee any substantial ethical issues as the PPI interactions have been very positive about the trial and our trial team are experienced in preparing similar applications.

The Chief Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) June 2017. Before enrolling patients into the trial, each site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients until the R&D department has confirmed Capability and Capacity and a site agreement is in place.

Trial staff will ensure that participants' anonymity is maintained. The participants will be identified by an ID number on all Case Report Forms (CRF), participant questionnaires and electronic database. Data will be entered into a secure online trial database provided by WCTU. Paper-based CRFs will be stored on site at WCTU under locked, secure conditions for the duration of the trial.

Direct access to source data and documents will be granted to authorised representatives from the sponsor, sites and regulatory authorities to permit trial related monitoring, audits and inspections.

6. Adverse Event Management

6.1 Definitions

6.1.1 Adverse events (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with the research.

An adverse device effect (ADE) is an adverse event related to the use of an investigational medical device, such as an insert. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation, or any malfunction of the investigational medical device (active or sham shoe inserts). This also includes any event that is a result of a user error or intentional misuse. For the purposes of the BigTOE trial, ADEs will be considered as AEs and recorded accordingly.

All AEs will be collected from the point of randomisation onwards, up to 12 months. Events occurring before randomisation will not be recorded.

Some events which occur during treatment (use of the inserts) will be considered normal outcomes from when using shoe inserts and will not be recorded as adverse events nor reported as a serious adverse event, unless in the opinion of the clinical team, they are considered untoward, excessive, or outside of what might normally be expected for insert use. These are events that are excluded from AE/SAE recording and reporting, this is not to be confused with known SAEs that are to be used for expectedness assessment and determining expedited reporting requirements. The events that do not require recording or reporting are listed below.

- Discomfort in foot or feet whilst wearing inserts
- Blisters or calluses
- Skin irritation
- Discomfort or muscle aches and pains in the legs e.g. as a result of altered gait
- New callus/corn formation
- Soft tissue musculoskeletal injury
- Tight shoes
- Feeling unstable whilst wearing inserts.
- Any elective or pre-planned treatment for a pre-existing condition, unrelated to the 1st MTPJ

Any event that is not listed above, or any event above that is considered untoward, excessive for insert use should be recorded by the treating clinical team, outcome assessors or study team, as appropriate. This will include events such as foot ulceration, foot infection requiring treatment, and/or falls. All AEs should be assessed to consider if they constitute a 'serious adverse event' below.

6.1.2 Serious adverse events

A Serious Adverse Event is an AE that fulfils one or more of following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition or immediate intervention was required to prevent one of the above.

.

Where participants are lost to follow-up, we will contact clinical teams to ask to document or record SAEs wherever possible e.g. from clinic records.

6.1.3 Assessing and reporting SAEs and related SAEs

All reportable **SAEs** occurring from the time of randomisation until one-year post-randomisation must be recorded on the SAE Form and emailed to WCTU (who will receive SAEs on behalf of the Sponsor), **within 24 hours** of the research staff becoming aware of the event.

For each **SAE** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to intervention), in the opinion of the investigator
- whether the event would be considered expected or unexpected (to be assessed and added by a delegate of the Sponsor).

Any change of condition or other follow-up information should be sent to WCTU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. An outcome of 'unknown' is not considered to be an acceptable final outcome. An outcome of 'not yet resolved' is an acceptable final outcome for non-serious AEs at the end of a patient's participation in a trial, and for SAEs at database lock.

SAEs, except for those listed as exemptions, will be reported using the SAE form. The PI or an appropriate delegate in each centre must report any SAEs to the trial coordinating centre within 24 hours of them becoming aware of the event. In the event that a clinical delegate of the PI is unable to assess causality within 24 hours, or is unavailable, any nominated person on the delegation log may send a partially completed SAE form. Further details should then be sent by site as soon as practically possible.

AEs or SAEs may be identified by the coordinating centre from the CRFs, either from specific questions or from answers within PROMs. If this occurs, the coordinating centre may query the site for details of the event either if it is unclear, or in the case of all SAEs (for the purposes of the sites own clinical governance). This will be determined on a case-by-case basis, and the potential to do so will be included in the participant information sheet (PIS).

The SAE form should be emailed to the study team: BigToeTrial@warwick.ac.uk and WCTU QA team: wctuqa@warwick.ac.uk. The TM will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected SAEs (i.e. events that are serious, related, and unexpected to the sponsor and REC within required timelines. Events which are possibly, probably or definitely related to the trial intervention and are unexpected **will be reported to the REC within 15 days**. To note, any adverse event which is serious and considered related to the insert would be unexpected and therefore reported to the REC.

The legal responsibility for reporting SAEs lies with the manufacturer or their authorised representative. However, the MHRA also has a voluntary reporting requirement for 'users' of devices i.e. where a device is being used in a trial in which the manufacturer has no involvement, and in this case, the coordinating centre would submit the appropriate reports and also inform the manufacturer of the event.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form using the following descriptions:

Table 3: Definitions of Causality

Relationship to trial device	Description
Unrelated	There is no evidence of any causal relationship

Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other co- treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

The following process will be used to review individual SAEs

- Clinical review (by a clinical TMG member) of a line listing of all life-threatening SAEs or SAEs resulting in death within one week of their occurrence.

The following process will be used to independently monitor trends in SAEs in addition to usual trial safety monitoring procedures.

- Cumulative review of all safety information by the DMC on a regular basis.

A member of the Principal Investigator's trial team will be instructed to closely monitor each participant who experiences an AE until the outcome of the AE has been determined.

6.2 Responsibilities

Principal Investigator (PI) or Delegate:

- Checking for AEs when participants attend for treatment / follow-up.
- Using medical judgement in assigning seriousness and causality.
- Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within two working days of initial reporting.
- Ensuring that AEs are recorded in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning causality.
- Assessment of expectedness

- Immediate review of all related and unexpected SAEs
- Review of AEs/SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

Sponsor (University of Warwick):

- All AEs (which meet the criteria in 6.1.1) will be recorded in the CRF
- Central data collection and verification of AEs, and SAEs, according to the trial protocol.
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit according to the Trial Monitoring Plan.
- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and/or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
- Expedited reporting of related and unexpected SAEs to the REC within required timelines.
- Notifying Investigators of related and unexpected SAEs that occur within the trial.
- The unblinding of a participant for the purpose of expedited reporting, only where strictly necessary.

TSC

- In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

DMC

- In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

6.3 Notification of deaths

All deaths where there may be a relationship between the trial interventions or the condition being studied will be reported by the CI to the sponsor. This report will be as soon as the CI becomes aware of the event. Reporting processes to other organisations (REC and the manufacturer) will be as documented above.

6.4 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than three days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

6.5 Assessment and management of risk

Carbon fibre shoe inserts are currently used in the NHS.

A risk assessment for the trial will be performed according to Warwick Standard Operating Procedures (SOP) and a monitoring plan developed depending on the risks identified. Risks specific to the trial include risks of data breaches, incorrect allocation, or failure to recognise safety concerns. These risks will all be carefully managed by following University of Warwick SOPs and careful adherence to the principles of Good Clinical Practice (GCP).

7. Data management

Personal data collected during the trial will be handled and stored in accordance with the 2018 Data Protection Act and UK GDPR. Confidential data will be handled in line with the Common Law Duty of Confidentiality.

Personal identifying information will be collected via the online database and stored electronically at WCTU. Participant details will be entered by staff at sites or WCTU, and will be stored and accessed via staff at WCTU to confirm eligibility and consent; allow postage of participant questionnaires; contact participants during the trial; and contact for qualitative interviews. Handling of personal and confidential data will be clearly documented in the participant information sheet and consent obtained.

Data containing of personal identifying information (participant contact details or consent forms) will be stored separately from the remaining trial data to safeguard it

Disclosure of confidential information will only be considered if there is an issue which may jeopardise the safety of the participant or another person, according to Warwick Standard Operating Procedures (SOP 15 part 1) and the UK regulatory framework. There is no reason to expect this situation to occur in this trial more than any other.

7.3 Data collection and management

The CRFs will be developed by the TM in consultation with CI, Trial Statistician, Health Economist and other relevant members of the trial team to collect all required trial data. In the first instance documents will be produced in English and other languages will be considered after the pilot phase.

All data will be entered directly either by participants, by site staff or by WCTU trial team members onto a secure online database hosted by WCTU as outlined in the data management plan and accordance with the Warwick SOPs.

Data entered onto the online study database by site staff or participants will be source data. This will be stored on Warwick secure servers. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

Various methods will be used to chase missing data including phone, text and email. Participants will receive a reminder to complete the online questionnaires at each study time point. Participants will also be offered paper-based questionnaires for completion if preferable. If a participant has not completed a study questionnaire following the reminder, the BigTOE trial team will contact the participant to encourage them to complete the questionnaire online, and to provide support where required. If data remains missing following this chase, the BigTOE trial team will contact the participant to attempt to collect the outcome measurements with priority on the core measures (MOXFQ and EQ5D-5L). Missing data at a timepoint will not preclude collection of data at subsequent

follow-up timepoints. The procedures for managing this will be outlined in the data management plan and appropriate consent will be sought to contact participants.

Data will still be collected for participants who discontinue or deviate from the intervention, unless they withdraw their consent (Section 3.9.1). Data that can identify participants by name and their contact details will be deleted once all analysis and participant dissemination is complete.

7.4 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff.

7.5 Data storage

All essential documentation and trial records will be stored at Warwick Clinical Trials Unit in conformance with the applicable regulatory requirements and access to stored information (paper and electronic) will be restricted to authorised personnel. All paper data will be stored in a designated ar facility within the WCTU (a restricted access building). Electronic data will be stored on password protected university computers in a restricted access building. Guidelines for data management will be outlined in the trial data management plan.

7.6 Data access and quality assurance

Most data will be received directly from participants who will enter their data into the online study database. After the collection of the baseline demographic data for each participant and following randomisation all data will be pseudonymised. Confidentiality will be strictly maintained and names, addresses or personal identifiable information will not be disclosed to anyone other than the staff involved in running the study. All electronic participant-identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Paper forms will be held in secure, locked filing cabinets within a restricted area of WCTU. Participants will be identified by a participant number only on the paper forms. Any identifiable participant hard copy data will be held separately in a locked filing cabinet and coded with the trial number to tag identifiable data to the outcome data.

Direct access to source data (online study database) will be available for study-related monitoring or audit by WCTU for internal audit or regulatory authorities. The PI must arrange for retention of study records on site in accordance with GCP and local Trust's policies.

Direct access to source data/documents will be required for study-related monitoring. For quality assurance, the data and results will be statistically checked. A full data management plan will be produced by the study Trial Manager and Statistician to outline the data monitoring checks required.

7.7 Data Shared with Third Parties

Requests for data sharing will be managed in accordance with Warwick Clinical Trials Unit SOP 15 Part 3. The datasets generated during and/or analysed during the current study are/will be available upon request after publication of the main study results. The publication of a study protocol, study

results and study data will comply with the NIHR standard terms and will follow Warwick SOP 22: Publication & Dissemination.

7.8 Archiving

Trial documentation (including the ISF) and data will be archived for at least five years after completion of the trial.

8. Statistical Analysis

8.3 Power and sample size

The MOxFQ is a 16-item questionnaire with three subdomains to assess standing/walking problems, pain and social interaction in people with foot and ankle problems. It was co-selected with our PPI partners. This scale is well accepted by patients with a range of foot conditions, including painful OA.[26, 39] We will use the Walking/Standing subdomain as our primary outcome, which comprises of seven items.

The standard deviation (SD) of the MOxFQ standing/walking subscale in a previous study of 1st MTPJ pathology was 23 points.[39] To our knowledge, there are no data on a worthwhile difference for conservative interventions for 1st MTPJ OA. However, Dawson *et al*. found that for people undergoing surgery for hallux valgus, the minimum clinically important difference was 16 points for the standing/walking subdomain. As this trial will assess a cheaper, non-surgical intervention, we have set a smaller value to be worthwhile. We have conservatively set the target difference to 8 points on the MOxFQ standing/walking subscale. This corresponds to an improvement in just over two item categories such as: a change from 'All of the time' to 'Some of the time' in one item, or a change from 'Most of the time' to 'Some of the time' in two items. Our patient partners agree that this modest change would be a worthwhile difference, particularly given the lack of other evidence-based treatment options for this condition. This also corresponds to a standardised effect size of 0.35, which is similar to other conservative intervention trials for musculoskeletal conditions (e.g. AIR[40], ARTISAN[41]).

Hence, to show a between group difference of 8 points on the standing/walking sub-score of the MOxFQ, assuming that the SD at three months post randomisation is 23 points, at 90% power and 5% significance, data are needed on 350 participants. Allowing for 20% loss to follow up, whilst aiming to keep this below 10%, 438 participants are required.

Table 4: Considered sample sizes

Between group difference in MOXFQ at 3 months	Effect size	n per group	N per group with 20% ltfu*	Total N (20% ltfu*)
7	0.30	228	285	570
8	0.35	175	219	438
9	0.39	139	173	346

*ltfu = loss to follow-up

8.3.1 Sample size re-estimation

As a robust estimation of the SD of the MOXFQ in this population is unknown, we will conduct a blinded sample size re-estimation to further inform study power. A blinded method will be used as this will not affect the type I error rate. At the end of the internal pilot, when approximately 50 participants have reported their primary outcome measure, the observed SD will be calculated from the blinded (pooled) data and used to re-estimate the sample size. The results will be presented to the oversight committees and the target sample, and if necessary, the sample reduced. An increase is not anticipated, as only large increases, such as 33% are considered worthwhile.[42]

8.4 Statistical analysis of efficacy and harms

8.4.1 Planned recruitment rate

We anticipate a recruitment rate of 1 participant per site per month. With a staggered opening of sites, we anticipate it will take 18 months across approximately 25 sites to complete recruitment.

8.4.2 Internal pilot study and progression criteria

The first nine months of randomisation will act as an internal pilot, with a green target of n=111 randomised, based on staggered opening of sites. We will apply stop-go rules with the same percentage thresholds as used for other recent musculoskeletal trials in our unit (e.g. ARTISAN and RACER (NIHR HTA 13/84/10 & 128768). We will collect follow up data for an additional month to ensure that sufficient data on the primary outcome are collected to inform sample size re-estimation.

If the study meets amber criteria, we will inform the TSC, review all trial processes, open additional sites or adapt trial processes, and review these again within three to six months. If the red criteria are met, we will consider stopping the trial after discussion with the TSC and funder.

Table 5: Feasibility criteria

	Red	Amber	Green
% Threshold	< 66%	66% to 99%	≥ 100%
Recruitment rate of sites per month	< 1	1 – 2	≥ 2
Number of sites opened	< 6	7 – 8	≥ 9
Total number of participants recruited	<73	73 – 110	≥ 111
Primary outcome data received	<36	36 – 54	≥ 55

8.4.3 Statistical analysis plan

A full and detailed Statistical Analysis Plan (SAP) will be developed and agreed with the DMC prior to the primary analysis taking place. Exact details of the sample size estimation procedure will be agreed *a priori* and rules to change the planned sample size agreed prior to the estimation analysis point. Treatment effects will be presented with appropriate 95% confidence intervals. Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level).

Analyses will be conducted as intention to treat basis unless otherwise specified, with exact details of the estimates given in the SAP.

Analyses will predominately carried out using R (www.r-project.org).

8.4.4 Summary of baseline data and flow of patients

Descriptive statistics of baseline and all follow up outcomes will be constructed, dependent on distribution (e.g. means and standard deviations for continuous data). Baseline data will be summarised to check compatibility between treatment arms. Screening data will also be summarised to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent for the study.

A CONSORT flow diagram will be produced and will be regularly updated for TMGs, TSCs and DMCs at the study progresses (http://www.consort-statement.org)

8.4.5 Primary outcome analysis

The primary analysis will be a conducted on an intention to treat basis, using a generalised linear model containing allocation group, recruitment site, baseline function and bilateral/unilaterality, along with any variables found to be meaningfully unbalanced at baseline by chance.

8.4.6 Secondary outcome analysis

Standard statistical summaries (e.g., medians and ranges or means and variances, dependent on the distribution of the outcome) will be presented for the primary outcome measure and all secondary outcome measures. Secondary outcomes will be modelled similarly to the primary outcome, dependent on distribution. Sensitivity analyses will be used to explore modelling assumptions, with both fixed and random effect models used.

Sensitivity analyses to explore the effects of nonadherence or treatment switching may also be conducted to aid inference. We will use per protocol or complier average causal effect analyses (CACE), as appropriate and note that these were the two most common approaches used in our recently published systematic review of adherence in NIHR funded trials.[36]

Missing data will be scrutinised and where possible, reasons for missingness collected. If judged necessary, missing data will be modelled using multiple imputation techniques as a sensitivity analysis.

We will conduct a subgroup analysis to investigate the impact of the Zammit clinical criteria[28], which are specific to the 1st MTPJ, versus NICE criteria for the diagnosis of OA[27], which are not joint-specific. This analysis will follow the primary analysis methods, with an additional interaction term incorporated into the mixed-effects regression model.

9. Health economic evaluation

A detailed health economic analysis plan (HEAP) in concordance with the SAP will be developed. The economic evaluation will aim to assess the cost-utility of carbon fibre shoe-stiffening inserts compared with sham inserts for the management of 1st MTPJ OA in the UK NHS setting. The analysis will be carried out from the perspective of the NHS and personal social services (PSS)[43]. The evaluation will be designed, conducted, and reported following best-practice guidelines conforming to the Consolidated Health Economics Evaluation Reporting Standards (CHEERS)[44].

Healthcare resource utilisation data will be collected from baseline to the 12-month follow-up for both groups using CRFs by site staff and by participants using self-report questionnaires during each follow-up assessment. The resource utilisation will aim to capture the key cost drivers associated with 1st MTPJ OA management including the costs of carbon fibre shoe-stiffening inserts, sham inserts, any healthcare visits, hospital admissions and medications. Healthcare resource use will be costed using appropriate cost data from local and national databases in £ sterling to the most relevant price year available at the time of the analysis. Any prices not in that financial year will be reflated to current prices.

To estimate quality-adjusted life years (QALYs), health-related quality of life (HRQoL) will be assessed at baseline, three, six, and 12 months using the EQ-5D-5L instrument. Using the trapezoidal rule, responses will be used to generate QALYs based on the UK value set (scoring algorithm) recommended by NICE at the time of analysis[45].

Descriptive statistics will summarise costs and QALYs by the intervention and comparator groups. The pattern of missing data will be examined and accounted for using suitable methods for multiple imputation. Using a bivariate regression for costs and QALYs, the base-case analysis will be conducted under an intention-to-treat (ITT) approach to calculate the incremental cost-effectiveness ratio (ICER), as the additional cost per QALY gained with carbon fibre shoe-stiffening inserts compared to sham inserts. Non-parametric bootstrapping will generate mean values and 95% confidence intervals (CIs) for costs, QALYs, and the ICER. The results will be presented using the cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) will be plotted to illustrate the likelihood of carbon fibre shoe-stiffening inserts being cost-effective compared to sham inserts at the typical willingness-to-pay thresholds. Net monetary benefit (NMB) analysis will also be generated, where a positive NMB indicates that the QALYs outweigh the costs. Secondary analyses will include a societal perspective to look at the wider impact on patients and their families. Deterministic and probabilistic sensitivity analyses will be conducted to explore uncertainties surrounding key parameters and

address concerns regarding the generalisability of the study. Subgroup analyses may be conducted to assess the impact of patient characteristics (e.g., age, gender, severity of OA) on the cost-effectiveness of carbon fibre shoe-stiffening inserts compared to sham inserts.

If costs and outcomes do not converge within 12 months, economic modelling will be undertaken to explore costs and benefits over an extended time horizon of using carbon fibre shoe-stiffening inserts and sham insoles. The time horizon and model type are still to be decided. The model will be populated using data from the trial, published literature and expert opinion. Any future costs and benefits will be discounted at 3.5%.

10. Trial organisation and oversight

10.3 Sponsor and governance arrangements

University of Warwick is sponsor for this trial.

10.4 Ethical approval

All required ethical approval(s) for the trial will be sought using the Integrated Research Application System. The trial will be conducted in accordance with all relevant regulations.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D agreement is received by Warwick Clinical Trials Unit.

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, analyses) will be communicated by the trial team to relevant parties i.e. investigators, RECs, participants, NHS Trusts, trial registries, journals, as appropriate.

The REC and sponsor will be notified of the end of the study (whether the study ends at the planned time or prematurely). The CI will submit a final report with the results to the Funder by the end of the contract.

10.5 Trial Registration

The study will be registered on the International Standard Randomised Controlled Trial Number (ISRCTN) Register.

10.6 Trial non-compliances and serious breaches to GCP and/or trial protocol

Deviations from clinical trial protocols, GCP, and the formal requirements in place for a clinical trial occur commonly in clinical studies. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. Violation is a failure to comply with or variance from GCP and/or the final approved protocol. This results from error, fraud or misconduct. These cases should be documented in the non-compliance section of the case report form for the trial and appropriate corrective and preventative actions taken. Non-compliances will be included and considered when the clinical trial report is produced, as they may have an impact on the analysis of the data.

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the study; or
(b) the scientific value of the study

The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase and will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that study; or
(b) the protocol relating to that study, as amended from time to time, within 7 days of becoming aware of that breach

10.7 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

10.8 Trial timetable and milestones

Table 6: Trial Timeline

	Month	Recruitment
Start date	01-06-2024	n/a
Set-up	1-6	n/a
Internal pilot study	7-15	111
Main trial recruitment	16-26	438
Follow up	27-38	n/a
Analysis	39-42	n/a

10.9 Administration

The trial co-ordination will be based at WMS/WCTU, University of Warwick.

10.10 TMG

The TMG, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

10.11 TSC

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one ‘lay’ representative. The TSC will have an independent Chairperson. Meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The membership of the TSC is shown on page 3. The membership of the TSC will be approved and appointed by the NIHR.

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

10.12 DMC

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC will meet at the start of the study, potentially together with the TSC and regularly thereafter, as agreed with the committee. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

The membership of the DMC is shown on page 3. The membership of the DMC will be approved and appointed by the NIHR.

DMC meetings will also be attended by the Chief Investigator and Trial Manager (for non-confidential parts of the meeting) and the trial statistician.

The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

10.13 Essential documentation

A Trial Master File will be set up according to Warwick SOP 11 and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

10.14 Financial support

The trial has been funded by a contract award from the NIHR Health technology Assessment programme (NIHR157097)

10.15 Safeguarding researchers and research participants

The trial and all personnel working on it will comply with the University of Warwick's Safeguarding policy https://warwick.ac.uk/services/wss/safeguarding/

11. Monitoring, audit, and inspection

The study will be monitored by the trial team with support from the Quality Assurance team at WCTU as representatives of the Sponsor, study coordinating centre and academic lead, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring will be specified in a study monitoring plan determined by the risk assessment undertaken prior to the start of the study. A Trial Monitoring Plan will be developed and agreed by the TMG based on the study risk assessment, including on site monitoring if applicable. Sites will be expected to assist in monitoring the study. This may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the study internally. Processes to be considered in the monitoring plan will include participant enrolment, consent, eligibility, and allocation to study groups; adherence to study interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. The plan will be available from the study coordination centre. Whilst any on-site monitors work in the same institution as the study team (WCTU), they will act independently in this role.

12. Patient and public involvement (PPI)

This trial has been developed following in depth patient and public involvement. At the heart of the trial leadership we have two patient partners on our TMG, and PPI representatives on our TSC to provide oversight.

We will also create a wider and more diverse PPI reference group of people with experience of living with 1st MTPJ OA.

Our patient partners and PPI representatives will be supported by the Chief Investigator, and PPI Lead, and through the peer support of lay partners on existing trials. Our patient partners are already experienced in their roles, being long standing members of the Keele Research User Group. Further training and support for all members is offered through WCTU and through University Hospitals Coventry and Warwickshire NHS Trust's R7D department who run regular lay seminars, group training, and other events through their Patient Research Advisory Group. All activity will be reimbursed at INVOLVE rates, for which there is adequate provision in the budget.

13. Dissemination and publication

The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication.

The success of the trial depends on the collaboration of participants, clinicians, and researchers from across the UK. Authorship confers credit and has important academic, social, and financial implications. Authorship also implies responsibility and accountability for published work. Therefore, credit for contribution will be determined using the ICMJE Criteria for authorship, and non-author contributions will be acknowledged (https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

Full results of the study will be prepared by the research team and lay partners and submitted to funders as a final report. Findings will be submitted to peer-reviewed journals and disseminated to the medical and exercise rehabilitation communities. We will publish papers in open-access journals including the study protocol, as per recommended guidance for transparent reporting, the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org), the

NIHR standard terms, and Warwick SOP 22: Publication & Dissemination. University of Warwick will review and approve all publications. We will submit abstracts to national and international conferences.

Our lay partners will help prepare the final report and assist with dissemination of study results. We will produce a lay summary for participants and the hospitals/centres involved. Results will be publicised via the study website and social media. At the end of the study, we will host a joint investigator and participant event to promote key findings. The trial results will be relevant to the NHS thus outputs will follow the usual route into the NHS system and wider society.

14. References

1. Roddy, E., et al., *The population prevalence of symptomatic radiographic foot osteoarthritis in community-dwelling older adults: cross-sectional findings from the clinical assessment study of the foot.* Ann Rheum Dis, 2015. **74**(1): p. 156-63.
2. Thomas, M.J., et al., *The population prevalence of foot and ankle pain in middle and old age: a systematic review.* Pain, 2011. **152**(12): p. 2870-2880.
3. Bergin, S.M., et al., *Impact of first metatarsophalangeal joint osteoarthritis on health-related quality of life.* Arthritis Care Res (Hoboken), 2012. **64**(11): p. 1691-8.
4. Bowen, C., et al., *Natural History of Radiographic First Metatarsophalangeal Joint Osteoarthritis: A Nineteen-Year Population-Based Cohort Study.* Arthritis Care Res (Hoboken), 2020. **72**(9): p. 1224-1230.
5. Quintana, J.M., et al., *Prevalence of knee and hip osteoarthritis and the appropriateness of joint replacement in an older population.* Arch Intern Med, 2008. **168**(14): p. 1576-84.
6. Menz, H.B., et al., *Effectiveness of Foot Orthoses Versus Rocker-Sole Footwear for First Metatarsophalangeal Joint Osteoarthritis: Randomized Trial.* Arthritis Care Res (Hoboken), 2016. **68**(5): p. 581-9.
7. Paterson, K.L., et al., *Effect of foot orthoses vs sham insoles on first metatarsophalangeal joint osteoarthritis symptoms: a randomized controlled trial.* Osteoarthritis Cartilage, 2022. **30**(7): p. 956-964.
8. Sornsakrin, P., et al., *Using flexible carbon fiber insoles for 1st metatarsophalangeal arthritis lead to pain reduction and high compliance rate: A Randomized Controlled Trial.* medRxiv, 2021: p. 2021.04.05.21253422.
9. Munteanu, S.E., et al., *Shoe-stiffening inserts for first metatarsophalangeal joint osteoarthritis: a randomised trial.* Osteoarthritis Cartilage, 2021. **29**(4): p. 480-490.
10. NICE, *Oateoarthtritis in over 16s: diagnosis and management (NG 226)*, N.I.f.H.a.C. Excellence, Editor. 2022: London.
11. Paterson, K.L., et al., *Management of first metatarsophalangeal joint osteoarthritis by physical therapists and podiatrists in Australia and the United Kingdom: a cross-sectional survey of current clinical practice.* J Foot Ankle Res, 2020. **13**(1): p. 14.
12. Torjesen, I., *Number of patients waiting 18 weeks for treatment in England passes three million.* Bmj, 2023.
13. England, N. *Consultant-led referral to treatment waiting times data 2022-23*. 2022-23 08/05/2023]; Available from: https://www.england.nhs.uk/statistics/statistical-work-areas/rtt-waiting-times/rtt-data-2022-23/.
14. Chapman, L.S., et al., *A survey of foot orthoses prescription habits amongst podiatrists in the UK, Australia and New Zealand.* J Foot Ankle Res, 2018. **11**: p. 64.
15. Munteanu, S.E., et al., *Interventions for treating osteoarthritis of the big toe joint.* Cochrane Database of Systematic Reviews, 2022. **Draft**.
16. Halstead, J., *Orthoses and their place in the treatment of painful great toe osteoarthritis - Taking the next steps.* Osteoarthritis Cartilage, 2022. **30**(7): p. 909-910.
17. Jerilyn, T.X., et al., *Effectiveness of Shoe Stiffening Inserts for First Metatarsophalangeal Joint Osteoarthritis: A Proof-of-Concept Study.* Am J Phys Med Rehabil, 2016. **95**(2): p. 103-11.

18. McClelland, J.A., et al., *Effects of Shoe-Stiffening Inserts on Lower Extremity Kinematics in Individuals With First Metatarsophalangeal Joint Osteoarthritis.* Arthritis Care Res (Hoboken), 2022. **74**(11): p. 1849-1856.
19. NICE, *Osteoarthritis: Care and Management*, N.I.f.H.a.C. Excellence, Editor. 2020: London.
20. International, F., et al., *International Foot and Ankle Osteoarthritis Consortium review and research agenda for diagnosis, epidemiology, burden, outcome assessment and treatment.* Osteoarthritis Cartilage, 2022. **30**(7): p. 945-955.
21. Alliance, J.L. *Foot Health Top 10 Research Priorities*. 2019; Available from: https://www.jla.nihr.ac.uk/priority-setting-partnerships/foot-health/top-10-priorities.htm.
22. Thomas, M.J., et al., *"Somebody to say 'come on we can sort this'": a qualitative study of primary care consultation among older adults with symptomatic foot osteoarthritis.* Arthritis Care Res (Hoboken), 2013. **65**(12): p. 2051-5.
23. Moher, D., K.F. Schulz, and D.G. Altman, *The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials.* Lancet, 2001. **357**(9263): p. 1191-4.
24. Chapman, L.S., et al., *Developing a core outcome set for foot and ankle disorders in rheumatic and musculoskeletal diseases: A scoping review and report from the OMERACT 2022 foot and ankle special interest group session.* Seminars in Arthritis and Rheumatism, 2023. **61**.
25. Morley, D., et al., *The Manchester-Oxford Foot Questionnaire (MOXFQ): Development and validation of a summary index score.* Bone Joint Res, 2013. **2**(4): p. 66-9.
26. Whittaker, G.A., et al., *Measures of Foot Pain, Foot Function, and General Foot Health.* Arthritis Care Res (Hoboken), 2020. **72 Suppl 10**: p. 294-320.
27. NICE, *NICE Guideline (NG226) Osteoarthritis in over 16s: diagnosis and management* 2022, National Insitute for Health and Care Excellence: London.
28. Zammit, G.V., S.E. Munteanu, and H.B. Menz, *Development of a diagnostic rule for identifying radiographic osteoarthritis in people with first metatarsophalangeal joint pain.* Osteoarthritis Cartilage, 2011. **19**(8): p. 939-45.
29. Garrow, A.P., et al., *The grading of hallux valgus. The Manchester Scale.* J Am Podiatr Med Assoc, 2001. **91**(2): p. 74-8.
30. Research, N.I.f.H.a.C. *Under-Served Communities*. 2024 03/06/24]; Available from: https://www.nihr.ac.uk/about-us/our-key-priorities/under-served-communities.htm#:~:text=%E2%80%9CA%20group%20that%20is%20less,population%20prevalence%20and%20healthcare%20burden.%E2%80%9D.
31. Research, N.I.f.H.a.C. *NIHR INCLUDE GUIDANCE*. 2024 [cited 2024 03/06/24]; Available from: https://sites.google.com/nihr.ac.uk/include/home/guidance.
32. Arnold, S., et al., *Meniscal Transplant surgery or Optimised Rehabilitation full randomised trial (MeTeOR2): a study protocol.* BMJ Open, 2024. **14**(6): p. e085125.
33. Felson, D.T., et al., *Recommendations for the conduct of efficacy trials of treatment devices for osteoarthritis: a report from a working group of the Arthritis Research UK Osteoarthritis and Crystal Diseases Clinical Studies Group.* Rheumatology (Oxford), 2016. **55**(2): p. 320-6.
34. McCormick, C.J., D.R. Bonanno, and K.B. Landorf, *The effect of customised and sham foot orthoses on plantar pressures.* J Foot Ankle Res, 2013. **6**: p. 19.

35. Jones, K., M.R. Backhouse, and J. Bruce, *Rehabilitation for people wearing offloading devices for diabetes-related foot ulcers: a systematic review and meta-analyses.* J Foot Ankle Res, 2023. **16**(1): p. 16.
36. Giovanazzi, A., et al., *Current practice in the measurement and interpretation of intervention adherence in randomised controlled trials: A systematic review.* Contemp Clin Trials, 2022. **118**: p. 106788.
37. Munteanu, S.E., et al., *Shoe-stiffening inserts for first metatarsophalangeal joint osteoarthritis (the SIMPLE trial): study protocol for a randomised controlled trial.* Trials, 2017. **18**(1): p. 198.
38. Ritchie, J. and L. Spencer, *Qualitative Data Analysis for Applied Policy Research*, in *Analyzing Qualitative Data*. 1994, Routledge: London.
39. Dawson, J., et al., *The MOXFQ patient-reported questionnaire: assessment of data quality, reliability and validity in relation to foot and ankle surgery.* Foot (Edinb), 2011. **21**(2): p. 92-102.
40. Kearney, R., et al., *Use of cast immobilisation versus removable brace in adults with an ankle fracture: multicentre randomised controlled trial.* BMJ, 2021. **374**: p. n1506.
41. Kearney, R.S., et al., *Acute Rehabilitation following Traumatic anterior shoulder dISlocAtioN (ARTISAN): protocol for a multicentre randomised controlled trial.* BMJ Open, 2020. **10**(11): p. e040623.
42. Gould, A.L., *Sample size re-estimation: recent developments and practical considerations.* Stat Med, 2001. **20**(17-18): p. 2625-43.
43. NICE, *Guide to the methods of technology appraisal*. 2013, London: National Institute for Health and Care Excellence
44. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations.* BMJ, 2022. **376**: p. e067975.
45. NICE. *Position Statement on use of the EQ-5D-5L value set for England*. 2019; Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l.
46. Magee, D., *Orthopaedic Physical Assessment*. 1987, Philidelphia: Saunders.
47. Menz, H.B., et al., *Validity of self-assessment of hallux valgus using the Manchester scale.* BMC Musculoskelet Disord, 2010. **11**: p. 215.

15. Appendix 1: Clinical criteria for assessment of 1st MTPJ OA

The criteria are:

- Duration of pain in 1st MTPJ in months
- Presence of a dorsal exostosis (bony lump) on dorsal surface of joint
- Hard end-feel to dorsiflexion
- Crepitus during dorsiflexion
- Range of 1st MTPJ dorsiflexion

Details of Assessment

Duration of pain: pain duration (in months) to be assessed using a single open-ended question "How long have you had pain in your big toe joint?"

Dorsal exostosis: the presence of a definite dorsal bony exostosis (lump) is to be determined via visual observation and palpation of the 1st MTPJ by the assessor.

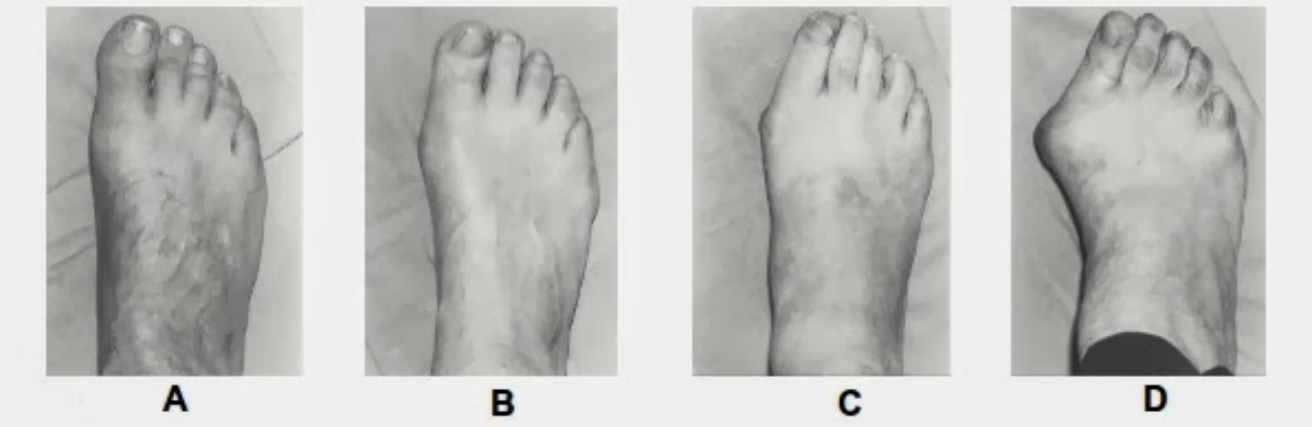
Hard end-feel: the assessor to grasp the proximal phalanx and dorsiflex the toe until movement is no longer possible. A positive test result will be concluded if a hard osseous end-feel was determined as opposed to a gradual end-feel of joint motion[46].

Crepitus during dorsiflexion: the assessor to apply compressive force while moving the joint through its full range of dorsiflexion motion. Any crepitus is to be considered positive.

First MTPJ dorsiflexion range of motion: the passive, non-weightbearing, dorsiflexion range of motion of the first MTPJ will be assessed.

Adapted from Zammit et al 2011[28]

16. Appendix 2: Manchester Hallux Valgus Scale



Grade 1	Grade 2	Grade 3	Grade 4
(no deformity)	(mild deformity)	(moderate deformity)	(severe deformity)

Figure 2: Hallux valgus (bunion) grading photographs. A, Grade 1 (no deformity); B, Grade 2 (mild deformity); C, Grade 3 (moderate deformity); D, Grade 4 (severe deformity)

Taken from Menz et al [47]