Trial Title: Comparing the effectiveness of computer-aided-design computer-aided-manufacture (CAD/CAM) insoles manufactured from foam-box cast vs direct scan on patient reported outcome measures: A double-blinded, randomised controlled trial

Short title: Comparing clinical outcomes using two insole manufacture techniques

London Stanmore REC Reference: 22/LO/0579
NHS GGC R&I No: GN22OR165

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Chief Investigator Signature:

Conflicts of interest: The Sponsor and investigation team have no conflicts of interest in this study

Confidentiality Statement:

This document contains confidential information that must not be disclosed to anyone other than the Investigator Team, HRA, participating site, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V2.0	08/09/2022	Laura Barr	Per recommendation from London-Stanmore REC: The term "Feasibility" removed from all trial documentation, in acknowledgement that this is a full clinical trial. The term "feasibility outcomes" changed to "tertiary outcomes".
2	V2.0	08/09/2022	Laura Barr	Page 1: REC reference added.
3	V2.0	08/09/2022	Laura Barr	Section 2: Start date, recruitment end date and trial end date updated to reflect approval dates from REC.

Protocol amendments will be listed here whenever a new version of the protocol is produced.

2. SYNOPSIS

Study Title	Comparing the effectiveness of computer-aided-design computer-aided-manufacture (CAD/CAM) insoles manufactured from foam-box cast vs direct scan on patient reported outcome measures: A double-blinded, randomised controlled trial
Internal ref. no.	R&I no GN22OR165
Type of study	A single centre, double blinded, randomised controlled trial
Trial Design	Interventional, equivalence Trial design.
Trial Participants	Participants with a medical condition or lower limb biomechanical deficit which would commonly be treated with the use of insoles, as per the NHS Greater Glasgow and Clyde MSK Foot and Ankle Pathway: http://www.clinicalknowledgepublisher.scot.nhs.uk/Published/PathwayViewer.aspx?fileId=119
Planned Sample Size	114 (57 per group)
Follow-up duration	Total duration of individual participant involvement: 14-16 weeks total. Including initial assessment and fitting 2-4 weeks, and 12-week follow-up.
Planned Trial Period	Total Project length: 12 Months Expected Recruitment Start date: 29/09/2022 Expected Recruitment End date: 29/06/2023 Anticipated Trial End Date (all participants completed recruitment, completed intervention, completed all follow up, all data collected and all issues resolved): 29/09/2023
Primary Objective	To compare the changes in pain in two groups of participants fitted with custom CAD/CAM insoles manufactured using different foot shape capture methods
Secondary Objectives	1. To compare the changes in foot function in two groups of participants fitted with custom CAD/CAM insoles manufactured using different foot shape capture methods 2. To compare the changes in foot health in two groups of participants fitted with custom CAD/CAM insoles manufactured using different foot shape capture methods 3. To compare the participant satisfaction in two groups of participants fitted with custom CAD/CAM insoles manufactured using different foot shape capture methods 4. To compare the time-in-transit and cost-time analysis of the custom CAD/CAM insoles manufactured using different foot shape capture methods 5. To compare the environmental impact of custom CAD/CAM insoles manufactured using different foot shape capture methods
Tertiary Objectives	1. Recruitment rate 2. Participant compliance with the study protocol / Adherence 3. Adverse events 4. Drop-out rate

Device Type	Custom, Computer aided design (CAD) Computer aided manufacture (CAM), Ethylene-vinyl acetate (EVA) Foot Orthoses (insoles)
Manufacturer Name	Manufactured in the NHS Greater Glasgow and Clyde Orthotic Department, at Gartnavel General Hospital. Manufactured using the Paromed Paromanager CAD/CAM system
Principle intended use	For the use of any persons with a medical condition or lower limb biomechanical deficit which would commonly be treated with the use of insoles, as per the NHS GGC MSK Foot and Ankle Pathway: http://www.clinicalknowledgepublisher.scot.nhs.uk/Published/PathwayViewer.aspx?fileId=119
Length of time the device has been in use.	These devices are currently used as a standard care across NHS services in the UK, and have been for many years. Both methods of shape-capture are standard clinical practice across the UK. No novel techniques or devices are under investigation within this trial.

3. ABBREVIATIONS

ACRT	Advanced Clinical Referral Triage
AE	Adverse event
AR	Adverse reaction
CAD	Computer aided design
CAM	Computer aided manufacture
CI	Chief Investigator
Co-I	Co-Investigator
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
EVA	Ethylene-vinyl acetate
FHSQ	Foot Health Status Questionnaire
GDPR	General Data Protection Regulation
GGC	Greater Glasgow and Clyde
GGH	Gartnavel General Hospital
GRI	Glasgow Royal Infirmary
MHRA	Medicines and Healthcare products Regulatory Agency
MSK	Musculoskeletal
NHS	National Health Service
OPUS CSD	Orthotic and Prosthetic User Survey Client Satisfaction with Device Module
PI	Principal Investigator
PIS	Participant Information Sheet
R&D	NHS Greater Glasgow and Clyde Research & Development Department
REC	Research Ethics Committee
RES	Research Ethics Service

SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure

4. BACKGROUND AND RATIONALE

Computer aided design (CAD) with computer aided manufacture (CAM) foot orthoses (insoles) represent 14% (n=2739, per annum 2020) of all Orthotic Department provision in NHS Greater Glasgow and Clyde (GGC), representing a significant proportion of Orthotic service users, and financial burden to the National Health Service (NHS). The production of CAD/CAM insoles relies on acquiring a digital model of the patient's foot from which the final insole can be produced. This digital model is created either by directly scanning the patient's foot in to the CAD/CAM system to produce a 3D model, or by taking a physical cast of the foot which is then scanned. These two methods of shape-capture are used interchangeably throughout NHS Orthotics services.

In the NHS GGC Musculoskeletal (MSK) Foot and Ankle pathway[1], patients receive insoles via fully digital design and manufacture, utilising direct foot scanning. Other NHS health-boards and Trusts across the UK have adopted a partially digitised approach, whereby shape-capture is achieved with a traditional foam-box casting method. To date, no work has been undertaken to determine the clinical outcomes and economic impact relating to these different treatment approaches.

Digitisation of medical devices in the orthotics industry conceptualised gains in production speed and reduction in waste materials when compared to traditional manufacture utilising physical shape capture[2]. Yet the continued interim stages of foam cast moulds and physical transportation of casts to manufacturers sacrifices these benefits. As services began adopting CAD systems in place of traditional manufacture, the standard service model for shape-capture has remained in place on some sites, despite the increased accessibility to mobile direct scanners over the past 10 years[3]. In NHS Scotland, the evolution of insole production with the introduction of CADCAM, has therefore lead to the creation of two industry standards; whereby a recent consultation with NHS Health boards across Scotland have shown some services continuing to use traditional foam-box casts, where others have chosen to utilise direct digital scanning on site.

Motivation and hesitation in transitioning to a fully digital work stream have been assumed, but are currently unsupported by research. A common reluctance to adopt direct scanning is based on the assumption that digital shape capture and foam-box casts do not produce like-for-like models, and therefore cannot result in the production of equally effective insoles. Although differences in volume have been shown[4], the effect on the final device production and ultimately the treatment efficacy and resulting effectiveness have not been evaluated.

Other concerns centralise on costs associated with the acquisition of direct scanning equipment. Although prior cost analyses have shown a fully digital supply chain to be more expensive than a fully traditional supply chain[2], this does not reflect the practices associated with a partially digital workflow as seen across NHS Scotland. Nor does this consider a cost comparison over the life span of a digital scanner, or the environmental impact of the manufacture and transportation of traditional cast materials.

Overall, the evidence base relating to CAD/CAM insoles, demonstrates little consistency or rationale behind the mode of shape-capture used during the process of manufacture. Often the shape-capture method is undocumented or unclear[5-7], or documented without any attributed clinical reasoning[8-16]. In 2019, Parker et al investigated the differences in a fully digital workflow compared with fully traditional manufacturing techniques, but did not investigate the specific impact of shape-capture in isolation. Furthermore, these studies

report no consideration as to the environmental impact of phenolic foam production and disposal required for traditional foot shape-capture[17-18], or the carbon footprint of transportation from manufacturer to digital upload of the foot shape from the foam-box cast, a step which is not required when utilising direct digital scan techniques. In line with NHS Net Zero targets 2020[19], and the recognition of Orthotic Services throughout the UK that largescale change is required to achieve this[20], the practice of single-use traditional shape capture techniques requires immediate scrutiny.

It is clear from the literature and current widespread indiscriminate practices across NHS Orthotic Services, that more research is required to assist with best practice in the manufacture of CAD/CAM insoles. Given the proportion of Orthotic Service users who receive insoles from the NHS, this trial has the potential to guide practice toward beneficial changes in patient outcomes, as well as providing NHS Orthotic departments with information to assist in the development of long-term service models in line with NHS and Government targets.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoints of evaluation of this outcome measure (as applicable)
• Primary Objective To compare the changes in pain in two groups of participants fitted with custom CAD/CAM insoles manufactured using different foot shape capture methods	Foot Health Status Questionnaire (*Appendix 1*) (FHSQ)[21-23] – Pain sub-domain. The minimal important difference has a threshold of a 12.5 point change for pain [24]	Completed at the Second Appointment, Third Appointment, Fourth Appointment and Fifth Appointment
Secondary Objectives 1. To compare the changes in foot function in two groups of participants fitted with custom CAD/CAM insoles manufactured using different foot shape capture methods	1. Foot Health Status Questionnaire – Function sub-domain. The minimal important difference has a threshold of a 7.1 point change for foot function [24]	1. Completed at the Second Appointment, Third Appointment, Fourth Appointment and Fifth appointment
2. To compare the changes in foot health in two groups of participants fitted with custom CAD/CAM insoles manufactured using different foot shape capture methods	2. Foot Health Status Questionnaire – foot health sub-domain. The minimal important difference has a threshold of a -0.4 point change for foot health [24]	2. Completed at the Second Appointment, Third Appointment, Fourth Appointment and Fifth appointment
3. To compare the participant satisfaction in two groups of participants fitted with custom CAD/CAM insoles manufactured using different foot shape capture methods	3. Orthotic and Prosthetic User Survey (OPUS) [25-28] Satisfaction with device survey (*Appendix 2*)	3. Completed at the fifth appointment
4. To compare the time-in-transit and cost-time analysis	4. Time-in-transit – Measurement of	4. Throughout duration of trial

of the custom CAD/CAM insoles manufactured using different foot shape capture methods	transit and delivery times associated with each arm of the trial will be compared. Cost analysis – Costs relating to time-in-transit for each arm of the trial will be compared	
5. To compare the environmental impact of custom CAD/CAM insoles manufactured using different foot shape capture methods	5. Analysis of annual custom insole production in NHSGGC in relation to the environmental impact of the required phenolic foam production[29] and carbon footprint of transportation from manufacturer to digital upload of foam-box cast using carbon foot print calculations[30].	5. Calculated retrospectively from April 2021 – April 2022
Tertiary Objectives Assessment of factors over a defined 9-month recruitment period including:		
1. Recruitment rate	1. Recruitment rate = *n*/recruitment period	1. Throughout recruitment period and calculated at the trial conclusion
2. Participant compliance with the study protocol / Adherence	2. Participants will keep a diary of daily wear time, in accordance with prior publications on measuring Orthotic Adherence[31]. The minimum threshold for adherence is >21 hours per week[32]	2. Data collected from participants at the third appointment, fourth appointment and fifth appointment
3. Adverse events	3. Adverse events	3. Self-reported by participants at any time throughout the trial period
4. Drop-out rate	4. Dropout rate = *n dropout*/duration of trial	4. Collected throughout trial and calculated at trial conclusion

6. TRIAL DESIGN

6.1 Summary of Trial Design

Type of Trial summary:

A single centre, double blinded, randomised controlled trial comparing the effectiveness of two methods of foot shape capture currently used in NHS Orthotic services in Scotland. This is an Interventional, equivalence trial using medical devices (insoles).

Trial Setting summary:

Participant assessment and treatment will be provided in a hospital setting, within the NHS GGC Orthotic Department. There will be one trial site, located at the Glasgow Royal Infirmary (GRI). This trial will minimise participant on-site visits by utilising telephone contacts throughout the participation period to collect relevant participant reported outcome measures (outlined in more detail below). At the conclusion of the participant involvement in the trial, they will transition back to usual care within the NHS GGC Orthotic Department.

Duration of participant involvement and visit summary:

From enrolment to exiting the trial, participants will be involved in the trial for 14-16 weeks.

During the study there will be 5 appointments. Participants will visit the Orthotic Department at GRI for the first appointment and second appointment as per standard practice in the NHS GGC Orthotic Department, and will receive telephone follow-up contact at the third, fourth and fifth appointments:

First appointment: Face-to-Face Hospital visit for screening, consenting, foot/clinical assessment and randomisation. Duration of appointment - 40 minutes.

Second appointment at week 2-4: Face-to-Face Hospital Visit for insole fitting and completion of baseline participant reported outcome measures. Duration of appointment - 40 minutes.

Third appointment at week 6-8: Telephone follow-up appointment to complete participant reported outcome measures and participant self-reporting of insole usage hours/day. Duration of appointment - 15 minutes.

Fourth Appointment at week 10-12: Telephone follow-up appointment to complete participant reported outcome measures and participant self-reporting of insole usage hours/day. Duration of appointment - 15 minutes.

Fifth Appointment at week 14-16: Telephone follow-up appointment to complete participant reported outcome measures and participant self-reporting of insole usage hours/day. Duration of appointment - 15 minutes.

Data collection summary:

Participant reported outcome measures:-

Eligible participants will complete the Foot Health Satisfaction Questionnaire (FHSQ) at their second appointment, third appointment, fourth appointment and fifth appointment. The Orthotic and Prosthetic User Survey (OPUS) questionnaire will be collected at the fifth appointment.

Tertiary outcomes:-

Participant self-reported insole usage will be collected by the PI at the third appointment, fourth appointment and fifth appointment to monitor compliance with insole use.

Outcomes relating to time in transit, cost-analysis, recruitment rate and dropout rate will be reported by the PI at the timescales as indicated in section 6. Objectives and Outcome Measures.

Assessment findings:-

Findings from the assessment as outlined in section 6.4.2 of this protocol will be collected at the first appointment. Any changes to medication throughout the trial will be collected during third appointment, fourth appointment, and fifth appointment.

Adverse events:-

Adverse events reported by participants at any time during the trial will be addressed as outlined in section 8 of this protocol.

6.2 Trial Participants

6.2.1 Overall Description of Trial Participants

Participants with a medical condition or lower limb biomechanical deficit which would commonly be treated with the use of insoles as a first or second line intervention, as per the NHS GGC MSK Foot and Ankle Pathway: http://www.clinicalknowledgepublisher.scot.nhs.uk/Published/PathwayViewer.aspx?fileId=1199

6.2.2 Inclusion Criteria

All participants:

- Are aged 18 years or above
- Are referred to the NHS GGC Orthotic service requiring a new assessment for insoles
- are deemed suitable for CAD/CAM insoles as assessed by the PI or Co-I on clinical assessment
- Are able to commit to five appointments over a 16-week period (two Face-to-Face appointments, three Telephone Appointments)
- Have suitable own footwear that can accommodate a CAD/CAM insole as assessed by the PI or Co-I, and as per standard practice can wear these for 12-weeks

- An adequate understanding of written and verbal information in English in order to provide informed consent and answer the study questionnaires

6.3.3 Exclusion Criteria

Potential participants will not enter the trial if any of the following apply:

- Scheduled elective surgery or other procedures which is likely to affect mobility during the trial.
- Scheduled steroid injection to the foot or ankle up to 3 months prior to joining the trial, or during participation in the trial
- Age <18 years
- Adult with Incapacity, under The Adults with Incapacity (Scotland) Act 2000
- Participant unable or unwilling to consent
- Medial longitudinal arch height of the foot exceeds depth of EVA blank (35mm)
- Clinical assessment concludes that the participant requires an insole material other than EVA
- Clinical assessment concludes that the participant does not require or will be unlikely to benefit from CAD/CAM insoles.
- The participant is unable to commit to the trial conditions.
- Peripheral Neuropathy present
- Active foot ulceration present
- Participant with life expectancy of less than 6 months.
- Any other significant disease or disorder which, in the opinion of the PI or Co-I, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
- Participants who have participated in another research trial involving an investigational foot orthosis in the past 12 weeks.

6.4 Study Procedures

6.4.1.1 Recruitment

Potential participants will be made aware of the trial and will receive a Participant Information Sheet (PIS) in the following way:

During the Advanced Clinical Referral Triage (ACRT) process, which is standard practice in the NHS GGC Orthotic service, all new patient referrals are reviewed by an Orthotist

and patients are contacted by telephone prior to being added to the waiting list. During the ACRT process Orthotists may mention the trial to potential participants, and post/email the PIS if requested. The PIS will invite potential participants to make contact with the research team for further information or to discuss eligibility or any questions that the potential participant may have. The PIS assures the potential participants that participation or otherwise in the research will not affect their care in any way.

For potential participants that respond indicating a willingness to be contacted, they will be contacted by the PI by telephone to provide more information about the study and if the potential participant(s) is still interested in the study, the PI will screen for eligibility. The research team will provide opportunities to answer any questions regarding the study, and the potential participant will be offered the choices of i) declining further participation, ii) arrange a date/time for the First Appointment at the time of the telephone contact or iii) to receive a follow-up telephone contact approximately one week later after initial contact has been made.

For those potential participants that do not respond to the invitation letter, after two weeks the PI, who is a member of the direct care team at the Orthotic Department in NHS GGC, will make one telephone call to the potential participant to see whether they have received the PIS and have any questions related to the study. The potential participant will be offered the choices of i) declining further participation, ii) a date/time for the First Appointment at the time of the telephone contact or iii) receiving a follow-up telephone contact approximately one week later, by a member of the research team, if the potential participant consents for their details to be shared with the PI.

6.4.1.2 Informed Consent

At the First Appointment, participants who wish to participate in the trial will be invited to provide informed, written consent, by personally signing and dating the latest approved version of the informed consent form before any study specific procedures are performed. Consent will be taken by the PI with a witness if required by the participant and recorded on a pre-printed consent form. The right of the participant to refuse consent without giving reason will be respected. Further, the participant will remain free to withdraw from the study at any time without giving reason and without prejudicing any further treatment. The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. A copy of the consent form will be given to the participant, one filed in the CRF, and one filed in the hospital notes. The written consent will be obtained by the PI, who is fully trained in Good Clinical Practice. The process of obtaining written consent will be clearly documented in the participant's medical notes.

6.4.2 Screening and Eligibility Assessment

Screening and Eligibility assessment will all take place at the First Appointment.

Protocol waivers are not permitted in this trial.

Rescreening will not be permitted, as it is unlikely that a participant who does not meet the inclusion criteria on first screening, will be able to meet this at a later date within the trial period.

Participants will be assessed and screened according to the inclusion and exclusion criteria in sections 6.2.2 and 6.3.3 of this protocol. This will involve:

- Review and recording of relevant medical history from the participant's medical record, which is standard practice in the NHS GGC Orthotic department.
- Review and recording of the following groups of medications routinely taken by the participant: Biologics, DMARDs, NSAIDs, oral steroids, or analgesics.
- Diagnosis of foot and ankle pathology i.e. Plantar fasciopathy, tendinopathy, arthropathy etc.
- Physical examination of the foot and ankle, including recording the outcomes of the following standard biomechanical tests –
    1. Foot Posture Index [33]
    2. Jacks test for Functional Hallux Limitus [34]
    3. Palpation technique for Subtalar Joint Axis Location [35]
    4. Passive assessment of ankle dorsiflexion stiffness by 'position of first detectable resistance [36]
    5. Supination resistance test [37]
    6. Visual gait analysis

6.4.3 Baseline Assessments

First Appointment – face-to-face visit at the NHS GGC GRI Orthotic clinic, as per standard practice

1. Participant physically attends the clinic
2. Participant is assessed by the PI and Co-I, using the assessment methods outlined above in section 6.4.2
3. Insole specification agreed between the PI, Co-I and participant
4. Participant is assigned a unique participant number.
5. ALL participants receive a direct scan and a foam-box cast, using the methods outlined above in section 9.2
6. PI exits – blinded to the randomisation group
7. Co-I randomises the participant to the treatment arm by opening one of the sealed envelopes: The treatment arm will indicate if the insoles will be manufactured using the direct scan or the foam-box cast.
8. Participant is not informed of the randomisation outcome – blinded to treatment arm
9. Participant is invited to a fitting appointment with the PI in 2-4 weeks and leaves the clinic
10. Co-I creates an insole order on the standard Orthotic department ordering system

11. Co-I sends ALL foam-box casts to Gartnavel General Hospital to be scanned into the CAD/CAM system. The CAD/CAM system records the time and date of each scan, which will be used to inform the time-in-transit aspect of the trial.
12. PI undertakes modelling of both the direct scan and the scanned foam-box cast.
13. Co-I documents the specific functional elements of the insole on the excel data spreadsheet against the unique participant number
14. Co-I documents the assessment findings for each of the biomechanical assessment methods (outlined in section 9.2 of the protocol) on the excel data spreadsheet against the unique participant number

6.4.4 Randomisation and Codebreaking

The trial has been registered on the web based registration system http://www.Clinicaltrials.Gov, and assigned trial number NCT05444192.

Randomisation:

All eligible participants will receive their randomised treatment/insole at the First Appointment, after they have been screened, assessed, and consented to join the trial. Randomisation will be conducted according to a random number algorithm, contained in pre-sealed envelopes, by the CI. The sealed envelopes will be sent to the Co-I and stored securely in a locked filing cabinet in the Glasgow Royal Infirmary Orthotic Department. The envelopes will be opened on a 1:1 basis by the Co-I during the assessment appointment. The PI and the participants will be blinded to the treatment arm.

Blinding:

The PI will be blinded to the allocation group for the duration of the trial. This will be achieved by the PI not being present during the randomisation process at the First Appointment, when the participant will be randomised into one of two treatment arms which will be allocated by the Co-I. Subsequently the PI will not have any access to the insole paperwork which will be removed by administration staff at Gartnavel General Hospital following insole manufacture. The insoles for each participant will be placed in clear plastic bags containing only the participants name and appointment time. The insoles will then be sent to Glasgow Royal Infirmary for the participant fitting appointment, as per standard practice. On arrival at the Glasgow Royal Infirmary, the Co-I will double check that the paperwork has been removed, and the bag contains only the insoles, participant name and appointment time. It is standard practice for the administration staff and the on-site orthotist to double check clinical goods in this way.

There will be no visible difference in the insoles for each treatment arm. CAD/CAM insoles manufactured from direct foot scans and foam-box casts are modelled and milled in the same way and have the same outward appearance.

The participants will be blinded to the allocation group for the duration of the trial. This will be achieved by the Co-I taking both a direct scan and a foam-box cast for each participant.

The participant will not be aware of which scan/cast has been used for the final manufacture of the insoles.

Code-Breaking:

If the clinical condition of a participant necessitates breaking the allocation code, the Co-I (not blinded) will access the CAD/CAM insole ordering system to confirm the treatment-arm. This process will not unbind the whole trial, nor will it disclose the randomisation schedule.

Out of hours code-breaking will not be required due to the low risk level of the intervention.

At the end of the study the data from the two groups will be analysed independently, after which the groups will be releveled.

6.4.5 Subsequent assessments

Second appointment – Fitting of insoles face-to-face visit at NHS GGC GRI Orthotic clinic, as per standard practice

1. Participant receives a reminder call from the PI the day before appointment to confirm attendance
2. PI fits the insoles
3. Participant is advised to wear the insoles for 10 minutes before leaving the clinic
4. If any issues arise during the 10 minutes, PI adjusts the insoles (repeat until no issues when leaving the clinic)
5. PI documents adjustments made against the unique participant number on the excel data sheet.
6. If the participant is unable to wear the insoles for any reason they will exit the trial at this stage which will be documented as “unable to proceed”. In these instances the participant will be transferred back to the standard orthotic clinic for ongoing treatment as appropriate, and an appointment will be offered within the standard waiting time of 12 weeks at the NHSGGC Orthotic Clinic unless unsuitable for the participant.
7. If continuing within the trial, the participant will be invited to attend a telephone appointment in 4 weeks with the PI
8. Participant completes the FHSQ and the PI calculates the FHSQ scores using the validated FHSQ calculation, and documents these against the unique participant number on the excel data sheet.
9. Participant is asked if there has been any change to their use any of the following groups of medications: Biologics, DMARDs, NSAIDs, oral steroids, or analgesics. This is documented by the PI on the CRF.
10. Participant is asked to keep a daily diary documenting the total number of hours per day that the insoles were worn for.

Third Appointment – 4 Week Review

1. Participant receives a reminder call from the PI the day before appointment to confirm attendance.
2. Participant attends the telephone clinic
3. If the participant is unable to wear the insoles for any reason they will exit the trial at this stage which will be documented as “unable to proceed”, in these instances the

participant will be transferred back to standard orthotic clinic for ongoing treatment as appropriate, and an appointment will be offered within the standard waiting time of 12 weeks at the NHSGGC Orthotic Clinic unless unsuitable for the participant.
4. If continuing with the trial the participant completes the FHSQ
5. Participant reports the daily wear-time of the insoles according to their diary over the past 4 weeks.
6. Participant is asked if there has been any change to their use any of the following groups of medications: Biologics, DMARDs, NSAIDs, oral steroids, or analgesics. This is documented by the PI on the CRF.
7. Participant invited to attend a telephone appointment in 4 weeks with PI
8. PI calculates the FHSQ scores using the validated FHSQ calculation, and documents these against the unique participant number on the excel data sheet
9. PI records the daily wear-time, documenting these against the unique participant number on the excel data sheet.

Fourth Appointment – 8 Week Review

1. Participant receives a reminder call from the PI the day before appointment to confirm attendance.
2. Participant attends the telephone clinic
3. If the participant is unable to wear the insoles for any reason they will exit the trial at this stage which will be documented as “unable to proceed”. In these instances participant will be transferred back to standard orthotic clinic for ongoing treatment as appropriate, and an appointment will be offered within the standard waiting time of 12 weeks at the NHSGGC Orthotic Clinic unless unsuitable for the participant.
4. If continuing with the trial Participant completes the FHSQ
5. Participant reports the daily wear-time of the insoles according to their diary over the past 4 weeks.
6. Participant is asked if there has been any change to their use any of the following groups of medications: Biologics, DMARDs, NSAIDs, oral steroids, or analgesics. This is documented by the PI on the CRF.
7. Participant is invited to attend a telephone appointment in 4 weeks with the PI
8. PI calculates the FHSQ scores using the validated FHSQ calculation, and documents these against the unique participant number on the excel data sheet.
9. PI records the daily wear-time, documenting these against the unique participant number on the excel data sheet.

Fifth Appointment – 12 Week Review

1. Participant receives a reminder call from the PI the day before appointment to confirm attendance.
2. Participant attends the telephone clinic
3. If participant unable to wear the insoles for any reason they will exit the trial at this stage documented as unable to proceed. In these instances participant will be transferred back to standard orthotic clinic for ongoing treatment as appropriate, and an appointment will be offered within the standard waiting time of 12 weeks at the NHSGGC Orthotic Clinic unless unsuitable for the participant.
4. If continuing with the trial Participant completes the FHSQ and OPUS

5. Participant reports the daily wear-time of the insoles according to their diary over the past 4 weeks.
6. Participant is asked if there has been any change to their use any of the following groups of medications: Biologics, DMARDs, NSAIDs, oral steroids, or analgesics. This is documented by the PI on the CRF.
7. The participant is thanked for their involved in the trial, and provided with contact details and self-referral information for the NHS GGC Orthotic Department so that they can continue to access standard care from the department in future on request.
8. PI calculates the FHSQ and OPUS scores using the validated FHSQ and OPUS calculation, and documents these against the unique participant number on the excel data sheet
9. PI records the daily wear-time, documenting these against the unique participant number on the excel data sheet.

6.5 Definition of End of Trial

The trial will conclude when either of the two conditions:

1. The recruitment phase has run for 9-months (plus 12-week follow up of all participants)
2. Participant recruitment = 114 (plus final 12-week follow up of all participants)

AND

- All the enrolled participants have concluded all 5 appointments, and all the data has been entered into the excel data sheet.

6.6 Discontinuation/ Withdrawal of Participants from Study Treatment

During the course of the trial a participant may choose to withdraw early from the trial at any time. This may happen for a number of reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with trial procedures
- Participant decision

The following options for withdrawal from the trial are included on the PIS:

1. Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.
2. Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis.

In addition, the PI may discontinue a participant from the trial treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility arising during the trial – i.e. development of a medical condition as outlined in the exclusion criteria.

- Significant non-compliance with treatment regimen or trial requirements – i.e. participant has not worn or unable to wear the insoles between appointments
- An adverse event which requires discontinuation of the CAD/CAM insoles or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the CAD/CAM insoles – i.e. medically too unwell to continue participation, or disease progression as outlined in the exclusion criteria

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

All participants withdrawn from the trial for any reason, will be offered an appointment at the general NHS GGC Orthotic service to resume their standard care. Contact information for the NHS GGC Orthotic Department is included within the PIS.

6.7 Source Data

Source documents are original documents, data, and records from which participants' Case Report Form (CRF) data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication as specified at each of the participant appointments in section 6 of this protocol, may be summarised into the CRF), diaries, medical imaging reports for relevant radiographs of the foot, MRI of the foot and CT of the foot, and correspondence from the participant. 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). In this study the CRF will be used as the source document for FSHQ data, OPUS data, physical assessment data, and diary of insole wear time data. All other participant information will be sourced from verifiable from source documents (e.g. hospital records, diaries, medical imaging reports for relevant radiographs of the foot, MRI of the foot and CT of the foot, and correspondence from the participant).
All CRF documents will be stored safely in a locked filing cabinet in the Glasgow Royal Infirmary. On all study-specific documents, other than the signed consent form, the participant will be referred to by the unique participant number, not by name.
Source data verification ensures accuracy and credibility of the data obtained. The PI will review the reported data to ensure they are accurate, complete, and verifiable from source documents. All data reported on the CRF will be supported by source documents. Data Verification will be carried out by the PI who will check the CRF for completeness and clarity, and crosscheck them with source documents

7. TREATMENT OF TRIAL PARTICIPANTS

7.1 Description of Study Intervention(s)

The treatment which will be supplied to all participants is a pair of custom, CAD/CAM ethylene vinyl acetate (EVA) foot orthoses (insoles). The insoles are manufactured either from a direct digital scan of the participants feet, or from a foam-box cast of the participants feet which will then be scanned into the CAD/CAM system. This is a standard treatment widely used across Orthotic Services in the UK.

7.2 Maintenance and storage of device

- All Direct Foot scans will be saved by the Co-I in the CAD/CAM insole system at the time of their first appointment, per standard clinical practice.
- All Foam-box casts will be sent by the secure internal NHS mail system to Gartnavel General Hospital to the Orthotic Technician, as per standard clinical practice. The foam-box cast will be scanned and saved by the Orthotic Technician in the CAD/CAM insole system, per standard clinical practice.
- All digital models will also be available for repeat prescriptions for participants attending the NHS GGC Orthotic department again in future once they return to standard care.
- Following manufacture, all physical insoles will be delivered to GGH Orthotic Administrators, as per standard NHS GGC Orthotic Department process.
- All insoles will be placed into clear plastic bags with the participant name and date of appointment attached. No other paperwork will be send to GRI with the insoles.
- Insoles will be sent to the GRI Orthotic Department using a secure internal courier, as per standard clinical practice.
- The Co-I will double check the insoles on arrival at GRI to ensure that only the participant name and date of appointment is contained in the bag with the insoles. It is standard practice for the Orthotist on site at GRI to double check the incoming goods for appointments.
- As per standard practice in the NHS GGC Orthotic Service, the insoles will be stored in the locked in an Orthotic Appointments Cupboard in Glasgow Royal Infirmary until the time of the participant fitting appointment.

7.3 Compliance with Trial treatment

Participant compliance with the trial treatment will be assessed at the Third Appointment, Fourth Appointment and Fifth Appointment by means of discussion with the participant regarding their use of the insoles over the preceding 4-weeks, and by collection of their diary of daily wear time.

7.4 Concomitant Medication

There are no contraindicated medications within the trial design. No medication changes are anticipated as a result of participating in this trial.

7.5 Post-trial treatment

All participants will be offered the opportunity to retain and continue use of the medical device (CAD/CAM insoles) after their participation in the trial has concluded.

8. SAFETY REPORTING

8.1 Definitions

Adverse events (AE)	An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note 1 to entry: This definition includes events related to the investigational medical device or the comparator. Note 2 to entry: This definition includes events related to the procedures involved. Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices.
Serious Adverse Event	An adverse event that led to any of the following: a. death, b. serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function including chronic diseases, or 3. in-patient or prolonged hospitalisation, or 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c. foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment Note 1 to entry: Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
Serious adverse device event (SADE)	A serious adverse device effect (SADE) is any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. A SADE may be anticipated or

	unanticipated.
Unanticipated Serious Adverse Device Effect (USADE)	Unanticipated serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

8.2 Recording and Reporting of Adverse Events

AEs must be recorded, assessed, reported, analysed and managed in accordance with the Research Governance Framework for Health and Community Care and the study protocol. All AEs must be assessed for seriousness. AEs for this study will be recorded within the participant's notes but are not considered reportable.

8.3 Recording and Reporting of Serious Adverse Events

Where an SAE requires recording; full details including the nature of the event, start and stop dates, severity, causal relationship to the device and/or trial procedures, and the outcome of the event will be recorded in the participant's medical notes. These events will be monitored and followed up until satisfactory resolution and stabilisation.

Assessment of causality
I.e., does the event have a "reasonable causal relationship" with any trial specific procedures or the investigational device?
The assessment of causality must be carried out by the PI or other medically qualified local investigator.

Assessment of expectedness
If the SAE is considered related to any trial specific procedures or the investigational medical device an assessment should be made of the expectedness i.e., is the SAE a recognised adverse effect of the investigational medical device or a trial procedure.

8.4 Reporting to Sponsor

The following events defined are considered reportable to the sponsor.

- Any Serious Adverse Event that is considered related to the trial specific procedures, or the medical device(s) that is considered unexpected by the Chief Investigator or their delegate. (USADE)

- Any device related serious adverse event that led or may have led to one of the following outcomes: (SADES)
    - The death of a participant
    - A serious deterioration in the health of a participant.
    - A serious deterioration in health may include (non-exhaustive):
    - Life threatening illness
    - Permanent impairment of a body function or permanent damage to a body structure
    - A condition necessitating medical/surgical intervention to prevent a) or b)
    - Foetal distress or death, or any congenital anomalies or birth defects.

SAEs meeting the above criteria must be reported to the Pharmacovigilance Office immediately (within 24 hours) using the SAE form for a non CTIMP found here: https://glasgowctu.org/Home/00-safety-reporting/. The SAE form should be completed and signed by appropriately delegated staff. The form should be e-mailed to the PV Office (pharmacovig@glasgowctu.org) and a copy placed in the Study Site File.

If all the required information is not available at the time of initial reporting, the CI (or designee) must ensure that any missing information is forwarded to the PV Office as soon as this becomes available. The report should indicate that this information is follow-up information for a previously reported event.

8.5 Reporting of USADEs to the REC

The Sponsor will report all USADEs to the ethics committee within 15 days of the PV office becoming aware of the event, via the 'report of serious adverse event form' for non-CTIMPs published on the Health Research Authority web site.
https://www.hra.nhs.uk/documents/2466/Non_CTIMP_Safety_Report_Form_Accessible_September_2020_AA.odt

The form should be completed in typescript and signed by the Chief Investigator.

8.6 Reporting of SADEs and USADES to IRIC

The CI or delegate must submit reports relating to the medical device that meet the above criteria to the Incident Reporting and Investigation Centre (IRIC – part of NHS National Services Scotland). Information about how to report an adverse incident can be found here: http://www.hfs.scot.nhs.uk/online-services/incident-reporting-and-investigation-centre-iric/how-to-report-an-adverse-incident/

8.7 Annual Reports

In addition to the above reporting the CI will submit once a year, throughout the trial, or on request a progress/safety report to the Research Ethics Committee and R&D.

9. STATISTICS

9.0.1 Responsibilities

The research team consisting of the PI and research investigators will perform the data analysis and complete the write up.

9.0.2 Hypotheses

We aim to evaluate the method of manufacturing CAD/CAM insoles from a direct-scan, compared to that of a foam-box cast. The null hypothesis is that the change in FHSQ Pain score pre and post-treatment will not differ between the treatment groups. The alternative hypothesis is that the change in FHSQ pain score will differ between groups.

9.1 Description of Statistical Methods

The change in FHSQ scores for the sub-domains of Pain, Foot Function, Foot Health and Footwear, will be compared between groups at the specified data collection time points: baseline, 4-weeks, 8-weeks and 12-weeks, using mix methods Analysis of Variance or Friedman tests with post hoc Wilcoxon tests for within group analysis and Mann-Whitney U tests for between group analysis if the data are not normally distributed.

The change in OPUS scores for the sub domain of Satisfaction With Device, will be compared between groups at the specified data collection time point of 12-weeks, using unpaired t-tests or Mann-Whitney U tests if the data are not normally distributed.

9.2 The Number of Participants

Power calculation for sample size: Based on data from Landorf et al.[24] regarding FHSQ, a sample size was calculated to detect a clinically important difference between groups of 13 (SD = 26.9) points in Foot Health Status Questionnaire scores using the pain sub-domain as the primary outcome, giving a required minimum sample size of 54 participants in each group plus 5% drop out rate = 57 per group. Total sample size n=114.

9.3 The Level of Statistical Significance

Significance will be considered at $P<0.5$

9.4 Criteria for the Termination of the Trial

If the medical devices (insoles) are found to cause serious adverse events

9.5 Procedure for Accounting for Missing, Unused, and Spurious Data.

If the level of missing data exceeds 5%, multiple imputation will be used to address this.

9.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan will be described and justified in the final report.

9.7 Inclusion in Analysis

All randomised participants, who have completed the trial and have not withdrawn their consent from their involvement in the trial, will be included in the analyses.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

11.1 Quality control and assurance

The study will be conducted in accordance with the current approved protocol, and standard operating procedures within the NHS GGC Orthotic Department.

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

11.2 Peer review

This protocol has been peer reviewed by the supervisory team at the University of Central Lancashire.

12. ETHICS

12.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations, with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996, and the UK policy Framework for Health and Social Care research.

12.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC) for written approval. No participants will be entered into the study until approvals have been received.
The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a unique participant number on the CRF and the excel data sheet. All electronic documents will be stored securely within a registered GDPR asset folder, and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act 1998 which requires data to be anonymised as soon as it is practical to do so.

13. DATA HANDLING AND RECORD KEEPING

All study data will be entered on a Microsoft excel spreadsheet, saved within a GDPR registered asset folder as per standard operating procedure in the NHS GGC Orthotics Department. Regular backups of the electronic data will be performed by the PI.
The participants will be identified by a unique participant number only. The name and any other identifying detail will NOT be included in any study data electronic file.
The Co-I will keep a list containing all subjects enrolled into the study. This list remains with the Co-I and is used for unambiguous identification of each subject. The list contains the unique participant number, full name, date informed consent signed, date of screening, the unique hospital number (CHI), and the randomisation group code. A copy of the participant's consent and enrolment in the study will be recorded in the participant's medical record. This data will identify the study and document the dates of the participant's participation.

Archiving:

Although not required by law for non-CTIMPs, in line with the principles of ICH GCP essential study documents will be retained for up to a minimum of 5 years following the completion of the study. Arrangements for confidential destruction will then be made. If a participant withdraws consent for their data to be retained, it will be confidentially destroyed immediately. No records/study documentation/data may be destroyed without first obtaining written permission from the Sponsor.
Essential documents could include (this list is not exhaustive):
Signed informed consent documents for all participants.
Participant identification code list, screening log and enrolment log.
Record of all communications between the Investigator, the REC and the Sponsor.
Composition of the REC, and the Sponsor
List of sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study and their signatures.
Copies of case report forms and documentation of corrections for all participants.
All other source documents (subject medical records, hospital records, etc.).
All other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial).
Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he or she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

14. FINANCING AND INSURANCE

The time and cost associated with the study has been agreed in kind by the NHS GGC Orthotic Service.

The PI has been funded for a 12-month Careers Fellowship by NHS Education Scotland, to support the PI's research activities associated with this trial.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The NHS Greater Glasgow and Clyde Health Board, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

15. PUBLICATION POLICY

All data and results will remain under the ownership of the research team and NHS GGC Orthotic Department.

16. REFERENCES

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17. APPENDICES

Appendix 1. Foot Health Status Questionnaire (FHSQ)

Appendix 2. Orthotic and Prosthetic User Survey (OPUS) Satisfaction with device survey

Appendix 3. Clinical CRF Template

Appendix 4. Schedule of Procedures:

Schedule of Procedures	Visits				
	First Appointment Screening and consent	Second Appointment Fitting	Third Appointment 4-week review	Fourth Appointment 8-week review	Fifth Appointment 12-week review
Informed consent	x				
Demographics	x				
Medical history including concurrent medications as outlined in section 6	x				
Physical Assessment	x				
Scan and cast of feet	x				
Insoles fitted		x			
FHSQ completion		x	x	x	x
Self-reported diary			x	x	x
OPUS completion					x
Review any relevant medication changes as outlined in section 6		x	x	x	x