Footwear and insole design parameters to prevent occurrence and recurrence of neuropathic plantar forefoot ulcers in patients with diabetes; - A series of N-of-1 trials.

Protocol Version 1.5

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# **Resources**

Prospective participants will be accessed through the High-Risk Foot Services (HRFS’s) within tertiary hospitals in the Sydney metropolitan area, NSW, Australia. The HRFS’s will provide ongoing treatment, consumables such as dressings and follow up for the post ulcer healing reviews and monitoring which are part of their regular service standards (1). F-scan in-shoe pressure analysis system (2), MobileMat barefoot static and dynamic plantar pressure analysis systems (3), and Orthotimer orthopaedic appliance wearing period measurements system (4) will also be required.

# **Funding**

As the footwear and insoles are part of the standard treatment for each participant, the funding will be provided by the funding source to which each participant has access. This includes HealthShare Enable NSW (5), private health funds, aged care packages, Closing the Gap or self-funded by participants’ based on their eligibility criteria. Foot Balance Technology (owned by the chief investigator), will provide support for the F-scan and Orthotimer systems and relevant sensors. There will be no cost to participants for the sensors.

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# 1. **Background**

## 1.1. Disease Background

Foot ulcers are a common consequence of diabetes due to the development of peripheral neuropathy, peripheral vascular disease, limited joint mobility and foot deformity (6-11). Nearly 34% of persons with diabetes will develop a foot ulcer in their lifetime (12). This can lead to infection and amputation; diabetes is the main reason for non-traumatic amputation (13, 14). Previous foot ulceration or amputation is a risk for future amputation (6, 8, 10, 15). Additional risk factors include a higher Body Mass Index (BMI), and structural foot deformities (7-9, 11), such as hammertoes and hallux valgus (16, 17).

Diabetic peripheral neuropathy (DPN) is a risk factor for the development of ulceration (18). Over 30% of persons with diabetes will develop DPN (19), the incidence increasing with age (20, 21). DPN can affect the autonomic, sensory and motor nervous systems. Sensory neuropathy interrupts the protective feedback mechanism of touch and pain (22). Motor neuropathy results in compromised muscle innervation, reduction in strength, and combined with limited joint mobility, the development of foot deformities. These deformities may lead to an increase in plantar foot pressures, particularly in the forefoot (23-26). Autonomic neuropathy leads to diminished sweating and changes to skin perfusion, leading to dry skin and hyperkeratosis. As skin integrity is compromised, patients are more susceptible to trauma which may predispose a diabetic foot ulcer (26-29).

Neuropathic foot ulcers in persons with diabetes occur mostly at the plantar forefoot (16, 30, 31) and correspond to areas of peak plantar pressure (32). Bennetts et al. (33) demonstrated that most peak pressure areas are located in the forefoot regions in this population. Limited range of motion at the forefoot joints is also likely to contribute to the increased peak plantar pressures (PPP) observed in this region (34). For this reason, plantar pressure mapping is used to guide footwear and insole manufacture and judge their effectiveness (35).

Reducing plantar pressures is considered a key factor for wound healing and prevention of ulcer recurrence (36, 37). Footwear and insoles are an important treatment modality for off-loading these pressures (38, 39). The desired off-loading threshold should be <200 kPa to ensure ulcer-free survival at the forefoot (40). Some studies also recommended that a pressure relief of 25-30% compared with the baseline to be effective (41, 42).

## 1.2. The rationale for performing the study

There is no existing, evidence-based recommendation for overall footwear design with all technical specifications to off-load the neuropathic diabetic foot. Several studies have suggested rocker sole profile as the preferred design feature of the footwear to be effective to off-load PPP at the forefoot (41, 43-47). Arts et al. (48) in the Netherlands and Rizzo et al. (45) in Italy conducted studies to test the effect of footwear design suggested by the consensus-based algorithm proposed by Dahmen et al. (49). Both studies found that the footwear and insoles design is effective in off-loading the neuropathic diabetic foot. However, Arts and colleagues (48) found that the algorithm is not as effective for footwear specifications when off-loading plantar pressure at the metatarsal heads is required.

Several studies (41, 45, 47, 50-52) have explored patient satisfaction and adherence to wearing footwear and insoles. Patient adherence to wearing therapeutic footwear is important to ensure improved off-loading and ulcer prevention (45, 47, 50).

# **2. Research questions/aims/objectives/hypothesis**

## 2.1. The research questions are:

1. What factors and parameters need to be considered when prescribing footwear and insoles for the people at risk of neuropathic forefoot plantar ulcer occurrence and recurrence?
2. How can participant’s preferences be incorporated into footwear and insole design to increase the adherence to prescribed footwear in people with diabetes and neuropathy who are at risk of plantar forefoot ulcer occurrence and recurrence?

## 2.2. Research aim

To identify clinically relevant footwear and insole design and modification parameters that effectively off-load forefoot peak plantar pressure in the neuropathic feet of people with diabetes.

## 2.3. Expected outcomes

The expected outcome of the study is an algorithm that can be personalised to prescribe footwear design and modifications based on pathologies, co-morbidities, and lifestyle in people with diabetic peripheral neuropathy who are at risk of plantar forefoot ulceration. This algorithm is expected to provide a clear guideline for referrers, patients, prescribers, and technicians to design or modify footwear and insole to ensure adequate and effective off-loading of the forefoot to prevent occurrence and recurrence of plantar neuropathic ulcers in people with diabetes.

# 3. Study Design

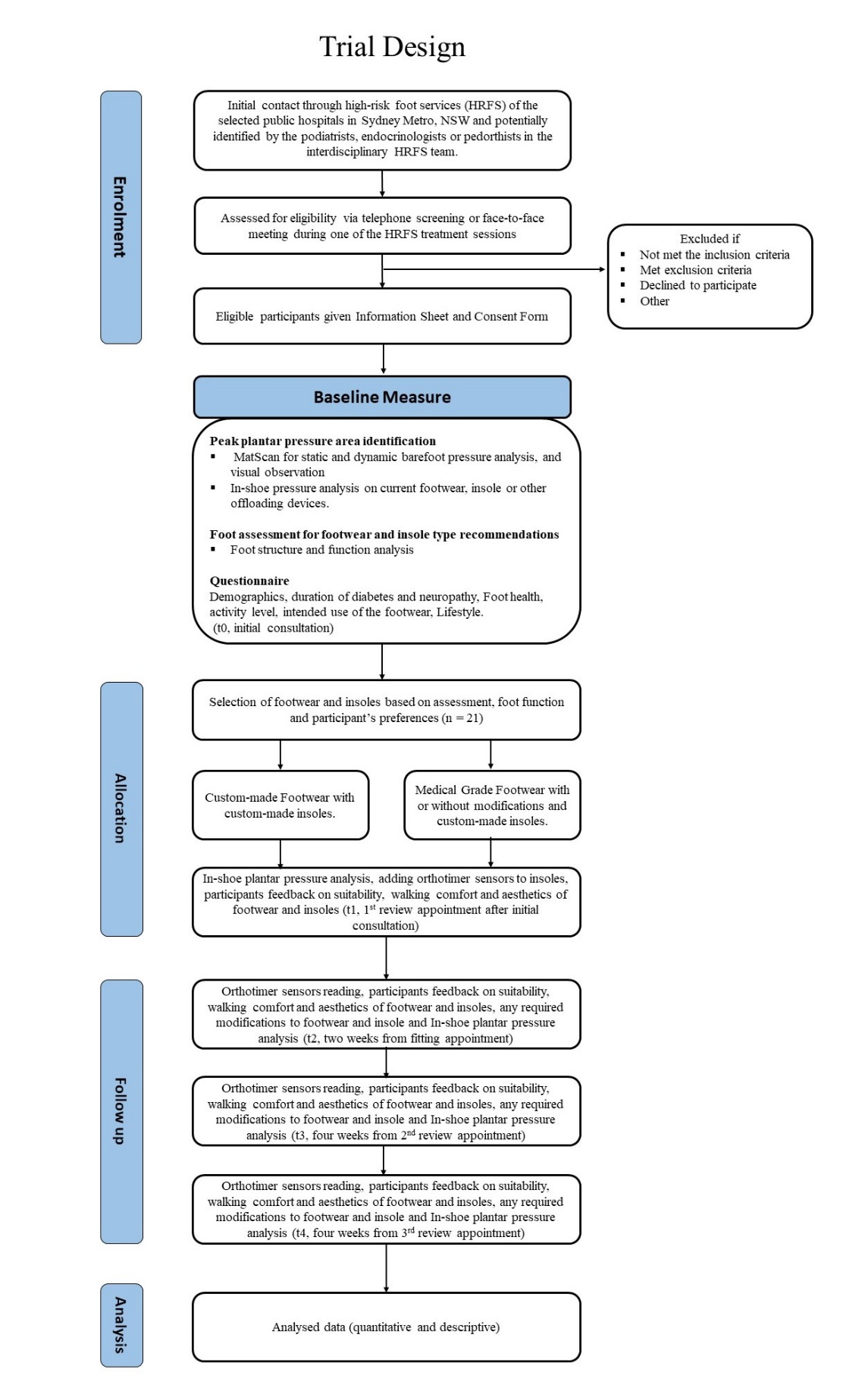


Fig-1: Study design flow for N-of-1 trial

## 3.1. Proposed physical sites are High-Risk Foot Services of the following hospitals

1. St Vincent’s Hospital Sydney, South Eastern Sydney Local Health District
2. St George Hospital Sydney, South Eastern Sydney Local Health District
3. Off-loading clinic of Nepean Hospital, Nepean Blue Mountains Local Health District

## 3.2. Methodological approach

The study will be comprised of a single patient or ‘N-of-1’ trials.

N-of-1 trials are randomised, double-blind, and multiple crossover comparisons of an intervention and a control treatment (53). Oxford Centre for Evidence-Based Medicine has recommended this trial as Level 1 evidence for treatment decision purposes (54). Double-blinding is not feasible in this study design, given the nature of the intervention and secondary outcomes. Participants will need to be aware of the prescribed footwear in order to provide feedback on acceptance. Features of the footwear and insoles may be easily identifiable by clinicians in the team. However, the statistician will remain blinded, and this study design can be termed as a single-blind trial (55).

N-of-1 trials provide a technique to guide evidence-based treatment decisions for an individual patient. They use common methodological components of large clinical trials to measure treatment effectiveness in a single patient. They are a practical alternative when circumstances do not allow for large scale trials, such as rare diseases, comorbid conditions, or when participants are using concurrent therapies (56). However, the findings from these trials can be used to inform the development of algorithms to guide complex treatments for other patients.

Methodologically robust N-of-1 trials objectively assess the effectiveness of treatments within individual participants. Aggregation of multiple cycles identically conducted N-of-1 trials yield a population estimate of effect, which approximates the similar effect that derived from other RCT designs. Trial participants contribute data for both intervention and control treatments creating matched data sets while using generally smaller sample sizes than conventional RCTs (53).

Single-patient or N-of-1 trials are commonly used for personalising the treatment options when participants have a chronic condition (57). Recent studies suggest that N-of-1 trials are effective tools for improving therapeutic precision, and they are widely accepted by patients and clinicians as an effective modality because they are patient-centred (57, 58). They also have proven value in guiding a more-effective prescription (58-60). In the era of ‘personalised medicine,’ they are becoming more popular as it is increasingly clear that ‘one size does not fit all’ particularly in complex interventions like diabetic footwear design and modifications.

In this proposed study, the participants will have a one to one consultation with the principal investigator for the initial assessment on pathology and co-morbidity, having a referral from the high-risk foot service. The initial assessment consultation will include the selection of appropriate footwear style, measuring, casting and 3D scanning of feet and technical specification of footwear and insole that reflects participant’s preferences. Barefoot static and dynamic pressure and in-shoe pressure measurements on the participant’s current footwear will be carried out at the initial assessment. Participant’s current (standard) footwear which may be a regular retail shoe, orthopaedic footwear, post-op shoes or cam-walkers or moon boots with or without insoles (custom or prefab) will be used as the control arm for the trial.

The second consultation will be done once the footwear and insole are ready for fitting (generally within four weeks after initial assessment and measurement). In-shoe pressure analysis will be carried out in the new footwear and insole, which may undergo minor or major modification to achieve desired off-loading efficacy. Participants will be assessed for walking comfort and satisfaction with their new footwear. Scores will be recorded on a Likert scale (61). Orthotimer sensors (to record active wearing period over a given period) will be added to the insoles before dispatching the shoes, and a third consultation will be arranged two weeks later. New footwear wearing instructions will be provided to the participants, including contact details for an emergency or experiencing any adverse effect from the new footwear.

In the third review, participants’ feet will be assessed for any redness or rubbing and any discomfort from the footwear. The Orthotimer data will be collected and analysed for wear patterns and frequency. The footwear will be assessed for any unusual wear marks or pressure/rubbing points. Necessary adjustments will be made, and the fourth review session will be booked for a monthly visit.

During the fourth review, participant’s feet and footwear will be assessed again, and participants’ satisfaction with the footwear will be recorded and compared along with the orthotimer sensor’s data for the previous month. A similar process will follow, and another monthly appointment will be made with the researcher.

In the fifth review, a similar process will follow as the previous review, and this is the endpoint of the study. Participants will be asked on the walking comfort and likeliness on footwear and suitability for the intended application. Overall feedback and any comments from the participants on the footwear will be recorded. Any repair or adjustments to the footwear and insoles will be carried out, and they will be given contact details for any future repair and follow up reviews.

## 3.3. Reporting standard

The quality of any study is dependent on the reporting standard of the study. To increase validity and acceptability, this N-of-1 trial will report data as per CONSORT extension for reporting N-of-1 trials (CENT) 2015 Statement (56).

## 3.4. The rationale for using N-of-1 trials method

From the literature review, it is evident that patient adherence is key for successful off-loading initiatives of the neuropathic diabetic foot. Footwear is an integral part of clothing. Patient preferences play a vital role in the usage of footwear and adherence to recommendations. So, a patient-centred study design that can recommend a precise prescription on personalised therapy/devices is important. The N-of-1 trial design is unique in that it allows focussed assessment of patient preferences and circumstances. This is also beneficial for personalised treatment decisions for patients with chronic conditions (57). There is a direct clinical application in individualising each participant’s treatment with outcomes generalisable to a broader patient population (57).

Effectiveness of off-loading will be measured by the in-shoe plantar pressure analysis system. Using in-shoe plantar pressure measurements and (62) analysis is the gold standard, and other studies with similar aims use the same method to measure this outcome (35, 63).

This trial methodology is preferable to participants as they feel more involved in treatment decisions and see changes being made in response to their feedback (53). This is also a more cost-effective approach than traditional phase iii clinical trials (59).

## 3.5. The rationale for the choice of any control arm

The primary outcome measure is in the reduction of forefoot peak plantar pressure. The control will be participants’ existing footwear, insoles in the form of regular, orthopedic or post-op footwear. This will form the baseline data of in-shoe plantar pressure measurements to be compared against in the new footwear and insole to evaluate off-loading efficacy. Hence, the choice of a control arm is essential, but in this case, the patient is their own control.

# **Participants**

Twenty-one participants (53) from the high-risk foot services of three major public hospitals and their affiliated community clinics in Sydney (Nepean hospital, St Vincent’s Hospital Sydney, St George Hospital,) will be recruited for the study. A sample size calculation is not possible due to the non-existence of a well-validated Quality of Life Scale (QOLS) for the target population. The QOLS measures an individual’s satisfaction, perceptions of control, involvement, commitment, and work-life balance, in terms of an individual’s personal perception. Previous studies (53, 64-66) utilising the N-of-1 methodology have recruited between 10 to 25 participants.

## Inclusion criteria

Participants will be adults (≥18 years) with type-1 or type-2 diabetes, peripheral neuropathy and recently healed plantar forefoot ulcer. Participants may have at least one or more forefoot deformities such as claw/hammer toes, cross over toes, hallux valgus, hallux amputation, limited joint mobility, pes planus or, pes cavus and bony prominences at metatarsal heads. Participants will have required referral for orthopedic footwear (either custom-made or prefabricated medical grade footwear with or without modification) and custom-made insoles, and have adequate English communication skills to provide informed consent and comprehend the study procedures.

## Exclusion criteria

Exclusion criteria will be bilateral amputation (proximal to the trans-metatarsal joint), active or inactive Charcot foot, healed heel ulcers, midfoot deformities, use of walking aid for off-loading the foot, or severe illness, such that the participant may not survive for the study period.

## Potential Participant recruitment strategies

Participants will be recruited from the aforementioned high-risk foot services. Potential participants will be identified by interdisciplinary team members of the high-risk foot services, including endocrinologists, pedorthists and podiatrists. Participants will then be invited to participate.

## Participant’s informed consent process

The participant will meet with the investigator prior to completing informed consent. The investigator will explain the rationale for the study, what participation will involve, follow-up requirements if applicable, and any side effects or risks. Questions from the participant will be encouraged. The Participant Information Sheet will be provided and explained. The participant may wish to consider their decision or discuss with other parties, and in that case, another visit with the investigator can be arranged. The participants will be advised that they can get a withdrawal from the study at any time without explanation or prejudice to future care. If willing, the participant will be asked to sign the Informed Consent Form.

## 4.5. Participant’s enrolment procedure

The participant will be enrolled in the study once the informed consent process has been completed in writing. The inclusion and exclusion criteria will be followed strictly for the enrolment. Once enrolled, every participant will be given a study enrolment number which will be documented in the participant's medical record and on all study documents.

## Study procedure risks

Risk in this study relates to the use of new footwear and insoles to the participant.

Participants may face the following risks:

1. Risk of fall or feeling unbalanced with wearing new footwear and insole to start.

Risk mitigation: Participants will be assessed carefully for any potential risk of falls and heel height, rocker profile will be adjusted accordingly in the footwear to mitigate the risk of fall or improve balance. At the initial fitting stage, the principal investigator will walk with the participant and will show the appropriate way of walking in the new devices.

1. Risk of developing a blister or pressure mark either on the plantar or dorsal surface of the foot and leg. This can be due to changes in volume in foot or leg for swelling or changes in medications.

Risk mitigation: The principal investigator will ensure that the footwear and insole fit well on the participant’s foot without putting any pressure on the foot and leg. The footwear comes with removable spacer inlays, and the thickness of the insoles can be adjusted if needed. The participants will be given a written wearing information sheet with contact details in case of any emergency and advice to stop wearing them until having a review with any of the investigators.

1. Risk of feeling discomfort or feeling depressed to wear a new kind of footwear and insole which may be quite different to what the participant is generally used to. Sometimes, participants may have perceptions that orthopaedic or therapeutic footwear may not be aesthetically as appealing compared to their regular footwear.

Risk mitigation: The participant will be explained thoroughly on the process of designing and manufacturing of the prescribed footwear and insoles relating to their foot conditions during the first appointment. They will have input on design, style and color selections for the footwear as per their intended activity. The footwear and insoles for the study will be used from premium orthopaedic brands and manufacturers to ensure the best possible quality and appearance.

# **Research Activities**

Each participant is required to commit to making him/herself available for the initial assessment and follow up appointments. Participants are also required to select a preferred style of footwear and report on the activities for which they intend to wear the footwear. Participants need to wear footwear and insoles as directed by the researcher. There will be an in-shoe sensor attached to the insoles to measure wearing period over the study periods. The participants will also undergo in-shoe plantar pressure measurements at each fitting and review appointments where they need to walk up to 12 meters at a self-selected pace that represents their regular pace of walking and consistent during each measurement. F-Scan sensors will be calibrated at “Walk” calibration and bodyweight of the participant will be recorded each time during the analysis.

## 5.1. Project duration

This project will last between three to four months, including the initial assessment, fitting of footwear and insoles, and then at least three reviews as outlined below.

## 5.2. Participant follow-up

First follow up will be done after two weeks of delivering and final fitting of the footwear and then at four-weekly intervals. During each follow-up, the participant will undergo for visual assessment of potential increased pressure from the footwear, in-shoe plantar pressure analysis and subsequent modifications if further off-loading is required. Orthotimer data will be recorded and analysed at each follow-up appointment as well. Participants will be asked about the suitability of the footwear in walking comfort, fit for purpose and about their level of satisfaction with appearance and feel.

## 5.3. Data collection

Each participant’s medical history, details of their foot assessment and co-morbidities will be recorded in Qualtrics software (67), either directly into Quaktrics or from paper-based case report form (CRF) to Qualtrics. This information will be obtained from the treating high-risk foot service with the participants’ consent. Participants’ preferences and adherence related information will also be recorded in the same software for analysis following a similar data entry process. Plantar pressure data and shoe wear period data will be collected at each appointment with the researcher. Persons will be de-identified/anonymised before sending the data to the statistician.

## 5.4. Data management and monitoring

Each participant will receive a study enrolment number, which will be used on an electronic spreadsheet. This way, participants can be re-identified by using the study enrolment number when further data collection or clarification is required. Once collated data will be non-identifiable.

Any hardcopy such as participant’s signed consent form, CRF’s will be scanned and stored in the form of an electronic copy, and hard copies will be disposed of in locked confidentiality bin. Electronic data will be stored on a password-protected computer with an up-to-date version of Trendmicro Maximum Security antivirus software.

Data will be achieved for a period of fifteen years after study completion. This period will allow conducting any follow-up study if the opportunity arises. After that period, electronic data will be securely erased.

## 5.5. Data analysis

Data will be analysed by using Analysis of variance (ANOVA), and a two-way ANOVA will be performed for the statistical analysis.

## 5.6. Matching and sampling strategies

The participants are their own controls, so all data (plantar pressure data) will be matched within the participants for the intervention and control arms of the study.

## 5.7. Accounting for potential bias, confounding factors and missing information

There is a potential risk of biasing the results for the researcher also being the treating clinician, and the researcher is aware of this situation. However, the statistician will remain blind to the condition of the participant. The order of intervention/control will be randomised, reducing any potential order effects. The in-shoe plantar pressure measurement will be done by using F-Scan system by Tekscan (2) and the F-Scan research software 7.0. The software generates the pressure analysis report without the clinician’s intervention. The report is based on sensors calibration data and actual interaction of pressure between the foot, insole and footwear. Thus, the report remains independent of external influence to give a true reflection of the off-loading efficacy of the footwear and insole’s design and subsequent modifications. Participant’s self-report on perceived clinical outcome regarding plantar pressure off-loading (<200kPa or 30% reduction from the baseline/control), suitability of the footwear and insoles and the review feedback from the treating podiatrists in the high-risk foot services will also reduce the risk of bias.

## 5.8. Statistical power calculation

This study will use G\*Power software (68) for statistical power calculation (53).

# **Outcome measures**

The primary outcome is a reduction of peak plantar pressure at the accepted level according to the protocol (<200kPa or 30% reduction from the baseline/control) (69). The outcome will be measured by using in-shoe pressure analysis (F-Scan system by Tekscan (2)).

The secondary outcome is adherence (to be measured by using Orthotimer (4) in-shoe sensor) and participant’s satisfaction with the provided footwear and insoles (in terms of walking convenience and aesthetics, to be measured by using a Likert scale (61)).

## 6.1. Plans for return of results or findings of research to participants

The participants’ will be asked on the consent form whether they wish to receive a summary of group findings, in which case you will take a contact email and or address to send them at the completion of the project.

## 6.2. Plans for dissemination and publication of project outcomes

Findings will be published in relevant scientific journals and presented at scientific meetings as well as in a PhD thesis.

## 6.3. Project closure processes

Once the project is completed, the participants will remain under the care of the respective HRFS and their affiliated community podiatry clinics or private podiatrist as appropriate. Participants will be advised to undergo twelve-weekly reviews with their pedorthists to ensure the footwear and insoles are repaired and optimally maintained.

# **Plans for future use of data**

## Anticipated secondary use of data

The data could be of interest to other patient groups with co-morbidities such as arthritis and lymphedema, where there is a need for therapeutic footwear and insoles.

# **Other Study Documents**

Participant Information Sheets

Consent Forms

Data Collection Sheet

Referral letter from the High-risk foot clinics

Study site checklist

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