Shear Load In-shoe Plantar Sensing/sTRain analysEs And Mapping in diabetic foot ulcers: SLIPSTREAM

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2. Contents

3. Glossary of terms

AE Adverse Event

CTRU Clinical Trials Research Unit

DFU Diabetic foot ulcer

DIC Digital image correlation

DPN Diabetic peripheral neuropathy

eGFR Estimated glomerular filtration rate

GCP Good clinical practice

IWGDF International working group for the diabetic foot

LCH Leeds Community Healthcare NHS Trust

LOPS Loss of protective sensation

MTH Metatarsal head

MRC Medical Research Council

PI Principal investigator

PIL Patient information leaflet

PSS Plantar shear stress

RGF Research Governance Framework

RUSAE Related Unexpected Serious Adverse Event

SAE Serious Adverse Event

SLIPS Shear load inductive plantar sensing

STAMP Strain analysis mapping of the plantar surface

SOPs Standard Operating Procedures

4. Background

Four hundred and sixty-three million adults live with diabetes globally, with prevalence expected to rise to 700 million by 2045.[1] Up to one quarter will develop a diabetic foot ulcer (DFU),[2] with 5-8% of these requiring a major amputation within 1 year.[3] Survival is poor, 5-year mortality following development of a DFU has been estimated at 30.5%, with half of patients undergoing a major amputation dead in 5 years. Ulceration is a multifactorial process with peripheral neuropathy and arterial disease playing central roles. Neuropathy leads to the loss of protective sensation and development of abnormal foot architecture.[4] Loss of protective sensation results in undetected, repetitive trauma to the foot.[4] This effect is compounded by the development of structural abnormalities, which increases plantar stress leading to inflammation and tissue breakdown.[5] Plantar pressure forms the vertical component of the load experienced during normal gait. Plantar shear stress (PSS) forms the tangential component of plantar load. It acts parallel to the foot, usually caused by friction between the foot-surface interface and comprises antero-posterior (AP) and medio-lateral (ML) components. [6] It is suggested that the repetitive, multidirectional nature of PSS, both at surface and subsurface levels is a significant contributor to ulcer formation. [7–12]

The authors have performed a systematic review and meta-analysis to summarise the literature on PSS in the diabetic foot. The results of this meta-analysis demonstrated that patients with diabetes and with a loss of protective sensation sustain greater levels of PSS than healthy controls. It also showed those with a current, or previous ulcer exhibit significantly greater levels of PSS compared with those with loss of protective sensation without a history of ulceration. However, it also identified a wide spectrum of methods of measuring PSS , with no validated gold standard. Most studies were performed ‘barefoot’; however, as the cornerstone of management of the diabetic foot is ensuring plantar tissue stress reduction through all weight bearing activities by using appropriate footwear, this form of analysis does not reflect the typical shear stresses that are sustained during a normal day. The review therefore highlighted the need for advances in technology to reliably measure ‘in-shoe’ shear stress and to transfer this to clinical studies investigating its relationship with ulcer formation.

Sensing platforms and insoles measure PSS and plantar pressure in real-time at the foot-surface interface. The technical challenges involved has led to the development of a new method of measuring the effects of PSS and plantar pressure at the foot-surface interface based upon Digital Image Correlation (DIC). DIC is an optical based technique used to measure displacement and strain. It involves comparing the image of the point or object of interest prior to loading, with those after or during loading. The method utilises DIC software employing algorithms to track blocks of pixels to measure displacement or strain. Strain is defined as the ratio between the deformation of a structure and its original length. In the context of an insole, the strain is determined by the plantar load, the product of both PSS and plantar pressure. Thus, it is hypothesised that the level of strain is a product of the cumulative effect of plantar pressure and shear stress during walking.

In-shoe technology

'STrain Analysis Mapping of the Plantar surface (STAMP)' is an untested method, designed by the University of Leeds to measure 'in-shoe' strain patterns on the plantar surface of the foot. The insole comprises a pseudorandom pattern applied to a plastically deformable insole using a temporary tattoo layer. STAMP utilises DIC to track the deformation of the pattern on the surface of the insole following a period of walking. This study will use STAMP to measure peak plantar strain. Peak plantar strain is defined as the maximum strain value within a region.

'Shear Load Inductive Plantar Sensing' (SLIPS) is a new system designed by the University of Leeds to measure 'in-shoe' shear and pressure. SLIPS is a wearable sensing insole which integrates 64 tri-axis soft force sensors, simultaneously measuring both plantar pressure and PSS. This study will use SLIPS to analyse peak PSS, mean peak plantar pressure and pressure time integral (PTI). Peak PSS is the largest shear value within a region per gait cycle. Peak plantar pressure is defined as the largest pressure reading within a region per gait cycle. PTI describes the cumulative effect of pressure over time and is calculated as the sum of the products of plantar pressure per time sample by the duration of that time sample.

Pedar (Novel gmbh, Munich), is a commercially available system used to measure in-shoe plantar pressure. The Pedar system will be used to compare the load measured by the novel systems (STAMP and SLIPS) with pressure data (peak plantar pressure and PTI) from Pedar.

The patient group of interest is those that have developed a plantar DFU as a result of abnormal biomechanical loading. The primary pathological process underlying this is diabetic peripheral neuropathy (DPN) which leads to the development of foot deformities, including hammer toe, claw toe, hallux valgus, prominent metatarsal heads, pes cavus, pes planus and pes equinus (IWGDF definition of diabetic foot deformity).[13] A subset of patients with DFUs may develop these as a result of significant ischaemia due to peripheral arterial disease in the absence of significant biomechanical abnormalities. These patients will not be eligible for inclusion, and will be excluded if they have an opening toe pressure of <40mmHg.

Patients with diabetes are classified as 'low', 'intermediate' and 'high risk' risk of ulceration by NICE (NG 19).[14] Patients at highest risk of ulceration are those with a recently healed ulcer; 40% of patients re-ulcerate within 1-year,[2] and we have therefore selected this group to represent the high-risk group for ulcer formation in this study. Those classified as 'low risk', have no risk factors for ulceration other than callus alone. With the lowest risk for ulceration and without DPN or foot deformities; this cohort of patients will be used as the comparison group. This study will investigate plantar strain, PSS and plantar pressure in these two patient groups.

5. Aims and objectives

The overall aim is to investigate whether patients with diabetes and a recently healed DFU demonstrate elevated levels of plantar strain, PSS and plantar pressure compared with patients at low risk for ulceration, without a history of DFU.

Primary objective

The primary objective is to compare peak plantar strain, peak PSS and peak plantar pressure in high-risk patients with diabetes who have a recently healed DFU (DFU group) with patients with diabetes who are at low risk of developing a DFU (Low risk group).

Secondary objectives

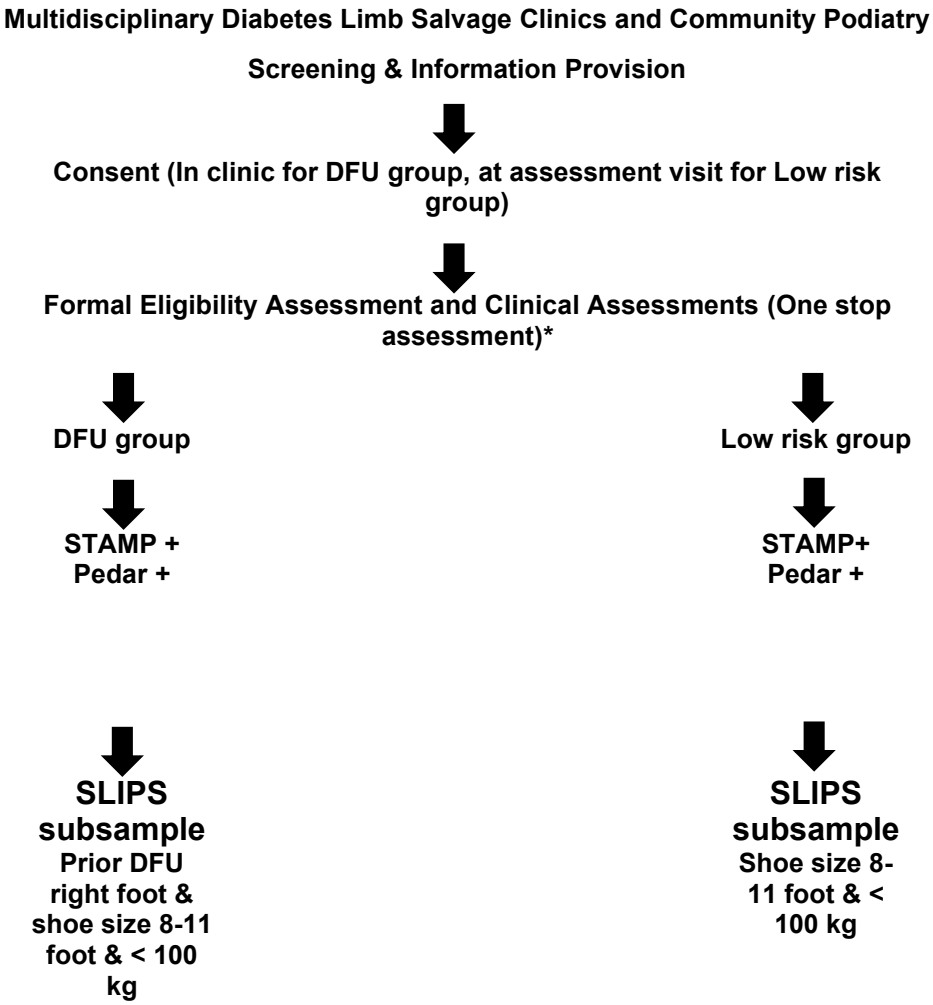
1) To report the relationship between location of peak plantar strain, peak PSS and peak plantar pressure with location of recently healed ulceration in the DFU group.

2) To investigate the relationship between peak plantar strain, peak PSS, peak plantar pressure and PTI at the 1st metatarsal head (MTH), 2nd MTH, 3rd MTH, 4th MTH, 5th MTH, hallux, second toe, toes 3-5, midfoot and heel, and to compare between the DFU and Low risk groups.

3) To inform research design for prospective studies investigating peak plantar strain, peak PSS and peak plantar pressure as risk factors for ulceration; including methodology, patient selection and modifications to the technology used.

Technology	Load measured	In-shoe/barefoot	Purpose
STAMP	Peak plantar strain	In-shoe	New technique used for the assessment of plantar strain
SLIPS	Peak PSS, peak plantar pressure and PTI	In-shoe	New insole designed to measure plantar shear and pressure
Pedar	Peak plantar pressure and PTI	In-shoe	Used to investigate the association between the measurements recorded by STAMP and SLIPS and plantar pressure recorded by the gold standard pressure system.

6. Flow Diagram



* Single visit unless technology failure requires a second visit

7. Study Design

The study design is a single centre case-control study. Cases will consist of patients with a recently healed DFU. The Low risk group (control group) will consist of patients with diabetes at low risk of ulceration (NICE NG19 definition).[14] The risk factor of interest is plantar strain, measured using the STAMP technique and PSS measured by the SLIPS insole system.

Upon enrolment, baseline clinical data will be collected for each patient. All patients will undergo assessment using STAMP and Pedar systems. If eligible, this will be followed by assessment with the SLIPS system within the same visit.

7.1 Blinding

To reduce the risk of measurement bias during data collection, the order of tests will be randomised using the Latin square method.

To reduce the risk of observer bias, data will be analysed in batches, with the assessor blinded to patient group.

A subsample of 10% of the patients will undergo analysis by a second assessor, also blinded to patient group and level of agreement analysed.

8. Eligibility

8.1 DFU group

Inclusion criteria

All patients with diabetes who have a recently healed plantar DFU will be identified by the clinicians within the Diabetes Limb Salvage Service and assenting patients will be assessed for eligibility by the research team. Patients will undergo STAMP and Pedar assessment if they fulfil the following inclusion criteria:

1) ≥18 years of age
2) A diagnosis of diabetes mellitus
3) A diagnosis of diabetic peripheral neuropathy (DPN)
4) Recently healed plantar DFU (healed within the last 3 months)
5) Provide informed written/witnessed verbal consent to participate

Exclusion criteria

Patients will be ineligible if they meet the any of the following exclusion criteria:

1) Those who are unable to mobilise independently 150m, without the use of walking aids and thus unable to complete the walking assessment
2) Previous ipsilateral minor amputation
3) Previous ipsilateral surgical offloading procedure
4) Previous contralateral major amputation
5) Ipsilateral toe pressure <40mmHg
6) Previous open or endovascular ipsilateral revascularisation

SLIPS assessment inclusion criteria

The SLIPS insole has been designed to measure the plantar load of the right foot, and due to its size, can only be accommodated by a size 8-11 shoe. The insole is also only able to accommodate patients weighing <100kg. Therefore, in addition to the above criteria, patients will undergo SLIPS assessment if the fulfil the following additional inclusion criteria:

1) Recently healed plantar DFU located on the right foot
2) The right foot can be accommodated in a size 8-11 shoe
3) Weight <100kg

8.2 Low risk group

Inclusion criteria

Potential patients will be identified by clinicians in the community podiatry service and assenting patients will be assessed for eligibility by either the attending clinical team or a member of the clinical research team. Patients will undergo STAMP and Pedar assessment if they fulfil the following inclusion criteria:

1) ≥18 years of age
2) A diagnosis of diabetes mellitus
3) Low risk for DFU according to the NG19 guidelines (no risk factors for ulceration except callus alone)
4) Provide informed written/witness verbal consent to participate

SLIPS assessment inclusion

Consenting patients will also undergo SLIPS assessment if they fulfil the following additional inclusion criteria:

1) The right foot can be accommodated by a size 8-11 shoe.
2) Weight < 100kg

Patients will be ineligible if they meet any of the following exclusion criteria:

1) Those who are unable to mobilise independently 150m, without the use of walking aids and thus unable to complete the walking assessments
2) Toe pressure < 40mmHg
3) Presence of a foot deformity
4) Previous ipsilateral minor amputation
5) Previous contralateral major amputation

9. Matching

Matching of DFU and Low risk groups will not be performed.

Rationale:

In a study by Yavuz et al., (2014), investigating PSS in neuropathic and non-neuropathic patients with diabetes, neither BMI nor age accounted for a significant proportion of the variance of shear between groups.

Furthermore, the effect of age, BMI, gender and walking speed can be adjusted for if appropriate in the analysis.

To ensure equal group sizes for SLIPS assessment, the proportion of patients per group will be monitored and selective sampling according to shoe size and weight will be performed and recruitment adjusted as appropriate.

10. Recruitment

10.1 Recruitment setting

Patients within the DFU group will be recruited from secondary care from the LTHT Diabetes Limb Salvage Service clinics. The service is run by podiatrists, diabetologists, vascular surgeons and orthotists specialising in care of the diabetic foot. Patients within the Low risk group will be recruited through the Leeds Community Healthcare NHS Trust (LCH) podiatry service which has diabetic foot protection clinics with podiatry led care.

10.2 Recruitment process

All patients with diabetes and a recently healed plantar DFU seen within the Diabetes Limb Salvage Service clinic will be considered as potentially eligible for this study. Where indicated by the attending clinical team and after agreeing to further information, patients will receive a full verbal explanation of the study and a Patient Information Leaflet (PIL) by either the attending clinical team or a member of the clinical research team at a time convenient to the patient during their routine clinic visit. Consenting patients will undergo an eligibility

assessment within their routine clinic appointment. An appointment will then be booked to attend the walking assessments. All data will be collected within a single visit.

The Low risk group will be recruited using the Leeds Community Healthcare podiatry service. The service will review their caseload and identify potentially eligible patients who will be sent a letter and the PIL. The letter will include a brief introduction to the study and patients will be invited to contact the research team by return of the form, email or via telephone if they are interested in participating. Assenting patients will then undergo an eligibility assessment via telephone and be invited to attend a research clinic visit for consent and study assessments. Community clinics may also be attended by the clinical research team to enable immediate referral of patients identified by the attending clinical team; all low risk patients will receive a full verbal explanation of the study and a Patient Information Leaflet (PIL) by a member of the clinical research team at a time convenient to the patient during their routine clinic visit. Consenting patients will undergo an eligibility assessment within their routine clinic appointment. An appointment will then be booked to attend the walking assessments. All data will be collected within a single visit. ;

10.3 Screening

A log will be kept of all patients who have had an eligibility assessment but have not been recruited for the study. Documented reasons for ineligibility or declining participation will be collected and monitored. The following anonymised data will be collected in the log:

1) Age
2) Gender
3) Ethnicity
4) Date screened
5) Reason not suitable for study OR
6) Reason for declining participation

10.4 Informed consent and eligibility

As per the recruitment section, patients will have received a PIL and a full verbal explanation of the study. Patients will have as long as they need to consider participation and will be given the opportunity to discuss the study with family and other healthcare professionals before they are asked whether they would be willing to take part. Patients will also be provided with the contact details of the research fellow where he/she may be able to obtain further information about the study. During the consent process, patients will have the opportunity to ask questions.,

The Chief Investigator (CI) retains overall responsibility for the informed consent of participants and must ensure that any person delegated responsibility to participate in the informed

consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

The informed consent process will be undertaken by the clinical research team or registered healthcare professional who is GCP trained.

The CI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

Informed consent must be obtained prior to the patient undergoing procedures that are specifically for the purposes of the study (including the collection of identifiable participant data). The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the study.

Should the participant be capable of giving consent but physically unable to complete the written aspects of the consent form, witnessed consent should be obtained. An appropriate witness would be a family member or friend of the patient, or another member of the participant's healthcare team who is not directly involved in the research study.

A record of the consent process detailing the date of consent and those present will be detailed in the patients' healthcare records. The original consent form will be filed securely by the clinical research team in a locked filing cabinet in a locked room at the Leeds Vascular Institute and a second copy uploaded to the electronic patient record (as per local practice).

11. Data collection

Following consent within the routine clinic appointment, patients within the DFU group will be invited will be invited to a research visit for the baseline clinical assessment and the strain, PSS and pressure assessment. Consent, baseline assessments and strain, PSS and pressure assessments for the Low risk group will be performed in one visit. All assessments are expected to be performed within a one-hour visit.

11.1 Clinical Characteristics

Following informed consent, demographics and clinical characteristics for each patient will be documented. A standardised proforma will be used to collect clinical characteristic data. History, examination and review of the medical records will be performed to collect information on: Age, sex, weight, height, duration of diabetes, presence of DPN, smoking status, duration of ulceration, time since ulceration, toe pressure, HbA1c (within the last 6 months), pre-ulcerative lesion at entry, presence and type of foot deformity.

Presence of co-morbidities including presence of chronic kidney disease, defined as an eGFR <60 for three months; heart failure, based upon clinic records. These characteristics are based upon reporting standards guidelines.[15]

Definitions:

Diabetic Peripheral Neuropathy – Diagnosed using 10g monofilament test. Methodology will be as described in the International Working Group for the Diabetic Foot guidelines on the prevention and management of diabetic foot disease.[5]

Pre-ulcerative lesion – Skin fissure, intra-cutaneous/subcutaneous haemorrhage or blister (IWGDF definition of pre-ulcerative lesion).[13]

11.2 Pressure and strain measurement

To reduce measurement bias, the order of tests performed will be randomised using the Latin square method.

11.3 STAMP

For the DFU group, the foot with the recently healed DFU will be analysed. For the Low risk group the right foot will be selected. Evidence suggests that there is no difference in vertical, or antero-posterior ground reaction force between dominant or non-dominant limb, therefore no bias should be introduced.[16]

To capture strain data an insole is created using plasticine and inserted into a trial shoe, a standard sock will be worn before donning the trial shoe the patient then undertakes a walking assessment.

The procedure is as follows:

A pseudo-random pattern will be marked onto a plasticine sheet of uniform thickness. An image of this will be taken prior to placing this onto the in-sole of a trial shoe. Each participant will be provided with a pair of disposable socks and be asked to wear the provided trial shoes. Participants will be asked to take 10 **steps** forward and then turn around to walk back to the initial position at their natural speed and step length before removing the STAMP insole. Three

repeats of this activity will be performed. Walking speed will also be recorded using an accelerometer.

An image will be taken of the pattern following the walking assessment. Pre- and post-walking assessment images will be compared using the software GOM Correlate, and analysis performed with the MATLAB analysis package.

11.4 Pedar

To capture pressure data the patient will undertake a walking assessment using the Pedar system.

The procedure is as follows:

The appropriately sized Pedar insole will be placed into the provided trial shoe the side of recently healed ulcer for the DFU group. The insole will be placed into the right shoe of the Low risk group. Each patient will be asked to walk 10 **metres** forward and then turn and walk back to the initial position at their natural speed and step length. Three repeats of this activity will be conducted.

11.5 SLIPS

To capture PSS data the patient will undertake a walking assessment using the SLIPS insole.

The procedure is as follows:

The sensing insole will be placed inside a commercial shoe (manufactured by Steeper Group, Leeds) for the right foot. A leather/foam insole (with the same size and thickness to the sensing insole) will be put into the shoe for the left foot. Each patient will be provided a pair of disposable socks and be asked to wear the provided shoes.

Patients will be allowed a short period of time to acclimatise to the shoes. Patients will then be asked to walk 10 **metres** forward and then turn around to walk back to the initial position at their natural speed and step length. Three repeats of this activity will be conducted.

12. Withdrawal of Consent

Patients may withdraw consent from the study at any time without explanation. The CI or PI or should make every effort to ensure that the specific wishes of any patient who wishes to withdraw from further involvement in the study are defined and documented using the withdrawal case report form. Patient withdrawal will be classified as follows:

a) Withdrawal following STAMP walking assessment
b) Withdrawal following Pedar walking assessment
c) Withdrawal following SLIPS walking assessment

For a), b) and c) patients will be offered to allow use of data up to the point of withdrawal. Patients can request complete withdrawal of data if it has not been included in an analysis; data utilised in analysis will not be withdrawn.

Patients who wish to discontinue performing the walking assessments will be allowed to at any point. Reasons for this will be explored and patients will be offered to return at another appointment if appropriate. Data that has been collected up to that point will be used in the analysis with the patient's consent.

13.Adverse and serious adverse events

13.1 General definitions

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical trial subject which does not necessarily have a causal relationship with the device/procedure.

A Serious Adverse Event (SAE) is an untoward occurrence that:

- Is fatal
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the Investigator

A Related Unexpected Serious Adverse Event (RUSAE) means for an SAE occurring to a research participant in the opinion of the Chief Investigator was:

- 'Related' that is, it resulted from the administration of any of the research procedures, and
- 'Unexpected' that is, the type of event is not listed in the protocol as an expected occurrence.

Medical and scientific judgement must be exercised in deciding whether an event is serious. These characteristics/consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

13.2 Definitions of (S)AEs and reporting

This is a study using three devices to measure plantar load, with no instigation of treatment, nor change to patients' standard care. Therefore, incidents will only be reported as AEs or SAEs if injury occurs during walking assessment.

14.Outcomes

Primary outcome:

The primary outcome is the difference in peak plantar strain and peak PSS between the DFU and Low risk groups as measured by:

1) STAMP
2) SLIPS

Secondary outcomes:

1) Regional peak plantar strain as measured in-shoe using the STAMP insole. Measured at the standard ten regions heel, mid foot, 1st MTH, 2nd MTH, 3rd MTH, 4th MTH, 5th MTH, hallux, second toe and toes 3-5. Mean regional peak plantar strain will be compared between DFU and Low risk groups.
2) Regional peak PSS measured at the standard ten regions heel, mid foot, 1st MTH, 2nd MTH, 3rd MTH, 4th MTH, 5th MTH, hallux, second toe and toes 3-5. Mean peak regional PSS will be compared between DFU and Low risk groups.
3) Global and regional peak plantar pressure, and PTI measured in-shoe using the Pedar system, compared between DFU and Low risk groups.

15.Statistical considerations

Sample size

The STAMP method is a novel technique, as such nil data exists in the literature to determine a sample size. SLIPSTREAM is a preliminary study and due to the time and resource constraints of an MD project it is not expected to be powered to detect statistical significance. Based upon preliminary work, it is expected the mean difference will be 4, with a standard deviation of 6. Therefore 28 patients per group are required for 90% significance at a power of 80%.

Planned recruitment rate

It is estimated 4 patients are identified with a healed plantar ulcer every week at the DLSS clinic. Assuming half of these consent to inclusion, and dependent upon the required sample size, recruitment is likely to be completed within one year.

16.Statistical analysis

Primary outcome analysis

The mean changes in coordinates and magnitude of principle strains on the plantar aspect of the foot will be calculated for each patient using GOM correlate and MATLAB. Linear regression will be used to compare mean peak plantar strain between DFU and Low risk groups. Bivariable analysis using Peason's correlation coefficient will be performed to investigate the relationship between the continuous independent variables and mean peak plantar strain. Multiple regression analysis will be used to explore the relationship between correlated continuous variables and the risk group.

Secondary outcome analyses

1) Regional analysis: A masking algorithm will be utilised to map the previously defined areas of interest (Measured at the standard ten regions heel, mid foot, 1st MTH, 2nd MTH, 3rd MTH, 4th MTH, 5th MTH, hallux, second toe and toes 3-5) following data acquisition. Intergroup comparisons will be performed comparing mean peak plantar strain at each region using linear regression. Multiple regression analysis will be used to explore the relationship between correlated continuous variables and the risk group. This method will also be utilised to perform regional intergroup comparisons for peak PSS, peak plantar pressure and PTI.
2) Peak PSS between DFU and Low risk groups will be compared using linear regression. Bivariable analysis using Peason's correlation coefficient will be performed to investigate the relationship between the continuous independent variables and mean peak plantar strain. Multiple regression analysis will be used to explore the relationship between correlated continuous variables and the risk group. This method will also be used to perform comparisons between groups for peak plantar pressure and PTI.
3) Multinomial regression analysis will be used to investigate the relationship between peak plantar strain and ulcer location.
4) ~~Regional analysis: A masking algorithm will be utilised to map the previously defined areas of interest (Measured at the standard ten regions heel, mid foot, 1st MTH, 2nd MTH, 3rd MTH, 4th MTH, 5th MTH, hallux, second toe and toes 3-5) following data acquisition. Intergroup comparisons will be performed comparing mean PSS at each region using ANCOVA, adjusting for factors matched…… Evidence of associated will be present if r > 0.3. Multiple regression analysis will be used including continuous variables with r > 0.3, risk group and the presence of joint deformity.~~

17. Data and monitoring

17.1 Data collection

All data will be collected and stored in accordance with Trust standards and procedures. When the data is collected it will be coded to pseudonymise the data. The patients' details and their coded data will be then separated and kept in the locations previously stated. The study database will be stored on a password-controlled computer in a locked access-controlled area in the Leeds General Infirmary. The patient files will be stored in a locked cabinet in a locked room in the Leeds Vascular Institute.

17.2 Data storage

All data will be handled, computerised and stored in accordance with the Data Protection Act 1998.

18. Quality Assurance and Ethical Considerations

18.1 Quality Assurance

The study will be conducted in accordance with the principle of Good Clinical Practice (GCP) in clinical trials as detailed by the Medical Research Council (MRC), the NHS research Governance Framework (RGF) and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006.

18.2 Ethical considerations

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland (1996 or later). Informed written/witnessed verbal consent will be obtained from the patients prior to inclusion into the study. The right of a participant to refuse

participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main REC prior to entering patients into the study. The CI will provide the main REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

19. Confidentiality

Collection of patient data that includes patient identifiers will comply with all aspects of the Data Protection Act 1998. Any information that would allow individual patients or clinicians to be identified will not be released into the public domain.

All data will be collected and stored in accordance with Trust standards and procedures. When the data is collected it will be coded to pseudonymise the data. The patients' details and their coded data will be then separated and kept in the locations previously stated.

Computers that are used to store electronic data will be password protected. Paper copies of data will be kept in a locked filing cabinet in a locked room. All new data will be backed up at the end of each data collection session. Weekly back up of all the data set will be stored both on and off site securely. Patient's details will not be exposed to the public at any stage and kept securely under the research team.

20. Archiving

At the end of the study, the data will be securely archived in line with Trust policy for 15 years. Following this, arrangements for confidential destruction will be made.

21.Statement of Indemnity

As sponsor, the Leeds Teaching Hospitals NHS Trust does not provide indemnification against claims arising from non-negligent harm.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical study. Therefore, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements under this duty of care.

22. Publication Policy

The study will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The success of the study depends upon collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the study, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- Conception and design, or acquisition of data or analysis and interpretation of data,
- Drafting the article or revising it critically for important intellectual content,
- And final approval of the version to be published,
- And that all these conditions must be met (www.icmje.org)