Research Protocol

Version 1. January 2017

Study Short Title: Evaluating plantar foot pressure in a novel diabetic offloading device

Study Full Title: Does a novel diabetic offloading boot (PulseFlow DF) reduce the plantar foot pressures compared to usual standard care? A proof of concept pilot study.

Sponsor Name: University of Leeds

Sponsor Number:

Protocol status:

Details of previous amendments

1. **NA**

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INVESTIGATOR DECLARATION AND SIGNATURE(S)

DFOBPS Protocol Version 1 18/01/2017

DECLARATION OF PROTOCOL ACCEPTANCE

I confirm that I am fully informed and aware of the requirements of the protocol and agree to conduct the study as set out in this protocol.

Thomas Dickie	01/02/2017
Principal Investigator	Date

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DFU	Diabetic Foot Ulcer
DMEC	Data Monitoring and Ethics Committee
DRMD	Division Of Rheumatic And Musculoskeletal Disease
DSUR	Developmental Safety Update Report
ECG	Electrocardiogram
GCP	Good Clinical Practice
GP	General Practitioner
IB	Investigator Brochure
ICH	International Conference On Harmonisation
IMP	Investigational Medicinal Product
LOCF	Last Observation Carried Forward
MHRA	Medicines And Healthcare Products Regulatory Agency
MRI	Magnetic Resonance Imaging
NIMP	Non-Investigational Medicinal Product
QA	Quality Assurance
REC	Research Ethics Committee
SAE	Serious Adverse Event
SD	Standard Deviation
SPC	Summary Of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCC	Total Contact Cast

PROTOCOL SYNOPSIS

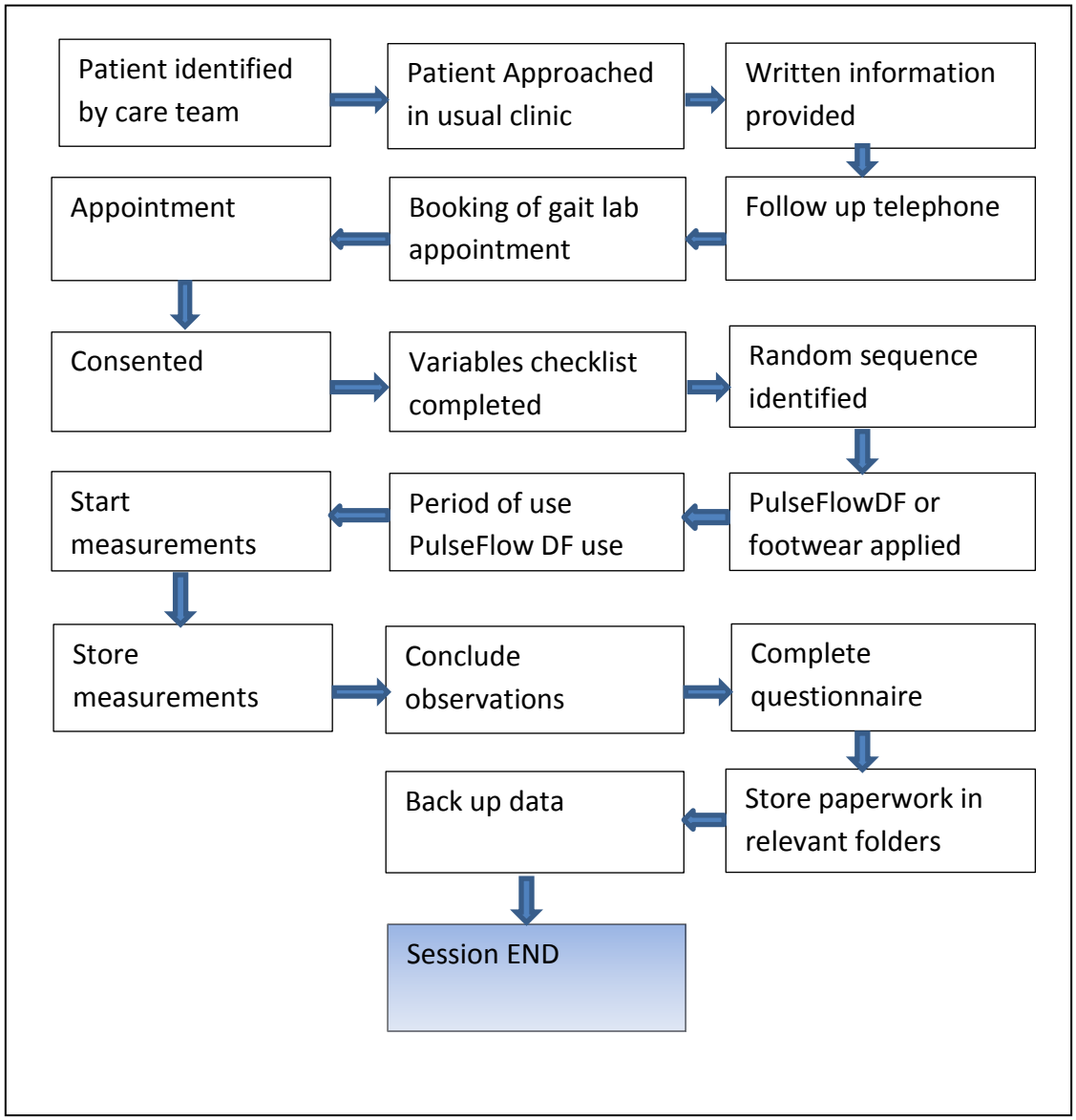
GENERAL INFORMATION	
Short Title	Evaluating plantar foot pressure in a novel diabetic offloading device
Full Title	Does a novel diabetic offloading boot (PulseFlow DF) reduce the plantar foot pressures compared to usual standard care? A proof of concept pilot study
Sponsor	University of Leeds
Sponsor ID	
MREC No.	
Chief Investigator	Professor Anne-Marie Keenan
Principal Investigator	Thomas Dickie
Co-ordinating Centre	University of Leeds, School of Healthcare
National / International	Local
STUDY INFORMATION	
Phase	Proof-of-concept
Indication	Evaluation of a new CE marked device (PulseFlow DF) for the treatment of diabetic foot ulcers
Design	Proof of concept
Number of sites	One
Study Objective	To compare plantar foot pressures between prescribed usual standard of care and the PulseFlow DF boot.
Secondary Objective(s)	Explore the effectiveness and acceptability of the novel device.
Study Endpoint	Collection of data from a single appointment.
Secondary Endpoint(s)	NA
STUDY TIMELINES	
Expected start date	February 2017
Subject enrolment phase	February 2017 to July 1st 2017.
Follow-up duration	No follow up
End of Study Definition	Numbers needed to recruit reached (n36)
Expected completion date	June 2017
STUDY SUBJECT INFORMATION	
Number of study subjects	36

Age group of study subjects	18 plus
Inclusion criteria	Diabetes Plantar forefoot diabetic foot ulcer over the 1st, 2nd, 3rd, 4th or 5th metatarsal joints Neuropathic or Neuro-Ischaemic classification foot ulcer Orthotic intervention for offloading/usual standard Plantar forefoot ulceration over the metatarsal heads
Exclusion criteria	Charcot Arthropathy ABPI of <0.8 and >1.29 Temporary footwear Accommodating or footwear not designed to offload. Clinically active Infection causing swelling Purely ischaemic classification foot ulcer Current active osteomyelitis Patients with forefoot trans metatarsal amputations Fractures of the foot Due to alterations in gait, patients with diagnosed vascular dementia, Parkinson's, alcoholism or other major medically related gait alterations i.e. intoxication, brain cancers, muscular degeneration diseases, inflammatory arthritis, etc. This does not include osteo-arthritis. Major amputees Pregnancy Participating in another trial regarding foot dressings or off loading

SCHEMATIC DIAGRAM

2017	Jan	Feb	Mar	Apr	May	Jun e	July	Aug-Dec
Submit ethical & R&D approval Audit Categories proportions Scoping able participants Non study Patient specific gait analysis testing								
Receive ethical & R&D approval Consent Identification of patients through database Approach patients in routine appointment Provide written literature								
Recruit Patients Contact and Consent Second follow up phone or appointment contact Written consent at laboratory appointment Data collection in gait lab								
Statistical Analysis Data analysis Statistical analysis Member checking usability outcomes								
Close Study Results writing Research conclusion with written research project Poster presentation PPI and research group meeting								

Patient Contact Schematic



1. INTRODUCTION

1.1. Background

Prevalence

Diabetes is an endocrine disorder which carries considerable health risks. Worldwide estimates from the International Federation of Diabetes (IDF 2016) estimate the prevalence of diabetes to be 387 million people. In the next twenty years this is set to rise to an estimated 582 million people which is 10% of all adults. Estimates (Gonzalez et al., 2009) show that from 1996 to 2005, the diabetic population rose by 50% in the United Kingdom (UK). Diabetes UK estimates currently 4 million people are living with diabetes (Diabetes UK, 2015)

Aetiology

Treating diabetes includes its co-morbidities and has proved challenging due to the rising population. Diabetes can cause damage to the nerves and circulation to the lower extremities which can result in the complication of Diabetic foot ulcers (DFU). It is estimated that 25% of the diabetic population will develop a DFU in their lifetime (Ndip and Jude, 2009). The prevalence of diabetic foot ulcers in a European based population of Type 1 and Type 2 Diabetes is 5.5% (Abbott et al., 2005). DFU's are linked to poorer quality of life, higher lower limb amputations and higher mortality rates following amputation (Singh et al., 2005). This is important as neuropathy is the highest cause of DFUs (Parisi et al., 2016), and a strong predictor of lower extremity amputations (Krishnakumar et al., 2015).

Other causes of developing a DFU can be helped by separating DFUs into different causes alongside neuropathy, which are:-

- Neuropathic (caused by lack of sensation)
- Ischaemic (caused by lack of blood supply)
- Neuro-ischaemic (caused by a mix of both sensation and blood supply deficits)

Common classifications have proven difficult to accept amongst clinicians. A widely used system has been incorporated into clinical practice which incorporates the above classification called the "Texas Classification" (Armstrong et al., 1998).

DFUs are consistently considered a chronic wound with increased risk of amputation, infection, suffering and death (Jeffcoate and Harding, 2003). Diabetic foot ulcerations are mainly caused by the damage to the peripheral nerves that causes a loss of protective sensation. This allows the insensate skin to be damaged from direct pressure or trauma without the patient realising (Konstantikaki, 2008). This pressure can increase over certain areas of the foot leading to tissue damage or a break in the skin resulting in the DFU. This is then perpetuated due to a lack of feeling (no pain) resulting in an inability to relieve

pressure over the ulcer site to allow appropriate healing. The DFU is a chronic wound caused by (Jeffcoate and Harding, 2003):-

- Nerves that help small blood vessels controlling microcirculation to the skin are damaged delaying new skin formation
- Motor function controlled by nerves are damaged changing the foot mechanics causing hard skin to build increasing pressure areas
- Poor medical management including diagnosis, access to the right specialists and patients being unaware of the condition

These and other factors related to diabetes such as depression, impairment of the inflammation process for healing due to hyperglycaemia and delayed access to a specialist treatment centre causes healing to be complex (Jeffcoate and Harding, 2003, Konstantikaki, 2008). The associated outcomes such as hospitalisation, infections, minor or major amputations can have a lasting impact. The estimated cost in socio-economic terms varies widely. One of the largest and most recent European study showed on average the total direct and indirect costs for treating an ulcer to healing and major amputation is €7,772 to €25,222 respectively (Prompers et al., 2008). This is in based on 2005 monetary treatment prices. The monetary cost burden to patients is also a factor but is rarely reported (Cavanagh and Bus, 2010). Other effects on patients include physical and emotional issues having negative impacts to their quality of life. This has been shown to be significantly reduced in diabetic patients with foot ulcerations (Jaksa and Mahoney, 2010).

The healing of DFU is therefore paramount to avoiding such devastating disease outcomes such as amputations, cost and other patient related factors. One of the priority interventions to promote healing of DFUs is allowing the foot to be rested or offloaded whilst the patient can continue a reasonable level of independence. The offloading of the foot relies on specific techniques guided by evidence based guidelines (NICE, 2015).

Previous Studies

Elevated diabetic plantar foot pressure has been identified as clinically significant in the development and deterioration of DFUs (Lavery et al., 2003). This is through tissue damage from numerous mechanical pressures on the foot (Yavuz et al., 2015). The clinical practice of pressure relief to treat DFUs is synonymous with offloading and relates to the pressure relief at sites of diabetic foot ulceration. This has been based on clinical experience and has lacked good quality research evidence. However, a recent systemic review (Bus et al., 2016a) has helped guide

clinicians on effectiveness of interventions chosen rather than rely on the historical experiences of clinicians. This review provides strong evidence towards the use of total contact casting, prefabricated irremovable and removable devices as the primary choices to offload DFUs. This is based on empirical research in studies using non complicated purely neuropathic ulcers in economically developed countries. Additionally reported with consistency in these studies is the evidence that poor adherence results in poorer clinical outcomes therefore further research is needed to measuring and improving adherence to offloading devices. This is important as there is such low use of total contact casting clinically. Ulcer healing relates to the time offloading devices are used and the quality of pressure relief provided by the devices used (Armstrong et al., 2003). The NICE Guidelines CG19 relating to off-loading is based on the Cochrane review on "Pressure-relieving interventions for treating diabetic foot ulcers" (Lewis and Lipp, 2013). This review identifies five out of seven studies showing an associated statistically significant improvement of the number of foot ulcers healed with non removable casts rather than removable. This was expressed as a risk ratio total at 1.41 as likely to heal ulcers (30days, 12weeks and 16weeks) in a non removable device versus a removable device.

The management of providing off loading is complex with many patients opting for removable devices due to lifestyle, job requirements, caring needs, driving and regular ulcer evaluations and/or re-dressings. Other removable pressure relieving devices included temporary therapeutic shoes and removable pressure relieving devices e.g. rigid rocker bottom sandals with non custom insoles, forefoot wedge/off-loading shoes, custom made therapeutic footwear and insoles, Aircasts and other removable casted walkers. It is likely that patients would prefer an option to use an aesthetically acceptable pressure relieving device such as the PulseFlow DF. However there is currently no such evidence for its efficacy in off loading.

Types of pressure affecting the skin

Since there are different types of pressures or forces that can cause damage to the skin there are different ways of measuring this in terms of the outcomes being researched. This study is observing plantar pressure over time which is described in section 1.2. However, offloading or pressure relief can be confused with terms such as force, friction and shear.

Friction and Shear Pressures

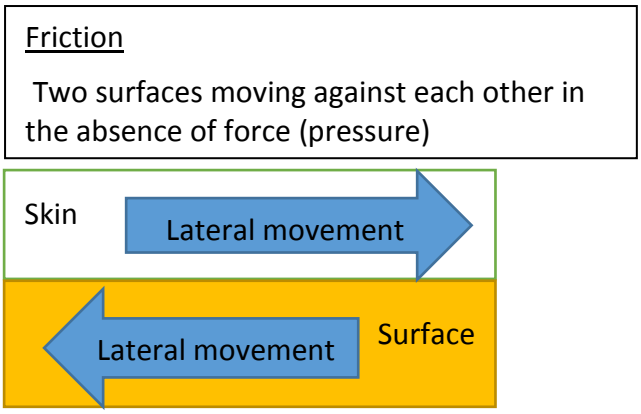
Recently there has been an association of shear and friction with DFU (Yavuz et al., 2015, Giacomozzi et al., 2008). Force is used as simply a measure of influence that changes movement or an interaction between structures. In the case of the foot this is measured in units of newtons (n) observing force vectors or lines of

pressure on the foot, Figure 1. Friction and shear are two other different forces compared to plantar pressures described in this study, which are associated with DFUs but often used in error describing pressure on the foot.

Friction

Friction is a mechanical force describing when two parallel surfaces pass one another i.e. skin of the foot, and its supporting structure (shoe or floor for example), Figure 1. Friction on a structure (foot on the floor) is associated by the pressure exerted from the downward force. The friction occurs when two surfaces in contact with each other move against each other. Although this is associated with DFUs, research has highlighted the importance that reducing friction force is associated more with preventing rather than healing of DFUs (Braun et al., 2014).

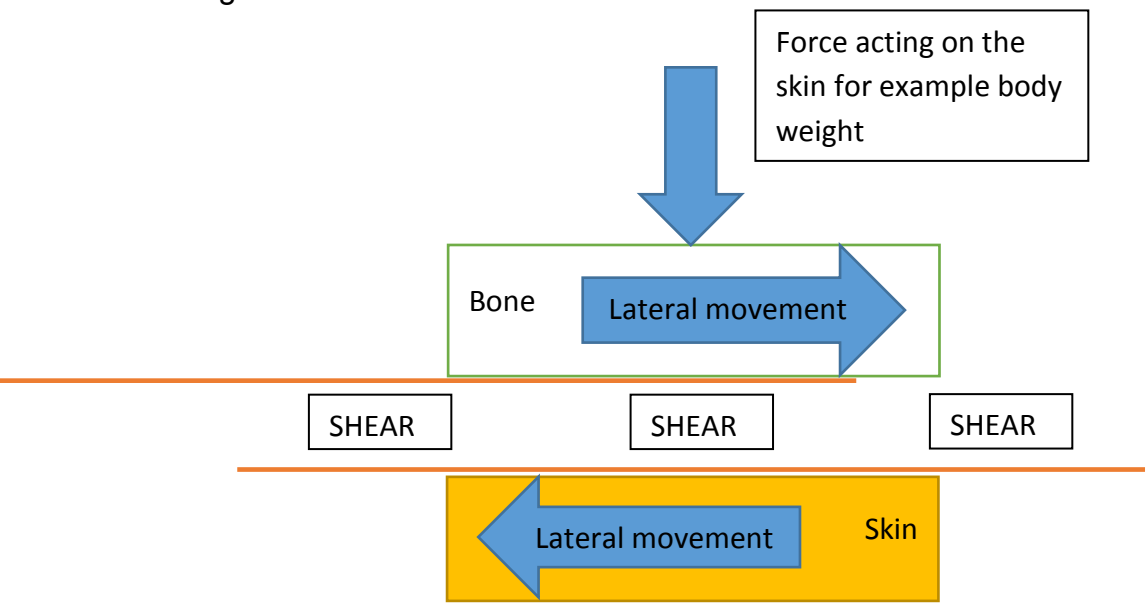
Figure 1.



Shear

Shear is a mechanical force exerted directly parallel to the body's surface (skin) which initiates a parallel shift causing shear within the tissues below or above it, Figure 2. Shear has only recently experienced interest from specialists in the treatment of DFUs (Yavuz et al., 2015, Giacomozzi et al., 2008). Clinically this can be evidenced regularly when dressings over macerated tissues covering a DFU cause separation of the macerated tissue from the dermal epidermal junction of skin (Braun et al., 2014). Shear is highlighted due to the diabetes effect on skin tissue mechanics and the role of skin biochemical changes related to ulcer formation and the inability to dissipate shear (Zhu et al., 2011).

Figure 2.



Shear and friction relating to DFU is difficult to measure. Custom built tools have had to be used previously to allow appropriate research (Yavuz et al., 2007). There is no common validated reliable device to perform shear or friction evaluations to show effectiveness on healing DFU compared to plantar pressure relief. Therefore it is unrealistic to be able to measure the shear and friction elements associated with DFU within this study and this study will measure downward or a vertical force.

1.2. Rationale for the proposed study

Diabetic Foot Ulcer impacts (including cost)

The impacts from diabetes are both patient related and healthcare based. DFU is associated with a high mortality rate at 34% at 1year. There is an associated higher limb amputation rate from DFU than other causes. The high mortality rate, high amputation rate and increased socio-economic burden means providing high quality evidence based DFU service provision should be a NHS priority. Offloading is recognised as the priority treatment for healing neuropathic and neuro-ischaemic plantar foot ulcers (NICE, 2015). Since the provision of non removable devices or total contact casts (TCC) is poor, options have to be available that are equivalent in effectiveness at off loading and healing DFU. By improving the quality of offloading choices and acceptability for devices this will improve healing rates and reduce the cost burden where currently in the UK diabetic foot care in 2015 accounted for 0.6%/585.5million pounds of the NHS budget (Diabetes UK, 2015, NHS England, 2016). The evidence for effectiveness of non removable devices is poor. Therefore any device that offloads to the equivalent or more than previous devices and current usual standard of care must be evidenced. The new PulseFlow DF boot is such a device which claims to off load but has little or no

evidence on DFU subjects. Thus the primary aim of this study is to observe forefoot plantar pressures in a cross sectional purposively selected sample compared to usual standard of care.

How pressure relief is studied

Pressure is measured in a standard unit of kilopascals (kPa). This can be measured by either a static plate embedded in the floor that a person walks across or an in-shoe device. There are several devices to measure pressure including the Pedar-xf analyser (novel, no date). The important considerations for use of such instruments are reliability and repeatability. The Pedar-xf has shown good levels of repeatability and reliability from linear loading with low errors measuring the coefficient of reliability at less than 10% for 93.4% of the parameters tested (Putti et al., 2007). This is practically due to the fact no two steps are identical to produce a 100% repeatable result. There is also good repeatability of loading at high pressures, seen in diabetic foot ulcer patients, as previous studies use healthy individuals (Hurkmans et al., 2006). The in-shoe device uses pressure cells imbedded in an insole which is placed between the foot and the device being measured. The insoles are 1-2mm in thickness. The senses imbedded in them can detect pressure in kPa. The Pedar-xf analyser being used in this study for example has 99 sensors imbedded in a single insole. Since the interest is measuring pressure between a foot and a new offloading diabetic boot the appropriate instrument would be an in-shoe device.

The Pedar-xf Analyser System

The Pedar-xf system allows dynamic plantar foot pressures to be collected in-shoe simultaneously in both feet. Once this has been achieved the software can be instructed to apply masks to parts of the foot (Putti et al., 2007). The masking helps measure specified regions of the foot (Lavery et al., 2003, Hughes et al., 1993) such as the first metatarsal phalangeal joint. This allows clinicians to identify specific areas targeting specific off loading treatments such as recurrent ulceration sites and explore potential changes to plantar pressures (Arts et al., 2012, Ledoux et al., 2013).

Generating Outcome Measurements

Since pressure can be measured, the outcomes can generate data on contact area (cm^2), area under the peak pressure time curve (pressure time integral or pti) and peak plantar pressure (ppp) known as the single highest pressure calculated in kPa. The parameter of pressure time integral is less significant than ppp in risk factors for ulceration i.e. preventing DFUs (Bus and Waaijman, 2013). However in reducing pressure over an ulcer site rather than reducing the risk of ulceration, the

pressure time integral could be considered to be of greater significance (Yavuz et al., 2007). Healing requires reducing the pressure over the DFU preventing further tissue damage and promoting healing by redistributing pressure measured by both ppp and pressure time integral. Specialist have debated the issue of both these measurements value and there is no consensus to which one or both to use especially with ppp showing low sensitivity and low specificity to ulcer risk factors (Yavuz et al., 2007, Yavuz et al., 2015, Bus et al., 2016b, Lavery et al., 2003). One of the conclusions was a hypothesis that there must be more complicated diabetic pathology to developing diabetic foot ulceration than just elevated ppp or pressure time integral. The degree of pressure deemed damaging to the DFU is from the length of time in contact (contact time) and the amount of pressure in kPa measured at the interested site(s). It has been highlighted (Ledoux et al., 2013) that here is no consensus on the range of kPa that causes damage (DFU) as studies show numerous variables that affect the measures such as size of pressure cells, static platform or in-shoe measuring devices, site of DFU and sampling techniques within research. Therefore concentrating on the devices used in DFU clinical practice to reduce pressure over DFU sites is more important to heal the skin damage than finding the DFU preventative range of kPa on a patient's foot. The priority is therefore identifying whether this new pressure relieving device changes (redistributes pressure effectively) plantar pressure distribution effectively at the common site (forefoot) of diabetic foot ulcerations.

Sampling Rationale

The Texas classification (Armstrong et al., 1998) of DFUs helps identify patients suitable for pressure relief, being neuropathic or neuro-ischaemic. As this is the classification system used at the study site it will be used within the context of this study. The proportion of wound classifications within the local population is as follows, purely ischaemic 10%, purely neuropathic 54%, neuro-ischaemic 36%. Ischaemic DFU prevalence in the UK ranges from 10% to 60% (Ndip and Jude, 2009). Therefore the maximum sample within this centre, 90% (Neuropathic plus Neuro-ischaemic), should be primarily treated by TCC or removable off loading devices (NICE, 2015). Within a 2015 audit within this centre only a small proportion (3%) of the neuropathic and neuro-ischaemic population are receiving the recommended standard of off loading with TCC. This is due to issues around patient consent, clinical capacity and funding making the PulseFlow DF boot and other removable devices as suitable alternatives.

While it is proven the non removable TCC is an effective modality for the successful treatment of diabetic forefoot plantar ulcers related to neuropathy, there are factors making it unsuitable for patients. This pragmatic approach to the sample population is supported by research (Wu et al., 2008) and also by the local

scoping audit showing poor utilisation of TCCs. Current comparative alternatives to TCCs (similar to the PulseFlow boot) show a low percentage of patient use (7% of the total possible). This highlights the reality of current clinical practice which is similar to the provision of pressure relief in the United States (US). According to specialist (Wu et al., 2008) DFU teams in the US show a lack of and even non existence of following standards on pressure relief for treating neuropathic related DFU's. The products used for pressure relief are bespoke devices, prefabricated devices or bespoke TCC's. There is a lack of products to choose from with limitations for devices used including financial constraints, stigma issues, quality of pressure relief, staff knowledge and skills needed to prescribe them. The direct material cost is lower for the TCC but demands more clinical time, highly experienced and trained staff with patient attending weekly applications. Patient consent to a TCC appears to be low aswell impacting on its use which has not been studied but only hypothesised that it is due to the lack of sensation (Piaggesi et al., 2007). Correct classification and providing appropriate pressure relief using the NICE guidelines CG19 needs to be considered carefully and closely monitored to facilitate efficient and effective use.

Hypothesis

Using the novel PulseFlow DF boot is as effective as usual standard care in off loading diabetic plantar forefoot ulcers.

Sample and Population

The population from the Diabetic Limb Salvage Service within Leeds will be used for the sample. This is a specialist centre based on the NICE CG19 guidelines (NICE, 2015) and provides a service to 252 diabetic foot patients (July 2016).

Outcome

To compare the pressure time integral data in kPa between usual standard care and the PulseFlow DF boot.

2. STUDY AIM AND OBJECTIVES

2.1. Study aim

The aim of the study is to assess the pressure relief in kPa for pressure time integral (PTI) (Melai et al., 2011) over the forefoot between the boot and usual standard of care.

2.2. Primary objective

To identify whether pressure time integral is equivalent or not to usual standard of care.

2.3. Secondary objective(s)

To measure the acceptability and effectiveness of the new boot.

3. STUDY ENDPOINTS

3.1. Primary endpoint

Due to the study design (proof of concept) the endpoint will be completion of data collection.

4. STUDY VARIABLES

4.1. Standard variables

Gender

Age

Ulcer location

Classification of Ulcer (Texas classification)

Ulcer duration

Previous history of foot ulcer

Previous foot ulcer at same site

Duration of diabetes

Weight

Height

5. STUDY DESIGN

5.1. Study description

Observational proof of concept study comparing the ability to redistribute forefoot pressure using a new foot offloading device compared to usual standard care. The sample will be purposively selected taken from a local population of active diabetic foot ulcer patients. The measurements will be taken from patients wearing usual standard of care, sham shoe (closest to barefoot or baseline pressures) and the PulseFlow DF boot. The measurements from each patient will be collated to compute pti averages for the comparison.

5.2. Study duration

Approximately four months or time to complete required maximum sample size of 36 or ending 1st July whichever arrives first.

5.3. Rationale for study design

The issue of a novel boot should not influence clinical practice or further research until data is produced to support it.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Target population

Patients currently undergoing treatment in the local Diabetic Limb Salvage Service who have diabetic neuropathic related plantar forefoot ulceration.

6.2. Estimated number of eligible participants

For this exploratory study formal methods for estimating sample size are inappropriate. The rationale for the size should be based on feasibility and the basis that this study will be used to justify the sample size of future studies. Therefore the rule of thumb modelling over three factors being explored will provide a sample size of 12 in each group (Julious, 2005). Therefore 36 in total are required. From a 2015 audit, theoretically there was a population size of 231 which identified 23% eligible patients for this study. The current population at January 2017 totalled 326 therefore approximately 74 patients should be eligible for this study. From the scoping exercise in December 2016, six patients were approached regarding the study to review possible challenges to taking part. All

six patients were satisfied with the proposal of taking part considering time required hospital location, travel arrangements and consenting. Therefore it is considered feasible to recruit the required sample of 36 participants (49% of available population following inclusion criteria).

6.3. Eligibility criteria

6.3.1. Inclusion criteria

(a) Plantar forefoot diabetic foot ulcer
    a. over the 1st, 2nd, 3rd, 4th or 5th metatarsal joints
(b) Neuropathic or Neuro-Ischaemic classification foot ulcer (taken from the TEXAS classification system)
(c) Orthotic intervention for offloading/usual standard
(d) English speaking and reading
(e) Palpable foot pulses and/or Ankle Brachial Pressure Indices of values 0.8 to 1.29.

6.3.2. Exclusion criteria

(a) Being treated for or having an active Charcot Arthropathy
(b) Ankle Brachial Pressure Indices of <0.8 and >1.29. Using a standardised reproducible instrument called the Huntleigh Dopplex Ability Unit (DA100PB).
(c) Temporary, accommodating or footwear not designed to offload.
(d) Clinically active Infection causing lower leg swelling
(e) Purely ischaemic classification foot ulcer
(f) Current active osteomyelitis
(g) Patients with forefoot trans metatarsal or major amputations
(h) Fractures of the foot
(i) Due to alterations in gait, patients with diagnosed vascular dementia, Parkinson's, alcoholism or other major medically related gait alterations i.e. intoxication, brain cancers, muscular degeneration diseases, inflammatory arthritis, etc. This does not include osteo-arthritis.
(j) Pregnancy
(k) Under another trial regarding foot dressings or off loading

6.4. Withdrawal criteria

If the participant wishes to withdraw from the study at any point they are free to do so. Information regarding this is on the patient information leaflet. If withdrawing consent from the study is after data collection the data and samples will remain on file and will be included in the final study analysis as this will be anonymised.

6.5. Recruitment, consent and randomisation processes

6.5.1. Recruitment

A verbal explanation of the trial and Patient Information Sheet will be provided by the authorised trial clinician in the patient's usual standard of care treatment for the patient to consider. This will include detailed information about the rationale, design and personal implications of the study. Following information provision, patients will have at least 48 hours to consider participation and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial. This process will be clearly documented into the patient's medical notes.

6.5.2. Consent

Identifying patients within their out patient appointments will be by the direct care team members with a GCP trained certification. Certification will be documented within the study folder. Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent.

Due to time and financial constraints of this educational study, it will not be possible to accommodate the communication needs of participants where English is not their first language. The right of the participant to refuse consent without giving reasons will be respected. Further, they will remain free to withdraw from the study at any time up to 24hours following (participant) data collection without giving reasons and without prejudicing any further treatment. Immediately after data collection participation will be pseudo anonymised. A copy of the consent will be given to the patient, one filed in the Study Files, and one filed in the hospital notes. The written consent will be taken by the principal investigator. The process of obtaining written consent will be clearly documented in the patient's medical notes.

6.5.3. Randomisation process

Due to the type of study design patients can not be randomised. However the process of measuring usual standard of care, standard shoe and PulsFlow DF can be randomised. This will be performed by using a Latin 3x3 square design below which will be randomly allocated from a computer programme at the appointment time of measuring the foot pressures.

Sequence 1	Usual standard care	PulseFlow DF Boot	Standard shoe
Sequence 2	B PulseFlow DF Boot	Standard shoe	Usual standard care
Sequence 3	Standard shoe	Usual standard care	PulseFlow DF Boot

6.5.4. STUDY BLINDING

Due to the type of study design, patients can not be blinded to the intervention.

6.5.5. Patients who withdraw consent

- As soon as the patient withdraws their consent either verbally or in writing this will be documented within their medical notes within the principal investigators normal working hours.
- If patient withdraws within 24 hours of data collection (of that patient) any data stored for that patient will be destroyed electronically following the organisational IT policy.

6.5.6. Definition for the end of the trial

Numbers completed to the original sample size of 36 or more or by1st July 2017.

6.6. General information on the products or interventions to be used

PulseFlow DF

The Diabetic Boot Company Ltd, Trading as PulseFlow Technologies, Midshires House, Midshires Business Park, Smeaton Close, Aylesbury, Buckinghamshire, HP19 8HL, United Kingdom.

UK Patent GB 2454089 - Dec 2009

US Patent US 8,388,562 - Mar 2013

FDA Registered Facility - Registration Number: 3012177215, Owner Operator Number: 10051096

PulseFlow DF is indicated for the treatment of active diabetic foot ulcer at the following sites: Plantar aspect of the 1st metatarsophalangeal joint (MTPJ), 2nd - 5th MTPJ, Heel, Plantar and dorsum aspects of the toes and the Dorsum of the foot.

Proof of concept and pilot studies using healthy and patients with diabetic foot ulcers were used without reporting any adverse reactions. Diabetic foot ulcer patients showed one loss to follow up and one excluded from a small nine patient study to healing. All seven out of the nine patients at study end healed within a six week period.

6.7. Use within the trial

PulseFlow DF Boot

- The PulseFlow DF boot is a trainer design with an integrated ankle foot orthosis. This is made of a metal design to immobilise the ankle and house the battery component around the calf region which will not be in use but with the same weight. Training of application and use of the device will be provided by the company producing the offloading device (Pulseflow Technology).
- The principal investigator will administer and supply the device at the time of data capture. This will be applied and then a recommended period of use will be given before data capture.
- Once the principal investigator and patient are satisfied with the safe use of the device it will be re-applied with the pressure sensing insole inserted.
- There will be no implementation or continuation of the offloading device following completion of data collection. However, information of the device, where it can be purchased from and how much will be offered to the patient as they are currently available to the public and healthcare practitioners.
- A test run will be applied by firstly using it on gait lab engineers and then testing the process on 3 active foot ulcer patients who will not be part of the study. These pre pilot testing phases for the principal investigator will enable training for the principal investigator and identify any anomalies when using the gait lab with study patients for the first time. The selection of the patients will be highly purposive due to the sampling methods and inclusion criteria.

Usual Standard Care

Management of the diabetic foot is guided by NICE with standards on DFU treatments modelled on best evidence (NICE, 2015). The basis of treatments other than TCC is worded as an alternative.

“Offer an alternative offloading device until casting can be provided.”
(NICE, 2015, section 1.5.5)

The alternative is anything available to the service using local protocols or policies and consented to use by the patient. This can be described as below and may be any of the following named devices but is not exhaustive:-

- Bespoke removable Boot (CROW meaning Charcot Restraint Orthotic Walker)
- Removable prefabricated boot e.g. Aircast, DH Walker, Rebound etc.

- Forefoot offloader
- Rearfoot offloader
- DH Shoe
- Scotch cast boot/shoe/slipper
- Made to measure footwear and total contact/bespoke insoles
- Total contact/bespoke insoles d plantar forefoot ulcer.

7. METHODS OF ASSESSMENT

This will be lab based data collection via electronic software, a modified validated questionnaire and demographic/variable list of specific identifying features of diabetic foot ulcers.

7.1. Efficacy assessment variables

1. Usual care (offloading) device name/description
2. PulseFlow DF
3. Standard shoe

7.2. Routine laboratory assessments

Gait laboratory

Pressure Time Integral

One laboratory will be used within the Leeds Teaching Hospitals NHS Trust. The Gait laboratory is situated within Chapel Allerton Hospital, Leeds. The measurements will be collected on pressure in kPa via the Pedar-xf analyser (novel, no date) automatically collected within self contained password protected computer software package and then held on the secure server of University of Leeds M Drive. This will be stored electronically, password protected (see 8.3.2 for full details) under patient identifiable data (participant study code) for analysis later. The first one collected will be analysed for quality analysis in efficacy and validity issues. Only the research team ill have access to this data.

Questionnaire

A modified validated Measure of Orthopaedic Shoes (MOS) questionnaire will be completed following the pressure measurements. Answers will be recorded on coded patient specific sheet to be collected and uploaded onto a prepared excel data base after the participant has left the appointment.

The first one collected will be checked for completion. The completed questionnaire documents will be scanned and stored electronically to improve and allow for quality assurance to the transfer of data. This questionnaire will be used for the description analysis of patient acceptability.

7.2.1.1. Gait analysis details

Patients will familiarise themselves with the lab with a walking tour taking approximately up to 10minutes with question and answer session on the process of measurement taking and a chance to ask any questions. Then the measurement phase of walk assessment will start approximately 10minutes into the visit. A further 30minutes (total of 40minutes) is allocated to acclimatisation of the novel walking boot before this is used for gathering the measurements.

The combined average of 3 steps or the middle one third of the 30 feet walkway will be used for assessment of PTI. The patient will be blinded from when the time the measurements are taken when walking for the measurement. This will be done by walking with the patient and taking a measurement after the patient has become acclimatised on the measured walkway. Acclimatisation will be quantified by the patient being able to walk and talk without the need of balance assistance i.e. hand on the patient's waist. The middle third of the walk will be used to acquire the measurements of PTI (approximately 3 steps of the foot)

7.2.1.2. Duration of gait analysis

Approximately 60 minutes will be given per patient visit to allow for technical and practical issues within the gait measuring room. The process for taking the electronic data measurements is estimated to take between 10 and 15minutes for all three devices however the overall practical process will take longer. The participant will then be allowed to complete the short questionnaire needed for the secondary analysis. This will take no longer than an additional 10minutes.

<u>General Safety</u>

Those experiencing hypoglycaemia from their diabetes at time of measurements will need to be addressed for patient safety reasons. Hypoglycaemia is measured or determined by the patient or the symptoms related to hypoglycaemia i.e. shaking, unbalanced walking, speaking incoherently, slow/slurred speech, sweating, feeling hot, disorientated and measured low blood sugars via the patient's blood sugar machine. When any participant has a hypoglycaemic event or becomes unwell the proceedings will be stopped. Hypoglycaemic events are not considered to

be caused by the intervention. The researcher will then seek appropriate medical care. The use of the nursing out patient hospital setting where the gait lab is situated will be used as support to any first aid issues. More serious events will be referred as appropriate to the nearest emergency care services. Rearranging the appointment will be offered following recovery.

7.2.1.3. Data capture

Data will be via the CE marked Novel Pedar Inshoe pressure analysis system. This system has been shown to have a higher accuracy than a similar competitor (Hsiao et al., 2002). It has also been piloted in a small study looking at sensitivity and valuable in post ulceration footwear analysis (Giacomozzi and Uccioli, 2013).

7.2.1.4. Data analysis

IBM SPSS Statistics 22 software will be used to analyse data. See 9.4.

8. STUDY MANAGEMENT AND ADMINISTRATION

8.1. Good clinical practice (GCP)

This clinical trial will be run in accordance with the Principles of ICH GCP and the Research Governance Framework 2005.

8.2. Adherence to protocol

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying the Sponsor and the REC in writing regarding the type of emergency and the course of action taken.

8.3. Data handling

8.3.1. CRF completion

The research team is responsible for prompt reporting of accurate, complete, and legible data in the CRFs and in all required reports. Any change or correction to the CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted. The Investigator is the sole authorizer to enter data into the CRF. Detailed instructions will be provided in the CRF Instructions.

8.3.2. Database entry and reconciliation

Case report forms and all electronic data will be entered/loaded in a password protected information technology platform internally secured by Leeds Teaching Hospitals and University of Leeds information technology infrastructure. This is on the NHS Leeds Teaching Hospitals F Drive which is a secured server only accessible by named individuals and password protected. The University of Leeds data will be stored on named individual password protected accounts on the secure server, M Drive. Regular backups of the electronic data will be performed after each entry on the secure One Drive at University of Leeds at https://leeds365-my.sharepoint.com/personal/hc15td_leeds_ac_uk/_layouts/15/onedrive.aspx

8.3.3. Screening and enrolment logs

Subject's Screening will be recorded in the Subject Screening Log.

The Investigator will keep a list containing all subjects screened and enrolled into the study. This list remains with the Investigator and is used for unambiguous identification of each subject. Subject's Screening will be recorded in the Participant Log Entry. The researcher will keep a list containing all subjects screened and enrolled into the study. This is the anonymised case report file. This is in addition to the Participant Name Study Identity Log. The list contains the subject identification number which links to the full name, date of birth and National Health Security number of each participant. This will be held in a separate password protected data sheet and folder within the infrastructure detailed in 8.3.2.

The subject's consent and enrolment in the study will be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

8.4. Archiving and data retention

Although not required by law for non-CTIMPs, in line with the principles of ICH GCP essential study documents will be retained for a minimum of 5 years following the completion of the study. For the purpose of a need for 5 year access this will be within the Principle Investigator's Leeds Teaching Hospitals NHS Trust F Drive not the University Of Leeds M Drive due to the Principle Investigators student role terminating in September 2017. The study will be removed from any university data storage and transferred to the Principle Investigator's NHS secured M drive via secure transfer, i.e. encrypted USB device or secure e-mail with password protected documents. Arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed immediately. No records/study documentation/data may be destroyed without first obtaining written permission from the Sponsor.

Essential documents include (this list is not exhaustive):

- Signed informed consent documents for all subjects.
- Subject identification code list, screening log (if applicable) and enrolment log.
- Record of all communications between the Investigator, the REC and the Sponsor.
- Copies of case report forms and documentation of corrections for all subjects.
- Investigational product accountability records.
- All other source documents (subject medical records, hospital records, laboratory 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.

8.5. Study suspension, termination and completion

Suspension or termination of the study may occur at any time for any reason, following discussion between the Investigator and the Sponsor. Upon study completion, the Investigator will provide the Sponsor with final reports and summaries as required by regulations, and will be responsible for completing a premature end of study report to the Research Ethics Committee (REC) within 15 days.

9. DATA EVALUATION

9.1. Responsibilities

The principal investigator will be the sole responsible person as part of the Master of Science qualification will perform all tasks in collecting, storing, analysing and reporting the data for the research.

9.2. Hypotheses

Using the novel PulseFlow DF boot is as effective as usual standard care in off loading diabetic plantar forefoot ulcers.

9.3. General statistical considerations

In general, summary statistics (number of available measurements), arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables and absolute and relative frequency tables for qualitative data will be presented.

9.4. Planned analyses

All data will be explored to check for assumptions of normality and homogeneity of variance for each variable, and to assess which statistical tests i.e. parametric or non-parametric test will be more appropriate to explore the data. The assumption of normality will be assessed graphically by histogram, box-plots and confirmed by statistical testing of significance of skewness and kurtosis. The spread, homogeneity and type of data will determine the type of statistical test. The paired t Test is predicted to be the statistical test of choice following statistician advice. This may change due to abnormal distribution of data once collection is complete.

Gait data will be checked for corruption or incomplete results associated with data capture or software error and rectified where possible either at the point of data collection or data analysis.

Exploratory statistical analyses will be performed to identify any potential associations between gait kinematics, clinical data and patient-reported outcomes. We will also explore the data for unexpected findings, including influential outliers, multicollinearity, truncation and missing data.

The primary outcome (section 2.2) will then be compared for systematic differences between the usual standard care and the PulseFlow DF boot using statistical tests based on the assumptions tested previously.

9.5. Data Handling

All electronic data will be stored on secure University IT systems with password protected documents backed after each participant entry. All electronic data will be entered in a password protected documented information technology platform internally secured by Leeds Teaching Hospitals and University of Leeds information technology infrastructure. This is on the NHS Leeds Teaching Hospitals F Drive which is a secured server only accessible by named individuals and password protected. In the University of Leeds data will be stored on named individual password protected accounts on the secure server, M Drive. Regular backups of the electronic data will be performed after each entry

on the secure One Drive at University of Leeds at https://leeds365-my.sharepoint.com/personal/hc15td_leeds_ac_uk/_layouts/15/onedrive.aspx.

All paper copy data will be immediately transferred to electronic format and paper systems shredded as confidential waste.

10. ETHICS AND REGULATORY REQUIREMENTS

10.1. Good Clinical Practice

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th General Assembly, Somerset West Republic of South Africa, October 1996. The Research Ethics Committee (REC) must review and approve the protocol and informed consent form before any subjects are enrolled. Before any protocol-required procedures are performed, the subject must sign and date the REC-approved informed consent form. The right of a patient to refuse participation without giving reasons must be respected. The patient 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 Research Ethics Committee (REC) and the appropriate regulatory authorities prior to entering patients into the study.

10.2. Subject information and informed consent

Before being enrolled in the study, subjects must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them.

An informed consent document (Patient Information Leaflet) that includes both information about the study and the consent form will be prepared and given to the subject at least 24 hours prior to the screening visit. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations.

At the screening visit, patients will be given the opportunity to ask questions and the nature and objectives of the study will be explained. A podiatry team member caring for the potential participant may help in this process but the principal investigator is responsible for the informed consent discussions.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

The original signed consent document will be retained in the study files. Other copies of the consent form are required:

- One copy of the informed consent document will be kept in the patient's clinical notes.
- One copy will be given to the patient.
- One copy will be stored in the master trial file

Consent is an ongoing process and will be reassessed at each study visit.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The Investigator must inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

10.3. Subject confidentiality

Only the subject number will be recorded in the case report form, and if the subject name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to anyone outside the clinical care team. The subjects will be informed that representatives of the Sponsor, Research Ethics Committee (REC) or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence.

All information collected during the course of the trial will be kept strictly confidential.

Information will be held securely on paper and electronically. All paper hard copies with patient identifiable data will be kept in the trial master file locked in a filing cabinet within a locked staff only access room on the NHS clinical site where consent is being taken (Chapel Allerton Hospital). All data transferable to electronic format will be performed directly after any paper data collection and the paper data destroyed as confidential waste. A site file at the recruiting centre (Leeds Teaching Hospitals NHS Trust) will store only copies of information for the participants and research protocol information accessible to staff within the team treating potential participants.

The University of Leeds via the Chief Investigator will comply with all aspects of the Data Protection Act 1998.

The Principle Investigator at each site will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

10.4. Approval of clinical study protocol and amendments

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the REC and the Sponsor with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met, including approval of the study by the NHS, the Sponsor Research and Development department and the REC.

Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should be revised, thus all protocol amendments and administrative changes must first be discussed with and approved by the Sponsor before being submitted to the REC, in accordance with legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should be revised.

The Investigator must keep a record of all communication with the REC and the Sponsor.

10.5. Protocol amendments

Requests for any amendments to the study must be sent to the Sponsor by the Principal and Chief Investigator. The Sponsor will determine whether said amendments are substantial or non-substantial prior to their submission to the appropriate bodies for approval. Patients should be re-consented to the study if the amendments affect the information they have received, patient safety, or if the change alters the type or quality of the data collected for the study. Patients should only be re-consented AFTER an amendment has been fully approved.

10.6. Ongoing information for Research Ethics Committee

Unless otherwise instructed by the REC and the Sponsor, the Investigator must submit to the REC and the Sponsor:

- Information on serious adverse events that are unexpected and related to study procedures (RUSAEs) from the Investigator's site, within 15 calendar days of the research team becoming aware of them.

- Expedited safety reports, as soon as possible.
- Annual reports on the progress of the study.
- The NRES Declaration of End of Study form.

11. FINANCE AND INSURANCE

11.1. Indemnity and insurance

UoL sponsored study: The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

11.2. Financial disclosure

None of the Investigators or members of the research team have any financial involvement with the sponsorship or funding bodies or will receive personal benefits, incentives or payment over and above normal salary.

12. PUBLICATION

Owning rights and any publication in relation to the study is by the Principal and Chief Investigator and/or the sponsor only.

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