EVALUATION OF LIGHTWEIGHT FIBREGLASS HEEL CASTS IN THE MANAGEMENT OF ULCERS OF THE HEEL IN DIABETES

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Short title: Fibreglass casts for heel ulcers in diabetes

Acronym:

Trial Registration:

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Trial Sponsor: Nottingham University Hospitals Trust

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SYNOPSIS

Title	EVALUATION OF LIGHTWEIGHT FIBREGLASS HEEL CASTS IN THE MANAGEMENT OF ULCERS OF THE HEEL IN DIABETES
Acronym	
Short title	Fibreglass casts for heel ulcers in diabetes
Chief Investigator	Professor William Jeffcoate
Objectives	To evaluate the use of fibreglass heel casts in the management of ulcers of the heel in diabetes
Trial Configuration	Observer-blind, randomised controlled trial
Setting	Primary and secondary care
Sample size estimate	529 randomised to two groups
Number of participants	529
Eligibility criteria	*Inclusion criteria* • type 1 or type 2 diabetes mellitus, • age 18 years or over, • an ulcer of the heel (below the malleoli and affecting the skin overlying the calcaneum) of NPUAP-EPUAP Grade 2-4, which has been present for two or more weeks and which has a cross-sectional area ≥25mm^2. If there is more than one heel ulcer, one will be selected as the index ulcer. • subjects who are both able and willing to give written informed consent. *Exclusion criteria* • frailty or disability which would mean that participation in the study might have an adverse effect of patient well being and mood, • the need for any off-loading device to be non-removable, • the likelihood of protocol violation because of planned travel • those who withhold consent • active participation in another study of a wound care product, and • the use of topical negative pressure or application of larvae to the index heel ulcer
Description of interventions	People with diabetes and chronic (>13 days) ulcers of the heel will receive either usual care (control arm) or usual care supplemented by the provision of a lightweight fibreglass heel cast.

Duration of study	Total study duration 5 years
Randomisation and blinding	Randomisation Web-based; Nottingham Clinical Trials Unit 1:1 Stratified by ulcer size and ulcer grade; using blocks of variable size Blinding Primary outcome will be confirmed by observers blind to randomisation group All outcomes will be analysed by researchers blind to randomisation group
Outcome measures	Primary The primary endpoint will be % of all ulcers healed at 24 weeks (6 months). Healing will be defined as epithelialisation maintained for 4 weeks and will be confirmed by an observer blind to randomisation group. Secondary outcome measures will include: (i) Ulcer-related outcomes – Time to healing, change in ulcer area, adverse device effects (including infection, major and minor amputation) and ulcer recurrence (ii) Patient-related outcomes – Local pain (visual analogue scale), mood and function (EQ-5D), Cardiff Wound Impact Schedule (CWIS) and survival (iii) Health economic analysis
Statistical methods	All analyses will be completed on an Intention to Treat (ITT) basis in the first instance. The primary analysis for outcome will be an uncorrected Chi-Square for the proportions of patients healed at 24 weeks. All secondary variables will be presented using appropriate descriptive statistics and analysed on the basis of the level of measures and the distribution of scores (where appropriate). Analyses will include t-tests for time to healing and difference in change of pain score; with EQ-5D and Cardiff Wound Impact Schedule data presented in line with the conventions for these tools.

ABBREVIATIONS

ADE	Adverse Device Effect
CI	Chief Investigator overall
CRF	Case Report Form
DAP	Data Analysis
DMC	Data Monitoring Committee
EOT	End of Trial
EPUAP	European Pressure Ulcer Advisory Panel
EQ-5D	Euroqol-5D
GCP	Good Clinical Practice
ICF	Informed Consent Form
ITT	Intention to treat (analysis)
NHS	National Health Service
NPUAP	US National Pressure Ulcer Advisory Panel
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development department
SADE	Serious Adverse Device Effect
TMG	Trial Management Group
TSC	Trial Steering Committee
CWIS	Cardiff Wound Impact Schedule

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STUDY BACKGROUND INFORMATION AND RATIONALE

Chronic ulceration of some part of the foot affects up to 15% of all people with diabetes at some stage, and is the source of considerable cost and suffering[7]. The average age at presentation is 67 years and many of those affected are thus elderly, with significant co-morbidities and often clinging to an independent existence. Only two-thirds of all ulcers heal without amputation within 12 months and in these, the median time to healing is 78 days[8,9]. 40% of patients whose ulcers heal will develop a recurrence within 12 months[10].

Ulcers of the heel present particular difficulties and it has often been said traditionally that "Heel ulcers don't heal". 7% heel ulcers result in amputation of the limb in diabetes and 20% persist until death[1]. Despite this, a single centre review of a consecutive series of 154 heel ulcers in 97 patients with diabetes managed in UK revealed that the eventual incidence of healing of heel ulcers without surgery was very similar to ulcers elsewhere on the foot. Despite this, the median time to healing was very much longer at 200 (24-1225 days)[1] – almost three times longer than ulcers elsewhere on the foot. Heel ulcers in diabetes also differ from ulcers elsewhere on the foot in that they are frequently painful.

Many heel ulcers arise as a result of the pressure of immobilisation, and pressure ulcers are very common in acute hospitals. Repeated prevalence surveys in UK suggest that 8-10% of all patients in acute hospital beds develop a pressure ulcer, of which one third are on the heel; half of all pressure ulcers are in people with diabetes[11,12]. Recurrent annual surveys of the prevalence of heel ulcers in Nottingham's two acute hospitals indicate that there are a total of approximately 40 at any one time (36, 40, 49, 36 and 39 in 2003-7 inclusive – in both those with and without diabetes (Nottingham Tissue Viability Nurse surveys, unpublished data). The prevalence of pressure ulcers is higher in long-stay hospitals and care homes.

The protracted course of heel ulcers causes considerable suffering from both physical and psychosocial factors. While the principles of care have been specified by NICE and the Royal College of Nursing[5], and by the International Working Group on the Diabetic Foot (International Diabetes Federation)[6], there are no specific interventions which have been shown to improve the outcome. The non-removable below-knee fibreglass (total contact) cast is recommended to hasten healing in ulcers caused by abnormal pressure loading on other parts of the foot[4], but it has been reported to be ineffective when the ulceration is on the heel[13].

Against the background of there being no specific treatment of proven effectiveness in heel ulcers, a small number of specialists in UK have recently started to use lightweight, fibreglass heel casts, and there is uncontrolled observational evidence that these devices result in both a reduced time to healing and a prompt improvement in pain and discomfort. Healing was observed in 42 (84%) of a consecutive series of 50 heel ulcers (in patients both with and without diabetes, but all of whom had peripheral arterial disease), with a median (range) time to healing of 6 (3-13) weeks[3]. Although the apparent benefit seems greater than would be expected for such a simple device, the findings of this uncontrolled study is mirrored by the clinical impression of the applicants. The mechanism for any positive effect is not known but may relate to the reduction of shearing and stretching forces applied to the surface of the ulcer. Current strategies to reduce local forces are confined to an effect on vertical forces with minimal effect, if any, on shear and on stretching.

Lightweight fibreglass heel casts take approximately 15 minutes to mould to the heel and can be easily fashioned in a domiciliary setting. They are applied over the primary wound dressing, and held in place with an outer dressing, being saved and re-used each time the dressing is changed. They are replaced when stained, damaged or lost, and can often be worn inside shoes. Health care professionals can be trained in their use in approximately 30

minutes, and the material cost of each cast is approximately £7. Casts need to be replaced on average each three weeks.

The purpose of the proposed study is to confirm the effectiveness and cost implications of this simple and apparently beneficial intervention.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

The purpose of the study is to evaluate the effectiveness of fibreglass heel casts in the healing of chronic ulcers of the heel in diabetes.

PRIMARY OBJECTIVE

The primary objective will be to determine whether the use of lightweight fibreglass heel casts for ulcers of the heel in people with diabetes results in a significant increase in the percentage healing within 24 weeks.

SECONDARY OBJECTIVES

The study will also provide information on:

- the time to healing (in those that heal),
- change in ulcer area
- incidence of amputation (major and minor)
- incidence of infection,
- incidence of recurrent or new ulceration
- adverse device effects,
- survival,
- well-being (using EQ-5D and the Cardiff Wound Impact Schedule, CWIS),
- local pain (visual analogue score, VAS), and
- costs associated with the use of the intervention compared with usual care.

Data for health economic analysis will be recorded at each fortnightly assessment by the researcher, and the participant or carer will be asked to keep a simple diary/calendar of relevant intervening events.

TABLE 1

International NPUAP- EPUAP Pressure Ulcer Classification System

Category/Stage I: Non-blanchable redness of intact skin

Intact skin with non-blanchable erythema of a localized area usually over a bony prominence. Discoloration of the skin, warmth, edema, hardness or pain may also be present. Darkly pigmented skin may not have visible blanching.
Further description: The area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Category/Stage I may be difficult to detect in individuals with dark skin tones. May indicate "at risk" persons.

Category/Stage II: Partial thickness skin loss or blister

Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled or sero-sanginous filled blister.
Further description: Presents as a shiny or dry shallow ulcer without slough or bruising. This category/stage should not be used to describe skin tears, tape burns, incontinence associated dermatitis, maceration or excoriation.

Category/Stage III: Full thickness skin loss (fat visible)

Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are *not* exposed. Some slough may be present. *May* include undermining and tunneling.
Further description: The depth of a Category/Stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and Category/Stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep Category/Stage III pressure ulcers. Bone/tendon is not visible or directly palpable.

Category/Stage IV: Full thickness tissue loss (muscle/bone visible)

Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. Often include undermining and tunneling.
Further description: The depth of a Category/Stage IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and these ulcers can be shallow. Category/Stage IV ulcers can extend into muscle and/or supporting structures (e.g., fascia, tendon or joint capsule) making osteomyelitis or osteitis likely to occur. Exposed bone/muscle is visible or directly palpable.

STUDY DESIGN

STUDY CONFIGURATION

This will be an observer-blind, randomised controlled trial. Randomisation will be stratified by ulcer grade (NPUAP-EPUAP Grade 2, 3 or 4, see Table 1), ulcer area greater than or equal to 25 mm^2 and less than or equal to1cm^2 or greater than 1cm^2 , using random permuted blocks of randomly varying size**,** . Randomisation will be undertaken by Nottingham CTU, using a web-based system.

Primary endpoint

The primary endpoint will be % of all ulcers healed at 24 weeks (6 months). Healing will be defined as epithelialisation maintained for 4 weeks and will be confirmed by an observer blind to randomisation group.

Secondary endpoints

(i) Ulcer-related outcomes –

Time to healing, change in ulcer area (measured by both acetate tracings and digital images analysed by using appropriate software to define area), infection, major and minor amputation, ulcer recurrence, secondary ulceration on either limb and adverse device effects .

(ii) Patient-related outcomes –

Local pain (visual analogue scale), mood and function (EQ-5D), Cardiff Wound Impact Schedule (CWIS) and survival
Hospital admission (relating primarily either to the heel ulcer or not), hospital length of stay, and death.

(iii) Cost-effectiveness –

Cost-effectiveness will be assessed by developing a decision-analytic model to estimate costs, from the perspective of the UK NHS and personal social services, and health outcomes, including % of healed ulcers and QALYs gained. The model will incorporate a range of time horizons, including a lifetime perspective, that reflect management of patients with diabetic ulcers of the heel. Costs will be compared between the two groups using a bottom-up approach from the perspective of UK NHS and personal social services. Data relating to the costs of training professionals and the costs of heel casts and their application will be collected by discussions with relevant clinical and finance staff. Costs associated with routine patient management (dressings, adverse device effects, etc) will be systematically logged for each patient by research nurses to obtain profiles of treatment costs for both groups. The use of EQ-5D will enable Quality Adjusted Life Years (QALYs) to be assessed. Incremental cost-effectiveness and cost-utility ratios will be generated for a series of time horizons and subjected to a series of one-way sensitivity analyses to determine the degree to which variation in parameter estimates affect the relative cost-effectiveness ratios. The findings from the trial will be used to model the likely effects over the particular time horizons and costs and effects will be discounted at 3.5%. A probabilistic sensitivity analysis will be conducted to investigate the joint uncertainty in parameter values and cost-effectiveness acceptability curves will be generated.

In addition, a budget impact analysis will be undertaken for 1-year and 5-year periods and will compare the costs to the health service of the use of heel casts in the management of ulcers of the heel in diabetes.

Safety endpoints

The study population is one which is elderly and which will have a high prevalence of co-morbidities, including renal, cardiac and cerebrovascular diseases. Moreover, ulcers of the foot may themselves worsen and lead to hospital admission because of infection or increasing necrosis. Although no specific safety issues are foreseen with the use of the heel cast, significant adverse events are listed among the secondary outcome measures. Other unexpected adverse device effects will be recorded and if considered serious (SADE) will be reported to the sponsor in accordance with the principles of GCP.

Stopping rules and discontinuation

The trial will be stopped when the last recruited subject reaches the end of the trial. However, premature termination of the clinical trial may occur because of a regulatory authority decision, change in opinion of the REC, or safety problems at the discretion of the Data Monitoring Committee (DMC) or Sponsor.

The DMC will have access to all trial data. It may request and will be provided with whatever data (blinded or unblinded) it deems necessary or useful for it to carry out its duties. The DMC will provide their recommendations to the TSC and to the NUHT over the course of the trial.

No formal interim analyses for efficacy are planned by the TMG. However the DMC may need to assess efficacy in relation to safety in order to advise the trial steering committee appropriately. Stopping for safety will be based on an informal assessment by the DMC of adverse device effects. To aid interpretation of efficacy, Haybittle-Peto type boundaries of +/- 3 standard errors ($P<0.0027$) will be adopted to permit the DMC to break the blind with negligible effect on the properties of the final analysis.

Recruitment at a centre may be stopped particularly for reasons of low recruitment, CIP violation or inadequate data recording.

RANDOMISATION AND BLINDING

Internet-based treatment assignment will be determined by a computer-generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham CTU. Trial participants will be allocated with equal probability to each treatment arm with stratification by, ulcer grade and ulcer size.

Maintenance of randomisation codes and procedures for breaking code

This will be an observer-blind study and the use of the heel cast in the intervention group will be apparent to both participant and any other health care professional. Although the randomisation code will be stored in the trial coordinating centre, it will not be necessary to have defined procedures for breaking it.

STUDY MANAGEMENT

This trial will be conducted in accordance with independent ethics committee (IEC), relevant informed consent regulations (Declaration of Helsinki), ISO-14155 Guidelines and the Data Protection Act 1998. In addition all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of trial subjects.

Before initiating a trial, the investigator/institution will have written and dated approval/favourable opinion from the REC for the trial protocol and any amendment(s), written informed consent forms, subject recruitment procedures and written information to be provided to subjects.

All investigators and research staff will be fully trained in ICH GCP, and the study will be conducted in line with these principles. Professor Jeffcoate is the Chief Investigator and the sponsor will be Nottingham University Hospitals NHS Trust.

There will be an independent Data Monitoring Committee and a Trial Steering Committee with an independent chairman, and both will be constituted according to MRC guidelines.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Duration of the study – 51 months

Start date	1st February 2011
Recruitment	1st February 2011-31st January 2014
End of intervention phase	Mid-August 2014
Final report	30th June 2015

Duration of participant involvement

If the ulcer remains unhealed, participants will have fortnightly assessments by the researcher and will remain in the study for 24 weeks. If the ulcer heals, they will continue to have two more fortnightly assessments. If the ulcer remains healed, they will then have only their 12 week and 24 week assessments, unless these have already been done. If the ulcer heals at 22 or 24 weeks, the participant will have two further fortnightly assessments to confirm healing.

End of the study

The study will end when the final patient has completed their final study visit.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Patients will have diabetes associated with an ulcer (NPUAP-EPUAP grades 2, 3 or 4 – see Table 1) on the heel (ie affecting the skin below the malleoli but overlying the calcaneum inferiorly, posteriorly, medially or laterally), which has been present for at least two weeks. Those affected may be identified by the health care professionals usually caring for them in hospitals, care homes or the community. The presence of peripheral arterial disease, wound infection and other particular co-morbidities (such as end stage renal failure of immobilisation) will not be regarded as specific contraindications.

Screening log

A log will be kept at each centre which will list patients screened but not included in the study. The data kept in the log will include only the date of screening, patient initials, age and reason for screen failure. The screen log will not leave the clinical centre. Data only on the absolute numbers of screened patients and reasons for screen failure will be collected by the investigators from each centre.

Inclusion criteria

- type 1 or type 2 diabetes mellitus,
- age 18 years or over,
- an ulcer of the heel (below the malleoli and affecting the skin overlying the calcaneum) of NPUAP-EPUAP Grade 2-4, which has been present for two or more weeks and which has a cross-sectional area ≥25mm^2. If there is more than one heel ulcer, one – which will be the largest or that judged most clinically significant – will be selected as the index ulcer
- subjects who are both able and willing to give written informed consent

Exclusion criteria

- frailty or disability which would mean that participation in the study might have an adverse effect of patient well being and mood,
- the need for any off-loading device to be non-removable,
- the likelihood of protocol violation because of planned travel
- those who withhold consent,
- active participation in another study of a wound care product,
- the use of topical negative pressure or application of larvae to the index heel ulcer

Removal of participants from assessments

Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis. Should a patient who had previously had capacity to consent for themselves lose capacity whilst still in the trial, they should be withdrawn from the trial and no more data will be collected on them. Any data collected up until that point will be used in the final analysis. A withdrawal form must be completed when a patient is withdrawn for any reason.

Informed consent

The investigator, or a person designated by the investigator, will explain the benefits and risks of participation in the trial to each subject, and provide a Participant Information Sheet, ensuring that the participant has sufficient time, and at least 24 hours, to consider participating or not. Written informed consent will be taken prior to the subject entering the trial (before initiation of non-routine tests and administration of investigational device).

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial
The researcher will be trained in the principles and practice of GCP and will be a temporary member of the direct care team, and will be collecting information on the status of the feet

which will be entered on the clinical record. The Patient Information Sheet will specify that their full clinical record will be made available to the researcher only after informed consent has been provided.

STUDY PROCEDURE

Study device

The study device is a fibre glass (3M) heel cast, moulded to the shape of the heel, and split for easy removal. The heel cast will be made according to a study specific procedure and applied over the primary dressing (and secondary dressing if appropriate) – which will be left at the discretion of the patient's usual carer, and a single layer of Softban or equivalent bandage and held in place by a retention layer. The cast will be marked with a research sticker to avoid accidental disposal with a contact telephone number. Written instructions on device usage will be given to patients and care givers. Heel casts will be refashioned when worn or stained.

Study plan

Participants who give written informed consent, will be asked either to attend a research clinic, or will have the necessary information and examination at another venue which is convenient for them and their carer.

The following procedures will be performed at the appropriate visit(s)

1 Prior to randomisation visit

The nature of the study will have been explained to the patient/carer by their usual doctor/nurse/podiatrist

2 Randomisation visit 1 (week 0)

Check inclusion and exclusion criteria
Explain study to patient
Written informed consent/agreement
Documentation of demographics and baseline clinical details, including;

Assessment of neuropathy (loss of protective sensation) using a 10g monofilament applied to three sites (hallux, 1st and 5th metatarsal heads) on the sole of the index foot
Assessment of peripheral arterial disease by palpation of pedal pulses and ABPI
Ulcer grade by NPUAP/EPUAP
Digital image of ulcer post debridement (if clinically indicated)
Local pain assessment by visual analogue scale
Patient well-being EQ5D and CWIS
Documentation of medication
Tracing of ulcer area with acetate sheet for the purposes of randomisation and stratification

Randomisation

For participants randomised to the intervention group, a fibreglass heel cast will be made according to agreed procedures by clinical research staff who have been trained to an agreed level of competence. Participants or carers will be provided with written and verbal instructions on its use. Dressings may be changed as often as patients/carers feel necessary

but this will be at least twice weekly. In addition, both groups will receive usual care recommended by the RCN and NICE, see Table 2.

A diary will be provided for the collection of activity data to use as the basis of health economic analysis.
Contact telephone numbers will be given.
Date and time of next visit will be agreed.

3 Visits 2-13 will be each two weeks (±4 days) to 24 weeks (visit 13)

Check healing – if healed, arrange for confirmation by blinded clinician within 4 days and review after 2 (±4 days) weeks and 4 weeks (±4 days).
Arrange for confirmation of healing by blinded clinician after 4 weeks (±4 days).
If the ulcer recurs during this period, the participant should continue in the study.
If the ulcer does not recur, the participant should continue to collect data for health economic analysis and should be reviewed by the research at 12 and 24 weeks, assuming these dates have not already passed

Digital image of ulcer post debridement (if clinically indicated)
Acetate tracing of ulcer area – to be imaged digitally
Documentation of medication
Documentation of adverse device effects
Collect diary for health economic assessment
Documentation of use of device if appropriate
Local pain assessment by visual analogue scale

Patient well-being and function will be documented by completion of EQ5D and CWIS (weeks 12 (±1) and 24 (±2) only. These may be completed by proxy.

For participants randomised to the intervention group, a fibreglass heel cast will be replaced as necessary by trained personnel and the patient/carer will be given written and verbal instructions on its use.

A diary will be provided for the collection of activity data to use as the basis of health economic analysis.
Contact telephone numbers will be given.
Date and time of next visit will be agreed.

Details of each visit are given in Table 3.

TABLE 2 Components of usual wound care

- Formal assessment of ulcer and surrounding skin
- Provision of any necessary off-loading
- Debridement (i) sharp, (ii) other as appropriate (but excluding the use of larvae)
- Appropriate dressing products
- Appropriate antibiotic therapy
- Nutrition and self care
- Optimal glycaemic control
- Revascularisation if deemed clinically necessary
- Continued close observation

TABLE 3 Fibreglass Casts for Heel Ulcers in Diabetes: Trial Profile

	Screening visit	Visit 1 Randomis-ation Week 0	Visit 2 Week 2	Visit 3 Week 4	Visit 4 Week 6	Visit 5 Week 8	Visit 6 Week 10	Visit 7 Week 12	Visit 8 Week 14	Visit 9 Week 16	Visit 10 Week 18	Visit 11 Week 20	Visit 12 Week 22	Visit 13 week24
Check inclusion/exclusion criteria	X	X												
Information about study	X													
Informed consent		X												
Patient Demographics		X												
ABPI		X												
Neuropathy		X												
Wound size by acetate tracing		X	x	x	x	x	x	x	x	x	x	x	x	x
Digital image after debridement		X	X	X	X	X	X	X	X	X	X	X	X	x
Cast applied if randomised to cast group		X	X	X	X	X	X	X	X	X	X	X	X	
Medication log		X	X	X	X	X	X	X	X	X	X	X	X	X
EQ5D		X						X						X
CWIS		X						X						X
Pain VAS		X	X	X	X	X	X	X	X	X	X	X	X	X
Non-blinded Assessment			X	X	X	X		X	X	X	X	X	X	X
Collect health economic diary		X	X	X	X	X	X	X	X	X	X	X	X	X
Blinded Assessment								X						x

If an ulcer is judged healed on or before Week 24, then healing should be confirmed by a blinded assessor as soon as possible, and within 4 days. If the ulcer breaks down within four weeks of first being judged healed, the participant should continue in the study. If the ulcer remains healed, the participant needs to have 12 Week and 24 Week visits – unless these have already been done.

	Visit at which ulcer is judged healed	Healing confirm-ation by blinded assessor	2 weeks after ulcer first judged healed	4 weeks after ulcer first judged healed		Visit 7 Week 12		Visit 13 Week 24
Digital image after debridement	X		X	X		X		X
cast applied if randomised to cast group	X		X	X		X		X
Medication log	X		X	X		X		X
EQ5D						x		X
CWIS						x		X
Pain VAS	X		X	X		x		x
Non-blinded Assessment	X		X	X		X		x
Collect health economic diary	X		X	X		x		x
Blinded Assessment		X		X		x		X

PROTOCOL VIOLATIONS

The following will be regarded as a protocol violation:

- Failure to use the study intervention (fibreglass heel cast) as recommended for more than 7 consecutive days, or for more than a cumulative total of 14 days during the course of the 24 week study. Those who violate the protocol in this way alone will not be withdrawn but will continue with fortnightly visits.

The following will be regarded as a protocol violation necessitating withdrawal from the study:

- Omission of more than one consecutive scheduled fortnightly assessment by the researcher, or omission of a total of three or more of these visits during the 24 week study, or until healing is confirmed.

WITHDRAWALS

Reasons for withdrawal will include;-

- Consent/agreement is withdrawn
- The patient loses capacity
- It is found that they were recruited in error
- They have omitted more than one consecutive scheduled fortnightly assessment by the researcher, or omission of a total of three or more of these visits during the 24 week study, or until healing is confirmed
- The participant is lost to follow-up

A withdrawal form must be completed in all cases

STATISTICS

Methods

Database lock will take place once all data entries had been checked and sufficient verification processes are completed (e.g. range checks on numerical data, logic checks and date comparisons and manual checks against source data in selected cases).

Analysis will be completed, blinded to group, with the latest version of SPSS (SPSS inc) available towards the end of the study (this is currently version 16). The baseline characteristics of both groups will be described using appropriate summary statistics, for the salient variables, to ensure that the randomization process has resulted in even distribution of factors related to healing and that the stratification process has been successful. All analyses will be completed on an Intention to Treat (ITT) basis in the first instance. The primary analysis for outcome will be an uncorrected Chi-Square for the proportions of patients healed at 24 weeks.

All secondary variables will be presented using appropriate descriptive statistics and analysed on the basis of the level of measures and the distribution of scores (where appropriate); time to healing will be taken from the clinical notes and based on time of recruitment to study to first date of healing (this date will be verified 28 days later

to ensure that the ulcer has remained healed: any ulcers found not to have maintained healing over the 28 day review period will be classified as 'not-healed' and returned to the study); the data from the digital images will be used to calculate reduction in surface area and volume over time. Analyses will include t-tests for time to healing and difference in change of pain score; with EQ-5D and CWIS data presented in line with the conventions for these tools.

In addition to the calculated values, confidence intervals and odds-ratios will be presented when appropriate. All clinical information including all adverse device effects will be presented in full. All secondary analyses will be interpreted with caution as the sample size calculation is based on the primary outcomes only. However, the level of power associated with secondary results will be investigated.

In addition to the ITT analysis, the data for those patients who are allocated to group correctly and remain in the study without incident will also be compared on a per protocol basis.

Sample size and justification

In order to detect a difference between groups of 15% (healing of 40% versus 55% at 24 weeks) with power on two-tailed analysis of 90% and alpha of 0.05, there would need to be 173 in each group and allowing 30% withdrawals, the total number of participants would be 529.

Assessment of efficacy

The primary endpoint will be % of all ulcers healed at 24 weeks (6 months). Healing will be defined as epithelialisation maintained for 4 weeks and will be confirmed by an observer blind to randomisation group. This confirmation will take place as soon as possible after first suspected by the non-blinded researcher. It will be repeated 4 weeks after the initial confirmation, unless the research identified skin breakdown in the interim. During this interim period, the participant will continue to use the heel cast (if in the intervention group) or appropriate protective dressings (if in the control group). If the skin breaks down within 4 weeks of initial healing, the ulcer will be regarded as still active and the participant will remain in the study.

ASSESSMENT OF SAFETY

Adverse Effects

Adverse Device Effect (ADE)
Any untoward and unintended response to a medical device

NOTE 1 This definition includes any effect resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device.
NOTE 2 This definition includes any effect that is a result of a user error.

Adverse device effects (ADEs) will be recorded as they are reported whether spontaneously volunteered or in response to questioning about well being at trial visits. The questioning about ADEs will cover the current visit as well as the period of time between the previous and the current visit. A note of any concomitant medication will also be made so that a full assessment of the ADE can be made.

All ADEs will be documented in the subject's medical records and CRF. All ADEs must be followed until resolution, or for at least 30 days after discontinuation in use of the device, whichever comes first.

The investigator will assess causal relationship of the ADE to the investigational device according to the following classification:

- None: No relationship with investigational device. Other factor(s) certainly or probably causative.
- Possible: Time relationship exists. Reasonable possibility that the event was caused by the device. Other possible causative factor(s) may exist.
- Probable: Time relationship exists. The event was certainly or probably caused by the device. Other possible causative factor(s) may exist.

The following definitions for rating severity of ADEs may be used:

- Mild: Awareness of signs or symptoms, but these are easily tolerated and are transient mildly irritating only. There is no loss of time from normal activities and symptoms do not require medication or a medical evaluation.
- Moderate: Discomfort enough to cause interference with usual activities or require therapeutic intervention e.g. concomitant medication.
- Severe: Incapacity with inability to do work or do usual activities.

Serious Adverse Device Effects

Serious Adverse Device Effects (SADEs)
Adverse device effect that has resulted in any of the consequences characteristic of the serious criteria or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Serious criteria
- Death χ
- Life threatening illness or χinjury
- Hospitalisation χor prolonged of hospitalisation
- Permanent χimpairment of body structure or body function
- Medical or surgical intervention required to prevent any of the above χ

An unexpected serious adverse device effect is any serious adverse device effect, the specificity or severity of which is not consistent with the current protocol.

SADE Reporting
All serious adverse device effects must be reported immediately to the Sponsor. Refer to the SADE form for contact details.

All SADEs will be documented in the subject's medical records and CRF. All SADEs must be followed until resolution, or for at least 30 days after discontinuation of device use, whichever comes first.

Foreseeable Adverse Device Effects

Foreseeable adverse device effects are those related to worsening of the clinical state of the ulcer and will be reported as secondary outcomes. These include

(i) Ulcer-related outcomes –

Increase in ulcer area,
Infection,
Major and minor amputation,
Ulcer recurrence,
Secondary ulceration on either limb

(ii) Patient-related outcomes –

Increase in pain
Worsening mood or function
Hospital admission (relating primarily to the heel ulcer),
Death from pre-existing medical conditions

ETHICS COMMITTEE AND REGULATORY APPROVALS

It is anticipated that there may be a number of patients who would be suitable for inclusion in the trial, but who may lack the capacity to consent as the inclusion criteria will include patients who have pressure ulcers from immobility, such as patients who are resident in nursing homes. After guidance from the research ethics committee these patients will not be included in the trial.

All necessary Ethics and R&D approvals will be obtained for all sites and Research Governance frameworks will be followed throughout. All investigators will be asked to sign a statement confirming training to ICH GCP. Patient data will be identified by initial and study code only. Study specific procedures will be used to guide the study at all sites to ensure standard practices are used.

The study will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study. The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

Confidentiality

The investigator shall maintain subject confidentiality during all audits and inspections of the study site and documentation. Trial subjects will be identified only by their initials and unique subject number on CRFs, in trial correspondence and on the trial database. The investigator will keep a list of identification codes in which each subject is named along with their assigned subject number.

All information provided to the investigator relevant to the investigational device, as well as information obtained during the course of the study, will be regarded as confidential. The investigator and members of his or her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol.

The investigator will take all measures to ensure subject confidentiality is maintained at all times. All subject data must be anonymised before retrieval from the trial site.

RECORDS

Electronic Case Report Forms

Each participant will be assigned a trial identity code number for use on eCRFs, other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen).

eCRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Study Recruitment Log), to permit identification of all participants enrolled in the trial, in case additional follow-up is required. eCRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Study Delegation Log.'

Any paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the eCRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. An eCRF may also completely serve as its own source data. Only trial staff as listed on the Study Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The investigator will allow inspections of the study site and documentation by clinical research and audit personnel from the Sponsor, the Sponsor Representative, the REC, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the case report forms. In order to do this direct access to medical or clinic records is necessary. The Investigator must inform the Sponsor if they are notified of a forthcoming audit by the REC or regulatory authorities.

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The eCRF will only collect the minimum required information for the purposes of the study. All paper files will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE AND AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

STUDY CONDUCT

Trial conduct will be in accordance with ICH GCP.

STUDY DATA

Study data will be treated as confidential documents. Data will be entered directly onto the web-based data entry form if possible. If the web-based data entry sheet is not immediately available, data will be recorded on standardised forms and transferred on to the web-based data entry form within one working day. All manual records will be stored as source data.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines and current regulations the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 5 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Study Master File and study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

The sponsor may terminate the study if they have reason to believe that the study is not being conducted in accordance with the principles of ICH GCP.

DISCONTINUATION OF THE STUDY BY THE DMEC

The study will be terminated if on the advice of the DMEC there is evidence of either a clear advantage of the study device over usual care such that it would no longer be ethical to continue or conversely evidence that the study device was harmful compared to usual care.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.
Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the sponsor, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The results of the study will be submitted for presentation at academic meetings, and for publication in a peer-reviewed journal and will be approved by the Trial Steering Committee. In order to avoid conflict and uncertainty, it has been decided that authorship of the eventual report will be based on the criteria published by the International Committee of medical Journal Editors (http://www.icmje.org/ethical_1author.html):

- Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript (3). These individuals should fully meet the criteria for authorship/contributorship defined above, and editors will ask these individuals to complete journal-specific author and conflict-of-interest disclosure forms. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments. The NLM indexes the group name and the names of individuals the group has identified as being directly responsible for the manuscript; it also lists the names of collaborators if they are listed in Acknowledgments.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

USER AND PUBLIC INVOLVEMENT

A user group at the specialist foot service at Dundee House will be asked to comment on the protocol.

STUDY FINANCES

Funding source

This study will be funded by the UK Department of Health, through the Health Technology Assessment (HTA) Clinical Evaluation and Trials scheme (Application number 09/01/53).

Participant stipends and payments

Participants will not be paid to participate in the trial. Travel expenses will be offered for any hospital visits in excess of usual care.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Professor William Jeffcoate

Signature:_____

Date: _____

Co- investigator: Dr Frances Game

Signature:_____

Date: _____

Trial Statistician: Professor Patricia Price

Signature:_____

Date: _____

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