Multiple Interventions for Diabetic Foot Ulcer Treatment Trial

(MIDFUT)

Version	v2.0
Date	21st July 2017
Sponsor	Leeds Teaching Hospitals NHS Trust
REC Reference	17/YH/0055
ISRCTN	64926597
IRAS reference	215194
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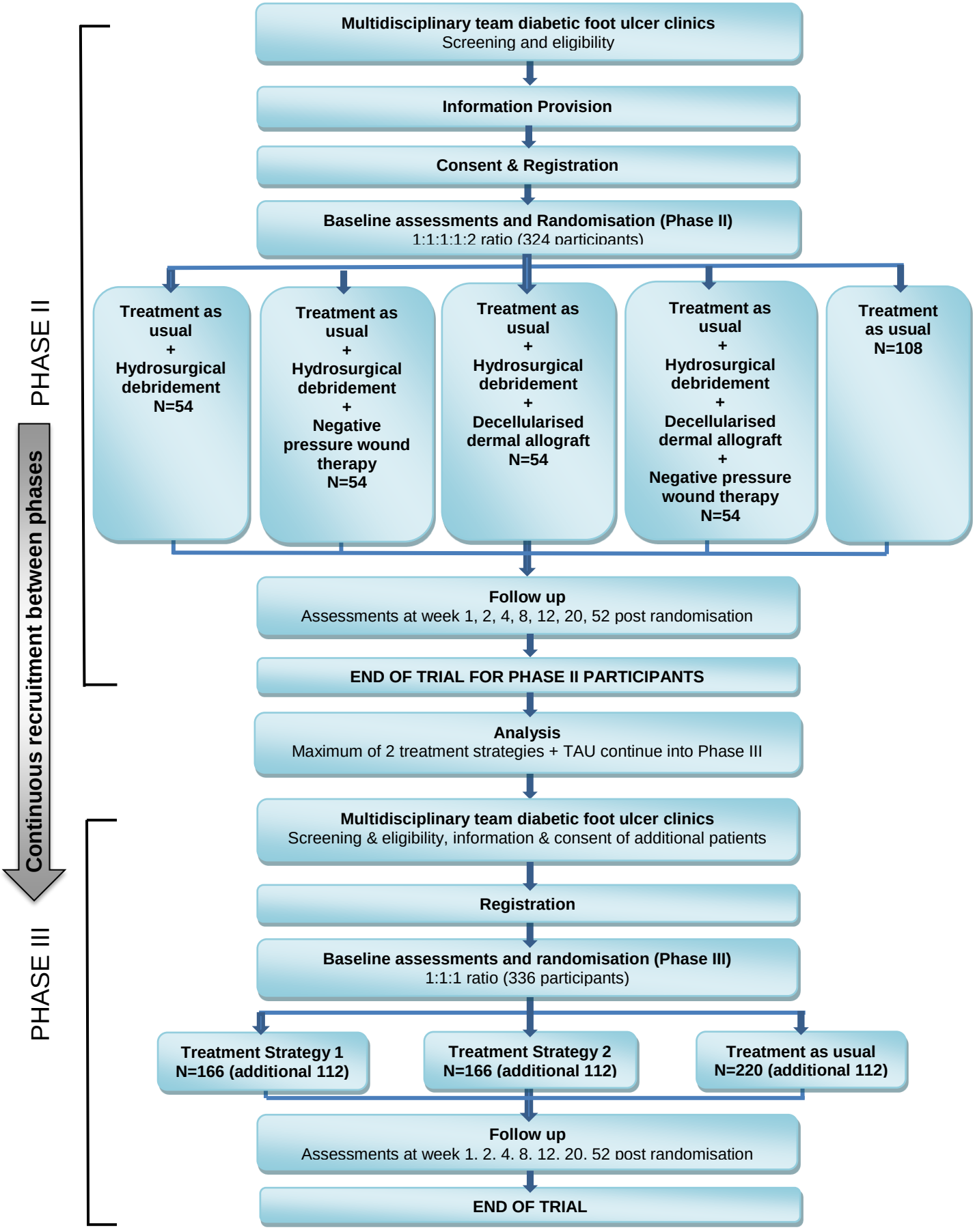
2. CONTENTS PAGE

3. FLOW DIAGRAM



4. GLOSSARY OF TERMS/DEFINITIONS

ABPI	Ankle Brachial Pressure Index
AE	Adverse Event
CCG	Clinical Commissioning Group
CEAC	Cost-effectiveness acceptability curves
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Nurse
CTRU	Clinical Trials Research Unit
DFS-SF	Diabetic Foot Ulcer Scale Short Form
DFU	Diabetic Foot Ulcer
DCD	Decellularised Dermis
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQol - five dimensions
GCP	Good Clinical Practice
GP	General Practitioner
HD	Hydrosurgical Debridement
HCPC	Health and Care Professions Council
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ISF	Investigator Site File
ITT	Intention to Treat
LICTR	Leeds Institute of Clinical Trials Research
LTHT	Leeds Teaching Hospitals NHS Trust
MAMS	Multi-Arm Multi-Stage
MAR	Missing At Random (MAR)
MDS	Minimum Data Set
MDT	Multi-Disciplinary Team
MRC	Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NPWT	Negative Pressure Wound Therapy
NRES	National Research Ethics Committee
PI	Principal Investigator
PIL/ICD	Patient Information Leaflet/Informed Consent Document
PP	Per-protocol
PPD	Preparation Process Dossier
PPI	Patient and Public Involvement
QALY	Quality Adjusted Life Year
QoL	Quality of Life (QoL)
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework
RHCP	Registered Healthcare Professional
RUSAE	Related Unexpected Serious Adverse Event
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TAU	Treatment As Usual
TMG	Trial Management Group
TSC	Trial Steering Committee

5. BACKGROUND

Diabetic foot disease is an increasing global health problem. Diabetes currently affects more than 387 million people worldwide [1]. By 2035 this number will have grown to 592 million - approximately 10% of the world's adult population [1]. 60-70% of diabetics will develop peripheral neuropathy or lose sensation in their feet [2] and up to 25% will develop a diabetic foot ulcer (DFU) [3]. More than 50% of DFUs (wounds) become infected requiring hospitalisation and 20% of infections result in amputation [4] contributing to approximately 80% of non-traumatic amputations performed in the developed world [5].

In the UK diabetes affects 3.2 million people [6] with approximately 2.5% (80,000) having a DFU. In 2010-11 NHS England spent an estimated £639-662 million, 0.6-0.7% of budget, or £1 in every £150 spent on DFU treatment [7]. This does not take into account the costs imposed on the public sector and society as a whole through working days lost, reductions in tax revenue, increases in benefit payments and social care resources.

The prevalence of current or past DFU is 5-7% of the diabetic population [6]. One third of DFUs require surgery [8-10] and up to 70% of patients will develop further ulcers over 5 year follow-up [9]. There were 25.1 major or minor lower extremity amputations per year per 10,000 diabetics in England during 2007-10 with figures remaining unchanged over the last 5 years [11]. Health-related quality of life (HRQoL) is significantly reduced in patients with DFUs versus those with healed ulcers or no foot complications [12].

Adverse outcomes for UK patients with DFUs are reported despite 'treatment as usual' (TAU) comprising provision of NICE recommended 'best' care through multi-disciplinary team (MDT) DFU clinics (podiatrists, diabetologists, vascular surgeons etc.) and concomitant treatment strategies including: optimising glycaemic control, non-surgical debridement, dressing application, off-loading, treatment of infection and ischaemia [13]. There are a number of advanced/adjuvant therapies but their use is limited by high unit cost and an absence of robust evidence.

Despite implementation of MDT care, healing rates for DFUs at 12 weeks with standard therapies are low, with control groups in randomised controlled trials achieving 7.7-46% healing. Of those patients who do not achieve 50% reduction in ulcer size at 4 weeks, only 9-30% will go on to heal at 12 weeks [14, 15] and this has been suggested as an intermediate outcome to determine ulcers that should have early adjuvant therapies.

DFUs have a major impact upon HRQoL, including physical function, mental wellbeing and social interaction. Delayed healing increases the probability of adverse sequela including infection and amputation. DFUs present for more than 30 days have a 5-fold increase in infection compared to those who heal and infection has a 55-fold increase risk of hospitalisation, and 154-fold increase in amputation when compared to non-infected DFUs [4]. Establishing efficacious adjuvant therapies to TAU for use in non-healing wounds is a priority to improve healing rates, QoL and reduce the risk of morbidity associated with infection. Trials assessing adjuvant wound therapies in DFU are of poor quality and recent NICE guideline NG19, highlights the need for randomised controlled trials of negative pressure wound therapy (NPWT) and other adjuvant therapies [13, 16]. We are interested in 3 adjuvant therapies as technological advances mean they are available for clinic use. NPWT is available in a small portable pump which doesn't restrict patient movement. Surgical debridement forming an acute wound can now be undertaken using hydrosurgical debridement (HD) under local anaesthetic in clinic, enhancing patient experience and reducing costs by avoiding additional hospital visits for day-case surgery. This also allows wound bed preparation to a "graft ready state" for advanced wound adjuncts, a state which cannot be achieved by less formal debridement with wound cleansing preparations such as Debrisoft®. HD has been shown to

be as effective as formal theatre surgical debridement in wound healing outcomes [17]. Decellularised dermal allograft (DCD), has been used in the US for treatment of DFU with improved healing vs standard care [18, 19] but cost has been prohibitive in the UK. A novel DCD, prepared from skin donated by voluntary UK donors has recently been developed within the NHS, is approved by the Human Tissue Authority (HTA) and available for use in the UK. DCD is prepared and supplied by NHS Blood and Transplant (a Department of Health Special Health Authority), from skin donated by volunteer donors in the UK. However, the application of DCD requires surgical debridement to a 'graft ready wound bed' and it is not known whether surgical debridement alone leads to improved healing in this setting.

Performing multiple RCTs to assess each intervention is time consuming and expensive. Further, these therapies are often used in combination. Our trial proposes an efficient and innovative, adaptive multi-arm, multi-stage (MAMS) design. This involves early evaluation of combinations of the candidate treatments in a Phase II/III design, stopping treatments which fail to demonstrate sufficient improvements in DFU healing (using an intermediate endpoint at 4 weeks post randomisation), evaluating only those treatments showing greatest efficacy in a Phase III trial. Advantages of MAMS design include comparing multiple treatment arms to a shared control group thereby requiring fewer patients; multiple stages with early evaluation allows potentially ineffective treatments to be stopped early; provides contemporaneous comparisons for each of the treatment arms to TAU; improved consent/ recruitment rates since patients are more likely to receive an active treatment; and in this study there are no major inclusion/exclusion criteria that relate to a specific treatment.

We are proposing to compare four treatment strategies comprising combinations of three adjuvant therapies against TAU including HD, NPWT and DCD. The evidence for adjuvant therapies for DFU treatment has been recently reviewed in NICE guideline NG19 [13] and concludes that the quality of trials is poor with dichotomous and early endpoints and small sample sizes. It recommends that future trials are sufficiently powered with outcomes including time to healing, incidence and extent of amputation (major or minor), recurrence, HRQOL, adverse events, hospital admissions and length of stay.

There is a paucity of quality data on the outcome of adjuvant therapies for DFU. A 30% increase in burden of disease anticipated over the next 20 years which will add to the already substantial costs to the NHS of DFU in a time of increasing fiscal demand. With the NICE guidance advocating the need for robust RCTs in this area, and opportunely, the availability of a clinic based method of surgical debridement, a Human Tissue Authority approved DCD graft now available for purchase from the NHS and a portable NPWT which does not restrict patient mobility, we believe this is the optimal time to perform a trial of this kind. We do not anticipate that there will be a rapid change in the technologies utilised in this trial, other than design changes aimed at increasing clinician and patient acceptance and utilisation, therefore increasing the potential adoption and generalisability of the trial outcomes.

The MAMS design will provide an efficient platform to determine an effective treatment strategy for DFU therapy, allowing multiple treatment strategies to be tested under the umbrella of a single trial, increasing value for money of this randomised controlled trial.

6. AIMS AND OBJECTIVES

In Phase II we will investigate the short-term efficacy of the 4 treatment strategies compared to treatment as usual (TAU) and in Phase III we will investigate the clinical and cost effectiveness of a maximum of two treatment strategies continued from Phase II compared to TAU in the treatment of hard to heal DFUs.

The specific objectives for each Phase are as follows:

Phase II

Aim:

In Phase II, to determine the efficacy of treatment strategies including HD alone or with NPWT or DCD or a combination of all as an adjunct to TAU compared to TAU alone using the short-term intermediate outcome of index ulcer area reduction at 4 weeks post randomisation in patients with a DFU not involving bone or joint at baseline.

Phase III

Aim:

In Phase III, to investigate the clinical and cost effectiveness of a maximum of two treatment strategies continued from Phase II (showing evidence of short term efficacy), compared to TAU alone, in the treatment of hard to heal DFUs, in terms of time to healing, re-ulceration of the index ulcer, infection, serious adverse events, patient quality of life and cost per quality-adjusted life year (QALY).

Primary objective:

To determine whether a maximum of two treatment strategies (continued from Phase II) as an adjunct to TAU reduces time to healing of the index ulcer compared with TAU alone.

Secondary objectives:

- To compare a maximum of two treatment strategies as an adjunct to TAU continued from Phase II to TAU alone in terms of:
    - healing status of the index ulcer at 12, 20 and 52 weeks
    - rate of ulcer infection in the foot of the index ulcer over 52 weeks post randomisation
    - re-ulceration following healing of index ulcer over 52 weeks post randomisation
    - quality of life using DFS-SF and EQ-5D-5L over 52 weeks post randomisation
    - incidence of adverse events (including for example amputation, infection in any ulcer on the foot of the index ulcer and hospital admission) over 52 weeks post randomisation
- To determine cost effectiveness over 52 weeks

Exploratory objective:

- To explore factors prognostic of ulcer healing

7. DESIGN

The trial is a multi-centre, seamless Phase II/III, open, parallel group, multi-arm multi-stage (MAMS) randomised controlled trial (RCT) in patients with a hard to heal DFU, with blinded outcome assessment.

The MAMS trial design will allow an early evaluation of the candidate treatment strategies in a Phase II/III design. The “drop-the-loser” approach will be employed to drop treatment strategies that fail to demonstrate sufficient improvement in index ulcer healing at the end of Phase II. Only those treatment strategies showing greatest early clinical efficacy will undergo clinical and cost-effectiveness assessment in Phase III.

A total of four treatment strategies will be compared to TAU in Phase II. Treatment strategies for which the probability of response is less than 10% greater than the probability for TAU (absolute difference in %) will be dropped at the end of Phase II (response defined as at least 50% reduction in area covered by the index ulcer). A maximum of two treatment strategies and TAU will be evaluated in Phase III. If more than two treatment strategies show a sufficient

response in Phase II, then the decision on which two treatment strategies to evaluate in Phase III will consider information on the safety profile, costs of the treatment strategies and clinical efficacy. Further details of the design and analysis are provided in the detailed Statistical Analysis Plan (SAP).

A maximum of 660 participants will be recruited, including 324 participants in Phase II and at most 336 participants in Phase III. In Phase II, randomisation will be in a 1:1:1:1:2 allocation ratio to the four treatment strategies and TAU group respectively, and in Phase III in a 1:1:1 allocation ratio to a maximum of two treatment strategies and TAU. Recruitment at centres will be seamless between Phase II and Phase III and will continue as usual.

The trial will include a 9-month internal pilot phase in Phase II to evaluate the feasibility of recruitment and therefore delivery of the trial (see section 7.2).

All participants from Phase II and III will be followed up at weeks 1, 2, 4, 8, 12, 20 and 52 post-randomisation (including those where healing of the index ulcer has been confirmed), or week 54 where healing of the index ulcer is first reported at week 52.

An interim analysis will be conducted after 33.3% patients have reached 52 weeks post-randomisation to re-estimate the overall loss to follow-up rate and the final sample size. The review will be conducted in a blinded manner.

7.1 BLINDING

Due to the nature of the treatment strategies it is not possible to blind a participant, the clinical team or the research nurse/registered healthcare professional to the treatment strategy (as the DCD is visible for an interim period after application and NPWT will be visible until removed). However the primary outcome assessments (index ulcer measurement at week 4 and confirmation of index ulcer healing visits) will be completed by an independent clinical assessor who will have no previous involvement with, or knowledge of, the participant's index ulcer treatment and as such will be blind to the randomised treatment strategy (as the DCD is not expected to be visible at 4 weeks and the NPWT device will have been removed). This blinded assessor can be a clinician, research nurse or registered healthcare professional who is suitably trained in the assessment of wound healing. To mitigate the risk of assessment bias the blinded assessor will also have no access to the participant's notes or the main trial Case Report Forms (CRFs). Tracings and photographs at week 4 and confirmation of the index ulcer healing assessments will be returned to the Clinical Trials Research Unit (CTRU) separate to the main trial CRFs, tracings and photographs.

For the Phase II primary outcome and Phase III exploratory objective, the blinded assessor at each site will complete an acetate tracing and take a 2D digital photograph of the index ulcer at week 4. These will be submitted to CTRU where measurements will be obtained from the index ulcer tracing using 'Image J' software by a member of the CTRU team who is independent of the research team at each site and blind to treatment allocation. A photograph of the index ulcer will be taken as a back-up in the event that a tracing cannot be taken or the tracing is of insufficient quality to determine the index ulcer outline. Photographs will be transferred electronically to CTRU (see section 11.7). Where required an independent clinician (for example, the Clinical Coordinator) will delineate the index ulcer margin on the photograph and use Image J software to calculate the index ulcer area. The clinician will be independent of the research team at each site and blind to treatment allocation and other outcomes. The measurements obtained using photographs will be used to inform imputed values for missing index ulcer area measurements when tracings are not available.

For the Phase III primary endpoint, all participants recruited to both Phase II and III will also have a photograph taken of the reported healed index ulcer by the blinded assessor within 3 days of healing being reported and two weeks later (+/- 3 days) as a confirmation assessment of healing which will undergo blinded central review (see below).

In addition, to assess the risk of under-reporting of healing, 25% of participants will be randomly selected at the point of randomisation for photographs of the index ulcer to be taken at weeks 12, 20 and 52. The CTRU will notify the research nurse/registered healthcare professional by email when these photographs are due.

All photographs will be submitted to CTRU. Photographs taken at first visit and confirmation of healing visits, and of unhealed index ulcers for randomly selected participants at baseline and weeks 12, 20 & 52, will be submitted for central blinded photography review by clinical members of the Trial Management Group who will not be aware of the participant's identity, treatment strategy or time point at which the photograph was taken.

7.2 INTERNAL PILOT PHASE

An internal pilot study has been planned in order to assess the feasibility of trial delivery to the maximum target recruitment within the planned timelines.

The internal pilot phase includes 66 patients recruited across 15 centres over 9 months and represents the minimum target to provide reassurance that recruitment to the trial will be feasible. Assuming a recruitment rate of 1 patient per centre per month, the maximum target of 660 patients in 36 months (across both phases of recruitment) will be feasible. The internal pilot represents 10% of patients recruited, across 75% of the target number of centres, after 25% of the recruitment period has been completed. The recruitment projection for this internal pilot phase takes into account a staggered opening of centres.

At the end of the internal pilot study at 9 months after the trial starts recruitment, if the number of actively recruiting centres is less than 15 or the overall number of patients recruited is less than 66, stopping will be considered by the TSC. The decision to continue the trial will remain with the funder in the event that the target is not met.

8. ELIGIBILITY

Patients attending the MDT-DFU service outpatient clinics will be screened for eligibility by the attending clinical/research team. Patients will be eligible for randomisation if they fulfil the following **inclusion** criteria:

1. Aged ≥ 18 years
2. Diagnosis of Diabetes Mellitus (according to WHO criteria [20])
3. Has a chronic DFU or surgical debridement wound or open minor amputation defined as having <40% reduction in index ulcer area in the preceding ≥ 4 weeks prior to randomisation
4. The index DFU has an area ≥1cm^2
5. Ankle brachial index for the leg of the index ulcer ≥0.7 or non-compressible (measurements available in the participants notes taken within 3 months of randomisation can be used if no change in intervention or vascular events have occurred)
6. Expected to comply with the treatment strategies and follow up schedule
7. Consent to foot and wound photography
8. Consent to participate (written/witnessed verbal informed consent)

Patients will be excluded if they fulfil any of the following **exclusion** criteria:

1. Has any current clinically infected DFU on the foot of the index ulcer (as per IDSA guidelines [21])
2. HbA1C>110mmol/mol (measurements available in the participants notes taken within 3 months of randomisation can be used if no change in intervention or vascular events have occurred)
3. Estimated glomerular filtration rate (eGFR) < 20mL/min/1.73m^2 (measurements taken within 3 months of randomisation can be used if no change in intervention or vascular events have occurred)
4. Index ulcer duration >2 years
5. Planned or previous treatment with corticosteroids to an equivalent dose of prednisolone >10mg per day or other immunosuppressive/immunomodulating therapy within 4 weeks prior to randomisation
6. Has evidence of connective tissue disorders as a cause of ulceration (e.g. vasculitis or rheumatoid arthritis)
7. Has evidence of dermatological disorders as a cause of ulceration (e.g. pyoderma gangrenosum or epidermolysis bullosa)
8. Planned or previous growth factor treatment within 4 weeks prior to randomisation
9. Planned or previous revascularisation or foot surgery affecting healing on the foot of the index ulcer within the 4 weeks prior to randomisation
10. Index ulcer base has bone or joint involvement
11. Previously received DCD for the index ulcer within 4 weeks prior to randomisation
12. Previously received NPWT for the index ulcer within 4 weeks prior to randomisation
13. Previously received hydrosurgical or surgical debridement for the index ulcer within 4 weeks prior to randomisation
14. Has previously been randomised to the MIDFUT study
15. Unable to receive one or more of the randomised treatment strategies for any reason at the discretion of the attending clinical team (e.g. risk of excessive bleeding, serious falls risk, known allergies to NPWT dressings or dCELL dermis preparation components)

Eligibility waivers to the inclusion/exclusion criteria are not permitted.

9. RECRUITMENT

9.1 RECRUITMENT SETTING

Patients will be recruited in secondary care and community clinics who provide an MDT-DFU service (which includes as a minimum a clinician trained in each trial intervention, podiatrist, diabetologist, vascular surgeon and orthotist). Research centres will be required to have obtained local confirmation of capability and capacity and undertake a site initiation meeting with the CTRU prior to the start of recruitment into the trial.

Randomised treatment strategies will be provided in MDT-DFU service clinics, with treatment as usual throughout the study provided through routine attendance at clinics providing a multidisciplinary team service and community services (as per local practice).

9.2 RECRUITMENT PROCESS

All patients under the care of the MDT-DFU outpatient clinics in participating services will be considered as potentially eligible for this study if they have a current DFU or amputation wound. Where indicated by the attending clinical team and agreeing to consider receiving

further information, patients will receive a full verbal explanation of the study and a Patient Information Leaflet (PIL) by either the attending clinical team or MIDFUT clinical research team, at a time convenient to the patient during their routine clinic visit.

In order to alert existing patients to the study we will display posters and/or leaflets in clinic waiting areas and any other appropriate location. With permission from consultant colleagues, patients will be sent a letter and patient information leaflet (PIL) with their out-patient appointment letter. This letter will include a brief introduction to the study and patients will be invited to ask further questions at their next clinic visit or to contact the MIDFUT research team for further details.

Assenting patients will have a formal eligibility assessment and be invited to provide informed consent (see Section 9.4 below).

Where suitable, information about the study will be included on relevant websites and research databases that can be accessed by members of the public who are interested in opportunities to take part in research. This information will include a brief synopsis of the study and detail of which MDT DFU clinics are participating in the MIDFUT study. Interested parties will be directed to enquire about the study at their next diabetic foot ulcer appointment at the clinic.

In addition, the study team will liaise with relevant organisations to circulate ethically approved tweets on Twitter to allow potential participants to become aware of the trial.

9.3 ELIGIBILITY SCREENING

Participating research sites will be required to complete a non-registration log of all patients presenting with a DFU who have been considered for the trial but have not been registered into the study. Documented reasons for ineligibility or declining participation will be collected and closely monitored by the CTRU as part of the regular review of recruitment progress. Non-registration logs should be returned to CTRU on a monthly basis. The following anonymised data will be collected on the non-registration log:

- Age
- Gender
- Ethnicity
- Date screened
- Reason not eligible for registration OR
- Reason declining participation

9.4 INFORMED CONSENT AND ELIGIBILITY

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

The assessment of eligibility will be confirmed and the informed consent process will be undertaken by the PI or registered healthcare professional who is GCP trained and has been approved by the PI as detailed on the Authorised Personnel Log. The PI or designate will confirm consent by countersigning the informed consent form.

Where a participant is required to re-consent or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU. The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

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

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

A record of the consent process detailing the date of consent and those present will be detailed in the patients' healthcare records. The original consent form will be filed in the Investigator Site File at the participating centre, a second copy included in the healthcare record (as per local practice) and a third copy will be returned to the CTRU.

Patients who provide written/witnessed verbal informed consent who subsequently lose capacity will be withdrawn from the trial.

Assenting patients will be seen by a member of the MIDFUT clinical research team who will provide a full verbal explanation of the study and Patient Information Leaflet 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 as long as they need to consider participation and will be given the opportunity to discuss the study with family and other healthcare professionals before they are asked whether they would be willing to take part in the study. Patients will also be provided with a contact point where he/she may obtain further information about the trial.

Full informed consent will be obtained for **all** participants prior to registration. All participants who consent will be registered into the trial. Participants eligible for randomisation will be asked to verbally reconfirm consent to continue in the trial prior to randomisation. Participants who provide written informed consent at the registration visit may withdraw consent at any time.

9.5 REGISTRATION

Informed written/witnessed verbal consent for entry into the trial must be obtained prior to registration. Following confirmation of written/witnessed verbal informed consent and eligibility for registration participants will be registered by an authorised member of staff at the research site. Registration will be performed centrally using the CTRU automated, secure, 24-hour registration/randomisation service which can be accessed via the web or telephone. For the telephone system, a site code, authorisation code and Personal Identification Number (PIN) will be required. To register using the web based system a staff site email address, site code

and PIN will be required. Authorisation codes and PINs will be provided by the CTRU to access the registration/randomisation service. These codes will only be issued once a site has been fully approved and all the necessary documentation has been received at CTRU.

The person telephoning or accessing the web address to register the participant must have the completed Registration Case Report Form (CRF) available at the time of registration as the following information will be required at registration;

- Participant details including initials, date of birth, and NHS number
- Site code
- Confirmation of informed consent
- Confirmation of consent to photography
- Index ulcer area measurement (as per Image J measurement)

Participants may only be registered into the trial by an authorised member of staff at the trial research site, as detailed on the Authorised Personnel Log.

Direct line for 24-hour registration: 0113 343 2290
Web address for 24-hour registration:
https://lictr.leeds.ac.uk/webrand/

After trial registration the research site will:

- Add the unique participant ID number to all CRFs
- Return a copy of the completed consent form to CTRU
- CTRU will email a Participant Registration Notification to the research site.

Participants may only be registered into the trial once

9.6 RANDOMISATION

An eligibility assessment period will take place between registration and randomisation. An eligibility assessment period is defined as 4 weeks between an initial tracing of an index ulcer and a subsequent pre-randomisation tracing (4 weeks -3/+7 days). At the end of the eligibility assessment period the research team will complete an eligibility for randomisation assessment CRF for **all** participants, including those who are not suitable to proceed to randomisation (and the reason why not suitable to proceed given). If a participant is not suitable to proceed to randomisation (including where the subsequent pre-randomisation tracing cannot be performed in the scheduled window), the eligibility assessment period can be repeated three times before the participant is considered as not proceeding to randomisation. A new initial tracing will be required at the start of each new eligibility assessment period with a pre-randomisation tracing taken 4 weeks later (-3/+7 days). The participant will only be registered once and will retain the same trial number.

Participants who have previously been registered, have confirmation of eligibility for randomisation and assent to continue in the study will be randomised into the trial by an authorised member of staff at the research site. Randomisation will be performed centrally using the CTRU automated, secure, 24-hour randomisation service which can be accessed via the web or telephone. For the telephone randomisation, the same site code, authorisation code and PIN used for registration (refer to Section 9.5) provided by CTRU, will be required

to access this system. For the web randomisation, a site staff email address, site code and PIN will be required.

Baseline questionnaires must be completed prior to randomisation.

Randomisation will be performed on the day of treatment by the research nurse/registered healthcare professional who will need to complete the Randomisation CRF prior to the time of telephoning/accessing the web, as the following information will be required:

- Site code
- Participant's unique trial number provided at registration
- Confirmation of eligibility for randomisation
- Confirmation of written informed consent
- Confirmation of consent to photography
- Confirmation of completion of baseline assessments
- Confirmation of completion of baseline questionnaires

Randomisation in both phases will use a minimisation algorithm incorporating a random element to ensure groups are well balanced for the following participant characteristics, details of which will also be required for randomisation:

- Aetiology (neuropathic or neuro-ischaemic)*
- Index ulcer duration (<6 months, ≥ 6 months)
- Anatomical site (forefoot, mid/hindfoot)
- Presentation (DFU, surgical debridement wound, open minor amputation)

* Neuropathic will be classified by a palpable pedal pulse or multiphasic hand held Doppler signal. All other patients will be classified as neuro-ischaemic.

In Phase II, participants will be randomised in a 1:1:1:1:2 treatment allocation ratio to one of five groups respectively:
i) Treatment As Usual (TAU) and Hydrosurgical Debridement (HD)
ii) TAU with HD and 2 weeks of Negative Pressure Wound Therapy (NPWT)
iii) TAU with HD and Decellularised dermal allograft (DCD)
iv) TAU with HD, DCD and 2 weeks of NPWT
v) TAU alone (control) (using Dunnett's recommendation for the allocation to the TAU arm of $\sqrt{}$(number of treatment strategies) [22])

In Phase III, participants will be randomised in a 1:1:1 allocation ratio to a maximum of two treatment strategies (that pass the threshold in Phase II) and TAU.

Direct line for 24-hour randomisation: 0113 343 2290
Web address for 24-hour randomisation:
https://lictr.leeds.ac.uk/webrand/

Following randomisation the research site will:

- Provide each participant with a trial ID card and inform them to keep this with them at all times and present to the attending clinical team if their index ulcer has healed or re-ulceration of the healed index ulcer has occurred during their time on the trial.
- Provide each participant with a Registered Healthcare Professional (RHCP) letter to present when required during a standard care appointment.
- Ensure that participants are notified of their appointment dates.
- Notify the patient's GP of participation in the trial.

Following participant randomisation, CTRU will fax or email a Participant Randomisation Notification to the member of the research team member who randomised the participant.

Participants may only be randomised into the trial once.

10. TREATMENT AS USUAL/ADJUVANT TREATMENT DETAILS

Please refer to the MIDFUT Treatment Strategy Study Site Operating Procedure (SSOP) for full details of the trial treatment strategy requirements. All randomised treatment strategies will be applied to the index ulcer on the day of randomisation in the MDT-DFU service clinic. Treatment of any other ulcers will continue as per the treating clinician decision.

At registration, baseline, randomisation and all follow-up visits all participants will receive TAU. At the randomisation treatment visit, the participant will be randomised to receive the treatment strategy specific to the arm of the trial for the index ulcer. This will include one or more of the following:

10.1.1 Treatment as usual (TAU)

For Treatment As Usual, the participant will receive the minimum standard care provided by the recruiting centre. This will be in line with NICE (NG19) guidelines and is likely to include attendance at the MDT-DFU service clinic(s) at least fortnightly for wound assessment (for healing/infection), sharp non-surgical debridement of callous/non-viable tissue, review of off-loading and other assessments and treatments to optimise diabetes management (through involvement of a diabetologist, vascular surgeon, podiatrist and orthotist) and community podiatry/district nurse/practice nurse visits for wound assessment and treatment as required (typically 1 to 2 times weekly).

In line with NICE guidelines use of removable below knee walking device or removable cast walker will be encouraged. Participants will have access to urgent advice between visits if required, either through DFU-MDT service clinic standard protocols or through the research team. Wound dressing changes will be performed between clinic visits as per local policies.

10.1.2 Hydrosurgical Debridement (HD)

Hydrosurgical Debridement utilises a high pressure jet of saline applied via a pump through a hand piece. This has an operating window located at the instrument's distal tip. During operation the flow of pressurised saline creates a local vacuum. As the operating window of the handset is passed over the tissue, non-viable material and debris are removed. The ulcer bed is debrided to healthy bleeding tissue which may require local anaesthetic.

10.1.3 Negative Pressure Wound Therapy (NPWT)

Negative Pressure Wound Therapy (NPWT) consists of a foam dressing cut to shape and applied to the wound. An air-tight seal is established with a film dressing; this is then connected to a pump which applies gentle suction to the wound. This allows the removal of fluid from the wound which is collected in a canister attached to the pump which is carried by the participant at all times in the bag provided. The dressing is usually changed at least once a week, and the NPWT will be applied for 2 weeks from randomisation during the trial. Disposable NPWT devices such as PICO are not authorised for use in the trial.

10.1.4 Decellularised Dermal Allograft (DCD)

Decellularised Dermal Allografts are produced from donated human tissue which is processed and sterilised. Processing keeps the normal skin structure, but removes donor cells meaning

the graft has a low rejection response and is considered a permanent allograft. The product will be stored at room temperature (between 0- 40^{o}C) upon receipt of delivery at participating sites until the expiry date stated on the product label.

Prior to application the product is soaked in a bowl of sterile saline solution for 15 mins. The graft is then cut to size using sterile scissors and applied directly to the debrided wound bed, epidermal side upwards. Following application, the wound is covered with a non-adherent contact layer and a secondary dressing or NPWT (as per randomisation).

10.2 CESSATION OF TREATMENT

In line with usual clinical care, cessation or alteration of treatment strategies at any time will be at the discretion of the attending clinical team or the participants themselves. Participants who do not receive or complete the protocol treatment strategies due to participant request or clinician decision are **NOT** classed as withdrawals. **Follow-up assessments will continue and case report forms will continue to be completed according to the protocol schedule unless consent for follow-up is withdrawn** (see section 10.3).

10.3 WITHDRAWAL OF CONSENT

Clinicians involved in the trial should not withdraw participants from the trial unless it is harmful for the participants to continue or unless the participant wishes to be withdrawn. Participants may withdraw consent from the trial at any time without explanation. The PI or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw from further involvement in the trial are defined and documented using the withdrawal case report form in order that the correct processes are followed by the CTRU and site. Withdrawal forms must be completed and returned to CTRU within 7 days.

Participant withdrawal will be classified as follows;

a) Withdrawal of consent to the study treatment strategy only but the participant is willing to be followed up according to the follow up schedule.
b) Withdrawal of consent to the study treatment strategy and wound photography but the participant is willing to be followed up according to the follow up schedule.
c) Withdrawal of consent for wound photography but the participant is willing to have/has completed the randomised treatment strategy and to be followed up according to the follow up schedule.
d) Withdrawal of consent to the follow up schedule but the participant is willing to have/has completed the randomised treatment strategy and is willing for further information to be collected only from healthcare records.
e) Withdrawal of consent to the study treatment strategy and the follow up schedule, but the participant is willing for further data to be collected only from healthcare records.
f) Withdrawal of consent to the follow up schedule and data collection (including healthcare records) but the participant has completed the randomised treatment strategy.
g) Withdrawal of consent to the study treatment strategy, the follow up schedule and data collection.

For a), b) and c) completion of CRFs will continue as per the protocol schedule and all of the participants' data will be used in the trial analysis.

For d) and e), data collection will continue for the duration of the trial when any further data become available in the healthcare record and all of the participants' data will be used in the trial analysis.

For f) and g), no further follow up data will be collected past the point of withdrawal and data collected up to the point of withdrawal will be used in the analysis.

10.3.1 Eligibility violations

Participants who have been randomised but found to be ineligible after randomisation (and were actually ineligible at the time of randomisation) are **NOT** withdrawn from the study and continue with the protocol follow-up schedule. Continuation with the randomised treatment strategy will be at the discretion of the treating clinician and participants may be withdrawn from the randomised treatment strategy but continue in the study (section 10.3). Eligibility violations will be recorded on the protocol deviation form and sent to CTRU.

11. ASSESSMENTS/SAMPLES/DATA COLLECTION

Registration, randomisation baseline assessments and follow up assessments at week 1, 2, 4, 8, 12, 20 and 52 weeks post randomisation will be undertaken by a member of the clinical research team (clinician, clinical research nurse or registered healthcare professional).

The outcome assessment at week 4 and confirmation of index ulcer healing visits will be completed by a blinded assessor (clinician, research nurse or registered healthcare professional).

The randomised treatment strategy and week 1 routine clinic assessment will be administered by the treating clinician/healthcare professional (who will not assess outcomes).

25% of participants will be randomly selected at the point of randomisation for photographs to be taken at weeks 12, 20 and 52. Please see section 11.2.

For full details of the process required to calculate wound measurement using the Image J software please refer to the relevant SSOP provided in the Investigator Site File (ISF).

For full details of the photography requirements and process please refer to the relevant SSOP provided in the ISF.

11.1 SUBMISSION OF TRIAL DATA

Trial data will be recorded by site research staff and participants on paper CRFs and participating sites will be expected to submit original wet ink copies to the CTRU at the University of Leeds. Following receipt, the CTRU will contact trial sites to resolve any missing or discrepant data and any outstanding CRFs will be chased by CTRU until received or the data is confirmed as unavailable.

It is the responsibility of each trial site to maintain a file of essential trial documentation in the ISF, which will be provided by the CTRU, and keep copies of all completed CRFs for the trial.

11.2 SCHEDULE OF EVENTS

Please see next page

WEEK	Eligibility Assessment Period			Follow up Assessments							Confirmation of healing (Ad hoc as required)	
Study Visit	-4 weeks	Day 0		Week 1	Week 2	Week 4	Week 8	Week 12	Week 20	Week 52	Initial visit	2 week follow up visit
	Registration (or date of initial tracing if eligibility assessment period is being repeated)	Eligibility & Baseline assessments **pre randomisation**	Randomisation & treatment strategy application									
STUDY VISIT WINDOW		-3/+7 days		+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	Within 3 days of healing being reported	+/-3 days
Informed consent	X†											
Assessment of suitability and registration	X†											
Registration clinical assessment	X†											
Photograph of foot indicating site of index ulcer	X†											
Photograph of index ulcer post sharp non-surgical debridement including scale with ruler	X	X			X	X*		X[1]	X[1]	X[1]	X*	X*
Index ulcer acetate tracing post sharp non-surgical debridement	X	X			X	X*						
Image J index ulcer measurement from acetate	X	X			X	X*						
Eligibility for randomisation assessment CRF		X										
Medical history		X										
Baseline clinical assessment		X										
SINBAD classification		X										
DFS-SF		X				X		X	X	X		
EQ-5D-DL		X				X		X	X	X		
Health resource questionnaire						X	X	X	X	X		
Confirmation of eligibility and randomisation			X									
GP letter sent			X									
Administration of randomised treatment strategy			X	X[2]								
Post HD debridement index ulcer area acetate tracing & photograph (where applicable)			X									
Administration & recording of index ulcer treatment	X		X	X	X	X		X	X	X		
Expected adverse events and SAEs	X		X	X	X	X		X	X	X		
Issue participant ID card			X									
Index ulcer status				X	X	X		X	X	X		
Recording of re-ulceration of the index ulcer (where applicable) including photography					X[3]	X[3]		X[3]	X[3]	X[3]		
Recording of revascularisation of the limb of the index ulcer (where applicable)				X	X	X		X	X	X		
Confirmation of compliance with NPWT (where applicable)				X[2]	X							
Removal of NPWT (where applicable)					X							

*Completed by the independent assessor at this visit

†Not required if the eligibility assessment period is being repeated

[1]Only for 25% of participants selected at random and where the index ulcer has not healed

[2] Only for NPWT where applicable

[3] Re-ulceration to be confirmed by the blinded assessor

= Blinded assessment visits

11.3 REGISTRATION VISIT

Following information provision, assenting patients will be screened for potential eligibility. Concomitant therapies, relevant medical history and planned/previous treatments for DFUs will be discussed with the patient and those who are potentially eligible will be asked to provide consent and will be registered as potentially eligible for trial participation.

Where patients are assessed as clearly not eligible or eligible but not consenting at the screening visit, they will be recorded on the anonymous Non-Registered Patients' log.

At registration, the following personal data will be collected (to be retained securely at site and not returned to CTRU);

- Patient name, hospital number, patient address and telephone number, patient email address, Pharmacy details, GP name and address.

The following information will be recorded on the CRFs completed at the registration visit:

- Participant details, including initials, date of birth, NHS number, confirmation of written informed consent, gender, ethnicity, confirmation consented to photography, Image J index ulcer area measurement from acetate. Confirmation of site of index ulcer
- Confirmation that a photograph of the foot indicating site of index ulcer has been sent to CTRU
- Confirmation that an acetate tracing of the index ulcer post sharp non-surgical debridement has been sent to CTRU
- Confirmation that a photograph of the index ulcer including grey scale with ruler has been sent to CTRU

11.4 ELIGIBILITY AND BASELINE ASSESSMENTS PRE RANDOMISATION

The aim of this visit is to confirm that the participant is eligible for the study and to collect baseline data for participants that are suitable for randomisation. This visit should take place 4 weeks (-3/+7 days) after the initial tracing of an index ulcer at the start of this eligibility assessment period.

For all registered participants the following information will be recorded on the Eligibility for Randomisation Assessment CRF:

- Data relating to the clinical assessment of eligibility
- Confirmation of eligibility

Where registered patients who attend the baseline visit are assessed as not eligible, or eligible but withdraw consent, or the participant is unable to attend this visit within the specified window, this information will be recorded on the Eligibility for Randomisation Assessment CRF as the reason for the participant not proceeding to be randomised into the study. The Eligibility for Randomisation Assessment CRF will then be returned to the CTRU. The baseline assessments should **not** be completed for participants that are ineligible.

For participants that are eligible to proceed to randomisation the following baseline data will be recorded on the Baseline CRF **prior to randomisation and receiving the randomised treatment strategy**:

- Verbal reconfirmation of consent to participate

- Verbal reconfirmation of consent for photography
- Clinical History: Duration of diabetes, type of diabetes, number of ulcers on both feet
- DFU clinical assessment: index ulcer characteristics (for example, first or recurrent ulcer, neuroischaemic/neuropathic aetiology and existing wound therapies)
- SINBAD classification (appendix 1)
- Smoking Status
- Quality of Life Questionnaires: DFS-SF and EQ-5D-5L (both participant completed)
- Administrative: Confirmation GP letter sent.

Baseline assessments and questionnaires pre-randomisation will be completed on the same day as randomisation and treatment strategy application.

11.5 RANDOMISATION & TREATMENT STRATEGY APPLICATION

Randomisation will be completed at the baseline visit by a member of the clinical research team after the baseline assessment and questionnaires have been completed. The following information will then be recorded on the appropriate CRFs **after randomisation and receiving the treatment strategy**:

- Participant ID/Trial number
- Treatment strategy allocation and details of application
- Date treatment strategy completed
- Post HD debridement index ulcer area acetate tracing and photography (where applicable)
- DCD reporting form completion (where applicable)
- Treatment strategy for all DFUs on the foot of the index ulcer
- Expected adverse and serious adverse events

11.6 FOLLOW UP ASSESSMENTS

Treatment as usual will continue throughout as per local practice. All participants will be followed up to week 52 (including participants recruited into Phase II and those where healing has been confirmed) or week 54 where index ulcer healing is first reported at week 52.

Routine clinic assessment at 1 week post randomisation:
The following information/ assessments will be recorded:

- Compliance with NPWT (where applicable)
- Index ulcer assessment including healing status (see 11.6.1) and infection status (IDSA criteria)
- Revascularisation of the limb of the index ulcer (where applicable)
- Index ulcer treatment
- Assessment for development of new DFU
- Expected adverse events and serious adverse events (see section 12)

***Follow up week 2 post randomisation*:**
The following information/ assessments will be recorded:

- Index ulcer assessment including healing status (see 11.6.1), re-ulceration of the index ulcer (see 11.6.2) and infection status (IDSA criteria)
- Revascularisation of the limb of the index ulcer (where applicable)

- Acetate tracing and photography of the index ulcer post sharp non-surgical debridement (where sharp non-surgical debridement is clinically indicated)
- Confirmation of compliance and removal of NPWT (where applicable)
- Index ulcer treatment
- Assessment for development of new DFU
- Expected adverse events and serious adverse events (see section 12)

Follow up week 4, post randomisation:
The following information/ assessments will be recorded:

- Index ulcer assessment including healing status (see 11.6.1), re-ulceration of the index ulcer (see 11.6.2) and infection status (IDSA criteria)
- Blinded assessor ulcer acetate tracing and photography post sharp non-surgical debridement (where sharp non-surgical debridement is clinically indicated)
- Revascularisation of the limb of the index ulcer (where applicable)
- Patient completed questionnaires (DFS-SF, EQ-5D-5L and healthcare resource utilisation)
- Index ulcer treatment
- Assessment for development of new DFU
- Expected adverse events and serious adverse events (see section 12)

Follow up week 8 post randomisation:

- Patient completed questionnaire (health resource utilisation)

Follow up week 12, 20 and 52 post randomisation:
The following information/ assessments will be recorded at weeks 12, 20 and 52 post randomisation:

- Index ulcer assessment including healing status (see 11.6.1), re-ulceration of index ulcer (see 11.6.2) and infection status (IDSA criteria)
- Revascularisation of limb of the index ulcer (where applicable)
- Patient completed questionnaires (DFS-SF, EQ-5D-5L and healthcare resource utilisation)
- Index ulcer treatment
- Assessment for development of new DFU
- Photography and wound tracing post sharp non-surgical debridement (where sharp non-surgical debridement is clinically indicated) only for the 25% of participants randomly selected at randomisation who remain unhealed
- Expected adverse events and serious adverse events (see section 12)

11.6.1 ASSESSMENT OF HEALING

Healing is defined as complete closure of the ulcer: 100% re-epithelialisation of the wound surface with the absence of drainage confirmed by blinded assessment of healing status at two consecutive assessments two weeks apart [23]. Healing of the index ulcer will be reported in one of the following scenarios;

- During the participant's routine appointment at the MDT-DFU service clinic, podiatry clinic, GP practice nurse and/or at home by district nurses as per treatment as usual (in between research visits). The index ulcer will be assessed for healing at each visit by the attending clinical team. In the event healing of the index ulcer is reported by the attending clinical team while the participant is being treated in the MDT-DFU service clinic, community podiatry clinic, and GP practice nurse or at home, the attending clinical team will contact the research team to report the date the index ulcer was first noted as healed.
- By the Research Nurse/Registered Healthcare Professional at a research visit.
- Patient self-reporting to the research team.

- Patient self-reporting to the attending clinical team in between routine appointments. The attending clinical team will inform the research team.

Following notification to the research team they will arrange an initial visit within 3 days of healing of the index ulcer first being reported and a 2 week follow-up visit (+/- 3 days) with the blinded assessor to assess index ulcer healing status and conduct photography.

11.6.2 ASSESSMENT OF RE-ULCERATION

Re-ulceration is defined as recurrence of a full thickness break in the epithelium at the same location as the index ulcer [24]. Re-ulceration of the index ulcer will be established either by participant self-referral to the research team, at a routine clinic or research appointment or by continuous screening of new referrals to the MDT-DFU service clinic where participants will be flagged to the research team by the attending clinical team. Re-ulceration of the index ulcer will be confirmed by a blinded assessor with reference to the photograph of the foot taken at the registration visit, photography undertaken and the date of re-ulceration of the index ulcer recorded.

11.7 PHOTOGRAPHY

Photography will be used to establish the index ulcer and is compulsory for all participants at the time of entering the study. This is made explicit in the patient information sheet. Verbal agreement will be confirmed before each photograph is taken and the participant can refuse to be photographed at any time yet still remain in the study (see section 10.3). All participants will have the following photographs taken at the following time points (where consent has been given);

- A photograph of the foot to establish the location of the index ulcer (by a member of the research team) at the registration visit.
- The index ulcer will be photographed at trial registration, post sharp non-surgical debridement (where sharp non-surgical debridement is clinically indicated) by a member of the research team.
- The index ulcer will be photographed at baseline post sharp non-surgical debridement (where sharp non-surgical debridement is clinically indicated) and before randomisation by a member of the research team.
- The index ulcer will be photographed post HD debridement (where applicable) by a member of the research team.
- The index ulcer will be photographed at week 2 post sharp non-surgical debridement (where sharp non-surgical debridement is clinically indicated) by a member of the research team.
- The index ulcer will be photographed at week 4 post sharp non-surgical debridement (where sharp non-surgical debridement is clinically indicated) by the blinded assessor.
- The site of the index ulcer will be photographed at the confirmation of healing initial and 2 week confirmation of visits (Blinded assessor).
- A photograph of the foot will be taken if re-ulceration of the index ulcer is reported to confirm the site of re-ulceration (by the blinded assessor).

A 25% sample of all participants will be randomly selected at randomisation to also have a post sharp non-surgical debridement (where sharp non-surgical debridement is clinically indicated) photograph taken of the index ulcer if unhealed at week 12, 20 and 52.

All follow up photographs will be taken after callous and non-viable tissue has been removed (where callous is present) by sharp non-surgical debridement.

A standard study camera will be supplied to each site together with a work instruction detailing the use of a standardised photographic method including the use of a scale with ruler. For the purposes of consistency and interpretation of photographic data it is imperative that only the study camera supplied is used to take photographs. In addition, the work instruction will provide clear instructions on the anonymisation, secure transfer and deletion of the photographs (that is, there will be no local storage of photographs on the camera or NHS computer) to ensure standardisation across all centres.

All photographs will be submitted to CTRU. Photographs taken at both the first and follow up confirmation of healing visits, and of unhealed index ulcers for randomly selected participants at baseline and weeks 12, 20 & 52, will be submitted for central blinded photography review by clinical members of the Trial Management Group who will not be aware of the participant's identity, treatment strategy or time point at which the photograph was taken.

11.8 PARTICIPANT QUESTIONNAIRES

No single patient-reported outcome measure (PROM) has been identified as a "gold standard" for assessing HRQOL in diabetes-related foot disease [12]. As a result, two different instruments are utilised both of which are completed by participants: 1) a preference-based utility measure - EuroQoL 5D (EQ-5D); and 2) a disease-specific questionnaire - Diabetic Foot Ulcer Scale - Short Form.

Diabetic Foot Ulcer Scale Short Form (DFS-SF) [25] questionnaire has acceptable psychometric properties for measuring quality of life for patients with DFUs. The DFS-SF will be administered by self-assessment at baseline, 4, 12, 20, and 52 weeks.

EQ-5D-5L is an accepted, five-item, generic, health-related quality of life measure that provides including 5 items that can be combined to provide a single assessment of utility of life in a particular for health state [26]. The EQ-5D-5L will be completed by self-assessment at baseline, 4, 12, 20, and 52 weeks. The EQ-5D is a generic instrument (www.euroqol.org) and forms part of the NICE reference case for cost per Quality Adjusted Life Years (QALY) analysis.

All participants should complete the quality of life (QoL) questionnaires in clinic. An authorised member of the trial team will check that the forms have been completed fully and will be able to provide clarification only if requested by the participant. They will be trained to avoid directing patients in their responses.

11.9 HEALTH RESOURCE UTILISATION QUESTIONNAIRE

Healthcare resource use information will be collected at the same time points as the clinical effectiveness data collection points (4, 8, 12, 20 and 52 weeks) and using the same methods as for the other outcome measures (participant self-completion in clinics). It will collect information on NHS and personal social care use in line with NICE guidelines [27]. This will include primary, secondary, and community resource use. This information will be collected for all participants in Phase II and Phase III of the trial up to 52 weeks post randomisation. In addition to number of visits, duration of appointment for delivering the randomised treatment strategy will be collected as part of the trial CRFs. Completion rates of the duration data will be assessed at 4 weeks. If completion is poor (<80%) we will adapt the CRFs or look to alternative methods to collect data following discussion with the research nurses and the study team.

11.10 PARTICIPANT TRIAL COMPLETION

Trial completion is defined as the end of follow up (i.e. 52 weeks post randomisation or 54 weeks post randomisation where healing is first reported at week 52), withdrawal or death.

11.11 PROTOCOL DEVIATIONS

The CTRU undertake to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the CTRU. All such deviations will be documented on the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the published report.

11.12 TRIAL MANAGEMENT END OF TRIAL

The end of the trial is defined as the date of the last participant's last data item.

12. ADVERSE AND SERIOUS ADVERSE EVENTS

12.1 GENERAL DEFINITIONS

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

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

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

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

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

Medical and scientific judgement must be exercised in deciding whether an event is serious (see protocol section 12.4 for Responsibilities). These characteristics/consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

12.2 OPERATIONAL DEFINITIONS OF (S)AEs AND REPORTING

This is a randomised controlled trial using well established treatment strategies with well-known safety profiles. In recognition of this, events fulfilling the definition of an adverse event or serious adverse event will not be reported in this study unless they are defined as:

1. Expected and related to DFUs and trial treatment strategies and classified as an AE (see 12.2.2)
2. Expected and related to DFUs and trial treatment strategies and classified as an SAE (section 12.2.2)
3. Related to DFU and trial treatment strategies and classified as a RUSAE (section 12.3)

12.2.1 Expected (S)AEs - Not Reportable

This is a randomised controlled trial in a patient population with high levels of morbidity and co-morbid diseases and as such in this patient population, acute illness resulting in hospitalisation, new medical problems and deterioration of existing medical problems are expected.

In recognition of this, events fulfilling the definition of an adverse event or serious adverse event will not be reported in this study unless they are classified as expected or 'related and unexpected'.

12.2.2 Expected (S)AEs - Standard Reporting

The following AEs and SAEs are expected within the patient study population and will be reported from randomisation to trial completion on standard Case Report Forms (CRFs):

AEs:
- Randomised treatment strategy related adverse event
- Falls in the 2 weeks after randomised treatment
- Development of new DFUs on the foot of the index ulcer
- Development of cast ulcers on the foot of the index ulcer
- Infection of any DFU on the foot of the index ulcer (as per IDSA guidelines [21])
- New factors affecting healing (for example treatment with corticosteroids to an equivalent dose of prednisolone >10mg per day or other immunosuppressive therapy, connective tissue disorders or dermatological condition as a cause of ulceration, growth factor treatment, revascularization or foot surgery)

SAEs:
- Hospital admission related to any DFU (including cause)
- Amputation (any site of either lower limb)
- Acute hospital admission any cause
- Death

As these events are expected within the study population they will not be subject to expedited reporting to the main REC.

12.2.3 Unexpected SAEs – Not reportable

Events fulfilling the definition of serious adverse event will not be reported in this study if they are **not related** to DFUs or trial treatment strategies. For example hospital admission for other co-morbid diseases **will not be reported.**

12.3 RECORDING & REPORTING RELATED & UNEXPECTED SAEs (RUSAEs)

All Related & Unexpected SAEs (RUSAEs) which are related to DFUs or trial treatment strategies which occur from the time of randomisation to end of follow up must be recorded

on the RUSAE form and faxed to the CTRU **within 24 hours** of the site research team becoming aware of the event. Once all resulting queries have been resolved, the original form should be posted to the CTRU and a copy retained on site. Please ensure that each separate event is reported on a separate RUSAE Form and not combined into one form.

For each RUSAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to the investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the CTRU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has been resolved or a final outcome has been reached. All RUSAEs will be reviewed by the Chief Investigator and will be subject to expedited reporting to the Sponsor and main REC by the CTRU on behalf of the CI within 15 days.

Fax Number for reporting RUSAEs:
0113 343 7985

12.4 RESPONSIBILITIES

Principal Investigator/Authorised individual:

- Checking for SAEs when participants attend for treatment / follow-up.
- Judgement in assigning:
  - Seriousness
  - Relatedness
  - Expectedness
- To ensure all RUSAEs are recorded and reported to the CTRU within 24 hours of becoming aware and to provide further follow-up information as soon as available.
- To report RUSAEs to local committees in line with local arrangements.

Chief Investigator (CI) or delegate:

- Assign relatedness and expected nature of SAEs where it has not been possible to obtain local assessment.
- Undertake SAE review.
- Review all events assessed as Related / Unexpected in the opinion of the local investigator. In the event of disagreement between local assessment and the CI, local assessment may be upgraded or downgraded by the CI prior to reporting to the main REC.

CTRU:

- Expedited reporting of Related / Unexpected SAEs to the main REC and Sponsor within required timelines.
- Preparing annual safety reports to main REC and periodic safety reports to TSC and Data Monitoring and Ethics Committee (DMEC) as appropriate.
- Notifying Investigators of Related / Unexpected SAEs which compromise participant safety.

TSC:
In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

DMEC:
In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

13. ECONOMIC EVALUATION

The paucity of quality data on the outcome of adjuvant therapies for DFU and a 30% increase in burden of disease anticipated over the next 20 years makes an evaluation of net benefit and clinical outcomes within the framework of the MAMS design a timely research undertaking.

Trial-based economic evaluation will be undertaken at week 52 of the trial. The proposed secondary endpoints and methods for the economic evaluation follow the reference case set out by NICE [27]. The primary economic analysis will be a cost-utility analysis presenting incremental cost-effectiveness ratios (ICER) for each treatment strategy versus control (TAU), with effects expressed in terms of quality-adjusted life years (QALY).

13.1 Perspective and time horizon

The cost utility analysis will adopt an NHS and Personal Social Services (PSS) perspective for cost and benefit evaluation. Costs and effect for each intervention will be calculated for the trial follow-up period of 52 weeks.

13.2 Measures of Effectiveness

Quality-Adjusted Life Years will be used as the main outcome measure. Utility weights will be derived from the EQ-5D questionnaire completed by the patients at 4, 12, 20 and 52 weeks.

13.3 Measures of resource use

The health resource use questionnaires will be administered to patients at the same time points as the clinical effectiveness and quality of life data collection points (4, 8, 12, 20 and 52 weeks). These questionnaires will collect information on NHS and personal social care use in line with NICE guidelines [27]. This will include primary, secondary, and community resource use. Unit cost data will be obtained from national databases such as the British National

Formulary and Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care.

13.4 Costing the interventions

Treatment costs include the cost of delivering each strategy (mainly given by person-time of health-care professionals) and the cost of the necessary equipment. The scope of resources considered includes the direct healthcare costs incurred for necessary patient care and excludes resources driven by the study protocol (eg, routine clinics will be included, whilst research visits that are just for checking for re-ulceration are excluded; also, the cost of photography and visit time for collecting data for study purposes will be excluded). To cost the treatment strategies, we will collect data on average duration of appointments for delivering the treatment strategy.

13.5 ICER and Net incremental monetary benefit (NMB)

The differences in mean costs and effects will be presented using incremental cost-effectiveness ratios, where ICER = Δ Cost / Δ effect. Net incremental monetary benefit (NMB) will also be computed. Net benefit combines cost-effectiveness and willingness to pay for health benefit. It is calculated by rearranging the ICER calculation such that:
NMB=(λ * ΔQALYs) – Δcosts, where λ is typically referred to as cost-effectiveness threshold.

The National Institute for Health and Care excellence considers a cost per QALY within the range of £20,000-£30,000 to be acceptable [25]. The lower limit of this threshold will be used such that, for λ=£20,000, an intervention with a positive mean incremental net monetary benefit (i.e. NMB >0) should be adopted.

13.6 Dealing with missing data

Our approach to missing data will follow good practice guidelines for cost effectiveness analysis alongside clinical trials [28]. Multiple imputation methods will be used to generate estimates of missing values based on the distribution of observed data. The multiple imputation approach is the recommended method of imputation for economic evaluation alongside clinical trials as it includes randomness to reflect the uncertainty inherent in missing data by using iterative multivariable regression techniques.

13.7 Sensitivity analyses

Alternative scenarios will be explored in the sensitivity analysis to test the robustness of the main trial analysis results. The effect of not imputing missing data will be considered with an analysis that includes only complete cases. Further sensitivity analyses may also be necessary to explore assumptions that are made during the primary analysis. ICERs from each of the scenarios will be presented and compared to the main trial results to identify areas of uncertainty.

13.8 Dealing with uncertainty

The level of sampling uncertainty around the ICER will be determined using a non-parametric bootstrap to generate 10,000 estimates of incremental costs and effects. Bootstrapped estimates will be plotted on the cost-effectiveness plane to illustrate the uncertainty surrounding cost-effectiveness estimates [29].

Bootstrapped estimates of cost and effects will also be used to compute the probability that each intervention is cost-effective for a range of cost-effectiveness thresholds. The results will be presented as cost-effectiveness acceptability curves (CEAC) [30]. Whilst the decision to fund or not fund a treatment should be made on the expected NMB, the CEAC provides decision makers with useful information regarding the risk that the option with the largest expected NMB is not the best alternative.

13.9 Exploratory economic analysis

Alongside the primary analysis an exploratory economic analysis to compare cost and quality of life outcomes, and the incremental cost effectiveness ratios using information on participants across all arms and the comparator (those in phase III and those only included in phase II) will be undertaken. This will provide valuable information as to the extent that the intermediate outcome of reduction in index ulcer area at 4 weeks relates to final outcomes and costs across all arms and the comparator (those in phase III and those only included in phase II). Uncertainty in the estimates will be examined using the same methods as for the primary economic analysis.

13.10 Future economic model

Due to a complicated interplay between predisposing factors in patients with DFUs there is a large amount of uncertainty around any outcomes after 52 weeks following randomisation, and their association with the initial trial treatment strategy. However, we plan to request funding to access routine NHS records to study long term outcomes and develop an updated economic model using these data.

14. ENDPOINTS

Phase II
Primary endpoint measure

- The primary (intermediate) outcome is whether the index ulcer achieved at least 50% reduction in ulcer area, relative to baseline, at 4 weeks post randomisation. Reduction in ulcer area at 4 weeks has been used as a predictor of healing at 12 and 20 weeks in previous studies [31, 32].

Reduction in index ulcer area at 4 weeks will be derived by measuring ulcer area using wound tracing and Image J software, at baseline (post sharp non-surgical debridement) and at 2 and 4 weeks post randomisation (post sharp non-surgical debridement where sharp non-surgical debridement is clinically indicated). A photograph will also be used to serve as a back-up in the event that a wound tracing cannot be taken or is of insufficient quality to measure the index ulcer area.
Phase III
Primary endpoint measure

- The primary outcome is ***time to healing of the index ulcer*** from randomisation to the date the index ulcer is confirmed as healed at the first confirmation visit conducted by the blinded assessor (providing index ulcer healing is confirmed at the 2 week follow-up clinical assessment).

Index ulcers that have not healed by 52 weeks post randomisation will be censored at 52 weeks in the analysis. Time to healing is an important outcome measure from both the clinical perspective and with regard to resource use and economic costs [23].

Healing is defined as complete closure of the ulcer: 100% re-epithelialisation of the wound surface with the absence of drainage confirmed by blinded assessment of index ulcer healing status at two consecutive assessments two weeks apart [23].

Time to healing of the index ulcer assessed via the central blinded photography review with and without magnification will be used as endpoint measures in the sensitivity analyses.

Secondary endpoint measures

- Healing status of the index ulcer at 12, 20 and 52 weeks post randomisation.
- Ulcer infection in the foot of the index ulcer over 52 weeks post randomisation: Incidence of infection will be defined in accordance with the IDSA criteria [21].
- Re-ulceration following healing of the index ulcer over 52 weeks post randomisation: Defined as recurrence of a full thickness break in the epithelium at the same location as the index ulcer [24]. Time to re-ulceration of the index ulcer will be measured from date of index ulcer healing defined as for the primary endpoint to the date of diagnosis of index ulcer re-ulceration.
- Quality of life using DFS-SF and EQ-5D-5L over 52 weeks post randomisation
- Hospital admissions and amputations over 52 weeks post randomisation: details of the amputation, including the date, extent and site of amputation (whether it includes the site of the index ulcer).
- Adverse events over 52 weeks post randomisation***:*** All DFU and treatment-related serious adverse events and device related adverse events.
- Cost-effectiveness over 52 weeks post randomisation.

Exploratory analysis

- Identification of factors that are predictive of time to healing

15. STATISTICAL CONSIDERATIONS

Sample size

The maximum sample size required and the apportionment of participants to phase II and phase III were estimated using a series of simulation studies. Full details of the sample size determination is given in the SAP.

Briefly, a maximum of 660 patients will be recruited, including 324 patients in Phase II (to 1 TAU and 4 treatment strategy arms) and 336 patients in Phase III (to 1 TAU and (at most) 2 treatment strategy arms).

In Phase II, 54 patients per treatment strategy arm and 108 patients in the control arm (total 324 patients) will be recruited. The proportion of patients achieving the Phase II endpoint will be assessed, and the two most promising treatment strategy arms will be selected together with TAU for evaluation in the phase III confirmatory trial.

The target effect size in Phase II is an absolute increase of 25% in the proportion of patients achieving at least a 50% reduction in wound area by 4 weeks post randomisation, assuming 39% reach at least a 50% reduction by week 4 in the TAU arm (based on local audit data of

patients meeting trial eligibility criteria) and 64% achieve this outcome in the experimental treatment arms.

An additional 112 patients will be recruited into each arm evaluated in Phase III, corresponding to a total (phase II and III combined) of 166 in the treatment strategy arm(s) and 220 in the TAU arm (total of 552 patients for evaluation in Phase III). The same number of additional patients will be recruited into the TAU arm as for the treatment strategy arms to allow for contemporaneous comparisons between the treatment strategy and TAU arms.
The minimum clinically important effect size in Phase III is a hazard ratio of 1.5, assuming a median time to healing of 21 weeks for the TAU arm (local audit data) and 14 weeks for the treatment strategy arms [18, 23, 33-35] and 18.0% and 7.6% ***un***healed at 52 weeks in the TAU and treatment strategy arms respectively (assuming exponential distribution for time to healing). A treatment strategy arm that progresses to phase III and which is significantly better than TAU at the 2-sided 2% significance level (to control the family wise error rate at 5%) on the time to healing endpoint will be declared clinically effective.

Several scenarios for the power of the trial have been considered. In all cases a 10% loss to follow-up by 4 weeks and 25% loss to follow up by 52 weeks is assumed. In the case where there is a single effective treatment strategy arm (providing a 25% increase in the Phase II endpoint from 39% to 64%, and a reduction in median time to healing from 21 weeks to 14 weeks), and the other treatment strategy arms have the same effect as TAU on both outcomes, this design has a 83% power to recommend the truly effective treatment strategy. In the case where two of the treatment strategy arms are effective, the power to recommend each one is 81.5% (see document entitled “MIDFUT trial simulations for sample size Estimation” for additional supporting information).

As the estimate of dropout rates is conservative, a formal sample size review will be conducted to re-estimate the proportion of patients lost to follow-up by 52 weeks post randomisation and hence the final sample size. A review conducted at 52 weeks after 220 patients have been recruited, corresponding to 33.3% of patients, will allow the overall loss to follow-up to be estimated to a minimum precision ±5.7% (corresponding to half width of the 95%CI), assuming a maximum loss to follow-up of 25%.

Planned recruitment rate

It is estimated that a total of 2640 patients will need to be screened of whom 50% are expected to be eligible and 50% of those eligible will consent.

In Phase II, to recruit a target of 324 patients will require an average recruitment rate of 1 patient per centre per month across 24 centres over a 22 month period.

To recruit an additional maximum target of 336 patients in Phase III, will require an average recruitment rate of 1 patient per centre per month across all 24 centres over a 14 month period. Previous trials that have used a MAMS design have reported high consent and recruitment rates compared to standard two-arm trials partly because patients are more likely to receive an active treatment [36].

Internal pilot phase
An internal pilot phase will determine the likelihood of achieving the planned recruitment rate and of opening the required number of actively recruiting centres, and therefore confirming feasibility of trial delivery to the maximum target recruitment within the planned timelines.

The internal pilot phase of recruiting 66 patients across 15 centres over 9 months represents the minimum target to provide reassurance that recruitment to the trial will be feasible. The internal pilot represents 10% of patients to be recruited, across 75% of the target number of

centres, after 25% of the recruitment period has been completed. The recruitment projection for this internal pilot phase takes into account a staggered opening of centres. At the end of the internal pilot study we will stop or continue based on the following stop/go decision rules below and with agreement of the HTA.

Stop/go decision rules:
If, at 9 months after trial recruitment starts, the number of actively recruiting centres is less than 15 or the overall number of patients recruited less than 66, stopping will be considered by the Trial Steering Committee.

16. STATISTICAL ANALYSIS

16.1 General Considerations

Statistical analysis is the responsibility of the CTRU Statistician. A full statistical analysis plan will be written before any analyses are undertaken.

The primary analysis will be on an intention-to-treat (ITT) basis where patients will be analysed according to treatment allocation determined by the randomisation process. A per-protocol population (PP) will also be defined, which will include all eligible randomised participants according to the treatment received but will exclude major protocol violations. This population will be defined in agreement with the Data Monitoring and Ethics Committee (DMEC) and the Trial Steering Committee (TSC) members. Results from both the ITT and the PP analyses will be presented.

16.2 Frequency of analyses

Statistical monitoring of safety data will be conducted throughout the trial and reported at agreed intervals to the DMEC. An efficacy analysis will take place at the end of phase II and the final analysis at the end of phase III. Otherwise no efficacy analyses are planned.

16.3 Interim analyses

The results of the sample size review will be presented to the DMEC who will provide recommendations to the TSC. When 220 (33.3%) patients have been recruited and reached 52 weeks post-randomisation the overall loss to follow-up rate will be calculated and the sample size will be re-estimated. The review will be conducted in a blinded manner.

16.4 Phase II Primary Endpoint Analysis

Primary analysis

Analysis of the primary endpoint, at least 50% reduction in index ulcer area by 4 weeks post randomisation, will be conducted on the ITT population using multivariable mixed-effects logistic regression analysis, including the minimisation factors: centre (random effect), index ulcer duration, aetiology, anatomical site and amputation; the effect of adding treatment group to this model will then be assessed using a likelihood ratio test. Contrasts for each treatment strategy to the TAU arm will be reported.

An augmented binary method [37] will be conducted as a secondary supportive analysis to inform the selection of treatment strategies to be evaluated in Phase III.

The minimum criterion for taking treatment strategies forward into Phase III will be defined as at least a 10% improvement in the probability of achieving ≥50% reduction in index ulcer area at 4 weeks post randomisation relative to TAU, corresponding to the minimum clinically important difference (clinical opinion). If more than two treatment strategies pass this threshold at Phase II then the selection criteria will be based on a combination of relative efficacy, cost of treatment and the safety profile. Further detail of the progression criteria is provided in the SAP.

If more than two treatment strategies satisfy the efficacy and safety profile criteria to a similar degree, the economic costs associated with the candidate treatment strategies will inform the decision of which to take forward. A rapid analysis of the costs associated with each will be undertaken. This will include both treatment costs and the cost of health care use by participants and will allow the treatment strategies to be ranked by the mean total cost. The mean per-patient cost of treatment and health care use for each candidate treatment strategy will be presented separately in addition to the total cost per patient. A measure of variance will be presented to illustrate uncertainty associated with the estimates. The final decision as to whether to drop treatment strategies with the highest cost and whether these are considered to be cost prohibitive will be made by the DMEC.

The trial will also have a futility rule to allow for stopping of the trial on the basis of no treatment strategy demonstrating superiority to TAU in Phase II. Superiority in this context is defined as at least 10% absolute difference in the success rate of the phase II primary outcome. This will be non-binding to allow the DMEC to make the final recommendations on whether or not to stop the trial.

16.5 Phase III Primary Endpoint Analysis

All analyses in phase III will consider the need for bias adjustment due to the two stage nature of the design. Details of bias adjustment will be finalised in the statistical analysis plan, which will be agreed with the DMEC and signed off before trial analysis.

Primary analysis:
Primary analysis on time to healing, using the clinical assessment conducted by the blinded assessor, will be conducted on the ITT population using Cox Proportional Hazards regression models (after confirming the proportional hazards assumption is valid) with covariates for the minimisation factors: centre (random effect), index ulcer duration, aetiology, anatomical site and presentation (DFU or surgical debridement wound or open minor amputation), and stratification for the phase in which the patient was recruited; the effect of adding treatment group to this model will then be assessed using a likelihood ratio test. Death and amputations will be considered as competing risks. Surgical revascularisation will be considered as a time dependent covariate. Estimated hazard ratios, corresponding confidence intervals and p-values will be reported.

A range of sensitivity analyses will be conducted to assess the assumption of independence of the distribution of time to healing and time to other events, i.e. amputation and death. Detailed information on competing risks will be captured to inform departures from the assumption of independence.

Further sensitivity analyses on time to healing using the blinded central photography assessment of healing with and without magnification will be conducted on the ITT population using Cox Proportional Hazards regression models (after confirming the proportional hazards assumption is valid) with the same covariates as specified for the primary endpoint analysis.

16.6 Phase III Secondary Endpoint Analyses

Healing status of the index ulcer at 12, 20 and 52 weeks post randomisation
Estimated hazard ratios and cumulative incidence of healing at 12, 20 and 52 weeks post randomisation conditioning on being selected at Phase II from the primary endpoint analysis model, corresponding confidence intervals and p-values will be reported.

Ulcer Infection
To compare each treatment strategy with TAU in terms of the rate of infection in the foot of the index ulcer over 52 weeks post randomisation, a multivariable Poisson-Gamma regression model will be fitted to infection status over time with an offset term for time at risk of infection, adjusting for the minimisation factors and phase in which recruited. The effect of treatment group will be assessed using a likelihood ratio test. Centre and patient random effects will be explored, assuming Gamma distributions for each. Contrasts for the rate of each treatment strategy relative to TAU, confidence intervals and p-values will be reported.

Ulcer re-ulceration
A comparison of time from healing to re-ulceration of the index ulcer, between each treatment strategy and the TAU, will be conducted on those patients where healing of the index ulcer is confirmed. After confirming validity of the proportional hazards assumption a Cox Proportional Hazard's model will be fitted to time to re-ulceration of the index ulcer adjusting for the minimisation factors and the phase in which recruited; the effect of treatment group will then be assessed using a likelihood ratio test. Centre will be fitted as a random effect. Death and amputations will be considered as competing risks. Hazard ratios, cumulative incidence of index ulcer re-ulceration at 12, 20 and 52 weeks post randomisation, corresponding confidence intervals and p-values will be reported.

Diabetic Foot Ulcer Scale Short Form (DFS-SF):
A comparison of each treatment strategy to TAU on the DFS-SF score will be conducted using a multivariable, repeated measures, random coefficients, linear regression model fitted to the DFS-SF score over time, adjusting for the minimisation factors, phase in which recruited and treatment group. Centre, patient and patient by time interaction random effects will be explored. Time, treatment and treatment by time interaction will be fitted as fixed effects. Contrasts for each treatment strategy compared to TAU at 12, 20 and 52 weeks post randomisation will be reported in terms of the difference in means, corresponding confidence intervals and p-values.

Hospital admissions and amputations:
Time to amputation, extent and site of amputation (whether it includes the site of the index ulcer) will be summarised by treatment strategy. Number of hospital admissions, time from randomisation to hospital admission, duration of hospital stay and reason for admission will be summarised by treatment strategy.

Safety:
All adverse events and serious adverse events, including amputations and admissions to hospital, will be recorded and summarised by treatment strategy.

16.7 Phase III Exploratory Analyses

To determine the extent to which the specified risk factors and reduction in ulcer area at 4 weeks predict time to healing, a multivariable Cox Proportional Hazards regression will be fitted (after confirming the proportional hazards assumption is valid). Pre-specified risk factors include for example, aetiology, index ulcer duration, anatomical site, presentation, baseline ulcer area, phase of study and reduction in index ulcer area at 4 weeks. Death and

amputations will be considered as competing risks. Estimated hazard ratios, corresponding confidence intervals and p-values will be reported.

17. TRIAL MONITORING

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment; this may include on site monitoring.

An independent DMEC will review the safety and ethics of the study. Detailed unblinded reports will be prepared by the CTRU for the DMEC at regular intervals. The DMEC will be provided with detailed unblinded reports containing the information agreed in the data monitoring analysis plan.

18. DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However missing data items will not be chased from participants (although missing questionnaires sometimes are). The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

18.1 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

19. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

19.1 QUALITY ASSURANCE

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

19.2 SERIOUS BREACHES

Investigators are required to promptly notify the CTRU of a serious breach (as defined in the latest version of the National Research Ethics Service (NRES) SOP). A ‘serious breach’ is

defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research. In the event of doubt or for further information, the Investigator should contact the Senior Trial Co-ordinator at the CTRU.

19.3 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland (1996 or later). Informed written/witnessed verbal consent will be obtained from the patients prior to randomisation into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main REC and the appropriate site specific assessor for each participating centre prior to entering patients into the study. The CTRU will provide the main REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

20. CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- Consent from participants to record personal details including name, date of birth, address and telephone number, NHS number, hospital number, GP name and address.
- Participant name, date of birth, NHS number, contact details and GP name and address will recorded by sites at the registration visit (subject to consent) and retained by them.
- Consent from participants for a letter to be sent to their GP to let them know they are taking part in the study.
- Consent from participants for the CTRU to receive a copy of their consent form (which includes their name and signature) and NHS number to check they have not been previously registered and to facilitate data collection for future research.
- Consent from patients to take photographs of their wound and for the electronic transfer of these images (with identifiers study number initials and date of birth only; the participant's name must be obliterated by site before sending).
- Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.

- All data collection forms that are transferred to or from the CTRU and AUHE will be coded with a trial number and two participant identifiers, usually the participants' initials and date of birth. The consent forms will be sent to the CTRU and stored separately from the clinical data.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to the CTRU.

If a participant withdraws consent from further trial treatment strategy and/or further collection of data their data will remain on file and be included in the final analysis.

20.1 ARCHIVING

At the end of the study, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at site. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

In addition, participating sites will retain written records of receipt, storage and use/disposal of the DCD for a period of 30 years including the following information:

(i) Identification of the supplier tissue bank and Order Number;
(ii) Identification of the user clinic or clinician;
(iii) The type of tissue;
(iv) The unique ISBT tissue identification number;
(v) The identity of the recipient;
(vi) Date of use or disposal

21. STATEMENT OF INDEMNITY

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

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

22. STUDY ORGANISATIONAL STRUCTURE

22.1 INDIVIDUALS AND INDIVIDUAL ORGANISATIONS

Chief Investigator (CI) – as defined by the NHS Research Governance Framework, the CI is responsible for the design, management and reporting of the study.

Trial Sponsor (LTHT) – The Sponsor is responsible for trial initiation and management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

Clinical Trials Research Unit – The CTRU will have responsibility for conduct of the study in accordance with the NHS Research Governance Framework (RGF), MRC GCP and CTRU SOPs. The CTRU will provide set up and monitoring of trial conduct to CTRU SOPs, MRC GCP and the RGF including randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring

schedule and statistical analysis for the trial. In addition the CTRU will support main REC, Site Specific Assessment and Health Research Authority (HRA) submissions and clinical set up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

22.2 OVERSIGHT / TRIAL MONITORING GROUPS

Trial Management Group – The TMG, comprising the CI, CTRU team and co-applicants will be assigned responsibility for the clinical set up, ongoing management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (III) obtaining approval from the Main REC and supporting applications for Site Specific Assessments, (iv) completing cost estimates on project initiation, (v) nominating members and facilitating the TSC and DMEC, (vi) reporting of serious adverse events, (vii) monitor of screening, recruitment, treatment and follow up procedures, (viii) auditing consent procedures, data collection, trial end point validation and database development and (viv) central review of photographs.

Trial Steering Committee – The TSC, with an independent chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an independent chair, not less than two other independent members and a consumer representative (PPI). The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet 6 monthly.

Data Monitoring and Ethics Committee – The DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data during recruitment. The Committee will meet annually as a minimum.

23. PUBLICATION POLICY

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

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

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

For core publications, co-applicants and members of the CTRU trial team will be given the opportunity to contribute to drafting and reviewing manuscripts; those who contribute as per the ICMJE guidance will be named authors on publications. For methodology papers, authorship will be discussed with the TMG and an authorship sub-team agreed.

To maintain the scientific integrity of the trial, data will not be released prior to the first

publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

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25. ADDITIONAL INFORMATION/APPENDICES

Appendix 1 – SINBAD wound classification

Category	Definition	SINBAD score	Equivalent S(AD)SAD categories
Site	Forefoot	0	—
	Midfoot and hindfoot	1	—
Ischemia	Pedal blood flow intact: at least one pulse palpable	0	0–1
	Clinical evidence of reduced pedal blood flow	1	2–3
Neuropathy	Protective sensation intact	0	0–1
	Protective sensation lost	1	2–3
Bacterial infection	None	0	0–1
	Present	1	2-3
Area	Ulcer <1cm^2	0	0-1
	Ulcer ≥1cm^2	1	2-3
Depth	Ulcer confined to skin and subcutaneous tissue	0	0-1
	Ulcer reaching muscle, tendon or deeper	1	2-3
Total Possible score		6	—