Multiple Interventions for Diabetic Foot Ulcer Treatment (MIDFUT) trial: benefits of involvement for patients and clinicians

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Article points

1. Despite implementation of NICE recommendations of 'best' care in multidisciplinary clinics, many patients experience adverse foot ulcer outcomes.
2. More research is needed on the effectiveness of adjuvant therapies for wound healing.
3. MIDFUT is a pragmatic randomised controlled trial with an efficient design to meet this need.
4. Implementing therapies in new clinical settings can be challenging; however, these can be overcome with benefits to patients and clinicians.

Key words

- Diabetic foot ulcer
- Randomised controlled trial
- Wound healing

Authors

Author details can be found on page 25.

Pragmatic diabetic foot ulcer research is key to enhancing clinical expertise and efficiency, patient experience and improved wound healing. Delivery of novel adjuvant therapies in a clinic setting can be challenging, both at clinical and organisational levels. There are many benefits to patients and clinicians from being involved in research. The aim of this article is to present the Multiple Interventions for Diabetic Foot Ulcer Treatment (MIDFUT) trial, describe its purpose, the project implementation and how it is overcoming the challenges of delivering novel therapies in a clinic setting, and the potential benefits to patients and staff.

Diabetes affects more than 4.8 million adults in the UK, 25% of whom will develop a diabetic foot ulcer (DFU) within their lifetime (Armstrong et al, 2017; Diabetes UK, 2020). Treatment of DFUs costs NHS England £1 billion per annum, not including societal costs, and is associated with significant reduction in health-related quality of life (Hogg et al, 2012; Kerr et al, 2019). The NICE recommended treatment for DFUs includes offloading, identification and treatment of infection and ischaemia, wound debridement and optimisation of glycaemic control within a multidisciplinary team (MDT) setting (NICE, 2019). Despite this, 48.3% of those included in the National Diabetes Foot Care Audit have persistent ulceration following 12 weeks of treatment in an MDT clinic (NHS Digital, 2019). Infection rates, hospitalisation and amputation rates are significantly higher in patients with non-healing DFUs (Lavery et al, 2006).

Healing rates <50% at 4 weeks are known to predict a reduced likelihood of healing at 12 and 24 weeks and have been proposed as an indicator for use of adjuvant therapies in these hard-to-heal DFUs (Margolis et al, 2003; Sheehan et al, 2003; Lavery et al, 2008). However, evidence to support many adjuvant therapies in DFU care is either lacking or of poor quality.

The Multiple Interventions for Diabetic Foot Ulcer Treatment (MIDFUT) trial seeks to provide evidence for the use of three available adjuvant therapies: hydrosurgical debridement (HD), negative pressure wound therapy (NPWT) and decellularised cadaveric dermis graft (DCD).

MIDFUT trial protocol

MIDFUT is a National Institute for Health Research (NIHR) Health Technology Assessment funded seamless phase II/III, multi-arm multi-stage (MAMS) randomised controlled trial in patients with hard-to-heal DFUs (defined as healing <50% in the previous 4 weeks as measured using local procedures). The trial compares the relative effectiveness of adjuvant therapies applied in addition to NICE recommended 'best' care (treatment as usual, TAU). Specifically, MIDFUT seeks to provide evidence for the use of HD, NPWT and DCD. The design of the trial uses an efficient and innovative method to enable these therapies, used in different combinations, to be compared under the umbrella of a single trial and a detailed trial protocol has been published elsewhere (Brown et al, 2020).

In Phase II, consenting patients are randomised to a treatment arm in a 1:1:1:2 allocation to one of the

intervention arms or TAU (*Figure 1*), and treatment applied the same day. Adjuvant therapies are applied as a treatment strategy: a single application of HD, either alone or in combination with DCD ± 2 weeks of NPWT. The primary outcome is achieving at least 50% reduction in index ulcer area in the 4 weeks following randomisation. The most effective treatment strategy will be taken forward to Phase III and compared with TAU in a 1:1 randomisation with a primary outcome of time to wound healing.

Eligible patients are recruited from MDT diabetic foot clinics (inclusion/exclusion criteria are shown in *Table 1*). Follow-up continues for 52 weeks, with information collected at weeks 1, 2, 4, 8, 12, 20 and 52 during routine clinic attendance. Ulcer size and evidence of healing are recorded with tracings and photographs, details of dressings and other treatments (e.g. offloading) applied are noted, any adverse events such as infection, hospitalisation, amputation and re-ulceration are recorded. At some timepoints additional questionnaires are completed to inform quality of life and cost-effectiveness. Outcomes of interest are time to healing, infection in the foot of the index ulcer, quality of life measures and cost-effectiveness.

The trial aims to recruit a maximum of 447 participants, 245 to Phase II and 202 to Phase III. Thus far, 122 have been recruited across 31 centres.

Summary of interventions

The three adjuvant therapies in MIDFUT, which are all available for routine NHS use, were selected for their potential to be delivered in an outpatient setting, thus enhancing acceptability to patients and reducing costs. We acknowledge that use in outpatient clinics may be limited, and to ensure their safe and effective application in MDT clinics (and potential follow-up in community), guidelines and training materials, e.g. videos (https://ctru.leeds.ac.uk/midfut-researchers), have been developed. On-site training for clinical staff has been delivered by the trial team and manufacturers' representatives, with ongoing support constantly available.

- NPWT: in line with our pragmatic and practical approach, the options for NPWT reflect standard care. Both portable pumps and disposable devices are suitable for use in the trial.
- HD (using the Versajet II system): the console is provided as a free of charge loan and the cost of disposable items is reimbursed (*Figures 2a and b*).
- DCD (an allograft with all human cells removed which acts as a scaffold for new tissue growth): provided free of charge (*Figures 2c and d*).

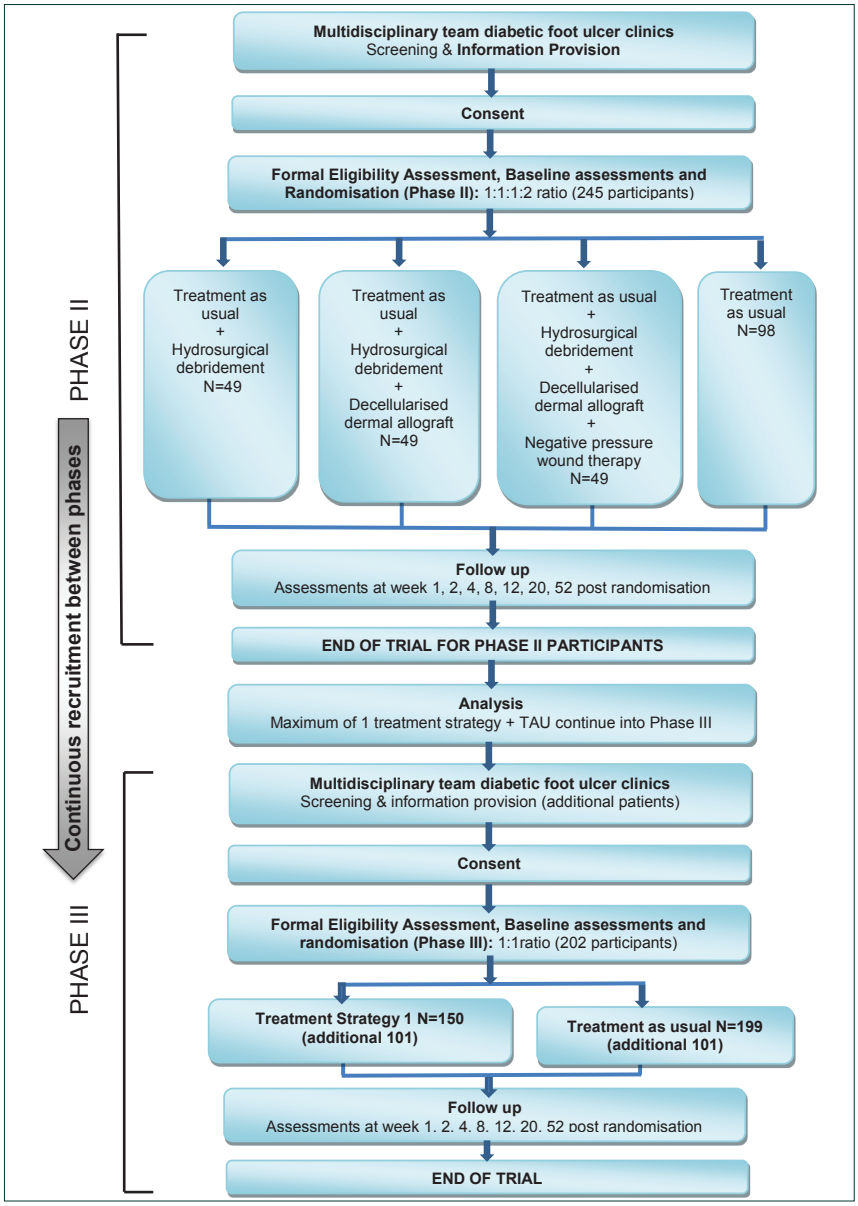

Figure 1. MIDFUT trial schematic.

Benefits of involvement for healthcare professionals

For clinical staff in diabetic foot clinics, the opportunity to deliver novel therapies through a funded study with rigorous evaluation of effectiveness can be both exciting and daunting.

Table 1. Inclusion and exclusion criteria for the MIDFUT trial.

Inclusion criteria
• Aged ≥ 18 years.
• Diagnosis of diabetes (according to WHO criteria).
• Has a chronic DFU, surgical debridement wound or open minor amputation and, in the opinion of the attending clinical team, is not on a healing trajectory* despite usual best care for a minimum of 4 weeks since initial presentation at the MDT DFU service. (*Defined as failure to achieve >50% reduction in index ulcer area over a minimum of 4 weeks using local wound measurement policies.)
• The index DFU has an area ≥0.8cm^2.
• Ankle brachial index for the leg of the index ulcer ≥0.7 or non-compressible. (Measurements available in the participant's notes taken within 3 months of randomisation can be used if no change in intervention or vascular events have occurred.)
• Expected to comply with the treatment strategies and follow-up schedule.
• Consent to foot and wound photography.
• Consent to participate (written/witnessed verbal informed consent).
Exclusion criteria
• Has any current clinically infected DFU on the foot of the index ulcer (as per IDSA guidelines)
• HbA_{1c} >110mmol/mol. (Measurements available in the participant's notes taken within 3 months of randomisation can be used if no change in intervention or vascular events have occurred.)
• Estimated glomerular filtration rate (eGFR) <20 ml/min/1.73m^2. (Measurements taken within 3 months of randomisation can be used if no change in intervention or vascular events have occurred.)
• Index ulcer duration >2 years.
• Planned or previous treatment with corticosteroids to an equivalent dose of prednisolone >10 mg per day or other immunosuppressive/immunomodulating therapy within 4 weeks prior to randomisation.
• Has evidence of connective tissue disorders as a cause of ulceration (e.g. vasculitis or rheumatoid arthritis).
• Has evidence of dermatological disorders as a cause of ulceration (e.g. pyoderma gangrenosum or epidermolysis bullosa).
• Planned or previous growth factor treatment within 4 weeks prior to randomisation.
• Planned or previous revascularisation or foot surgery affecting healing on the foot of the index ulcer within 4 weeks prior to randomisation.
• Index ulcer base has bone or joint involvement.
• Previously received DCD for the index ulcer within 4 weeks prior to randomisation
• Previously received NPWT for the index ulcer within 4 weeks prior to randomisation
• Previously received hydrosurgical or surgical debridement for the index ulcer within 4 weeks prior to randomisation.
• Has previously been randomised to the MIDFUT study.
• 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 DCD preparation components).

> Many podiatrists have little or no exposure to research. It may be difficult to find out how to start a trial, ensuring correct procedures are followed, obtaining support and the necessary equipment from research delivery staff, and setting up clinics to ensure safe delivery of the interventions. However, our friendly, experienced trials team are always on hand to support new investigators through these processes.

During the set-up of the study, there had been little experience of using DCD on patients with DFUs across the UK, and a particular concern was their ongoing care in the community. The team spent time with the manufacturer (NHS Blood and Transplant), learning about how to adapt the DCD preparation techniques used in operating theatres to clinic environments, how to apply it to ulcers and options for keeping it in place, e.g. suturing or gluing the edges. The practical aspects were important because it was anticipated few podiatrists would be happy suturing the allograft.

The team members were also aware that once in place, the graft that initially resembled a piece of skin could look different sometime later and resemble slough or necrotic tissue. Staff who were likely to change the ulcer dressings would need information about the visual appearance of the wound and how to not damage the graft. Podiatrists involved in the trial report that learning and delivering these new techniques is a professionally rewarding addition to their scope of practice.

Benefits of involvement for patients

There are many benefits to patients from taking part in pragmatic research. They can carry on their life as usual and there is no need to attend specialist facilities; patients traditionally feel closer attention is being paid to their care during their involvement in a trial; they can provide valuable insight into the acceptability of interventions and impact on lifestyle; and outcomes that are important to patients, such as pain, discomfort, convenience and other quality of life issues, will be measured. When patients were surveyed about research, 87% said they had a positive experience and 83% would be happy to take part in another study (NIHR, 2020).

Anecdotally, patients have an increased awareness and/or enthusiasm for their own self-care and a sense of pride in being asked to take part in a project that could not only benefit themselves, but also others. Patients who previously struggled to comply with their prescribed treatment and offloading regimens find that being part of a study encourages them to follow recommendations more

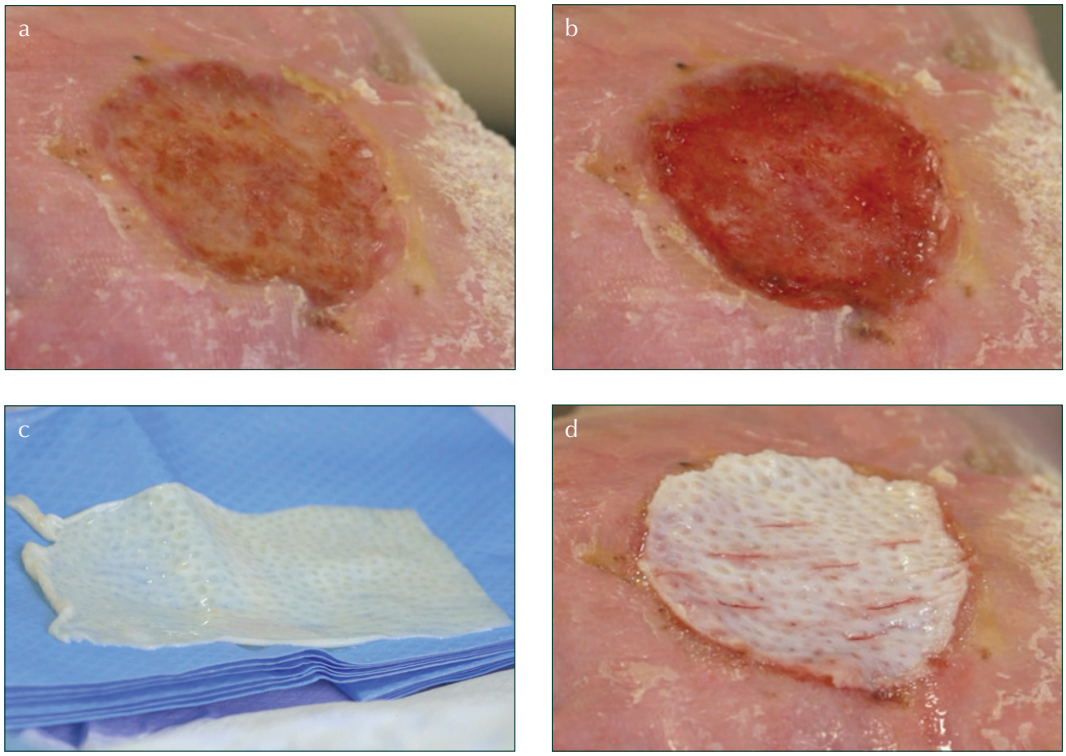

Figure 2. Hydrosurgical debridement and application of decellularised cadaveric dermis (DCD) graft. Figure 2a. DFU prior to hydrosurgical debridement (HD). Figure 2b. DFU following HD. Figure 2c. The DCD graft. Figure 2d. DFU following application of DCD.

carefully. Some patients go on to take part in other trials, become involved in research design and delivery, and provide valuable contributions to trial investigator days.

MIDFUT in the COVID-19 era

At the time of writing, the UK situation is fluid and changeable. However, the initial signs for MIDFUT are promising, with feedback from microbiology leads that peripheral tissues are deemed low risk for COVID-19, and as such hydrosurgical debridement in MIDFUT study may continue using pre-COVID-19 protocols.

The trial will contribute towards improving outcomes for patients with DFUs. If you would like to contribute by becoming a recruiting centre or would like more information, please email us at midfut@leeds.ac.uk. The websites https://ctru.leeds.ac.uk/midfut and https://www.isrctn.com/ISRCTN64926597 have further details. ■

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