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The Leeds Teaching Hospitals NHS
NHS Trust

Development and Design of a Multi-Arm Multi-Stage Trial in Diabetic Foot Ulcers

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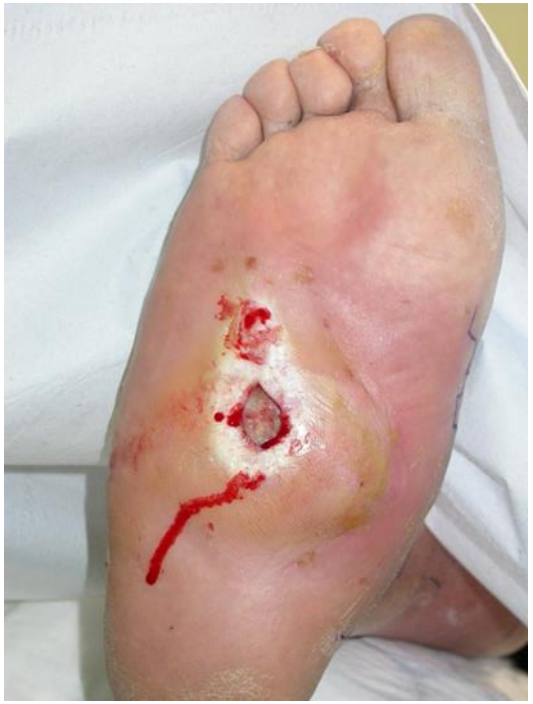
Background

- Diabetes affects 4.5million adults in UK
- 2.5% (112,500) have a DFU at any one time
- HRQoL similar to those with major amputation
  - Physical function
  - Mental wellbeing
  - Social interaction
- Significant financial burden on NHS
  - 2010/11 £639-662M spent on DFU healing
  - £1 in every £150 spent by NHS



Background

- Healing rates at 12 weeks for DFUs are low
  - 7.7-46% in control arms of RCTs
- Healing by 50% at 4 weeks is a predictor of outcome
  - Failure associated with only 9-30% healing at 12 weeks
- Delay in healing increases risk of adverse sequelae
  - DFUs still open at 30 days have 5-fold increased risk infection
  - Infection associated with:
    - 55-fold increased risk of hospitalisation
    - 154-fold increased risk of amputation
- Adjuvant therapies suggested for “hard-to-heal” ulcers

Background

- Treatment as usual (TAU) for DFUs[1]
  - Should be within MDT DFU clinics
  - At least fortnightly visits
    - Community dressing changes between visits
  - Sharp, non-surgical debridement
  - Off-loading (ideally below knee walker or TCC)
  - Management of infection
  - Identification and management of ischaemia

1. NICE NG19; 2015

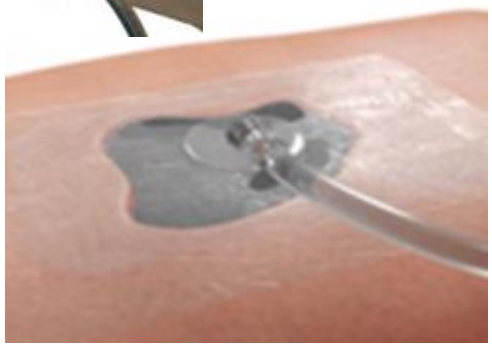
Background

- Original concept for RCT of dCELL® Human Dermis (DCD) in hard to heal diabetic foot ulcers
- Compounding factors with intervention[1]
  - Hydrosurgical debridment (HD) creating acute wound
  - Negative pressure wound therapy (NPWT)
- Little evidence available for HD in DFU healing
- One RCT NPWT vs TAU (n=342) to healing or 16 weeks[2]
  - Improved healing (43.2% vs 28,9%)
  - Reduced amputations (4.1% vs 10.2%)
  - NICE concluded good quality studies are required[3]

1. Greaves NS et al. Wound Regen Repair 2013; 21(6): 813-822
2. Blume PA et al. Diabetes Care 2008; 31: 631-636
3. NICE NG19; 2015

Clinical Research Question

- 3 interventions, potentially additive, plus TAU
  - HD
  - NWPT
  - DCD
- Options:
  - Test combination vs TAU in RCT
  - Multiple RCTs
  - Multi-arm multi-stage trial design
    - Cost-effective
    - Efficient patient recruitment



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Multiple Interventions For Diabetic Foot Ulcer Treatment

(MIDFUT) Trial

MIDFUT

Comparing treatments for diabetic foot ulcers

Design

- Multicentre, seamless Phase II/III, open, parallel group multi-arm multi-stage randomised controlled trial (blinded outcome assessment)
- Multiple treatments to be tested under the umbrella of a single trial
- Allows for early evaluation of treatment strategies and the least effective treatment strategies in Phase II will not continue into Phase III
- Phase II participants will be randomised on a 1:1:1:1:2 basis to receive one of the following treatment strategies;
  - HD + TAU
  - HD + NPWT + TAU
  - HD + DCD + TAU
  - HD + DCD + NPWT + TAU
  - TAU
- Two treatment strategies showing greatest efficiency at the end of Phase II will continue to Phase III along with TAU on a 1:1:1 basis

Methodological Considerations

- Sample size
  - Maximum of 660 participants, 324 in Phase II, 336 in Phase III
- Phase II – Primary Objective
  - To determine the efficacy of treatment strategies compared to TAU using index ulcer area reduction at 4 weeks post randomisation
- Phase III – Primary Objective
  - To determine whether a maximum of two treatment strategies as an adjunct to TAU reduces time to healing of the index ulcer compared to TAU alone
- Phase III – Secondary Objectives
  - Comparison of treatment strategies v TAU alone in terms of;
    - Healing status at 12, 20 & 52 weeks
    - Rate of infection
    - Re-ulceration
    - QoL – DFS-SF and EQ-5D
    - Adverse events
- Cost effectiveness
- *Exploratory objective: Explore factors prognostic of ulcer healing*

Statistical Considerations

- Phase II
  - Target effect size: absolute increase of 25% in the proportion of participants achieving ≥50% reduction in wound area by 4 weeks post randomisation
    - Assumption: 39% reach ≥50% reduction by week 4 in the TAU arm
    - 10% loss to follow-up
- Phase III
  - Effect size: hazard ratio of 1.5
    - median time to healing 21 weeks and 18% unhealed at 52 weeks with TAU
  - 2-sided 2% significance level (to control the family wise error rate at 5%)
  - 25% loss to follow-up
- Overall power
  - 83% and 81.5% for recommending single and each of two effective interventions respectively

Progression Rules to Phase III

- "Drop the loser" approach:
  - Recommend dropping any arms failing to show ≥10% absolute improvement in Phase II outcome vs TAU
  - If no treatment arms remain then recommend stopping trial
  - If more than 2 arms remain consider:
    - Safety profile
    - Cost-effectiveness at 4 weeks
    - Top 2 arms as assessed by efficacy

Inclusion/Exclusion Criteria

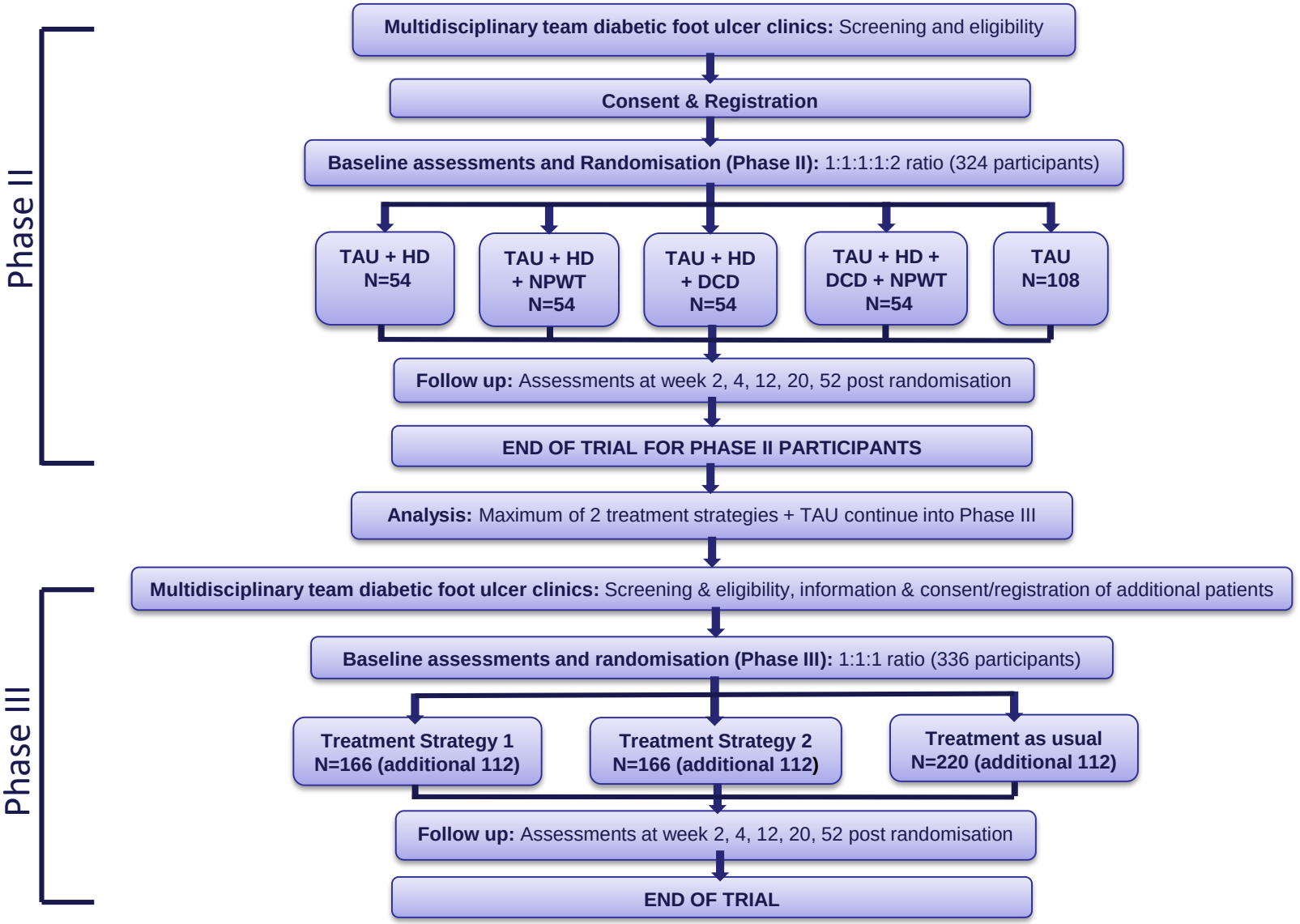
Inclusion

- Aged >18 years
- Diagnosis of Diabetes Mellitus
- Has a chronic DFU or surgical debridement wound or open minor amputation (<40% reduction in index ulcer area in the preceding 4 weeks prior to randomisation)
- The index DFU has an area >1cm2
- Ankle brachial index ≥0.7
- Expected to comply with the treatment strategies and follow up schedule
- Consent to foot & wound photography
- Consent to participate (written / witnessed verbal informed consent)

Exclusion

- Has any current clinically infected DFU
- HbA1C>110mmol/mol or eGFR < 20mL/min/1.73m2
- Index ulcer duration >2 years
- Recent immunosuppressive therapy or connective tissue disorders or dermatological disorders as a cause of ulcer
- Planned or recent growth factor treatment or revascularisation or foot surgery affecting healing
- Index ulcer base has bone or joint involvement
- Recent DCD, NPWT or HD for the index ulcer
- Has previously been randomised to the MIDFUT study

Trial Schematic



Blinding

- Unable to blind participant, clinical or research team due to the nature of the treatment strategies
- Primary outcome assessments will be completed by an independent assessor who is blind to the randomised treatment strategy

- Photography
  - Photograph of index ulcer at baseline, week 2, week 4 & confirmation of healing visits
  - 25% of participants will be randomly selected for the index ulcer (unhealed) to be photographed at week 12, 20 & 52
  - Photographs taken at confirmation of healing and baseline, week 12, 20 & 52 for a random selection of participants will undergo blinded central review by clinical members of the trial management group

Internal Pilot

- To confirm feasibility of trial delivery
- Minimum target specified:
  - 66 patients recruited across 15 centres over 9 months
    - 10% of patients recruited across 75% of centres, after 25% of the recruitment period has been completed
    - accounts for staggered opening of centres
- Aiming for recruitment start date 1st July 2017
- Application for funding from NIHR HTA

MIDFUT Team

Chief Investigator: Mr David Russell,
CTRU Lead: Professor Jane Nixon
Trial Statistician: Dr Sarah Brown, Principal Statistician, Leeds CTRU
Methodology Oversight: Professor Linda Sharples, Professor of Medical Statistics
Statistical Consultant: Dr James Wason, Programme Leader MRC Biostatistics Unit
Trial Co-ordinator: Rachael Gilberts
Clinical Members:

Professor Frances Game, Consultant Diabetologist
Professor Peter Vowden, Honorary Consultant Vascular Surgeon
Dr Richard Lomas, Senior Clinical Development Scientist, NHSBT Tissue services
Dr Akila Chandrasekar, Consultant in Transfusion Medicine
Dr Edward Jude, Consultant Diabetologist & Endocrinologist
Dr Paul Chadwick, Consultant Podiatrist
Professor Shervanthi Homer-Vanniasinkam, Consultant Vascular Surgeon
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Health Economics:

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