PROTOCOL INFORMATION

FULL/LONG TITLE OF THE TRIAL – A Multifactorial Intervention to Improve Cardiovascular Outcomes in Adults with Type 2 Diabetes and Current or Previous Foot Ulcers - randomised controlled trial (MiFoot RCT)

SHORT TRIAL TITLE / ACRONYM **– MiFoot RCT**

PROTOCOL VERSION NUMBER AND DATE **2.0 19/07/2024**

IRAS NUMBER: **322098**

SPONSOR: **University of Leicester**

SPONSOR REFERENCE NUMBER: **0922**

TRIAL REGISTRATION: **IRSCTN13413505**

FUNDER(S) – **NIHR202021**

FUNDED BY
NIHR | National Institute for Health and Care Research
DIABETES UK
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This protocol has regard for the HRA guidance

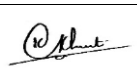
Confidentiality Statement:

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given. Any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Chief Investigator:	
Signature: 	Date: 19.08.2024
Name: (please print): Professor Kamlesh Khunti	
Principal Investigator:	
Signature: 	Date: 19.08.2024
Name: (please print): Professor Kamlesh Khunti Study site name: UHL NHS Trust	

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Funder start and end date(s)	Programme 01/10/2021 - 31/12/2026 Final report due 14/01/2027
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NIHR Portfolio adopted	Yes

CONTENTS

LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
BRC	Biomedical Research Centre
CI	Chief Investigator
COVID-19	Coronavirus Disease 2019
CRN	Clinical Research Network
CVD	Cardiovascular Disease
DCTSU	Derby Clinical Trials Support Unit
DFS SF	The Diabetic Foot Ulcer Scale Short Form
DFUD	Diabetes-related Foot Ulcer Disease
DMSC	Data Monitoring and Safety Committee
DMSES-15	Diabetes Management Self-Efficacy Scale
DUK	Diabetes UK
ECG	Electrocardiogram
e-CRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EQ-5D-5L	European Quality of Life -5 Dimensions
GP	General Practitioner
GDPR	General Data Protection Regulation
HADS	Hospital Anxiety Depression Score
HbA1c	Glycated Haemoglobin
HCP	Health Care Professional
HDL-C	High-density lipoprotein-cholesterol
HRA	Health Research Authority
ICF	Informed Consent Form
ICH-GCP	International Committee on Harmonization of Good Clinical Practice
ID	Identification
IMD	Index of Multiple Deprivation
IRAS	Integrated Research Application System
ISF	Investigator Site File
ITT	Intention-to-Treat
LDC	Leicester Diabetes Centre
LDL-C	Low-density lipoprotein-cholesterol
LADA	Latent Autoimmune Diabetes in Adults
MACE	Major Adverse Cardiovascular Event
ModRUM	Modular Resource-Use Measure

MODY	Monogenic Diabetes
MVPA	Moderate to Vigorous Physical Activities
NIHR	National Institute for Health and Care Research
NHS	National Health Service
PAID	Problem Areas in Diabetes
PGfAR	Programme Grants for Applied Research
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI/E	Patient and Public Involvement/Engagement
PSC	Programme Steering Committee
QALY	Quality Adjusted Life Year
QC	Quality Control
QoL	Quality of Life
R&I	Research and Innovation
RE-AIM	Reach; Effectiveness; Adoption; Implementation, and Maintenance
RCT	Randomised Control Trial
RDE	Research Data Extraction
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGLT2i	Sodium-Glucose Cotransporter-2 Inhibitors
SME	Structured Self-Management Education
SOP	Standard Operating Procedure
SPHR-T2DMT	School for Public Health Research Type 2 Diabetes Treatment
T2D	Type 2 Diabetes
TC	Total Cholesterol
TG	Triglycerides
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
WS	Work Stream

KEY WORDS

Diabetes-related foot ulcer disease; cardiovascular disease; disease management; randomised controlled trial; lifestyle behaviours.

STUDY SUMMARY

Study Title	A Multifactorial Intervention to Improve Cardiovascular Outcomes in Adults with Type 2 Diabetes and Current or Previous Diabetes-related Foot Ulcers - randomised controlled trial (MiFoot RCT).	
Study Design	Pragmatic single-blind RCT with internal feasibility study, process evaluation and health economic analyses.	
Study Participants	Adults aged ≥18 with diagnosed Type 2 Diabetes (T2D) and current or previous Diabetes-related Foot Ulcer Disease (DFUD) defined as diagnosed with DFUD in the previous 5 years.	
Planned Sample Size	Participants (n=392) will be randomised 1:1 to intervention or control conditions. The internal feasibility study will be 20% of the total recruitment target (n=78). The process evaluation will carry out interviews with participants from the intervention group and HCPs/Facilitators (the intervention delivery team) involved in intervention delivery.	
Follow up duration	24 months	
Planned Study Period	01/August/2023 - 31/December/2026	
	Objectives	**End Points / Outcome Measures**
Primary	Compare the complex intervention (MiFoot) with usual care for preventing CVD events in people with T2D and current or previous (within the last 5 years) DFUD	Difference between groups in rate of occurrence of Extended MACE (myocardial infarction, stroke, cardiovascular death, peripheral arterial bypass, coronary artery bypass, coronary angioplasty or peripheral artery angioplasty) at 24 months
Secondary	Monitor recruitment and stop-go criteria (internal feasibility study)	Number of patients recruited (consented and randomised) at 3 months
	Evaluate the sustainability of the MiFoot intervention (Process Evaluation)	Interviews with intervention participants and the intervention delivery team (qualitative) and questionnaires (quantitative)
	Estimate cost-effectiveness of the MiFoot intervention in a real-world setting via health economic analyses	Quality adjusted life years (QALYs)
Intervention	Brief: Usual care plus tailored complex intervention (MiFoot) will have 3 components: Individualised appointment ; group sessions (combined education and exercise sessions); digital programme. MiFoot intervention aims to reduce multiple modifiable risk factors integral to CVD prevention	
Comparator	Usual care	

FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
NIHR under PGfAR and DUK	As detailed in the award letter

ROLE OF STUDY SPONSOR

The Sponsor of this research is the University of Leicester.

The University of Leicester is responsible for the design, management and outputs of the research. Participating NHS sites are responsible for the conduct of the study within their organisation.

The Research Governance Office review and approve all iterations of the protocol as part of their initial Sponsor review and amendment review process. Further information is available from our Sponsor Standard Operating Procedures webpage.

ROLE OF COLLABORATOR(S)

Collaborators are "jointly involved" with study Chief Investigator (CI) in the scientific development and/or execution of the proposed work.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

- **Programme Steering Committee (PSC)**

  The PSC will meet regularly (e.g., annually or more often as required) and will consist of the Chief Investigator, an independent Chair, an independent statistician, independent external members and independent Patient and Public Involvement (PPI) representative. Additionally, the study team will attend the PSC when required. The PSC will act as an independent strategic oversight and will ensure transparency and that the work is reaching the relevant milestones.

- **Trial Steering Committee (TSC)**

  A TSC with an independent chair will be convened. The committee will meet regularly (e.g., annually or more often as required). The TSC will monitor the conduct of the study, provide advice, and ensure patient safety.

- **Data Monitoring and Safety Committee (DMSC)**

  The DMSC will meet regularly (e.g., every six months) and report to the PSC. The DMSC will be appointed by the CI and the Statistical Team and will comprise members who are independent of the trial, to include at least one statistician and at least one clinician. The CI and/or trial statistician may be invited to attend to provide specific input by the DMSC Chair. The DMSC will review safety data regularly and make recommendations as to whether the trial should continue, be modified or terminated. A log of all AEs will be provided to the DMSC for this purpose. The DMSC will also review any statistical analysis plans.

- **Trial Management Group (TMG)**

  Trial conduct will be overseen by a TMG. The TMG will meet regularly (e.g., monthly) to discuss all aspects of the trial and report directly to the PSC. Senior investigators, the core/trial management team and other members where appropriate, are invited. The meeting will be chaired by the Chief Investigator. Trial targets/milestones and progress (including details and logistics of recruitment, retention and follow-up data collection and participant safety) will be reviewed, and risk assessment and troubleshooting undertaken. At strategic points of the trial, longer and more in-depth TMG meetings could be held in order to ensure attendance of all investigators.

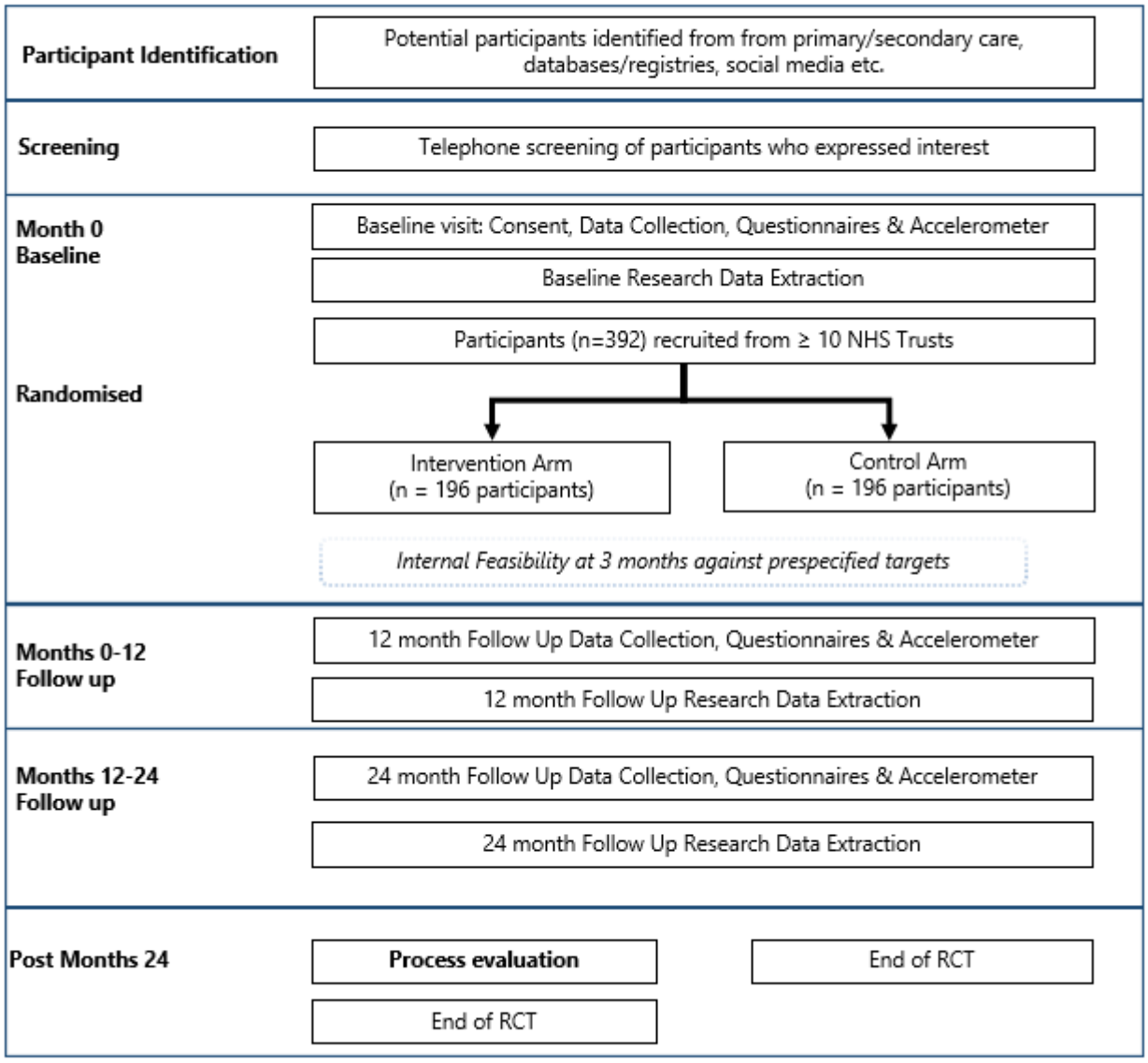
- **Responsibilities of the Principal Investigator(s)**

The Investigator and delegated Investigator staff undertake to perform the study in accordance with this RCT protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The PIs are required to ensure compliance with all procedures required by the RCT protocol and with all study procedures provided by the Sponsor (including security rules). The PIs agree to provide reliable data and all information requested by the RCT protocol (with the help of the CRF or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives. With any data transfer, particular attention should be paid to the confidentiality of the subject's data.

The PIs may appoint such other individuals as he/she may deem appropriate as co-investigators to assist in the conduct of the study in accordance with the RCT protocol. All co-investigators shall be appointed and will have been delegated by the PI and will have signed the delegation log prior to commencing work on the study. The co-investigators will be supervised by and work under the responsibility of the PI. The PI will provide them with a copy of the RCT protocol and all necessary information.

TRIAL FLOW CHART



1. BACKGROUND

Diabetes-related foot ulcer disease (DFUD; an ulcer below the malleoli) puts people at extremely high risk of cardiovascular disease (CVD) events and premature mortality. It is life-changing, common, and associated with persistent suboptimal control of glycaemia (1). In the UK, 50-60,000 people with diabetes have active DFUD, whilst annual incidence is 40-50,000 cases (2). Five-year survival is worse than many cancers at 40-50% in those with DFUD (3), and only 30% in those whose DFUD led to amputation (4, 5), yet it is consistently perceived as less life-threatening than cancer (6). DFUD costs the NHS more than breast, prostate and lung cancer combined (7).

This is all particularly important in Type 2 Diabetes (T2D); 90% of DFUD patients have T2D, and total DFUD prevalence and disease burden are substantially higher in T2D than T1D (8, 9). Data suggests that health outcomes in DFUD have worsened during the COVID-19 pandemic (10) due to various factors, including reduced medication adherence (11), worsened lifestyle behaviours including reduced physical activity (12), worsened mental health (13), and reduced ability to disease self-manage or seek medical treatment (14).

Research in DFUD tends to focus on DFUD prevention and management (15), whilst the profound CVD risk in DFUD (16) is under-researched. CVD is the leading cause of death in DFUD (17), with elevated CVD burden beyond that in diabetes alone causing accelerated cardiovascular events and mortality (18). Whilst imposed physical inactivity and immobilisation associated with many long-term conditions drives CVD risk (19), it does not completely account for the excess CVD risk in DFUD. Additional causational mechanisms include cardiac autonomic neuropathy (20), atherosclerotic disease acceleration, physical deconditioning, inertia to preventative treatments (21), high prevalence of peripheral arterial disease (22), and poor medication adherence (23). Accordingly, research has called for investigations into aggressive CVD risk modification in DFUD (18).

CVD-related mortality decreases with medication-driven cardiovascular risk factor control in T2D populations with high CVD risk. There is also improved CVD risk from structured self-management education (SME) in people with T2D and microalbuminuria (24, 25).

However, these may not translate to, and have not been widely adopted for, people with T2D and DFUD. Instead, they are managed to diabetes quality and outcomes framework targets. T2D with DFUD represents a unique population due to: significantly elevated CVD risk compared with T2D alone (26); specific DFUD treatment requirements (e.g. SGLT-2 inhibitors, specifically canagliflozin, may increase amputation risk (27), though not in closely monitored patients (28); inability to undertake load-bearing exercise; mental and social impact of DFUD including worsened depression and quality of life (QoL) with associated poor adherence and risk factor control (29, 30); demographics (typically older, less active, longer diabetes duration); more sedentary (31). Model of care delivery may also impact CVD prevention in this group; the time-demanding nature of DFUD care and prevention/treatment of ulcers may prevent time and energy being spent on CVD prevention.

Furthermore, these previous studies pre-date modern T2D treatment recommendations and novel glucose-lowering agents that improve cardiovascular outcomes (30) and may reduce amputation risk in T2D with DFUD (32). Including these treatments may augment the effects of intensive risk factor control in those trials (25, 33). Building upon previous high-quality T2D trials by re-designing them specifically for the unique needs of T2D with DFUD in the most at-risk patient groups provides huge opportunity for clinical benefit in this extremely high-risk group. For example, seated arm ergometer exercise could replace traditional physical activity (31). This provides previously unavailable opportunities to those with DFUD to safely reap the cardiovascular benefits of exercise without risking further foot problems (32).

Therefore, in this trial, we will investigate the impact of a complex intervention targeting multifactorial CVD risk reduction strategies in those with current or previous DFUD, including physical activity and exercise, group disease self-management education and medication optimisation.

2. RATIONALE

We urgently need to address the substantial clinical and economic burden of DFUD-related CVD and identify and minimise prevailing health inequalities. The NHS Long Term Plan highlights multidisciplinary care in DFUD (sections 2.16, 3.81), addressing T2D health inequalities (2.16), and the importance of preventing CVD-related death as "the single biggest area where the NHS can save lives over the next ten years" (3.66), particularly in high-risk conditions (3.69) such as DFUD.

This trial will address this by testing a multifactorial complex intervention to prevent or slow the progression of CVD-related complications in the most at-need patients within an extremely high-risk population (DFUD). The anticipated outputs are: reduced CVD-related morbidity and mortality; reduced health inequalities in DFUD; reduced unnecessary CVD-related healthcare expenditure; and, unwarranted clinical variation. These are all important NHS and research targets (34).

People with DFUD are significantly underserved regarding CVD prevention compared with other chronic conditions such as hypertension and chronic kidney disease; accordingly, there is huge capacity for rapid (within the next 5 years) and meaningful clinical and financial benefit. Additionally, given the high number of prevalent (50-60,000) and incident (40-50,000/year) active DFUD cases in the UK, this benefit would extend to a very large number of people.

As such, there is clear rationale for a multifactorial complex CVD risk reduction intervention in those with T2D and DFUD that addresses specific needs and health inequalities. There is particular need for investigations into contemporary medication optimisation, improvement in adherence, and seated physical activity, which shows significant potential cardiovascular benefit (35); both are under-researched in DFUD. This kind of novel intervention would have huge clinical and cost benefit; however, current literature largely focuses on ulcer prevention and management, with little attention given to long-term CVD risk reduction. This represents an important research priority. The importance of this has only increased with the COVID-19 pandemic given that many people with DFUD are still managed remotely, which may exacerbate their risk factors and psychological outcomes, including medication adherence and physical activity levels.

3. RESEARCH QUESTION /OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Research question:

Can a complex intervention aimed at medication optimisation and behaviour change be effective, cost effective and sustainable in preventing CVD events in people with T2D and current or previous (within last 5 years) DFUD?

3.1 Primary objective

Compare the complex intervention (MiFoot) with usual care for preventing CVD events in people with T2D and current or previous DFUD in a randomised controlled trial.

3.2 Secondary objectives

- Monitor recruitment and stop-go criteria with an internal feasibility study
- Evaluate sustainability via completion of a process evaluation
- Estimate cost-effectiveness in a real-world setting via health economic analyses

3.3 Outcome measures/endpoints

Primary outcome is extended major adverse cardiovascular events (MACE) defined as (myocardial infarction, stroke, cardiovascular death, peripheral arterial bypass, coronary artery bypass, coronary angioplasty, or peripheral artery angioplasty) by 2 years. Event date taken as the earliest post-baseline date when one of the components occurred.

Extended MACE was chosen because CVD prevention is the primary aim, and all of the components are serious, potentially life-threatening and/or have a huge patient burden. MACE is a common outcome in CVD trials, therefore using it will allow comparability with other trials. Our Extended MACE definition is context-specific and newly defined. Other CVD trials have similarly added components to traditional MACE. The components were chosen because they are appropriate for this population; for example, it is important to include peripheral bypass and angioplasty given the high risk of this in T2D and DFUD.

An end-point committee of three blinded clinicians (not part of the trial research team; overlap with the PSC allowed) will adjudicate the primary endpoint by ensuring that it is consistent with the participant's other data (hospital admissions, biomedical values, etc). Each event will be independently adjudicated by two of the three clinical reviewers. For disagreements, the final deciding vote will be made by the third clinician.

3.4 Primary endpoint/outcome

Extended MACE (myocardial infarction, stroke, cardiovascular death, peripheral arterial bypass, coronary artery bypass, coronary angioplasty, or peripheral artery angioplasty) by 2 years. Event date will be taken as the earliest post-baseline date when one of the components occurred.

3.5 Secondary endpoints/outcomes

- Health outcomes
  - Composite renal endpoints: end-stage kidney disease (defined as dialysis, transplantation, or a sustained (>3 months) eGFR of <15 ml/minute/1.73m^2), doubling of the serum creatinine level, or death from renal causes
  - 3P-MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) and individual components of the Extended MACE composite: non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, peripheral arterial bypass, coronary artery bypass, coronary bypass, coronary angioplasty, peripheral artery angioplasty
  - All-cause mortality
  - Lower-limb major amputation
  - Self-reported re-ulceration

- Patient reported outcomes
  - Distress (PAID-20)
  - Self-efficacy (DMSES-15)
  - QoL: DFUD (DFS-SF), generic (EQ-5D-5L)
  - Depression and anxiety (HADS)
  - Health resource use, such as primary care visits, emergency department visits, hospitalisations and medication use (ModRUM)
  - Medication adherence
  - Diet (short-form food frequency questionnaire
  - Sleep duration/quality and physical activity volume/intensity measured objectively using wrist worn accelerometers

- Biomedical markers

- Blood pressure (systolic, diastolic, heart rate) (mmHg, BPM)
- Low-density lipoprotein-cholesterol (LDL-C) (mmol/L)
- High-density lipoprotein-cholesterol (HDL-C) (mmol/L)
- Total cholesterol (TC) (mmol/L)
- Triglycerides (TG) (mmol/L)
- Glycated haemoglobin (HbA1c) (% and mmol/mol)
- Estimated Glomerular Filtration Rate (eGFR) (ml/min/1.73m^2)
- Urine albumin: creatinine ratio (AUCR)

- Anthropometric
  - Weight
  - Body mass index (BMI)

- Safety measures
  - Myocardial infarction
  - Stroke
  - Cardiovascular death
  - Peripheral arterial bypass
  - Coronary artery bypass
  - Coronary angioplasty
  - Peripheral artery angioplasty
  - Hypoglycaemic events

- Demographic variables (collected for exploratory stratified analyses)
  - Age
  - Sex
  - Ethnicity
  - T2DM duration
  - DFUD duration
  - Socio-economic score (Index of Multiple Deprivation (IMD); a postcode-based measure of socio-economic score)
  - Medications (glucose-lowering, lipid-lowering, blood pressure-lowering, anti-platelet, anti-depressants)

3.6 Exploratory endpoints/outcomes

The effectiveness of the MiFoot intervention in persons with T2D and DFUD compared to standard care will be tested at the 12-month and 24-month marks on the following exploratory outcome:

- Measures related to glycaemic level:
  - Continuous Glucose Monitor- assessed:
    - percentage of time spent within target range [3.9-10mmol/l] (optional to minimise burden)
    - percentage of time spent above target range [over 10 mmol/l] (optional to minimise burden)
    - percentage of time spent below target range [below 3.9 mmol/l] (optional to minimise burden)

3.7 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective Compare the complex intervention (MiFoot) with usual care for preventing CVD events in people with T2D and current or previous DFUD in a randomised controlled trial.	Extended MACE (myocardial infarction, stroke, cardiovascular death, peripheral arterial bypass, coronary artery bypass, coronary angioplasty, or peripheral artery angioplasty) by 2 years. Event date will be taken as the earliest post-baseline date when one of the components occurred.	Extraction of CVD event data from routine healthcare records at following timepoints: 0, 12 and 24 months.
Secondary Objectives • Monitor recruitment and stop-go criteria with an internal feasibility study • Evaluate sustainability via completion of a process evaluation • Estimate cost-effectiveness in a real-world setting via health economic analyses	Recruitment rates (consented and randomised), intervention delivery and attendance rates, qualitative interviews, health-outcomes (listed in section 3.5), biomedical markers, anthropometrics, questionnaires, physical activity data (accelerometers), safety measures. For the health economic analyses health resource use data will be collected, including primary care visits, emergency department visits, hospitalisations and medication use, via electronic records and supplemented with patient self-reported data.	Collected via combination of clinic visits, extraction of test results and event data from routine health records, postal questionnaires and accelerometer data.

4. TRIAL DESIGN

Multicentre, pragmatic, single-blind RCT with internal feasibility study, process evaluation and health economics analyses. Participants cannot be blinded due to the nature of the intervention. To reduce bias, analysis will be conducted by investigators blinded to randomisation allocation. Additionally, the primary outcome is objective and will be ascertained from routinely collected data.

5. TRIAL SETTING

The MiFoot RCT is a multi-site, two arm trial consisting of an evaluation of effectiveness, an internal feasibility study (described in section 5.1), a process evaluation (described in section 5.2), and a health economic evaluation (described in section 5.3). Participants will be randomised to receive intervention or usual care and followed up at month 12 and 24. Participants will be recruited from sites across UK.

Participating research sites:

The participating research sites include secondary care sites University Hospitals of Leicester NHS Trust University Hospitals of Derby and Burton, NHS Greater Glasgow & Clyde, Imperial College Healthcare NHS Trust, Sheffield Teaching Hospitals NHS Foundation Trust and other sites yet to be identified, these will be added via an amendment.

5.1 Internal Feasibility study

An internal feasibility study will be undertaken within the larger MiFoot RCT, with analysis based on the first 3 months of recruitment data, when recruitment should be 25% complete (i.e., 98 participants). To allow for a slower start, feasibility criteria will be set as 20% of the total recruitment target (i.e., 78 participants). Patient inclusion/exclusion criteria will be identical to that of the main trial. Based on the actual number of patients recruited (consented and randomised) after 3 months compared with the target of 78 participants (red: ≤49; amber: 50-77; green: ≥78). Information from the internal feasibility assessment will be used to inform subsequent action planning to ensure the trial meets key milestones. The options will be to:

- continue as planned (for example, if recruitment is in the green zone)
- consider whether changes to the RCT protocol or recruitment process would aid recruitment (for example, if recruitment is in the amber/red zone and sites are unable to meet target recruitment rates)
- add sites (for example, if recruitment is in the amber/red zone and recruiting sites are meeting their target recruitment rates but not all sites are actively recruiting, or if sites are unable to meet target recruitment rates)
- extend recruitment period (for example, if recruitment is in the amber/red zone and there are no additional sites to recruit, which is unlikely to happen; if possible and necessary then adding additional sites will take precedence over extending the recruitment period to maintain projected timelines)
- stop study (if recruitment is in the red zone and only if entirely unfeasible and additional funding cannot be obtained).

5.2 Process evaluation

To investigate individual experiences with the intervention, potential barriers and facilitators to intervention delivery, attendance (including delineation of these factors based on each different element of the intervention) and intervention fidelity. A mixed methods process evaluation will be completed, using both qualitative (described in section 7.8.1) and quantitative (described in section 7.8.2) data collection methodologies. This is based on using the RE-AIM framework (section 7.8.3).

5.3 Health economics

We will conduct two health economic analyses. We will do an analysis of resource use data collected within the trial and a long-term economic modelling analysis. We envisage that the primary analysis will be long-term health economic model, as we expect that MiFoot will have an effect on patient outcomes beyond the trial period.

Resource use data collection

During the RCT, health resource use data will be collected, including primary care visits, emergency department visits, hospitalisations and medication use, via electronic records and supplemented with patient self-reported data.

For medication data, a list of glucose lowering and cardio-protective medications will be provided to the data extraction provider, who will extract any incidents of prescribing (including dose and date) from primary care systems over the period of interest. We will also ask the participant to report usage of the same list of medications to allow cross-checking between the two sources (e.g., total count of prescriptions). The questionnaire data can then add information on any additional medication use (e.g., emergency prescription by another general practice; over the counter medications).

The intervention cost will be compiled from the costs mobilised to implement it, including staff, space, and consumables.

Within trial analysis

Within-trial cost-effectiveness analyses will be conducted for all study outcomes unless the intervention proves unfeasible or harmful (reported as cost/QALY, and cost per unit change/event reduction). Cost-utility analysis will be conducted using preference-based health utility scores from EQ-5D-5L. Within-trial discounted cost and discounted QALYs measured using EQ-5D-5L will be analysed using a "seemingly unrelated regression" model. Intention-to-treat (ITT) analyses will be used as with the main trial analyses, with baseline costs, baseline utility, and stratification factors as covariates, and multiple imputation using the chained equations approach will be used to impute missing data. This method assumes data are missing at random and creates multiple predictions for each missing value, thereby allowing for uncertainty to be accounted for. A sensitivity analysis will be used with complete cases.

Model based analysis

We will develop a new health economic model to examine the effects of MiFoot versus usual care. This model will be based on our existing health economic model, the School for Public Health Research Type 2 Diabetes Treatment Model (SPHR-T2DMT), which has been used to assess the cost-effectiveness of psychological therapies in people with T2DM and is currently been used in NIHR programme grants to assess the cost-effectiveness of technologies in people with early onset type 2 diabetes and the addition of weight management to structured education for people with type 2 diabetes (36-38). For MiFoot we plan on updating SPHR-T2DMT or creating a new model based on the SPHR-T2DMT structure to reflect the epidemiology risk equations (work still in progress) developed in earlier stages of the MiFoot programme grant and to include the treatment effects estimated from the trial data. We envisage that the updated model will still be an individual level simulation in line with other models of diabetes, and as such the characteristics of simulated patients will come from the MiFoot trial baseline population. We will simulate two cohorts, one cohort who receives the MiFoot intervention and another who does not.
We will estimate the duration of sustained effect using the differences between the 12- and 24-month RCT follow-ups, and the clinical plausibility of different methods of extrapolating this benefit assessed with topic experts.

Health Economic results

The key health economic outcome in both analyses will be incremental cost per QALY gained by MiFoot versus usual care, incorporating discounting and a full probabilistic sensitivity analysis. We will take a lifetime horizon and an NHS and personal social services perspective.

6. PARTICIPANT ELIGIBILITY CRITERIA

As outlined in the inclusion and exclusion criteria below, we will recruit participants with T2D and current or previous DFUD. Eligibility criteria will be identical for the RCT, internal feasibility study and process evaluation.

6.1 Inclusion criteria

The participant inclusion criteria are as follows:

- Males and Females aged ≥18 years
- Diagnosed with T2D
- Current or previous DFUD (defined as diagnosed with DFUD in the previous 5 years)
- Ability to understand and communicate in English
- Participant is able (in the Investigators opinion) and willing to fulfil all the study requirements

At the baseline visit, physical activity screening will be undertaken to assess safety considerations as a precaution prior to physical activity as part of the intervention. The participant may be excluded from the physical activity part of the intervention, but not the remaining intervention elements. Participants with both vascular and neuropathic ulcers will be eligible.

6.2 Exclusion criteria

The participant exclusion criteria are as follows:

- Diagnosed with other forms of diabetes (e.g., type 1 diabetes, monogenic diabetes (MODY), gestational diabetes or latent autoimmune diabetes in adults (LADA)
- Other, non-diabetic forms of ulceration (e.g., venous)
- Serious illness or event with life-expectancy <1 year or other significant illness which, in the opinion of a study clinician, precludes involvement
- Planned major surgery
- Requirement for renal replacement therapy
- Current pregnancy, or actively trying to conceive
- Unwilling or unable to give informed consent to participate in the study
- Current participation in a CTIMP or any other disease management or lifestyle-related intervention study (as determined by study investigator)

Inability to participate in physical activity part of the intervention will not preclude inclusion in the study or the rest of the intervention, in order to represent the real-world situation. We will collect data concerning this as part of the process evaluation (section 5.2.2). The intervention will be delivered in English language and as such any participants who do not speak or read English to a sufficient standard will be excluded from the study. Every effort will be made to support participants with minimal English proficiency to participate.

7. TRIAL PROCEDURES

Eligible potential participants will be identified and recruited as described in section 7. The trial procedures are described within section 7.

Table 1. Schedule of Procedures

Procedures	Visits					
	Pre-screening	Baseline visit month 0	Intervention period Intervention arm	Usual care arm	Remote 12 month Follow Up	Remote 24 month Follow Up
Invitation and EOI	x					
Telephone screening[1]	x					
Informed consent		x				
Face to face eligibility screening[2]		x				
Demographics and additional information (e.g.: age, sex, ethnicity, post code, familial history)[3]		x				
Medical history and medications (cardiometabolic, anti-depressants)[4]		x				
SINBAD total score and components (if active ulcer present)		x				
Randomisation[5]		After consent				
Health outcomes data collection[6]		x			x	x
Biomedical markers: Blood pressure, Lipids, HbA1c, eGFR, Urine albumin: creatinine ratio		x			x	x
Anthropometric: Weight, Height, Body mass index		x			x	x
Questionnaires[7]		x			x (±4 weeks)	x (±4 weeks)
Accelerometer[8]		x (±4 weeks)			x (±4 weeks)	x (±4 weeks)
Physical activity screening*		x				
ECG*		x				
Continuous Glucose Monitor		After consent				
MiFoot programme*			x		x	x
Adverse event assessments Safety measures		x			x	x
Inform GP of study participation		x				
Process evaluation observations*			x			
Process evaluation feedback surveys*			x**			
Process evaluation questionnaires*					x	
Process evaluation interviews*						After month 24

* Intervention group only

** after each one-to-one and group session and 4 weeks into the digital programme, collected up to month 9 of the intervention delivery

[1]Telephone screening includes checks for: age, T2D and DFUD diagnosis, planned major surgery, renal replacement therapy, current pregnancy, involvement in CTIMP

[2]Face to face screening includes: confirmation of full inclusion and exclusion criteria via medical records, participant interview/discussion

[3]Demographic and medical history includes: sex, date of birth, ethnicity, employment, education, marital status, socio-economic status

[4]Detailed past medical history including previous or current diseases and surgical interventions will be recorded along full medication history and allergy status will also be collected

[5]Randomisation will occur on completion of baseline measures

[6]Health outcomes includes: renal endpoints: end-stage kidney disease (defined as dialysis, transplantation, or a sustained eGFR of <15 ml/minute/1.73m2), doubling of the serum creatinine level, or death from renal causes, individual components of the Extended MACE composite: myocardial infarction, stroke, cardiovascular death, peripheral arterial bypass, coronary angioplasty, peripheral artery angioplasty; all-cause mortality, lower-limb major amputation, self-reported re-ulceration

[7]Questionnaires booklet to be issued. HADS questionnaire **must** be completed, collected and scored at baseline and passed onto HCP delivering 121 session*

[8]Site staff will demonstrate to participant how to use the accelerometer, lead site will post it to participant. At Lead site these will be given to participant who attend the lead site at baseline visit.

7.1 Recruitment

The Chief Investigator will ensure that all regulatory approvals, confirmation of capacity and capability from NHS sites and Sponsor Green Light are in place before participants are identified and approached. People who may be interested in taking part in the study will be invited to contact the study team to express this interest. Interested people will return the reply slip/scan the QR code or call the team directly to register their interest and they will be advised that a member of the research team will be back in touch. On the reply slip or online registration form individuals confirm whether or not they consent to a member of the research team accessing their medical records to confirm T2D and DFUD diagnosis. If they are not happy for their records to be accessed prior to consent, this can be checked and confirmed at the baseline visit.

The number of potential participants identified will be collated for Consolidated Standards of Reporting Trials (CONSORT).

We will work with the local CRNs and specialist and community foot and podiatry clinics and HCPs to support the participant identification and recruitment from primary and secondary care.

7.1.1 Participant identification

7.1.1.1 Participant identification through primary and secondary care

Research sites will closely work alongside their local CRN to support recruitment from primary and secondary care PIC sites. Potential participants will be identified primarily through database searches of clinical systems/Electronic Health Records (e.g., SystmOne). Database searches will initially screen for eligibility (using the criteria outlined in section 6). An invitation letter, participant information sheet and pre-paid reply envelope will be provided to potential participants. A remailing will be conducted where appropriate. If willing, sites can add notes or reminders to patient records within Electronic Health Records to aid recruitment and display posters and banners. The study teams will work with the CRN, Specialist Services, Community Podiatry, Community Foot Clinics and GP practices to add notes and/or set-up reminders on eligible medical records for a GP, Diabetes Specialist Nurse or other health care provider to inform them about the study during routine appointments. In addition, where willing, individual clinicians, GPs and other health care professionals may engage in opportunist identification of potentially eligible participants with the provision of study materials and the participant information leaflet.

Potential participants will be approached through hospital-based foot clinics via their usual clinical carers, and through community podiatry/GP records. Healthcare professionals will screen their clinic lists for

potentially eligible participants and promote the study either verbally in clinic, over the phone/videocall text-message, email or via mail-out of an invitation letter, participant information sheet and pre-paid reply envelope. Searches and screening may be done periodically to enable newly potentially eligible patients to be invited.

Alternatively after seeking consent to do so, contact details of interested people identified by healthcare professionals from either primary or secondary care will be shared with the research team, who will then contact the potential participants and share study materials. Whether approached in primary or secondary care, non-clinical members of the research team, or clinical members not involved in the person's usual care, will not identify participants or access medical records before consent has been obtained. Researchers may however visit clinical sites to promote the study to clinical teams and potential participants where the site has given permission for this to take place. The first approach will be via the direct care team, i.e., asking eligible participants for permission to be approached by a research team member to discuss the study. This will be documented within the potential participant's health records.

Potential participants will be also approached through hospital inpatient wards via their usual clinical carers. Healthcare professionals will screen their admission lists for potentially eligible participants and promote the study verbally and by provision of study materials to invite them to take part in the study. Recruitment activity (including but not limited to display of study posters, banners, leaflets, GPs text messages, newsletters, PPI groups, social media, attendance by research team etc.) may be carried out in various health care settings, including but not limited to:

1. Primary care and community clinics, for example:
    a. GP practices
    b. Local hospitals
    c. Community groups
    d. Health Services Providers
2. Secondary care
    a. Local outpatients' clinics
    b. Local inpatients' clinics

7.1.1.2 Participant identification through participant and volunteer database

If applicable, study sites may use participant and volunteer databases containing individuals who have consented to be informed of and invited to future research studies. These may be participants that have completed studies previously and are known to have T2D and DFUD, or volunteers that have not previously been involved in studies but have expressed interest to be considered for future studies at the corresponding study site.

7.1.1.3 Participant identification through the community and networks

The Leicester Diabetes Centre participates in community events and open days to publicise their research studies and distribute information. This may consist of having a stand and or banner/poster with all the study information and/or presenting this study at these events. Relevant events at the other research sites will also be used to distribute study information.

Local social events, health and community support groups, online communities and networks will be utilized to advertise and publicise the study within the community and networks.

7.1.1.4 Participant identification through other methods

This study will be advertised via several formats, including but not limited to creation of the website, social media (e.g. Facebook, Twitter, forums etc.), local radio (local to each site), television stations, and press releases. Participant case studies (with media consent in line with the research sites' Trust policies), which will be used to promote the study on social media, websites and press releases. Study information, including a brief leaflet about the study, will be distributed by email to various mailing lists held by the research sites, included but not limited to, local registries, newsletters, Trust members, PPI groups, and Trust staff, local intranets and internal mailing lists. The research team will also distribute posters, banners and information to publicise the study within the community at each site e.g. pharmacies, supermarkets, libraries, gyms and community centres.

7.1.1.5 Recruitment from Diabetes Research Register (Scotland only):

The NHS Research Scotland (NRS) Diabetes Research Network permission will be utilised to contact research register of people with who have expressed a willingness to be involved in research. This register has a large cohort of people with diabetes (>20,000) who have given permission to be approached directly via email, letter, text-message and or phone. People with diabetes in Scotland who are part of this system will be approached via email, letter, text-message and or phone to take part.

7.1.2 Screening

Identification by usual clinical care team to be initially approached about the study

Potential participants will be initially screened (pre-screened) for their eligibility (all relevant information will be obtained from routine existing healthcare records by the clinical care team) using following criteria:

- Males and Females aged ≥18 years
- Diagnosed with T2D
- Current or previous DFUD (defined as diagnosed with DFUD in the previous 5 years)

Telephone screening

Following a participant's expression of interest, a screening call will be arranged to provide further information about the study and, subject to the participant consenting to it on their expression of interest form (paper, online or verbal over the phone), screening of their medical records by a research team member to confirm T2D and DFUD will take place. If they are not happy for their records to be accessed prior to consent, this can be checked and confirmed at the baseline visit. During the screening call, participants will be able to ask any questions they have, and the team will confirm whether they are eligible to take part prior to coming for a baseline visit.

For those that do not wish to participate in the study, we will collect the patient initials, DOB and where possible for monitoring purposes, the reason for not wishing to participate.

Screening at baseline visit

Potential participants will be screened for their eligibility by the research team. Eligible participants must meet all the inclusion criteria and not meet any of the exclusion criteria described in section 6.

Participants will be screened on the pre-specified criteria only; all relevant information will be obtained from routine existing healthcare records by the clinical care team.

For those that do not wish to participate in the study, we will collect the patient initials, DOB and where possible for monitoring purposes, the reason for not wishing to participate.

7.1.3 Reimbursements

Participants travel and parking for all study visits (measurement and intervention) will be reimbursed on the production of receipts. Participants randomised to the Control group will receive up to £10 in reimbursement for attendance of the baseline visit. Intervention group participants will be attending approximately 14 face to face visits and will receive up to £140 in reimbursement. The amount will be reviewed on a case-by-case basis, depending upon circumstance.

In line with NIHR guidance, good practice for payment and recognition for participant involvement will be followed and each participant may receive incentives of up to £60 for their participation in the study in recognition of their time commitment in RCT. An additional £20 incentive is for participation in the process evaluation. This payment is only available for trial participants and not HCP (refer to section 7.8 for information on HCP involvement).

All payment to participants will be made by the relevant research site. Sites will invoice the Lead centre to be reimbursed quarterly keeping local records for audit trails as required by the NIHR.

7.2 Consent

Consent procedures for the study will be undertaken at the baseline visit. Participant information sheets, consent forms and any amendments will be approved by Research Ethics Committee (REC), Health Research Authority (HRA), Study Sponsor and the local trust R&I department prior to implementation. Prior to participation in the study, participants will be required to give their written informed consent.

After confirmation of eligibility, written informed consent will be received after individual discussion between the participant and a member of the research team, with the participant having had sufficient opportunity to consider the participant information sheet and ask any questions related to the study. Where possible and acceptable to the participant, we will obtain written informed consent at baseline visit in order to prevent the need for another visit to the research site for the consent process, and therefore minimise the burden of study participation in this group that already experience significant disease and treatment burden. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who completed consent procedures.

The person obtaining informed consent will be a suitably trained and competent person who, in the opinion of the Principal Investigator (PI) at each site, will be able to give a full and unbiased explanation of the study (including benefits and risk) to the potential participant. As part of the process, they will make an informed judgement on the persons capacity to provide informed consent, by checking the participant understands:

- the purpose and nature of the research
- what the research involves, including its potential benefits risks and burdens
- the alternatives to taking part

and that they can:

- retain the information long enough to make an effective decision
- make a free choice
- make this decision at the time it needs to be made.

The person obtaining consent will also have been named on the delegation of authority and signature log of staff as undertaking this duty and approved as study personnel by the relevant governance procedures. Written and verbal versions of the participant information sheet and informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known potential risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Each participant will be provided with a contact point where they may obtain further information about the study, a copy of the consent form and participant information leaflet; a copy will be placed in their hospital medical records and the original copy held in the trial master file/investigator site file.

The PI will retain overall responsibility for the conduct of research at their site, including the receipt of informed consent of participants. Where a participant is required to re-consent or new information is required to be provided to a participant it will be the responsibility of the PI to ensure this is done in a timely manner.

For participants already taking part in the study prior to the addition of the optional CGM component, additional consent will be sought.To reduce participant burden, consent to this optional additional componentmay be conducted face-to-face or remotely via telephone and/or video visits. The method of participant: study personnel interaction will be recorded at the visit. An addendum consent form will be used. The remote consent method is used in the Qualitative element of the RCT.

7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies

Not applicable

7.3 Randomisation

Stratified blocked randomisation will occur on completion of baseline measures.

Participants will be randomly allocated in a 1:1 ratio to participate in:

1) Intervention – Intervention plus usual care

or

2) Control Conditions - Usual care.

7.3.1 Method of implementing the randomisation/allocation sequence

Participants will be informed of their randomisation assignment during the baseline visit and this will also be confirmed via a letter. A letter will be sent to the participant's GP notifying them of their patient's participation in the study.

The person using the randomisation system must be suitably trained and have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the study, using a validated web-based system. Eligible participants will be randomly assigned in a 1:1 ratio to one of two study arms, as detailed in section 7.3.

Participants will be allocated using stratification factors of site, sex (male; female) and age (<50; ≥50). Further details can be found in the Statistical Analysis Plan. Each participant will be given a unique participant identification (ID) number at screening. This participant ID number will be used to identify the individual participant throughout the study and will not be re-assigned to any other participant. Due to the nature of the intervention, blinding of the participants and the study team to randomisation is not possible.

Core members of the team at each site e.g., site lead, study clinician and research nurse will receive new participant/randomisation alerts at each given site. Core members of the team at the lead site e.g., CI,

trial manager and lead co-investigators will receive alerts for all randomisation irrespective of site. The allocation will be documented within the site and trial master files and participant medical notes.

7.4 Baseline data

First, a screening call (section 7.1.2) to assess eligibility and provide the individual with further information about the study, including the participant information sheet will take place, then participants will attend a baseline clinic visit. At the baseline visit participant eligibility will be confirmed by a nurse.

At the baseline visit informed consent will be taken before any other procedures take place. To join the study, individuals will need to give the research team permission to access their GP and hospital records to collect clinical baseline and follow-up data at month 12 and 24. This will be fully explained as part of the consent process. After providing consent, baseline data will be obtained, namely demographics, medical history, family history, SINBAD components and total score of any active ulcers, and the primary and secondary outcome measures, including the questionnaires (described in detail in section 7.5). Height and weight will be measured and used to calculate Body Mass Index (BMI). Resting pulse and blood pressure (BP) following a 5 minute seated rest will also be recorded. Participants will also have their pulse checked, followed by the completion of an electrocardiogram (ECG) in order to identify any potential undiagnosed cardiac problems (this is considered as an adjunct to the intervention and so will be completed in intervention participants only . If any previously unknown issues are detected, this will be recorded in the eCRF along with any resulting actions such as treatments or referrals. If the participant's most recent blood test results taken as part of usual care (HbA1c, lipids, eGFR, liver function tests) are greater than 6 months old, the participant will be referred for further blood tests in order to ensure that their results are up to date. This will be accomplished via the routine process for the completion of bloods at each site; either completion at the site/clinic/hospital, or participants will be given a blood request form and will be asked to request that these blood tests be completed by their GP; in this instance GPs will also be informed of this requirement in the letter informing them of their patient's participation in the study). For participants in the intervention group, these blood test results will then be available to the clinician leading the individualised appointment within the intervention (described in section 7.5.1.1) in order to inform potential changes to patient care. Participants will be shown a wrist-worn accelerometer and advised they need to wear this for 8 days to measure habitual activity. The lead site research team will post the accelerometers and questionnaires with a pre-paid, addressed envelope to return the accelerometer and questionnaires back to the Lead site research team, who will then process the data in line with standard protocols.

Participants will be assessed for safety and any precautionary measures, to take part in the physical activity component of the intervention as described in section 7.4.1.

7.4.1 Health outcomes

Health outcomes will be collected from medical records. Collection/measurement period is defined as existing records prior to and inclusive of the baseline date. Baseline data will be obtained from the medical records and provided to the research team for the period prior to the baseline visit, this will include: renal endpoints: end-stage kidney disease (defined as dialysis, transplantation, or a sustained eGFR of <15 ml/minute/1.73m2), doubling of the serum creatinine level, or death from renal causes, individual components of the Extended MACE composite: myocardial infarction, stroke, cardiovascular death, peripheral arterial bypass, coronary angioplasty, peripheral artery angioplasty; all-cause mortality, lower-limb major amputation, self-reported re-ulceration. For participants who take the optional CGM, 12th-month, and 24th- month glycaemic level data will be downloaded if participants have worn the device for long enough.

7.4.2 Safety measures

Baseline data will be obtained from the medical records and self-reported by participants and provided to the research team from the baseline visit, this will include: myocardial infarction, stroke, cardiovascular death, peripheral arterial bypass, coronary artery bypass, coronary angioplasty, or peripheral artery angioplasty.

7.4.3 Questionnaires

Participants will be asked to complete the following questionnaires at their baseline visit:

- QoL: generic EQ-5D-5L
- Depression and anxiety (HADS)
- Health resource use, such as primary care/emergency department visits, hospitalisations and medication use (ModRUM)
- QoL: DFUD (DFS-SF)
- Self-efficacy (DMSES-15)
- Distress (PAID-20)
- Medication adherence (Morisky)
- Diet (short-form food frequency questionnaire)

The paper-based questionnaire booklet will be provided and collected by the study team at this baseline visit. Should participants wish, they will be able to take questionnaires home for completion along with a prepaid envelope in order to return them. The HADS questionnaire at the baseline visit will be a questionnaire required to complete in person with the study team. The HADS must be scored at baseline, and the score must be captured on the e-CRF. Scoring for each item ranges from zero to three, with three denoting highest anxiety or depression level. A total subscale score of >8 points out of a possible 21 denotes potential symptoms of anxiety or depression. GP or local mental health services will be notified of those participants who score more than or equal to 8 points. This will aim to inform the individualised appointment of the intervention.

7.4.4 Accelerometer

Participants will be shown an accelerometer whilst in clinic and then the lead site team will send it in the post to be worn for 8 days to measure habitual activity and returned in a pre-paid envelope. Outcomes will include sleep duration and quality, overall physical activity volume and intensity profile, along with time spent sedentary, in light-intensity physical activity and in MVPA (moderate to vigorous physical activities).

Wrist-worn accelerometers are suitable for measuring habitual ambulation, as well as arm-based exercise. If the participant's accelerometer has not been received two weeks after the due date, the study team will contact the participant to remind them to return the device. Multiple attempts will be made within the determined window (± 4 weeks) or until resolution.

7.4.5 Continuous Glucose Monitor

The Continuous Glucose Monitoring (CGM) is a wearable technology that allows individuals to track their blood sugar levels at any time, day or night. The device has a tiny sensor that sits under the skin and transmits blood sugar readings, data and alerts to a reader or a smartphone so that individuals with T2D can better manage their diabetes.

We will perform exploratory analyses of sensor glucose levels from CGM devices for those who take part in the optional CGM part of the study. We will evaluate CGM metrics as per the ATTD guidance including – 1) Time in range 3.9-10mmol/l; 2) Time above range (> 10mmol/l; 3) time below range (< 3.9 mmol/l); 4) sensor usage data (proportion of time the sensor is used).

The FreeStyle Libre 2 CGM System will be available to all participants for this study; participants will be free to choose if they want to use the device or not based on their preference, participants will be given access to paper and/or online education and videos showing how to use the sensor.

Participants will be provided with the CGM during their baseline appoinment and shown how to use it. For participants who were already taking part in the study prior to the additional optional CGM aspect, participants will be made aware of the additional aspect by notification letter, email or text. If interested they will be invited to get in touch with the study team. They will then be sent a copy of the updated participant information sheet. If they consent to take part in this component, where consent occurs remotely, individuals will be sent the devices alongside links on how to set up the device. Participants will be asked to wear the CGM for as long as they like during the study; if they choose to wear them for the duration of the study, then will be provided with a supply regularly (i.e., for 3 months at a time).

For participants with a smartphone, the CGM can be linked to their smartphone devices and participants can monitor their blood glucose levels daily. However, a reader will be made available to participants who do not have smartphones or who will prefer to have the readers. Data from the devices will be downloaded remotely via Libre link. We will set up a separate "clinic" in libreview that will allow data (identified by study subject number) to be viewed and shared with the research team.

7.4.6 Physical activity screening (Intervention group only)

We aim to mimic real world settings, for exercise and physical activity sessions conducted within the NHS. Therefore, a specifically designed physical activity assessment form will be used to safely determine participant's readiness and ability for physical activity, prior to the SME (structured self-management education). The aim of the physical activity component of MiFoot is to increase people's ability and motivation to adhere to the recommended physical activity guidelines (39, 40), within the constraints of any health limitations (e.g., non-weight bearing exercises if they have an active foot ulcer). The physical activity sessions will be conducted by participants at a level suited to their abilities and focus on breaking up sedentary time and moderate activity. All intervention participants will be screened for any contraindications, precautions or considerations for exercise in line with clinical judgement and guidelines (41, 42). Further assessment and referral to other services/healthcare professionals will be carried out where necessary, subject to clinical judgement at the time.

If a contraindication is identified, the participant will be excluded from the physical activity part of the intervention, but not the remaining intervention elements. This will be recorded to inform the analyses and process evaluation. The physical activity intervention will include both weight-bearing and non-weight-bearing exercises, in order to allow tailoring and exercise selection based on the participant's functional status and guidance concerning avoidance of weight-bearing where required.

7.4.7 Routine health data (via research data extractions)

Patient data will be collected from relevant routine medical records at baseline (month 0 - defined as month of participant baseline visit). The collection/measurement period for the baseline data extraction is defined as any existing records prior to and inclusive of the baseline date (variables collected detailed in table 2).

Table 2: Research Data Extraction variables collected in this study.

Variable	Value of Interest	To be extracted
Type 2 diabetes diagnosis	First recorded	Value and date
DFUD diagnosis	First recorded	Value and date
Age	Last recorded	Value
Sex	Last recorded	Value
Ethnicity	Last recorded	Value
Smoking status (Current/Never /Ex-Smoker)	Last recorded	Value and date
SINBAD total score and components	Last recorded within measurement period	Value and date
Body mass index (BMI)	Last recorded within measurement period	Value and date
Weight	Last recorded within measurement period	Value and date
Height	Last recorded	Value and date
Total cholesterol (TC)	Last recorded within measurement period	Value and date
LDL cholesterol	Last recorded within measurement period	Value and date
HDL cholesterol	Last recorded within measurement period	Value and date
Systolic blood pressure	Last recorded within measurement period	Value and date
Diastolic blood pressure	Last recorded within measurement period	Value and date
Heart rate (HR)	Last recorded within measurement period	Value and date
Triglycerides (TG)	Last recorded within measurement period	Value and date
HbA1c	Last recorded within measurement period	Value and date
Estimated Glomerular Filtration Rate (eGFR)	Last recorded within measurement period	Value and date
Urine albumin: creatinine ratio (AUCR)	Last recorded within measurement period	Value and date
Myocardial infarction	All recorded within measurement period	Value and date
Stroke	All recorded within measurement period	Value and date
Cardiovascular death	All recorded within measurement period	Value and date
Peripheral arterial bypass	All recorded within measurement period	Value and date
Coronary artery bypass	All recorded within measurement period	Value and date
Coronary angioplasty	All recorded within measurement period	Value and date
Peripheral artery angioplasty	All recorded within measurement period	Value and date
Hospital admissions	All recorded within measurement period	Value and date
All-cause mortality	All recorded within measurement period	Value and date
Lower-limb major amputation	All recorded within measurement period	Value and date
Self-reported re-ulceration	All recorded within measurement period	Value and date
Medication: Glucose lowering	All recorded within measurement period	Value and date
Medication: Lipid-lowering	All recorded within measurement period	Value and date
Medication: Blood pressure-lowering	All recorded within measurement period	Value and date
Medication: Anti-platelet	All recorded within measurement period	Value and date
Medication: Anti-depressants	All recorded within measurement period	Value and date
Medication: CVD	All recorded within measurement period	Value and date

7.5 Trial assessments

7.5.1 Description of study intervention and comparator

7.5.1.1 Intervention – *MiFoot programme*

The MiFoot programme has 3 components, comprising:

- One individualised appointment with an HCP
- Seven weekly SME group sessions (one hour of physical activity and one hour of education); followed by 8 monthly booster sessions (45 minutes of physical activity and 45 minutes of

education, alternating between virtual and face-to-face delivery); and one final booster session between 18-24 months (45 minutes of physical activity and 45 minutes of education, face-to-face delivery)
- Access to a digital-based programme, 'MiFoot MyDesmond'.

MiFoot aims to address multiple modifiable risk factors integral to CVD prevention. Some risk factors (e.g., glycaemia, lipids, blood pressure, anti-platelets) will be predominantly managed one to one via an assessment of current levels, target setting and action planning as a joint patient-HCP activity, medication initiation/adjustment, and supported medication adherence. Other factors (e.g., weight, physical activity, smoking cessation, diet) will be predominantly managed via SME group sessions and a digital-based programme (MiFoot MyDesmond). More details around these components follows. All sites and participating staff involved in intervention delivery will be provided with training in order to support the delivery of the intervention, and to ensure that it is structured and standardised across study sites. Any required actions resulting from the ECG completed in the intervention participants at baseline will be at the discretion and clinical judgement of the physician reviewing the ECG and will not be predefined as part of the Mifoot intervention.

Individualised appointment with an HCP with foot knowledge (i.e. clinician, diabetes specialist nurse, registrar etc.)

These sessions will focus on medical management and intensive multifactorial CVD risk factor control aimed at achieving optimal clinical targets, evidence-based medication initiation, and supported adherence (to polypharmacy). Where relevant this will also include review of medications, and considerations given to prescription of novel therapies for glycaemic control and CVD risk reduction, such as sodium-glucose co-transporter-2 (SGLT2) inhibitors (whilst avoiding canagliflozin and maintaining compliance with contemporary clinical guidelines that may evolve over time) and glucagon-like peptide-1 receptor agonists, based on contemporary clinical guidelines. These clinical discussions will be based on the latest blood test results (either completed as part of routine care or requested specifically for the purposes of this study if the most recent blood test results were completed over six months previously), the existing knowledge of the clinician and the training and support provided by the main study team. The HADS score completed as part of the baseline assessments will inform the clinician as to whether or not the participant needs mental health support, and if so they will be signposted to either their GP or local mental health services. The programme PPI/E panel was specifically involved in discussions and vote on potential formats and delivery options for these sessions during the PPI/E discussion groups.

The sessions also offer the opportunity to learn about the face to face SME sessions and digital programme, allow for physical activity risk stratification, and reflect on the programme and signpost to services. Virtual consultations using remote technology to manage conditions is becoming the new norm in clinical care. To reduce treatment burden for patients, particularly in vulnerable groups, these sessions will be offered as face to face or video/phone consultations.

SME group sessions

These sessions build on previous SME research and provide a secure, non-judgmental environment whereby people with T2D and current/previous DFUD can discuss how well or not so well things are going, try seated arm-based exercises, and engage with peers. The aim is to facilitate peer support and increase self-efficacy. SME sessions include a tailored physical activity session followed by an education component, held within a hospital or suitable community venue, and will include the following topics (among others):

- Increase knowledge about T2D, foot ulcers and high CVD risk
- Improve risk factor control (medication adherence, smoking, cholesterol, blood pressure, weight, wellbeing)
- Explore diet and weight management

- Explore physical activity benefits and provide guidance on suitable home-based exercises
- Emotional management (e.g. mindfulness techniques, resilience)
- Goal setting

Based on our background work and PPI/E feedback, the SME will comprise seven weekly sessions lasting 2 hours, and 9 booster sessions, each lasting 1.5hours. The weekly sessions will be face to face to allow supervision of physical activity. The physical activity component will be tailored according to ability and health status, consisting of seated and standing options for light-moderate physical activity, and strength and balance to encourage adherence towards the Physical Activity guidelines (39) where possible given potential physical function and limitations. There will be 8 monthly booster sessions after the weekly programme has ended and a further booster session at approximately 18 months to review and refine participant's goals. These boosters will continue to consist of education and physical activity components and aim to be alternatively delivered face to face and virtually (where possible) to minimise treatment burden whilst also allowing individual tailoring of advice and supervision of physical activity (if for example, health status changes during the study period).

Training package for facilitators

SME sessions will be delivered by trained facilitators, who will have previous experience in long-term conditions and facilitation skills.

Based on our previous SME research and implementation work, a training programme has been developed to train facilitators, at each site involved in intervention delivery. This training package includes components such as:

- Expanding knowledge of T2D, CVD risk and foot ulcers
- Understanding the theories underpinning the SME
- Understanding of seated physical activity and arm-based exercises
- Expanding skills on motivational interviewing
- How to deliver the SME programme

This training package will be delivered by experienced trainers from the LDC.

Input and feedback from the PPI/E panel also contributed to and refined the training package.

The MiFoot MyDesmond digital-based programme

Leicester Diabetes Centre has developed a digital self-management platform for diabetes (MyDesmond; www.MyDesmond.com), which is live on the NHS Apps Library website, and contains three programmes (managing T2D; preventing T2D; managing gestational diabetes). MyDesmond platform is compatible with mobile devices (smartphones, tablets etc.) and personal computers.

Much of the information in the "Type 2 Diabetes" programme of MyDesmond is relevant to people with T2D and DFUD. However, some of it, particularly regarding physical activity and CVD prevention, is not.

With the PPI/E panel, we have therefore designed a digital-based programme, 'MiFoot MyDesmond', for the target population so that participants can re-visit topics covered in the SME programme, have ongoing support, support, access tailored information for their needs and connect with other participants and HCPs. A separate homepage for MiFoot MyDesmond was developed because the current MyDesmond programme for type 2 diabetes focusses on increasing step count, which is unsuitable for the DFUD population.

The MiFoot MyDesmond programme consists of:

- Learning sessions
- Booster sessions
- Example exercises to reinforce the SME physical activity sessions
- Health trackers - self reported blood pressure, weight etc.
- Ask the expert

- Chart Forum
- Buddies

MiFoot Intervention refinement

The MiFoot intervention will be delivered as part of the RCT with user experience feedback surveys given to intervention participants so that the intervention can be iteratively tested and refined up until the major refinement after 9 months of intervention delivery.

The feedback surveys will be given to all intervention participants after the following:

- Completion of their individualised appointment
- 4 weeks into the digital programme (week five of the group sessions since the digital programme is introduced to the group at week one)
- Completion of week 7 of the face-to-face group sessions

Based on this, participants will be asked to complete a total of four feedback surveys: one relating to the individualised appointment, one relating to the digital programme, one relating to the SME sessions, and one relating to the physical activity sessions. If required, an independent researcher (not part of the intervention delivery team) will attend to help participants complete the surveys. All survey responses will be anonymous (no personal identifiable collected on the surveys).

The MiFoot surveys are based on surveys that the Leicester site uses effectively and further adapted and developed with the intervention development team and PPI input. Survey responses will be regularly collated and monitored throughout the intervention delivery. If potential improvements to the intervention are identified then they will be explored further with the PPI input and/or further data will be collected, depending on what is appropriate and feasible. Appropriate changes will then be made to the intervention. We have found with other interventions that required changes are typically minor, given the extensive development work. Refinements will be delivered within the study as soon as they are available.

Although feedback surveys will not consist of any personal identifiable data, they will be kept in a locked drawer in a secure office environment office at the Leicester Diabetes Centre. Once the surveys have been collated and the refinements implemented, the feedback surveys will be destroyed.

Informal verbal feedback will be obtained from the intervention delivery teams through existing communication between sites (e.g. through intervention delivery team mentorship meetings).

7.5.1.2 Control – *Usual care*

Usual care for people with DFUD typically focuses on prevention of re-ulceration, rather than prevention of CVD (although NICE guidelines include glycaemic management, BP and lipid control, direct ulcer treatment or prevention tends to dominate), and varies greatly between centres. Usual practice within each centre will be captured as part of the site recruitment process, and then described within the final programme report. Given the heterogeneity of the clinical care needs of the DFUD population, it is difficult to accurately represent 'routine' usual care in this population for any given patient; this is a key rationale for stratifying by site to ensure that any potential variations in care are balanced across allocation groups.

7.6 Follow-up assessments

Follow up will last for 24 months after baseline visit. Participants are not required to attend on site for any of the follow-up visits at 12- and 24-months. Follow-up data will be collected remotely from relevant routine medical records via data extraction and by an online/postal questionnaire and accelerometers. Data extraction will be used to reduce participant burden, maximise existing data, and eliminate possible noncompliance with study visits in the control group.

Collection/measurement period is defined as existing records within the measurement periods (baseline to month 12 and month 12 to month 24).

7.6.1 Questionnaires

Participants will be asked to complete the following questionnaires at month 12 and 24 (±4 weeks):

- QoL: generic EQ-5D-5L
- Depression and anxiety (HADS)
- Health resource use, such as primary care/emergency department visits, hospitalisations and medication use (ModRUM)
- QoL: DFUD (DFS-SF)
- Self-efficacy (DMSES-15)
- Distress (PAID-20)
- Medication adherence (Morisky)
- Diet (short-form food frequency questionnaire)

A link to the web-based follow-up questionnaires will be provided by email. For those who prefer paper, copies will be posted. The paper-based questionnaire will include a pre-paid envelope so that it can be easily returned to the Lead centre. If the participant's follow-up questionnaires have not been received two weeks after the due date, the research team will contact the participant to remind them to complete these online or on paper and to find out whether they need any assistance. Multiple attempts will be made within the determined window (± 4 weeks).

7.6.2 Accelerometer

Participants will be sent an accelerometer in the post to be worn in the same way as for the baseline visit, and again returned in a pre-paid envelope. If the participant's accelerometer has not been received two weeks after the due date, the research team will contact the participant to remind them to return the device. Multiple attempts will be made within the determined window (± 4 weeks) or until resolution.

7.6.3 Continuous Glucose Monitor

Participants who consent to use the optional CGM systems will be provided with a starter pack with 2 sensors. If they decide to continue using the sensors, we will send them sensors regularly (i.e., every 3 months). They will be set up in a bespoke "libre-view" clinic using their study ID details. This will allow data to be downloaded remotely.

7.6.4 Routine health data

Patient data will be collected from relevant routine medical records at month 12 and month 24. Where relevant blood test results (listed in section 7.4.4) are not available or are significantly out of date (>6 months), patients will be contacted to prompt them to see their GP to request that these blood tests be completed in line with good clinical practice. Participants will be contacted by telephone, and if not available one additional follow-up call will be made. It will be beyond the scope of this project to check if these blood tests have been completed and this data will not be extracted by the research team for the purposes of trial data.

7.6.5 Health outcomes

Health outcomes will be collected from relevant routine medical records at month 12 and month 24. Follow up data will include: renal endpoints: end-stage kidney disease (defined as dialysis, transplantation, or a sustained eGFR of <15 ml/minute/1.73m2), doubling of the serum creatinine level, or death from renal causes, individual components of the Extended MACE composite: myocardial infarction, stroke, cardiovascular death, peripheral arterial bypass, coronary artery bypass, coronary angioplasty, peripheral artery angioplasty; all-cause mortality, lower-limb major amputation, self-reported re-ulceration.

7.6.6 Safety measures

Follow up data will be obtained from the medical records and self-reported by participants and provided to the research team for the period of 24 months after the baseline visit, this will include: myocardial infarction, stroke, cardiovascular death, peripheral arterial bypass, coronary artery bypass, coronary angioplasty, or peripheral artery angioplasty).

7.6.7 Unscheduled contact

Participants will be advised that they may be contacted throughout the 24 month-follow-up period should any issues arise.

Should the research team be unable to contact a participant throughout the 24 month-follow-up period (lost to follow up) or for any reason a participant has not completed questionnaires/returned accelerometer (non-attendance), the research team will ask that we are able to access data from existing health records (hospital, GP), where study visit data may exist in lieu of completion of the study Follow up visits. Participants will be given the option to opt in or out of this on the consent form.

When the 24-month questionnaire and accelerometer are returned, a letter and or email (as per participant preference) will be sent to the participant thanking them for taking part in the study. Regardless of the method of communication, the content of the thank you correspondence will be the same.

7.7 Post-trial follow-up assessments

No post intervention follow-up is currently planned, but we will seek consent for long-term follow-up via electronic health records.

7.8 Process evaluation

Table 3: Summary of Process evaluation dimensions, data collected, time-point collected

Process evaluation				
Implementation	**Element assessed**	**Data source**	**Team responsible**	**Time-point collected**
Reach	The number of intended audience that participate in the intervention (i.e. number proportion, representativeness of individuals willing to participate in intervention, proportion of participants in the intervention group who participated in the study)	-Study records (participation rate, drop out rate) -Questionnaires with intervention participants	Study Team	Baseline 12months 24months 24months
Effectiveness	How do we know our intervention is effective, e.g., impact and efficacy of MiFoot on important outcomes, including potential negative effects, QoL, and economic outcomes	- Participant related outcome questionnaires - Interviews with delivery intervention team and participants	Psychology / Study Teams	Baseline 12months 24months 24months
Fidelity (training, delivery, participant receipt)	The extent to which the intervention was delivered as planned	-Observations -Interviews with delivery intervention team and participants	IMPACT/ Psychology Teams	During the intervention delivery period 24months

Implementation	Element assessed	Data source	Team responsible	Time-point collected
Adoption	How do we develop organisational support to deliver our intervention, e.g., number, proportion, and representativeness of the settings and intervention agents (implementation team) willing to initiate MiFoot	Interviews with delivery intervention team	Psychology Team	24months
Implementation	Factors external to the intervention, which may influence intervention implementation	-Interviews with intervention delivery team and participants -Observations -Records	Psychology/ IMPACT Teams	24months During the intervention delivery period Baseline 12months 24months
Implementation	Consistency of delivery as intended; and the time and cost of the intervention	Records	Health Economy/ Study Teams	
Maintenance	The extent to which a program or policy becomes institutionalised or part of organisational practices and policies	Interviews with delivery intervention team and participants	Psychology Team	24months

7.8.1 Qualitative study for the process evaluation

One-to-one in-depth interviews (face to face for Leicester site only, for other participating sites either via telephone, video call depending on convenience and participant preference) will be conducted with intervention-arm participants who have reached the 24-month follow-up point of the main RCT (to explore individual experiences), and the intervention delivery team (to explore barriers/facilitators to intervention delivery and implementation).

7.8.1.1 Participants

Intervention-arm participants who have attended a minimum of 1 session and reached the 24-month follow-up point of the main RCT, and HCPs/Facilitators involved in intervention delivery. Participants will be recruited from all sites participating in the main RCT.

7.8.1.2 Consent procedures

Patient participants will be identified and recruited as described for the main study (see section 7.2). A separate consent process will not be undertaken, to reduce participant burden, but participants will be made aware that they may not be asked to take part in the interviews and will have the ability to opt-out of this component if they wish.

Eligible HCPs/Facilitators will be approached by the qualitative research team and invited to take part in a semi-structured interview. Those interested in taking part will be provided with an information sheet. When a participant has indicated willingness to be interviewed, the researcher will arrange a convenient time and location to obtain written informed consent. Where possible and acceptable to the participant we will obtain written informed consent on the same day. A participant information sheet and consent for HCPs/Facilitators will be submitted as a planned amendment during the progress of the study.

The researcher will have received appropriate training In obtaining consent and have been delegated this task by the PI. Before proceeding, they will check that the interviewee has understood the information and has had opportunity to ask questions.

For participants already taking part in the study prior to the addition of the optional IF component, additional consent will be sought. To reduce participant burden, additional consent may be conducted face-to-face or remotely via telephone and/or video visits. The method of participant: study personnel interaction will be recorded at the visit. An addendum consent form will be used.

7.8.1.3 Interview procedures

The interviews will be conducted by a suitably qualified and experienced Qualitative Researcher who have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the study.

7.8.2. Quantitative elements of the process evaluation (study logs, observations and questionnaires)

The quantitative element of the process evaluation embedded within the MiFoot RCT will investigate processes related to the delivery of the intervention. The main aims will be:

- To assess the number of the intended audience that participated in the intervention
- To assess the impact of the intervention
- To assess the delivery of the intervention
- To assess implementation of the intervention
- To assess participants' responses and interactions with the intervention

The fidelity of the MiFoot sessions will be observed and measured using structured, quantitative observation tools (checklist and coding manual) to further explore intervention delivery, including, HCP

and facilitators' behaviours, key components of the programme (content and key messages) and behaviour change techniques. The content of these tools will be informed by the content of behavioural guidance for facilitators, intervention training package, , and resources and materials - detailed in section 7.8.2.1 below.

Participant receipt will be investigated using programme-specific, self-report process evaluation questionnaires, containing a mix of multiple-choice and Likert scaling questions. Opportunity for free text responses will also be included. To ensure these questionnaires accurately reflect the final MiFoot intervention, they will be developed after the refined version of MiFoot is in use and therefore will be submitted for regulatory approval as a planned amendment to the study. Data collection will be via the postal/online questionnaire completed by participants at the 24-month follow up timepoint.

Data from questionnaires, data logs and the observation tool will be analysed using simple descriptive analyses, e.g. counts (percentage) or means (standard deviation).

7.8.2.1 Intervention Fidelity

The fidelity of the MiFoot sessions will be observed and measured using structured, quantitative observation tools (checklist and coding manual). The quality of the delivery will be observed by marking key indicators as either; present, absent, attempted or not applicable. Key indicators will include (but are not limited to); application of content use of resources, facilitator behaviours, facilitation skills, and behaviour change techniques facilitated during the session .

Observers trained in the use of the MiFoot intervention fidelity tools will then observe subsequent cohort sessions by either attending in-person, for a direct observation; or through a remote observation. Remote observations will be conducted via recording or live stream; which participants will have been informed of, and consented to, during their baselineor re-consent visit.
A sample of each component will be observed across the five initial confirmed sites (as follows):

- Individualised appointments -10% of individualised appointments will be observed (~19 observations)
- Core SME and physical activity sessions – each of the seven weekly SME/physical activity sessions will be observed at least twice (a total of fourteen core sessions)
- Booster sessions – four of the eight monthly booster sessions will be observed, ensuring a mix of both virtual and face to face deliveries are observed
- Final booster session – this will be observed twice

These observations will be undertaken by 1 or 2 trained observers, with a third observer available if there are discrepancies to resolve. inter-rater reliability will be measured using Cohen's Kappa or percentage agreement; when inter-rater reliability is established, observations may continue with a single observer.

7.8.3 RE-AIM framework

The mixed-methods data collected for the process evaluation (described in sections 5.2.1 and 5.2.2) will then be considered, along with the RCT data (section 5.1) and health economics data (section 5.3), to examine how the intervention was delivered and received to explain study findings, and plan for sustainable implementation in a real-world setting. The mixed-methods data will be evaluated for each of the following framework indicators: Reach; Effectiveness; Adoption; Implementation, and Maintenance (RE-AIM) - detailed in the table below. We will also measure intervention fidelity, by assessing training, delivery, and patient receipt through mixed methodology (explained above).

Table 4. RE-AIM

RE-AIM Indicators	Detail
Reach	How do we reach the targeted population, e.g., number, proportion, and representativeness of individuals willing to participate in intervention
Effectiveness	How do we know our intervention is effective, e.g., impact and efficacy of MiFoot on important outcomes, including potential negative effects, QoL, and economic outcomes
Adoption	How do we develop organisational support to deliver our intervention, e.g., number, proportion, and representativeness of settings and intervention agents willing to initiate MiFoot
Implementation	How do we ensure the intervention is delivered properly, e.g., intervention fidelity, trained facilitators can deliver sessions, any observed implementation barriers Exploration of implementation barriers, including implementation within the NHS?
Maintenance	What is the potential cost and sustainability of the intervention in practice, e.g., quantity of intervention received (face to face sessions attended/digital programme sessions completed)

7.9 Trial implementation measures

Objectives:

1. Assess uptake and retention to the MiFoot randomised controlled trial
2. Assess compliance with the research-related visits and completion of outcome assessments

Methods:

To assess uptake and retention to the MiFoot RCT, data (including number of participants screened, approached and consented, as well as anonymous participant demographics) will be extracted from the study screening and enrolment logs. Similarly, compliance with the research visits and the outcome assessments (questionnaires and accelerometers) will be assessed using study management and intervention delivery logs.

7.10 Withdrawal criteria

Withdrawal from trial

Participants may withdraw from (a) complying with the allocated study treatment and/or (b) providing data to the study, at any time for any reason without affecting their usual care. Participants in the intervention group who wish to revert to usual care will be asked if they are willing to continue to provide outcome data, which will be included in the analysis. Withdrawals from the study will be recorded in the e-CRF and medical records. Participants will be sent a letter thanking them for their participation and informing them that we would like to continue collecting information about their health from NHS, hospital and GP records, if they do not want this to happen, they can inform us, and we will stop. Additionally, we will emphasise that their usual care will not be affected by their withdrawal from this study and that they will return to usual care. Furthermore, they will be informed that the data collected up to the time point they withdrew will be included in the study analysis and that they will not be contacted again with regards to this study. Participants who have withdrawn but consented to be part of the long-term follow up will be given the option to remain in the long-term follow up.

The Investigators may withdraw a participant or stakeholder if they consider it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at recruitment)
- Significant protocol deviation
- Lost to follow up
- Loss of capacity

For participants who fail to return to the site or return questionnaires/accelerometers, the research team should make reasonable effort to re-contact the participants (e.g., contacting participant's GP, reviewing available registries or health care databases) and to determine their health status, including at least their vital status. Participants may be contacted until the resolution of retrieval of the accelerometer by a number of methods (including phone, letter, email or text-message). Attempts to contact such participants must be documented on the study trackers participant's records (e.g., times and dates of attempted telephone contact, copy of an email, text-message or a letter).

Discontinuation of intervention

Inability to participate in any specific element of the intervention (e.g., the exercise element due to contraindications, or the digital element due to lack of digital access) will not preclude inclusion in the study or the rest of the intervention to represent the real-world situation. We plan to collect data concerning this as part of the process evaluation.

All efforts should be made to document the reasons for intervention discontinuation, and this should be documented in the e-CRF.

7.11 Assessment and management of risk

Risk to participants

All study procedures including risks involved will be explained clearly to the participant in the Participant Information Sheet and at Baseline and subsequently before each procedure is performed.

Although there are many benefits of physical activity, it can pose some risks. For example, participants may experience delayed onset muscle soreness. Physical activity carried out as part of MiFoot will be light-moderate, which can equate to walking upstairs or completing housework; therefore, the participant's risk should not be increased over and above their usual day to day activities. However, to reduce risk, all participants will be assessed at the individualised appointment before physical activity commences and any appropriate adaptations suggested. Participants will also be screened briefly prior to commencing the weekly group sessions and will be monitored throughout the session and for a period of 15 mins afterwards, by trained facilitators using a combination of heart rate, observation, RPE and any reported symptoms from the participant. The overall care and comfort of the participant will be considered paramount at all times during the study.

Risk to staff

There are no anticipated risks to staff.

7.12 End of trial

The end of trial is the date of when all data has been collected, analysed and final report have been submitted to NIHR.

8. Storage and analysis of clinical samples

No samples will be taken as part of this study.

9. Recording and reporting of SAEs

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study, whether or not considered related to the study.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above. Detailed guidance can be found here: http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

9.2 Expected Adverse Events and Serious Adverse Events

Due to the study population age group and morbidities, the following events could be expected to occur during this study and will not be collected and reported to the sponsor as an AE/SAE unless it is deemed to be related to the study procedures:

- Hypoglycemia
- Amputation
- Falls
- Musculoskeletal injury
- Diabetic Ketoacidosis (DKA)
- Acute kidney injury (AKI)
- Elective or planned routine surgery for ongoing conditions that were present at the start of the study
- Outpatient appointments or treatments for ongoing conditions that were present at the start of the study

- Age related conditions such as cancer where the event is not directly linked to the study objective to increase physical activity
- Foreseeable and predefined SAEs, including terminal illness
- Congenital anomalies or birth defects
- Any life-threatening medical occurrence that is not related to the study procedures or participation in this study

The following Safety measures will be captured as main outcomes and therefore not reported to the sponsor as a SAE:

- Myocardial infarction
- Stroke
- Cardiovascular death
- Peripheral arterial bypass
- Coronary artery bypass
- Coronary angioplasty
- Peripheral artery angioplasty

The expected events listed above will therefore not be subject to expedited reporting to the Sponsor. Whether or not Serious Adverse Events are reasonably related to the study procedures will be judged by a medically trained delegated study team member (e.g., PI of the study) and if deemed related these will be reported to the Sponsor.

Structured exercise training

The adverse events associated with structured exercise training that are expected for safety reporting purposes are fainting (excluding pre-emptive feelings of faintness which are relieved through appropriate treatment), hypoglycaemia, and musculoskeletal injury. Blood glucose and blood pressure monitors and pulse oximeters will be available for use during structured exercise sessions for safety monitoring purposes.

Participants will be closely monitored during supervised sessions, and the exercise intervention will be progressive, starting with an appropriately low volume and intensity to avoid excessive risk. Participants will be instructed to contact the study team at the earliest opportunity (they will have contact details to telephone) to report AEs occurring during unsupervised sessions.

Any Serious Adverse Events that are deemed to be related to the study procedures by medically trained person (e.g., PI of the study) will be reported to the Sponsor.

9.3 Reporting procedures for All Adverse Events and Serious Adverse Events

All AEs/SAEs occurring during the study that are deemed to be related to the study procedures by medically trained person (e.g., PI of the study) or reported by the participant, attributed to study, will be recorded on the e-CRF.

The information must be recorded as described in section 9.4. Follow-up information should be provided as necessary.

AEs/SAEs considered related to the study as judged by a medically qualified investigator will be followed until resolution or the event is considered stable. All related AEs/SAEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE/SAE is of sufficient severity to require the participant's removal from the physical activity/exercise part of the intervention. A participant

may also voluntarily withdraw from the physical activity/exercise part of the intervention due to what he or she perceives as an intolerable AE/SAE. If either of these occurs, the participant must undergo an end of physical activity/exercise assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

The relationship of AEs/SAEs to the study will be assessed and signed off by a medically qualified person (e.g., PI of the study).

Adverse Events will be recorded on e-CRF and periodically discussed by the study Steering Group Committee and Data Safety and Monitoring Committee as required. Any safety concerns arising from the team will be reported to the Sponsor as soon as possible.

9.4 Reporting Procedures for Serious Adverse Events

All SAEs except those identified as expected within section 9.2 occurring from the time of **written informed consent at** baseline visit until month 24 must be reported to the Sponsor immediately and within 24 hours of becoming aware of the event. The SAE will be reported using appropriate forms and according to the Sponsor SOP for reporting serious adverse events. Additional information will be provided if requested to the Sponsor and main Research Ethics Committee (REC). The Principal Investigator or another delegated physician (as agreed by the Sponsor) is responsible for the review and sign off of the SAE and the assessment of causality (e.g., whether an event is related to a study procedure or intervention).

The Sponsor will perform an initial check of the information and ensure that the SAE line listing is reviewed by the Director of Research & Innovation. All SAE information must be recorded on an SAE form and sent to the Sponsor. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form and sent to the Sponsor.

Copies of all documentation and correspondence relating to SAEs will be stored in the TMF and / or ISF

For each **SAE*** 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
- relationship to the study procedure or intervention

Any change of condition or other follow-up information should be emailed to the Sponsor 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 resolved or a final outcome has been reached.

The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, the CI shall submit once a year throughout the study or on request an Annual Report to the Ethics Committee which lists all SAEs / SUSARs that have occurred during the preceding 12 months.

9.5 Responsibilities

Trial Steering Committee (TSC):

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

Data Monitoring and Safety Committee (DMSC):

In accordance with the Trial Terms of Reference for the DMSC, periodically reviewing 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.

9.6 Reporting urgent safety measures

Not applicable

10 STATISTICS AND DATA ANALYSIS

A statistical analysis plan (SAP) will be written by the trial statistician with oversight from the lead statistician (Gray). It will be finalised and signed off by the CI, lead statistician and Programme Steering Committee (PSC) chair and DMSC prior to the database lock. Any deviations from the statistical analysis plan will be explained and justified in the final report and resulting publications. The SAP will not cover the internal feasibility study. Therefore, a brief description of the proposed analysis strategy is given below.

10.1 Sample size calculation

392 participants will be recruited. This is based on detecting a 20% improvement in the survival rate for Extended MACE (i.e. time without Extended MACE; a much smaller reduction than a similar intervention in another high risk T2D population (33)) at 2 years from 65.6% (i.e. 34.4% experience an Extended MACE event) to 78.7% (i.e. 21.3% experience an Extended MACE event). The 65.6% rate in the control arm at 2 years was extrapolated from two of our studies in this population (16, 43) which had 12% event rate by 6 months; this was reduced to 10% as a conservative estimate and it was assumed that the event rate is constant over the 2 years. These numbers, and assuming 80% power and 5% alpha, gives a required sample size of 372 participants. This increases to 392 to be recruited to allow for 5% drop-out (low because primary outcome collected by data linkage; similar to another of our studies (44).

10.2 Planned recruitment rate

A 12-month recruitment period gives a recruitment rate of <1 participant/week/site (approximately 10 sites).

10.3 Statistical analysis plan

Summary measures (e.g., change from baseline, number of events) by treatment group, effect size, 95% confidence interval and two-sided p-value will be presented for the primary and for the key secondary outcomes. To limit issues of multiple testing, a descriptive analysis will be undertaken for other secondary outcomes. Statistical significance will be assessed at the 5% level. The amount of missing data will be presented for each endpoint.

10.3.1 Summary of baseline data and flow of patients

A CONSORT diagram showing the flow of participants through the study will be produced. Baseline demographics will be summarised by treatment group and for the total population using number (percentage) for categorical variables and mean (standard deviation) for continuous variables (unless they are found to be skewed in which case median and interquartile range will be presented).

10.3.2 Primary outcome analysis

The primary analysis will compare the primary outcome (Extended MACE) between treatment groups using a Cox proportional hazards regression model. The model will be fitted with Extended MACE as the outcome and treatment group as the main explanatory variable. The stratification factors (site, age,sex) will be adjusted for, and participants lost to follow-up will be censored at the last date at which they were known to be event free. Therefore, by definition, the primary analyses will use the intention-to-treat population because the covariates will be known for all and missing data for the outcome will result in censoring. The assumptions required for the proportional hazards model will be assessed, primarily through graphical methods. If the assumptions are not met, then another appropriate model will be selected.

10.3.3 Secondary outcome analysis

Key secondary outcomes will be compared between the treatment groups using the intention to- treat population to align with the primary analysis. For the event outcomes, the analysis approach will be a Cox proportional hazards model adjusted for the stratification factors in line with the primary outcome analysis. Continuous priority secondary outcomes will be compared between treatment groups using linear regression (or another suitable model if model assumptions are not met) adjusted for the stratification factors and with separate models for the 12- and 24-month follow-ups. Missing data will imputed using multiple imputation. No corrections for multiple testing will be made, and P values and 95% confidence intervals are presented for priority secondary outcomes only. Priority secondary outcomes will be defined in the SAP, prior to analysis. For all other secondary outcomes, only descriptive analyses with no statistical testing will be performed: continuous data that are approximately normally distributed will be summarised as means and standard deviations, and skewed data with medians and interquartile ranges. Ordinal and categorical data will be summarised using frequency counts and percentages.

Listings of AEs/SAEs will be produced sorted by treatment group, date, and participant ID. AEs/SAEs will also be summarised by treatment group, if appropriate.

10.4 Subgroup analyses

Sub-group analyses will be pre-specified in a trial-specific statistical analysis plan and will likely include but not be limited to age, sex, ethnicity, deprivation, co-morbidities, blood glucose levels, depending on data availability and quality.

10.5 Adjusted analysis

Secondary analyses of the primary outcome will 1) estimate the complier average causal effect (CACE) using the complier population to estimate the impact of the intervention in the participants who comply with their assigned treatment, and 2) use a competing risks approach with non-CVD death as the competing risk.

10.6 Interim analysis and criteria for the premature termination of the trial

The internal feasibility study will happen over the first 3 months of the trial. The criteria for continuation is based on the number of participants recruited at this time. The criteria for continuation without further actions is a minimum of 78 participants (20% of expected recruitment target to allow for a slower start). There will be no further analysis conducted at this time point.

The DMSC will be provided with unblinded summary data at each meeting, main outcomes and safety measures will be provided by arm. No formal interim analyses will be conducted unless specifically requested by the DMSC. There are no pre-specified stopping guidelines for the main trial.

10.7 Participant population

All analyses will analyse participants in the group to which they were randomised and will be fully defined in the statistical analysis plan.

10.8 Procedure(s) to account for missing or spurious data

Missing data will be imputed using multiple imputation. Sensitivity analysis which analyses data on a complete case basis will also be undertaken.

10.9 Other statistical considerations

Accelerometer data analysis

Analysis will include sleep duration and quality, overall physical activity volume and intensity profile, along with time spent sedentary, in light-intensity physical activity and in MVPA. This will be coordinated by the Lifestyle theme of the NIHR Leicester BRC.

The MiFoot programme back-end data analysis

Back-end website data on the extent of user engagement (group reports) will be collected. Analysis will include the registration details, user activity (anonymised e.g., length of time for which individual pages were viewed and the number of occasions etc.) and google analytics (page views, device used, browser, operating system).

10.10 Process evaluation

10.10.1 Qualitative

The aim of the qualitative study is to explore barriers/facilitators to intervention implementation and participant experience and satisfaction. One-to-one in-depth interviews (either via telephone, video call or face to face depending on convenience and participant preference) will be conducted with intervention group participants who have reached the 24-month follow-up point of the main RCT (to explore individual experiences), and staff involved in intervention delivery (including but not limited to physiotherapists, HCPs, SME facilitators etc).

Sampling

We anticipate that approximately 10 sites will take part in the qualitative study, with approximately 3-4 participants per site. Therefore, a total of approximately 40 participants will take part, including those delivering and receiving the intervention. The total numbers for the qualitative study will depend on the analysis progress and availability of participants. We aim to recruit patient participants and staff involved in the intervention delivery. Information power will be applied, thus the final sample size will be determined by meeting the components of the information power approach (Malterud, 2006).

Qualitative analysis

The audio files of the interviews will be transcribed verbatim by an external transcription company. A Transcription Agreement will be signed between the transcription company and the University of Leicester. Data will be organised using NVivo (QSR International) software. The qualitative research team will analyse the data using reflexive thematic analysis. The qualitative team have experience mapping findings to an implementation/behavioural framework. This will be decided once the qualitative team familiarise themselves with the data.

10.10.2 Quantitative

Data from questionnaires and the structured observation tool will be analysed using descriptive statistics. We will also analyse trial management logs and electronic case report forms to attendance/compliance with the 1-to-1 sessions, SME sessions, and the digital programme. Number (percentage) will be used for categorical variables and mean (standard deviation) for normally distributed continuous variables. Skewed data will be reported using medians and interquartile ranges. Interim analysis will be conducted after half of the participants have completed their 12-month visit, and the findings may be used to refine intervention delivery.

10.10.3 Trial implementation measures

Number (percentage) will be used for categorical variables and mean (standard deviation) for normally distributed continuous variables. Skewed data will be reported using medians and interquartile ranges.

10.11 Economic evaluation

A full health economic analysis plan will be drafted, reviewed, and signed off before cost-effectiveness analyses commences. We will conduct two health economic analyses. We will do an analysis of resource use data collected within the trial and a long-term economic modelling analysis.

Within-trial cost-effectiveness analyses will be conducted for all study outcomes unless the intervention proves unfeasible or harmful (reported as cost/QALY, and cost per unit change/event reduction). Cost-utility analysis will be conducted using preference-based health utility scores from EQ-5D-5L. Within-trial discounted cost and discounted QALYs measured using EQ-5D-5L will be analysed using a "seemingly unrelated regression" model. Intention-to-treat (ITT) analyses will be used as with the main trial analyses, with baseline costs, baseline utility, and stratification factors as covariates, and multiple imputation using the chained equations approach will be used to impute missing data.97 This method assumes data is missing at random and creates multiple predictions for each missing value, thereby allowing for uncertainty to be accounted for. A sensitivity analysis will be used with complete cases.

Model based analysis

We will develop a new health economic model to examine the effects of MiFoot versus usual care. This model will be based on our existing health economic model, the School for Public Health Research Type 2 Diabetes Treatment Model (SPHR-T2DMT). In particular, we plan on updating SPHR-T2DMT to reflect the epidemiology risk equations developed in earlier stages of the MiFoot programme grant and to include the treatment effects estimated from the trial data. We envisage that the updated model will still be an individual level simulation in line with other models of diabetes, and as such the characteristics of simulated patients will come from the MiFoot trial baseline population. We will simulate two cohorts, one cohort who receives the MiFoot intervention and another who does not.

We will estimate the duration of sustained effect using the differences between the 12- and 24-month RCT follow-ups, and the clinical plausibility of different methods of extrapolating this benefit assessed with topic experts.

Health Economic results

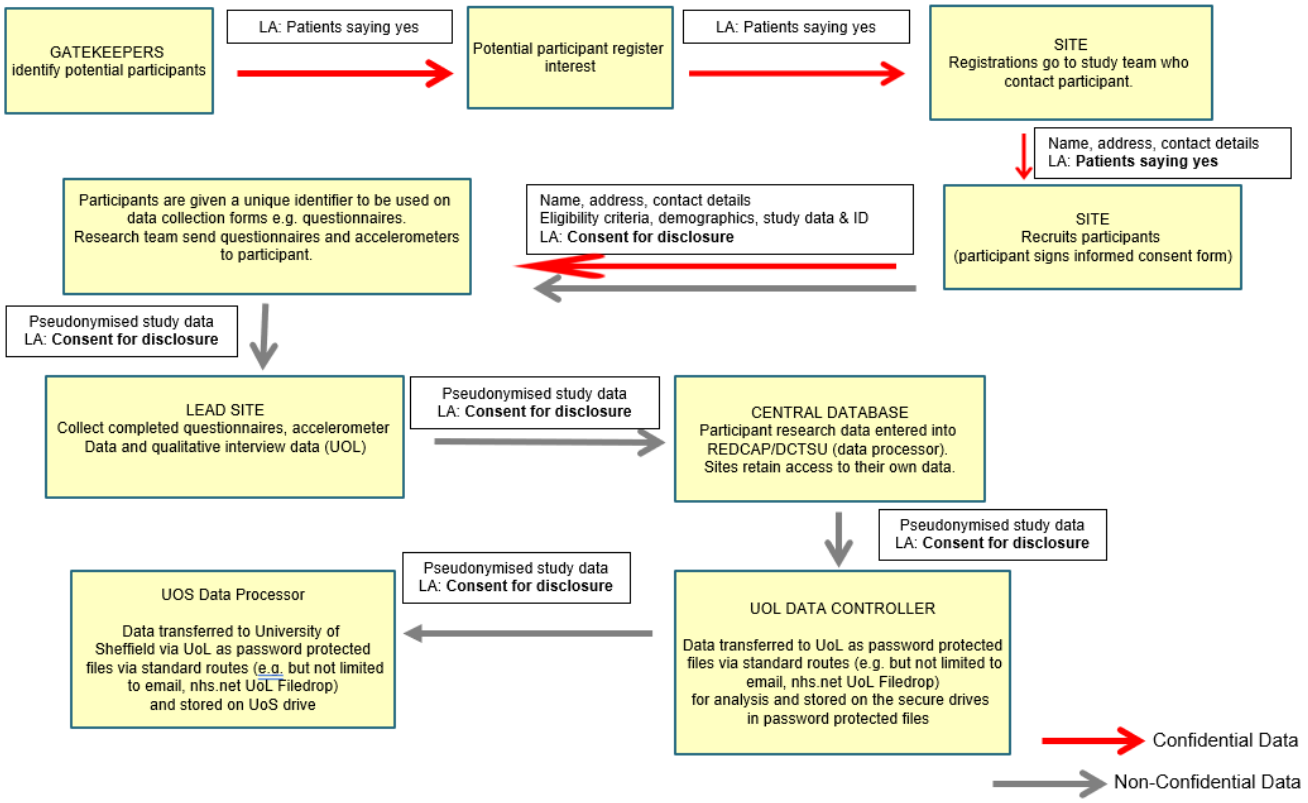
The key health economic outcome in both analyses will be incremental cost per QALY gained by MiFoot versus usual care, incorporating discounting and a full probabilistic sensitivity analysis. We will take a lifetime horizon and an NHS and personal social services perspective.

11. DATA MANAGEMENT

Data Flow Diagram

The sponsor (University of Leicester) is the data controller. Gatekeepers will identify and NHS sites will recruit participants. Data will be collected by the sites and entered into the central database. Sites will have visibility and access to their own data but no other data on the eCRF. The pseudonymised data from the accelerometers will be downloaded on each visit and added to the central database.

Pseudonymised data will be shared with the University of Leicester and University of Sheffield or approved delegate for analysis.



11.1 Data collection tools and source document identification

Electronic Case Report Forms (e-CRF) are the primary data collection instruments and treated as source data. All data requested in the e-CRF will be recorded. All data specified as required in the Data Validation Plan which is missing will be explained via data query.

Data capture will be via a web-based, fully validated system, compliant with 21 CRF Part 11; Electronic records; Electronic signatures and EU Commission Directive 2005/28/EC with comprehensive audit trials.

Each enrolled participant will be allocated a unique study ID at screening to reduce the risk of identification from data stored in the e-CRFs or other electronic systems.

A copy of the patient consent form and information sheet will be placed in the hospital notes of all participants and in the Investigator Site File and Trial Master File. A sticker will be placed on the cover of the notes (or inside cover) detailing the trial title, contact details of the PI and the fact that the notes should not be destroyed. All study visits and AEs/SAEs will be recorded in the hospital notes.

In case of multiple records for a certain data or duplication of collected data, the data collected via RDE would take precedence over data collected via other means i.e. self-reported. Study statistician or health economist will review and de-duplicate datasets.

Research Data Extractions (RDEs)

Data extraction will be used to reduce participant burden, maximise existing data, and eliminate possible noncompliance with study visits in the control group. RDEs are data collection instruments and treated as source data. Patient data will be collected via extraction from relevant routine medical records at following time points: baseline, month 12 and month 24. Timepoints for data extraction will be defined as:

- Month 0 is defined as month of participant baseline visit. RDE to take place from date of baseline visit.
- Baseline timepoint as month 0 (data collected is all existing data prior and inclusive the baseline date)
- Month 12 timepoint (data collected for months 1-12 inclusive)
- Month 24 timepoint (data collected for months 13-24 inclusive)

Variables collected are outlined in section 7.4.4.

Data extractions can be performed using different methods. Programme's oversight team will regularly review the contemporary options available for data extraction.

- NHS Digital
- 3rd party agencies
- Manual – there is also sufficient capacity within the programme's research team, with support from core-funded staff, to manually extract the data directly from hospital/GP systems.

Standardised, rigorous searches will be used to identify patients accurately. Pseudonymisation or anonymisation of data can also be provided. Informed consent will be required for the data extraction element of the study.

We have included sufficient statistician and data management time to link the extracted data with the participant's baseline and questionnaire data. Finally, to test and finalise our data extraction procedures, we have included two data extraction points prior to the final data extraction. This will allow administrative coding and data cleaning procedures to be put in place, which will help to ensure the timeliness of the final data extraction.

RDE files will be pseudonymised prior to transfer to the Lead site for analysis. We intend to use a secure transfer service to transfer data securely. The flow of patient data is shown in Data Flow Diagram (section 11).

Accelerometer data

Accelerometers will be used as data collection instruments and treated as source data, and will record raw movement data in milligravitational units (m*g*), which will be processed to assess sleep duration/quality and physical activity volume/intensity measured objectively using wrist worn accelerometers. This will be coordinated by the Lifestyle theme of the NIHR Leicester BRC.

Wrist-worn accelerometers are suitable for measuring habitual ambulation, as well as arm-based exercise. Participants will be asked to wear the accelerometer at following time points: baseline, month 12 and month 24 as described in section 7.

Continuous Glucose Monitoring Data

The FreeStyle Libre 2 CGM System will be used as a data collection instrument and treated as source data and will record blood glucose levels in mmol/L.

Questionnaires

Questionnaires are data collection instruments and treated as source data, whether paper or electronic (via REDCap) depending on participant preference. Participants will be asked to complete the questionnaires at following time points: baseline, month 12 and month 24 as described in section 7.

Health Economics Tracker

A tracker capturing the cost of staff time and training, consumable and room costs for any education components will be maintained, and we will use patient self-reported medications to capture any increase in uptake of medications in the intervention group.

Source Documents

Source documents are where data are first recorded, and from which participants' CRF data are obtained. This protocol allows data to be entered directly onto the electronic Case Report Forms (e-CRF), as such the e-CRF would be considered a source document. When the e-CRF is then transmitted to the sponsor, it is necessary for the study site to retain a copy to ensure that the PI has an independent account from the sponsor as to what has occurred during the study at their site.

Self-reported data including paper questionnaires and questionnaires entered onto REDCap by participants will be considered source data.

The FreeStyle Libre 2 CGM System will be considered as source data.
Study trackers and logs, transcriptions of audio files and notes taken during the intervention observation will be considered source data if these are the site of the original recording.

11.2 Data handling and record keeping

All data handling and record keeping will be kept in adherence to the organisational policies of the organisation responsible for that study data as specified in the following section (i.e. University of Leicester's, Derby Clinical Trials Support Unit and study sites - NHS Organisation(s) policies. Participants will be allocated a unique study ID number which will be used on all hard and electronic copies of research documentation and data collected from the point of consent onwards.

All study documentation containing identifiable patient data will be managed in accordance with ICH-GCP, the UK Policy Framework for Health and Social Care Research and the Data Protection Act (or its subsequent legislation) and made available for inspection, monitoring or audit purposes by the Sponsor, host, regulatory authorities or the funder.

Information will only be obtained from the participant if necessary for the study.

The contacts database (which contains participant contact details) will be held separately from the study database. This will be password protected and managed at site by the research team. Contact details will be passed onto the Lead site to allow for posting of questionnaires and accelerometers.

All electronic data will be stored on secure network drives, apart from that collected in the e-CRF which will be held on Dacima Software's secure servers. Only the relevant study staff will have access, to any study data, which is granted by the IT services or the research team. Network drives are backed up daily by the organisations IM&T departments.

11.2.1 Database

11.2.1.1 Dacima™ Software (DCTSU responsibility)

The Derby CTSU Data Management team will maintain the Electronic Data Capture and the data will be hosted by the EDC supplier according to General Data Protection Regulation guidance. The study database (Dacima™ Software) will be designed to capture the clinical data in accordance with the best principles of clinical data management and the relevant SOPs on Research Electronic System Specification, Selection, Validation and Implementation and Case Report Form and Database Selection, Development & Release and Data Security & Access Control developed by the Derby CTSU.

Data will be entered into the database by site staff. Validation checks will be automatically performed on the data to ensure accuracy and consistency according to the Data Validation Plan. All data queries generated by these checks will be available for resolution by the site online. After data entry is complete, all data queries have been resolved, medical coding is complete and all forms have been signed by the PI, the database will be locked and released for statistical analysis after Investigator sign off.

11.2.1.2 RedCap (UoL responsibility)

The online questionnaire will be built and reproduced using REDCap web application which should run on any PC with a modern browser. For details and documentation about the software, please see: https://www.project-redcap.org.

The application is hosted on a University of Leicester vitual 'LAMP' server. The physical servers are located at the University of Leicester main site. Servers are backed up nightly and the backups are sent to a University of Leicester remote site. Physical access to the servers access is restricted to IT Services and Estate Staff. Access to the Operating System is restricted to the BRC IT and University of Leicester Research Computing Support teams. Servers are monitored and regularly patched for security vulnerabilities. The servers are regularly penetration tested using Nessus. Connections to the server pass through a reverse proxy, that strips out requests and request content which may compromise security. Information on the UoL information governance can be found at https://bit.ly/3fqXxda.

Authentication is provided by the application. Users log in with a username and password. Passwords must be at least 9 characters and must consist of at least one lower-case letter, one upper-case letter, and one number. REDCAP research database will identify participants by their unique identification ID number.

The application is visible to computers on the Internet. All communication between client computers and the application are encrypted using HTTPS.

Upon receipt of the returned paper-based questionnaire, the data will be transcribed into the REDCap database.

Electronic records will be stored on secure drives at the University of Leicester, University Hospitals of Leicester, participating NHS sites and University of Sheffield. Paper records will be stored in locked filing cabinets in offices at the University of Leicester, University Hospitals of Leicester, participating NHS sites and University of Sheffield.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections - in line with participant consent.

Access to the study database will be restricted by role-based permission to authorised study personnel. Users will be suitably trained on the system prior to being granted access. Individual user accounts will be password protected and will not be shared between members of the study team.

11.4 Archiving

Archiving will be authorised by the Sponsor following submission of the final programme report.

All study documents and data will be kept for 6 years, or the minimum determined by the regulatory authorities, whichever is the longer. Archived files will kept in a secure location and storage will comply with the University of Leicester archiving Standard Operating Procedure. Details can be found at: http://www2.le.ac.uk/offices/ias. Destruction of essential documents will require authorisation from the Sponsor.

Please note, we are not able to archive source data or the ISF for participating sites, however we can arrange for the payment for an archiving facility to be used.

Long-term storing will comply with the UoL archiving SOP.

12. MONITORING, AUDIT & INSPECTION

The University of Leicester, as Sponsor operates a risk-based monitoring programme which this study will be subject to.

A Trial Monitoring Plan will be developed by Derby CTSU, based on the study Risk Assessment. A division of responsibilities document will be signed ahead of Sponsor Green Light to confirm that DCTSU are responsible for conducting this monitoring. This will detail the procedures and anticipated frequency and format for monitoring. Both central and remote monitoring will be conducted, with appropriate triggers outlined in the Monitoring Plan to determine when additional monitoring visits are required. Expectations for source data verification will be outlined in the monitoring plan, in line with the Risk Assessment.

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures (SOPs). Direct access to appropriate study documentation and medical records will be granted to authorised representatives from the Sponsor and host institutions for monitoring and/or audit of the study to ensure compliance with regulations. The informed consent form will include a statement by which the patient allows such access.

The delegate will be responsible for maintaining the Trial Master File (TMF). Principal Investigators at each site will be responsible for ensuring their Investigator Site File (ISF) is kept up to date.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Once the initial sponsor review process is complete and a sponsor reference number has been allocated, and all requested documentation has been received and checked, authorisation from the University of Leicester's Research Governance Office will be issued to book further review of the proposed research. The NHS Research Ethics Committee and the Health Research Authority will then review the proposal. Agreement in principle is subject to the research receiving all relevant regulatory permissions. Submission for regulatory

approvals will be submitted via Integrated Research Application System (IRAS). The Chief Investigator will ensure that all regulatory approvals, confirmation of capacity and capability from NHS sites and sponsor greenlight are in place before participants are approached.

For any required amendment to the study, the Chief Investigator, in agreement with the sponsor will submit information to the appropriate body for them to issue approval for the amendment. Amendments will be implemented upon receiving Sponsor Approval and/or Green Light.

The Research Governance Office's Standard operational procedures will be followed for the duration of the study.

Amendments will be submitted to the sponsor in the first instance for review and approval.

Annual progress reports will be submitted to the Ethics Committee annually on the anniversary date of when favourable opinion is given by the Chief Investigator.

The Chief Investigator will notify the REC when the study has ended by completing the end of study notification form and will submit a final report of the results within one year after notifying REC.

A trial master file will be maintained for the duration of the study and will be stored for 6 years after the study has ended. The only time this could be exceeded, is if there is consent for future research, then these are being retained beyond the scope of the original study.

Participants will be free to withdraw at any time from the study without giving a reason and without their legal rights being affected. All study procedures including risks involved will be explained clearly to the participant at screening and subsequently before each procedure is performed.

The overall care and comfort of the participant will be considered paramount at all times during the study.

13.2 Peer review

This protocol has been peer-reviewed by two individual experts external to the investigators institution. To ensure that this trial it is both scientifically robust and clinically meaningful the development of the trial as part of the programme application have been supported by the NIHR Research Design Service East Midlands, who are experts in the field of healthcare research. The RCT protocol has been reviewed by Programme Streering Committee members as well as Trial Management, Clinical, Real World Evidence Unit Physical activity and Complex intervention Teams at the Leicester Diabetes Centre to ensure propriety from a trial management and delivery standpoint.

13.3 Public and Patient Involvement and Engagement

PPIE members have informed the design of the MiFoot intervention and RCT, including reviewing and refining patient-facing documentation, lay summaries and dissemination strategies. PPIE members will be proactively involved throughout the duration of the trial to support and inform participant recruitment, data collection, results interpretation and production of resources for dissemination purposes. PPIE members of the MiFoot programme and the Trial Steering Committee will also provide oversight and guidance from a PPIE perspective.

13.4 Regulatory Compliance

Approvals

The trial will not commence until Favourable REC opinion and HRA Approval are obtained.

Before any site can enrol participants into the trial, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. The trial will commence upon receipt of Sponsor Green Light for each site.

Sponsor Standard Operating Procedures

All relevant Sponsor standard operating procedures will be followed to ensure that this study complies with all relevant legislation and guidelines.

Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

ICH Guidelines for Good Clinical Practice (GCP)

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for GCP (CPMP/ICH/135/95) July 1996.

13.5 Protocol compliance

If a protocol breach occurs, then the CI will document this in adherence to the University's Standard Operational Procedure SOP Identifying and Reporting Deviations and Serious Breaches of GCP and/or the Protocol for Trials. The CI will seek advice from the research supervisors and the sponsor

Protocol non-compliances are departures from the approved protocol.

A deviation is a change or departure from the clinical trial protocol and/or Good Clinical Practice (GCP) that does not result in harm to the study participants or significantly affect the scientific value of the reported results of the study.

Deviations may be identified by routine quality control procedures or may be reported directly from the PI or other site staff, as a spontaneous written notification or by submission of a protocol deviation form included as part of the e-CRF. All such deviations should be documented in-line with Sponsor SOP's and retained within the Trial Master File and notification sent to Sponsor when serious breaches occur (as detailed in Sponsor SOPs). An assessment will be made by the PI as to whether the deviation is deemed to be serious or substantial (see below).

The deviation report should include:

- The title (full or accepted abbreviation) of the clinical trial
- The name of the CI and the PI
- A brief explanation of how the deviation was identified
- Details of initial corrective actions

Actions that result from a deviation may include:

- Alerting the investigator and asking for further explanation or data verification
- Audit of the investigator site or the study database (as applicable)
- Examination of data from the site by a statistician as a central monitoring procedure
- Review of other trial data
- Involvement of an DMSC or the PSC (if and as applicable)

Prospective, planned deviations or waivers to the protocol must not be used e.g., it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the study protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.5.1 Notification of Serious Breaches to GCP and/or the protocol

If research misconduct or a serious breach is confirmed by clear and unequivocal evidence, it is the responsibility of the Sponsor (or delegate) to notify the main REC in the UK in writing within 7 days of the Sponsor becoming aware of the breach using the Serious Breach Notification Form and to investigate or take action simultaneously or after initial notification.

Deviations from the protocol and/or GCP that are assessed as serious are to be reported to the REC as a serious breach by the study Sponsor (or delegate).

A "serious breach" is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the participants of the study; or
b) the scientific value of the study

The sponsor will be notified immediately of any case where the above definition applies during the study conduct.

Research misconduct is the deliberate reporting of false or misleading data or the withholding of reportable data. Concluding that an individual is responsible for misconduct in research relies on a judgement that there was an intention to commit the misconduct and/or recklessness in the conduct of any aspect of a research project. Misconduct includes: fabrication; falsification; misrepresentation of data and/or interests and or involvement; and plagiarism. It also includes a failure to follow accepted procedures or to exercise due care in carrying out responsibilities to avoid unreasonable risk or harm to participants in research, and/or a failure in the proper handling of information on individuals collected during the research.

13.6 Data protection and patient confidentiality

All information collected in the study will be kept strictly confidential.

The Chief Investigator will have access to the study documentation and will be the data custodian.

The investigator will comply with the requirements of the General Data Protection Regulation (and other applicable regulations) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The study staff will safeguard the privacy of participants' personal data.

Analysis of the generated RCT data will be undertaken by the Trial Statistician at University of Leicester or delegated to a freelance medical statistician and academic writer (with extensive statistical and writing expertise to NHS and academic departments, MedTech/BioTech companies, CROs, and research agencies) with whom University has a contract.

Health Economic analysis will be carried out by University of Sheffield delegates and Process evaluation analysis will be carried out by process evaluation team at University of Leicester and Deakin University.

Any printed confidential material will be kept in a folder in a locked drawer in a secured room in a secure office environment office at the Leicester Diabetes Centre and University of Sheffield.

Anonymised research data will be stored for 6 years after the study has ended, unless there is explicit consent for the data to be retained beyond the scope of the original research project, then it should be

defined how long the data would be retained for i.e., indefinitely, or for as long as the data is to be retained. If the study is a data only study, then the duration of the data retention timelines should be made clear in the PIS and ICF. Long-term storing will comply with the University of Leicester archiving Standard Operating Procedure. Details can be found at: http://www2.le.ac.uk/offices/ias.

Each participant will be assigned a unique identification number (ID) upon recruitment. Participant's contact details will be held on a database separate to the study visit data and used to arrange data collections. The database will be password protected and only researchers collecting data will have access. Participant's contact details will be used to contact the participant throughout the study, to arrange questionnaires and equipment collections also to reimburse participants.

All data collected during the study will be stored pseudonymously on a separate database. Again, access will be password protected and restricted to relevant members of the research team. Consent forms and any identifiable information required will be stored separately from any clinical or self-reported data. Self-reported data will be entered on to a study-specific database.

Paper copies of the questionnaires will be stored in a locked filing cabinet in the relevant research office. Neither hard copies nor electronic files containing personal information will be removed from the research office. Quality control checks will be conducted by the lead site (Leicester) or DCTSU these documents will be pseudonymised and stored in a secure manner. The study's team will comply with the Data Protection Policy of the University of Leicester and local NHS Trusts.

The digital programme is developed according to NHS Digital's standards for acceptance onto their health applications library (https://digital.nhs.uk/services/nhs-apps-library), which covers a range of components to ensure that applications are appropriate, accurate, safe and secure, whilst also meeting national standards, regulations and industry best-practices. Areas of assessment include available evidence on outcomes, clinical safety, and data protection.

Data will be encrypted and stored on UK servers fully compliant with the latest industry standards for security and GDPR.

13.7 Financial

The MiFoot site agreement will set out site level costs approved in funding application. Site agreements will be agreed for all sites and as such will be documented through this process. Note that site agreements, once agreed will provide details of the funds available for each site and any associated performance related requirement.

In addition, the approved SOECAT provides detailed costs.

13.8 Indemnity

University insurance applies for this study.

If participant wishes to make a complaint about any aspects of the way they have been treated or approached during the study, the standard National Health Service complaint system will be available to them.

13.9 Post trial care

Access to the online element of the intervention will continue after the study if the study site in question is already a DESMOND-licensed site or becomes a DESMOND-licensed site during or at the end of the study. If attending a DESMOND-licensed site, participants randomised to the intervention group will have

continued access to the online element of the intervention after the conclusion of the study, whilst interested participants randomised to the usual care control group will be offered new access.

13.10 Access to the final trial dataset

Chief Investigator and study team will have access to the full dataset.

The data generated during and/or analysed during the RCT are/will be available to the individuals responsible for study analysis and report writing.

The data generated or analysed during this RCT will be included in published NIHR Final report. The data that supports the findings of this study will not be publicly available. The datasets generated and/or analysed during the RCT will be available from the Chief Investigator on reasonable request.

The PPI member involved in the analysis stage, will not have access to the final study dataset, they will however have input in the analysis discussions of the data.

Direct access will be granted to authorised representatives from the Sponsor and host institutions for monitoring and/or audit of the study to ensure compliance with regulations.

14. DISSEMINIATION POLICY

The study will be registered prior to initiation on ISRCTN registry. The study will develop a comprehensive dissemination plan fully involving PPI/E colleagues and members of the PMG, including academic and non-academic outputs.

The findings of the RCT will be presented at conferences and will be submitted for publication in relevant peer-reviewed journals. All activity and findings will be submitted and available via open-access in the final report to the NIHR at the end of the programme. A portfolio of three core outputs from RCT, comprising open-access peer-reviewed publications reporting the results of intervention 1) effectiveness, 2) health economics, and 3) process evaluation analyses. Some or all of these results (minimum the effectiveness analyses) will also be presented at diabetes-specific international conferences (IDF/ADA/EASD etc.) to reach a related academic and clinical audience.

Neither the sponsor nor the funder will have intellectual or editorial control of the journal articles. Other non-academic outputs will include and are not limited to press releases, radio stations, social networks, open days and work with relevant charities.

Authorships and acknowledgements will be in line with the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations 2018). The process of preparation, presentation, publication and dissemination of the research findings will also be conducted in line with the University of Leicester policy and best practice for publication of research.

Complementing our academic and clinical dissemination via publication/conference presentation, we will inform and engage patients, the NHS and the wider public through a series of diverse strategies, including:

- Press releases and TV/radio interviews with local/national media
- Social networks, open days and public lectures to share programme results and PPI/E guide
- Work with local/national charities (including Diabetes UK who will be part of the PSC)
- We will have direct policy-level discussions
- Utilising relevant clinical studies groups and the new NIHR DUK national diabetes research forum
- Articles for informed public audiences (e.g., The Conversation)

We will also create a public programme-specific website, which will form a 'hub' for all programme-specific information, including collating news and outputs. We will do this in collaboration the PPI/E panel and the LDC Creative team or a private vendor.

15. REFERENCES

1. Hokkam EN. Assessment of risk factors in diabetic foot ulceration and their impact on the outcome of the disease. Primary care diabetes. 2009;3(4):219-24.
2. Leese G, Stang D, Pearson D. A national approach to diabetes foot risk stratification and foot care. Scottish medical journal. 2011;56(3):151-5.
3. Jupiter DC, Thorud JC, Buckley CJ, Shibuya N. The impact of foot ulceration and amputation on mortality in diabetic patients. I: from ulceration to death, a systematic review. International wound journal. 2016;13(5):892-903.
4. Holman N, Young R, Jeffcoate W. Variation in the recorded incidence of amputation of the lower limb in England. Diabetologia. 2012;55(7):1919-25.
5. Icks A, Claessen H, Morbach S, Glaeske G, Hoffmann F. Time-dependent impact of diabetes on mortality in patients with stroke: survival up to 5 years in a health insurance population cohort in Germany. Diabetes care. 2012;35(9):1868-75.
6. Coffey L, Mahon C, Gallagher P. Perceptions and experiences of diabetic foot ulceration and foot care in people with diabetes: A qualitative meta-synthesis. International wound journal. 2019;16(1):183-210.
7. Kerr M, Barron E, Chadwick P, Evans T, Kong W, Rayman G, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabetic medicine [Internet]. 2019; 36(8):[995-1002 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02090247/full.
8. Chatterjee S, Davies MJ, Stribling B, Farooqi A, Khunti K. Real-world evaluation of the DESMOND type 2 diabetes education and self-management programme. Practical Diabetes. 2018;35(1):19-22a.
9. Rasmussen A, Almdal T, Nielsen AA, Nielsen K, Jørgensen M, Hangaard S, et al. Decreasing incidence of foot ulcer among patients with type 1 and type 2 diabetes in the period 2001–2014. Diabetes research and clinical practice. 2017;130:221-8.
10. Caruso P, Longo M, Signoriello S, Gicchino M, Maiorino MI, Bellastella G, et al. Diabetic foot problems during the COVID-19 pandemic in a tertiary care center: the emergency among the emergencies. Diabetes care. 2020;43(10):e123-e4.
11. Kretchy IA, Asiedu-Danso M, Kretchy J-P. Medication management and adherence during the COVID-19 pandemic: perspectives and experiences from low-and middle-income countries. Research in social and administrative pharmacy. 2021;17(1):2023-6.
12. Lippi G, Henry BM, Sanchis-Gomar F. Physical inactivity and cardiovascular disease at the time of coronavirus disease 2019 (COVID-19). European journal of preventive cardiology. 2020;27(9):906-8.
13. Li LZ, Wang S. Prevalence and predictors of general psychiatric disorders and loneliness during COVID-19 in the United Kingdom. Psychiatry research. 2020;291:113267.
14. Banerjee M, Chakraborty S, Pal R. Diabetes self-management amid COVID-19 pandemic. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(4):351-4.
15. Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K. Prevention and management of foot problems in diabetes: a Summary Guidance for Daily Practice 2015, based on the IWGDF Guidance Documents. Diabetes/Metabolism Research & Reviews. 2016;32:7-15.
16. Iversen MM, Tell GS, Riise T, Hanestad BR, Ostbye T, Graue M, et al. History of foot ulcer increases mortality among individuals with diabetes: ten-year follow-up of the Nord-Trøndelag Health Study, Norway. Diabetes Care. 2009;32(12):2193-9.
17. Chammas N, Hill R, Edmonds M. Increased mortality in diabetic foot ulcer patients: the significance of ulcer type. Journal of diabetes research. 2016;2016.
18. Brownrigg J, Davey J, Holt P, Davis W, Thompson M, Ray K, et al. The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis. Diabetologia. 2012;55:2906-12.
19. Dhatariya K, Fox M. Should patients with active foot ulcers be non-weight bearing or take exercise to improve cardiovascular fitness? Diabetic Foot. 2014;17(3).

20. Menon AS, Dixit A, Garg M, Girish R. Cardiac autonomic neuropathy in patients with type 2 diabetes mellitus at high risk for foot ulcers. Indian Journal of Endocrinology and Metabolism. 2017;21(2):282.
21. Bain SC, Bekker Hansen B, Hunt B, Chubb B, Valentine WJ. Evaluating the burden of poor glycemic control associated with therapeutic inertia in patients with type 2 diabetes in the UK. Journal of Medical Economics. 2020;23(1):98-105.
22. Hinchliffe R, Brownrigg J, Apelqvist J, Boyko E, Fitridge R, Mills J, et al. IWGDF guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes. Diabetes/metabolism research and reviews. 2016;32:37-44.
23. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient preference and adherence. 2016;10:1299.
24. Davies MJ, Heller S, Skinner T, Campbell M, Carey M, Cradock S, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. Bmj. 2008;336(7642):491-5.
25. Crasto W, Jarvis J, Khunti K, Skinner T, Gray L, Brela J, et al. Multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: the Microalbuminuria Education and Medication Optimisation (MEMO) study. Diabetes research and clinical practice. 2011;93(3):328-36.
26. Pinto A, Tuttolomondo A, Di Raimondo D, Fernandez P, La Placa S, Di Gati M, et al. Cardiovascular risk profile and morbidity in subjects affected by type 2 diabetes mellitus with and without diabetic foot. Metabolism. 2008;57(5):676-82.
27. Li D, Yang JY, Wang T, Shen S, Tang H. Risks of diabetic foot syndrome and amputation associated with sodium glucose co-transporter 2 inhibitors: a meta-analysis of randomized controlled trials. Diabetes & metabolism. 2018;44(5):410-4.
28. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New England Journal of Medicine. 2019;380(24):2295-306.
29. Pearson S, Nash T, Ireland V. Depression symptoms in people with diabetes attending outpatient podiatry clinics for the treatment of foot ulcers. Journal of foot and ankle research. 2014;7(1):1-8.
30. Ribu L, Hanestad BR, Moum T, Birkeland K, Rustoen T. A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population. Quality of life research. 2007;16(2):179-89.
31. McCarthy M, Yates T, Webb D, Game F, Gray L, Davies M. Health impacts of seated arm ergometry training in patients with a diabetic foot ulcer: protocol for a randomised controlled trial. BMJ open [Internet]. 2020; 10(6):[e039062- pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02142051/full.
32. Dhatariya K, Bain S, Buse J, Simpson R, Tarnow L, Kaltoft M, et al. The Impact of Liraglutide on Diabetes-Related Foot Ulceration and Associated Complications in Patients With Type 2 Diabetes at High Risk for Cardiovascular Events: results From the LEADER Trial. Diabetes care [Internet]. 2018; 41(10):[2229-35 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01664773/full.
33. Gæde P, Vedel P, Parving H-H, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. The Lancet. 1999;353(9153):617-22.
34. NHS. NHS Long Term Plan. 2019.
35. Bresnahan JJ, Farkas GJ, Clasey JL, Yates JW, Gater DR. Arm crank ergometry improves cardiovascular disease risk factors and community mobility independent of body composition in high motor complete spinal cord injury. The Journal of Spinal Cord Medicine. 2019;42(3):272-80.
36. Winkley K, Upsher R, Stahl D, Pollard D, Kasera A, Brennan A, et al. Psychological interventions to improve self-management of type 1 and type 2 diabetes: a systematic review. Health Technology Assessment (Winchester, England). 2020;24(28):1.
37. NIHR. Type 2 Diabetes (T2D) in 16 40 year olds: A Multifactorial Management Intervention to Address Multimorbidity in Early-Onset T2D in Adults (The M3 Research Programme) 2021 [Available from: https://fundingawards.nihr.ac.uk/award/NIHR201165.
38. NIHR. Scalable behavioural weight management programmes for the prevention and treatment of type 2 diabetes 2017 [Available from: https://fundingawards.nihr.ac.uk/award/RP-PG-0216-20010.
39. Department of Health and Social Care. Physical activity guidelines. 2022.
40. Harrington D, Henson J. Physical activity and exercise in the management of type 2 diabetes: where to start? Practical Diabetes. 2021;38(5):35-40b.

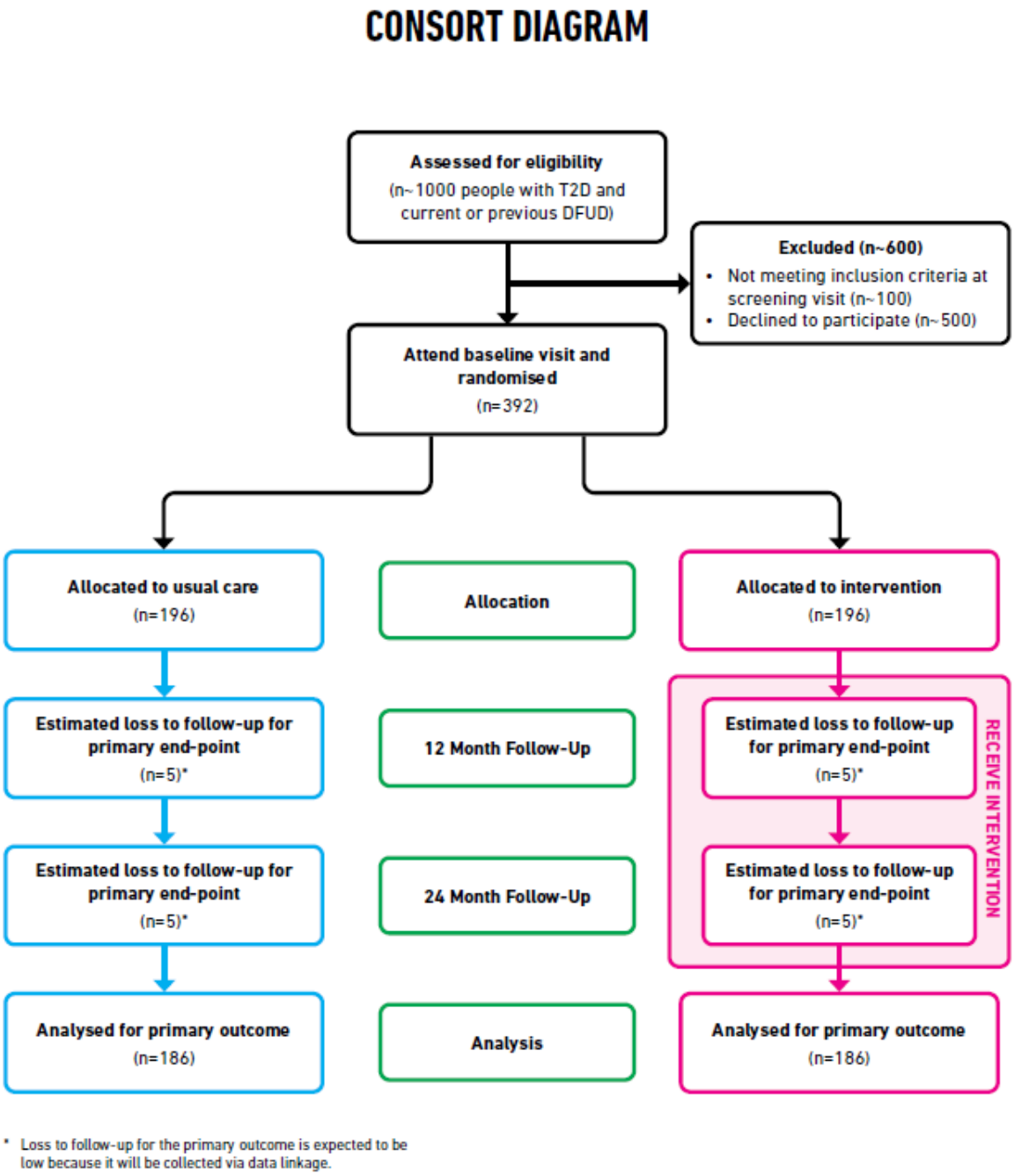
41. Association of Chartered Physiotherapists in Cardiac Rehabilitation. Standards for Physical Activity and Exercise in the Cardiovascular Population. 2015.
42. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, et al. Exercise/physical activity in individuals with type 2 diabetes: A consensus statement from the American College of Sports Medicine. Medicine and Science in Sports and Exercise. 2022.
43. Jeffcoate W, Game F, Turtle-Savage V, Musgrove A, Price P, Tan W, et al. Evaluation of the effectiveness and cost-effectiveness of lightweight fibreglass heel casts in the management of ulcers of the heel in diabetes: a randomised controlled trial. Health technology assessment (Winchester, England) [Internet]. 2017; 21(34):[1-92 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01454253/full.
44. Webb D, Dales J, Zaccardi F, Hill S, Moore C, Farooqi A, et al. Intensive versus standard multifactorial cardiovascular risk factor control in screen-detected type 2 diabetes: 5-year and longer-term modelled outcomes of the ADDITION-Leicester study. Diabetes/Metabolism Research and Reviews. 2019;35(3):e3111.

16. Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NSA06	1.1	04/04/2024	M. Hadjiconstantinou M. Caba V. Hull A. Glab P. Highton	• Update to the assessment for the internal feasibility study • Update and clarification to inclusion and exclusion criteria • Clarification on randomisation terminology. • Addition of scoring instructions for the HADS questionnaire. • Changes to the description of the study intervention, also called 'MiFoot programme'. • The blood test results timeframe, as part of the baseline data collection, has been increased from 3 to 6 months. • Further clarification of the mixed-methods process evaluation component of the trial and the MiFoot Intervention refinement exercise. • Updates to the participant information sheet and consent form to include additional information relating to recordings, allowing participants the opportunity to consent to being observed and recorded. The protocol and relevant study documents have been updated to reflect these changes.
SA01	2.0	19/07/2024	P. Highton T. Onuwe M.Funnell M. Hadjiconstantinou M. Caba A. Glab	• Sponsor address change • The provision of continuous glucose monitors (CGMs) to all participants within the MiFoot RCT, regardless of which group they are assigned to (i.e., intervention or usual care groups). The provision of CGM devices to populations with diabetes is becoming increasingly common in routine practice, and is likely to become the norm within the

				population of interest (people with diabetic foot ulcer disease) within the next 3-5 years, or around the time that the MiFoot RCT will be finished and the results published. As such, the aim of this amendment is to future proof the RCT findings by offering CGMs to all participants in order to ensure that the results are in the context of these devices being readily available to patients. As CGM devices may improve glucose and diabetes control, ensuring that the MiFoot intervention is beneficial to patients above and beyond the support provided by CGM devices is crucial for the long-term impact of the intervention findings. This will not affect any other proposed element of the study, including the intervention design/delivery and the data collection processes. CGM use and outcome data will be collected from each CGM device via link to a study-specific virtual clinic, allowing remote collection of data. Devices and sensors etc will be provided by Abbott and no additional cost or resource demand will be placed on the participating sites. • Identification and approach of participants updated • Intervention refinement protocol section updated. • Re-consenting following the amendment process aligned with the study design. The remote consent method is used in the Qualitative element of the RCT.

16. Appendix 2 Consort diagram



* Loss to follow-up for the primary outcome is expected to be low because it will be collected via data linkage.