Reducing the impact of diabetic foot ulcers (REDUCE): A effectiveness and cost-effectiveness Randomised Controlled Trial

Short title: Reducing the impact of DFUs (REDUCE): RCT

Version and Date of Protocol:	V3.3, 13 August 2024
Sponsor:	University Hospitals of Derby & Burton NHS Foundation Trust
Chief Investigator:	Professor Fran Game
Sponsor Reference:	UHDB/2022/015
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This protocol has regard for the HRA guidance	

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust, regulatory authorities, and members of the Research Ethics Committee.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.
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 investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Protocol (v3.3, 13th August 2024) authorisation signatures:

Chief Investigator:

Signature: DocuSigned by: Prof Fran Game A84078C3A4E045F... Date: 19-09-24

……/……/……

Name (please print): Prof Fran Game ……

For and on behalf of the Study Sponsor (if required):

Signature: DocuSigned by: Kate Threapleton 4EFEA8CA9C3E4C4... Date: 19-09-24

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Position: Sponsor Trial Manager ……

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STUDY SUMMARY

Study Title:	Reducing the impact of diabetic foot ulcers (REDUCE): Randomised Controlled Effectiveness Trial
Short Title:	REDUCE Trial: Reducing the impact of DFUs (RCT)
Sponsor Reference:	UHDB/2022/015
Study Design:	Multi-centre randomised controlled trial with a process evaluation study, health economic evaluation, and biological mechanisms sub-study
Study Participants:	***Trial and biological mechanisms sub-study:*** People with diabetes, two lower limbs and a recently healed DFU (fully epithelialised with no drainage, healed for a minimum two weeks up to a maximum of twelve weeks). ***Process Evaluation:*** Intervention participants and healthcare professionals involved in the delivery of the REDUCE intervention.
Planned Number of Sites:	Up to forty NHS Trusts will recruit patients and deliver the intervention. Follow up data will be collected from secondary care, primary care and community health including podiatry and wound care medical records.
Planned Sample Size:	N=544 (of which n=100 to be recruited into biological mechanisms sub-study). Up to twenty healthcare professionals involved in the delivery of the REDUCE intervention.
Treatment Duration:	3 months
Follow Up Duration:	18 months
Planned Start Date:	01/05/2022
Planned Recruitment End Date:	31/10/2024
Planned Study End Date:	30/11/2026
Research Question/ Aims:	The primary outcome of this trial is total ulcer free time with limbs intact over 18 months. The secondary outcomes of this trial are: 1. Clinical outcome data (days to re-ulceration; number of ulcers; days in hospital; amputations, mortality). 2. Psychological/behavioural risk factors targeted in REDUCE to examine mechanisms; 3. Economic outcomes to examine cost-effectiveness. 4. The biological mechanisms underpinning REDUCE and psychological/behavioural risk factors to clinical outcomes via immune and gene expression pathways.

FUNDING AND SUPPORT IN KIND

Funder(s)	Financial and Non-Financial Support Given
NIHR PGfAR (Reference: RP-PG-0618-20001) NIHR PGfAR (Reference: RP-PG-0618-20001) – Variation to Contract Extension NIHR EME (Reference: NIHR154807)	£2,531,202 £97,315 £352,791

ROLES & RESPONSIBILITIES

Sponsor

The Sponsor, University Hospitals of Derby & Burton NHS Foundation Trust, take on overall responsibility for appropriate arrangements being in place to set up, run and report the research project. The Sponsor is not providing funds for this study, but has taken on responsibility for ensuring finances are in place to support the research.

Funder

The study is funded by the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research (PGfAR), reference RP-PG-0618-20001. Further funding for the additional mechanistic sub-study was obtained from the NIHR Efficacy and Mechanism Evaluation Programme (NIHR154807).

Study Management Committees

Trial Management Group (TMG)

The day to day running of the work described in this protocol will be overseen by the TMG which consists of all the applicants and collaborators involved in the pilot trial. This group will have face-to-face meetings every quarter (where able) and monthly teleconferences. Any problems with study conduct will be raised and addressed during TMG meetings.

Joint Trial Steering and Independent Programme Steering Committee (JT-IPSC)

The JT-IPSC will oversee and supervise the progress of the trial and ensure that it is being conducted according to the protocol and the applicable regulations. The JT-IPSC is an independent body that includes members who are not involved with the running of the trial. The JT-IPSC consists of five members; an independent Chair with expertise in health psychology, an independent clinician with expertise in diabetes, an independent member with expertise in podiatry, an independent statistician and an independent patient and public involvement (PPI) representative. Representatives from the Trial Management Group will attend the JT-IPSC to provide the updates, to include Chief Investigator, Trial Manager, Trial Statistician, Programme Manager, Sponsor representative(s) and a Funder representative. Other members will be invited on an 'as required' basis. A separate Data Monitoring and Ethics Committee will not be convened for this trial. The JT-IPSC will be responsible for all data monitoring and ethics issues raised throughout the trial. The JT-IPSC will meet bi-annually over the duration of the Trial.

Programme Management Group (PMG)

The study is part of a larger programme of work, which will be overseen by the REDUCE PMG. The PMG consists of all the applicants and collaborators on the wider programme (including members of this TMG), and one lay/PPI member. The PMG will meet bi-annually over the programme to oversee the management of all work packages (WPs), including the work described here. The PMG will be notified of any problems with study conduct. A representative from the sponsoring organisation and the University of Nottingham Technology Transfer Office will also attend these meetings, where able/required, to ensure any new intellectual property (IP) is captured in a timely fashion.

Protocol Contributors

A number of protocol contributors have been involved in the development of this protocol. These include the Chief Investigators, named Co-applicants and Collaborators, Programme Manager, Senior Research Fellow, Research Fellows, Psychologists, Statistician, Data Manager, Trial Manager, Health Economist, Sponsor Representative, Patients and Carers. Protocol contributors are responsible for inputting into the design of the study, ensuring that it is designed transparently and efficiently.

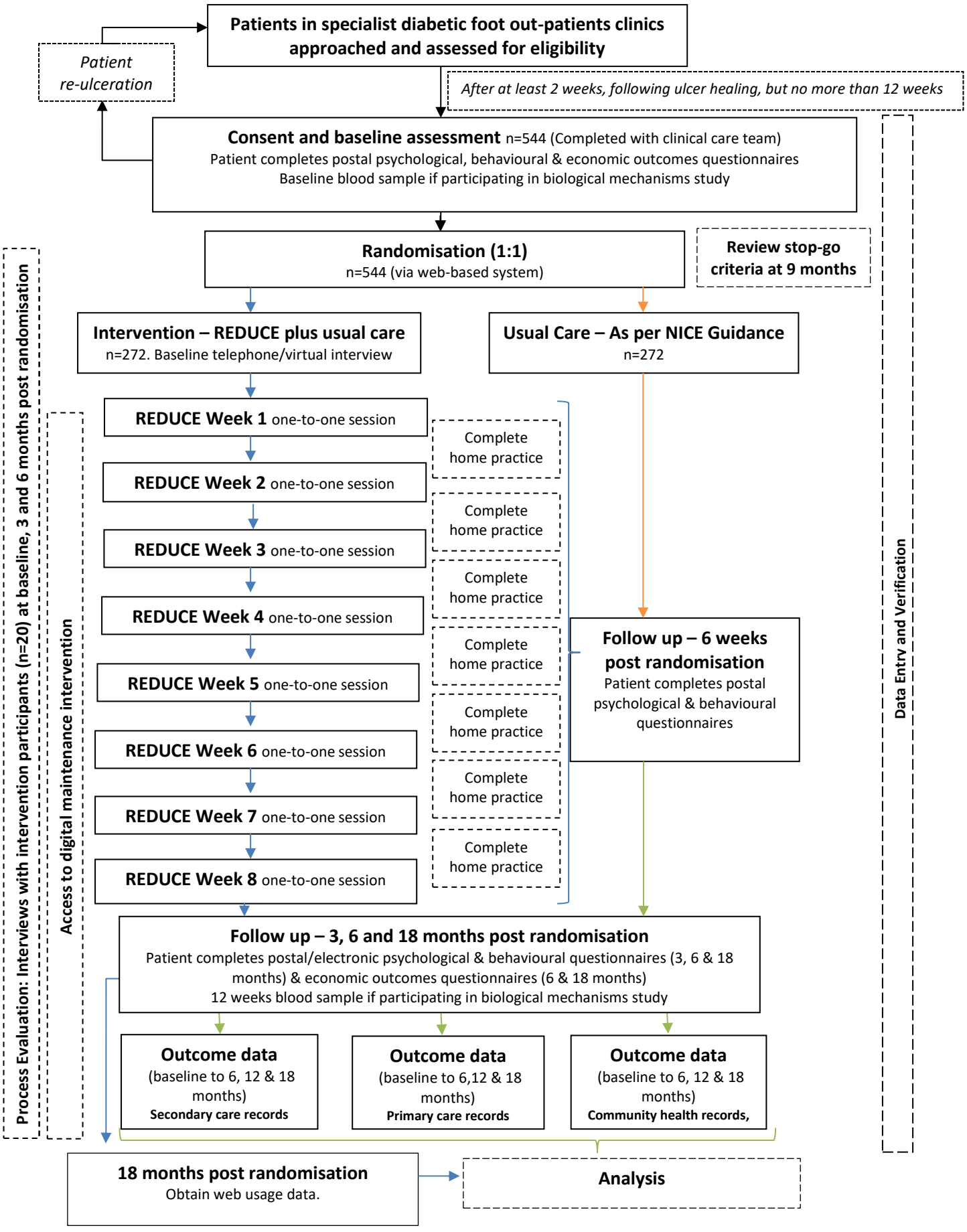
Contents

LIST OF ABBREVIATIONS

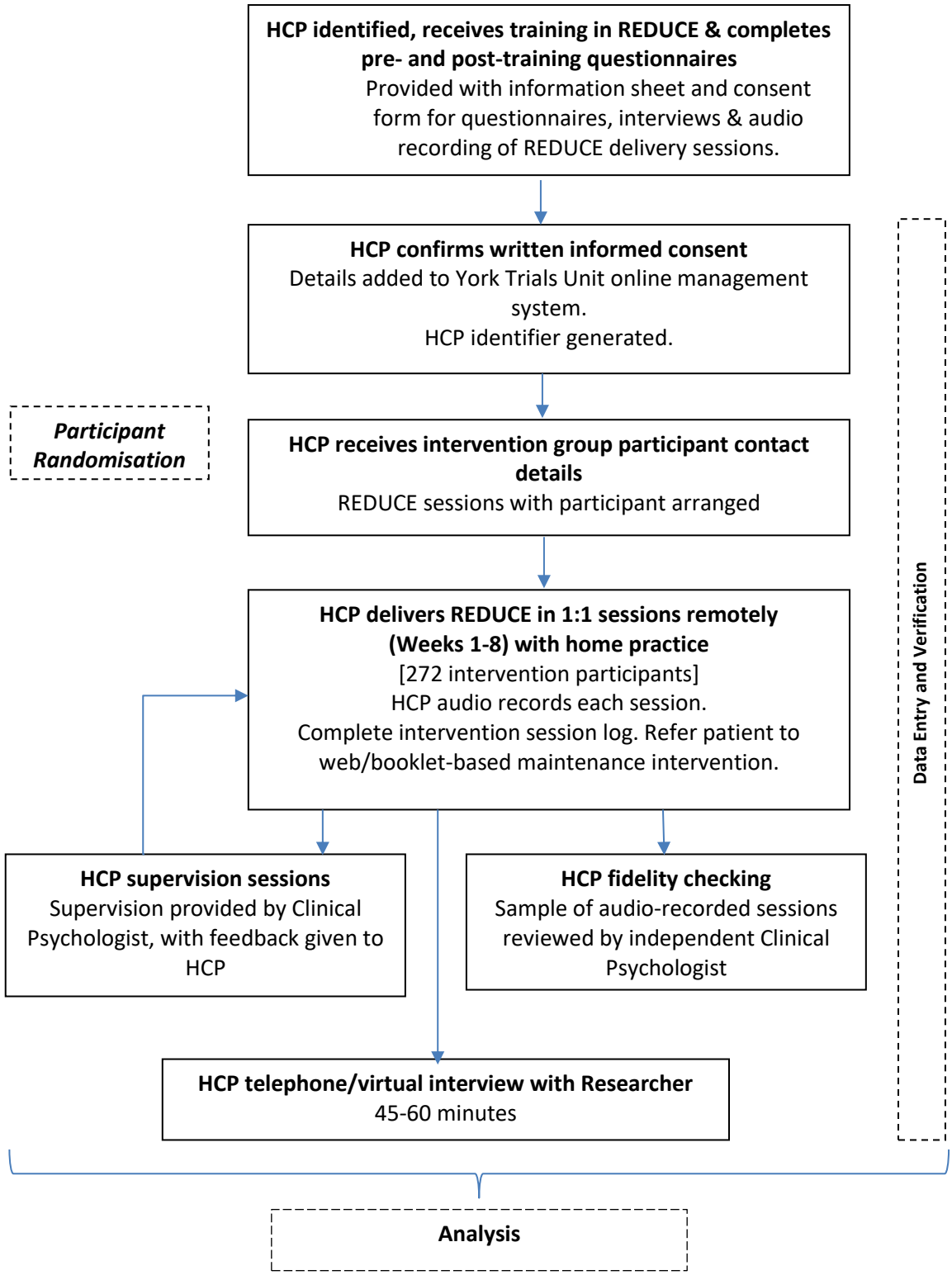
AE	Adverse Event
APR	Annual Progress Report
B-IPQ	Brief Illness Perception Questionnaire
CBRQ	Cognitive and Behavioural Responses Questionnaire
CBT	Cognitive Behavioural Therapy
CACE	Complier average causal effect
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTRA	Conserved Transcriptional Response to Adversity
DFU	Diabetic Foot Ulcer
DMI	Digital Maintenance Intervention
DMP	Data Management Plan
EQ-5D-5L	EuroQol five level version
FBS	Fetal Bovine Serum
GCP	Good Clinical Practice
GI	Global Initiative
GP	General Practice/Practitioner
HCP	Healthcare Professional
HEAP	Health Economic Analysis Plan
HRA	Health Research Authority
ICECAP-A	ICEpop CAPability measure for Adults
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
ICJME	International Committee of Journal Medical Editors
IP	Intellectual Property
IPAQ-E	International Physical Activity Questionnaire - Elderly
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials
JT-IPSC	Joint Trial and Independent Programme Steering Committee
KCL	King's College London
MI	Maintenance Intervention
MRC	Medical Research Council
NAFF	Nottingham Assessment of Functional Footcare
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PAD	Peripheral Arterial Disease
PBA	Person Based Approach
PBMCs	Peripheral Blood Mononuclear Cells
PBS	Phosphate-Buffered Saline

PGfAR	Programme Grants for Applied Research
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PMG	Programme Management Group
PPI	Patient and Public Involvement
PSS	Personal Social Services
QA	Quality Assurance
QC	Quality Control
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RUM	Resource Use Measure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPANE	Scale of Positive And Negative Experience
SPS	Social Provisions Scale
SWAT	Studies Within A Trial
TMG	Trial Management Group
TMF	Trial Master File
UCLA	University of California, Los Angeles
UHDB	University Hospitals of Derby and Burton NHS Foundation Trust
UK	United Kingdom
UoE	University of Edinburgh
UoN	University of Nottingham
VAS	Visual Analogue Scale
WHO	World Health Organization
WP	Work Package
YTU	York Trials Unit

STUDY FLOW CHART – PARTICIPANTS



STUDY FLOW CHART – HEALTHCARE PROFESSIONALS



STUDY PROTOCOL

1. BACKGROUND AND RATIONALE

One in 15 people in the UK has diabetes [1]. Foot ulceration is a common, chronic and costly complication of the disease: affecting a quarter of patients [2]; Less than half of ulcers are healed after 12 weeks [3] and 80% of the 2,200 major amputations in patients with diabetes per-annum are preceded by foot ulcers [4]. The physical and emotional burden of ulceration is considerable: 32% of patients are depressed and this is associated with a three-fold greater risk of mortality [5]. In 2014–2015 it is estimated that the NHS spent between £837 million and £962 million on diabetic foot care: equivalent to £1.50 in every £150 of NHS spending [6].

Despite the fact that diabetic foot care has been identified as a priority by the National Institute for Health and Care Excellence (NICE), the NHS and Diabetes UK [4,7,8], there is currently a lack of evidence-based treatments which prevent ulceration. NICE guidance for ulcer prevention in diabetic patients with a history of ulceration focuses on risk assessment in primary care; referral to foot protection teams and 'basic foot care education' (undefined). For active ulceration, the guidance is rapid referral to multidisciplinary foot care teams [4]. However, successive systematic reviews have found no evidence that education alone improves clinical outcomes [9-15]. NICE have consequently called for further research in this area and the development of new interventions targeting psychological and behavioural factors, which research suggests may play a central role in the healing and prevention of foot ulcers [16,17].

A complex intervention [17] has previously been developed in accordance with the MRC's guidance on complex interventions [18]. This intervention aimed to (i) reduce re-ulceration risk by modifying associated psychological and behavioural factors and (ii) improve ulcer healing in the event of re-ulceration, by encouraging rapid self-referral and effective self-management. This intervention originally consisted of two phases conducted face-to-face over five months: an initiation phase of ten weekly sessions, which established the foundations for psychological and behavioural change, and a maintenance phase involving two additional sessions held one and three months later, which encouraged the patient to sustain the changes made in the initiation phase.

The intervention was tested in a small feasibility RCT (n=15) which: (i) established the feasibility of training nurses and podiatrists to deliver the intervention; (ii) established that patients would consent to participate in an RCT; and (iii) that the intervention is acceptable (no withdrawals post randomisation and all participants attended at least 80% of sessions). Refinements to the content of the intervention also indicated that the components of the initiation phase of the intervention could be delivered in eight, rather than 10, weekly sessions. Qualitative research with patients suggested that that the intervention seemed to modify the psychological and behavioural precursors of re-ulceration risk and ulcer healing; with changes sustained for eight months. However, feedback from participants indicated that support for long-term change may be more effective if available indefinitely, and as and when patients require it.

In follow up work [19] the investigators have examined the acceptability and feasibility of providing this long-term support through a digital platform. People with a history of prior ulceration reported that a digital solution would be acceptable, but that an alternative (i.e., a written handbook) should also be available. Also, within this work, the first phase of developing this digital intervention was

completed, in accordance with the Person Based Approach (PBA) to intervention development [20]. This involved identifying the key issues that need to be addressed in the intervention:

- Managing difficult feelings.
- Promoting and sustaining moderate and stable levels of activity.
- Promoting and sustaining regular and effective checking of feet for early signs of ulceration.
- Facilitating rapid self-referral in the event of changes in foot health.

Theoretical modelling of the intervention has also been completed to identify the key determinants of the above areas of psychological and behavioural functioning and these have been mapped on to the behaviour change wheel to identify appropriate theory-based behaviour change techniques [21].

1.1. The REDUCE Intervention

The REDUCE intervention consists of an eight week initiation phase delivered weekly (in sessions of approximately 60 minutes), with access to a web-based digital package or hard copy handbook (for those without internet access, a suitable device or who indicate a preference to use a handbook) which will provide long-term support for the psychological and behavioural changes achieved in the initiation phase. The *behavioural goals/outcomes* are to improve foot-checking, physical activity, manage low mood and encourage rapid self-referral (in the event of changes in foot health); and, in so doing, increase ulcer-free days. We hypothesise that the mechanisms (our '*mechanisms of change'*) by which REDUCE will achieve these goals, will be improved mood, reduced social isolation, development of new foot-care behaviours and changes in illness beliefs. The delivery of the intervention will be carried out remotely by HCPs trained in the REDUCE intervention in accordance with routine NHS processes. Sites are currently engaged in remote delivery of many aspects of patient care, therefore the delivery of the intervention remotely is now more likely to be familiar and acceptable to participants.

The first ('Initiation') phase of REDUCE starts the process of modifying these *'mechanisms of change'*. This will be achieved through a suite of intervention techniques delivered in eight weekly remote online/telephone sessions with a supporting handbook and digital platform (website). Comparable techniques will be utilised in the second ('Maintenance') phase although with a focus on sustaining change, delivered via the handbook and the digital platform.

Thus, the two phases of REDUCE are intended to flow together but with a slightly different emphasis in their intervention techniques given their respective focus on the initiation, versus maintenance, of behaviours. For example, the 'Initiation' phase will provide detailed information about the benefits of making behaviour changes (e.g., to avoid future ill-health) and will aim to increase perceptions of risk, whilst supporting self-efficacy. It will also provide guidance and support on how to perform key behaviours (e.g., foot checking, activity scheduling for behavioural activation). In contrast, the 'Maintenance' phase will provide only brief guidance on how to perform these behaviours, in order to serve as reminders and reinforce messages from the 'Initiation' phase. Similarly, the 'Maintenance' phase will include brief reminders about the benefits of behaviour change to reinforce messages about risk, and thus support motivation.

The 'Initiation' phase will also seek to modify illness beliefs (e.g., positive outcome expectations, self-

efficacy, perceived control over illness), mood, key behaviours and social isolation through the use of Cognitive Behavioural Therapy (CBT) techniques (positive reframing, behavioural experiments, behavioural activation). In contrast, the 'Maintenance' phase will provide resources to facilitate the continued use of these techniques (e.g., thought diaries, spaces to reflect on behavioural experiments, diaries for activity scheduling). Both phases will also use self-monitoring, with feedback on progress with goals/action plans. In the 'Initiation' phase the feedback will include Socratic questioning if the participant is facing barriers to behaviour change. This is a well-established therapeutic approach which involves the use of probing questions which encourage the treatment recipient to become aware of and reflect on their reasons for engaging in specific behaviours. This in turn enables them to develop appropriate solutions. Within the 'Maintenance' phase the participant will ask themselves Socratic questions when reviewing goals/action plans.

The delivery of the 'Initiation' sessions will be structured as follows, supported by the handbook and digital platform:

- Assessment of current difficulties and strengths and motivators;
- Identify problematic behavioural, cognitive and emotional responses;
- Socialisation to the therapeutic model;
- Explore the role of personal values, thoughts and behaviours and their link with mood and/or health status;
- Negotiate individualised values-based goals and agree weekly actions as home practice;
- Increasing awareness of activity patterns and behaviours which impact on ulcer outcomes;
- Negotiating appropriate behaviours including increasing appropriate physical activity, social contact and regular foot checking;
- Increasing awareness and exploring of unhelpful cognitions (e.g. hopelessness);
- Identifying sources of social support and problem-solving barriers to change;
- Discussing how to be more assertive/test out with behavioural experiments;
- Taking responsibility, strengthening commitment to new behaviours and maintenance of these including engaging with the digital maintenance programme;
- Planning for the future and empowering continued change.

The 'Maintenance' phase will be delivered on the digital platform and through the handbook and focuses on supporting four key areas of psychological and behavioural functioning:

- Managing difficult feelings.
- Promoting and sustaining moderate and stable levels of activity.
- Promoting and sustaining regular and effective checking of feet for early signs of ulceration.
- Facilitating rapid self-referral in the event of changes in foot health.

1.2. Biological Mechanisms Sub-study

Multiple psychological and behavioural factors have been reliably associated with diabetic foot ulcer outcomes. Several of these (e.g., mood, activity, social isolation) are the targets of REDUCE. In this mechanistic sub-study we will use the opportunity of the REDUCE trial to elucidate the molecular mechanisms by which REDUCE, and the psychological and behavioural risk factors it changes, impact diabetic foot ulcer outcomes.

Molecular biological research reveals that epithelial repair and inflammatory responses, which are critical in preventing ulcer recurrence and promoting healing, are both unfavourably altered in people living with diabetes. These processes, in turn, are driven by circulating immune cells and proteins: in particular, prolonged production of pro-inflammatory cytokines and reduced type 1 interferon responses have been observed in diabetic wounds.

Genes that produce pro-inflammatory cytokines and type 1 interferons are influenced by psychological factors. Circulating immune cells from people exposed to chronic stress show a characteristic pattern in the expression of genes encoding these proteins, specifically an increase in activity of pro-inflammatory genes and decreased activity in those encoding type 1 interferon responses. This pattern of gene expression, termed the Conserved Transcriptional Response to Adversity (CTRA), has been shown to be modifiable by psychological interventions such as cognitive behavioural therapy.

This mechanistic sub-study will involve venous blood samples from patients in the ongoing REDUCE trial to test the hypothesis that REDUCE impacts this CTRA pathway. Specifically, we hypothesize that REDUCE reduces the expression of pro-inflammatory genes and increases the expression of genes involved in type 1 interferon responses, and thereby influences the circulating immune environment, and ultimately DFU outcomes.

2. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

2.1. Objectives

To investigate the effectiveness and cost-effectiveness of the REDUCE intervention in patients with healed diabetic foot ulcers compared with patients who receive usual care following their healed diabetic foot ulcers.

2.2. Primary Outcome

The primary outcome of this trial is total ulcer free time with limbs intact over 18 months as measured in days.

2.3. Secondary Outcomes

1. Clinical outcomes to include:
    a. Whether the patient remained ulcer-free
    b. Time to re-ulceration
    c. Total number of ulcers
    d. Proportion of patients deceased
    e. Time to death
    f. Whether patient had major amputation
    g. Time to major amputation operation
    h. Whether patient had minor amputation operation
    i. Time to minor amputation
    j. Days in hospital related to foot ulcer disease

k. Days in hospital not related to foot ulcer disease

2. Psychological/behavioural risk factors targeted in REDUCE to examine mechanisms.
3. Economic outcomes to examine cost-effectiveness.
4. Molecular mechanisms: expression of pro-inflammatory genes and genes involved in type 1 interferon responses .

3. STUDY DESIGN

A multi-centre, parallel group, randomised controlled trial with process evaluation, and biological mechanism sub-study.

4. STUDY SETTING

This is a multi-centre randomised controlled trial involving up to twenty-four clinical sites recruiting 544 participants. It is anticipated that the participant population will be recruited from specialist multidisciplinary diabetic foot clinics at participating NHS Trusts. The intervention will be delivered remotely by Healthcare Professionals (HCP) who are independent of the participating Trusts.

Usual care for both arms of the study will be provided by the clinical care teams in primary care, secondary care and community health including community podiatry teams.

Clinical outcome data will be extracted from any relevant healthcare records including (but not limited to) primary care, secondary care, community health and podiatry records.

5. ELIGIBILITY CRITERIA

5.1. Participant Inclusion Criteria

We will include adults who fulfil all of the following inclusion criteria:

- Has diabetes [according to World Health Organization (WHO) criteria].
- Is aged 18 years or over.
- Has two lower limbs (i.e. has not had major amputation of either lower limb).
- Has a recently healed diabetic foot ulcer (if more than one, all must be healed), defined as fully epithelialised with no drainage, healed for a minimum two weeks and up to a maximum of twelve weeks.
- Has cognitive capacity to provide informed consent, to engage with the study intervention (as digital and written handbook versions), to take part in interviews (if randomised to the intervention and selected as part of a sub-sample), and to provide follow-up data
- Has sufficient command of English language and is able to engage with the intervention and to provide follow-up data.

5.2. Participant Exclusion Criteria

We will exclude all adults who meet any of the following exclusion criteria:

- Has active Charcot Neuro-osteoarthropathy.
- Presence of active diabetic foot ulceration.
- In the acute phase of a diagnosed mental illness where being approached about participation could be an extra burden (e.g. currently under the care of MH crisis team or admitted to hospital at the time of recruitment).

- Has previously been randomised to the REDUCE pilot trial.
- Has previously been randomised to this REDUCE trial.
- Is currently taking part in another study which would affect the outcomes of this study (e.g. diabetic foot ulcer wound healing medicinal product trial or other behavioural intervention study).
- Has a healed diabetic foot ulcer, defined as fully epithelialised with no drainage, healed for more than twelve weeks.

5.3. Healthcare Professional Inclusion Criteria

- A Healthcare Professional involved in the delivery of the REDUCE intervention.
- Willing to take part in questionnaires, an interview and have their sessions audio recorded for fidelity assessment.

5.4. Healthcare Professional Exclusion Criteria

- Unwilling to provide informed consent.

5.5. Biological Mechanism Sub-study Inclusion Criteria

- Participating in the main REDUCE trial (thus meeting all criteria in 5.1).

5.6. Biological Mechanism Sub-study Exclusion Criteria

- Unwilling to provide informed consent and undergo venepuncture.
- Venepuncture contraindicated.
- Recruited at sites not participating in the biological mechanisms sub-study (e.g., site does not have the personnel required for phlebotomy).

6. STUDY PROCEDURES

6.1. Recruitment

6.1.1. Participant Identification

6.1.1.1 Trial Participants

Over a 30-month recruitment period potential participants will be identified from and screened by their clinical care team in specialist multidisciplinary diabetes foot clinics at the participating NHS Trusts. Medical records will be accessed only by a member of the existing clinical care team (not by the research team) in order to establish whether they are eligible to be invited to take part in the study. No details about patients will be passed on to the research team at this stage.

Potential participants on clinical caseloads will be screened against the eligibility criteria in the trial sites. Those eligible will be approached about the trial in clinic by their usual clinical carers and given some details about the study, including an information sheet, during a scheduled clinic visit. Participants will be provided with information regarding the trial as soon as possible after healing of all their foot ulcers, but will only be recruited and consented at a separate clinic visit after the ulcer has remained healed for a period of at least two weeks (i.e., clinical definition of healing). If their

foot ulcer however, breaks down during this two-week period, potential participants can be re-screened for eligibility into the trial three further times. Potential participants with a healed foot ulcer can be approached about taking part in the trial up to twelve weeks after their foot ulcer is defined as healed.

It will be clearly stated that the potential 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 a reason for withdrawal. Should new information arise during the study, which may affect a participant's willingness to take part, this will be reviewed for addition to the participant information sheet and a revised consent form will be completed as necessary.

The participant information sheet will also include details on the optional elements of study including qualitative interviews and, where relevant (e.g., in participating sites), the biological mechanisms sub-study.

The potential participant will be allowed as much time as they wish to consider the information, and will be given the opportunity to question the Principal Investigator, the research team, their GP or other independent parties to decide whether they will participate in the study.

6.1.1.2 Healthcare Professionals

Participating healthcare professionals will be known to the study researchers as they will be centrally employed by the sponsoring NHS Trust to deliver the REDUCE intervention remotely to the participants at the participating NHS sites. HCPs delivering the REDUCE intervention will be provided with an information sheet about taking part in pre- and post-training questionnaires, a telephone/virtual interview and the audio recording of the REDUCE intervention sessions they will deliver, together with a consent form and contact details form.

6.2. Participant Consent

6.2.1. Trial Participants

Where potential participants are willing to participate in the study they will be shown the consent form and will be given the opportunity to ask questions about the study.

Informed consent will be obtained by a suitably qualified and experienced local research nurse, healthcare professional or practitioner who has been authorised to do so by the Chief or Principal Investigator, as detailed on the study Delegation of Authority and Signature Log for the study site, and who is deemed to be trained and competent according to the REC approved protocol and applicable guidelines and regulations. The participant must personally sign and date the latest approved version of the informed consent form before any study specific, baseline procedures are performed.

Consent to participate will include participation in the trial, and, if randomised to the intervention consent for the eight REDUCE intervention sessions to be audio recorded and to take part in up to three telephone/virtual interviews (at baseline and approximately 3 months and 6 months – or earlier if there are changes in a participant's circumstances). All participants will be asked to consent to an interview but only a sub-sample of participants will be interviewed (participants will be made

aware of this when they are consented into the interview study). The information sheet will indicate that the audio recording of the REDUCE intervention sessions is for the purposes of assessing the healthcare professional delivery of the intervention sessions, quality assurance and checking fidelity. In addition to written consent, verbal permission for the interviews and intervention sessions to be audio-recorded will be obtained prior to the interviews and each session. In sites that are recruiting for the biological mechanisms sub-study, participants will be asked for consent to take venous blood samples on 2 occasions (baseline and 12 weeks).

Specific consent will be sought to enable the sharing of identifiable data with York Trials Unit (YTU) as part of the study in order to facilitate the collection of outcome data and to receive study reminders (ie. telephone/email/SMS). Research staff at the Universities of Nottingham (UoN) and Edinburgh (UoE) will have access to relevant identifiable data for the processing of the questionnaires, provision of the intervention handbook and website log-in and arranging intervention sessions with HCPs (UoN) and to contact participants to arrange and undertake the interviews (UoE) or support in the arrangement of blood sampling appointments. Participants will be asked to consent to the recording of the intervention sessions, if randomised to the intervention group, as part of the trial consent form and for the recordings to be reviewed by the clinical/health psychologists at King's College London (KCL). HCPs delivering the REDUCE sessions will also have access to contact details to undertaken the sessions. Consent will be sought for de-identified data to be shared with Swansea University for the health economic analysis and with other collaborators at Cardiff University, and the Universities of Bristol and Manchester.

The original copy of the participant consent forms will be stored at the participating NHS Trust. A copy will also be sent securely (by email) to York Trials Unit for storage in the Trial Master File and to enable centralised monitoring. York Trials Unit will verify consent on behalf of University of Nottingham, University of Edinburgh and Kings College London for participant interviews; administration of questionnaires; arranging of intervention sessions and materials (intervention arm only); and audio recording during delivery of intervention sessions.

6.2.2. Healthcare Professional Participants

Healthcare professionals will be appointed to deliver the REDUCE intervention, verbal consent will be obtained by the UHDB team to pass contact details to the University of Nottingham research team, who will make contact with the study documents. Healthcare professionals will be provided with an information sheet and consent form via email and/or post and will have their questions answered by a researcher from the University of Nottingham. Freepost envelopes will be provided for the consent form and contact details form return. Prior to the interview commencing the interviewer will verbally re-check consent for the interview and it's audio-recording.

The original signed form(s) will be retained at UoN while copies will be given to the participant, UHDB and the York Trials Unit. The UoN research team will verify the completion of the consent form for the research teams at Kings College London and University of Edinburgh to minimise the transfer of consent forms.

6.3. The Randomisation Scheme

After obtaining consent and following the completion of all baseline data collection and assessments, trial participants will be randomised. Participants will be notified of which arm they

have been allocated to at the point of randomisation by a member of the unblinded research team, where possible, otherwise they will be notified by a delegated unblinded member of the team as soon as possible.

Participants will be allocated to either:

- ***REDUCE Intervention plus usual care (intervention arm)***
  Eight weeks of one hour one-to-one sessions with a healthcare professional trained to deliver the REDUCE intervention. Participants will also be able to access the web- or booklet-based maintenance intervention. During the intervention period participants will continue to receive usual standard care.
- ***Usual care alone (control arm)***
  Participants will receive usual standard care.

The randomisation schedule will be stratified by ulcer history (one previous ulcer versus more than one previous ulcer) and formed of randomly-permuted blocks of randomly-varying sizes using a 1:1 allocation ratio.

6.3.1. Method of Implementing the Allocation Sequence

Randomisation will be performed by a remote, centralised, online randomisation service provided by the York Trials Unit. Telephone back up will be available if required. The allocation sequence will be generated by a statistician not involved in the study.

Authorised staff at the research will access the online randomisation service hosted by YTU. Staff will be required to provide the participant's trial identification number (obtained from a pre-numbered screening form) and eligibility details to confirm participant eligibility and obtain the allocation. These authorised staff will inform the participant of which trial arm they have been allocated to.

6.4. Blinding and Un-blinding

The blinding of participants and clinicians is not possible in this study due to the nature of the intervention. As a result emergency un-blinding will not be required.

All outcome assessors will, however, be blinded and strategies employed to minimise risk of un-blinding. Outcome assessors will not be delivering the intervention, or involved in the participant's usual care. Although the participant's involvement in the trial will be recorded in the medical notes at the site at which they are recruited, in line with requirements of GCP this will not include allocation arm, which will only be recorded in the case report forms (CRFs). Participants will be instructed on whom they can discuss their allocation with, and from whom they should withhold this information. Should the participant inadvertently reveal their allocation to an outcome assessor, or the assessor become un-blinded for any reason, that assessor will no longer continue to assess outcomes for that participant and this will be recorded in the outcome assessment CRF at the relevant time (6, 12 or 18 months). Additionally, we will ask assessors to indicate which arm they thought participants were in and why at each of the data collection time points.

The YTU statistician conducting the analyses will not be blinded. The primary analysis will be verified by a second statistician at YTU.

6.5. Study Intervention

Following randomisation, consenting participants allocated to the intervention arm will have their details passed to the REDUCE intervention delivery team (UoN) to arrange the intervention sessions. The University of Nottingham research team will provide participants with a copy of the handbook and the website log-in details. The team will liaise with the UoE research team to arrange the baseline interview (where required) and with HCPs delivering REDUCE to arrange the first intervention session (following the baseline interview, where possible, for the sub-sample selected for interview). Participants will receive eight one-to-one sessions (one session per week, where able, over a maximum of 12 weeks) with a REDUCE-trained healthcare professional. The sessions will take place as an online video- or tele-conference via an NHS approved system. Each session will last approximately one hour. The content of the sessions will be as described in section 1.1 The REDUCE Intervention.

Participants in the intervention arm will be provided with access to the maintenance intervention in handbook and website format. The website is accessible by mobile phone, tablet and computer. The website is developed and hosted by a commercial company, Global Initiative (GI), experts in developing and hosting digital interventions for NIHR clinical trials. Content for the website was developed by the University of Southampton Co-Investigator and researchers, with members of the study team.

Participants allocated to the control arm (usual care) will not receive access to the REDUCE intervention one-to-one sessions or the web- or booklet-based maintenance intervention but will continue to receive treatment as usual.

6.6. Data Collection/Study Assessments

6.6.1. Clinical Team Completed Case Report Forms (CRFs)

Case report forms will be used to collect the following clinical and demographic data:

- Screening:
  - Inclusion and exclusion criteria;
- Baseline:
  - Participant contact details – name, address, telephone number and email address
  - Demographics (date of birth) and NHS number;
  - Previous medical history – duration (years) and type of diabetes, most recent HbA1c value if available, depression, documented peripheral neuropathy, documented peripheral arterial disease (PAD), visual impairment, other relevant conditions;
  - Diabetic foot ulcer (DFU) history – single ulcer versus multiple ulcers, most recent episode confirmed healing date, activity/education/footwear;
- Clinical outcomes (via notes review by blinded outcome assessors)
  - Ulcer-free days;
  - Days to re-ulceration (if re-ulceration occurs);
  - Number of new ulcers;
  - Days in hospital (related and not related to foot ulcer disease);
  - AEs;
  - SAEs;
  - Amputations – major and minor;
  - Mortality.

The clinician baseline CRF will be completed on paper; a copy of the completed CRF will be securely stored in the site ISF and the original CRF will be posted to YTU.

Healthcare professionals who are not involved in delivering the REDUCE intervention, the research outcome assessors (nurses or practitioners) will support the collection of clinical outcome data at six, 12 and 18 months post randomisation. Data will be collected from relevant health care records, to include but not limited to, secondary care, GP, community health and community podiatry records. Paper forms will be provided, a copy of the completed CRF will be securely stored in the site ISF and the original CRF will be posted to YTU.

Intervention session details will be collected and will include:

- Session number;
- Date;
- Attendance;
- Session delivered by;
- Length of session;
- Interventions/modalities delivered;
- Completion of home practice.

6.6.2. Participant completed CRFs

All participants will be asked to complete demographic and general information about their health following consent including: declared ethnicity, marital status, highest level of education, and employment status.

To assess the psychological and behavioural outcomes, they will be asked to complete the following validated questionnaires at baseline (prior to randomisation), and at six weeks, three months, six months and 18 months post randomisation:

- Brief Illness Perception Questionnaire (B-IPQ):
  Examines the participant's perception of their illness [22].
- Cognitive and Behavioural Responses Questionnaire (CBRQ) – short version; sub-set of items:
  Examines participant's beliefs about their symptoms [23].
- Patient Health Questionnaire-9 (PHQ-9):
  Assesses depression [25].
- International Physical Activity Questionnaire - Elderly (IPAQ-E) – short form:
  Assesses participant physical activity [26].
- Nottingham Assessment of Functional Footcare (NAFF):
  Examines foot self-care behaviours [28].
- Scale of Positive And Negative Experience (SPANE-P) - positive items only:
  Examines positive feelings [29].
- Social Provisions Scale (SPS) 5-item scale:
  Examines social relationships and support [30].

For the health economic analysis, participants in both arms will be asked to complete the following questionnaires at baseline six months and 18 months post randomisation:

- ICEpop CAPability measure for Adults (ICECAP-A):
  Measures capability in adults including attachment, stability, achievement, enjoyment and autonomy [31].

- EQ-5D-5L consisting of the EQ5D descriptive system and the EQ Visual Analogue Scale (EQ VAS): Measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression [32].
- Items on resource use.

All participants will be asked at baseline, 6 weeks, 3, 6 and 18 months about time taken to contact a healthcare professional when last noticing changes in their feet. Participants in the intervention arm will also be asked a couple of questions about recent usage of the handbook (at 3, 6 & 18 months) and about practicing what they have learned during the intervention session period (at 6 weeks and 3 months).

The baseline participant questionnaire will be provided as a paper copy along with a freepost envelope to facilitate return. Participant follow-up questionnaires will be completed on paper, returned by freepost envelope, or electronically subject to participant preference. There will be up to three reminders per questionnaire where a questionnaire is not received by the research team. The first reminder via SMS (or telephone if only a landline contact number is given) will take place 14 days after due date. A second reminder will be via a letter by post and sent after 21 days after due date, where required. A final reminder by telephone will be made by a member of the research team after 28 days after due date, contact with the participant will be made over 3 attempts (varying time and day). Telephone completion of follow-up questionnaires with a member of the research team will be offered if required. In addition to the retention strategies above, participants will receive a pre-notification SMS up to 1 week before their questionnaire is due to alert them of the upcoming questionnaire.

Participants will take part in the trial for up to eighteen months. Participants will be considered lost to follow up if attempts to contact them fail repeatedly (i.e., participant does not respond to telephone, postal and/or email contact over a two-month period).

Intervention participants will receive a telephone/email/SMS reminder for their REDUCE one-to-one sessions. Where required, the healthcare professionals/University of Nottingham research team may contact the participant regarding any missed intervention appointments, and to re-book the intervention session.

6.6.3. Web-based Maintenance Intervention (MI)

Intervention participants will access the web-based MI using an assigned sign-up code, used to identify their website accesses. Access and usage data is accessible by the commercial company (Global Initiative) via website analytics, e.g. Matomo Analytics. Members of the research team at the University of Nottingham have access to the usage data, which includes data on visits to the website, pages views, duration of views on each page, etc. which can be used for analysis of website usage as part of the trial. The participant IP addresses and location information are visible in Matomo Analytics, however on downloading these data, prior to storage or sharing, these personal details will be removed as participant identifier is available. Participants in the intervention arm will be able to access the website during the follow-up period of 18 months post-randomisation.

6.6.4. Interviews with Participants in Intervention Arm

A sub-sample of approximately 20 participants who are randomised to the REDUCE intervention arm

will take part in the interview study. Purposive sampling will be used so there is diversity in the sample with respect to age, gender, occupation/socio-economic status and diabetes duration. Sampling decisions may also be informed by emerging findings arising from analysis of initial interviews. Where possible, individuals will be interviewed at baseline and approximately three months and six months later. However, some individuals may be offered a one-off interview at the 6-month time point only; for example, if an individual is recruited to replace a participant who withdraws from the longitudinal interviews. The interviews will examine: participants' expectations of the REDUCE programme and their illness perceptions and self-management practices pre-trial; participants' engagement with the different elements of REDUCE Intervention (initiation and maintenance phases) and whether, how, and, why, this engagement leads psychological and behavioural changes; and, barriers/facilitators to maintenance of key self-management behaviours over time. Findings will be used to aid interpretation of trial results by establishing whether the initiation and maintenance phases of the intervention work as intended and whether any unintended consequences arise from delivery and receipt of the intervention. Findings will also be used to inform recommendations for rollout of the REDUCE intervention post-trial.

These interviews will be undertaken by an experienced qualitative researcher at the University of Edinburgh, by telephone or virtually at a time convenient to participants. They are expected to last around 45-60 minutes each (although this will depend on what participants have to say) and will be audio recorded using an encrypted digital device, and later transcribed.

6.6.5. Interviews with HCPs

All healthcare professionals involved in intervention delivery will be given the opportunity to take part in an interview in the later stages of the REDUCE trial (by which stage they should have a substantial body of experience upon which they can draw). However, some interviews may take place earlier – if, for example, a healthcare professional leaves their post early. The interviews will explore healthcare professionals' experiences of delivering the 1-to-1 sessions (including any difficulties and challenges encountered), their views about which patients benefit most/least from receiving REDUCE, and why, and their views about the resourcing and support colleagues would need to deliver the REDUCE programme in routine clinical care. These interviews will be undertaken by an experienced qualitative researcher at the University of Edinburgh, by telephone or virtually at a time convenient to health professionals. They are expected to last around 45-60 minutes each (although this will depend on what interviewees have to say) and will be audio recorded using an encrypted digital device, and then transcribed.

6.6.6. Assessing Intervention Fidelity

It is the aim that all intervention sessions will be audio-recorded. Assessment of intervention fidelity will be conducted at the individual level and will focus on randomly selected sessions, whilst ensuring that all eight treatment sessions are covered to ensure all components of the treatment, and all items of the scale, are examined. The selected sessions will be rated using the fidelity tool by two skilled assessors. A proportion (10%) of sessions will be rated twice to establish inter-rater reliability. Construct validity will be assessed by ensuring items on the scale match the content of the intervention and by examining the scores on the items of the scale and supervisor observations. Competency will also be examined by determining how sensitively the interventions are used with individual clients. The tool contains item descriptors and numerical scores. A Guideline for Assessors has been produced, piloted and refined. We will report overall integrity as well as component

integrity. The Fidelity Tool will also be used to provide descriptive feedback to HCPs to enhance their supervision and refine skills. This may positively improve the reported integrity ratings, if HCP skills are influenced by feedback and skills practice as part of supervision.

6.6.7. Biological Mechanism Sub-study

Non-fasting peripheral blood samples (3 vacutainers, approx. 15-20ml total) will be taken via venepuncture at baseline and 12 weeks post-recruitment. Research/clinical staff (e.g., nurse, phlebotomist or other suitably qualified person) will take baseline samples in diabetic foot clinics, or other appropriate settings (e.g., hospital phlebotomy clinic, GP surgery), at the point participants are randomised in the main REDUCE trial, but prior to receiving any REDUCE intervention sessions. The follow-up 12-week sample will be collected as part of an additional study visit, typically at the same diabetic foot ulcer clinic and participants' travel expenses will be reimbursed.

The primary objectives of this sub-study are as follows:

To quantify changes in CTRA gene transcriptional responses among patients in both arms of the REDUCE trial – to examine whether REDUCE influences CTRA gene expression.

To measure (a) levels of pro-inflammatory and pro-healing/regulatory cytokines (e.g., interleukin-1beta, interlukin-6, interlukin-8, tumor necrosis factor, transforming growth factor beta) and (b) levels of the cells that secrete them (e.g., monocyte/macrophages and dendritic cells). This will allow us to investigate if REDUCE affects the circulating immune environment.

To conduct analyses exploring the relative contribution of biological, psychological and behavioural pathways on ulcer outcomes, among patients participating in the REDUCE trial.

A flow diagram showing how and where samples are collected, processed, and transported is presented in Appendix 4.

For RNA analyses, samples will be collected into PAXgene RNA tubes, refrigerated at recruiting sites and shipped overnight to University of Nottingham on gel packs (e.g., 4c), before being sent in batch for RNA sequencing and analysis to the University of California, Los Angeles (Co-applicant Professor Steve Cole's Lab). For circulating immune profile analysis, sera will be collected in serum advance SST2 vacutainers, separated, and shipped overnight to the University of Nottingham on gel packs (e.g., 4c) for analysis (Co-applicant Professor Amir Ghaemmaghami's Lab). If required, sites can store separated sera overnight at 4c, before shipping the next day. Alternatively, if the site prefers and has existing capacity to do so, sera can be stored frozen (at -20c or -80c) for a longer period and returned with other samples in batch at the end of recruitment.

We will also collect peripheral blood mononuclear cells (PBMCs) in EDTA vacutainers. Samples will be refrigerated at recruiting sites and shipped overnight to University of Nottingham on gel packs (e.g., 4c). PBMC's will then be isolated, frozen at -80c and stored to the University of Nottingham for storage and use in potential future research where participants have consented for this (after appropriate ethical approval).

6.7. Methods to Enhance Recruitment and Retention

The importance of ensuring trials are able to recruit and retain participants is important for the quality of the trial. Strategies can be included to support the recruitment and retention of

participants. However, it is also important to rigorously evaluate these strategies by embedding them in actual clinical trials [33, 34]; also known as Studies Within A Trial (SWATs). The REDUCE trial will include a SWAT to evaluate whether sending a birthday card improves the retention of participants in trials involving an adult population. A separate protocol has been developed for this SWAT using the methodology of embedding trials developed and published by the MRC START (Systematic Techniques for Assisting Recruitment to Trials) initiative [35]. Please refer to Appendix 3 for details of this SWAT.

6.8. Withdrawal Criteria

Participants will have the right to withdraw from the study any time, without giving a reason. In addition, the Investigator may advise that a participant be discontinued from the study at any time if the Investigator considers it necessary for any reason; however the decision on full withdrawal will remain with the participant at all times. It will be made clear in the PIS that should they wish to withdraw this will not affect their future clinical care, although data collected to that point as part of the research will be retained.

The reason for withdrawal will be recorded within study documentation. If the participant is withdrawn due to an adverse event, the Investigator (or appropriate nominee listed on the delegation of responsibilities log) will complete follow-up visits or telephone calls until the adverse event has resolved or stabilised.

Participants who request to withdraw during a study assessment or by contacting the research team will be asked which elements they would like to withdraw from. This could be:

I. Withdrawal from intervention - Where a participant wishes to withdraw from the intervention (proposed pathway), but is prepared to complete the follow-up questionnaires, complete any interviews (if randomised to the intervention arm and selected for interview) and is happy for their medical records to continue to be accessed with relevant outcome data extracted. This is pertinent only to the intervention arm of the study.
II. Withdrawal from follow-up questionnaires - Where a participant wishes to withdraw from completing the follow-up questionnaires only. This is applicable to both arms of the study. Outcome data will continue to be accessed and extracted from the participant's medical records.
III. (For the process evaluation sub-sample only.) Withdrawal from baseline and/or follow-up interview(s) only – Where a participant wishes to withdraw from taking part in any of the interviews. This is applicable to the intervention arm only. The participant will continue to receive follow-up questionnaires (as appropriate) and outcome data will continue to be accessed and extracted from the participant's medical records.
IV. Full withdrawal (including outcome data extraction) - Where a participant wishes to withdraw from the study, from the intervention (where applicable), from completing any follow-up questionnaires, from completing any interviews (if randomised to the intervention arm and identified for interview) and does not wish their medical records to be accessed or for outcome data to be extracted. This is applicable to both arms of the study.
V. Full withdrawal (excluding outcome data extraction) - Where a participant wishes to withdraw from the study, from the intervention (where applicable), from completing any follow-up questionnaires, and from completing any interviews (if randomised to the

intervention arm and identified for interview). The participant does consents to their medical records being be accessed or for outcome data to be extracted. This is applicable to both arms of the study.

Where researchers are informed about a participant's loss of capacity during their time in the study, they will be withdrawn from further follow up; however data collected until this point will be retained for use. No further data would be collected or any other research procedures conducted in relation to the participant.

Healthcare professionals will have the right to withdraw from the questionnaires and interviews at any time without giving a reason. Any study data provided up to that point will still be used and healthcare professionals will be notified of this prior to consent.

6.9. Storage and Analysis of Samples

Samples will be stored and labelled using the participants' unique study identifier, time point, initials and study name.

Blood samples will be collected in 3 types of vacutainers for later analyses: (1) Serum Advance SST2: approximately 5ml; (2) EDTA: approximately 5ml; (3) PAXgene RNA tubes: approximately 2.5ml. As appropriate, samples will be centrifuged on site, serum isolated, aliquoted, and shipped overnight (next day delivery) to the University of Nottingham in compliant packaging on gel packs. All shipments will contain a complete inventory of all samples, along with the name of the person responsible for sending the samples. If required, sites can store separated sera overnight at 4c, before shipping the next day in the same manner. Alternatively, if the site prefers and has existing capacity to do so, sera can be stored frozen (at -20c or -80c) for a longer period and returned with other samples in batch, on dry ice, via courier at the end of recruitment.

RNA tubes will be analysed at authorised laboratories at the University of California, Los Angeles. The analysis of serum will take place at the University of Nottingham within the School of Life Sciences, and also at other authorised laboratories within the University of Nottingham. PBMCs will be stored and potentially analysed, subject to adequate funding, at the same laboratories. If participants are agreeable and sign the optional clause on the consent form, remaining samples will be placed into storage at the University of Nottingham for potential use in future research. Where participants do not agree to the future use of the samples, they will be destroyed in accordance with the Human Tissue Act, 2004.

6.1. LABORATORY ANALYSES

Blood Samples will be assessed for a variety of immunological parameters relevant to skin repair and wound healing (e.g., pro-inflammatory cytokines). RNA analyses will also be conducted to examine gene expression (specifically relating to CTRA profile). The analyses will be conducted by the study team, overseen by co-investigators Professor Steve Cole (University of California, Los Angeles) and Professor Amir Ghaemmaghami (University of Nottingham). All analyses will be completed at UCLA or University of Nottingham using equipment and laboratories serviced and managed at those institutions.

6.2. End of Study

The end of study will be defined as 'last participant last visit' i.e., the date at which the last participant has completed their final study process. The CI will notify the Sponsor, participating sites and REC within 90 days of the end of study.

7. SAFETY REPORTING

7.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a trial participant (i.e., any unfavourable and unintended sign, symptom or disease), which is related to study ulcer and/or to the study treatments (intervention or control).
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.

7.2. Operational Definitions for (S)AEs

An adverse event (AE) in this trial is any untoward medical occurrence in a participant to whom a trial intervention or procedure has been delivered, including occurrences which are not necessarily caused by or related to that intervention or procedure.

AEs which might be expected among DFU participants include:

- Re-ulceration
- New ulcer
- Ulcer infection

Adverse events which may be expected, do not need to be reported as part of the trial, however sites will need to follow their usual reporting procedures for the recruiting site. AEs which are NOT considered related to the intervention or procedure do not need to be reported unless they are considered SAEs. Only SAEs which are related to the trial intervention or procedure which are unexpected need to be reported using the REDUCE AE/SAE Form.

7.3. Recording and Reporting SAEs

Adverse events should be entered onto the AE/SAE form and reported to York Trials Unit within five days of discovery or notification of the event by clinical sites. In addition, sites should follow their own local procedures for the reporting of any adverse events linked to clinical care.

SAEs should be entered onto the REDUCE AE/SAE form and reported to York Trials Unit within 24 hours of discovery or notification of the event. Once received, causality and expectedness of the SAE will be confirmed by the Chief Investigator or another clinical member of the Trial Management Group (if the CI is unavailable).

SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) and Sponsor within 15 days. All such events will be reported to the Trial Steering Committee at their next meeting.

All events will be followed up until the event resolves or a decision is made for no further follow up. Participants experiencing SAEs which are deemed to be related to the trial treatments (intervention or control) and which remain ongoing at the time of participant trial exit will be followed up for one further month beyond trial exit.

Where repeated adverse events (serious or non-serious) of a similar type are observed, these will be discussed with the TMG and other relevant groups and will be onward reported to the REC and Sponsor should concerns be raised in relation to the type of event and/or frequency observed.

7.3.1. Assessment of AEs and SAEs

7.3.1.1 Severity

The Investigator will determine the severity of the AE;

- Mild: no interference with daily activities.
- Moderate: moderate interference with daily activities.
- Severe: considerable interference with daily activities (e.g. inability to work).

NOTE: to avoid confusion or misunderstanding the term “severe” is used to describe the intensity of the event, which may be of relatively minor medical significance, and is NOT the same as “serious” which is described in the safety definitions.

7.3.1.2 Causality

Clinical judgement will be used to determine the relationship between the study procedures and the occurrence of each AE;

- Not-related: There is no evidence of a causal relationship between the event and study procedures.
- Related: There is evidence of a causal relationship between the event and study procedures, i.e., a relationship to the study procedures cannot be completely ruled out.

Assessment of causality must be made by the PI or other delegated member of the study team suitably qualified to complete this activity.

7.3.1.3 Expectedness

The assessment of expectedness is only required if the event is deemed to be related to study procedures.

- Expected: Event previously identified and described in the protocol.
- Unexpected: Event not previously described in the protocol.

The expectedness assessment is delegated to the local PI.

7.4. Pregnancy Reporting

Not required.

7.5. Reporting Urgent Safety Measures

If any urgent safety measure is required UoN & York Trials Unit will notify the Sponsor within 24 hours using the Sponsor's safety incident reporting form. Any immediate actions will be advised to the study teams at recruiting sites in writing. Study teams will be asked to confirm receipt and implementation of any action

The Sponsor will inform the REC and in conjunction with YTU and the Chief Investigator will advise participating sites. This will be followed up within three days by notice in writing setting out the measures taken and the circumstances giving rise to those measures on implementation of the urgent safety measure, with a plan for further action.

8. DATA HANDLING

A separate Data Management Plan (DMP) will be in place for the handling of the data between participating NHS sites, York Trials Unit and the research team.

8.1. System and Compliance

Completion of participant-completed follow-up questionnaires may be undertaken (subject to participant preference) using the web-based survey tool, Online Surveys (formerly JISC). Online Surveys will also be used for the healthcare professionals' pre- and post-training questionnaires. A copy of the data protection and security information from the tool's website will be obtained and stored in the Trial Master File. The survey tool displays the data security, back-up and encryption information on their website, (e.g., Online Surveys is certified to ISO 27001 standard, see: https://www.onlinesurveys.ac.uk/ [Accessed 23 December 2021]).

Electronic-completed follow-up questionnaire data at 6 weeks, 3 months, 6 months and 18 months will be considered source data, as will telephone-completed questionnaires for which hard copy questionnaires will be completed and entered. The electronic-completed healthcare professionals' pre- and post-training questionnaire data will also be retained as source data.

8.2. Data Handling and Record Keeping

Each site will hold data according to the current Data Protection Act (2018) and the General Data Protection Regulation (2018). Data will be collated in CRFs identified by a unique identification number (i.e. the participant identification number) only. A Trial Enrolment Log held at individual sites will list the participant identification numbers. YTU will maintain a list of participant identification numbers for all trial participants at each site.

All information collected during the course of the study will be kept strictly confidential. Personal addresses, postcodes and other contact details of consenting participants will be stored on the study specific participant management system at YTU, for the purposes of assisting in follow-ups during the study. Only relevant members of the research team will have access to this system, accessible via individual password. Permissions for access of this information will be detailed within the study delegation log. All participant data will be coded by a participant number in all manual and electronic files to ensure confidentiality.

Data from the participant-completed paper forms will be manually entered into a database and data from the participant-completed electronic forms will be stored directly into the database. Online Surveys will be used to record and store the data from both paper and electronic forms.

A proportion of paper forms will be second checked against the hard copy of the questionnaire, using a continuous sampling procedure. One in ten forms entered will initially be second checked, however if on any check the error rate exceeds 2% the following ten will each be second checked. Only where the following ten forms are below this error rate will second checks return to a rate of one in ten. Data is error checked and then validation checks are run against the database. Discrepancies identified during validation which require resolution will be communicated to the relevant person who is in a position to obtain the information required to rectify the discrepancy.

Information will be held securely on paper and electronically at the above mentioned departments, including appropriate storage, restricted access and disposal arrangements of participant personal and clinical details. Participants will not be identified in the results of the study. Personal data will be processed under Article 6 (1) (e) (Processing necessary for the performance of a task carried out in the public interest) and Special Category data under Article 9 (2) (j) (Processing necessary for ... scientific ... research purposes) of the General Data Protection Regulation (2018).

Anonymised copies of the data (e.g. questionnaires, intervention session recordings, fidelity tool data, training and attendance records) will be retained for a period of five years and thereafter destroyed. Data with personal information (including contact details forms and audio recordings) will be deleted after the study period and write-up are complete (maximum three years after study end). Personal data considered source data, e.g. names on consent forms and in the enrolment log will be retained for five years.

8.2.1. Trial Participant Data

Anonymised case report form data will be stored in a database held at the University of York. This data is only accessible by relevant members of the data management team who are responsible for checking and validating the data. This will be accessible via individual password. Permissions for access of this information will also be detailed within the study delegation log. The server on which the database will be housed is secure and is subject to rigorous testing and continued backup. Once finalised and locked, the dataset will be transferred to those responsible for the analyses.

The REDUCE Trial Management system will be used to record participant details, and CRF completion. This will be accessible via individual password to those listed on the study delegation log. The server on which the management system will be housed is secure and is subject to rigorous

testing and continued backup. Once finalised and locked, the dataset will be transferred to those responsible for the analyses.

All documents will be stored safely in confidential conditions. Any paper forms containing participant identifiable information (e.g. patient contact details form and consent form) will be held in a location separate to the questionnaire data. Identifiable information will be stored securely in a locked filing cabinet, in an office only accessible via registered swipe card access held by the York Trials Unit research team (As per YTU Standard Operating Procedure [YT03]).

8.2.2. Health Economic Data

For the health economic analysis, unit cost information will be identified from the pilot CRFs prior to the main trial, where costs items cannot be identified from published sources, the REDUCE research team will be asked to provide estimates. The finalised and locked dataset will be stored on the Swansea University network, accessible by user id and password.

8.2.3. Process Evaluation Data

Interviewee names and contact details will be relayed to the qualitative research team via encrypted and password-protected electronic files sent using the University of York secure encrypted drop off service (see section 8.3) and retained by the qualitative team for no longer than necessary for them to complete the interviews.

Interviews will be audio-recorded using an encrypted digital recorder and stored as digital audio-files and (once transcribed) as Word files. Recordings and transcripts will be given a unique reference, which will not include any identifying information (e.g., names or initials).

The digital audio-files will be transcribed by a professional transcription company with whom a data processing agreement is in place. The audio-files will be transferred to that company using an SSL secure file upload service or similar, and transcripts returned using an encrypted email system, such as Egress.

Identifying information such as names (of people and places) will be removed during the transcription process. Access to the full/raw qualitative data, i.e., transcripts, will be limited to the qualitative research team. This data will be stored in electronic form in a secure folder on the University of Edinburgh network, accessible only to named users with an appropriate user ID and password. Any paper copies of transcripts will be stored in a locked cabinet in a locked office.

8.2.4. Fidelity Assessment Data

Intervention session audio recordings will be obtained by the healthcare professional delivering the REDUCE intervention via an encrypted digital audio recorder. Recordings will be uploaded and stored initially on NHS computers. Healthcare professionals will transfer the audio files to the King's College London research team via email from their nhs.net email addresses using NHS encryption or, where file size exceeds that which can be transferred via NHS email, using a Secure Online Cloud Storage facility, provided by the University of Nottingham, only accessible by relevant members of the research teams from King's College London, University of Nottingham and the healthcare professionals.

Intervention session audio recordings and fidelity assessment data will be given identifiers to ensure confidentiality. Data will be stored on Kings College London servers, backed up and accessible only by members of the research team on the delegation log who have university usernames and passwords. Independent assessors follow a data handling protocol which ensures recordings remain securely held and are used only for the purposes of fidelity assessment and supervision, or for training purposes; permission is obtained from both the participant and the HCP. Recordings are destroyed at the end of the trial.

8.2.5. Web-based Maintenance Intervention Usage Data

The data will be transferred from the University of Nottingham to the University of York using secure file transfer protocol. IP addresses and location information of participants will not be stored or transferred.

8.2.6. Biological Samples Data

Samples will be analysed by authorised laboratories at the University of Nottingham and the University of California, Los Angeles (UCLA). The samples to the University of California, in the United States will be transferred by secure courier, with a strict confidentiality agreement in place. Appropriate checks and risk assessments have taken place to ensure the University of California have the necessary controls in place which means samples are looked after in a similar way to as they would be at the University of Nottingham. Samples will be securely disposed of by the University of California once the analysis has been completed. Data generated from analyses at UCLA will be transferred as required back to the University of Nottingham using secure encrypted email or file transfer protocol for use in statistical analyses.

8.3. Data Access and Security

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. The research team includes collaborating investigators from outside of the Sponsor/host institution who may require access to data (including personal data).

York Trials Unit will have access to data entered by the participating NHS Trusts (screening and enrolment logs, consent forms, clinical assessment CRFs, participant contact details), healthcare professionals (intervention attendance records) and University of Nottingham research team (participant questionnaire data).

York Trials Unit will provide access to limited datasets for research staff at the University of Nottingham to enter and review questionnaire management data and to update participant contact details. Research staff at UoN will require access to participant contact details to update these as necessary and to contact participants to provide the follow-up questionnaires and reminders. HCP contact details are required for arranging of REDUCE sessions. The University of Nottingham research staff will scan hard copy participant questionnaires and enter the questionnaire data into Online Surveys (see 8.2). Scanned copies of questionnaires will be stored on University of Nottingham cloud-based servers, backed up regularly and accessible by those on the delegation log

via usernames and passwords. YTU will receive the questionnaire data for analysis using their secure encrypted drop off service.

York Trials Unit will receive the web-usage data from the University of Nottingham research team via the secure encrypted University of York drop off service and will provide to the University of Edinburgh, King's College London and Swansea University research teams.

The University of Edinburgh research team will require access to the contact details of intervention participants and HCPs to arrange and conduct the interviews. This will be provided by York Trials Unit using an encrypted Microsoft Excel spreadsheet, sent using the University of York secure encrypted drop off service. The University of Edinburgh will share de-identified data from the interviews, e.g. quotes and themes with the University of Nottingham, Swansea University and King's College London research teams where appropriate to the analyses.

The Swansea University research team will require access to the de-identified questionnaires, clinical assessments and resource use data including from the intervention session logs. This will be provided by York Trials Unit using the University of York secure encrypted drop off service.

The King's College London research team will require access to healthcare professionals' contact details, pre- and post- training questionnaire data and website usage data. They will also require access to recordings of participant sessions.

As part of the biological mechanisms study, co-investigators at The University of Bristol and Cardiff University will require access to limited datasets covering questionnaire data collected, biological samples results and clinical outcome data. This will be provided, as required, using a secure file protocol from York Trials Unit and the University of Nottingham as appropriate.

The TMG and JT-IPSC will have sight of relevant de-identified aggregate data as part of their oversight at the management group and steering committee.

8.4. Archiving

At the end of the study, following completion of the end of study report, York Trials Unit will securely archive all centrally held study related documentation in the Trial Master File for a minimum of five years. At the end of the defined archive period arrangements for confidential destruction will be made.

It is the responsibility of each PI to ensure that data and all essential documents relating to the study are retained securely for a minimum of five years after the end of the study, and in accordance with national legislation. In conjunction with the Sponsor, York Trials Unit will notify sites when study documentation held at sites may be archived, and then destroyed. All archived documents must continue to be available for inspection by appropriate authorities upon request.

9. STATISTICS, HEALTH ECONOMICS AND DATA ANALYSIS

9.1. Sample Size Calculation

We have limited data on number of ulcer-free days on which to base a sample size including the standard deviation and potential difference we will observe. Thus, our calculation is based on the difference in percentage of participants remaining ulcer-free over follow-up. We acknowledge that it is unconventional that our sample size calculation does not match our primary analysis (i.e., using a sample size calculation for proportions when the primary outcome 'ulcer free days' is measured as continuous count variable). However, the approach we have adopted can be regarded as conservative as it will underestimate the power of our analysis.

Approximately 60% of patients will still be ulcer-free at 12 months[9] (40% within 3 years). Thus, we assume that 55% of control participants will remain ulcer-free over the 18 month follow-up. Our target sample size will permit detection of a 15% increase in patients remaining ulcer-free over follow-up i.e., from 55% to 70% (risk ratio=1.3). An intervention effect of this size, with 90% power and 5% significance, requires 217 patients per group (Stata v15, chi-squared test comparing two independent proportions). Allowing for 20% loss to follow-up increases the total sample size to 544 (i.e., 272 in each group). Experience from previous trials with comparable patient groups suggests that the 20% estimate is not unreasonable. For example, the Heels trial reported 11% loss to follow-up over 6 months and Venus III 12% at 12 months[36, 37].

9.2. Biological Mechanisms Sub-study Sample Size Calculation

No previous studies have examined the effect of a psychological and behavioural intervention on CTRA gene responses in diabetic patients. However, previous research by the applicants have examined CTRA gene responses to a cognitive-behavioural intervention in non-diabetics, demonstrating a between group effect size of d=0.7 on a single composite measure combining the 53 CTRA gene-set [50].

Using G*Power 3.1, we calculated that using the same outcome to reliably detect a more conservative effect size of d=0.5, with 80% power, in a two tailed independent samples t-test would require a total sample size of 128 participants (64 per arm). Allowing for 10% attrition, we initially proposed a target sample size of 142 patients (71 per arm). However, recruitment into the sub-study was hindered by delays in approvals and study set-up. Consequently, the target sample size was revised to n=100 participants in Protocol version 3.3 (13th August 2024). This revised sample size is estimated to detect an effect size of d=0.6, with 80% power, in a two tailed independent samples t-test, allowing for 10% attrition.

9.3. Trial Stop-Go Criteria

Recruitment and data collection will be assessed against pre-defined stop-go criteria.

We propose the following criteria to determine trial progression at 9 months (based on target recruitment of n=200):

- Green (continue):

1. Recruit ≥ 140 participants (70% of predicted sample-size).
2. Complete outcome data collection at 6 months post-randomisation in ≥ 80% of eligible participants.

- Amber (discuss remedial plan with PGfAR and continue subject to approval):
  1. Recruit 100-140 participants (50-70% of predicted sample-size);
  2. Complete outcome data collection at 6 months post-randomisation in 50-80% of eligible participants.

- Red (halt trial unless credible plan to increase recruitment is agreed with PGfAR):
  1. Recruit <100 participants (50% of predicted sample size);
  2. Complete outcome data collection at 6 months post-randomisation in 50% of eligible participants.

9.4. Planned Recruitment Rate

We will enlist up to 40 sites to recruit 544 participants over a 30-month period. This would mean a recruitment yield of approximately 18 participants per month. The TMG will monitor recruitment and will determine whether recruitment estimates need to be refined. The recruitment rate will be adjusted to reflect the gradual/phased/stepped opening of recruiting sites.

9.5. Statistical Analysis

A statistical analysis plan (SAP) giving full details of the planned analyses will be drafted and reviewed by the Trial Management Group and the Trial Steering Committee. Analyses will be conducted in Stata version 17 or later. Treatment effects and corresponding 95% confidence intervals will be reported, and statistical significance will be assessed at the 5% level.

9.5.1. Summary of Baseline Data and Flow of Patients

Baseline characteristics will be presented descriptively by group. Continuous data will be presented using means and standard deviations or medians and ranges as appropriate, and categorical data will be presented using frequencies and percentages.

For the analysis of the trial a CONSORT flow diagram will be provided to display the flow of participants through the study, including patients:

- Assessed for eligibility,
- Frequency of each reason for not being eligible
- Found eligible,
- Excluded before consent (and the frequency of each reason for exclusion),
- Consented,
- Excluded before randomisation (and the frequency of each reason for exclusion),
- Randomised,
- Allocated to each randomisation group,
- That received each allocated intervention,
- That did not receive each allocated intervention,

- Lost to follow-up (and the frequency of each reason for loss to follow-up) for each analysis group,
- Analysed for each analysis group,
- Not analysed (and the frequency of each reason for not being analysed) for each analysis group.

9.5.2. Outcome Analysis

All outcomes will be reported descriptively at all collected time points. The primary analysis will be on an intention-to-treat (ITT) basis, analysing patients in the groups to which they were randomised. The number of ulcer-free days will be analysed using a mixed-effects Poisson regression model, or negative binomial model as appropriate. The model will adjust for ulcer history and other relevant baseline covariates as fixed effects. Centre will be adjusted for as a random effect. Length of follow-up will be incorporated into the model to take into account participants who are lost to follow-up before 18 months post-randomisation. The total number of days spent in hospital will be analysed in a similar manner.

The proportion of participants remaining ulcer-free will be compared between the two groups using a mixed-effect logistic regression including the same fixed and random effects used in the primary analysis. Other binary secondary outcomes will be analysed in a similar manner.

Time to re-ulceration will be analysed via a Cox Proportional Hazards regression model adjusting for the same fixed and random effects used in the primary analysis. Other time-to-event secondary outcomes will be analysed in a similar manner.

Psychological/behavioural outcome measures will be analysed using mixed-effect linear regression models adjusting for relevant baseline covariates as fixed effects and centre as a random effect.

Economic outcomes will examine cost-effectiveness of the REDUCE intervention.

9.6. Subgroup Analyses

Subgroup analyses will be pre-specified in the statistical analysis plan.

9.7. Adjusted Analyses

Details on adjusted analyses are provided in Section 9.4.2.

9.8. Interim Analysis and Criteria for the Premature Termination of the Study

There are no planned interim analyses, and as there will not be a Data Monitoring Committee for this study it is not anticipated that there will be any interim analyses, other than the analysis of the internal pilot as detailed in Section 9.2.

9.9. Analysis Groups

The analysis of the primary and secondary outcomes will be carried out on an intention-to-treat basis. Complier-average-causal-effect (CACE) analysis will be carried out to assess the effectiveness of the intervention in participants who complied with their allocated treatment.

9.10. Procedure(s) to Account for Missing or Spurious Data

Missing data patterns and reasons for missingness will be explored. Multiple imputation by chained equations will be used to explore the impact of missing data on the primary analysis.

9.11. Health Economic Analysis

A health economic analysis plan (HEAP) outlining the details of the planned analyses will be drafted before the main trial data collection has been completed, conforming to the best practice for HEAPs [38] and reviewed by the Trial Management Group and the Trial Steering Committee. This will include preliminary work, a structured review of relevant economic evaluations and an initial plan for a model-based analysis. The framework for the economic evaluation will be developed based on the initial pilot trial analysis, and refined prior to completion of the main trial data collection. The detailed for the planned analyses will be defined based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERs) [39].

A healthcare service/personal social services perspective (PSS) will be adopted for the primary analyses; this will be extended to a broader perspective (patient/carer and societal) including non-healthcare resource use and estimation of lost productivity. A resource use measure has been developed using a modified Delphi process involving patients and healthcare professionals who work with people with DFUs. This was tested in the pilot trial to determine completion levels, and to identify any additional resources to include. This allows us to capture the range of costs related to DFUs including personal and societal costs. The intervention and usual care resource use will be calculated based on the intervention sessions logs and interviews with the trial clinical team. Published unit costs will be used to value resource use in £ sterling [40].

Two health economic outcome measures, EQ-5D-5L [41] and ICEpop CAPability measure for Adults (ICECAP-A)[42], were tested in the pilot trial (WP2) to assess participant completion and missing items. Based on review of the baseline pilot trial data both measures were consistently completed with no missing data. Both measures will be included in the main trial to allow assessment of the benefits on patients' well-being as well as health-related quality of life.

The health economic analyses will be developed using STATA v16 or later and Excel 2016 or later. Resource use measures and patient reported outcomes (e.g. EQ-5D-5L and ICECAP-A) will be collected at baseline, six- and 18-months with discounting applied at 3.5% as a base case [43]. The EQ-5D-5L will be translated into the EQ-5D-3L for calculation of QALYs [44].

Regression methods will estimate incremental costs and effects, with appropriate baseline adjustment. The impact of missing data will be determined using suitable methods [45]. The primary analysis will be a cost-utility analysis presenting an incremental cost per Quality Adjusted Life Year (QALY) gained over 18-months. Sensitivity analyses will include parameter variation in costs and effects, and selected scenario analyses. Uncertainty will be explored using bootstrapping, with cost-

effectiveness acceptability curves presented. We will estimate the net monetary benefit gained from REDUCE. Appropriate societal willingness to pay thresholds [46] will be used to determine whether REDUCE could be considered an effective use of NHS resources. Additional analyses will present the ICER based on the ICECAP-A. An incremental cost per ulcer free days gained at 18 months will be calculated based on the primary trial endpoint with deterministic sensitivity analysis to examine the effect of parameter variation. Other outcomes will be presented as part of a cost-consequence analysis. Using the trial data, supplemented by best available evidence and informed by good practice [47] we will estimate the likely impact of using the REDUCE intervention on UK NHS budgets.

The potential for economic modelling to extrapolate longer-term cost-effectiveness beyond the trial period will be assessed on the clinical and cost effectiveness of REDUCE at 18 months (based on statistical significance, range of confidence intervals, and clinically important differences over time), availability and plausibility of data inputs identified from a structured literature review and expert elicitation, and, where necessary, plausibility of assumptions. The conditions to inform the model development will be detailed in the HEAP. The decision to develop the economic model will be made with the Programme Management Group, Independent Trial Steering Committed, and Data Monitoring and Ethics Committee. A modelling plan, model schema, and main assumptions will be prepared prior to final analysis of the clinical and in-trial economic analysis. A base-case ICER will be produced, with sensitivity analyses conducted and presented as described above. We will also consider appropriate value methods (e.g. Expected Value of Perfect Information) as part of addressing uncertainty and value of additional research [48].

9.12. Qualitative Data Analysis

Data will be analysed using a combination of thematic and framework analytical approaches. To maximise rigour and conform to qualitative data reporting standards e.g. (COREQ), at least two experienced qualitative researchers will be involved in the analysis. A qualitative software package, NVivo, will be used to support data retrieval and coding.

9.13. Fidelity Assessment Data Analysis

The intervention session fidelity assessment data will be analysed descriptively. The data will be analysed descriptively with analysis for inter-rater reliability.

9.14. Biological Mechanisms Sub-Study Analysis

A detailed statistical analysis plan, describing the analyses for the biological mechanisms sub-study, will be developed, and made public, in advance of undertaking the analyses. In brief, all analyses will be based on comparisons of the randomly allocated groups, with treatment effects estimated using appropriate regression models and presented with 95% confidence intervals and two-tailed p-values.

The primary research questions for this biological mechanisms sub-study will examine between group differences in CTRA responses and cytokine levels at 12 weeks using an analysis of covariance

(ANCOVA), comparing composite CTRA response scores at 12 weeks, with baseline CTRA response scores included as a covariate.

Further to these, additional analyses will explore the evidence for a treatment effect on the trial primary outcome of ulcer free days with limbs intact, being mediated at least in part by a treatment effect on CTRA response scores. To allow separation of cause and effect, CTRA response scores will be established at 12 weeks and, for this analysis, ulcer free days with limbs intact will be recorded between 12 weeks and 18 months. The total effect of treatment on ulcer free days, and the effect of treatment on ulcer free days that is not mediated by CTRA score will be estimated, the difference between these indicating the treatment effect that is mediated by CTRA score – a structural equation model approach. We will conduct a naïve analysis using extensions of the ANCOVA models described above, but will be clear that these are subject to confounding of the relationship between CTRA score and ulcer free days, as both these measures are post-randomisation. We will also conduct a causal analysis in an attempt to control that confounding. This analysis will be adapted to focus on the recurrence of ulceration as the outcome measure, as ulcer free days is a composite of recurrence and speed of recovery. Further extensions of this analysis will consider the mediating role of specific circulating immunity measures, and the mediating role of psychological and behavioural factors measured at 12 weeks. We will also consider using multistate modelling approaches to examine mechanisms underlying re-ulceration and healing, should the frequency of re-ulceration provide us with sufficient power to do so. These analyses are only worthwhile if there is evidence of a treatment effect on the potential mediator and outcome measure, and hence the exact analyses conducted will follow from the findings of the primary research questions.

10. MONITORING, AUDIT & INSPECTION

The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the REC or regulatory authority inspectors. Authorised representatives of the Sponsor and YTU may visit the participating sites to conduct audits/ inspections as indicated in the Sponsor's risk assessment of the study.

Monitoring and source data verification will be conducted by YTU on behalf of the Sponsor according to the study monitoring plan. The extent and nature of monitoring will be determined by the study objectives, purpose, design, complexity, blinding, number of patients and sites, and endpoints.

The Sponsor may suspend or prematurely terminate either the entire study, or the study at an individual site, for significant reasons that must be documented (e.g. an unacceptable risk to participants or serious repeated deviations from the protocol/ regulations). If this occurs the Sponsor shall justify its decision in writing and will promptly inform any relevant parties (i.e. participants, investigators, participating sites, REC, regulatory bodies).

A study specific monitoring plan will be developed to outline any monitoring or audit considerations.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1. Assessment and Management of Risk

No formal monitoring visits will be planned for this study. A monitoring plan will however be generated for the study, to outline the range of centralised monitoring activities (e.g. eligibility, consent, safety checks), which will be undertaken in this study.

11.2. Peer Review

This study has been peer reviewed as part of the NIHR PGfAR application process.

11.3. Public and Patient Involvement

Patients and carers have been involved in the design of the trial and will be involved in the management of the research, analysis of results and the dissemination of findings. Our participant information sheet has been co-developed with our patient and public involvement (PPI) group. In addition, members of the PPI group have provided feedback on the content of participant-facing study documents, the digital and handbook versions of the MI and have tested the feasibility and duration for completing the psychological, behavioural and health economic questionnaires.

The PPI group meet three times per year. The group will also be consulted on the findings of this trial and their advice will be sought regarding any changes to participant-facing documents throughout this clinical and cost-effectiveness trial.

11.4. Research Ethics Committee (REC) & Regulatory Considerations

The study will be conducted in compliance with the approved protocol and the Declaration of Helsinki. The protocol and all related documentation (e.g. informed consent form, participant information sheet, questionnaires) have been reviewed and received approval by a Research Ethics Committee (REC). The Investigator will not begin any participant activities until approval from the HRA and REC has been obtained and documented. All documentation and correspondence must be retained in the Trial Master File/Investigator Site File. Substantial amendments that require HRA and REC (where applicable) review will not be implemented until the HRA and REC grants a favourable opinion (with the exception of those necessary to reduce immediate risk to participants).

It is the responsibility of the CI to ensure that an annual progress report (APR) is submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, annually until the study is declared ended. The CI is also responsible for notifying the REC of the end of study (see Section 6.9) within 90 days. Within one year of the end of study, the CI will submit a final report with the results, including any publications/abstracts to the REC.

Before any site can enroll a participant into the study confirmation of capacity must be sought from the site's research and development (R&D) department. In addition, for any amendment that will potentially affect the site's permission, the research team must confirm with the site's R&D department that permission is ongoing (Section 11.10).

11.4.1. Participant Payments

Participants will receive a £5 shopping voucher for completion of the baseline questionnaire. A £5 voucher will be sent with each questionnaire at 6 week, 3 month, 6 month and 18 month post-

randomisation. A final £5 shopping voucher will be sent to participants for completion of all study questionnaires at the end of the study, as a "thank you". (A maximum of £30 will be provided). This process will be managed by the University of Nottingham research team.

For those participants involved in the biological mechanisms sub-study reasonable travel expenses will be covered for additional trips to appropriate locations where blood sampling is taking place. The specific form this payment will take will differ according to participating site and/or participant preference and may be paid in advance in the form of cash or vouchers, reimbursed following production of receipts/mileage claims, or booked and paid for directly by the central or site study teams.

11.5. Protocol Compliance / Non-compliance Reporting

The Investigator is responsible for ensuring that the study is conducted in accordance with the procedures described in this protocol. Prospective, planned deviations and/or waivers to the protocol are not acceptable. Accidental protocol deviations may happen and as such these must be reported according to the York Trials Unit SOP. Deviations from the protocol which are found to frequently recur are not acceptable, and will require immediate action. Where events are repeated this may constitute a serious breach.

11.6. Notification of Serious Breaches to GCP and/or the Protocol

A "serious breach" is a departure from the protocol, Sponsor procedures (i.e. SOPs), or regulatory requirements which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the study; or
(b) The scientific value of the study.

If a serious breach is identified the Investigator should notify York Trials Unit immediately (i.e. within 1 working day) using the 'Non-CTIMP Notification of a Serious Breach' form. The report will then be reviewed by the Sponsor and CI, and where appropriate, the Sponsor will notify the REC within 7 calendar days of being made aware of the breach.

11.7. Data Protection and Patient Confidentiality

The study will be conducted in accordance with the Data Protection Act 2018. The Investigator must ensure that participant's anonymity is maintained throughout the study and following completion of the study. Participants will be identified on all study specific documents (except for the informed consent form and enrolment log) only by the participants study specific identifier (and initials where deemed necessary). This identifier will be recorded on documents, and the database. Initials will not be used in the study identifiers for the qualitative or fidelity components of the trial. The Investigator Site File will hold an enrolment log detailing the study specific identifier alongside the names of all participants enrolled in the study.

All documents will be stored securely with access restricted to study staff and authorised personnel. Transcribers will have a signed data processing agreement with the appropriate University.

Professor Fran Game will act as the custodian of the data generated in the study.

11.8. Financial and Other Competing Interests for the Chief Investigator, Principal Investigators at Each Site and Committee Members for the Overall Study Management

No financial or other competing interests identified.

11.9. Indemnity

As UHDB is acting as the research Sponsor for this study, NHS indemnity applies. NHS indemnity provides cover for legal liabilities where the NHS has a duty of care. Non-negligent harm is not covered by the NHS indemnity scheme. UHDB, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

11.10. Amendments

Changes to the protocol will be documented in written protocol amendments; the Sponsor is responsible for deciding if an amendment should be deemed substantial or non-substantial. Substantial amendments will be submitted to the relevant regulatory bodies (REC, HRA) for review and approval. The amendments will only be implemented after approval and a favourable opinion has been obtained. Non-substantial amendments will be submitted to the HRA for their approval/ acknowledgment. Amendments will not be implemented until all relevant approvals are in place.

11.11. Access to Final Study Dataset

Access to the final full anonymised version of the dataset will be given to relevant individuals on the delegation log at York Trials Unit, the Chief Investigator, the Sponsor and, where requested, members of the Programme Steering Committee, and other relevant individuals as permitted by the PSC and recorded on the research site delegation log. The data generated by the trial will be owned by University Hospitals of Derby and Burton NHS Foundation Trust.

12. DISSEMINATION POLICY

12.1. Dissemination Policy

On completion of the trial, data will be analysed and tabulated and a final study report prepared for the funder. Following Funder approval, a copy of the final study report will be made available on the NIHR journals library website (or equivalent): https://www.journalslibrary.nihr.ac.uk/pgfar/#/ [accessed 23 December 2021].

The findings from this research will be disseminated in the following ways:

- To the scientific community through presentation at national & international conferences and publication in peer reviewed journals.
- To clinical and academic colleagues via professional societies: key stakeholders will be sent a summary of the findings.
- To participants: All participants will be asked whether they would like to be sent a summary of the results. Those that do will be sent an accessible summary of the findings from the study that they took part in within six months of study completion to their preferred contact address/email address.

The findings of this research will also be used to educate students.

All presentations and publications will include the relevant current funding body and sponsoring organisation acknowledgement. Prior to any publication or presentation (oral or written) a copy of the proposed publication or presentation will be provided to the funder, UHDB as sponsor and all collaborating parties on the award at the same time as submission for publication or at least twenty-eight days before the date intended for publication (whichever is earlier).

12.2. Authorship Eligibility Guidelines and any Intended Use of Professional Writers

It is expected that any first drafts of publications for academic journals and the final study report will first be authored by the TMG on behalf of the PMG. Final authorship shall be in accordance with the International Committee of Journal Medical Editors (ICJME) guidance [49].

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14. APPENDICES

14.1. Appendix 1 – Schedule of Assessments: Participants

Procedures		Visits												
	Screening	Baseline	Treatment Phase *Post randomisation*								Follow up *Post randomisation*			
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	6 weeks	3 months	6 months	12 months	18 months
Inclusion/Exclusion criteria	X	X													
Discuss study with patient	X	X													
Informed consent		X													
Demographics/ Contact information		X													
Web-based randomisation		X													
Brief IPQ		X									X	X	X		X
CBRQ-SF		X									X	X	X		X
SPANE-P		X									X	X	X		X
PHQ-9		X									X	X	X		X
IPAQ-E-SF		X									X	X	X		X
NAFF		X									X	X	X		X
SPS-5		X									X	X	X		X
ICECAP-A		X											X		X
EQ5D-5L & EQ VAS		X											X		X
Blood Sample (biological mechanisms study)		X										X (12 weeks)			

Procedures		**Visits**												
	Screening	**Baseline**	**Treatment Phase** *Post randomisation*								**Follow up** *Post randomisation*			
			Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**6 weeks**	**3 months**	**6 months**	**12 months**	**18 months**
Resource use questionnaire		X											X		X
Telephone/virtual interview (sub-sample)*		X										X	X		
REDUCE intervention 1:1 sessions*			X	X	X	X	X	X	X	X					
Complete home practice*			X	X	X	X	X	X	X						
Website access data*											X	X	X	X	X
Clinical data collection													X	X	X
Audit and monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events and SAs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Approximate Time Estimate (mins)	30	90	90	100	90	90	90	90	90	75	120	120/ 180*	150	60	150

* Intervention arm only

14.2. Appendix 2 – Schedule of Assessments: Healthcare Professionals

Procedures	**Pre-trial**	**Delivery Phase**								**Follow up[a] (Post delivery of intervention)**
		Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	
Inclusion/Exclusion criteria	X									
Informed consent	X									
Demographics/ Contact information	X									
Receive training in REDUCE	X									
Complete pre- and post- training questionnaires	X									
Deliver and record REDUCE intervention 1:1 sessions		X	X	X	X	X	X	X	X	
Record participant attendance at REDUCE 1:1 sessions		X	X	X	X	X	X	X	X	
Record participant home practice compliance			X	X	X	X	X	X	X	
Fidelity assessment (random sample of REDUCE sessions)		X	X	X	X	X	X	X	X	
Telephone/virtual interview(s)										X
Approximate Time Estimate (mins)	60	110	120	120	120	120	120	120	120	60

[a]Either at end of allocated intervention delivery or up to when the HCP leaves the intervention delivery team.

14.3. Appendix 3 – Birthday Card SWAT Protocol

Title: Effect of sending a birthday card on the retention of participants in an adult healed diabetic foot ulcer trial

Objective of this SWAT
To evaluate whether sending a birthday card improves the retention of participants in trials involving an adult population (aged 18 and above).

Study area: Retention, Follow-up
Sample type: Participants

Background
Randomised controlled trials are regarded as the gold standard for evaluating healthcare interventions. However, trialists often experience poor participant retention (i.e., poor questionnaire responses) and these have serious consequences on the validity, reliability, and generalisability of study results [1],[2]. Hence, it is important to rigorously evaluate participant recruitment and retention strategies to produce evidence on effective (and ineffective) strategies to help trialists make better-informed decisions in conducting trials [3]. The REDUCE trial aims to include a SWAT to evaluate the effectiveness of sending a birthday card on participant retention in a diverse adult population. A number of studies have explored the use of non-monetary incentives (e.g., providing pens or using Post-it notes to encourage retention) [3],[4]; this SWAT would further contribute to the existing body of research that aims to enhance participant retention in trials. Moreover, the inclusion of more participants as a result of this SWAT gives it the potential to be incorporated into a meta-analysis with similar studies, such as SWAT 79 [5].

Interventions and comparators
Intervention 1: A birthday card for the whole of the trial (i.e., if a participant has two birthdays during their 18-month follow-up, they will receive birthday cards twice).
Intervention 2: No birthday card

Index type: Birthday cards, follow-up

Method for allocating to intervention or comparator
All participants recruited into the host trial will be eligible to take part in this SWAT. At the point of recruitment to the main trial, participants will be randomly allocated 1:1 to either receive birthday cards throughout the trial (i.e., until the participant exits the trial at final follow-up or fully withdraws) or not to receive birthday cards throughout the trial. Block randomisation will be stratified by the main trial allocation using randomly-permuted blocks of randomly-varying sizes. The allocation sequence will be generated by the trial statistician who is not involved in the follow-up of participants.

Outcome Measures
The primary outcome of this SWAT is whether the questionnaire was returned at the first-time point following receipt of the first birthday card. Secondary outcomes include:

1. Whether the questionnaire was returned at the first-time point following receipt of the second birthday card.
2. Response rate at each timepoint (6-weeks, 3 months, 6 months and 18 months).
3. Time to response (number of days from date due to date returned) at the first-time point following receipt of the first birthday card.

4. Time to response (number of days from date due to date returned) at the first-time point following receipt of the second birthday card (where applicable).
5. Needed an initial reminder at the first-time point following receipt of the first birthday card.
6. Needed an initial reminder at the first-time point following receipt of the second birthday card (where applicable).
7. Needed a telephone reminder at the first-time point following receipt of the first birthday card.
8. Needed a telephone reminder at the first-time point following receipt of the second birthday card (where applicable).
9. Cost per participant retained at the first-time point following receipt of the first birthday card.
10. Cost per participant retained at the first-time point following receipt of the second birthday card (where applicable).

Analysis Plans

The sample size for this embedded trial will be constrained to the number of participants recruited into the host trial. All participants recruited into the host trial and who are currently participating in the study, at the point at which their birthday card is due to be sent out, will be eligible to take part in this embedded trial.

Analyses will follow the principles of intention to treat, including all participants in the groups they were originally allocated. The primary outcome will be analysed using mixed-effect logistic regression including SWAT allocation, main trial allocation, age, and gender as fixed effects. Recruitment site will be adjusted for as a random effect. Binary secondary outcomes will be analysed in a similar manner. Time to response will be compared between the groups using the frailty extension of the Cox proportional hazards regression including SWAT allocation, main trial allocation, age and gender as fixed effects and recruitment site as a random effect. Subgroup analyses for age and gender will be undertaken for the primary outcome via the addition of an interaction term between the relevant factor and SWAT allocation.

Possible problems in implementing this SWAT

The major challenge associated with the study may be the staff time required to administer this SWAT. Hence, the costs associated with the SWAT will relate to 1) designing, printing, & posting the birthday card (and associated stationary); and 2) staff time for randomisation and administering these activities [5]. Additionally, as the host trial serves a diverse population, some groups – such as Jehovah's Witnesses that do not celebrate birthdays [6] – may be averse to receiving birthday cards; and care must also be taken to create a birthday card which is not offensive to participants. Therefore, we will liaise with the recruiting site teams to help identify anyone who may be offended to participate in this SWAT or any participant feedback about receiving a birthday card.

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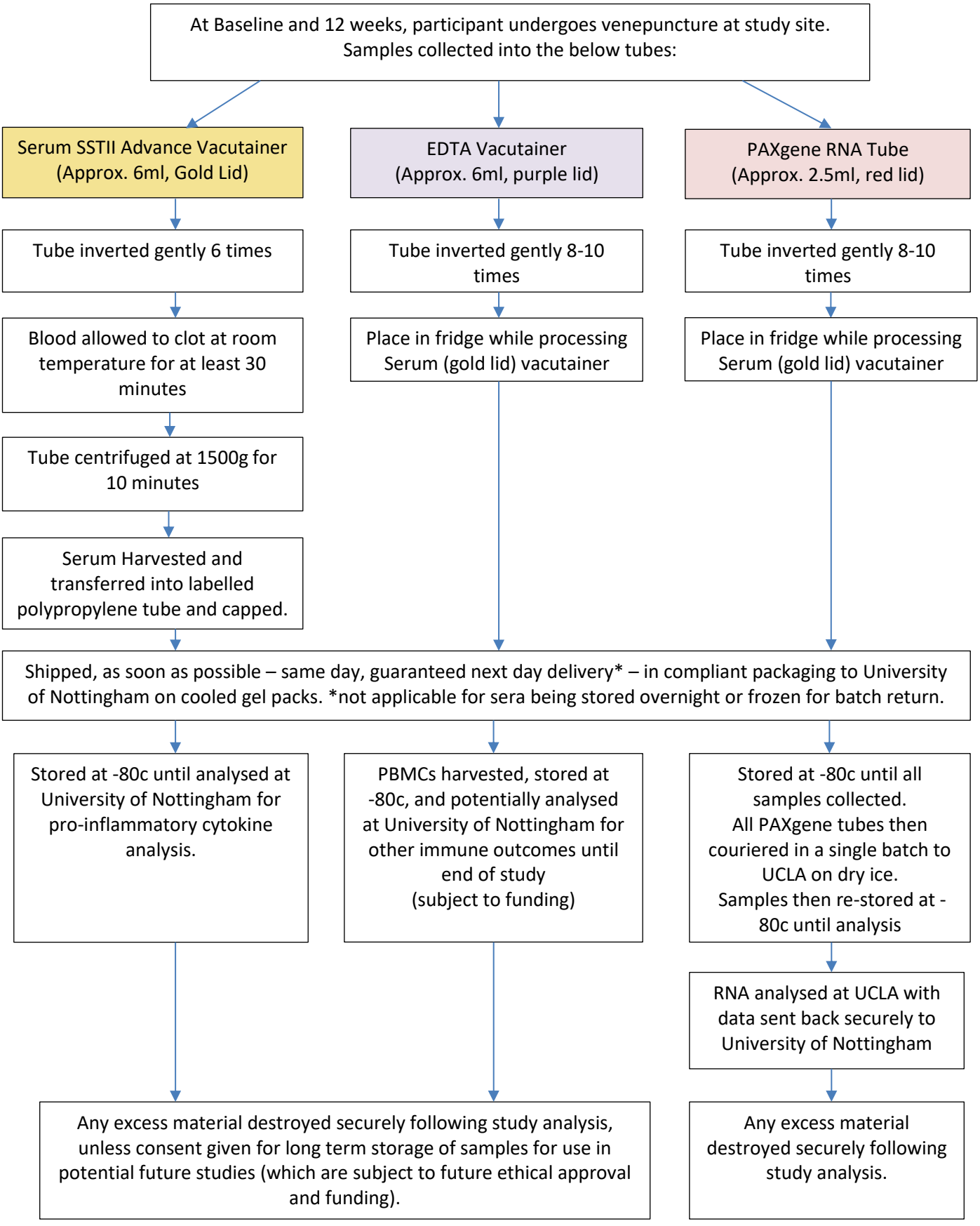
14.4. Appendix 4 – Flow Diagram of Biological Mechanisms Study Sample Processing



14.5. Appendix 5 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
Substantial Amendment 1	2.0	15/10/2022	Natasha Mitchell	• Amendment to inclusion & exclusion criteria. Provided an upper limit in which healed diabetic foot ulcer patients can be approached.
Substantial Amendment 2	3.0	22/08/2023	Kieran Ayling, Natasha Mitchell, Adenike Okanlawon	• Updating the protocol for the inclusion of the newly funded biological mechanisms sub-study. The changes include updating the background, method, inclusion/exclusion criteria, blood sample collection, and analysis. • Updating the SWAT section, including removing the PIS SWAT and adding more details about the birthday card SWAT. Adding the birthday card SWAT protocol as Appendix 3. • Updating the process of how intervention session recordings are transferred from HCPs to the Kings College London team.
Non-substantial 24	3.1	10/12/2023	Kieran Ayling	• Clarification to protocol relating to the return of blood samples process for the Biological Mechanisms Sub-Study within the trial - in addition to same day shipping, participating sites can where necessary choose to retain separated sera samples refrigerated overnight prior to shipping

				in the following day or at the end of recruitment.
Non-substantial 27	3.2	08/02/2024	Natasha Mitchell	• Adjusting the recruitment window from 23 months to 30 months. Updating the final follow-up dates to reflect the change in recruit time.
Non-substantial 29	3.3	13/08/2024	Kieran Ayling	• Revising the target sample size for the Biological Mechanisms sub-study from 142 to 100 due to parent trial being close to completing recruitment preventing original target from being reached.

Detail all protocol amendments. Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC.