Reducing the impact of diabetic foot ulcers (REDUCE): Pilot trial

Short title: Reducing the impact of DFUs (REDUCE): Pilot trial

Version and Date of Protocol:	v1.1, 25 May 2021
Sponsor:	University Hospitals of Derby & Burton NHS Foundation Trust
Chief Investigator:	Professor Fran Game
Sponsor Reference:	UHDB/2020/037
IRAS Number:	274356
ISRCTN number:	15460422
Funder(s):	National Institute for Health Research (NIHR) Programme Grant for Applied Research (PGfAR) Reference: RP-PG-0618-20001
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 publically 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 (v1.1, 25th May 2021) authorisation signatures:

Chief Investigator:

Signature: ..... Date: 02/06/2021

Name (please print): PROF F. GAMG.

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

Signature: Dr Teresa M. Grieve Digitally signed by Dr Teresa M. Grieve Date: 2021.06.04 13:02:31 +01'00' Date: 04/06/2021

Name (please print): Dr Teresa M Grieve

Position: Ass. Director Research & Development

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STUDY SUMMARY

Study Title:	Reducing the impact of diabetic foot ulcers: Pilot trial
Short Title:	Reducing the impact of DFUs: Pilot trial
Sponsor Reference:	UHDB/2020/037
Study Design:	Multi-centre randomised controlled pilot trial with nested qualitative study
Study Participants:	***Pilot trial:*** People with diabetes, two lower limbs and a recently healed DFU (fully epithelialised with no drainage, for a minimum two weeks). ***Nested qualitative study:*** Intervention participants and healthcare professionals delivering REDUCE.
Planned Number of Sites:	Two secondary care 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=23, consisting of: 20 participants and three healthcare professionals
Treatment Duration:	3 months
Follow Up Duration:	4 months
Planned Start Date:	19/04/2021
Planned Recruitment End Date:	18/07/2021
Planned Study End Date:	31/03/2022
Research Question/ Aims:	The primary objectives of this pilot trial are to investigate the following prior to conducting a larger clinical and cost-effectiveness trial: 1. Feasibility of the recruitment strategy for participants, to include numbers of eligible patients approached, numbers not eligible (and why), and proportion of eligible patients consented. 2. Adherence to and attrition from the REDUCE intervention and to the trial (to include reasons for attrition and how this is documented). 3. Feasibility of obtaining outcome data from primary, community and secondary care patient medical records. Completeness of data collection. 4. Feasibility of collecting the planned economic outcome measures. Completeness of data collected. 5. Identify whether adaptations are required to the REDUCE intervention. 6. Test out and refine data collection methods for the mixed-methods process evaluation to be undertaken in the main trial. 7. Determine if refinements are required to the intervention fidelity tool. 8. Determine if modifications are needed prior to the clinical and cost-effectiveness trial to: a. the REDUCE intervention and/or training programme; b. the logic model.

FUNDING AND SUPPORT IN KIND

Funder(s)	Financial and Non-Financial Support Given
NIHR PGfAR (Reference: RP-PG-0618-20001)	£2,531,202

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 Research (NIHR) Programme Grants for Applied Research (PGfAR), reference RP-PG-0618-20001.

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 and monthly teleconferences. Any problems with study conduct will be raised and addressed during TMG meetings.

Trial Steering Committee (TSC)
The TSC 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 TSC is an independent body that includes members who are not involved with the running of the trial and will meet bi-annually during the pilot trial. The TSC 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 TSC to provide the updates, to include Chief Investigator, Trial Manager, Trial Statistician and Programme Manager. Other members will be invited on an 'as required' basis. A Data Monitoring and Ethics Committee will not be convened for this pilot trial.

The Trial Steering Committee will also meet as the Independent Programme Steering Committee (IPSC). For IPSC meetings, a Sponsor representative and a Funder representative may also be in attendance. The IPSC will meet annually over the duration of the Programme.

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, 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, Statistician, Data Manager, Trial Manager, Sponsor Representative, Patients and Carers.

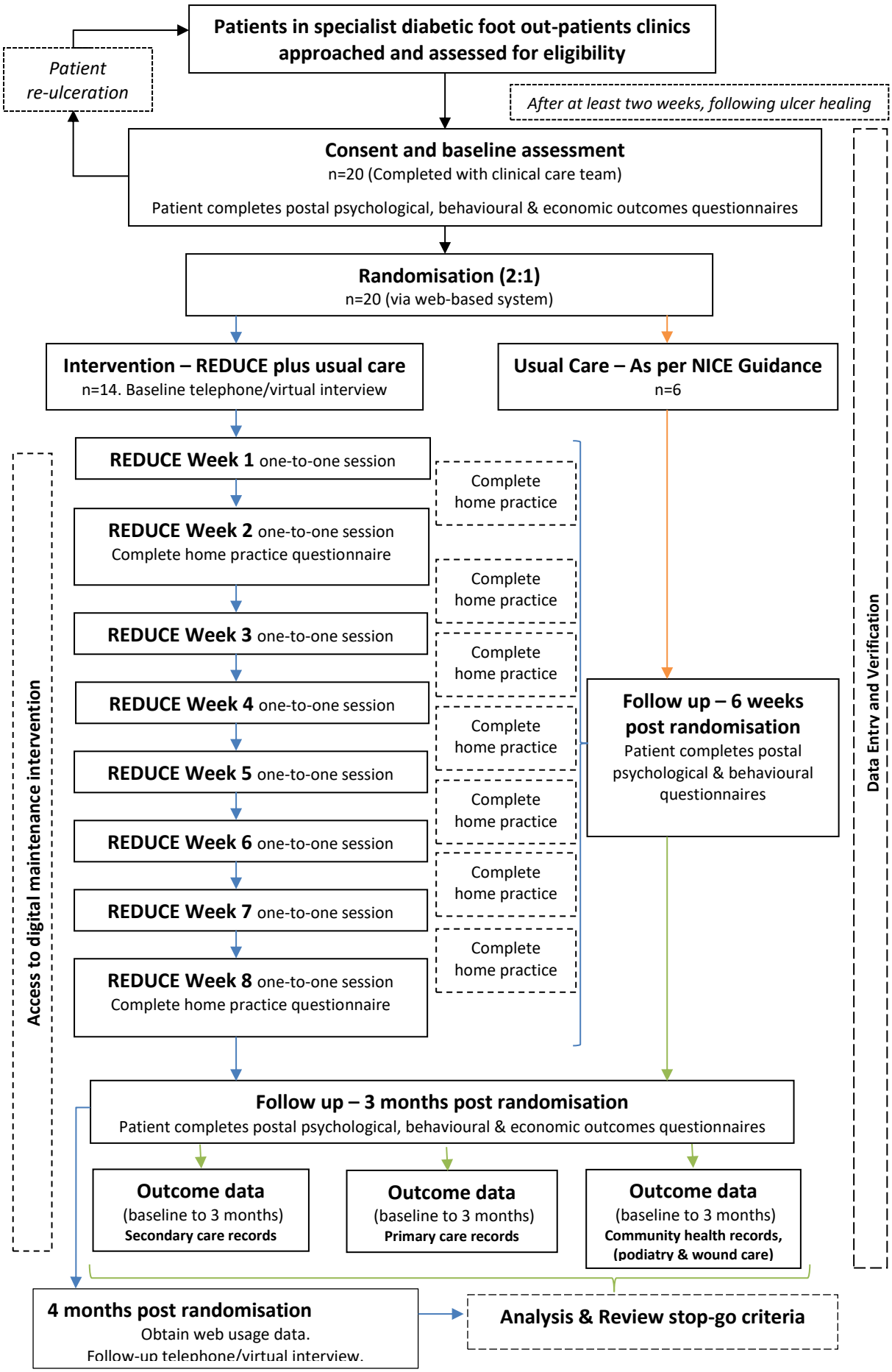
Contents

LIST OF ABBREVIATIONS

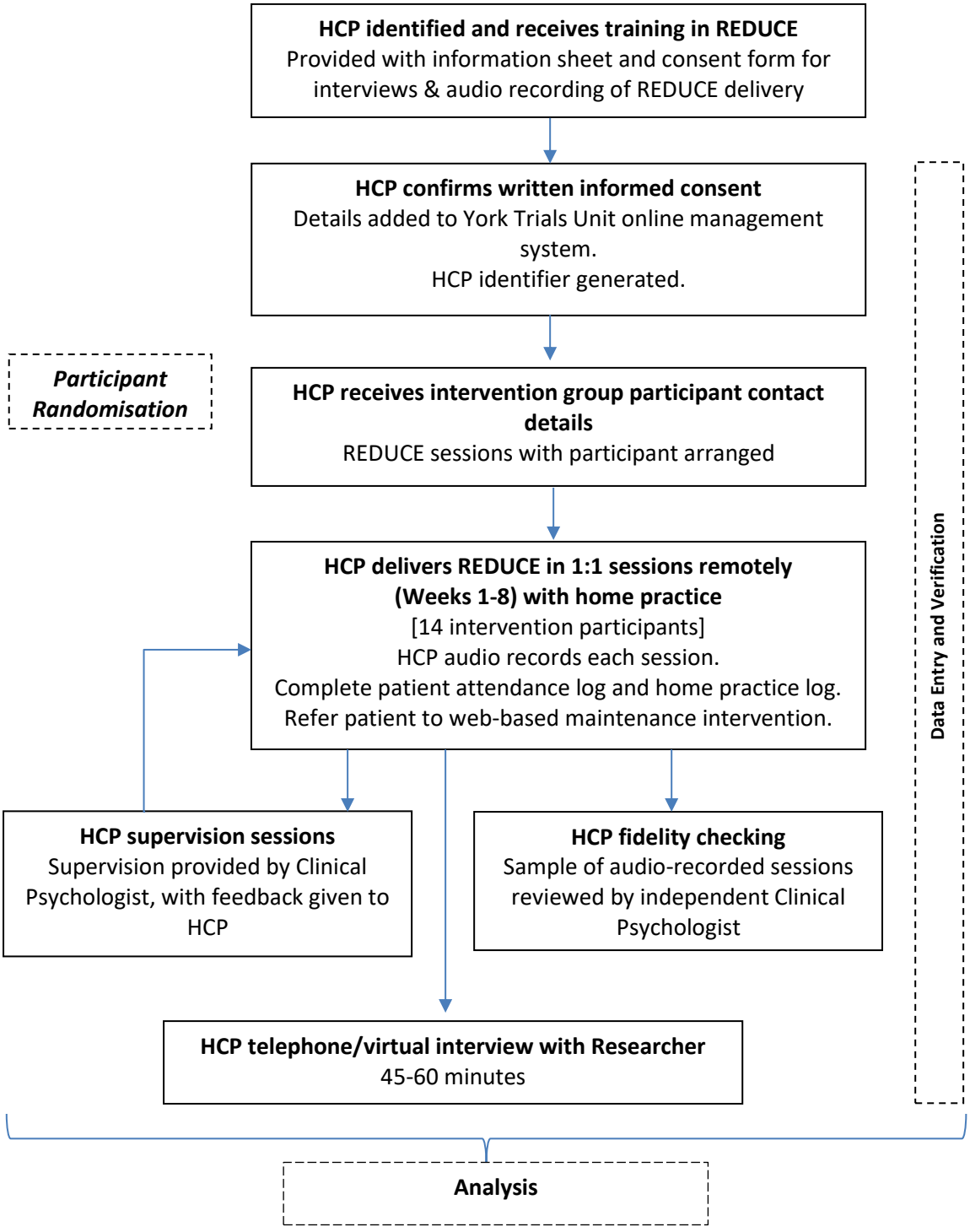
AE	Adverse Event
APR	Annual Progress Report
B-IPQ	Brief Illness Perception Questionnaire
CBRQ	Cognitive and Behavioural Responses Questionnaire
CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DDS	Diabetes Distress Screening
DFU	Diabetic Foot Ulcer
DMP	Data Management Plan
GAD	Generalised Anxiety Questionnaire
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
IPSC	Independent Programme Steering Committee
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials
KCL	King's College London
MHC-SF	Mental Health Continuum – Short Form
MI	Maintenance Intervention
MRC	Medical Research Council
NAFF	Nottingham Assessment of Functional Footcare
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PAD	Peripheral Arterial Disease
PBA	Person Based Approach
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
QA	Quality Assurance
QC	Quality Control
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
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
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
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]; 70% of ulcers remain unhealed after five months [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 2010-11 the NHS spent approximately £650 million on diabetic foot care: equivalent to £1 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 Revised REDUCE Intervention

Thus, the revised 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 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 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 face-to-face sessions. Comparable techniques will be utilised in the second ('Maintenance') phase although with a focus on sustaining change, delivered via a digital platform (and handbook).

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:

- Assessment of current difficulties;
- Identify problematic behavioural, cognitive and emotional responses;
- Socialisation to the therapeutic model;
- Explore the role of thoughts and behaviours and their link with mood and/or health status;
- Negotiate individualised goals, a stepped approach 'homework';
- Increasing awareness of activity patterns and behaviours which impact on ulcer outcomes;
- Negotiating appropriate behaviours;
- Increasing awareness and exploring of unhelpful cognitions (e.g., hopelessness);
- Identifying sources of social support;
- Discussing how to be more assertive/test out with behavioural experiments;
- Taking responsibility, strengthening commitment to new behaviours and planning for the future.

The 'Maintenance' phase will be delivered on a digital platform and through a 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. Development of REDUCE Maintenance Intervention

Prior to this study, the *think aloud* methodology has been used to obtain feedback from our PPI members to explore their perceptions of the maintenance intervention to ensure the content was as acceptable, feasible, persuasive and motivating as possible. The feedback has been used to update the maintenance intervention for the pilot trial.

1.3. Pilot Trial

An external pilot trial will be completed to examine recruitment and retention rates and inform estimates regarding the number of recruiting centres and the recruitment period required for the clinical and cost-effectiveness trial. We will also examine the viability of primary and secondary outcome data collection. The design of this pilot will therefore mirror the main features of the clinical and cost-effectiveness trial.

As findings could result in changes to the intervention, the training programme, and/or the study design and processes, an external, rather than internal, pilot is most appropriate. However, should findings from this pilot not result in significant changes to REDUCE or the REDUCE training programme, we would consider treating this pilot trial as an internal pilot, with patient and HCP data contributing to the main trial and the process evaluation.

1.3.1. Health Economic Evaluation

The pilot trial will assess the feasibility of collecting the economic outcomes in preparation for the main trial, drawing upon our findings from previous work including the perspectives of commissioners and service providers and as noted in 1.2 Development of REDUCE Maintenance Intervention. We will pilot the methods to collect resource use data from patient-level questionnaires and other data collection sources (e.g. primary, community and secondary patient medical records). We will also consider what are the most relevant and important drivers of health and social care costs (and additionally, costs to patients and society) so that these can be accurately collected within the main trial. Finally, we will also consider what are the key drivers of resource use and costs associated with the REDUCE intervention, with appropriate face validity checks, to ensure we have understood and accounted for the treatment pathways of both arms.

2. OBJECTIVES

2.1. Primary Objectives

The primary objectives of this pilot trial are to investigate the following prior to conducting a larger clinical and cost-effectiveness trial:

1. Feasibility of the recruitment strategy for participants, to include numbers of eligible patients approached; numbers not eligible (and why); and proportion of eligible patients consented.
2. Adherence to and attrition from the REDUCE intervention and to the trial (to include reasons for attrition and how this is documented).
3. Feasibility of obtaining outcome data from primary, community and secondary care patient medical records. Completeness of data collection.
4. Feasibility of collecting the planned economic outcome measures. Completeness of data collected.
5. Identify whether adaptations are required to the REDUCE intervention.
6. Test out and refine data collection methods for the mixed-methods process evaluation to be undertaken in the main trial.
7. Determine if refinements are required to the intervention fidelity tool.
8. Determine if modifications are needed prior to the clinical and cost-effectiveness trial to:
    a. the REDUCE intervention and/or training programme;
    b. the logic model.

3. STUDY DESIGN

A multi-centre, parallel group, randomised controlled external pilot trial with nested qualitative study.

4. STUDY SETTING

This is a multi-centre randomised controlled pilot trial involving at least two clinical sites recruiting 15-20 participants (i.e., 7-10 participants per site). It is anticipated that the participant population will be recruited from specialist multidisciplinary diabetic foot clinics at participating secondary care NHS Trusts. The intervention will be undertaken at 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, for a minimum two weeks.
- Has cognitive capacity to provide informed consent, to engage with the study intervention (both as digital and written handbook versions), to take part in interviews if randomised to the intervention, and to provide follow-up data.
- Has sufficient command of English language 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.
- Diagnosis of a current severe mental illness which could hinder engagement with the trial and/or intervention (e.g., psychosis).
- Has previously been randomised to this pilot 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).

5.3. Healthcare Professional Inclusion Criteria

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

assessment.

5.4. Healthcare Professional Exclusion Criteria

- Unwilling to provide informed consent.

6. PROCEDURES

6.1. Recruitment

6.1.1. Participant Identification

6.1.1.1 Pilot Trial Participants

Over a three-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 pilot trial sites. Those eligible will be approached about the trial by their usual clinical carers and given some details about the study, including an information sheet. 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).

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 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. After they have received training in the REDUCE intervention they will be provided with an information sheet about taking part in 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. Pilot 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 pilot trial, and, if randomised to the intervention consent to take part in two telephone/virtual interviews at baseline and at four months, and for the eight REDUCE intervention sessions to be audio recorded. 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 training sessions to be audio-recorded will be obtained prior to the interviews and each training session.

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. 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). Participants will be asked to consent to the recording of the intervention sessions, if randomised to the intervention group, as part of the pilot 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. A copy will also be sent securely (by email) to University of Edinburgh to verify consent to interview, University of Nottingham to verify consent for the questionnaires and, for the intervention arm, to arrange intervention sessions and provide intervention materials, to University of Edinburgh to verify consent to interview and to Kings College London for audio recording of intervention delivery.

6.2.2. Healthcare Professional Participants

Healthcare professionals will be recruited to deliver the REDUCE intervention and 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. Interview dates and times will be arranged after the healthcare professional has completed delivery of all face-to-face sessions at their site.

The original signed form(s) will be retained at UoN while copies will be given to the participant and to the York Trials Unit, and will be accessible to the research teams at Kings College London, UHDB and University of Edinburgh.

6.3. The Randomisation Scheme

After obtaining consent and following the completion of all baseline data collection and assessments, pilot trial participants will be randomised 2:1 to the intervention to maximize the number of participants receiving REDUCE and, therefore, the depth and extent of information we can glean on their experiences of receiving it. Participants will be notified of which arm they have been allocated to whilst in clinic.

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-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 non-stratified and formed of randomly permuted blocks with a 2:1 allocation ratio favouring the intervention arm.

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 sites 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

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 relevant.

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 CRF. At the end of the trial we will ask assessors to indicate which arm they thought participants were in and why.

The YTU statistician conducting the analyses will not be blinded. Analysis code will be replicated by an un-blinded 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 to arrange the intervention sessions. The University of Nottingham research team will provide participants with a copy of the handbook, the website log-in details and home practice questionnaires with freepost envelopes. The team will liaise with the UoE research team to arrange the baseline interview and with HCPs delivering REDUCE to arrange the first intervention session following the baseline 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 1.1 The Revised REDUCE Intervention.

Participants in the intervention arm will be provided with access to a web-based maintenance intervention (website accessible by mobile phone, tablet and computer). The website will be developed and hosted by a commercial company, Global Initiative (GI), experts in developing and hosting digital interventions for NIHR clinical trials.

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

6.6. Data Collection

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 ulcers;
  - Days in hospital;
  - AEs;
  - SAEs;
  - Amputations – major and minor;
  - Mortality;

- Resource use data.

The clinician baseline CRF will be completed on paper, a copy will 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 three 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 will 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: sex, declared ethnicity, marital status, smoking status, COVID-19 exposure, income, 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 and three 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].
- Generalised Anxiety Questionnaire (GAD-7):
  Assesses anxiety [24].
- Patient Health Questionnaire-9 (PHQ-9):
  Assesses depression [25].
- International Physical Activity Questionnaire - Elderly (IPAQ-E) – short form:
  Assesses participant physical activity [26].
- Mental Health Continuum Short Form (MHC-SF):
  Examines emotional, psychological and social well-being [27].
- 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):
  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 and three months only:

- ICEpop CAPability measure for Adults (ICECAP-A):
  Measures capability in adults including attachment, stability, achievement, enjoyment and autonomy [31].
- EQ5D-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

Participants in the intervention arm will also be asked by the healthcare professional delivering the REDUCE intervention to complete a paper homework rating scale [33] questionnaire at their second and eighth REDUCE intervention sessions. These will be sent with freepost envelopes to the intervention participants with the intervention materials. A replacement copy will be sent where required. A postal reminder will be sent after one week and a final telephone reminder at two weeks, where a questionnaire is not received by the research team.

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 and returned by freepost envelope. There will be up to two postal reminders per questionnaire where a questionnaire is not received by the research team. The first reminder will be sent after two weeks. A second reminder will be sent, where required, after a further two weeks which will offer paper or telephone completion of the questionnaire with a member of the University of Nottingham research team.

Participants will take part in the trial for up to four 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 reminder for their REDUCE one-to-one sessions. One of the objectives of this pilot study is to establish attrition rates and completeness of follow-up data. These will be recorded and used to inform the main trial. Where required, the healthcare professionals may contact the participant regarding any missed intervention appointments, and to re-book the intervention session.

6.6.3. Web-based Maintenance Intervention

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 will be able to access 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 pilot trial. The participant IP addresses and location information are collected in Matomo Analytics, however on downloading these data, these personal details will be removed and participant identifier added. Participants in the intervention arm will be able to access the website for approximately three months.

6.6.4. Interviews with Participants in Intervention Arm

All participants in the intervention arm will be invited to be interviewed at baseline and approximately four months in order to examine: their understandings and expectations of the intervention and recruitment experiences; their likes/dislikes of the initiation and maintenance components of REDUCE; reasons for engagement and non-engagement with these components; and their views about how REDUCE might be further refined to optimize uptake and engagement. 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 (although this will depend on what participants have to say) and will be digitally audio recorded using an encrypted device and transcribed.

6.6.5. Interviews with HCPs

All staff involved in intervention delivery in the external pilot will be invited to be interviewed after the 'Initiation' phase of the intervention has been delivered to all participants at their site. These interviews will examine HCP views about: a) the intervention and b) their training, including any improvements which could be made. 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 (although this will depend on what interviewees have to say) and will be digitally audio recorded using an encrypted device and transcribed.

6.6.6. Assessing the Intervention Fidelity Tool

It is the aim that all intervention sessions will be audio-recorded. Assessment of the 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 observers. Each session will be rated twice to assess 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. Any items not working well (i.e., causing confusion, low inter-rater reliabilities) will be discussed with a view to refining or removing. We will report overall integrity as well as component integrity.

6.7. 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 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, and participants will continue to take part in interviews (if randomised to the intervention arm).

III. Withdrawal from baseline and/or follow-up interview only – Where a participant wishes to withdraw from taking part in an interview. 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 - 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 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.

Where participants lose capacity to consent 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 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.

6.8. Storage and Analysis of Samples

Not applicable.

6.9. 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. If the data collected in this pilot trial is considered an internal pilot rather than an external pilot we will use the data in the main trial.

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 pilot 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.

Examples of AEs which may be expected would be:

- Re-ulceration
- New ulcer
- Ulcer infection

AEs which are NOT considered related to the intervention or procedure do not need to be reported unless they are considered SAEs.

7.3. Recording and Reporting SAEs

HCPs will record all directly observed AEs and all SAEs reported by the trial participants up to the final follow-up assessment. In addition, sites should follow their own local procedures for the reporting of any adverse events linked to clinical care.

Adverse events should be entered onto the Adverse Event reporting form and reported to York Trials Unit within five days of discovery or notification of the event.

SAEs should be entered onto the Serious Adverse Event reporting 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 a medically qualified doctor (usually the Principal Investigator).

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 the research team should inform the Sponsor within 24 hours. The participating site will notify York Trials Unit within 24 hours. York Trials Unit will notify the Sponsor using the Sponsor's safety incident reporting form. Any immediate actions will be advised to the research teams at 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 within three days 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. Data Collection Tools and Source Document Identification

Data collected as part of this research includes questionnaires, clinical assessments, web-usage data and interview audio recordings. Data will be collected through designed questionnaires paper CRFs.

Baselines clinical assessment CRFs will be completed on paper at the participating NHS Trust/site and the data will be managed by York Trials Unit. A copy will be retained for the trial site file. Follow-up clinical assessment will be completed in a paper format by the outcome assessors at the research site and the data will be managed by YTU.

The participant completed CRFs (baseline, 6 week and 3 month follow-up) and home practice questionnaires, will be received and entered by the University of Nottingham research team and returned to York Trials Unit at regular intervals.

Web-usage data is collected via Matomo Analytics. Information regarding data security is available here: https://matomo.org/gdpr-analytics/ [accessed 25 January 2021]. This data will be provided to York Trials Unit for the final dataset, and will be accessed by research teams at the University of Nottingham, King's College London, University of Edinburgh and Swansea University.

8.2. Source Data

Source documents are original documents, data, and records from which participants' study-specific data are obtained. These include, but are not limited to, medical records (from which medical history and previous and concurrent medication may be summarised into the study-specific documentation, clinical observation records, diaries, correspondence, completed scales, quality of life questionnaires, interview audio recordings, interview transcripts and web-usage data). Study documentation entries will be considered source data if the form is the site of the original recording (e.g., there is no other written or electronic record of data). In this study, the study documentation will be used as the source document as outlined in the Source Data Verification form.

All documents will be stored safely in confidential conditions. Any paper forms containing participant identifiable information (e.g. participant details form and consent form) will be held in a location separate to the questionnaire data. Outside of the NHS Trust, 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).

Personal data held electronically, will be stored on the study specific participant management system which will record identifiable information and participant activity to enable study coordination. This will be accessible via individual password. Permissions for access of this information will also be detailed within the trial delegation of responsibilities log. The server on which the management system will be housed is secure and is subject to rigorous testing and continued backup.

The original copy of the participant consent forms will be stored at the participating NHS Trust. A copy will also be sent securely electronically to York Trials Unit for storage in the Trial Master File

and to enable centralised monitoring. A copy will also be sent (securely) to University of Nottingham to verify consent for the questionnaires and, for the intervention arm, to arrange intervention sessions and provide intervention materials, to University of Edinburgh to verify consent to interview and to Kings College London for audio recording of intervention delivery.

8.3. 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 paper forms will then be manually entered into a database which will be second checked against the hard copy of the questionnaire. 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.

8.3.1. Pilot 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 Pilot 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).

8.3.2. Health Economic Data

For the health economic analysis, unit cost information will be collected or estimated to ensure these costs are available or can be generated (e.g. from local financial records or literature) prior to the main trial.

8.3.3. Nested Qualitative Study Data

All interview recordings and transcripts will be given a unique participant identifier.

The interviews will be audio-digitally recorded on an encrypted audio recorder and stored as digital files and transcribed into Word files. All identifying features (e.g., names, places) will be removed during the transcription process. There will be no identifying information (names, etc.) used to denote these digital files.

The audio-digital files will be transcribed by a professional transcription agency. The researcher of UoE will use the DataSync cloud service (or equivalent) operated and hosted by the University of Edinburgh (see: https://www.ed.ac.uk/information-services/computing/desktop-personal/datasync [Accessed 4 March 2020]. Files on DataSync are only visible to other people if they are shared. Digital audio recordings of interviews will be uploaded to DataSync and an encrypted and time-limited link sent to a professional transcription company to enable the file to be downloaded. Transcripts of audio files will be returned to the researcher using password-encrypted Word files. The transcription company will be asked to sign a confidentiality agreement, including a section which acknowledges that any recordings downloaded or transcript files will be deleted after being sent to the researcher. Following transcription, only the research team will have access to the raw data or transcripts.

Data will be stored on the University of Edinburgh network, accessible by user id and password. Data will be password protected. At no point will digital or paper files of the final transcript contain any identifying information. Files containing contact details will be encrypted and password-protected.

8.3.4. Fidelity Assessment Data

Intervention session audio recordings will be obtained by the healthcare professional delivering the REDUCE intervention via an encrypted digital audio recorder or via an NHS approved system, e.g.

Microsoft Teams. 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.

Intervention session audio recordings and fidelity assessment tool 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.

8.3.5. 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.

8.4. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections. 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 and enter and update HCP 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 enter the participant questionnaire data into a secure database held on University of Nottingham Microsoft cloud-based servers, backed up regularly and accessible by those on the delegation log, via usernames and passwords. YTU will receive and transfer 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 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. 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, home practice questionnaire results and website usage data.

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

8.5. 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 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 AND HEALTH ECONOMICS

9.1. Sample Size Calculation

This study is an external pilot RCT and as a result the sample size has not been calculated to assess the effectiveness of the intervention. We will enlist two sites to recruit 15-20 participants over a three month period. This would mean a recruitment yield of approximately four participants per site per month, which is comparable to the yield we would require in a main trial, and will provide an opportunity to determine whether recruitment estimates need to be refined. In addition, this sample size, together with a 2:1 allocation ratio, will provide a sufficient number of intervention participants for the qualitative study.

9.2. External Pilot Stop-Go Criteria

Recruitment and data collection will be assessed against pre-defined stop-go criteria The primary criterion is the number of participants recruited, with the secondary criterion being the collection of primary and secondary outcome data (as measured by extraction of relevant data from clinical records related to the primary outcome and questionnaire return rates).

9.3. Planned Recruitment Rate

A planned recruitment rate is not required for this pilot feasibility study.

9.4. Statistical Analysis

A statistical analysis plan (SAP) giving details of the planned analyses will be drafted before data collection has been completed, and reviewed by the Trial Management Group and the Trial Steering Committee. A brief description of the planned analyses is given below.

The statistical analysis will be carried out by a statistician at York Trials Unit, using Stata v16 or later. The analysis and reporting of this pilot trial will follow CONSORT guidelines [34,35]. A flow diagram will be produced, depicting the flow of participants through the trial. The number of participants screened, eligible, consenting and randomised will be summarised, with reasons for ineligibility and non-consent given where available.

Baseline data will be summarised by randomised group, with no formal statistical comparisons being undertaken [36]. Continuous variables will be summarised using descriptive statistics (n, mean, standard deviation, median, minimum, maximum), while categorical variables will be summarised using counts and percentages. Participant outcomes will be summarised descriptively by randomised group and time point, including the amount of missing data. This study is a pilot trial, and as a result statistical hypothesis testing of outcomes will not be carried out.

For the intervention group, attendance of the one-to-one sessions and use of the web-based maintenance intervention will be summarised descriptively.

Adverse events will be summarised descriptively by treatment group.

9.5. Outcome Measures

The primary outcome for a future main clinical and cost-effectiveness trial will be 'ulcer-free time with limbs intact'. The secondary outcomes are:

- Clinical: days to re-ulceration; number of ulcers; days in hospital; amputations, mortality.
- Psychological/behavioural risk factors targeted in REDUCE to examine mechanisms and economic outcomes to examine cost-effectiveness.

The pilot will allow trial procedures (e.g., recruitment, randomisation, delivery of the intervention and collection of outcome measurements) to be tested prior to the main effectiveness trial.
The key outcomes of the external pilot trial will include:

- rates of recruitment and retention
- data on the viability and variability of primary and secondary outcome data collection;
- nature and extent of any modifications to the REDUCE intervention, training programme, logic model, mixed-methods process evaluation data collection methods and/or intervention fidelity tool.

9.6. Health Economic Analysis

The baseline and three-month information on resource use and patient reported outcomes will be analysed (e.g. EQ-5D and ICECAP-A) to assess whether the measures can be completed by participants and/or research team (e.g. completion rates, missing items). We will use the information from this pilot trial, alongside the previous work where we obtained perspectives from commissioners and service providers and conducted *think aloud* interviews to finalise a framework for the economic evaluation for the main trial including a first draft of the health economics analysis

plan (HEAP). We anticipate that careful attention to these design and conduct issues will reduce bias and enhance the accuracy, reliability and completeness of data for a full economic analysis within the main trial.

9.7. Qualitative Data Analysis

All interviews will be recorded, transcribed and analysed, potentially using a combination of thematic and framework analysis and critical incident techniques [37,38]; we may also try out other data analysis approaches at this stage in order to inform decisions about the most appropriate analytical approaches to use in the main trial process evaluation.

9.8. Fidelity Assessment Data Analysis

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

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 pilot 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 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 will meet three times per year. The group will also be consulted on the findings of this pilot trial and their advice will be sought regarding any changes required for the main 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 £20 gift voucher for completion of questionnaires at the end of the study, as a "thank you" for their time. This process will be managed by the University of Nottingham research team.

11.5. Protocol Compliance

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 confidentiality 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 pilot 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 pilot 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 22 January 2020].

We will notify participants of the outcome of the pilot trial via the dedicated REDUCE website (website address to be confirmed). The website will include lay summaries of the results, dissemination activities and academic publication access information.

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.

The findings of this research will also be used to educate students and inform the clinical and cost-effectiveness trial.

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 [39].

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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	4 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	
CBRQ-SF		X									X	X	
SPANE-P		X									X		
GAD-7		X									X	X	
PHQ-9		X									X	X	
IPAQ-SF		X									X	X	
MHC-SF		X									X	X	
NAFF		X									X	X	
SPS		X									X	X	
ICECAP-A		X										X	
EQ5D-5L & EQ VAS		X										X	

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	3 months	4 months
Resource use questionnaire		X									X	
Telephone/virtual interview*		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			
Homework Rating Scale				X						X		
Website access data*												X
Clinical data collection											X	
Audit and monitoring	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
Approximate Time Estimate (mins)	30	90	90	100	90	90	90	90	90	75	120	75

* Intervention arm only

14.2. Appendix 2 – Schedule of Assessments: Healthcare Professionals

Procedures	**Pre-trial**	**Baseline**	**Delivery Phase**								**Follow up (Post delivery of intervention)**
			Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	
Receive training in REDUCE	X										
Inclusion/Exclusion criteria		X									
Informed consent		X									
Demographics/ Contact information		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											X
Approximate Time Estimate (mins)	1440	60	110	120	120	120	120	120	120	120	60

14.3. Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
Non-Sub 1	1.1	25 May 2021	Natasha Mitchell	Removal of word 'draft' from table on first page; inclusion of ISRCTN number on table on first page, update all footers with ISRCTN number inclusion

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