# HeLP-Diabetes: Randomised Controlled Trial Research Protocol.

Study Title: Randomised controlled trial of an interactive internet-based intervention compared with a standard information website to improve self-management skills in people with type 2 diabetes in primary care.

REC Number: 12/LO/1572

UKCRN Portfolio number: 13563

ISRCTNO: 2123133

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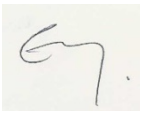
## Protocol Signatures

I give my approval for the attached protocol

## Chief Investigator

Name: Prof Elizabeth Murray

Signature: 

Date:

## Site Signatures

The trial will be conducted in compliance with the approved protocol, trial related procedures and all applicable regulatory requirements, including the NHS Research Governance Framework for Health and Social Care (April 2005), the World Medical Association Declaration of Helsinki (1996), the Human Tissue Act (2004) and the Data Protection Act (1998), and any subsequent amendments made.

## Principal Investigator

Name:

Signature:

Date:

## Glossary of Abbreviations:

| | |
|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| DESMOND | Diabetes Education and Self-Management for Ongoing and Newly Diagnosed |
| DMEC | Data Monitoring and Ethics Committee |
| DMSES | Diabetes Management Self-Efficacy Scale |
| DTSQ | Diabetes Treatment Satisfaction Questionnaire |
| EQ-5D | European Quality of Life Five Dimension Scale |
| HADS | Hospital Anxiety and Depression Scale |
| HbA1c | Glycated haemoglobin |
| HeLP-Diabetes | Healthy Living for People with type 2 Diabetes |
| HDL | High-density lipoprotein |
| IMP | Investigational Medicinal Product |
| NHS | National Health Service |
| NICE | National Institute of Health & Clinical Excellence |
| NIHR | National Institute of Health Research |
| NoCLor | North Central London Research Consortium |
| PAR | Possible Adverse Reaction |
| PCRN | Primary Care Research Network |
| PRIMENT CTU | Primary Care and Mental Health Clinical Trials Unit |
| QALY | Quality-Adjusted Life Year |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SDs | Standard Deviations |
| SMP | Self-Management Programme |
| SOPs | Standard Operating Procedures |
| T2DM | Type 2 Diabetes Mellitus |
| TMG | Trial Managing Group |
| TSC | Trial Steering Committee |
| URL | Uniform Resource Locator |

# Table of Contents

# 1 Trial Personnel

## Trial Management Group:

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## Funding Organisation:

National Institute for Health Research (Grant Reference Number RP-PG-0609-10135)

# 2 Summary

| Study synopsis | |
|---|---|
| Short title | HeLP-Diabetes: RCT in primary care |
| Study design | In a multi-centre, two-arm individually randomised controlled trial, an internet-based interactive self-management intervention (HeLP-Diabetes) is compared with a text-based information website. |
| Rationale | Type 2 Diabetes (T2DM) is one of the commonest, and costliest long terms conditions in the UK and internationally, with a rapidly increasing prevalence. Structured education is known to promote self-management and improve health outcomes; however few people in the UK with T2DM report receiving such education. An internet-based self-management intervention could potentially help address this unmet need. HeLP-Diabetes is a theoretically informed, evidence-based internet intervention developed using participatory design and addressing Corbin & Strauss' three tasks for managing a long-term condition: medical, role and emotional management. |
| Primary outcome | Change in Glycated haemoglobin (HbA1c) and diabetes related emotional distress scores (PAID) between baseline and 12 month follow up |
| Secondary outcome | Change in blood pressure; body mass index; lipids, depression and anxiety (HADS), diabetes-related self-efficacy (DMSES) and satisfaction with treatment (DTSQ). A health economic analysis is included. |
| Number of participating sites | 20 GP practices in England |
| Number of participants | 400 |
| Main Inclusion Criteria | Over 18 years old with a diagnosis of type 2 diabetes |
| Proposed Start Date | 01.03.2013 |
| Proposed End Date | 31.08.2015 |
| Study Duration | 30 months |

# 3 Introduction

## 3.1 Background

Type 2 diabetes (T2DM) is one of the commonest long term conditions in the UK, affecting over 2 million adults (1). T2DM can cause severe complications including cardiovascular disease, blindness, renal failure and neuropathy, and can reduce life expectancy by 8 – 10 years. Approximately 12% of deaths of people between the ages of 20 – 79 years are attributable to diabetes and about 10% of the NHS budget (£9 billion per annum) is spent on diabetes(2). Many of these costs are due to preventable complications. The key to good clinical outcomes in people with diabetes is self-management which can reduce both the incidence and impact of complications. Structured education is known to promote self-management and reduce the incidence of diabetes complications(3-5), and in 2008, the National Institute of Health and Clinical Excellence (NICE) advised that a key priority for implementation was the offer of structured education to every patient and / or their carer at the time of diagnosis with diabetes with annual reinforcement (1). NICE advised that such structured education or self-management programmes (SMP) should improve outcomes

through addressing health beliefs, optimising metabolic control, addressing cardiovascular risk factors, facilitating behaviour change, improving quality of life and reducing depression as well as enhancing the relationship between the patient and their healthcare professionals (1).

### 3.2 Rationale

Examples of existing self-management programmes for people with type 2 diabetes in the UK include DESMOND (5), X-PERT (6) and Co-Creating Health. Although these programmes have shown initial benefits, there are concerns that benefits may not be sustained in the long term (7). There are additional concerns that group-based programmes such as these may not suit all patients who need self-management training. People who work, have caring responsibilities at home, have mobility problems, or who find group interactions difficult may all have difficulty attending. Recent data from the National Audit Office suggests that less than 5% of people with T2DM have attended structured education (NAO, 2012). Thus there is an urgent need to find cost-effective and acceptable methods of delivering sustainable self-management education for people with type 2 diabetes in the UK. One possibility is the use of web-based or computer-based self-management programmes. These have many potential advantages, including convenience, accessibility and anonymity. For people with home access to the internet (73% of the UK population in 2011 (8)), such programmes can be accessed at any time of day or night so can be fitted in around responsibilities at home or work. Information can be presented accessibly using simple graphics or audio-visual techniques and can be easily updated as new research becomes available. Programmes can be highly interactive, responding to data entered by individual users to provide a tailored, personalised experience. They can offer structured behaviour change support including self-assessment, goal-setting, monitoring and feedback. Users can gain emotional support from reading about others' experiences with similar problems (personal stories), participating in online forums, or using online support tools such as computerised cognitive behavioural therapy or mindfulness training. Unlike face-to-face interventions, computerised programmes can be permanently available and provide both on-going support as well as meeting changing needs as the disease progresses. The marginal costs per additional user are low, so such interventions have the potential to be highly cost-effective. A recent Cochrane systematic review of such programmes suggested they can improve some health outcomes including glycaemic control and lipids, but there were insufficient data to draw any conclusions about their impact on emotional well-being, quality of life or cost-effectiveness. None of these programmes addressed all the areas specified by NICE for self-management education, and none were developed in the UK (9).

We have developed a internet-based self-management programme for people with type 2 diabetes, HeLP-Diabetes, or Healthy Living for People with type 2 diabetes. HeLP-Diabetes was developed as part of a National Institute for Health Research (NIHR) Programme Grant for Applied Research. The content and development of HeLP-Diabetes was based on five main principles: first, we adopted the Corbin and Strauss model of the work required for self-management of a long-term condition, which includes medical management (e.g. adopting healthy behaviours, working with health professionals, managing medicines), emotional management (e.g. managing the strong negative emotions resulting from being diagnosed with a long term condition including anger, guilt, shame and despair), and role management (e.g. managing the disruption of one's biographical narrative) (10). This model gave us an overarching framework of patients' requirements. Secondly we undertook extensive qualitative work with our target users, defined as patients with type 2 diabetes and health professionals who care for these patients, to identify user needs and wants from such a programme. Effective self-management requires a partnership between patients and health professionals so it was important to ensure that the programme was acceptable to both groups of users. User input continued throughout the development process with user panels providing iterative comments on materials as they were developed and refined (participatory design), ensuring that the final programme was highly acceptable to both

patients and health professionals. Thirdly, we reviewed the behaviour change literature to identify behaviour change techniques that were most likely to be effective in helping patients achieve sustainable behaviour change. Fourthly, we applied the principles of Normalization Process Theory to maximise the likelihood of the programme being easily implemented and integrated into routine NHS care (11). Finally, we ensured that all information provided in the programme was evidence-based and compatible with current NICE guidelines.

# 4 Objectives

The aims of the trial are to:

1. Determine the effect of HeLP-Diabetes on clinical outcomes and diabetes-related emotional distress in people with T2DM;
2. Determine the incremental cost-effectiveness of the intervention compared to usual care from the perspectives of health and personal social services and wider public sector resources.

Hypothesis: that use of the intervention will reduce diabetes-related emotional distress and improve glycaemic control.

# 5 Trial Design

**Design: This will be** multi-centre, two-arm individually randomised controlled trial of approximately 400 patients in primary care (200 patients intervention arm; 200 patient control arm).

***Setting:*** Approximately 20 general practices in 5 Primary Care Research Networks (PCRN) across England will recruit the patients and conduct the study, with support from the UCL coordination centre.

# 6 Selection of participants

*6.1 Inclusion criteria*:

- Adults, aged 18 or over, with type 2 diabetes.

*6.2 Exclusion criteria*:

- Unable to provide informed consent, e.g. due to psychosis, dementia or severe learning difficulties;
- Terminally ill with less than 12 months life expectancy;
- Unable to use a computer due to severe mental or physical impairment;
- Insufficient mastery of English to use the intervention i.e. requires an interpreter in consultations;
- Current participation in a trial of an alternative self-management programme.

NB
Participants do not have to have home internet access or prior experience of using the internet to participate.
Participants with previous or current experience of self-management education are eligible to participate.

# 7 Recruitment

**Stage 1: Practice Recruitment**
Approximately 20 practices will be recruited through 5 Primary Care Research Networks (PCRN) in England (South West, Central, East of England, South East, Greater London) and the North Central London Research Consortium (NoCLOR). Practices will be assessed for their feasibility (e.g. large enough diabetes register to be able to invite a minimum of 300 eligible participants; staff are GCP trained; 2 members of staff available to carry out the study) prior to agreement to act as a participating site. Once a practice has agreed to participate and completed site set-up procedures they will commence patient recruitment.

**Stage 2: Patient recruitment**
20 patients will be recruited by each practice following standard opt-in procedures. Each practice will have a register of patients with type 2 diabetes as they need this for the Quality and Outcomes Framework. A nurse or other qualified health professional at the practice will review the electronic medical record of each of the patients on this register with a view to screening out ineligible patients. To take part in the trial the practice must have at least 300 eligible participants after screening of the diabetes register has taken place. All remaining, potentially eligible patients will be sent a letter from their GP inviting them to participate in the study. A participant information sheet, expression of interest and stamped addressed envelope will be included. Patients who are interested in participating will be asked to return the expression of interest form to the practice nurse or trial manager.

Follow up invitation letters will be sent 2 weeks later to all non-responders by the practice if the recruitment target of 20 letters of interest has not been met. 2 weeks later if the practice/trial manager has still not received 20 letters of interest a sample of 50 non-responders will be chosen from the eligible patients to receive a follow up phone call from the practice. Reasons for non-response will be recorded by the practice on a pro-forma provided by the research team.

In addition posters advertising the study will be put up in each practice so that patients can ask the nurse directly for more information about taking part.

# 8 Study procedures and schedule of assessments

## 8.1 Screening
See section 7, Stage 2: Practice recruitment

## 8.2 Informed Consent (Visit 1)
Informed, written consent will be sought prior to conducting any trial procedures. On receipt of the expression of interest form, the nurse will contact the patient and offer them an appointment at the practice. This will ensure that following identification, participants will always be given at least 24 hours from receiving the participant information sheet to giving informed consent. At this first study visit (baseline), the nurse will confirm with the participant that they have read and understood the participant information sheet. The nurse will also verbally explain the study and answer any questions the patient might have. The voluntary nature of participation and the ability to withdraw at any time will be emphasised. If there is any doubt about the participant's ability to give informed consent, they will not be recruited onto the study. Those that agree to participate will be asked to sign the written consent form. The nurse will also sign to confirm they are the person taking consent. The original signed consent form should be kept in the site file. Three copies should be taken: one to be given to the patient, one to put in the patient's medical record, and one for the coordinating site (UCL).

After signing the consent form, all baseline data collection will be completed prior to randomisation. Randomisation marks the point of entry into the trial.

### 8.3 Baseline assessments (visit 1)

At the baseline visit (visit 1) to the GP practice informed consent must be taken before any data can be collected (see 8.2 Informed consent). Once this has been taken all nurse completed baseline assessments will be completed. These include the patient's height (cm), weight (kg), systolic and diastolic blood pressure will be recorded. A blood test will be taken to determine glycated haemoglobin (HbA1c), total cholesterol and HDL cholesterol. This will be processed at local laboratories through the GP practices. When the results of the blood test are returned to the practice the nurse should enter them directly to the online Case Report Form and also into the patient's medical record.

In addition the following data will need to be extracted from the patient's electronic medical record:

- date of diagnosis of diabetes;
- HbA1c, blood pressure, total cholesterol, HDL cholesterol and smoking status at time of diagnosis;
- presence or absence and date of diagnosis of complications of diabetes including ischaemic heart disease, myocardial infarction, congestive cardiac failure, atrial fibrillation, peripheral vascular disease, amputation, cerebro-vascular disease, retinopathy, renal failure and neuropathy;
- a list of current medications.
- Current smoking status
- Health Service Utilisation in the 12 months prior to baseline visit

During the baseline assessment (visit 1) at the practice the nurse will send an email to the patient containing a secure link to complete their baseline patient reported outcomes, demographic data and health service use when they get home. Demographic data will include: age, gender, highest educational attainment, ethnicity, current employment status, presence or absence of home internet access, level of expertise in computer use, current or previous participation in diabetes self-management education, smoking status.

Baseline patient reported outcomes include:

- PAID,
- HADS,
- DTSQ,
- EQ-5D,
- Diabetes self-efficacy scale
- Health Service Use in the past 12 months

### 8.4 Randomisation

Randomisation will be performed only after all (nurse and patient) baseline data assessments has been completed. Randomisation will be at the level of the individual participant. It will be stratified by recruitment centre and will be performed centrally using a web-based randomisation system provided by the PRIMENT Clinical Trials Unit (Sealed Envelope http://www.sealedenvelope.com/). This system will send an email to the trial manager when a patient has been randomised detailing which arm the patient has been allocated to. This will then be forwarded to the nurse who will be introducing the control and intervention websites to the patients in visit 2.

### 8.5 Delivery of intervention and comparator (visit 2 & supportive phone calls)

**Trial arm 1: The intervention group**

1. ***Visit 2***

Visit 2 will take place at the GP practice. Practice nurses will give the patient a booklet containing the url for the programme, the participant's log in details, and information about the content of the website and how best to use it. Nurses will register the patient, show them how to login to the website, and introduce them to the main content areas. The nurse will discuss with the patient what the patient's most pressing needs are and use this to guide the patient toward certain sections (for example, improving diet, being more physically active, or managing emotions).

2. ***Supportive follow-up phone calls***

Follow-up phone calls will be offered to support the patient in use of the programme. Nurses will phone patients once every fortnight (3 phone calls in total) over the first 6 weeks after visit 2.

**Trial arm 2: The comparator**

1. ***Visit 2***

Visit 2 will take place at the GP practice. At this visit practice nurses will also give participants a booklet with the url of the control website and user log in details. Practice nurses will register each participant on the website, show them how to login and how to use the website.

Follow up phone calls are not offered to participants in the comparator arm.

### 8.6 Subsequent assessments

Follow up assessments will be collected at 3 and 12 months after visit 2 (delivery of the intervention or comparator website).

**Patient completed assessments**

Participants will be sent an email by the trial manager containing a secure link to complete their patient reported questionnaires (demographics, PAID, HADS, DMSES, DTSQ and EQ-5D), prior to the visits 3 and 4 with the nurse.

**3 month follow up assessments (visit 3)**

As soon as the patient has completed their 3 month questionnaires at home the trial manager will notify the nurse to arrange visit 3. Visit 3 will take part at the GP practice. At this visit the nurse will record the patient's weight (kg) and systolic and diastolic blood pressure. A blood test will be taken to determine glycated haemoglobin (HbA1c), total cholesterol and HDL cholesterol. The blood samples will be processed at the local laboratory through the GP practice.

In addition the nurse will need to extract the following data from the patient's electronic medical record:

- a list of current medications.
- current smoking status
- Health Service Utilisation in the 3 months prior to 3 month visit

**12 month follow up assessments (visit 4)**

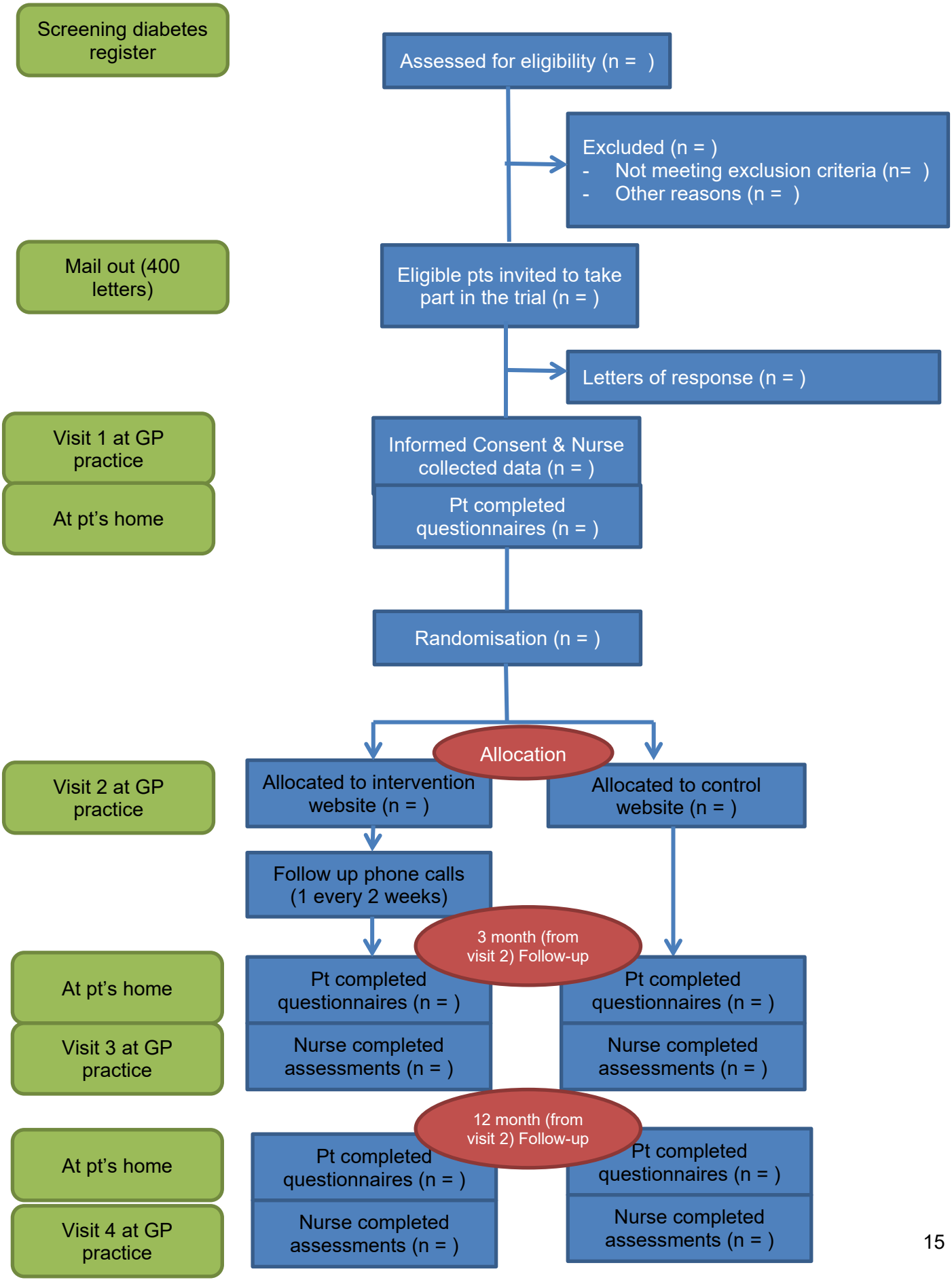
As soon as the patient has completed their 12 month questionnaires at home the trial manager will notify the nurse to arrange visit 4. Visit 4 will take part at the GP practice. At this visit the nurse will record the patient's weight (kg) and systolic and diastolic blood pressure. A blood test will be taken to determine glycated haemoglobin (HbA1c), total

cholesterol and HDL cholesterol. The blood samples will be processed at the local laboratory through the GP practice.

In addition the nurse will need to extract the following data from the patient's electronic medical record:

- a list of current medications.
- current smoking status
- Completion of the "9 essential processes" for the 12 months prior to randomisation and the 12 months after randomisation at the 12 month follow-up visit

### 8.7 Flowchart of study assessments



# 9 Definition of end of trial

The end of the trial will be when the last patient has completed visit 4 (12 month follow up assessments).

### 9.1 Withdrawal

A participant can withdraw from the trial at any point without giving a reason. Participant withdrawal should be recorded by a member of the practice on the participant's online case report form. Any data that has already been provided will be kept in the study but no further data will be collected.

# 10 Intervention and comparator

### 10.1 The Intervention

The intervention consists of facilitated access to an interactive website. There are three components to the facilitated access:

1. an introductory appointment with a nurse (visit 2: see section 8.5)
2. 3 supportive follow-up phone calls,
3. on-going discussion of the website in routine appointments for diabetes-related matters.

Participants in the intervention arm will have access to detailed interactive web-based programme with multiple components. There are information sections on diabetes, how diabetes is treated, possible complications of diabetes, possible impacts of diabetes on relationships at home and at work, dealing with unusual situations like parties, holidays, travelling or shift work, and what lifestyle modifications will improve health. There are sections addressing skills and behaviour change, including behaviour change modules on eating healthily, losing weight, being more physically active, smoking cessation, moderating alcohol consumption, managing medicines, glycaemic control and blood pressure control. These all include motivating information on the benefits of behaviour change, self-assessment quizzes for patients to assess whether and how much they need to change, and opportunities for goal-setting and self-monitoring. Users can arrange for automated SMS messages to remind them of specific behaviours or provide encouragement. The third strand of components focuses on emotional well-being and contains self-help tools based on cognitive behavioural therapy and mindfulness. There are multiple personal stories (used with license from health talk online), and a moderated forum for users to interact with each other. This all makes for a large and complex programme which could potentially be overwhelming or hard to find one's way around. We have worked with a web designer to ensure that navigation is intuitive and user friendly. Engagement with the intervention website will be promoted through regular, SMS, emails and newsletters.

### 10.2 The comparator

From an NHS perspective, the important research question is whether the proposed intervention can improve health outcomes when compared to current practice. However, to improve acceptability to participants, all participants will have access to a website. The control consists of facilitated access to a simple information website, based on the information available on the Diabetes UK and NHS choices websites. This facilitated access will involve an introductory appointment (visit 2) with the nurse but no follow up phone calls. Discussion about the website during consultations will be left to the discretion of the health professionals and participating patients.

# 11. Data management and quality assurance

## *11.1 Outcome measures and other measurements*

*Primary outcomes.*
The outcomes reflect our aims of improving clinical outcomes and health related quality fo life. We have selected two joint primary outcomes: **glycated haemoglobin (HbA1c)** and diabetes-related emotional distress, measured by the **Problem Areas in Diabetes (PAID) scale** (12). PAID has 20 items focusing on areas that cause difficulty for people living with diabetes, including social situations, food, friends and family, diabetes treatment, relationships with health care professionals and social support. It has been the subject of a number of reviews comparing available quality of life measures for diabetes. Eigenmann assessed available measures against criteria of reliability; content, face, construct, criterion and convergent validity; responsiveness to change; interpretability; response burden; acceptability and availability and concluded that PAID was one of three measures that met all criteria (13). It is sensitive to change and has been widely used to evaluate self-management programmes for people with T2DM including the influential DESMOND trial (5).

*Secondary outcomes*
Secondary outcomes have been selected to reflect the proposed pathway of action of our intervention and allow health economic analysis and can be categorised as clinical, patient-reported, or economic.

Clinical outcomes collected by the nurse:

- Systolic and diastolic blood pressure;
- Body mass index;
- Total cholesterol and HDL (not fasting);
- Completion of “9 essential processes” (= weight, BP, smoking status, measurement of serum creatinine, cholesterol and HbA1c, urinary albumen and assessment of eyes and feet). This data is to be obtained from the patients notes for the 12 months prior to randomisation and the 12 months after randomisation at the 12 month follow-up point by the research nurses.

Patient-reported outcomes:

- Depression and anxiety, measured using the Hospital Anxiety and Depression Scale (HADS) (14);
- Diabetes-related self-efficacy measured using the Diabetes Management Self-Efficacy Scale (DMSES) (15);
- Satisfaction with treatment, measures using the Diabetes Satisfaction with Treatment Questionnaire status and change version (DTSQs & DTSQc) (16).

Economic outcomes:

- Cost of developing the intervention;
- Cost of supported access;
- Costs of training NHS staff both in using the intervention and training patients to use the intervention;
- Costs of maintaining and updating the intervention;
- Health service utilisation during and 12 months before the study period;
- EQ-5D to calculate QALYs (17);
- Clinical parameters required for modelling long term cost-effectiveness of the intervention (detailed below).

Other measurements:
Data to describe our patient population will be collected at baseline and will include demographic and clinical data. In addition we will use automated software to automatically record each participant's use of the intervention (number and frequency of log-ins, pages visited).

### *11.2 Data collection tools and source document identification*

Table 1 below outlines the data that will be collected at each visit/appointment. Table 2 shows the procedures and sources for data collection.

Table 1: Shows the scheduling and data collected at each visit/appointment

| | Baseline | | Introductory Session | 3 month follow up | | 12 month Follow up | |
|---|---|---|---|---|---|---|---|
| | Baseline Visit (apt 1) | Baseline Email | Showing intervention or control website | 3 month Email | 3 month Visit | 12 month Email | 12 month Visit |
| Who will collect data | Nurse 1 or 2 | Patient | Nurse 1 | Patient | Nurse 2 | Patient | Nurse 2 |
| Scheduling | | | As soon as possible after randomisation | | | | |
| Informed Consent | X | | | | | | |
| Assignment of patient ID | X | | | | | | |
| Height (cm) | X | | | | X | | X |
| Weight (kg) | X | | | | X | | X |
| Systolic & Diastolic Blood Pressure | X | | | | X | | X |
| HbA1c | X | | | | X | | X |
| Total Cholesterol | X | | | | X | | X |
| HDL Cholesterol | X | | | | X | | X |
| Date of diabetes diagnosis | X | | | | | | |
| HbA1c; blood pressure; total cholesterol; HDL cholesterol and smoking status at time of diabetes diagnosis | X | | | | | | |
| Presence or absence and date of diagnosis of complications of diabetes | X | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| List of current medications | X | | | | X | | X |
| Health service Use | X* | | | | X** | | X*** |
| Demographic Data | | X | | | | | |
| PAID | | X | | X | | X | |
| HADS | | X | | X | | X | |
| DTSQ | | X | | X | | X | |
| EQ-5D | | X | | X | | X | |
| DMSES | | X | | X | | X | |
| Health Service Use | | X* | | X** | | X*** | |
| Smoking status | | X | | X | | X | |
| Randomisation | | X**** | | | | | |
| Intervention or Control | | | X | | | | |

*In the 12 months prior to baseline visit
**In the 3 months prior to visit 3 (3 month follow up)
***In the 9 months prior to visit 4 (12 month follow up)
****Randomisation actually occurs after completion of all baseline data (visit and email)

Standard operating procedures (SOPs) will cover every aspect of data collection and nurses will be trained in these procedures. Nurses will enter the data collected into an electronic case report form for each patient provided by sealedenvelope.com (see data management below).Adherence to SOP will be monitored

### 11.3 Confidentiality

All data will be handled in accordance with the data protection act. The electronic case report form for each participant will not include any patient identifiable data.

### 11.4 Adherence and loss to follow-up

Fidelity of the intervention will be promoted and monitored. Use of the intervention and control websites will be recorded automatically. A random sample of nurse-delivered training sessions and follow-up phone calls will be recorded and reviewed by the study team.

Every effort will be made to promote follow-up which will be co-ordinated by the trial manager centrally. The trial manager or practice nurse will send participants up to two e-mails at weekly intervals at each follow-up point (3 and 12 months) containing an embedded hotlink to the online questionnaires. Participants who have not responded after the second email will be sent a letter through the post, explaining that we have sent emails requesting follow-up data. This letter will also contain a pencil-and-paper version of the questionnaires with a stamped addressed envelope for returning it, in case participants prefer to complete the questionnaires offline. A second version of this letter will be sent two weeks later. If participants do not respond after this second letter, the trial manager will contact the relevant practice nurse to see if there is any reason for non-response. If no compelling reason is identified, a member of the research or practice team will contact the patient by phone to explore reasons for non-response, encourage response, and if necessary, ask the patient to complete the PAID verbally over the phone.

Once the trial manager has received self-reported follow-up data from the participant, she will notify the practice nurse and ask the nurse to arrange an appointment with the participant to record clinical and economic outcome data

### *11.5 Data Handling and Record Keeping*

Clinical outcome data (height, weight, blood pressure, HbA1c, total cholesterol, HDL cholesterol) will be entered directly into a secure online case report form (CRF, provided by sealed envelope) by the nurse. The results of these assessments will also be added to the patient's medical record. Data from the patient's medical record (Health service use; Date of diabetes diagnosis; HbA1c, blood pressure, total cholesterol, HDL cholesterol and smoking status at time of diabetes diagnosis: Presence or absence and date of diagnosis of complications of diabetes; List of current medications will first be extracted by the nurse and then entered into the online case report form. All trial data in the CRF must be extracted from and be consistent with the relevant source documents (see Table 2). Patient reported outcomes (Demographic Data; PAID; HADS; DTSQ; EQ-5D; DMSES; Health Service Use; Smoking status) will be completed by patients online and will automatically be recorded in the online case report form.

The principal investigator at each site has overall responsibility in ensuring the accuracy and completeness of the data entered into the electronic case report form. In addition the principal investigator is also responsible for delegating responsibilities such as data collection to staff members and maintaining an up to date delegation log recording these decisions.

Table 2: shows the procedures for data collection

| Data Collected | By Who? | Location of Source Data | Data Collection Tool/Method |
|---|---|---|---|
| Clinical Data | Nurse | Lab results | Online Case Report Form and patient medical record |
| Patient Reported Data | Patient | Electronic Questionnaire (via email) | Online Case Report Form |
| Data from patients medical Record | Nurse | Patients medical record | Online Case Report Form |
| Data collected via websites | Intervention & Control website | Websites secure server | Google analytics |

**Data checks**

The validity and quality of the data is ensured by having required fields and range checks built in to the online case report form. These validation rules are triggered during data entry. Rules can be overridden where necessary as long as a justification is provided. The online Case Report Form displays a listing of forms for each patient showing at a glance both incomplete forms and those that have queries raised against them. Queries can be raised at any time against questions within a form or against the form itself. The online Case Report Form also displays an overview chart that helps quickly identify overdue forms and problem sites.

**Source Data**

To enable peer review, monitoring, audit and/or inspection, each site will agree to keep records (i.e. a recruitment log) of all participating patients (sufficient information to link records e.g, eCRF, and medical records), all original signed informed consent forms and any paper copies of the CRF. It is the principal investigator at each site responsibility to make sure this data is complete, accurate and secure.

**Patient Identifiable Data Transfer from Local Site to Coordinating Centre**
All identifiable data (Pt ID, Gender, Name, Home Address and Postcode, Date of Birth, Telephone number, email) will be securely sent to the Coordinating Centre by recorded delivery or fax (020 7794 1224) and stored in a locked filing cabinet and/or in a separate, password encrypted database in compliance with the Data Protection Act, with permission for access given to delegated study-staff. The Coordinating Centre will keep a log of when data was transferred and by which site.

**Archiving**
All documents contained in the TMF, Investigator Site File should be archived within 12 months of the end of the study for a period of not less than 5 years. Source data will also be archived. For external sites, it is the responsibility of the PI to clarify local Trust policies on retention of medical records. The source data (i.e. any source data not contained in the medical records, such as completed Case Report Forms) and the TMF and ISF and PF should be archived together. Any essential trial documentation, that was stored somewhere other than the TMF or the ISF during the study, should be returned to the CI (for filing in the TMF) or PI (for filing in the ISF) once the study finishes so that all documents can be archived together. All archived documentation should be complete, legible and available to auditors, other researchers or anyone with a legitimate need to access them.

On completion of the trial, the individual(s) responsible for archiving should check the TMF against the TMF index to ensure that all of the essential documents are in the file and are in the correct order.

### 11.6 Blinding
Baseline data (visit 1) will be obtained prior to randomisation so there will be not risk of bias. Randomisation will be performed centrally and allocation will not be revealed to the participants who will have been informed that the trial is comparing two forms of web-based education for diabetes (one simple website and one detailed website). The nurse (nurse 1) who is responsible for running the introductory sessions (visit 2) with the patients to show them either the control or the intervention website will not be blinded. The risk of bias in collection of follow-up data will be minimised by using standardised data collection instruments with participants completing self-assessment questionnaires before seeing the nurse to record clinical data. The nurse who will be collecting follow up data (visit 3 and 4) will be a different nurse to the nurse who runs the introductory session (visit 2) and will therefore be blinded to website (control; intervention) each patient has been allocated to. The trial manager will not be blinded to the website the participants have be allocated to so any follow up phone call to non-responders will be carried out by a member of the research team who is blind to patients allocation.

### 11.7 Other measures to avoid bias
There are potential problems with contamination (e.g. two members of the same household being randomised to different interventions with individual randomisation but cluster randomisation has greater potential to introduce bias by affecting GP behaviour (which patients they refer to the trial) and patient behaviour (participation). We will monitor the extent to which contamination occurs by determining the proportion of participants who had contact with another trial participant with a different treatment allocation. Blood pressure will be recorded using automated electronic sphygmanometers.

### 11.8 Training
Clinical data will be collected by the nurses who will be trained by the trial manager to adhere to detailed SOPs developed in collaboration with PRIMENT CTU. In particular these SOPs will cover data collection and how to introduce the control and intervention websites to patients

# 12. Safety Reporting

## 12.1 Definitions

*Adverse Events (AE)*

Adverse Events are defined as an adverse change in health that occurs while a patient is taking part in a study. This is any unfavourable or unintended sign, symptom, syndrome or adverse illness that develops or worsens during the period of observation in the study. It does not necessarily have a causal relationship with the research.

Includes:

- an exacerbation of a pre-existing illness
- increase in frequency or intensity of a pre-existing episodic event or condition
- condition detected or diagnosed after being introduced to the HELP-Diabetes website even though it may have been present prior to the start of the trial
- continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

Not included (Expected):

- a medical or surgical procedure (e.g. surgery, endoscopy, tooth extraction, transfusion) unless the condition that leads to the procedure is an AE
- pre-existing disease or conditions present or detected at the start of the trial that did not worsen
- situations where an untoward medical occurrence has not occurred (e.g. hospitalisations for elective surgery, or other elective admissions)
- disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the patient's condition (For example: hypoglycaemic episode)
- overdose of concurrent medication without any signs or symptoms.

*Serious Adverse Event (SAE)*

Any adverse event during participation in the study that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation or prolongation of existing hospitalisation;

(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect;

(f) any other serious medical occurrence

### 12.2 Recording adverse events

Only adverse events (AEs) resulting directly from any study procedures will be reported. As HeLP-Diabetes is a low risk study it is anticipated that the vast majority of AEs will be unrelated to study participation.

AEs that are not considered serious should be logged in the case report form by the site PI (or delegate).

### 12.3 Procedures for recording and reporting Serious Adverse Events

AEs that are considered to be serious will be recorded in the CRF by the site PI or delegate, and reported to the study coordinating centre/trial manager using the study SAE form by fax or email within 24 hours of awareness of the event.

Serious adverse events will be documented from the point of enrolment until the patient has completed the study. Information recorded and reported will include:

- A description of the event
- The date of event onset
- The relatedness of the event to the procedure
- The expectedness of the event
- Actions taken as a result of the event
- The outcome of the event
- The date the event was first noticed by, or reported to the Investigator

All ongoing SAEs will be followed up until the last study visit.

SAEs need to be reported to the patients GP by the PI or nurse.

The PI must provide the reason why the event qualifies as an SAE and assesses the causality and expectedness of the event in relation to the intervention is the study.

Upon receipt of an SAE at the study coordinating centre, the CI will review causality and expectedness and report as follows:

**Sponsor**

All Serious Unexpected Adverse Events must be reported immediately to the Sponsor using the following email address: research-incidents@ucl.ac.uk

**Research Ethics Committee**

An SAE occurring to a research participant should be reported to the main REC using the Serious Adverse Form where in the opinion of the Chief Investigator the event was:

- Related – that is, it resulted from the administration of any of the research procedures, and

- Unexpected – that is, the type of event is not listed in the protocol as an expected (not included) occurrence.

Reports of related and unexpected SAEs should be submitted **within 15 days** of the Chief Investigator becoming aware of the event.

The form should be completed in typescript and signed by the Chief Investigator. The co-coordinator of the main REC will acknowledge receipt of safety reports within 30 days.

# 13. Statistical considerations

### 13.1 Outcomes

Primary endpoints:

- Change in mean glycated haemoglobin (HbA1c) between baseline and 12 month follow up.
- Change in mean Problem Areas in Diabetes (PAID) scale (12) between baseline and 12 month follow up.

Secondary endpoints:
Change in the following parameters between baseline and 12 month follow-up:

- Blood pressure
- Lipids
- Body Mass Index (BMI)
- Health Service Use
- Smoking status
- Anxiety and Depression Score (HADS)
- Treatment satisfaction (DTSQ)
- Self-efficacy (DMSES)
- Completion of 9 essential processes

### *13.2 Sample size*

We hypothesise that use of the intervention will improve both PAID scores and HbA1c. The analyses will gain power through adjustment for baseline levels. We have back-calculated the relevant effective standard deviations (SDs) from a previous trial as 0.676 for HbA1c and 10.75 for PAID, substantially lower than the SDs of cross-sectional measures of around 1.4 and 16 respectively because of the correlation between baseline and subsequent measures. We intend to recruit 350 participants; with attrition of up to 15% we anticipate at least 300 patients for the primary analysis. This will give us 90% power of detecting at a 5% significance level a true average difference in the PAID score of 4.0 and 0.25% change in HbA1c. These are both small effect sizes.

### *13.3 Analysis*

The analysis will follow a pre-specified analysis plan, based on comparing the groups as randomised (intention-to-treat). Follow-up HbA1c will be adjusted for initial levels and other baseline covariates including age, gender, participation in other self-management programmes, pre-existing cardiovascular disease and duration of diabetes. PAID and other outcome measures will be analysed similarly. Sub-group analysis of patients with poor glycaemic control (HbA1c 7.5% or greater) will be undertaken. Pre-specified sub-group effects by age and gender will be assessed for HbA1c using tests of interaction. Missing follow-up data will be multiply imputed where possible using other outcome data (e.g. 3m data when 12 m data are missing) and other sensitivity analyses investigating the potential for bias undertaken. The role of potential mediators (e.g. extent of use of the SMP) will be investigated employing the randomised design to obtain unbiased estimates.

If contamination (where members of the control group have access to the active intervention, e.g. through a family member in the intervention group) does occur it will be dealt with in the analysis by:

a) Our main (primary) analysis will be a full intention-to-treat analysis on the whole trial population;
b) We will report the extent of any contamination;
c) We will undertake a sensitivity analysis using non-contaminated controls in the control arm only. However, as this loses the benefits of randomisation we will also
d) Undertake a Complier Average Causal Effect (CACE) analysis which respects randomisation. For this CACE analysis we would label contaminated control participants as potential non-compliers (18).

### *13.4 Economic analysis*

*Incremental cost-effectiveness*

The incremental cost-effectiveness of facilitated access to HeLP-Diabetes compared to usual care for patients with T2DM will be assessed following NICE guidance both from a health and personal social services and a wider public sector resource perspective (19;20). The components of the analysis are health outcomes, costs of the active and control intervention, and the potential impact on diabetes care and complications. QALYS will be calculated using area under the curve analysis from the baseline, 3- and 12- month follow-ups, adjusting for baseline levels. Intervention costs will be measured directly and other NHS costs will be calculated from the patient record.

*Costs of the intervention*

Costs of the intervention to the NHS are made up of two major components: development of the intervention and facilitation / implementation costs. The resources required for the development of the intervention will be monitored during the development process and a careful analysis made to separate treatment from research costs. Once the intervention has been developed it will need ongoing maintenance and updating; these costs will be recorded. There may also be additional costs per participant to obtain access to the GP electronic medical record.

*Facilitated access and implementation costs*

Implementation costs will be largely made up of staff time, health professional time, and patient time. A proforma will be constructed so that time spent by the implementation staff in the project can be attributed to the different stages of the implementation process. The individual help given to each patient and health professional will be collected and coded to each practice, and costed on the basis of the full economic costs of the staff involved. Estimates of the additional time required from the general practice staff will be obtained. The costs of health professional input from the practices will be based on national average rates using PSSRU estimates. Costs calculated for the different implementation and facilitated access activities will be estimated for each participating practice and compared to patient activity. The data will be used to construct models of the potential implementation costs and population benefits for a “typical” Clinical Commissioning Group and how these costs and effects may vary with different levels of implementation.

*Probabilistic decision model*

We will construct and test a probabilistic decision model following best-practice guidelines. We will undertake a literature review of existing relevant models and economic evaluations and build a model which evaluates the expected outcomes of the intervention and captures all relevant impacts from a health service perspective over the medium - long term. Parameter estimates will be determined from systematic reviews and synthesis of available evidence.

# 14. Regulatory issues

### 14.1 Non-CTIMP Status
This research project does not constitute a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC.

### 14.2 Ethical Approval
The HeLP-Diabetes study has been reviewed and given favourable opinion by the Camden and Islington National Research Ethics Committee (12/LO/1572)

### 14.3 Direct access to source data/documents
The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents if necessary. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

### 14.4 Sponsor
University College London will act as sponsor for this study

### 14.5 Funding
This study is funded by a National Institute of Health Research Programme Grant (RP-PG-0609-10135).

### 14.6 Audit and monitoring requirements
The study may be subject to inspection and audit by University College London under their remit as sponsor and other regulatory bodies to ensure GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

### 14.7 Trial Management Group
The PI is Elizabeth Murray and the Trial Manager is Charlotte Dack. They will take day to day responsibility for the trial. We will have a trial management group (TMG) whose role will be to support EM and CD in managing the trial, including reviewing procedures, recruitment, data collection, follow-up and responding to unforeseen issues. The TMG will meet quarterly, using a mixture of face-to-face and teleconference meetings. Membership of the TMG will include:

Michael Sweeting (statistician)
Steve Parrott (health economist)
Andrew Farmer
Susan Michie
Lucy Yardley
Maria Barnard
Bindie Wood (Patient representative).

### 14.8 Trial Steering Committee
We have established an independent Trial Steering Committee (TSC) to oversee the overall conduct of the trial. Membership of the TSC will include:

- Frances Mair (Chair)
- Nick Freemantle (statistician);
- Joni Inniss (patient representative);
- Peter Hindmarsh (paediatric endocrinologist).

### 14.9 Data Monitoring and Ethics Committee (DMEC).

As this is a low risk trial we will not have a DMEC.

### 14.10 Incident Reporting

All incidents must be reported through the appropriate Trust incidents reporting system. Where no Trust is involved, the incident should be reported by completing the form at http://www.ucl.ac.uk/jro/postapproval

An incident in a research study is:

- something that should not have happened OR
- something that should have happened but didn't

which significantly affects any of the following:

- the rights and well-being of the research subject
- the scientific value of the study
- the compliance of the study with all relevant legal rules or ethical guidance including the Data Protection Act and the Human Tissue Act
- the reputation of UCL

This includes a requirement to report all serious breaches of the protocol or GCP.

### 14.11 Complaints and Insurance

**Complaints**
In the event of complaint about the conduct of the study, the complaint should be reported immediately to the Joint Research Office research-incidents@ucl.ac.uk who will decide which complaints policy applies and who will be the lead organisation. The NHS complaints policy can only apply where the research subject is recruited through an NHS Trust. In other circumstances the UCL complaints policy will apply.

**Insurance**
University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Potential insurance claims should also be reported immediately to the Joint Research Office.

## 15. PROJECT TIMETABLE & MILESTONES

| Date | Task / Milestone |
|---|---|
| | |
| 1 March 2013 | Start of trial |
| March – December 2013 | Recruit practices |
| September 2013 – August 2014 | Recruit patients (screening, patient invitations, visit 1, randomisation & visit 2) |

| | |
|---|---|
| Nov 2013 - Dec 2014 | 3 month follow up (visit 3) |
| September 2014 – August 2015 | 12 month follow up |
| August 2015 | Close follow up |
| September 2015 – February 2016 | Analysis, Writing up and dissemination |

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