

## **Title page**

Title: Protocol for the feasibility study testing a wearable digital diabetes prevention programme in people at high risk of type 2 diabetes-Diabetes Stopwatch Study: a randomised controlled trial.

Authors: Khalida Ismail<sup>1</sup>, Adam Bayley<sup>1</sup>, Jennifer Rundle<sup>1</sup>, Stephen Thomas<sup>3</sup>, Neel Basudev<sup>4</sup>, Emily Staite<sup>1</sup>, Kurtis Stewart<sup>1</sup>, Natalie Zaremba<sup>1</sup>, Ebaa Al Ozairi<sup>5</sup>, David Hopkins<sup>2</sup>

### Affiliations:

1. King's College London, Western Education Centre, 10 Cutcombe Road, London, SE5 9RJ
2. King's College Hospital NHS Foundation Trust/King's Health Partners, Denmark Hill, SE5 9RS
3. Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, London, SE1 9RT
4. Springfield Medical Centre, 110 Union Road, London, SW8 2SH
5. University of Kuwait, Dasman Diabetes Institute, Kuwait

Corresponding author: Khalida Ismail, [khalida.2.ismail@kcl.ac.uk](mailto:khalida.2.ismail@kcl.ac.uk)

Protocol version and date: 1.5 2018-04-23

Trial sponsor: King's College London

Trial sponsor contact information: Denmark Hill, London, SE5 8AF, 020 7848 0251,

[Susan.dickson@kcl.ac.uk](mailto:Susan.dickson@kcl.ac.uk)

## **Abstract**

**Background:** Diabetes has been described by the World Health Organisation as an epidemic and is costly to the NHS, accounting for approximately 10% of healthcare resources in the UK. Intensive lifestyle interventions are effective in reducing the risk of type 2 diabetes but the implementation of research findings from landmark studies is expensive, time consuming for the patient and for health systems, and the uptake is often by those with the lowest risk. Translational research has found that the implementation and uptake of less intensive and therefore cheaper interventions has been suboptimal. The evidence for e-health lifestyle interventions using wearable technologies and online programmes by commercial providers is increasing but the evidence of their effectiveness in reducing the risk of type 2 diabetes is limited. Advantages of digital health include providing efficient, cost effective, safe, adaptable and scalable interventions to improve health.

**Methods:** This is a feasibility study (n=200) for a two-arm, parallel, single-blind randomised controlled trial for people at high risk of type 2 diabetes. The two arms are the intervention group (n=100), who will receive wearable technology delivering an e-lifestyle advice combined with personalised/biofeedback instant messaging, and the control group (n=100), who will receive the wearable technology and the same e-lifestyle advice but not the instant messaging.

**Discussion:** We have described the study design for a feasibility as a method for testing the technology and examining the barriers and facilitators in preparation for conducting a full-scale RCT.

**Trial registration:** Registered with [clinicaltrials.gov](https://clinicaltrials.gov) (NCT02919397).

**Keywords:** Type 2 Diabetes, prevention, wearable technology, instant motivational messages, theory of planned behaviour, lifestyle intervention, biofeedback

## **Background**

Intensive lifestyle interventions are effective in reducing the risk of type 2 diabetes [1], but the implementation of research findings from landmark studies is expensive, time-consuming for the patient and for health systems, and the uptake is often by those with the lowest risk [2]. The number of e-health lifestyle interventions using wearable technologies and online programmes by commercial providers is increasing, but the evidence of their effectiveness in reducing the risk of type 2 diabetes is limited [3].

The prevalence of pre-diabetes, a HbA1c value between 42 and 47 mmol/mol, is approximately 10% in the UK population [4]. Prevalence of pre-diabetes varies by age from 3% between the ages of 16 and 39 years to 26% for over 70 years and by ethnicity, with higher proportions of the populations of Asian (14.2%) and black ethnic groups (13.1%) having a pre-diabetic HbA1c than those of a white ethnic background (10.4%). Diabetes accounts for approximately 10% of healthcare resources in the UK, and this is set to rise to 17% and an estimated cost of £39.8 billion by 2035 when direct healthcare costs and indirect costs on productivity are taken into account [5]. Therefore, the development of a type 2 diabetes prevention programme is a current priority for the NHS.

Face-to-face diabetes prevention programmes have been successful in improving outcomes through trials in other countries; the major examples being the Diabetes Prevention Program (DPP) in the United States [6], and the Finnish Diabetes Prevention Study (DPS) [7]. The DPP research group found that, compared to a placebo, intensive lifestyle interventions (encouraging the loss of weight through diet and physical activity) reduced the risk of diabetes by 58%, compared to metformin which reduced the risk by 31% at follow-up (average 5.7 years). However, further evidence is required to translate and implement these intensive and expensive interventions to routine primary care [3].

Components of behavioural change techniques considered to be most effective in improving diet and physical activity in pre-diabetes patients are based on self-regulatory behaviours, such as goal setting, self-monitoring, giving feedback, utilising social support, and motivational interviewing (MI) [8]. Interventions based on a psychological theory (such as the theory of

planned behaviour [9]) are more effective, and high-risk populations have better outcomes. There is less evidence to support a case for any minimum threshold of intensity, mode of delivery, intervention provider, and setting for behavioural interventions [8,10,11]. Strategies to prevent relapses and to increase the maintenance of healthier lifestyles over longer periods remain poorly understood and understudied.

Translational research using digital interventions has found that less intensive interventions based on the DPP and DPS can be feasible and produce improved outcomes in pre-diabetic patients in primary care settings [12]. In a randomised controlled trial of 588 Asian working men aged 35–55 years in southeast India with impaired glucose tolerance, those who received 1-2 weekly short messaging service (SMS) texts giving lifestyle advice tailored to the transtheoretical stage of change had a lower cumulative incidence of type 2 diabetes compared with controls who received standard lifestyle modification advice at baseline only [13]. Similarly, a pilot trial of a 16-week internet-based diabetes prevention programme found long-term maintenance of reduced weight and lower HbA1c at two-year follow-up [14]. These are examples of how intensive lifestyle interventions may be adapted to a more cost-effective, scalable model which makes use of technologies widely available.

We propose to test the feasibility of an intensive diabetes prevention intervention that includes an online diabetes prevention educational programme integrated with instant messaging incorporating MI techniques, and biofeedback delivered via wearable technology and a smartphone application over 12 months in reducing the risk for developing type 2 diabetes in those at high risk, compared to a control group using a randomised controlled trial (RCT). We primarily aim to assess the potential size of the study population, the proportion of uptake for eligibility screening, the proportion who are eligible, consented and randomised, the proportion who complete the intervention, and the data collection rates. We plan to recruit and randomise 200 participants to the intervention. Our secondary aims are to compare the change in biomedical outcomes, including reducing weight and increasing physical activity, to inform the possible range of effect sizes and obtain outcome variance estimates required for sample size calculations in a full-scale trial. We will conduct a process evaluation to assess the barriers and facilitators of uptake by conducting focus groups with participants in both groups. Finally, we aim to produce a

protocol for a full-scale trial (if supported by this feasibility trial) and assess the proposed data analysis techniques to uncover potential problems.

## **Methods/Design**

### **Study design**

This is a feasibility study for a two-arm, parallel, single-blind RCT for people at high risk of type 2 diabetes. The two arms are the intervention group, who will receive wearable technology delivering an e-lifestyle intervention combined with personalised/biofeedback instant messaging, and the control group, who will receive the wearable technology and will be directed to the same lifestyle advice. The study flow chart in Figure 1 shows progression through the study.

### **Setting**

The study is set in the south London boroughs of Lambeth, Southwark and Lewisham, which comprise a population of n=912,687 residents and has one of the highest prevalence rates of type 2 diabetes, as well as representing wide socio-economic and ethnic diversity. Subjects will be recruited from participating primary care surgeries with list sizes greater than 6,000 patients.

### **Sample selection**

The target population are adult residents in the three boroughs who are identified as being at high risk of type 2 diabetes. Two hundred participants will be recruited for this study. They will be identified by a two-stage screening process. In the first stage, patients at high risk of type 2 diabetes will be identified by the general practitioner (GP) who will conduct a search using HbA1c results recorded in previous 12 months. The GP will invite those potentially eligible to be invited for HbA1c screening in the practice. In the second stage, those patients attending screening for eligibility who have a current HbA1c in the range 39-47 mmol/mol will be invited to volunteer. We will use the minimum threshold for HbA1c of  $\geq 39$  mmol/mol because research has found increased health risk above this level [15].

The inclusion criteria will be: adults aged between 18-65 years, selected because of the increasing prevalence of pre-diabetes in younger age groups and detecting diabetes in older

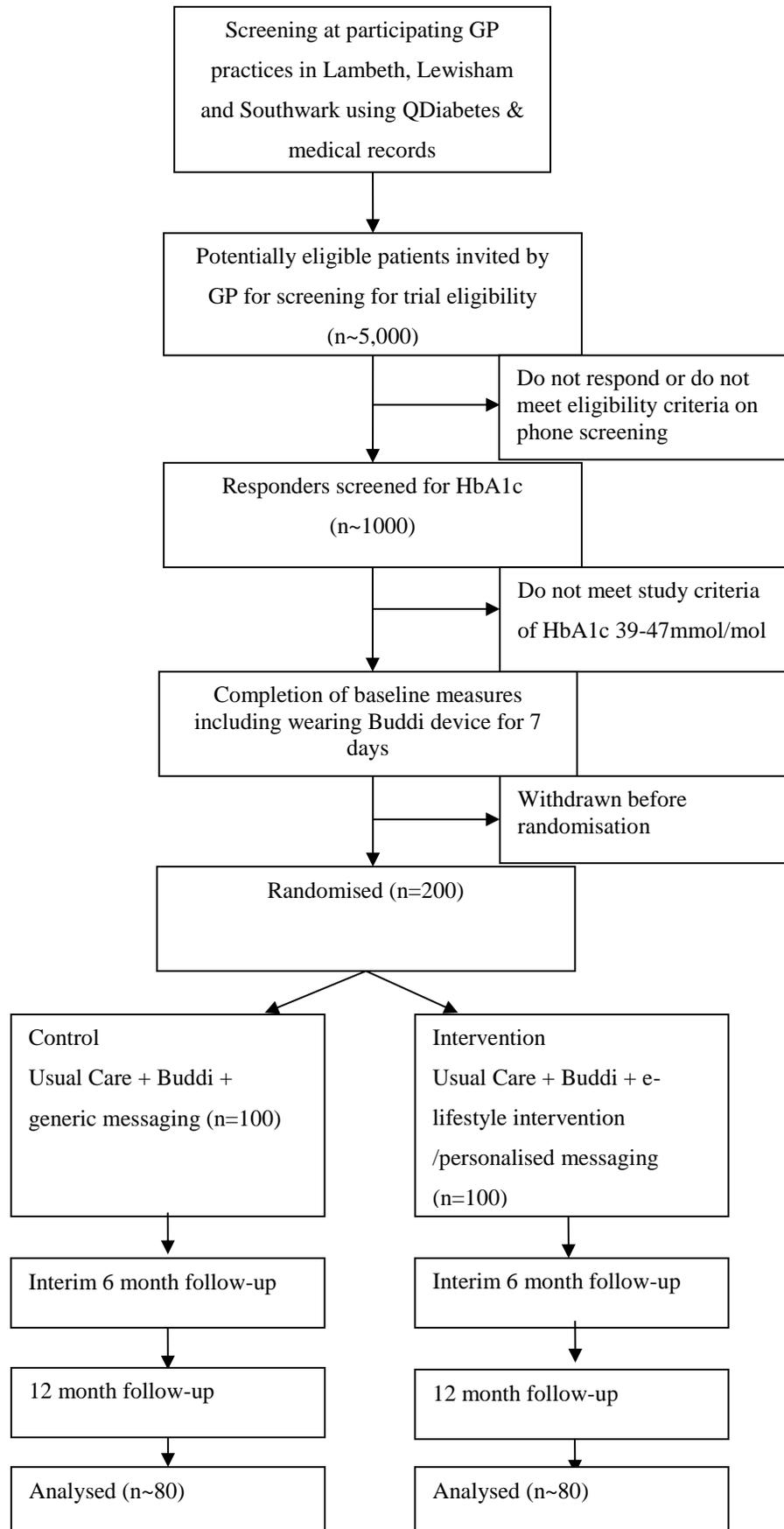
people is not associated with improved outcomes; HbA1c between 39 and 47 mmol/mol; BMI  $\geq$  25 kg/m<sup>2</sup> ( $\geq$  23 kg/m<sup>2</sup> in Asian participants as found to be more practical in identifying those who go on to develop type 2 diabetes in this population [16]); permanent resident in Lambeth, Southwark, or Lewisham; ownership of a smartphone (either iPhone or Android only) for communication defined as logging on at least once/day to the internet; being fluent in conversational English; and ambulatory.

The exclusion criteria will be: known diabetes (not including past history of gestational diabetes), pregnancy or planning pregnancy or lactating during the duration of the study; severe mental illness (severe depression with suicidal ideation, psychosis, bipolar affective disorder, dementia, learning difficulties, substance problem use or dependence); severe physical disability (e.g., that would prevent any increased uptake of physical exercise); advanced active disease, such as cancer or heart failure; any other condition which requires glucose-altering drugs; super-obese (BMI  $\geq$  50 kg/m<sup>2</sup>); and current participation in a weight loss or diabetes prevention programme. When in doubt, we will seek the GP's opinion and approval.

### *Sample size*

The primary endpoints of this feasibility trial are factors that affect successful trial conduct, rather than measures of intervention effects. Hence, power analyses for intervention outcomes were not undertaken in advance. A minimum of 100 participants will be recruited for each intervention arm, for a total of at least 200 randomised participants in the trial. We aim for 100 participants per arm because we anticipate this will be a large enough sample to inform the practicalities of delivering the intervention, recruitment, uptake, and attrition. Based on our previous work, we expect a follow-up rate of approximately 80%, yielding n=80 analysed in each arm, which will be sufficient to obtain stable estimates of population variances for future power calculations.

Figure 1. Trial Flow Chart



### ***Baseline and outcome measures***

We will collect the following sociodemographic data: age, gender, postcode of residence, employment status, educational level, and self-reported ethnicity.

Physical activity will be measured objectively using the wearable Buddi device (Buddi, Rickmansworth, UK). The Buddi will be worn as a wristband, and physical activity (number of steps per day) will be recorded for the first 7 days wear as a baseline measure. Self-reported physical activity will be assessed using the International Physical Activity Questionnaire (IPAQ) [17].

The following biomedical data will be collected: haemoglobin A1c (HbA1c) level (mmol/mol), fasting blood glucose will be measured by affinity chromatography using the Primus Ultra 2 analyser (Primus Corporation, Kansas City, MO) and an Advia 2120 analyser (Siemens Diagnostics) respectively. Lipid profile (total and non-HDL cholesterol, fasting triglycerides) will be measured using an Advia 2400 (Siemens Diagnostics) analyser, detection limit 0.1 mg/L and 0.01 mmol/L respectively. Weight will be measured in light clothing, without shoes, on a Class 3 Tanita SC240 weighing digital scale (Tanita, Tokyo, Japan) to 0.01 kg for weight and body fat composition. Height will be measured to 0.1 cm using stadiometers (Tanita, Tokyo, Japan) with the supported stretch stature method. Weight and height measurements will be used to calculate BMI ( $\text{kg/m}^2$ ). Waist circumference will be measured horizontally halfway between the lowest rib and the upper prominence of the pelvis using a non-extensible steel tape against the bare abdomen. Waist-to-hip ratio will be measured using the BMI calculator (<http://www.bmi-calculator.net/waist-to-hip-ratio-calculator>). Blood pressure (BP) and resting heart rate will be measured with digital Omron BP monitors (Omron, Kyoto, Japan) using standardised procedures of the average of two readings taken one minute apart while seated. We will collect concomitant medication data for the duration of the trial.

Psychological measures will include: depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9) and health-related quality of life (QoL) using the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) [18]. Readiness to change will be measured using the University of Rhode Island Change Assessment Scale (URICA) [19]. Self-efficacy will be

measured using the Self-Efficacy for Exercise (SEE) Scale [20]. We will collect data on smoking status and, if current, how many cigarettes per day. Alcohol intake will be measured using the Alcohol Use Disorders Identification Test (AUDIT) [21].

Dietary intake will be assessed using a standardised multiple-pass 24-hour dietary recall as it can be more objective and more reliable as a measure of change in intervention studies [22].

Researchers will be trained to follow a standardised protocol, ask neutral probing questions to encourage recall of food items, and taught about different methods of food preparations and brands in different cultures. Portion size will be assessed with food photographs to estimate daily calorie intake [23].

### ***Randomisation and allocation concealment***

Prior to randomisation all patients will be asked to wear the Buddi wristband for one week to familiarise themselves with the technology and to collect baseline activity data. All patients will be offered a brief educational session on the use of the Buddi device and standard advice on exercise and diet relevant to type 2 diabetes prevention. Randomisation of participants will be conducted by the data manager from an independent Clinical Trials Unit using computer generated randomisation blocks of random sizes and stratified by General Practice. Allocation concealment will be ensured, as the randomisation list will be held in a password-locked computer and ACCESS programme. The data manager can only reveal to him/herself and then the researcher the next allocation after entering the details of the next participant recruited. As this is a complex intervention, it is not possible to conceal the allocation to the participants, but outcome assessors and laboratory technicians will be blind to the allocation for the primary and secondary outcomes.

### ***Interventions***

#### ***Intervention arm***

The intervention will be based on the theory of planned behaviour [9] for initiation of behaviour change, which states that, in order to change behaviour, people need to form an intention.

Intention formation is influenced by three constructs: expected value or positive attitude (people see the value in making the change); subjective norm (significant others and peers also value the

change) and self-efficacy (people believe they are capable of making the change). Our intervention will deliver Short Message Service (SMS) messages underpinned by these constructs using principles and techniques from motivational interviewing [24]. Motivational Interviewing (MI) will be used to support participants in forming healthy intentions, encourage self-monitoring of lifestyle behaviours, give biofeedback on behaviours and utilise social support. MI is normally a face-to-face collaborative conversation style for strengthening a person's own motivation, belief and commitment to change. We will adapt the principles of MI into a virtual setting with targeted motivational messages into diabetes prevention course; specifically, on diet and activity; and real-time biofeedback on lifestyle behaviours.

A programme of education related to diabetes prevention will be delivered as 22 online over 12-months targeting diet, physical activity and mental resilience. The curriculum will be based on the newly developed Centers for Disease Control and Prevention (CDC) PreventT2 curriculum and handouts [25], which is itself the implementation version of the original DPP and follow-up studies [6,26,27]. The online sessions will be available through the smartphone application as online interactive sessions, with portable document format (PDF) transcripts available for each session. The contents of instant messaging via the smartphone application will be temporally coordinated with the contents of the educational programme.

Participants will receive instant messages five days per week for 12 months; these will include standard targeted messages that everyone receives, and four types of messages based on the biodata received:

- 1) Targeted behaviours: this will consist of automated messages; encouraging 'how' to make lifestyle changes (self-efficacy) and 'why' messages (expected value) as reinforcement. The message content will be coordinated with the contents of the diabetes educational programme sessions.
- 2) Biofeedback: data received from the wearable technology on step count will be fed back to the participant, and messages designed to reinforce or encourage increase in activity sent in response.

- 3) Automated messages will introduce new modules of the diabetes prevention education programme materials, which participants will have access to via the smartphone application.
- 4) Responsiveness: participants will be invited to interact with the application by pressing a button on the wristband to indicate when they are eating, as a measure of eating habits. They are also able to select CRAVE or LAPSE in the application when they are feeling particularly vulnerable to a relapse of their lifestyle. They will be able to select ACHIEVE in the application when they feel they have achieved a goal. CRAVE will indicate that the participant is thinking about pursuing an unhealthy behaviour (e.g., eating a high calorie food or avoiding their exercise regime) but have not acted upon it yet. LAPSE will indicate that patients have acted upon their cravings and need support to reengage with their good intentions. Participants will also have the opportunity to record their achievements within the application. Message content will be designed to remind participants of the ability to select CRAVE, LAPSE and ACHIEVE, as well as in response to each selection.

### ***Control arm***

The control group will be provided with the Buddi device for the duration of the study and will have access to their activity data via the application. They will be directed to the educational materials on diet, exercise, and lifestyle changes available via automated messaging on the smartphone application. They will not receive any motivational or biofeedback messages. See Appendix 1 for a list of the standard messages the control group received.

### ***Analysis plan***

The primary outcome measures will be change in weight (kg) and physical activity (average steps per day) from baseline to 12 months, with an interim measure at six months.

The secondary outcomes are change in HbA1c, diabetes risk score, waist circumference, waist:hip ratio, lipid levels, sleep duration and quality, and BP. HbA1c will be analysed as a continuous and a categorical variable, with the following categories: normal (<42mmol/mol),

pre-diabetic (42-47mmol/mol) and diabetic (>47mmol/mol). We will collect interim HbA1c levels at six months.

A process evaluation will aim to identify, describe, and where appropriate quantify, factors and processes that affect the delivery, receipt and outcome of the study to aid the interpretation and translation of the observed findings. Process data will be analysed before outcome data wherever possible to reduce bias in interpretation. The main themes will be:

- 1) Reach: we will collect anonymised data on those who were invited to take part but did not respond, to allow analysis of participation biases. We will also invite patients who dropout of the study to attend a focus group to give feedback on the programme.
- 2) Processes of change: we will conduct meditational analyses to identify whether changes in weight and physical activity were associated with the dose of intervention received. Change in dietary habits and depression at six and 12 months will be assessed as measures of mediating processes. We will administer a detailed process questionnaire at 6-month and 12-month follow-ups that requires all randomised participants to list in both open-ended and structured questionnaires which techniques they had found most or least helpful. Participants will receive a message via the smartphone app directing them to an online questionnaire. They will be asked to identify themselves using their participant ID number. We will also conduct three focus groups: i) with those who received the intervention, ii) with those who dropped out of the intervention, and iii) with those who were in the control group, to further understand the processes of change.
- 3) We will aim to describe the technical and mechanical issues in delivering the intervention and how they were resolved.

We will request informed consent for access to participants' Hospital Episodes Statistics data, for a period of five years for the purposes of an economic evaluation pending funding and resources to complete this.

The feasibility of trial procedures will be examined using proportions and exact Clopper Pearson 95% confidence intervals [28]. Analysis and reporting will be in line with the Consolidated

Standards of Reporting Trials (CONSORT) guidelines [29], including its extensions for pilot and feasibility trials, with primary analyses being on an intention-to-treat basis and a two-sided significance level of 5% used. Estimates of population variances and intra-cluster correlations for future power calculations will be based on Browne (1995) [30], who suggests using the upper 80th percentile of confidence intervals around the estimates.

Statistical analyses will be mainly descriptive in nature, aiming to provide estimates of key feasibility parameters and to inform power calculations for a future definitive trial. A description of the sample will be presented using means and standard deviations for continuous data. Frequencies and proportions will be used to analyse categorical variables. Feasibility of trial procedures will be examined using proportions and exact Clopper Pearson 95% confidence intervals for rates of consent and intervention adherence. Reasons for non-adherence will be examined where information is available. Descriptive sub-analyses (chi-squared and Fisher's exact tests) will be used to explore participation rates among participants based on ethnicity, education level, index of deprivation score, and BMI. In addition, completion rates for demographic, clinical and health economic measures will be assessed at baseline and follow-up. The amount of missing data for individual items and entire measures will be examined to determine the suitability of instruments and level of burden for a future full-scale trial. Baseline characteristics of those who were eligible but decline to participate with those who consent to participate and those who dropped out of follow-up will be compared with participants who complete the study.

### Primary analyses

Our study was not formally powered to assess treatment effects and does not provide meaningful effect size estimates for assessing efficacy or for planning subsequent studies [31]. The aim was, therefore, to estimate the likely range of intervention effects at follow-up by estimating 95% confidence intervals.

The primary outcome analyses will be analyses on an intention-to-treat basis. The differences in treatment effect for the primary and secondary outcomes between the two arms at 12 months will

be analysed using mixed-effects models with pre-randomisation values as a covariate [32]. This approach provides valid inferences under the assumption that the missing data mechanism can be ignored (or missing at random). An analysis of covariance (ANCOVA) approach will be utilised as the model accounts for the possible imbalance due to random sampling in baseline measurement of the outcome variable to control for pre-treatment differences. An ANCOVA approach is preferred because of a usually increased statistical power to detect any treatment effects, since baseline and post-treatment measurements are assumed to be correlated. Furthermore, the ANCOVA approach is known to deal better with possible regression to the mean effects.

The main outcome values are assumed to arise from normal distributions (this will be checked and, if necessary, appropriate transformations will be used). A linear mixed model using STATA's *mixed* command will be used for estimation. The fixed parts of the model will be: 'treatment group', the interaction 'treatment group by time', and the pre-randomisation value of the respective outcome. 'Time' will be entered as a categorical variable to avoid making parametric assumptions of the outcome values over time.

To model the dependency of the repeated observations of the same patients at six and 12 months, we will model the covariance between the residuals within the lowest level group 'patients' to be correlated by using an unstructured covariance pattern model. If necessary, a different covariance structure will be estimated for each group. For the final model, the group difference estimates and associated confidence intervals will be reported for six and 12 months post-randomization.

### Sensitivity analyses

A sensitivity analysis will investigate if any imbalances in the pre-randomisation characteristics between the two groups are associated with the primary and secondary outcomes. The primary analyses above will be repeated, adjusting for the following pre-randomisation variables: age, sex, education, ethnicity, smoking status, marital status, and BMI.

The following sensitivity analysis will be conducted to determine if any violations of the assumption of data missing at random (MAR) affect the outcomes: Any demographic or clinical

baseline variables that are predictors of outcome missingness, then such variables will be included as covariates in the primary analysis model and post-treatment group difference estimates and associated confidence intervals will be reported.

#### *Moderator analyses*

We will also conduct an analysis of moderators of treatment effectiveness if significant differences are found in the primary analyses, but, as this is a feasibility study, we recognise this will not be powered. We will test age, sex, ethnicity, education, employment, marital status, IMD and BMI as possible moderators of the treatment effect.

#### *Mediation analyses*

As part of the process evaluation, we will investigate if dose of intervention received or changes in depression or diet mediate the treatment effect on the outcomes at 12 months.

#### ***Data management***

Patient data will be anonymised and stored on an Access database on a password-protected computer. All trial data will be stored in line with the Data Protection Act (2018). The research data will be stored in a locked filing cabinet and in a locked room. Patients can only be identified by a unique and anonymous study number. Electronic data will be password protected and any direct quotations will be anonymised.

The Buddi Ltd. company will retrieve activity data via the smartphone application. They will have access to participant ID number and treatment allocation, in order for the intervention to be set up and delivered. This data, along with activity data, will be stored securely on a web server. However, the company will not have access to personal identifiable information.

Anonymised demographic data for those patients invited to take part in the trial, but did not respond, will be collected from medical records in order to estimate reach. This data will include age, sex, ethnicity, postcode (index of deprivation) and diabetes risk score. All personal identifiers will be removed from this data and data will not be collected if the patient has an 'informed dissent' code in their case notes.

Each participant is expected to be involved in the trial for a minimum of one year after taking consent and baseline data. It is anticipated that recruitment of participants will take three months. The trial will start in October 2016 and finish in May 2018.

A copy of patient consent forms will be kept for five years after the study has ended. Personal data that are identified by patient name or address will be destroyed five years after the study has ended. Other trial records will be archived for five years after the trial ends before being destroyed.

### ***Service Users***

We will work with the scientific and practical resource that Users (consumers or patients as stakeholders) can offer and aim to develop Patient Public Involvement (PPI) pathways.

Drawn from participating general practices, we would like to recruit a core group of patient researchers who will help to improve the contents of our intervention, network with local communities and provide local information. We will ask patients whether they understand the rationale of the study and think it is of value, and we will ask for their thoughts on the intervention.

While we will not be able to pay a salary, we will offer them training in research and administrative skills, opportunity to conduct research and contribute to analyses and manuscript preparation, networking opportunities such as access to resources within KHP. We will be looking to recruit people who can offer their time while looking for work, those recently retired, homemakers trying to improve their skills and confidence to return to the workplace. Our experience of volunteers is that for some this has led to substantive employment.

### ***Regulatory Approval***

The Investigator(s) will permit trial-related monitoring, audits and REC in full first review by providing the Sponsor(s), and REC direct access to source data and other documents (e.g. patients' baseline and outcome data and blood test reports).

The trial protocol will be submitted for ethical review to a Research Ethics Committee. The main ethical consideration is to ensure that the risk of harm to participants is minimised and that they are fully informed of any risks. We will take into account literacy and cultural sensitivities in obtaining informed consent. Other ethical considerations are ensuring that recruitment and informed consent are handled in such a way that potential participants are not put under pressure to take part and that confidentiality is preserved.

The database that contains the patients' names, addresses and unique identifier will be held by the research team and accessible only by the trial manager and the principal investigator. All other data will be stored separately in a locked room where patients can only be identified by their unique study identifier and electronic data will be password protected.

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Mental Capacity Act 2005. Any changes to the study protocol or related study documents will be submitted to the Research Ethics Committee.

Each member of the research team will have a research passport which states that all material connected with their presence in the Trust(s) is in accordance with the NHS Confidentiality Code of Practice and the Data Protection Act (1998) which covers information concerning individuals which are stored in any of the Trust(s)' systems. The Chief Investigator will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor.

### *Assessment of safety*

In general, regular physical activity is associated with improved health outcomes and this outweighs the risk of sedentary lifestyles. However, sudden increase in vigorous physical activity in otherwise sedentary individuals is associated with a higher risk of myocardial infarction and of musculoskeletal injuries. However, one of the components of behaviour change techniques is to deliver the message that physical activity should be increased in a graded manner rather than

suddenly. We will be discouraging excessive and/or sudden changes to lifestyles. We consider this risk to be small and it will be minimised by excluding subjects with existing comorbidities. There is a small risk that some participants may undergo rapid weight loss. Rapid weight loss or fasting may pose a risk by reducing body fluids, preventing the body from burning fat and increases metabolism of lean muscle mass, and diarrhoea and fatigue. Weight loss could worsen frailty by accelerating the usual age-related loss of muscle that leads to sarcopenia but combining weight loss with increased physical activity can actually ameliorate frailty. Importantly, our intervention is based on healthier diets, and gradual and sustainable weight loss as opposed to commercial weight loss programmes.

A serious adverse event is defined as an untoward occurrence that is related to the intervention and is unexpected. All serious adverse events and laboratory values will be reviewed by the trial manager and the PI will be responsible for reporting any adverse events related to the study to the Research Ethics Committee using the National Research Ethics Service guidance ([www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports](http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports)). We will register the participants in the study with the NHS register after obtaining informed consent to link our records with mortality and Hospital Episodes Statistics data.

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a therapy has been administered including occurrences, which are not necessarily caused by or related to that therapy.

Adverse Reaction (AR): Any untoward and unintended response in a subject to a therapy which is related to any duration of therapy administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information known about the therapy in question in the view of the investigator.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

All SAEs, SARs and USARs (except those specified in this protocol as not requiring reporting) that occur from randomisation until the 30 days post final therapy session will be reported immediately by the Chief Investigator to the R&D office.

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the regulatory authority. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

## **Discussion**

We describe here the design and protocol for a feasibility RCT to compare the effectiveness of a wearable technology and e-diabetes prevention programme delivered via a smartphone app, including biofeedback instant messaging, with a control group who do not receive the biofeedback instant messages, in reducing weight and increasing physical activity in people at risk of developing type 2 diabetes.

### ***Strengths and limitations***

The strengths are that this is the first UK feasibility testing a standalone self-help digital complex intervention delivering as an application consisting of educational modularised information about how to prevent type 2 diabetes over 12 months matched temporarily with motivational text messages on diet, activity, emotional wellbeing and receiving biofeedback about activity levels from a wearable technology measuring activity. We have also included a detailed process evaluation to capture reach, responders versus non responders, and barriers and facilitators and strategies to improve the intervention. The limitations are that this a feasibility study therefore not powered to test effectiveness at this stage. Another limitation is that as this is a new technology there may be mechanical or technical failures that resulted in receiving less of the dose. We will not be conducting an economic evaluation but we have asked for consent to access health service use in order to be able to do so if the feasibility findings suggest any evidence of potential effectiveness.

### ***Research/clinical implications***

The feasibility findings will allow us to address problems and optimise the technology for a full scale or phase 3 RCT to either compare the intervention with standardised usual care or a gold standard face to face diabetes prevention including a cost effectiveness evaluation. This will provide greater evidence to inform the development and optimisation of the NHS diabetes prevention programme which is crucial for slowing the rising tide of type 2 diabetes.

## **List of abbreviations**

AE: Adverse Event

ANCOVA: An analysis of covariance

AR: Adverse Reaction

AUDIT: Alcohol Use Disorders Identification Test

BMI: Body Mass Index

BP: Blood pressure

CDC: Centers for Disease Control and Prevention

CONSORT: Consolidated Standards of Reporting Trials

DPP: Diabetes Prevention Program

DPS: Diabetes Prevention Study

EQ-5D-5L: EuroQol-5 Dimensions-5 Levels

GCP: Good Clinical Practice

GP: general practitioner

HbA1c: haemoglobin A1c

HDL: High-density lipoprotein

IMD: Index of Multiple Deprivation

IPAQ: International Physical Activity Questionnaire

KHP: King's Health Partners

MAR: Missing at random

MI: motivational interviewing

NHS: National Health Service

PDF: Portable document format

PHQ-9: Patient Health Questionnaire-9

PPI: Patient Public Involvement

QoL: quality of life

RCT: Randomised controlled trial

REC: Research Ethics Committee

SAE: Serious adverse Event

SAR: Serious Adverse Reaction

SEE: Self-Efficacy for Exercise

SMS: short messaging service

UAR: Unexpected Adverse Reaction

URICA: University of Rhode Island Change Assessment Scale

USAR: Unexpected Serious Adverse Reaction

## **Declarations**

### ***Ethics approval and consent to participate***

The trial has been reviewed and given favourable opinion by the London City and East Research Ethics Committee (16/LO/1505) and approval has been granted by the Health Research Authority.

### ***Consent for publication***

Not applicable.

### ***Availability of data and material***

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### ***Competing interests***

Not applicable

### ***Funding***

Funding for this study was provided by Innovate UK. The funder had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. K.I. is part funded by the NIHR Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

### ***Authors' contributions***

Khalida Ismail is the Chief Investigator and responsible for the conduct of study and together with David Hopkins, Stephen Thomas and Neel Basudev as the Co-Investigators developed the protocol. Jennifer Rundle prepared the intervention. Adam Bayley (between June 2016 and September 2017) and then Emily Staite (between October 2017 to present) are the Clinical Trial Managers. Natalie Zaremba reviewed the text messages. Kurtis Stewart prepared and is responsible for the statistical analysis. Daniel Stahl is the statistical advisor who reviewed the protocol.

### ***Acknowledgements***

We would like to thank the Buddi team who provided the technology, developed the app and installed the text messages. We would also like to thank Jill Locket for her help on the operational side.

Appendix 1. List of the standard messages the control group received.

- Being part of this study helps everyone in the future. Thanks for your help!
- Thanks for taking part! The study is important and is funded by the UK's innovation agency, Buddi and King's Health Partners.
- You are participating in the Diabetes Stopwatch study-this is very much appreciated.
- This study is joint project between Buddi and King's College London.
- Participating in research studies is important to find out about new treatments.
- The results of this study will help improve the management of diabetes.
- We are grateful for your participation in this important study.
- We will be contacting you regularly to collect information about your health.
- If there are any changes to your contact details please let us know. Thanks once again!
- The study is run by a team of researchers at King's Health Partners led by Professor Khalida Ismail.
- Your participation is voluntary so we highly value your time to this project.
- We will let you know the results of the study when they are ready.
- Thanks for taking part! Without your input, the study could not have gone ahead!
- Please keep Bluetooth turned on for your nujjer wristband and app to work!
- Please do not quit or swipe away your nujjer app - it needs to be on and running in the background for your wristband to work!
- Don't forget to keep Bluetooth switched on for your nujjer wristband and app to work properly.
- Don't forget to keep Bluetooth turned on for your nujjer wristband to work!
- Please do not quit your nujjer app on your phone – it needs to be on and running in the background for your wristband to work correctly!
- Your nujjer app needs to be working in the background for you to receive messages and for your wristband to work.
- Bluetooth needs to be switched on for your nujjer to work, please leave it on all of the time.

- Please keep your nujjer app running in the background all of the time - if you swipe the app to close it will not work!
- Please remember to keep bluetooth switched on - it's needed for the app and your wristband to work correctly!
- Don't forget you can use your note book to record activity and create action plans.

## References

- 1 Venditti, E.M. (20017). Efficacy of lifestyle behavior change programs in diabetes. *Current diabetes reports*, 7(2), 123-127.
- 2 Aguiar, E. J., Morgan, P. J., Collins, C. E., Plotnikoff, R. C., & Callister, R. (2014). Efficacy of interventions that include diet, aerobic and resistance training components for type 2 diabetes prevention: a systematic review with meta-analysis. *Int J Behav Nutr Phys Act*, 11(2).
- 3 Ma, J., Yank, V., Xiao, L., Lavori, P. W., Wilson, S. R., Rosas, L. G., & Stafford, R. S. (2013). Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial. *JAMA internal medicine*, 173(2), 113-121.
- 4 Public Health England (2015). NHS Diabetes Prevention Programme (NHS DPP) non-diabetic hyperglycaemia. Retrieved from <https://www.gov.uk/government/publications/nhs-diabetes-prevention-programme-non-diabetic-hyperglycaemia>
- 5 Hex, N., Bartlett, C., Wright, D., Taylor, M., & Varley, D. (2012). Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabetic Medicine*, 29(7), 855-862.
- 6 Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England journal of medicine*, 346(6), 393.
- 7 Lindström, J., Peltonen, M., Eriksson, J. G., Ilanne-Parikka, P., Aunola, S., Keinänen-Kiukaanniemi, S., & Finnish Diabetes Prevention Study (DPS). (2013). Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). *Diabetologia*, 56(2), 284-293.

- 8 Baker, M.K., Simpson, K., Lloyd, B., Bauman, A.E., & Singh, M.A.F. (2011). Behavioral strategies in diabetes prevention programs: a systematic review of randomized controlled trials. *Diabetes Res Clin Pract.* 91(1), 1–12.
- 9 Azjen I. (1991). The theory of planned behavior. *Organ Behav Hum Decis Process*, 50, 179–211.
- 10 Ebrahim, S., Taylor, F., Ward, K., Beswick, A., Burke, M., & Davey, S.G. Multiple risk factor interventions for primary prevention of coronary heart disease. (2011). *Cochrane Database Syst Rev.* DOI: 10.1002/14651858.CD001561.pub3.
- 11 Greaves, C., Sheppard, K., Abraham, C., Hardeman, W., Roden, M., Evans, P.H... (2011). Systematic review of reviews of intervention components associated with increased effectiveness in dietary and physical activity interventions. *BMC Public Health*, 11, 119.
- 12 Johnson, M., Jones, R., Freeman, C., Woods, H. B., Gillett, M., Goyder, E., & Payne, N. (2013). Can diabetes prevention programmes be translated effectively into real-world settings and still deliver improved outcomes? A synthesis of evidence. *Diabetic medicine*, 30(1), 3-15.
- 13 Ramachandran, A., Snehalatha, C., Ram, J., Selvam, S., Simon, M., Nanditha, A., & Oliver, N. (2013). Effectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modification in men in India: a prospective, parallel-group, randomised controlled trial. *The Lancet Diabetes & Endocrinology*, 1(3), 191-198.
- 14 Sepah, S. C., Jiang, L., & Peters, A. L. (2015). Long-term outcomes of a web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. *Journal of medical Internet research*, 17(4).
- 15 Huang, Y., Cai, X., Chen, P., Mai, W., Tang, H., Huang, Y., & Hu, Y. (2014). Associations of prediabetes with all-cause and cardiovascular mortality: a meta-analysis. *Annals of medicine*, 46(8), 684-692.

16 Hsu, W. C., Araneta, M. R. G., Kanaya, A. M., Chiang, J. L., & Fujimoto, W. (2015). BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. *Diabetes Care*, 38(1), 150-158.

17 Booth, Michael L., et al. (2003). International physical activity questionnaire: 12-country reliability and validity. *Med sci sports Exerc*, 3508-1381.

18 Williams, A. (1995). *The role of the EuroQol instrument in QALY calculations*. University of York Centre for Health Economics.

19 Dozoisa, D.J.A., Westra, H.A., Collins, K.A., Fung, T.S., & Garry, J.K.F. (2004). Stages of change in anxiety: psychometric properties of the University of Rhode Island Change Assessment (URICA) scale. *Behaviour Research and Therapy*. 42(6), 711-29.

20 Resnick, B., & Jenkins, L.S. (2000). Testing the Reliability and Validity of the Self-Efficacy for Exercise Scale. *Nursing Research*. 49(3), 154-9.

21 Saunders, J., Aasland, O., Thomas, B., de la Fuente, J., & Grant, M. (1993). Development of the Alcohol Use Disorders Test (AUDIT): WHO collaborative project on the early detection of persons with harmful alcohol consumption. *Addiction*. 88, 791–804.

22 Slimani, N., Ferrari, P., Ocke, M., Welch, A., & Boeing-Messing, H. (2000). Standardization of the 24-hour diet recall calibration method used in the European prospective investigation into cancer and nutrition (EPIC). *European Journal of Clinical Nutrition*, 54, 900–917.

23 Nelson, M., & Haraldsdóttir, J. (1998). Food photographs: practical guidelines I. Design and analysis of studies to validate portion size estimates. *Public Health Nutr*. 1, 219–30.

24 Miller, W., & Rollnick, S. (2002). *Motivational interviewing: preparing people to change addictive behaviour*. 2nd ed. New York: Guildford Press.

25 Centers for Disease Control and Prevention (2016). Retrieved from <http://www.cdc.gov/diabetes/prevention/lifestyle-program/t2/t2faq.html>

26 Diabetes Prevention Program Research Group, (2009). 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*, 14, 1677-86.

27 Group DPPR. (2015). Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *The Lancet Diabetes & Endocrinology*, ;3(11), 866–75.

28 Vollset, S.E (1993). Confidence intervals for a binomial proportion. *Stat Med*, 12(9), 809-24.

29 Campbell, M.K., Elbourne, D.R., & Altman, DG. (2004). CONSORT statement: extension to cluster randomised trials. *BMJ*, 328(7441), 702–8.

30 Browne, M.W., & Arminger, G. (1995). Specification and Estimation of Mean- and Covariance-Structure Models. *Handbook of Statistical Modeling for the Social and Behavioral Sciences*, 185-249.

31 Leon, A.C., Davis, L.L., & Kraemer, H.C. (2011). The role and interpretation of pilot studies in clinical research. *Journal of Psychiatric Research*. 45(5), 626–9.

32 Bauer, D., Sterba, S., & Hallfors, D. (2008). Evaluating group-based interventions when control participants are ungrouped. *Multivariate Behav Res*, 43, 210–36.