propels

The PRomotion Of Physical activity through structured Education with differing Levels of ongoing Support for those with prediabetes (PROPELS): *randomised controlled trial in a diverse multi-ethnic community*

Protocol v10
27/11/2018

IRAS project ID: **96298**

Chief Investigator
Professor Kamlesh Khunti

Co-Investigators
Professor Melanie Davies
Dr Tom Yates
Professor Simon Griffin
Dr Wendy Hardeman
Professor Stephen Sutton
Dr Helen Eborall
Dr Laura Gray
Dr Danielle Bodicoat
Mike Gillett

Study Co-ordination Team
Dr Emer Brady
Dr Charlotte Edwardson
Siân Hill
Jacqui Troughton
Helen Dallosso

PROPELS is funded by the National Institute for Health Research's HTA Programme

CONTENTS

1. Study Background……... 3
    1.1 Type 2 diabetes and Impaired glucose regulation…… 3
    1.2 Physical activity and health 4
    1.3 Physical activity for the prevention of type 2 diabetes…… 4
    1.4 Structured education…… 5
    1.5 Follow-up support…… 5
    1.6 National policy for diabetes prevention……... 6

2. Study Objectives…… 6

3. Pre-intervention pilot development work ……..… 7
    3.1 Aim…… 7
    3.2 Focus group recruitment…… 7
    3.3 Content of focus groups…… 7
        3.3.1 Text messages…… 8
    3.4 Analysis of focus groups……... 8
    3.5 Storage and security of data…… 8
    3.6 Trialling of Text messaging system…….. 8

4. Randomised controlled trial…… 10
    4.1 Recruitment…… 10
    4.2 Inclusion criteria…… 11
    4.3 Exclusion criteria…… 12
    4.4 Randomisation…… 12
    4.5 Groups..... 12
        4.5.1 Group 1…… 12
        4.5.2 Group 2…… 12
        4.5.3 Group 3…… 15
            4.5.3.1 Maintenance support …….. 15
    4.6 Outcome measures…… 18
        4.6.1 Primary outcome…….. 18
        4.6.2 Secondary outcomes…….. 19

5a. Safety Reporting
5a.1 Definitions
5a.2 Reporting procedures for adverse events
5a.3 Reporting procedures for serious adverse events

5b. Sample size…….. 27
6. Process evaluation…….. 27

7. Cost effectiveness modelling…… 29

8. Data handling……... 31
9. Data analysis…… 3
10. Trial Steering Committee (TSC)
and Data Monitoring and Ethics Committee (DMEC)…… 32

11. Ethical issues…….. 32

References…… 36

1. Study Background

1.1 Type 2 diabetes and impaired glucose regulation

The world is faced with a growing diabetes epidemic – since 1980 the number of adults with diabetes has risen from 153 million to 347 million people world-wide (Danaei et al., 2011). According to the World Health Organisation (WHO), diabetes is the fourth main cause of mortality globally (WHO, 2009). In the UK, diabetes currently affects over 2 million people in England alone and prevalence is predicted to rise to over 4 million by 2025 (Diabetes UK, 2010). Type 2 diabetes (T2DM) is most common and accounts for around 80-90% of all people with diabetes. T2DM is a chronic and debilitating disease characterised by an inability to adequately regulate blood glucose levels. This condition leads to considerable morbidity and mortality and the direct costs of managing and treating this disease are estimated to be around 7-12% of total NHS expenditure (National Collaborative Centre for Chronic Conditions, 2008). T2DM is more prevalent among South Asian people than white Europeans and they are up to six times more likely to have T2DM (Diabetes UK, 2009).

T2DM is at one end of a continuous glycaemia spectrum with normal glucose control at the other. In between there exists a state where blood glucose levels are elevated above the normal range but do not satisfy the criteria for T2DM; this has been labelled impaired glucose regulation (IGR). IGR is used to describe the presence of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and is characterised by insulin resistance and/or impaired insulin secretion, features that precede and predict the development of T2DM. In most countries around 15% of adults have IGR based on WHO criteria (WHO, 2006; Santaguida et al., 2005), of which an estimated 5 to 12 % develop T2DM per year based on traditional classification (WHO, 2006; Santaguida et al., 2005). However, the prevalence of IGR varies among the population depending on different ethnic backgrounds, for example UK data suggests that South Asians progress to diabetes at three times the rate of White Europeans (Srinivasan et al., 2007). Research has also shown that the risk of cardiovascular disease is significantly elevated with IGR (WHO, 2006; Santaguida et al., 2005).

Targeting those with IGR provides an opportunity for preventing the future burden of T2DM. There is good evidence to suggest that T2DM can be prevented or delayed in people with IGR through lifestyle change (Gillies et al., 2007). International best practice recommends that this population should receive more intensive lifestyle interventions than those available to the general population (Paulweber et al., 2010).

T2DM and IGR have traditionally been defined through analysis of fasting and 2-hour post-challenge glucose; however recent international and national recommendations in the diagnostic criteria for T2DM have been revised to include the use of HbA_{1c}, with a value of 6.5% or greater indicating the presence of T2DM (WHO, 2011). Although controversial, there has also been emerging consensus that values lower than 6.5% can be used to identify those with a high risk of developing T2DM in the future. For example, an international expert committee and the American Diabetes Association recommend that HbA_{1c} at levels of 6.0 to 6.5% or 5.7 to 6.5 % respectively may be used to identify a high risk state (ADA, 2010; Nathan et al. 2009). In the UK, an HbA_{1c} level in the range of 6.0 to 6.49% will be adopted as indicating a high risk of future diabetes with recommendations that those

meeting this criteria should receive the same level of prevention treatment as those traditionally defined IGR (NHS Diabetes, 2012; NICE, 2012)

1.2 Physical activity and health

There is clear evidence from observational cohort studies that level of physical activity and cardiorespiratory fitness are inversely associated with mortality and morbidity in a dose-response manner (Kodama et al., 2009; Lee & Skerrett, 2001). This is consistent with evidence compiled by the Department of Health which found that those classified as physically active, because they met the current physical activity recommendations, have a 30% reduced risk of all-cause mortality and up to a 50% reduced risk of developing chronic disease compared to those who are inactive. However, the latest Health Survey for England shows that only 39% of men and 29% of women meet the physical activity recommendations when measured using self-report and only 5% when measured objectively by accelerometer (Health Survey for England, 2008). Physical inactivity has been identified as contributing to over 20 diseases and health conditions (Department of Health, 2004) and the World Health Organisation has recently estimated physical inactivity to be the fourth leading cause of mortality globally, ahead of both obesity and dietary factors (WHO, 2010). Furthermore, physical inactivity has been estimated to directly cost the NHS over £1 billion annually with the indirect cost as high as £8 billion (Allender at al., 2007; DoH, 2011).

1.3 Physical activity for the prevention of diabetes

Physical inactivity is directly involved in the pathogenesis of IGR and T2DM and has consistently been associated with an increased risk of the disease in observational cohort studies (Bassuk & Manson, 2005). Physical activity may slow the initiation and progression of T2DM and its cardiovascular sequelae via favourable effects on body weight, insulin resistance and glucose regulation, blood pressure, lipid profile, endothelial function, and chronic low-grade inflammation (Bassuk & Manson, 2005). Consequently, increasing physical activity is a cornerstone of diabetes prevention initiatives.

There is now clear evidence that intensive multi-factorial lifestyle interventions aimed at weight loss, a healthy diet and increased physical activity successfully reduce the risk of diabetes by 30-60% in those with IGR and are likely to be cost-effective in the longer-term (Gillies et al., 2007; Gillies et al., 2008).

However, prevention programmes have been unable to demonstrate clinically significant increases in physical activity over the longer term (> 12 months) and to date there have not been any long-term interventions primarily focused on physical activity in those with IGR (Yates et al., 2007), suggesting that physical activity has not been fully harnessed in the prevention of diabetes. Furthermore, many physical activity randomised controlled trials have failed to adequately assess the impact of increased physical activity on health through the collection of relevant biochemical data (Ogilvie et al., 2007). Consequently, evidence for the clinical effectiveness of physical activity that has been used to guide public health recommendations and policy has, to date, been reliant on observational rather than causal evidence. Therefore, randomised controlled trials are needed to investigate the effectiveness of interventions aimed at promoting physical activity both in terms of the impact on behaviour change and metabolic health. This is important because physical activity is hypothesised to be the most important

lifestyle determinant in the development of insulin resistance and T2DM (Telford, 2007), therefore it is potentially a highly effective therapeutic treatment in the prevention of diabetes. This should be fully investigated to establish the long-term effectiveness and cost-effectiveness of an intervention that is suitable for implementation in a routine health care setting.

1.4 Structured education

Previous diabetes prevention trials have utilised intensive one-to-one counselling strategies to promote behaviour change, but due to current resource limitations within primary care, these may be unsuitable for direct implementation.

Structured education has been widely advocated in England as a cost-effective method of promoting self-management and behaviour change in individuals with chronic disease (Department of Health; Diabetes UK, 2005). The National Institute for Health and Clinical Excellence (NICE) advises that structured education should be available to all individuals with T2DM mellitus at the time of diagnosis (National Institute of Health and Clinical Excellence, 2008). Structured education is an alternative to one-to-one counselling and refers to group-based, patient-centred educational programmes that: have a clear philosophy; a written curriculum that is underpinned by appropriate learning and health behaviour theories; are evidence based; and are delivered by trained, quality assessed, educators (Department of Health; Diabetes UK, 2005). The DESMOND programme for individuals with T2DM has recently demonstrated that a structured education programme, along with educator training and quality assurance protocols, can be delivered within the NHS at a national level and promote behaviour change (Davies et al., 2008). Therefore within primary care there is an existing infrastructure for delivering education programmes that could feasibly be utilised and extended for promoting behaviour change in individuals at a high risk of diabetes.

In addition to treating chronic disease, there is also emerging evidence which suggests structured education can also be utilised in populations who have IGR. The PREPARE (Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement) programme was a small pilot study informed by, and modelled on, the person-centred philosophy and learning techniques developed for the DESMOND programme (Davies et al., 2008). The PREPARE programme was designed to promote walking activity in individuals with pre-diabetes and participants assigned to the intervention group increased their ambulatory activity by 2000 steps per day and decreased their 2-hour glucose levels at 3, 12 months and 24 months (Yates et al., 2009; Yates et al., 2011). Therefore, preliminary evidence in a pilot setting suggests that structured education may be effective for those with IGR but more evidence is needed from larger randomised controlled trials.

1.5 Follow-up support

It is well recognised that individuals need continued support from health care professionals in order to effectively promote sustained behaviour change. However, the effect of different methods or doses of follow-up support has not been tested experimentally in physical activity interventions. A recent European review and guidelines on the prevention of diabetes state that a greater number of patient contacts up to 36-months are associated with greater intervention effectiveness, and consequently recommend that the number of patient contacts should be maximised (Paulweber et al., 2010).

However, this comes with the caveat that follow-up needs to be conducted/planned within the scarce resources available to health care organisations.

In contrast to the review-level evidence, we have recently shown that the biochemical changes observed following the PREPARE programme were sustained at 24-months (Yates et al., 2011) despite the fact that participants only received brief follow-up counselling at 3 and 6 months. However, we have also shown that health behaviour changes observed 12 months after a one off structured education programme in those with newly diagnosed T2DM were not sustained at 36 months (Khunti et al., 2010). Therefore within the UK there is a need to investigate differing levels of support using methods that are suitable for implementation within the NHS. This will allow health care commissioners and policy advisers to accurately assess the impact of providing an intensive compared to minimal support package following a physical activity behaviour intervention.

1.6 National policy for diabetes prevention

Within the UK, the prevention of chronic disease is a stated health care priority through the NHS Health Checks programme. This programme is specifically aimed at screening adults between 40-74 years of age within primary care for vascular disease risk and then treating high risk individuals accordingly; the identification of IGR and subsequent promotion of physical activity and a healthy lifestyle is a core component of the programme. The National Institute for Health and Clinical Excellence (NICE) were commissioned by Department of Health to complement and enhance this programme by producing specific public health guidance on preventing of T2DM among high-risk groups (NICE, 2011). The draft guidance advocates that high risk individuals should be identified through a two-stage approach involving risk score technology followed by an HbA_{1c} or fasting plasma glucose blood test. High risk individuals should then receive an evidence-based quality assured lifestyle intervention, such as a group-based structured education programme.

2. Study Objectives

1. To develop an intervention package to support maintenance of behaviour change.

2. To investigate whether an intervention to support physical activity behaviour change and maintenance, offered to an ethnically diverse population at high risk of T2DM, can lead to sustained increases in physical activity over four years.

3. To investigate the effectiveness of the intervention when delivered at two levels of intensity.

4. To investigate the effect of the intervention within White European and South Asian sub-groups.

5. To conduct a within-trial and long-term economic evaluation of both intervention conditions using the costs and benefits arising from the

study, rates of progression to diabetes, biomedical outcomes, NHS resource use, and quality-of-life.

3.0 Pre-intervention pilot development work (0-12 months)

3.1 Aim

The pre-intervention pilot development work will cover the following elements:

- Optimising the use of strategies to facilitate behavioural maintenance; frequency of contacts and mode of delivery through piloting the intervention in focus groups in a multi-ethnic cohort at high risk of diabetes in Leicester.
- Tailoring the text messaging system to an ethnically diverse population.

12 months has been allocated to fine tune the delivery and content of the intervention package to support maintenance of behaviour change provided by text messaging and by telephone. This is to ensure that the proposed support is feasible and acceptable to our ethnically diverse target group.

3.2 Focus group recruitment

In order to inform the development of the intervention maintenance, focus groups will be conducted with people who have recently attended a similar self-management group intervention. Participants will be recruited from ongoing studies within the Leicester Diabetes department such as Walking Away from Diabetes (09/H0408/32) and Let's Prevent (08/H0406/139). Participants in the control group and intervention group from these studies will be included. Participants in these studies have previously provided consent to be contacted by the research team with regard to other research within the department. Potential participants will be sent an information leaflet including a statement to indicate willingness to be contacted about the focus groups. This form will clearly state that at this stage they are not consenting to take part in the focus group, only to being approached about taking part. A PROPELS researcher will telephone participants who have expressed interest (by returning the reply slip); he/she will explain details of the focus groups, check willingness to participate, and arrange attendance at a focus group. Written informed consent will be taken by the PROPELS researcher conducting the focus group immediately prior to the focus group starting. We anticipate conducting up to 6 focus groups in a representative sample (of between 4-8 participants in each focus group). However, if we reach the point of data saturation where no new themes are emerging from fewer focus groups then a smaller number will be conducted. Focus groups will be led and moderated by an experienced qualitative PROPELS researcher, with support and supervision from a more senior researcher. Focus groups will take place in a mutually agreeable location in Leicester.

3.3 Content of focus groups

A topic guide will be used to facilitate data generation, but this will be used flexibly, with scope for discussion of additional relevant topics that may arise and revision of the topic guide in line with any additional emergent issues. The focus groups will firstly cover participants' views and experiences of the intervention they have recently received, and their ideas about post-intervention support and follow-up. Second, following a brief explanation of the PROPELS intervention and follow-up, their views about the different types

of maintenance support will be sought. Third, in order to develop maintenance support by entering steps walked from a pedometer and receiving tailored feedback by text messaging, participants will give feedback and discuss their reactions to receiving example text messages. Participants will be invited to bring their mobile telephones to the focus group and to give their mobile telephone number to the researcher in advance. During the focus group, example text messages will be sent to participants (at no cost to the participant). The messages will give advice about setting goals for pedometer steps and feedback about performance against these goals. Participants will be asked their views on the content and style of the messages, as well as views about the timing and frequency of receiving such messages.

3.3.1 Text messages

Text messages to be sent to the focus group participants will be generated by a member of the research team based in Cambridge entering the phone numbers and text messages manually into a computer program running on the University of Cambridge server which will send the messages via the internet to a company called FastSMS (www.fastsms.co.uk) who will transmit them over the mobile phone network; the internet transfer and network transmission happens automatically with no involvement of company personnel. The telephone numbers will not be sent to the Cambridge team until written informed consent has been received by each participant. The company's privacy policy states that all information will remain confidential and will not be disclosed to any third parties. The phone numbers will be deleted from the University of Cambridge server and the paper records of these numbers will be destroyed after the focus group has ended.

3.4 Analysis of focus groups

Focus groups will be audio-recorded and transcribed verbatim. Analysis will be iterative and informed by the constant comparative method. Preliminary open codes will be generated from the first two focus groups, as will initial ideas about the content and style of the text messages. The message ideas will be tested, developed and refined throughout subsequent focus groups. Ongoing analysis will lead to the development and refinement of the codes into a coding framework. Analysis will be facilitated with NVivo8, a qualitative data-indexing package.

3.5 Storage and security of data

The researcher conducting the focus groups will be responsible for both the recording and the storage of the recorded focus group data during the developmental stage of the trial. Recordings will be downloaded onto an encrypted memory key and a secure hard drive at the University of Cambridge until the end of the developmental stage of the trial. Anonymised transcriptions of recordings will be kept for five years on the secure servers at the University of Cambridge and the University of Leicester.

3.6 Trialling of text messaging system

Purpose: This pilot phase will:

1. Ensure that the computer based text-messaging system is fully operational, i.e. participants are receiving messages as and when intended and the system can recognise and respond appropriately to incoming text messages from participants.

2. Gather participant feedback on the text messaging intervention in 'real time' and in the 'real-life' setting. Although the focus groups are imperative to the development of the content, type and language of the text messages for the intervention, they cannot provide data concerning the acceptability of the intervention in 'real-life' settings and over an extended period of time reflecting what would happen in the initial stage of the main trial.

Participants: We will require between 10 and 20 participants for this pilot phase. The participants will be individuals who participated in the developmental focus groups and indicated that they are keen to be involved in further development/piloting work relating to this study. (Most of our focus group participants were very interested in the text-messaging and asked about trying it out.)

Recruitment:
We will send an invitation letter and a participant information leaflet outlining the purpose of the trial phase to all focus group participants who expressed an interest in being involved in further development work. A PROPELS researcher will telephone the participant approximately one week after sending the letter. The researcher will explain more about the trial phase and will answer any questions that participants have. If the participant is interested in taking part, the researcher will take informed consent according to the telephone script*. (*Note: given that these people will have already participated in the development focus groups (conducted by the same researchers) and expressed an interest in helping to further develop the PROPELS intervention, telephone consent is deemed suitable.)

The consent process will be audio recorded. Following the consent process, the recording will be stopped and the participant will be asked for their mobile telephone number to which the trial text messages will be sent. The researcher will then post a pedometer and a step-diary booklet to the participant. On a date agreed between the researcher and participant (approximately one week after the telephone call), the participant will receive a text message welcoming them to the pilot study.

Piloting: Mirroring the plan for the main trial, participants will be asked to record daily step counts using a step-diary. They will be sent *up to* 3 text messages per week (for example, reminding them to wear their pedometer) and each week one text message will ask them to respond with their total weekly step count. At the end of the 8-week pilot phase, a PROPELS researcher will telephone each participant to arrange a short (10-15 minute) telephone interview to gain their feedback.

Data storage and analysis: Data storage will be exactly the same as storage of focus group data as per the protocol. The researchers conducting the pilot study will be responsible for the recording and the storage of: a) the informed consent by telephone, b) participants' mobile phone numbers, and c) the recorded interview data.

- Recordings of each participant's informed consent by telephone will be downloaded onto a secure hard drive at the University of Cambridge or University of Leicester.

- Participants' mobile phone numbers will be stored for the duration of the 8 week pilot phase. At the end of the 8 week pilot phase, mobile numbers will be deleted from the system.
- Recordings of interviews will be downloaded onto a secure hard drive at the University of Cambridge until the end of the developmental stage of the trial. Anonymised transcriptions of recordings will be kept for five years on the secure servers at the University of Cambridge and the University of Leicester.

4.0 Randomised controlled trial (12-60 months)

A multi-centre randomised controlled trial will compare two different modes of physical activity intervention with control conditions.

4.1 Recruitment

This study involves two centres, Leicester and Cambridge. A total of 1308 participants will be recruited with 66% (n=863) recruited from Leicester. We aim to have at least 25% (n=327) of the total cohort from a South Asian ethnic origin to allow for increased generalisability and the ability to stratify results by ethnicity (see Section 5.0 Sample Size), This study will recruit individuals with IGR or previous IGR through several defined strategies that will be used in parallel with priority given to those that are best tailored to each centres individual circumstances.

Strategy one: Utilisation of existing datasets. Participants from other screening studies conducted by our group, who have consented to be contacted about other research and who meet the inclusion criteria, will be recruited from existing databases held by our research centres. Only study staff on the original research studies will have access to participant's data.

Strategy two: Risk score technology. With the support of the primary care research network, GP practices will be recruited to take part in the study. Risk scores such as the Cambridge Risk Score (Griffin et al., 2000) and the Leicester automated risk score (Gray et al. 2012) will be used to identify those individuals within the practice who are at risk of type 2 diabetes. This will involve enabling practices to run an established automated diabetes risk score within their practice database (Gray et al., 2012). For example, the Leicester automated risk score uses the Morbidity, Information Query and Export Syntax (MIQUEST) programme to extract data from six variables (age, ethnicity, sex, family history of diabetes, antihypertensive therapy and BMI) commonly coded within primary care computerized medical records. By assigning pre-validated weighting to each variable, individuals are ranked for their risk of IGR or undiagnosed T2DM with a higher score indicating higher risk. In addition, the risk score also has the capability of identifying all individuals who have had a previous blood glucose or HbA_{1c} result recorded. In this study, those above the 90^{th} percentile of the calculated risk score and who meet the inclusion criteria will be invited to take part in the study. Anyone who has a recorded plasma glucose or HbA_{1c} value in the IGR range (see Table 1) within the last five years and is not currently diagnosed with T2DM will also automatically be invited to take part. We will train staff employed by the GP practice to run the risk score and record high risk individuals. No patient data will leave the practice and research staff will not be able to

approach high risk individuals directly until such individuals have expressed an interest in taking part (see Participant Invitation below).

Strategy Three: NHS Health Checks programme. The NHS Health Check Programme (formerly known as vascular checks) is designed to identify and treat vascular disease risk (heart disease, stoke, diabetes and kidney disease) in all individuals aged 40-74. This programme currently has differing rates of coverage throughout the country, but is formally taking place within some locations across both Leicestershire and Cambridgeshire. We will work in collaboration with those practices running the health checks programme to recruit those found to have a high risk of T2DM or IGR but who are not receiving a systematic diabetes prevention pathway.

Participant invitation: For all recruitment strategies, a letter of invitation, an initial study brochure and a reply slip will be sent to the identified individuals. This initial invitation pack will be sent from the relevant authority which will be dependant on the strategy used (Strategy 1 = Principal Investigator of the screening study database used for identification; Strategy 2 = Practice GP; Strategy 3 = Practice GP). If potential participants are interested in the study, the reply slip will be returned directly to the PROPELS research team in the provided stamped addressed envelope. Contact with the invited participant will then be made by phone to arrange a baseline visit. A member of the PROPELS team will then send the individual the full study Patient Information Sheet with the appointment letter.

4.2 Inclusion criteria

Adults within the age range eligible for the NHS Health Check Programme (40-74 years old) or 25-74 years old if South Asian and confirmed to have IGR at baseline or normal glucose levels at baseline but with the addition of any previously recorded plasma glucose or HbA_{1c} value in the IGR range at any time over the previous five years (see Table 1 for IGR definition and the Outcome Measures section below for details on participant flow at baseline).
Participants will also be informed that access to a mobile phone is necessary given the nature of the intervention provided to those randomised to Group 3 (see Page 15).

Table 1: Categories of glycaemic control used for the purposes of this study

	Normal glycaemia	**Impaired glucose regulation (IGR)****		**Type 2 diabetes**
	Upper value	*Lower value*	*Upper value*	*Lower value*
HbA_{1c} (%)	< 6.0	≥ 6.0	< 6.5	≥ 6.5 **(≥48mmol/mol)**
Fasting plasma glucose (mmol/l)	< 5.5*	≥ 6.0	<7.0	≥ 7.0
2-hour post challenge glucose (mmol/l)	< 7.8	≥ 7.8	< 11.1	≥ 11.1

***** NICE (2012)

**Required of PROPELS participation

4.3 Exclusion criteria

In order to make the study findings generalisable to primary care, we will have as few exclusion criteria as possible. However, given the primary outcome, those unable to undertake ambulatory-based activity will be excluded. Pregnant women, those currently involved in other related intervention studies, and those with diagnosed diabetes, or with screening-detected diabetes at baseline will also be excluded from the study. Those screened at baseline that have normal glycaemia with no previous record of IGR in the previous five years will also be excluded (see Outcome Measures section for details on the criteria for screening detected T2DM, IGR and normal glycaemia). The intervention will be delivered in English; therefore participants without a basic understanding of written or spoken English will be excluded. If individuals are able to demonstrate that they have understood the consenting procedure, they are eligible for the study. Due to the content of the additional text message support offered as part of the study for those in Group 3, any participant without access to a mobile phone will be unable to participate in the study.

4.4 Randomisation

Once baseline data have been collected, participants will be randomised (stratified by sex and ethnicity) by an independent bio-statistician at Leicester CTU. Individuals will be randomised (1:1:1) to: 1) Detailed advice leaflet (control). 2) A behaviour change intervention with annual support or 3) a behaviour change intervention with ongoing behavioural change maintenance support. The exception to this will be for individuals from the same household who will be randomised to the same group.

4.5 Groups

4.5.1 Group 1: Detailed advice leaflet (control)

Individuals randomised to this group will be sent a detailed advice leaflet detailing the likely causes, consequences, symptoms and timeline associated with IGR, along with information about how physical activity can be used to reduce the risk of developing diabetes. This leaflet will be developed in line with the same psychological theories underpinning the active interventions, particularly Leventhal's common sense model, with input from behavioural scientists. In addition participants will receive usual care through their GP practice.

4.5.2 Group 2: A behaviour change intervention with annual support (Walking Away)

Participants will be invited to our Walking Away structured education programme (formally known as the PREPARE programme) within three months of their baseline clinic visit. The programme is a group-based, person centred, education programme which promotes holistic lifestyle messages by targeting perceptions and knowledge of impaired glucose tolerance, understanding of the link between diet and metabolic dysfunction, physical activity self-efficacy, barriers to physical activity, and self-regulatory skills. The content and structure of the programme is underpinned by robust psychological theories that were identified during the development of the PREPARE programme. These theories include:

- Bandura's (1986) Social Cognitive Theory, including self-efficacy and self-regulation.
- Gollwitzer's (1999) implementation intentions - identified as an important framework for developing successful strategies around self-regulation and translating intentions into behaviour.
- Leventhal's (1980) Common Sense Model - thought to be relevant and instructive for targeting illness perceptions.
- Chaiken's (1987) Dual Process Theory.

The programme is delivered using simple non-technical language, analogies, visual aids and open questions to encourage the participants to become actively involved in their learning experience. The programme is delivered in one 3.5 hour session (comprising 3 hour's active content and 0.5 hours for house-keeping and coffee break) to 5-10 individuals per group by two trained educators in English. The programme is based on four modules; the content of each module, example activities and the underlying theoretical structures are presented in Table 2.

The key aim of the programme is to increase participants' physical activity, predominantly through increased ambulation and the use of self-monitoring/feedback from pedometers. Prior to the intervention, participants' habitual steps/day are calculated from accelerometer data collected during their baseline measurement visit (see primary outcome). Using these values, participants are helped to set personalised activity goals and are provided with a pedometer (Yamax SW200) as a motivational and self-monitoring tool. Specifically, sedentary participants will be encouraged to increase their activity levels by at least 3000 steps per day, equivalent to around 30 minutes of walking. Those achieving more than 6000 steps per day will be encouraged to try to reach at least 9000 steps per day, an amount that is likely to include 30 minutes of walking activity in addition to usual daily activity (Yates et al., 2009). Those achieving more than 9000 steps per day will be encouraged to at least maintain their current activity levels and will be informed that health benefits could be achieved by increasing their activity levels further. It is anticipated that, based on pilot data, the average physical activity level of recruited participants at baseline will be between 5000 - 7000 steps/day. Goal attainment will be encouraged through the use of proximal objectives, such as increasing ambulatory activity by 500 steps per day every two weeks. Participants are enabled to set an action plan detailing where, when and how their first proximal goal will be reached and encouraged to repeat this process for each new proximal goal and encouraged to wear their pedometer on a daily basis and self-monitor their ambulatory activity using a specifically designed steps-per-day log.

All participants in this group will be also be given the same advice leaflet as the control group.

Table 2: Outline of the Walking Away programme

Module:	**Main aims:**	**Example activity:**	**Theoretical underpinning:**	**Time weighting:**
Patient Story	Give participants a chance to share their knowledge and perceptions of IGR and highlight any concerns they may want the programme to address.	Participants are asked to share their story, how they were diagnosed with IGR and their current knowledge of IGR.	Common Sense Model (50)	10% (20 minutes)
Professional	Use simple non-technical	1) The following model for	Common Sense	35% (60

story	language, analogies, visual aids and open questions to provide participants with an overview of healthy glucose metabolism, the aetiology of IGR, the risk factors and complications associated with IGR, the possible causes of IGR, possible symptoms associated with IGR and the meaning and accumulative nature of risk and associated risk factors (i.e. cholesterol, blood pressure etc)	insulin resistance is used: Glucose moves from the blood into cells to be used as energy via a door with a lock on it. Insulin keys are used to open the lock; insulin resistance occurs when the cell locks get rusty. 2) Individuals are given their individual glucose, cholesterol and blood pressure scores and a risk chart and helped to work out their individual risk areas.	Model (50) Dual Process Theory (51)	minutes)
Diet	Give participants an accurate understanding of the link between dietary macro-nutrients and metabolic dysfunction	Participants are asked to group food models into their dominant macro-nutrient groups (i.e. carbohydrate, fat, protein). Fats and oils are divided into saturated, polyunsaturated and monounsaturated categories.	Social Cognitive Theory (49) Dual Process Theory (51)	15% (25 minutes)
Physical activity	Use simple non-technical language, analogies, visual aids and open questions to help participants: identify how physical activity improves glucose control; understand the current physical activity recommendations; explore options for incorporating physical activity (primarily walking) into everyday life; identify barriers to exercise; form action plans; encourage participants to use their provided physical activity diaries; and set personal goals (based on baseline pedometer counts for the pedometer version of the programme and generic exercise recommendations for the non-pedometer version).	1) Participants are encouraged to share their knowledge of the various exercise recommendations and to work out how each recommendation may affect their health. 2) Participants are provided with a physical activity diary and encouraged to set their first action plan.	Social Cognitive Theory (49) Implementation Intentions (48) Dual Process Theory (51)	40% (75 minutes)

Follow-up support: Participants will be offered annual follow-up support through the attendance at a 3.5 hour group-based session aimed at re-visiting the key messages of the initial structured education programme; particular emphasis will be placed on discussing encountered barriers to behaviour change and the volitional elements of the intervention (i.e. goal setting, pedometer use and self-monitoring). In addition, follow-up discussions will place a strong emphasis on relapse prevention, or behaviour change re-initiation if relapse has occurred. Participants will also be helped to identify and highlight any benefits experienced (in particular affective benefits associated with walking) Educators delivering the annual follow-up maintenance sessions will be trained and quality assessed using the same approach described for the initial programme.

4.5.3 Group 3: A behaviour change intervention with ongoing tailored maintenance support (Walking Away Plus):
Participants in this group will receive the same advice leaflet as group 1 and the same structured education and annual follow-up group sessions as Group 2, ensuring equivalence between groups. In addition, they will receive ongoing tailored maintenance support delivered by mobile phone text messaging, and brief telephone calls by trained educators or other members of staff approximately one week after the education session and then another halfway between the annual group sessions e.g. every six months (see Table 3). The higher frequency of contacts than in group 2 (see Table 2) is aimed at facilitating maintenance of behaviour change using a pragmatic approach that could be replicated within the NHS if found to be effective.

4.5.3.1 Maintenance support
The behaviour change techniques used during the maintenance contacts will be consistent with the person-centred approach used in the structured education programme and with the underlying theoretical model.

Telephone calls: All intervention educators will be enabled through an existing training programme developed by the DESMOND collaborative to deliver brief telephone-based counselling. Telephone contact is undertaken using the same person-centred philosophy as the initial structured education programme and includes elements that are based on motivational interviewing to help establish a positive rapport, explore and enhance motivation for and confidence about behaviour change and help participants to continue to formulate goals and action plans which are relevant to the context of their day-to-day lives (Miller & Rollnick, 2002). In particular, the educator will help the participant to problem-solve around any physical and affective barriers; identify and highlight any benefits experienced (in particular affective benefits associated with walking), help ensure that the experiences of behaviour change are satisfying and reinforcing; review the participant's progress over time; help the participant set new goals and action plans; and provide ongoing social support.

Text messaging: Text messaging support will be based on the number of steps recorded at baseline and the subsequent short-term and long-term goals identified in the education programme. The anticipated timings and frequency of text and phone call support is discussed below and in Table 3; the exact timing of the contact timings may be subject to minor changes following feedback from the pilot work

In the week following the education programme, participants will receive a brief phone call from the educator who will log the participant's 'tailoring variables' onto the database (i.e., confirm long term and short term goal, confirm action plan, log participants level of self-reported confidence to achieve goal and their previous PA level).

For the next 8 weeks (2 months), participants will receive one text message per week reminding them to wear their pedometer and self-monitor steps. Participants will also receive one text message per week prompting them to enter their weekly step totals (via text) at the end of each week. Once participants have responded, they will receive immediate feedback tailored to goal achievement (e.g., achieved, not achieved, surpassed), and their level of confidence and previous levels of PA

The minimum frequency of text messaging contacts will be once per week, and the maximum frequency will be 3 per week during the first two months. For example, if participants are not making sufficient goal progress they will receive an additional 'problem-solving' text message that enables us to elicit information about potential barriers to PA and provide participants with tailored responses (e.g., tips for getting more active, general supportive messages etc.). After 2 months, the frequency will be once per week (months 2-6; incoming messages only; participants not required to text in step count), then once per month from month 6-12 (see Table 3). If participants do not enter step counts via text each week (for the first 2 months), they will receive an additional text prompting them to text in, followed up by a phone call from the educator if they do not respond after 3 weeks. If however, participants do not want to receive text messages they can opt out at any time and will still be offered the annual group sessions and the follow up phone calls following each of the annual sessions (see Table 3).

Educator recruitment, training and quality assurance: Educator recruitment will take place from local NHS centres and other suitable settings. Through LNR CLAHRC we have successfully trained suitable non-NHS staff, such as local gym instructors, to deliver Walking Away to the same standard as practice nurses. A mix of NHS and non-NHS personnel will therefore be included in order to make the study as pragmatic and generalizable as possible. We will use the infrastructure developed through the DESMOND collaborative to train a pool of around 10 educators per site. Educator training consists of a full day training programme for practice nurses or healthcare professionals who are accredited DESMOND educators, or two full days for registered health care professionals. Previous work on the DESMOND lay educator study has identified that non-registered healthcare professionals will require an extra day of training. The training programme has been developed by the DESMOND collaborative who have proven national success. Training aims to familiarise educators with the content and resources of the curriculum. Training enables educators to become confident and competent to deliver the programme in accordance with the learning theory and philosophy of the programme. Post training, educators will be supported by a mentorship programme.

In order to ensure that the programme philosophy and content are being adhered to, a full quality-development (QD) programme has been developed by the DESMOND national curriculum and training team. The QD tools assess content covered and educator behaviour to ensure that the programme is being delivered according to the underpinning philosophy of empowerment. Part of the QD process involves an assessor sitting quietly and unobtrusively at the back of the room, with a CD playing into a headphone whilst observing the programme. The CD is silent, except for a beep sounding every 10 seconds. When the beep is sounded, the assessor indicates on a response sheet who is talking at that point (whether an educator or a participant), with other activity classed as 'miscellaneous' (indicating silence, laughter or multiple conversations during learning activities). At the same time the assessor fills in a prompt sheet indicating whether or not key learning points within each module were covered. It has been shown that this system, particularly the amount of time educators or participants spend speaking, is predictive of the changes observed in the participants' illness perceptions: less educator talk leads to a greater change

in participants' beliefs about their condition (Skinner et al., 2008). All quality-assured educators will receive structured and instructive feedback from their assessor and key goals and action plans are developed in order to help the educator improve/maintain their performance.

For the purpose of QD, the study team will video record some of the education sessions that are delivered. The camera will be focused and directed on at the educators and not the participants. Permission, through written consent, will be obtained from participants attending the session and the educators delivering the session. If participants are unwilling to take part, the course will be delivered without recording. Video recording has been successfully implemented in other research studies (DESMOND Ongoing Study, REC ref 10/H0406/54, and SUCCESS Study, REC ref 11/EM/0141) carried out at the Leicester Diabetes Centre as a helpful means of continuous improvement of educators' skills and overall improvement of the programme being delivered. In addition, a random sub-sample of '1-week' and '6-month' telephone calls (in group 3) will be audio-recorded (with permission of the participants). The tapes will be used to check fidelity to the intervention protocol (e.g., were the expected behaviour change techniques delivered as planned), receipt by the participants (e.g., understanding and engagement in the phone call) and the time taken to deliver the phone call.

Table 3: Behaviour change intervention with ongoing tailored maintenance support for group 3
NB: This annual structure will be repeated each year (as presented in Table 3) following each education attendance, for the 4 year time period. Clinical visit at 12month is to occur prior to education attendance.

Time point from education attendance	Type of contact and frequency*	Content
0 months	First group session; 3.5 hrs	• As group 2 plus extra 15-20 minutes at end of WA session to discuss 'next-steps' and what to expect over the next 12 months in terms of on-going text messaging and phone calls. • 1 week self-monitoring (using the activity diary) and 'text in' weekly step total at the end of the week (i.e., record 'baseline' steps).
1 week	First telephone call from educator (15 minutes)	• In this initial phone call the educator will confirm the participant's **action plan** and individual long term and short term **goals** (calculated from the person's baseline amount), record the participant's self-reported **confidence** to achieve goals and also their **previous levels of physical activity**. **These 'tailoring variables' will be logged into the educator database by the educator.**
0-2 months	Text message contact (1-3 per week)	• Self-monitoring of activity (pedometer step counts) each week (using an activity diary and the use of a converter to convert other activities into 'steps'). • Participants receive message asking them to 'text in weekly step count total. • Participants receive feedback tailored to goal achievement, confidence, previous PA via text message. • 'Problem solving' text: if participant's not making progress (asks about barriers and sends tailored replies).
2-6 months	Text message contact (one per week)	• Weekly **tailored** messages targeting attitudes and beliefs, motivation, self-efficacy and self-regulation of PA behaviours. • Participants asked to self-monitor and record steps for 1 week

		and text in weekly amount (ahead of 6 month telephone call)
6 months	Telephone contact; 15 mins	• Educator feedback on goal progress / goal review. • Problem solving in relation to barriers. • Identify and highlight benefits experienced. • Ensure that experiences of behaviour change are satisfying and reinforcing. • Social support. • Goal setting and action planning (review goals and action plan; update if required).
7-12 months	Text message contact once per month	• Monthly **tailored** messages targeting attitudes and beliefs, motivation, self-efficacy and self-regulation of PA behaviours. • Participants asked to self-monitor and record steps for 1 week and text in weekly amount (ahead of 12 month group session)
OPTIONAL	Telephone contact; 15 mins	• Where participants do not respond to text requests for step counts, an additional call is triggered for educator to contact using mobile and/or other contact number to encourage and troubleshoot non participation
12 months	Group session; 3.5 hrs	• As per intervention group 2

***** The possible timings and frequency of text and phone call support described will be informed by the pilot work carried out.

4.6 Outcomes measures to be measured at baseline, 12 months and 48 months

4.6.1 Primary outcome

The primary outcome is change in ambulatory activity (steps per day) at 48 months. Ambulatory activity was chosen as the primary outcome because data from epidemiological and intervention studies have consistently shown walking to be the most popular and preferred choice of activity among the general public (Health Survey for England, 2009). The assessment of ambulatory activity (steps/day) is also acceptable to researchers and clinical practitioners alike as it allows for a simple interpretation of habitual activity levels.

Ambulatory activity will be measured using the triaxial Actigraph GT3X accelerometer. ActiGraph accelerometers are the most widely used research grade accelerometers and they have shown to correlate reasonably with a doubly-labelled water measurement of physical activity energy expenditure (Plasqui & Westerterp, 2007) and have good reliability (McClain et al., 2007). ActiGraph accelerometer accelerometers detect a step whenever accelerations on the vertical axis are detected above a minimum threshold (0.30*g*). This threshold allows incidental steps to detected through everyday activities undertaken (i.e. house work), as well as purposeful walking activity. The unique ability of the ActiGraph accelerometer is that it includes a measure of the intensity level at which any accelerations are recorded. This allows the distinction between steps taken incidentally (any acceleration above 0.030g) and those taken during purposeful ~~mobility~~ walking activity above specific intensity thresholds. We will use best-practice analysis techniques to interpret the findings of the output data (Tudor- Locke & Katzmarzyk, 2009). For example, steps/day will be reported as total measured steps (uncensored analysis) as well as steps taken above a certain intensity thresholds (censored analysis). The primary outcome will total uncensored analysis.

Participants will be asked to wear the accelerometer on a waistband (in the right anterior axillary line) for seven consecutive days during waking hours following attendance at their clinical visit and prior to their attendance at the

education. A total of at least three days valid wear will be required to count as a valid recording and a 'valid day' will consist of at least 10 hours of accelerometer movement data. Non-wear time will be determined by one hour or more of consecutive zero counts. Due to the potential for bias between groups in factors used to acquire valid accelerometer data, average wear time and the number of valid days will be included as covariates in the analysis (see section 9).

4.6.2 Secondary outcomes
Physical activity:

- Accelerometer data
- ActivPAL
- Recent Physical Activity Questionnaire (RPAQ)

ActiGraph accelerometers, used for the primary analysis, convert the detection of vertical accelerations into activity counts based on the intensity of the acceleration undertaken; this allows time spent in different activity thresholds to be quantified. For this study, time spent in sedentary, light-, moderate- and vigorous-intensity physical activity will be determined from the ActiGraph by applying the published cut points proposed by Freedson et al (1998).

The ActivPAL is a thigh worn accelerometer which measures the angle of the thigh, providing valuable data on participant posture (i.e. sitting or lying vs. standing). The data obtained from this device will provide invaluable information about the time spent sitting. The ActivPAL will be worn on the thigh for the same 7 day period as the GT3X accelerometer and will be an optional assessment determined by local capacity and participant preference.

RPAQ (Besson et al. 2006) is a self-administered questionnaire containing questions about usual physical activity over the past four weeks in four main domains: activity at home, during work, during transport, and during leisure time. In each domain, questions are closed rather than open-ended to make them easy to complete and to facilitate large-scale data entry. RPAQ is closely based on the previously validated EPAQ2 questionnaire (Wareham et al. 2002). Estimates of energy expenditure for the four different domains (home, work, travel and leisure time) can be calculated by multiplying participation (h/week) by the metabolic cost of each activity, expressed in metabolic equivalents (MET) obtained from the Physical Activity Compendium (Ainsworth et al. 2000). Total energy expenditure (TEE) and physical activity energy expenditure (PAEE) measured using doubly labelled water were significantly associated with TEE and PAEE from the RPAQ (r=0.72 and r=0.43 respectively).

Biochemical variables:

- Fasting and 2-hour glucose (Oral Glucose Tolerance Test)
    - Leicester site only, see site specific methodology below
- HbA_{1c}
- Diagnosis of Type 2 diabetes
- Insulin, HOMA-B, HOMA-IR
- Urea & Electrolytes (U & E)

- Liver Function Tests (LFTs)
- Lipid profile (LDL, HDL & Triglycerides)
- Novel Biomarkers (Adiponectin, leptin, IL-6, hs-CRP)
- Vitamin C and D
- Urine sample
- Genetics

HbA_{1c}
All participants from both Leicester and Cambridge sites will have HbA_{1c} assessed. HbA_{1c} values will be used in the diagnosis of screening detected diabetes at baseline and at subsequent follow-up visits at both sites, conforming to new criteria set out by WHO (2011) and NICE (2012) (see below section titled "Screening detected diagnosis of diabetes at baseline or follow-up"). HbA_{1c} collection will be undertaken according to standardised best practice and analysis. This will be conducted using stable methodology standardised to external quality assurance reference values with the Leicester Royal Infirmary (for the Leicester centre) and Addenbrooke's Hospital (for the Cambridge centre).

Screen-detected diagnosis of Type 2 diabetes at baseline or follow-up:
Anyone self-reporting a diagnosis of diabetes between study visits or found to have an HbA_{1c} value of greater than or equal to 6.5% (48mmol/mol) will be classed as having diabetes. In Leicester, a repeat test to confirm the result will be carried out by the study team and the participants GP informed of these results and diagnosis. This is due to the variability of the test and to ensure validity of the methodology being used, in concordance with international recommendations from the World Health Organisation (WHO, 2006). In Cambridge, the participants GP will be informed of the need for diagnosis to be confirmed as they see appropriate. At both sites, the recommendation will be that diabetes treatment should be initiated and the GP informed that the study team will not be providing any clinical care for the participant's diabetes.

At baseline individuals diagnosed with Type 2 diabetes will be excluded from the study, Figure 1 shows the flow of participants based on the baseline HbA1c values

Individuals diagnosed with diabetes at the 12 month follow-up clinical measurement session will be invited to attend the final measurement clinic at 48 months and will continue to be offered any intervention as stated in their randomisation.

Fasting, 2-hour post-challenge glucose, and Insulin (Leicester site only)
The Leicester site has a track record for undertaking oral glucose tolerance tests (OGTT) within research studies. Participants recruited from the Leicester site will therefore have their metabolic health extensively phenotyped using OGTT to measure fasting and 2-hour glucose and insulin value. The OGTT results will be used to provide greater clinical insight into how the promotion of physical activity affects metabolic health in high risk individuals. The OGTT will involve a fasting blood sample being taken from the patient before they are then given a glucose load of 75g in the form of Lucozade original (410mls). Timing of the 2-hour interval will be taken from the start of the Lucozade drink. After 120 minutes a second blood sample will be taken to

determine the 2-hour post challenge glucose and insulin values. Plasma glucose and insulin samples will be taken at each clinical visit and stored in a -80^{o}C freezer and analysed after the final study visit (48 month) using standardised, stable methodology within the Leicester Diabetes Research Centre. Glucose and insulin measures will be combined to calculate indices of insulin resistance (i.e. HOMA-IR) and β-cell function (HOMA-B).

Given that the new WHO guidelines (2011) have led to local clinical practice basing diagnosis of type 2 diabetes on HbA_{1c} criteria, the routine use of OGTTs have been phased out of primary care. Therefore, in order to comply with local guidelines and to avoid confusing clinical management strategies in recruited practices, OGTT samples taken in Leicester at each clinical visit will be frozen and analysed after the final study visit (48 month) and will not form part of a diagnosis of diabetes.

Standard biomedical outcomes
Fasting lipid profile, urea & electrolytes (sodium, potassium, urea, creatinine) and liver function tests (Albumin, Total Bilirubin, Alkaline Phosphatase (ALP), Alanine Transaminase (ALT)) will be measured by venous sampling.

Novel biomedical outcomes
This study includes markers of chronic low grade inflammation and adipokines (Adiponectin, leptin, IL-6, hs-CRP) because these variables have been hypothesised to be directly involved in the pathogenesis of T2DM (Tataranni 2005) and have been shown to be inversely associated with overall physical activity and walking activity (Panagiotakos 2005, Yates 2008). However, prospective data with objective measures of physical activity is lacking. Therefore this study will further our understanding of the effect of physical activity behaviour change on markers of chronic low-grade inflammation.

Vitamin D and C
Vitamin D deficiency has been consistently associated to poor glycaemic control (Pittas et al., 2007) but prospective data are lacking and the potential interaction with increased physical activity is unknown. Vitamin C will be used as an objective marker of dietary quality.

Urine sample
A urine sample will be taken to allow for the assessment of oxidative stress in relation to glucose tolerance and fruit and vegetable intake. Furthermore, the presence of protein albumin in the urine (microalbuminuria) will also be tested.

Anthropometric and demographic measures:
- Body weight
- Body Mass Index (BMI)
- Body fat percentage
- Waist circumference
- Blood pressure
- Medication status
- Smoking status
- Muscular/skeletal injury

Body weight, body fat percentage (Tanita, West Drayton, UK), and waist circumference will be measured to the nearest 0.1kg, 0.5%, and 0.1cm respectively. Waist circumference will be measured using a soft tape mid-way between the lowest rib and iliac crest. BMI will be calculated once body weight and height are measured. Arterial blood pressure (Omron, Healthcare, Henfield, UK) will be obtained from the right arm whilst the patient is seated. Three measurements will be obtained and an average of the last two will be calculated. Information on current smoking status, medication history, and muscular skeletal injury that prevents physical activity will be interview administered.

Psychological variables and other questionnaire data:

- Illness perceptions (Brief Illness Perceptions Questionnaire)
- Self-efficacy
- Self regulation
- Health utility (EQ-5D); Short Form-8 (SF-8)
- Depression
- Dietary questions (validated questions adapted from EPIC and Navigator)
- Sleep
- Health resources
- Neighbourhood Environmental Walkability Survey (NEWS)

Illness perceptions

Perceptions and perceived knowledge of diabetes risk will be measured with the validated Brief Illness Perceptions Questionnaire (BIPQ) (Broadbent 2006). This eight item instrument uses an 11 point Likert scale (0 = no effect, 10 = complete effect) to measure five cognitive illness representations (consequences, timeline, personal control, treatment control, and identity), two emotional representations (concern and emotion) and illness comprehensibility (perceived knowledge). BIPQ provides a practical and comprehensive measurement of determinants identified in Leventhal's (1980) common sense model, one of the key theoretical models underpinning the content and structure of the education programme. BIPQ has been shown to have reasonable test-retest reliability and concurrent validity (Broadbent 2006).

Self-efficacy

Exercise self-efficacy will be measured using the 100% confidence rating scale (from 0% = no confidence to 100% = complete confidence) (Keller 1999). This self-efficacy questionnaire (six items) measures participants' confidence in their ability to undertake any form of moderate- to vigorous-intensity physical activity for 10 minute periods, increasing incrementally from 10 minutes to one hour each day. An overall score is calculated by summing the efficacy scores for each time period and dividing by the number of time periods. Exercise self-efficacy measures using the 100% confidence rating scale have been shown to have good ($\alpha > 0.8$) internal reliability (McAuley 2003, Cox 2003).

Self regulation

A six item questionnaire will assess individuals' self-regulation habits around physical activity. A 5 point likert scale will be used to assess how much of the time individuals set goals, form action plans, use a pedometer, keep an exercise log, are aware of their activity levels and really try to be physically active. This questionnaire will only be completed at 12 and 48 month follow-up in groups 2 and 3.

Health Utility
Health-related quality of life will be measured using EQ-5D (Kind et al. 1998) and SF-8 (Ware et al. 2001). EQ-5D is a standardized questionnaire that was developed for use as a measure of health outcomes and defines health in terms of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Data from EQ-5D can be represented either as a health profile ($EQ\text{-}5D_{profile}$) or a health index ($EQ\text{-}5D_{utility}$) based on time trade-off data from England, which was used to elicit utility weights for the EQ-5D. This instrument can be used to calculate 'quality adjusted life years' (QALYs) which are essential to cost-effectiveness analysis. SF-8 is a self-administered questionnaire measuring eight health domains (general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health and emotional roles) with eight questions. The standard (4 week) recall format will be used. Data from SF-8 is represented as a physical component score and a mental component score.

Depression and anxiety
Depression and anxiety will be measured with the widely used 14 item Hospital Anxiety and Depression Scale (Zigmond 2006). There are independent subscales for anxiety and depression. Scores on each scale can be interpreted in ranges: normal (0-7), mild (8-10), moderate (11-14) and severe (15-21).

Dietary Questions
In order to capture dietary behaviour two short questionnaires used in previous research studies by our group will be administered to the participants for self completion. These questions are based on dietary questionnaires developed for the EPIC study and the international NAVIGATOR study (McMurray et al. 2010, Bingham et al. 1997)

Sleep
Participants will self-report on two questions concerning sleep duration over the past 24 hours and on a usual week. There is accumulating evidence for an association between short sleep duration (<6 hours per 24 hours) and long sleep duration (≥10 hours per 24 hours) and metabolic dysfunction (Gangwisch, 2007).

Health resources
A health resources questionnaire will be used to assess the cost effectiveness of the randomised controlled trial. This questionnaire looks at the number of times over the past 12 months that the participant has seen a health care practitioner such as a GP, nurse or other health workers, the number of times they have been to hospital as well as the total costs of these visits.

Neighbourhood Environment Walkability Survey (NEWS)

This questionnaire captures the environmental context in which participants live and will be used to establish environmental determinants of physical activity and physical activity behaviour change (Panter et al. 2010, Panter et al. 2011).

4.6.3 Explanatory variables

Maintenance support – group 3 participants only
The number of text messages received by the system will be recorded.

Optional Assessments:
Dual energy X-ray* absorptiometry (*DEXA) assessment of body composition
Those participants who are agreeable in the Leicester and Cambridge cohort and where capacity allows will be offered a whole body dual energy X-ray absorptiometry (DEXA) to assess regional (arms, legs, trunk, android, gynoid) and total adiposity and muscle mass. This study measurement will be undertaken at each measurement time point (0, 12 and 48 months). Scans will be conducted within one month of their baseline and follow-up clinical measurement sessions.

Genetics
A blood sample for genetic analysis will also be collected in those who provide their consent. The aim of this sample will be to investigate group level associations and interactions of physical activity, obesity and genes in the development of T2DM. The genetic assessments will be focused on genes for which there are biological plausibility for interaction. The choice of genes and polymorphisms of interest will be decided by an experienced group of researchers. We will genotype all consenting participants for genetic variants in key genes and analyse the data for gene-lifestyle interaction. The demonstration of differential response to lifestyle change by genotype will not only provide greater aetiological understanding, but will also present the opportunity to investigate possibilities to use genotypic data in risk stratification and identification of individuals who have the potential to benefit most from targeted lifestyle modification. We will store the samples in our secure freezers for up to 10 years, after which time the samples will be sent to a national officially recognised ‘tissue bank’ for future research if they have not already been used.

Long-term Follow-up
Participants will provide consent to enable access their future health status through records maintained by the Health and Social Care Information Centre, together with other central UK NHS bodies. This data will be used to quantify whether the investigated interventions affect long-term morbidity and mortality outcomes. Physical has been associated with reduced risk of morbidity and mortality, however evidence from intervention studies is limited. This study will help address this research gap.

Summary of study measures

All primary and secondary outcomes will be measured 0, 12 and 48 months. Tables 4 and 5 present a summary of blood samples and measures taken at each clinic visit. All participants will be sent a results letter highlighting their main clinical results after each measurement session. Furthermore, all participants' results will be sent to their GP.

Table 4. Summary of blood samples taken at 0, 12 and 48 months

Samples Taken	Amount taken
Fasting Samples	
Fasting Glucose (Leicester only)	2.7ml Fluoride
Lipids	4.7ml Serum Gel
HbA_{1c}	2.7ml EDTA
LFTs, U & Es	included in 4.7ml SG
Insulin and inflammatory biomarkers	2 x 9ml EDTA & 9ml Serum Gel
Genetic Whole Blood	9ml EDTA
120 Minutes Samples	
Glucose (Leicester only)	2.7ml Fluoride

Table 5. Summary of measures taken at each clinical study visit

Measurements	Time Points		
Clinical Assessment	0	12	48
Family History of Disease	X	X	X
Medication Status	X	X	X
Smoking Status	X	X	X
Muscular/skeletal injury	X	X	X
Anthropometric			
3 x Blood Pressure	X	X	X
Height	X		
Weight	X	X	X
Waist Circumference	X	X	X
Arm and leg length	X		
Body Fat Percentage	X	X	X
DEXA (optional)	X	X	X
Blood Tests			
Fasting and 2-hr Glucose (Leicester only)	X	X	X
HbA_{1c}	X	X	X
Insulin	X	X	X
Lipids	X	X	X
Urea & Electrolytes	X	X	X
Liver Function Tests	X	X	X
Novel Biomarkers	X	X	X
Vitamin D and C	X	X	X
Urine sample	X	X	X
Genetics	X		
Questionnaires & Lifestyle Measures			
7 Day Step Count & Physical Activity	X	X	X
RPAQ	X	X	X

Dietary questions	X	X	X
BIPQ		X	X
Exercise Self-Efficacy	X	X	X
Self Regulation (Groups 2 & 3 only)		X	X
EQ-5D; SF-8	X	X	X
HADS	X	X	X
Sleep	X	X	X
NEWS	X		
Health resources	X	X	X
Text messaging		X	X

Clinic visit procedures:

In Leicester, participants will attend a baseline clinic visit after a ~~12~~ minimum 8 hour fast and having taken part in their normal amounts of physical activity for 48 hours prior. The research nurse will conduct group consent and, if happy to, the participants will provide written consent for the study. Once they have consented, a fasting blood sample will be taken and lucozade will be consumed. During the 2 hours between blood samples participants will complete their questionnaire booklet and have their clinic assessment and anthropometric data taken. Once the 2 hour blood sample has been taken participants will be able to leave the clinic.

In Cambridge, participants will attend a baseline clinic, and a consent trained member of the study team will conduct consent and, if happy to, the participants will provide written consent for the study. Blood samples will be taken and the participant will be given time to complete their questionnaire booklet, have their clinic assessment and anthropometric data taken, before being able to leave clinic.

Following the baseline clinic participants will be randomised to one of three groups and will be informed of the assigned group once their 7 days of accelerometer wear have been completed. Whichever group participants are assigned to all participants will be invited back for a 12 and 48 month clinic visit and undergo the measures outlined above. The clinical staff will be blind to the randomisation groups.

Missing clinic visits

If a participant is unable to attend their 12 month clinic visit but is still willing to be involved in the study, on agreement from the participant an accelerometer and questionnaire booklet will be sent to the participant and any relevant data will be collected from their GP. The participant will be invited back again for their 48 month follow up appointment. Similarly, if a participant is unable to attend their 48 month clinic visit but is still willing to be involved in the study, on agreement from the participant an accelerometer and questionnaire booklet will be sent to the participant and any relevant data will be collected from their GP. Attendance and any study data collected will be within +/- 3months of expected time point.

Withdrawal from the study

If a participant withdraws their consent during the study and requests for their data not to be used, all samples and data will be destroyed. The participant will be withdrawn from the study and their GP will be informed. If a participant withdraws from the study, but not their consent, because they are no longer able to take part in future visits, data already obtained will be used for the

study but the participant will not be invited to any future visits. The GP will be informed of their withdrawal from the study. As the participant has not withdrawn their consent for the study, future data will be collected from the GP during the course of the study.

5a. Safety reporting
All safety reporting will be made in line with study sponsor and Leicester CTU SOP guidelines and processes. Copies will also be placed in the study CRF, study database to allow affective analysis to take place and be included in any DMEC and TSC, HTA (as funder), Ethics (as regulator) and other study reporting as part of monitoring of study activity**.**

5a.1 Definitions

An AE or adverse event is:
Any untoward medical occurrence in a patient or clinical investigation, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study, whether or not considered related to the study

Adverse Reaction (AR)
All untoward and unintended responses related to the intervention.
All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study qualify as adverse reactions.

Serious adverse events (SAE)
To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Serious Adverse Event or Serious Adverse Reaction
A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or

- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Expected Serious Adverse Events/Reactions

No serious adverse events/reactions are expected in this study; all participants are recruited as healthy volunteers who are high risk of developing Type 2 diabetes where the study aims to increase the participant's physical activity as a primary outcome. Therefore, the study team will not report any elective or planned surgeries, or outpatient appointments or treatments for ongoing conditions that were present before the start of the study or any aged related conditions such as cancer, stroke, and heart attack where the event is not directly linked to the study activity to increase physical activity. All muscular-skeletal injuries or cardiovascular diseases that occur or are diagnosed during study participation will be reported and assessed in isolation as being study related or not. All deaths will be reported as SAEs. Events that are not reported as SAEs will be reported as AEs. The decision on whether or not to report as an SAE will be the PI's.

Suspected Unexpected Serious Adverse Reactions

A serious adverse reaction, the nature or severity of which is not consistent with the mild to moderate increase in physical activity as part of the study intervention offered.

5a. 2 Reporting procedures for adverse events

All AEs occurring during the study observed by the investigator or reported by the participant, attributed to the study, will be recorded on the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary.

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

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

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

The relationship of AEs to the study will be assessed by a medically qualified investigator.
If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate if applicable) and the CRF.

Adverse Events will be recorded on the AE Record Sheet and periodically discussed by the study steering group committee as required. Any safety concerns arising from the team will be reported to the Sponsor as soon as possible.

5a.3 Reporting procedures for serious adverse events

All deaths will be reported to the Sponsor. SAEs other than death will be reported to the Sponsor if it is deemed to be related to the study intervention (see above). The report will be made within 24 hours of the study team being made aware of the SAE. The Sponsor will perform an initial check of the information and ensure that it is reviewed at the next R&I management meeting. All SAE information must be recorded on an SAE form and sent to the Sponsor using the appropriate reporting form and the contact details on there. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form which must be sent to the Sponsor using the appropriate reporting form and the contact details on there.

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

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

5b~~.0~~ Sample size

Primary outcome

For 1-beta=0.8, alpha=0.025 (allowing for 2 *a priori* comparisons against control conditions), SD = 4000 steps/day and a drop-out of 30%, we require 436 per group (1308 in total) to detect a 1000 steps/day difference in change in ambulatory activity (equivalent to 10 mins walking/day or 70 mins walking/week) between intervention groups and between the intervention and control group. Assuming 25% of participants in the total cohort are SA we have an 80% power to detect around a 2000 steps/day difference when comparing two intervention comparisons to the control group (alpha = 0.025) in the SA population.

Several intervention studies with a follow-up of between 3 to 12-months, including unreported data from the PREPARE study, reported a standard deviation of change in ambulatory activity of around 3000-4000

steps per day in individuals with T2DM, impaired glucose control or in sedentary individuals (Yates et al., 2009; Chan et al., 2004; Merom et al., 2007; Tudor-Locke et al., 2004).Therefore we have anticipated a standard deviation of change of 4000 here.

Secondary outcomes

Given that around 95% of the general population fail to meet the CMO's physical activity guidelines when measured objectively by accelerometers (Health Survey for England, 2008); this study will also allow for the 10% difference in those meeting the current physical activity recommendation to be detected at follow-up based on 1-beta=0.8, alpha=0.025.

Consistent with the calculation for ambulatory activity, this study will also have sufficient power (1-beta=0.8, alpha=0.025) to measure a 10 minute/day difference in change in the time spent in moderate-to-vigorous intensity physical activity based on previous work undertaken by our group (Kinmonth et al., 2008).

This study will have sufficient (1-beta=0.8, alpha=0.025) power to allow for clinically meaningful differences for change in the biochemical measures to be detected in the entire study cohort and after stratification by ethnicity; fasting (0.3 mmol/l) and 2-h glucose (1 mmol/l) and HbA_{1c} (0.25%). 2-h glucose data is based on sample recruited at the Leicester site only.

Furthermore assuming a conversion rate to T2DM in the control group of at least 25% over the course of the entire study (4 years), we will have an 80% power to detect a 40% reduction in the relative risk of diabetes in both intervention groups compared to the control group. The estimated conversion rate is at the lower level reported for traditionally defined IGR using oral glucose tolerance tests (WHO, 2006; Santaguida, 2005). We anticipate that the inclusion of an HbA_{1c} defined IGR state in this study will act to marginally lower the conversion rates, whilst the inclusion of a large South Asian group will act to increase the conversion rates. Therefore a conversion rate of 6.25% per year seems reasonable.

6.0 Process Evaluation

Aim

A qualitative sub-study will be conducted to contribute to the evaluation of the intervention by observing education sessions (at different time points), exploring the perspectives of participants in the different arms of the intervention after the 12 month educations sessions and by exploring the perspectives of educators delivering the education sessions and telephone calls. The process evaluation will provide in-depth qualitative data on how people engage with the two levels of intervention – in particular how and why the more intense level of intervention helps (or does not help) participants to increase and sustain physical activity. In doing so, it will provide critical information for understanding the results of the trial itself – notably how and why differences between groups occur (or not). The qualitative findings will also contribute to areas of theoretical interest such as how participants make sense of IGR, their risk of developing and capability for preventing diabetes, and their perceptions around increasing physical activity and pedometer use.

Sampling and recruitment

Observations: We will observe a sample of annual group education sessions (including up to five of the initial session (depending on availability) and approximately five at the 12-month time point), maximising the range in terms of study site, educator, and – where possible – participant demographics.

When booking participants onto a group education session which a researcher is scheduled to observe, the administrator will advise the participant that there may be a researcher observing the session. If a participant is not happy to attend a session in which a researcher is observing, where available they will be allocated to a different session, or the researcher will not attend. On the day of the sessions the researcher will introduce themselves to participants and explain the purpose of the observations. The researcher will introduce themselves to participants and explain the purpose of the observations. The researcher will sit at the back of the room and take anonymised handwritten field notes (Brewer, 2000; Wolfinger 2002) They will not interfere with the education session and will not audio/video record the sessions.

The focus of the observations is likely to be on two key modules in the curriculum: 'The Participants' Story' and 'Physical Activity'. The researcher will observe how participants talk about their activity levels, pedometer use and (in groups 3) text messaging during their first year of the PROPELS study, including the goals they set, the challenges they faced, the strategies they used to overcome these, the challenges that they haven't overcome, etc. The field notes will inform the topics to be explored in the qualitative interviews (below).

Qualitative interviews and focus groups (trial participants):

A number of study participants in the two intervention arms will be invited to take part in interviews and focus groups after the final follow-up at 48 month – at this point delivery of all the education sessions will have finished as will collection of the final set of follow-up data. Participants from both sites will be invited and selected based on the degree to which they engaged in the education programme namely

1. The number of sessions they attended, We also hope to include some who chose not to attend the programme
2. Whether they continued to accept the text messages or requested them to stop

Attempts will be made to interview a cross section of ages and ethnic groups. If a focus group is held then ideally similar participants would attend (for example those who engaged in several sessions or those who only attended one session). However for logistical reasons this may not always be possible. A letter of invitation together with a patient information leaflet will be sent to the participant. The letter asks them to return a reply slip if they are interested in taking part in an interview or focus group.

A member of the PROPELS research team will contact participants who return the reply slip to discuss the plan for the interview/focus group, confirm their willingness to participate and arrange a date and time for the interview/focus group. Ideally we would like to collect the information using a focus group format, but if the participant would prefer to do an interview or is not available on the dates of the focus groups then a face to face interview will be held. If the participant is not able to travel or does not have the time then a

telephone interview will be offered. Focus groups or face to face interviews will be held in the research department where the participant attended the clinic or an appropriate community venue. Participants will also be offered the option of having the face to face interview at their home.

Written informed consent will be taken before the interview/focus group starts by the experienced qualitative researcher. Participants taking part in a telephone interview will also provide informed consent to the interviewer before the interview starts. This will include asking the participant if they have understood the PIL, and answering any queries they may have. The interviewer will explain that they are not obliged to take part and can withdraw at any time. The interviewer will then read out every statement on the consent form and ask the participant to confirm they are happy with the statement. The researcher obtaining consent will document that each statement was discussed by initialling each statement on the form, and then signing and dating the form. A copy of the completed form will be sent to the participant.

Interviews/focus groupswill be semi-structured and informed by a topic guide.. It is anticipated that interviews and focus groups will last 30 minutes to one hour and telephone interviews will last 15 to 20 minutes.. Interviews will be audio-recorded and transcribed verbatim by the researcher or a transcription service approved by the sponsor.

We anticipate interviewing approximately 20 to 30 participantsin total. . The number included in the final sample will be dependent on pragmatic issues (availability), but will aim to reach theoretical saturation in the analysis of data generated through the interviews.

Qualitative interviews and focus groups (educators): We will invite all educators who are involved in delivering education sessions and telephone calls in the PROPELS study to be involved as follows. 1) Initial individual interviews (during the period of the trial when the 12-month education sessions are being delivered): we will email educators to invite them to participate in an initial individual interview (either face-to-face or telephone according to convenience for the educator). A participant information sheet will be attached to the email. Educators will be asked to indicate their interest by replying to the email. A member of the PROPELS research team will then contact the educator to answer any questions they may have about the interviews and, if they are happy to proceed, to arrange a date for the interview. Written informed consent will be taken immediately prior to the interview. As part of the consent process for the initial interview, educators will also be asked to indicate their consent to be contacted about follow-up interviews and focus groups later in the PROPELS trial. 2) Follow-up interviews and focus groups with educators will be conducted (during the period of the trial when the 24- and 36-month education sessions are being delivered). Educators who indicate willingness to be contacted about follow-up interviews and focus groups (in the consent process for their initial interview) will be invited by email to the follow-up interviews/focus groups. New educators (who joined the trial after the initial interviews) will also be invited by email and sent a participant information sheet. Arrangement of the follow-up interviews/focus groups will be via the same procedure as the initial

interviews. Written informed consent will be taken immediately prior to each interview/focus group.

Analysis
Analysis will be informed by the constant comparative method; initially open codes will be generated from the data, which will be subsequently refined and developed into a coding framework comprising thematic categories and sub-categories. Analysis will be facilitated with NVivo10, a qualitative data-indexing package.

Data storage and security
The PROPELS research team will be responsible for recording and storage of the recorded interview data during the qualitative sub-study. Recordings will be downloaded onto an encrypted memory key and a secure hard drive at the University of Leicester or University Hospitals of Leicester (depending on the base of the researcher)and destroyed once the interviews have been transcribed.. Anonymised transcriptions of recordings will be kept for 6 years on a secure hard drive at the University of Leicester.

7.0 Cost-effectiveness modelling

We will undertake a costing exercise to determine the cost of delivering the initial interventions covering expenditure such as educator time, educator training and quality assurance. In addition we will determine the cost of the follow-up maintenance support group-sessions and the staff and other costs of the individually tailored telephone and text messaging package for maintenance support. Resource use incurred will be costed using actual costs and/or standard unit costs such as Unit Costs of Health and Social Care (Curtis, PSSRU). In addition to the primary endpoint, we will analyse the within-trial impact of the interventions during the trial on other outcomes in Table 5 that are pertinent to the economic analysis, i.e. use of antihypertensives and lipid-lowering therapies, blood pressure, health utility and incidence of diabetes.

Long-term costs and benefits of the interventions will be evaluated through a combination of the within-trial outcomes and decision-analytic modelling to simulate long-term conversion to diabetes, microvascular complications arising from diabetes and cardiovascular events. Specifically for progression to diabetes, estimating long-term progression will require a statistical model built on incidence data from the trial. The underlying incidence curve will be based on rates of conversion in the control arm, and a survival model with time-varying hazards will be built to demonstrate the effect of a unit change in physical activity on risk of diabetes over time. This will allow the impact of alternative assumptions about the degree of maintenance of physical activity beyond the 4-year follow-up period to be modelled. The underlying progression of diabetes beyond the 4-year follow-up will be estimated by the above 4-year survival curve and assumptions about medium-term maintenance of physical activity, but also informed by the trajectory of survival curves from long-term diabetes prevention studies such as the Finnish Diabetes Prevention study. We will undertake sensitivity analyses using a range of plausible assumptions about how behaviour change might affect other risk factors and hence indirectly influence future diabetes risk.

An important input for the modelling will be the effect of reducing physical activity on cardiovascular risk. As we anticipate that evidence for this from intervention studies may still not exist, we will draw on evidence from epidemiological analyses, in particular of walking-based interventions such as (Hamer and Chida, 2008) and any subsequent emerging evidence. We will supplement this with a targeted search for relevant publications including economic evaluations of physical activity interventions. We expect that heterogeneity, in terms of the form, intensity and measures of activity, is likely to be a barrier to a robust formal evidence synthesis of such epidemiological studies. We will therefore critique the evidence retrieved in order to determine, in conjunction will clinical colleagues, the most appropriate evidence to use in the model, in particular taking into account the similarity or otherwise of definitions and intensity of walking compared to that specified in this study, as well as the achievement or otherwise of concomitant changes in weight or BMI.

The above relationship between changes in physical activity and cardiovascular risk will be incorporated into the existing Sheffield T2DM Model (already adapted for prevention of diabetes). The Sheffield T2DM Model is a health state simulation model of the natural history of diabetes and complications which replicates participants' risk of progression through five co-morbidities: retinopathy, nephropathy, neuropathy, heart disease (including heart failure), and cerebrovascular disease. The model aggregates the costs of therapy, the costs of one-off treatments (e.g. cost of amputation), and on-going treatment of complications (e.g. treatment following stroke). The cardiovascular risks of participants' with pre-diabetes and diabetes are estimated using the UKPDS risk engines (UKPDS56, UKPDS60, UKPDS66). A further adjustment will be made so that the risk can be adapted for the South Asian population using evidence advised by clinical colleagues.

Separate evaluations will be undertaken for the overall group and for the South Asian subgroup. Cost-effectiveness will be reported in terms of incremental costs and QALYS, the incremental cost-effectiveness ratio and uncertainty will be reported on a cost-effectiveness acceptability curve and cost-effectiveness plane.

8.0 Data handling

Data will be treated as confidential and stored securely. All data will be entered (through secure web-based access) and held within a specifically designed database within Leicester CTU. Data will be released at predefined time-points to the study statistician. The data will not be used or given to any other third party without written permission of the participant, as defined in their consent form. Biological samples (blood) taken for the study will be destroyed once analysed in a Human Tissue Act compliant site. Every effort will be made by the investigators to adhere to the ethical principles described by the UK Good Governance Procedures and as enshrined in the Declaration of Helsinki.

9.0 Data analysis

Analysis of primary outcome

Analysis will involve two *a priori* comparisons; both intervention groups will be compared to the control group. Should any of these comparisons reveal a significant difference, then a third *a priori* comparison will be undertaken by comparing the difference between intervention groups - this will be included

as a secondary analysis. The primary analyses will be based on the complete case population. The intention-to-treat and per-protocol populations will be analysed as secondary analyses. Those withdrawn from the study due to diagnosis of diabetes at baseline visit will have their last observation carried forward. This will not be required for those diagnosed after their baseline visit as they will continue with the study.

Regression analysis will be used to investigate the differences in the change in physical activity level achieved between groups, after adjusting for potential areas of bias between groups, such as valid accelerometer wear time and the number of valid wear days. Due to the relatively high numbers of participants recruited into this study and the minimisation strategy used, it is anticipated that physical activity levels will be well matched between groups. However, following best practice, baseline values will be entered into the model to rule out the possibility that small discrepancies were affecting the results due to regression to the mean. The modelling assumptions inherent in undertaking regression analysis will be rigorously assessed; for example extreme outliers will be assessed and removed if behaviourally implausible and the dependent variable (change in ambulatory activity) assessed for normality with correction techniques applied if necessary. Unlike self-reported methods (i.e. questionnaire), objectively measured physical activity levels describing a continuous variable are generally normally distributed at the population level.

Analysis will be conducted on the cohort as a whole and stratified by ethnic group. We will also assess the effects of gender, age, ethnicity, and family history of T2DM through interaction analyses.

Although the primary analysis time point is at 48 months, interim follow-up analysis will be conducted at 12 month following the above procedures. Given these are secondary time points, adjustment for multiple comparisons will not be undertaken. The results from these interim analyses may be disseminated, with the appropriate caution explicitly stated and in agreement with the DMEC, at national and international conferences.

Sensitivity analysis

We will undertake sensitivity analysis to analyse the effect of excluding those with data lost to follow-up. This will be done using multiple imputation involving several commonly used imputation methods; this method has been used previously by our group (Kinmonth et al., 2008). Sensitivity analyses will also be carried out using the per protocol definition to analyse the treatment effect in those who adhered to their randomised treatment. The per protocol population will be defined as follows. In the Control arm, all participants will be included in the per protocol sample. In the Walking Away arm, the per protocol sample will be participants who attended all education sessions. In the Walking Away Plus arm, the per protocol sample will be participants who attended all education sessions, registered to the text message programme, and received all of their follow-up education phone calls.

Analysis of secondary outcomes

Analysis of secondary biochemical outcomes will be analysed using the same strategy and at the same time-points as that described for the primary outcome. As these are secondary outcomes, adjustment for multiple measures will not be undertaken; therefore observed significant differences

resulting from these measurements will be interpreted with caution and in relation to the over-all pattern of results.

Differentials in the time to diabetes between groups will be calculated using the Kaplan–Meier method for comparing survival curves.

Other secondary analysis

We will undertake pooled analysis of the study cohort to determine, through linear regression analysis, the extent to which various intensities and types of physical activity (baseline and change) are associated with key biochemical and anthropometric variables (baseline and change); this will help provide additional information quantifying the extent to which physical activity and sedentary behavior are associated with metabolic health; any such analysis will be reported with the caveats inherent with this type of analysis. Mediation and moderator analyses will be conducted using collected psychological variables and intervention processes, such as pedometer use, in order to determine whether hypothesised mediators explain any behaviour change and which individuals gain the greatest benefit, respectively. We will explore whether there is a dose-response relationship between adherence to the interventions and change in the outcome(s).

The finalised analysis plan will be written by the Trial Statistician and reviewed and agreed with the DMEC prior to database lock.

10.0 Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC)

The TSC will comprise of the Chief Investigator (Prof. Khunti) an independent chair (Prof. Simon Heller), two other independent member, a service user advisor, as well other key investigators who may be asked to contribute. The three named independent delegates, who make up the majority, and the study CI will share a vote on any decisions requiring voting (to avoid domination by the research team). A HTA representative will be invited to each meeting. The trial statistician and health economist may attend as needed.

We will appoint a fully independent Data Monitoring and Ethics Committee which will report to the trial steering committee. This will comprise at least two members, an independent chair and a statistician.

11.0 Ethical issues

Main Research Ethics Committee approval and University Hospitals of Leicester R & D approval will be sought before the study commences and where appropriate Primary Care Trust approval will be sought. This will ensure that all ethical and indemnity issues are dealt with.

An internal Data Safety Monitoring Committee will be established to oversee all activities required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. The committee will meet on a regular scheduled basis to review data collection. Issues raised will be addressed with the Principle Investigators and reports and recommendations will be provided.

Figure 1: Design and flowchart for the PROPELS study

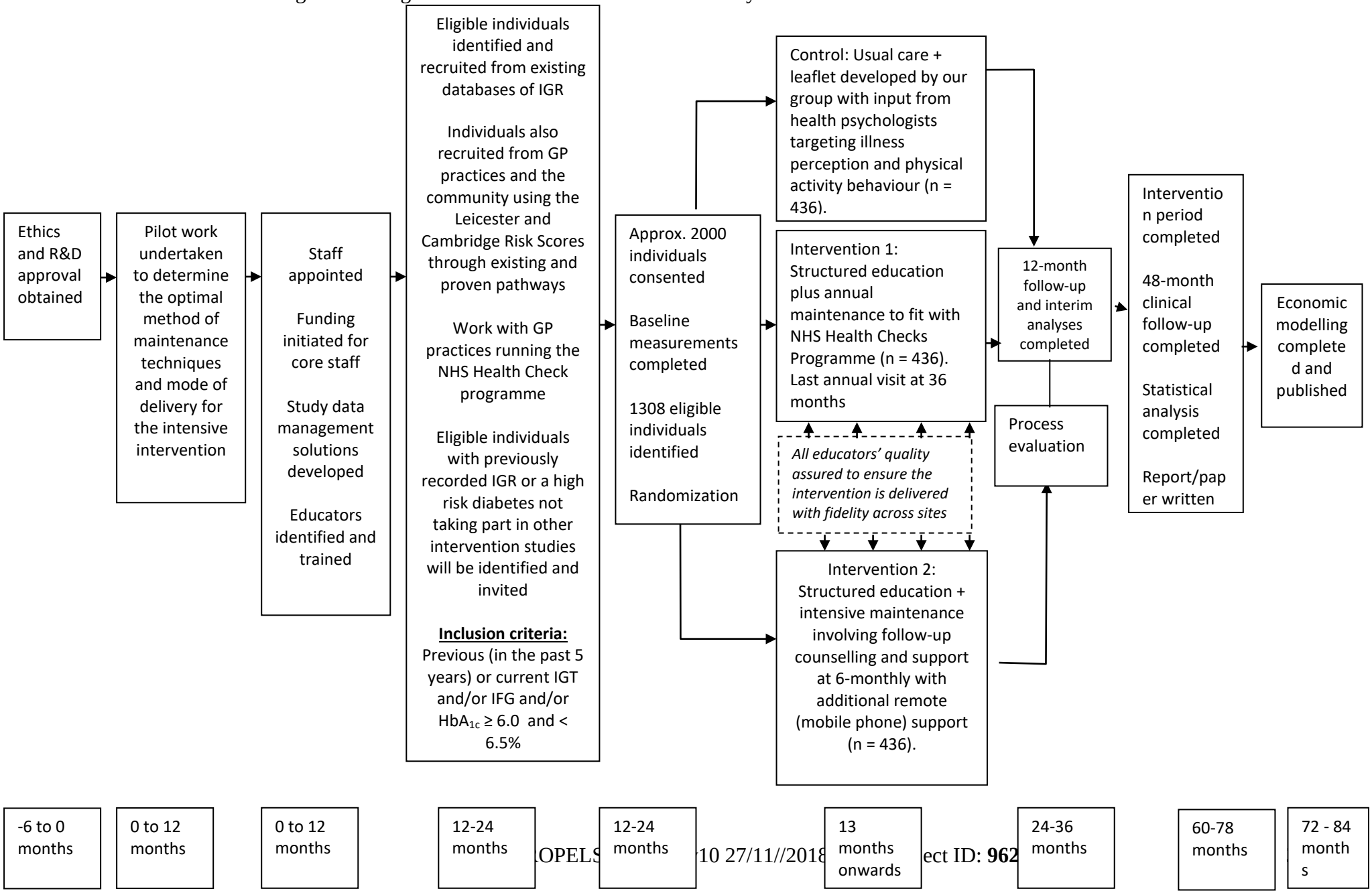
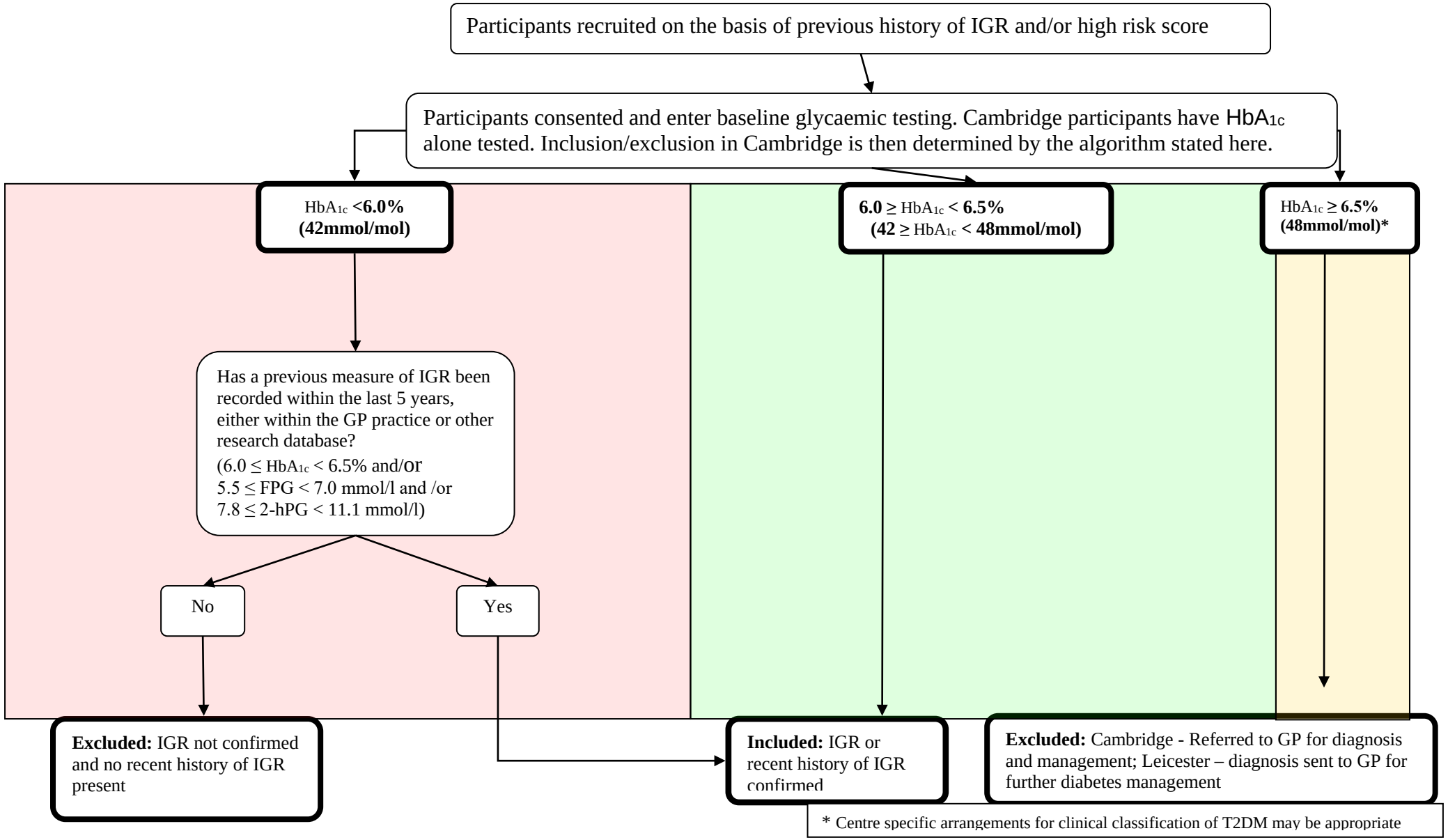


Figure 2: Baseline algorithm for PROPELS



References

Ainsworth, BE., Haskell, WL., Whitt, MC., Irwin, ML., Swartz, AM., Strath, SJ., et al. (2000). Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 32(9 Suppl):S498-S504.

Allender, S., Foster, C., Scarborough, P., Rayner, M. (2007). The burden of physical activity-related ill health in the UK. Journal of Epidemiology and Community Health 61: 344–348.

American Diabetes Association (2010). Diagnosis and classification of diabetes mellitus. Diabetes Care33(suppl 1):S62-S69

Besson H, Brage S, Jakes R, Ekelund U, Wareham N. (2006). Validation of the recent physical activity questionnaire (RPAQ). Objective measurement of physical activity Satellite meeting of the ICDAM6 Conference University of Southern Denmark, Odense: Denmark.

Bingham, S. A., Gill, C., Welch, A., Cassidy, A., Runswick, S. A., Oakes, S., ... & Day, N. E. (1997). Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. International journal of epidemiology, 26(suppl 1), S137.

Brewer JT. (2000) Ethnography (understanding qualitative research). Philadelphia: Open University Press.

Broadbent, E., Petrie, KJ., Main, J., Weinman, J. (2006). The brief illness perception questionnaire. Journal of psychosomatic research 60:631-637.

Chan, C., Ryan, D., Tudor-Locke, C. (2004). Health benefits of a pedometer-based physical activity intervention in sedentary workers. Preventive Medicine 39(6):1215-22.

Cox, KL., Gorely, TJ., Puddey, IB., Burke, V., Beilin, LJ. (2003). Exercise behaviour change in 40 to 65-year-old women: The SWEAT study (sedentary women exercise adherence trial). British journal of health psychology 8:477-95.

Danaei, G., Finucane, MM., Lu, Y., Singh, GM., Cowan, MJ., Paciorek, CJ., et al. (2011). National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. The Lancet 378:31-40.

Davies, MJ., Heller, S., Skinner, TC., Campbell, M., Carey, ME., Dallosso, HM., et al. (2008). Effectiveness of a structured education programme on individuals newly diagnosed with type 2 diabetes: a cluster randomised

controlled trial of the DESMOND programme. British Medical Journal 336:491-5.

Department of Health (2011). Start active, stay active: a report on physical activity from the four home countries' Chief Medical Officers [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_128209].

Department of Health (2006). *Turning the corner improving diabetes care* www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4136141.

Department of Health; Diabetes UK. (2005). Structured patient education in diabetes: Report from the Patient Education Working Group.

Department of Health. (2004). At least five a week: Evidence on the impact of physical activity and its relationship to health. A Report from the Chief Medical Officer.

Freedson, PS., Melanson, E., Sirard, J. (1998). Calibration of the computer science and applications, inc. accelerometer. Med Sci Sports Exerc 30:777-781.

Gangwisch, JE., Heymsfield, SB., Boden-Albala, B., Buijs, RM., Kreier, F., Pickering, TG., et al. (2007). Sleep duration as a risk factor for diabetes incidence in a larger US sample. Sleep 30(12):1667-1673.

Gillies, C., Lambert, P., Abrams, K., Sutton, A., Cooper, N., Hsu, R., et al. (2008). Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. BMJ 336(7654):1180-5.

Gillies, CL., Abrams, KR., Lambert, PC., Cooper, NJ., Sutton, AJ., Hsu, RT., Khunti K. (2007). Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 334:299.

Gray, LJ., Davies, MJ., Hiles, S., Taub, NA., Webb, D., Srinivasan, BT., et al. Detection of impaired glucose regulation and/or type 2 diabetes mellitus, using primary care electronic data, in a multiethnic UK community setting. DOI: 10.1007/s00125-011-2432-x

Hamer, M., Chida, Y. (2008). Walking and primary prevention: a meta-analysis of prospective cohort studies. British Journal of Sports Medicine 42(4):238-43.

NHS Information Centre. Health Survey for England. 2009.

Hein JR, Evans J, Jones. (2008) Mobile methodologies: theory, technology and practice. Geography Compass 2008; 2(5):1266–1285. Health Survey for England (2008). Volume 1. Physical activity and fitness.

Keller, C., Fleury, J., Gregor-Holt, N., Thompson, T. (1999). Predictive ability of social cognitive theory in exercise research: An integrated literature review. The online journal of knowledge synthesis for nursing 6:2

Khunti, K, Walker, N, Sattar, N, Davies, M. (2011) Unanswered questions over NHS health checks. BMJ 342:316-318.

Khunti, K., Heller, S., Skinner, T., (2010). Randomised Controlled Trial of the DESMOND structured education programme for people newly diagnosed with type 2 diabetes. Diabetologia 53(suppl 1):S411.

Kind, P., Dolan, P., Gudex, C., Williams, A. (1998). Variations in population health status: Results from a United Kingdom national questionnaire survey. BMJ 316:736-741.

Kinmonth, A., Wareham, N., Hardeman, W., Sutton, S., Prevost, A., Fanshawe, T., et al. (2008). Efficacy of a theory-based behavioural intervention to increase physical activity in an at-risk group in primary care (ProActive UK): a randomised trial. Lancet 371(9606):41-8.

Knowler, WC., Barrett-Connor, E., Fowler, SE., Hamman, RF., Lachin, JM., Walker, EA., Nathan, DM. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin N Engl J Med 346: 393– 403.

Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., et al. (2009). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA 301(19):2024-35.

Lee, I., Skerrett, P. (2001). Physical activity and all-cause mortality: what is the dose-response relation? Medicine & Science in Sports & Exercise 33(6 Suppl):S459-71.

Leventhal, H., Meyer, D., Nerenz, D. (1980). The common-sense representation of illness danger. In Rachman S (eds) Contributions to Medical Psychology. New York, Pergamon, pp7-30.

McAuley, E., Jerome, GJ., Marquez, DX., Elavsky, S., Blissmer, B. (2003). Exercise self-efficacy in older adults: Social, affective, and behavioral influences. Annals of Behavioral Medicine 25:1-7.

McClain, J., Sission, S., Tudor-Locke, C. (2007). Actigraph accelerometer inter-instrument reliability during free-living in adults. Medicine & Science in Sports & Exercise 39:1509-14.

McMurray, J. J., Holman, R. R., Rutten, G. E. H. M., & Califf, R. M. (2010). Effect of valsartan on the incidence of diabetes and cardiovascular events. New England Journal of Medicine, 362(16), 1477-1490.

Merom, D., Rissel, C., Phongsavan, P., Smith, B., Van Kemenade, C., Brown, W., et al. (2007). Promoting walking with pedometers in the community: the step-by-step trial. American Journal of Preventive Medicine 32(4):290-7.

Miller, W., Rollnick, S. Motivational Interviewing: preparing people for change. Guilford Press, 2002.

Nathan, D on behalf of the International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes (2009). Diabetes Care. 32(7):1327-34

NHS Diabetes 2012. Use of Haemoglobin A1c (HbA_{1c}) in the diagnosis of diabetes mellitus: The implementation of World Health Organisation (WHO) guidance 2011. http://www.diabetes.nhs.uk/our_publications/reports_and_guidance/national_guidelines/

National Institute for Health and Clinical Excellence. Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. Public Health Draft Guidance. 2011. http://guidance.nice.org.uk/PHG/Wave19/62/Consultation/Latest

National Institute for Health and Clinical Excellence. Type 2 diabetes: National clinical guideline for management in primary and secondary care. 2008.

Ogilvie, D., Foster, C., Rothnie, H., Cavill, N., Hamilton, V., Fitzsimons, C., et al. (2007). Interventions to promote walking: systematic review. British Medical Journal 334(7605):1204.

Panagiotakos, DB., Pitsavos, C., Chrysohoou, C., Kavouras, S., Stefanadis, C., ATTICA Study. (2005). The associations between leisure-time physical activity and inflammatory and coagulation markers related to cardiovascular disease: the ATTICA Study. Preventive Medicine 40:432-437.

Panter JR, Jones AP, van Sluijs EM, Griffin SJ (2010) Attitudes, social support and environmental perceptions as predictors of active commuting behaviour in school children. Journal of epidemiology and community health 64(1):41-48.

Panter JR, Jones AP, van Sluijs EM, Griffin SJ, Wareham NJ (2011) Environmental and psychological correlates of older adult's active commuting. Medicine and science in sports and exercise. 43(7):1235-1243.

Paulweber, B., Valensi, P., Lindstrom, J., Lalic, NM., Greaves, CJ., McKee, M., et al. (2010). A European evidence-based guideline for the prevention of type 2 diabetes. Horm Metab Res 42(suppl 1):S3-36.

Pittas, AG., Lau, J., Hu, FB, Dawson-Hughes, B. (2007). The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-anaysis. J Clin Endocrinol Metab 92:2017-2029.

Plasqui, G., Westerterp, K. (2007). Physical activity assessment with accelerometers: an evaluation against doubly labeled water. Obesity 15(10):2371-9.

Santaguida, P., Balion, C., Hunt, D., Morrison, K., Gerstein, H., Raina, P., et al. (2005). Diagnosis, prognosis, and treatment of impaired glucose tolerance and impaired fasting glucose. Evidence Report: Technology Assessment (128):1-11.

Skinner, T., Carey, M., Cradock, S., Dallosso, H., Daly, H., Davies, M., et al. (2008). 'Educator talk' and patient change: some insights from the DESMOND (Diabetes Education and Self Management for Ongoing and Newly Diagnosed) randomized controlled trial. Diabetic Medicine 25(9):1117-20.

Srinivasan, BT., Davies, MJ., Webb, D., et al. (2007). Baseline characteristics and risk of progression from pre-diabetes to Type 2 diabetes in a multi-ethnic population based screening. Diabetes Medicine 24(Supplement 1): 73.

Telford, RD. (2007). Low physical activity and obesity: causes of chronic disease or simply predictors? Medicine & Science in Sports & Exercise 39:1233-1240.

Tudor- Locke, W., Johnson, WD., Katzmarzyk, PT. (2009). Accelerometer-determined steps per day in U.S. adults. Medicine & Science in Sports & Exercise 41:1384-91.

Tudor-Locke, C., Bell, R., Myers, A., Harris, S., Ecclestone, N., Lauzon, N., et al. (2004). Controlled outcome evaluation of the First Step Program: a daily physical activity intervention for individuals with type II diabetes. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesitym28(1):113-9

Tataranni, PA., Ortega, E. (2005). Does adipokine induced activation of the immune system mediate the effect of overnutrition on type 2 diabetes? Diabetes 54, 917-927.

Tuomilehto, J., Lindstrom, J., Eriksson, JG., Valle, TT., Hamalainen, H., Ilanne-Parikka, P., et al. (2001). Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance. N Engl J Med 344:1343-1350.

Ware, JE., Kosinski, M., Dewey, JE., Gandek, B. How to Score and Interpret Single-Item Health Status Measures: A Manual for Users of the SF-8 Health Survey. Lincoln RI: QualityMetric Incorporated, 2001.

Wolfinger NH. (2002) On writing fieldnotes: collection strategies and background expectancies. Qualitative Research; 2(1):85-95.

World Health Organization (2012). Use of Glycated Haemoglobin (HbA_{1c}) in the Diagnosis of Diabetes Mellitus
http://www.who.int/diabetes/publications/report-hba1c_2011.pdf

World Health Organization. Global Recommendations on physical activity. 2010.

World Health Organization: Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risk Factors. Geneva, Switzerland: World Health Organization. 2009.

World Health Organisation Diabetes Development Committee. Definition and diagnoses of diabetes mellitus and intermediate hyperglycemia. 2006.

Yates, T., Davies, MJ., Shemi, S., Gorely, T., Khunti, K. (2011). The Pre-diabetes Risk Education and Physical Activity Recommendation and Encourgament (PREPARE) programme study: are improvements in glucose regulation sustained at 2 years? Diabetic Medicine 28(10):1268-1271.

Yates, T., Davies, MJ., Gorely, T., Bull, F., Khunti, K. (2009). Effectiveness of a Pragmatic Education Program Designed to Promote Walking Activity in Individuals With Impaired Glucose Tolerance. A Randomised Controlled Trial. Diabetes Care 32:1404-1410.

Yates, T., Davies, M., Brady, E., Webb, D., Gorely, T., Bull, F., et al. (2008). Walking and inflammatory markers in individuals screened for type 2 diabetes. Preventive Medicine 47(4):417- 421.

Yates, T., Khunti, K., Bull, F., Gorely, T., Davies, M. (2007). The role of physical activity in the management of impaired glucose tolerance: a systematic review. Diabetologia 50(6):1116-26.

Zigmond, AS., Snaith, RP. (2006). The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361-70.