CLINICAL TRIAL PROTOCOL

A pragmatic and scaleable strategy using mobile technology to promote sustained lifestyle changes to Prevent Type 2 Diabetes in India and the UK
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General Information

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Background The current burden of diabetes in both India and the UK is high and it is expected to increase over the next 20 years. In India, the problem is especially bad with a prevalence in adults of 20% in urban and 10% in rural populations[1]. In the UK, 5% of the population is known to have diabetes[2]. Sub-groups can be defined to be at high risk of developing diabetes, especially those with impaired glucose regulation (IGR) historically defined on the results of an oral glucose tolerance test (OGTT). In India the prevalence of IGR is 18% of the adult population, again with an urban/rural split, and in the UK, the figure is 15% with higher values in those of Indian ethnic origin. Some people with IGR will revert to normal glucose tolerance but progression rates to diabetes are 4-9% per year in published series[3,4]. Several clinical trials, including the Indian Diabetes Prevention Program (IDPP), have shown that intensive lifestyle modification in people with IGR can reduce the progression to diabetes by up to 58%[5-8].

There are 2 main challenges in applying diabetes prevention strategies to the population as a whole. Firstly, the lifestyle modification interventions employed in clinical trials are labour intensive and expensive (the US Diabetes Prevention Program[8], for example, cost over $200million) and such trial-based interventions are unrealistic on a population level in any country. Secondly, the OGTT used to identify those in the population at high risk is a poorly reproducible and time-consuming test, both for the participant and for health care workers. More practical means of defining individuals who would benefit from lifestyle intervention are required.

We propose more practical solutions to these two issues. Firstly, our diabetes prevention strategy will employ a lifestyle modification programme delivered by text messaging in both India and the UK. Text messaging has been successfully used to modify behaviour in other contexts and the current proposal will assess the efficacy, acceptability and cost effectiveness of mobile phone based lifestyle intervention in IGR in India and the UK. The primary outcome will be progression to diabetes. Secondary outcomes will be physical activity, other cardiovascular disease (CVD) risk factors and quality of life. An economic analysis will be performed. Secondly, we propose to employ HbA1c measurement instead of the OGTT as the basis for intervention. This has the advantage of a single sample taken non-fasting. It reflects average circulating glucose levels over the preceding 4-8 weeks and has similar biological significance (in terms of the complications of diabetes) to that of OGTT glucose values. Since standardisation by the International Federation of Clinical Chemistry (IFCC), it has been recognised as a diagnostic test for diabetes by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF), with a cut-off at 6.5%[9]. For impaired glucose regulation, the ADA has recommended the HbA1c range of 5.7-6.4%[9]. International consensus has not yet been reached for IGR and we propose to use a range of 6-6.4% for recruitment into this study in both India and the UK to ensure that only patients at high risk are recruited. Baseline HbA1c has been found to be a better predictor of incident diabetes than the glucose values in the Indian population.

Specific objectives of the project are:

• To assess the efficacy in terms of progression to diabetes, and user acceptability, of a mobile phone-based lifestyle modification programme for people at risk of type 2 diabetes,

evaluating acceptable frequency and user selected content of the intervention in India and the UK

• to assess the effectiveness of such a lifestyle modification programme on change in objectively measured physical activity levels and on other CVD risk factors

• to assess the cost-effectiveness of this mobile phone-based lifestyle modification programme on the progression to diabetes and on improvement of the physical activity level over a 2 year period

• to develop and evaluate a pragmatic and scalable approach to identifying people at high risk of developing type 2 diabetes based on HbA1c in India.

Diabetes is projected to cause an estimated 4 million deaths globally in people aged between 20-79 years in 2010, which is equal to 6.8% of all expected deaths[10]. The potential for lifestyle interventions to reduce the progression to diabetes from high risk states has been demonstrated in a number of RCTs in different countries, with a meta-analysis of RCTs suggesting that lifestyle intervention in high risk subjects can halve the incidence[11]. The lifestyle modification RCTs showing reduced progression to diabetes in high risk subjects have given impressive results. They have however been expensive and labour intensive, with multiple personal contacts (including in some instances home visits) for those in the trial that were deemed to be failing to achieve their goals. Such intensive input is not practical on a large scale. Alternative methods to induce behavioural change, including contact via mobile phones or home computer, have been employed with success in other clinical situations.

A randomized controlled trial assessed ‘Sweet Talk’, a text messaging system designed to support young people with diabetes[12]. Subjects aged between 8y and 18y were randomized to conventional therapy, conventional therapy and ‘Sweet Talk’ or intensive insulin therapy with ‘Sweet Talk’. Conventional goal setting was reinforced by daily text messages containing personalized prompts and tailored messages. HbA1c only improved in subjects randomized to intensive therapy and ‘Sweet Talk’. However ‘Sweet Talk’ was associated with improvements in diabetes self-management and self reported adherence; 82% of subjects felt that ‘Sweet Talk’ had improved their diabetes self- management and 90% wanted to continue to receive messages. In a recent meta- analysis of text messaging in the management of established diabetes (both type 1 and type 2), 22 trials covering 1657 participants were selected for review[13]. Although criticisms could be made about publication bias, results from pooled data suggested that significant improvements in glycaemia and self-management were possible using mobile phone intervention.

Similar degrees of success and acceptability have been observed in other trials of the effectiveness of mobile telephone text messaging, for example as a reminder tool for improving adherence to sunscreen application[14] and in a weight management programme in African American women[15]. The proof of principle for lifestyle modification using text messaging interventions in other clinical situations has therefore been established.

In the UK, recruitment of high risk subjects will be from GP databases following HbA1c measurement as part of the NHS Health Checks and from routine screening of at-risk adults. NHS Health Checks, a cardiovascular risk assessment programme for all adults aged 40-74 years in England, was introduced in 2009 at an annual cost of £250 million. This

government-funded population-based programme aims to both accelerate overall reductions in CVD and diabetes incidence, and reduce known socio-economic and ethnic inequalities in cardiovascular health and diabetes. Delivered in primary care, the programme involves the systematic measurement of CVD risk factors and we shall select practices (the majority) in which HbA1c has been chosen as the indicator of glucose homeostasis.

The UK limb will be centred on a multi-ethnic population in London. There are 42,000 people eligible for the NHS Health Checks in this area. Between 8,000 and 14,000 people will be identified with IGR during the five year roll out of the National screening programme, that is between 1,600 and 2,800 people with IGR identified per year. Neighbouring areas in London will also participate as required.

Potential risks and benefits The potential risks and burdens for research participants are as follows:

At screening, visits 3,4 and 5 there is a venous blood test. These have the potential to cause discomfort. This will be minimised by experienced research personnel and appropriate use of equipment. The text messaging intervention may be irritating to subjects though the evidence base suggests that health interventions delivered in this way are welcomed. Subjects will be able to choose which day and which time of day they receive their messages to improve acceptability and minimise disruption.

The study requires minimal visits and only the randomisation and 6 month visits are over and above usual care for people at high risk of developing diabetes. All visits will be arranged according to subject preference for time and location.

The delivery of an education package for IGR at the start of the study for all participants is an advantage and is additional care above that usually delivered for people diagnosed with IGR.

The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

Population to be studied Subjects with impaired glucose regulation aged 18-74

Trial Objectives and Purpose This study assesses the efficacy, acceptability and cost-effectiveness of a text messaging system for delivering lifestyle advice to people with impaired glucose regulation.

Trial Design Subjects with impaired glucose regulation (defined as an HbA1c of 6.0-6.4%) will be randomised to usual care or usual care with text messaging. Text messages will be delivered three times weekly and will contain educational, motivational and supportive content on diet, physical activity, lifestyle and smoking. The content will be appropriate to the stage of the transtheoretical model of behavioural change that the subject is in (see appendices for transtheoretical model questionnaire, assessment scale and text messages). The primary outcome is progression to type 2 diabetes as defined by an HbA1c of 6.5% or over. Secondary outcomes are:

- Change in physical activity as measured by Actigraph and Recent Physical Activity Questionnaire (RPAQ)
- Change in weight, BMI, waist circumference, hip circumference and waist:hip ratio
- Change in fasting plasma glucose and HbA1c
- Change in lipid profile (total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol)
- Liver function as measured by alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT)
- Change in diet assessed by validated food frequency questionnaire
- Quality of life assessed by EQ-5D questionnaire
- Acceptability of text message intervention assessed by questionnaire
- Cardiovascular biomarkers including hsCRP, adiponectin, PAI (plasminogen activator inhibitor), uric acid, white cell count, albumin, IL-6, IL-1, TNF-α, monocytes chemotactic protein-1, leptin, resistin, endothelin-1, E-selectin, soluble vascular cellular adhesion molecule-1 (sVCAM-1) and soluble interstitial cellular adhesion molecule-1 (sICAM-1)
- Insulin secretion and sensitivity

Lifestyle modification targets in the study are in line with previously published type 2 diabetes prevention studies:

1. A minimum of 150 minutes moderate intensity exercise per week
2. A minimum of 7% weight loss or achievement of a BMI of 25kg/m^2 (23kg/m^2 in South Asian subjects)
3. Less than 30% of total Kcal intake from fat
4. Less than 10% of total Kcal intake from saturated fat
5. Greater than 15g fibre per 1000Kcal intake

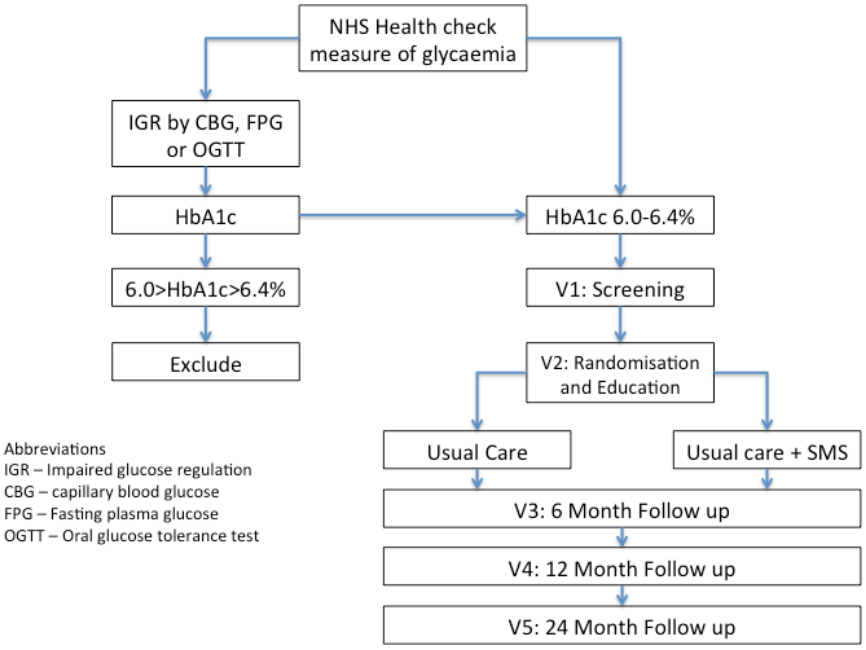
Methodology Randomised, controlled trial.

Timescale It is anticipated that the study will take 3 years with each subject being enrolled for 2 years with a total of 5 visits in that period.

Population n=2268 across the UK and India. n=1134 in UK sites randomized equally to 2 groups of 567.

Recruitment will be undertaken in both primary and secondary care targeting people with impaired glucose regulation (IGR). Identifying this group of people will be done by searching existing pathology databases held in NHS laboratories or GP records for fasting plasma glucose, HbA1c or an oral glucose tolerance test. These glycaemic measurements are done as part of the NHS Health check programme or other routine screening and are performed in NHS hospital labs. Access to the record of laboratory results will be done by only authorised personnel in the pathology department. Potential participants meeting the inclusion criteria for the study will be sent letters of invitation by the study team. Existing samples will not be used in the study. In addition, adverts and face to face talks to potential participants can be used where appropriate. An invitation letter and a participant information sheet together with a reply slip will be sent to potential participants. Those who have shown interest in the reply slips are encouraged to ask questions about the study. Only those who have agreed to take

part will be invited for screening. Informed consent will be taken before conducting any study procedures. During screening, glycaemic status will be confirmed with an HbA1c.



No concomitant medical therapies are contra-indicated. All study visits will take place in a local clinic at one of NHS research collaborating sites for the study.

Visit 1: Screening

- Attend fasting
- Routine clinical examination including measurement of height, weight, waist circumference, hip circumference
- Measurement of blood pressure and heart rate
- 15mL (approximately 3 tablespoons) of venous blood taken for glucose, HbA1c, lipids, Creatinine, ALT, AST, GGT, insulin, cardiovascular biomarkers and serum save
- Urine pregnancy test in female subjects of childbearing age
- Random urine sample for microalbumin:creatinine ratio
- EQ-5D, RPAQ, TTM and food frequency questionnaires completed
- Actigraph physical activity monitor fitted according to manufacturer's instructions and worn for 7 days. Pre-paid addressed envelopes will be provided for the return of the Actigraph device or subjects may return them to the clinic.

Visit 2: Education and Randomisation

- Delivery of structured education for IGR including:
    - Define IGR
    - Implications of IGR in progression to diabetes
    - Prevention of type 2 diabetes
    - Healthy lifestyle advice
    - Dietary advice
    - Physical activity advice

    - Written material given (see appendix)
- Randomised to control (usual care) or text message arm with randomisation minimised by gender and age in decades.

Visit 3: 6 Month Follow-up

- Attend fasting
- Routine clinical examination including measurement of height, weight, waist circumference, hip circumference
- Measurement of blood pressure and heart rate
- 15mL (approximately 3 tablespoons) of venous blood taken for glucose, HbA1c, lipids, Creatinine, ALT, AST, GGT, insulin, cardiovascular biomarkers and serum save
- Urine pregnancy test in female subjects of childbearing age
- Random urine sample for microalbumin:creatinine ratio
- EQ-5D, RPAQ, TTM, food frequency and acceptability questionnaires completed
- Actigraph physical activity monitor fitted according to manufacturer's instructions and worn for 7 days. Pre-paid addressed envelopes will be provided for the return of the Actigraph device or subjects may return them to the clinic.

Visit 4: 12 Month Follow-up

- Attend fasting
- Routine clinical examination including measurement of height, weight, waist circumference, hip circumference
- Measurement of blood pressure and heart rate
- 15mL (approximately 3 tablespoons) of venous blood taken for glucose, HbA1c, lipids, Creatinine, ALT, AST, GGT, insulin, cardiovascular biomarkers and serum save
- Urine pregnancy test in female subjects of childbearing age
- Random urine sample for microalbumin:creatinine ratio
- EQ-5D, RPAQ, TTM, food frequency and acceptability questionnaires completed Actigraph physical activity monitor fitted according to manufacturer's instructions and worn for 7 days. Pre-paid addressed envelopes will be provided for the return of the Actigraph device or subjects may return them to the clinic.

Visit 5: 24 Month Follow-up

- Attend fasting
- Routine clinical examination including measurement of height, weight, waist circumference, hip circumference
- Measurement of blood pressure and heart rate
- 15mL (approximately 3 tablespoons) of venous blood taken for glucose, HbA1c, lipids, Creatinine, ALT, AST, GGT, insulin, cardiovascular biomarkers and serum save
- Urine pregnancy test in female subjects of childbearing age
- Random urine sample for microalbumin:creatinine ratio
- EQ-5D, RPAQ, TTM, food frequency and acceptability questionnaires completed

- Actigraph physical activity monitor fitted according to manufacturer's instructions and worn for 7 days. Pre-paid addressed envelopes will be provided for the return of the Actigraph device or subjects may return them to the clinic.

Data During the course of the study visits some data will be stored on laptop computers, not connected to the internet, for later statistical analysis. These data will be coded and non identifiable. Participant data will be stored in a locked filing cabinet in a secure room in Imperial College Healthcare NHS Trust. Only the research team (clinical research fellow and research nurse) will have access to the filing cabinet. Electronic data will be stored by subject number only on NHS desktop computers which are in the same locked room. At the end of each visit the anonymised data will be transferred immediately to the secure NHS computers and will be deleted from the laptop. Access to NHS computers is only by members of NHS staff with appropriate login privileges.
All data will be stored in an anonymised form by using study numbers for identification of participants. The NHS code of confidentiality will be followed and all activity will meet the requirements of the data protection act.
Only members of the clinical research team and those responsible for direct care will have access to subjects' data during the study. The data generated by the study will be analysed by the research team from Imperial College. The analysis will be on anonymised data and will take place in Imperial College Healthcare NHS Trust and in Imperial College academic buildings in the Faculty of Medicine.

Subject inclusion criteria Subjects may be recruited if:
Adults 18 yrs or over and less than 75 yrs
HbA1c between 6.0-6.4% (42-47 mmol/mol)
(HbA1c test performed within a week before full screening date can be used for inclusion criteria.)

Subject exclusion criteria Subjects are excluded if:
FPG equal or greater than 7.0 mmol/l
Pregnant or planning pregnancy
Breastfeeding
Enrolled in other clinical trials
Have active malignancy or under investigation for malignancy
Are unable to follow the protocol for any other reason

Subject withdrawal criteria Subjects will be withdrawn from the study in the case of:
1. Loss of capacity to give informed consent
2. Terminal illness
3. Diagnosis of type 2 diabetes by any validated criteria in any care setting (see **Efficacy** for more details)

Withdrawal will be immediate and subjects will be followed up in the appropriate care setting.

Efficacy
The primary outcome will be progression to type 2 diabetes as measured by FPG (Fasting Plasma Glucose) or HbA1c at visits 3, 4 and 5 or by any validated criteria in any other care setting. The WHO/IDF criteria for diagnosis of diabetes will be used throughout.

1. If participant presents symptoms of diabetes and, FPG (Fasting Plasma Glucose) ≥ 7.0 OR HbA1c ≥ 48 then no repeat test is needed. The participant is diabetic.
2. If the participant does not present symptoms of diabetes;
    - If FPG ≥ 7.0 and HbA1c ≥ 48 then repeat both tests after 4 weeks. If the repeat results are FPG ≥ 7.0 or / and HbA1c ≥ 48, the participant is diabetic.
    - If FPG < 7.0 and HbA1c ≥ 48 then repeat HbA1c after 4 weeks. If the second result is ≥ 48, the participant is diabetic.
    - If FPG ≥ 7.0 and HbA1c < 48 then repeat FPG after 4 weeks. If the second result is ≥ 7.0, the participant is diabetes.

Secondary outcomes will be:

- Change in physical activity as measured by Actigraph and Recent Physical Activity Questionnaire (RPAQ)
- Change in weight, BMI, waist circumference, hip circumference and waist:hip ratio
- Change in fasting plasma glucose and HbA1c
- Change in lipid profile
- Liver function as measured by alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT)
- Change in diet assessed by validated food frequency questionnaire
- Quality of life assessed by EQ-5D questionnaire
- Cardiovascular biomarkers including hsCRP, adiponectin, PAI (plasminogen activator inhibitor), uric acid, white cell count, albumin, IL-6, IL-1, TNF-α, monocytes chemotactic protein-1, leptin, resistin, endothelin-1, E-selectin, soluble vascular cellular adhesion molecule-1 (sVCAM-1) and soluble interstitial cellular adhesion molecule-1 (sICAM-1)
- Insulin secretion and sensitivity as calculated from fasting plasma glucose and insulin measurements

Safety Adverse events will be reported to the REC, the sponsor and the Principal Investigator immediately. Subjects will be followed-up after one week following an adverse event and thereafter in the clinically indicated follow up setting.

Statistics Missing, unused, and spurious data will be assessed on an individual basis and may be ignored, withdrawn or the visit may be removed from the analysis with appropriate justification adjudicated by the Principal Investigator.

Direct Access to Source Data/Documents The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

Regulatory Issues

Ethics Approval The Chief Investigator has obtained approval from the Westminster Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on

human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Consent Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Confidentiality The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Indemnity Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Sponsor Imperial College Academic Health Science Centre will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

Funding The Medical Research Council of the UK is funding this study.

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

Study Management The day-to-day management of the study will be co-ordinated by Professor D Johnston. Weekly research meetings and monthly data reviews will be chaired by the chief investigator or other senior researcher. Annual reports to the funder and sponsor will be written and submitted. A data monitoring committee will be convened including a lay member with diabetes and appropriate experts not involved with the study.

Publication Policy The study will be registered on the clinicaltrials.gov system and results will be disseminated by peer reviewed scientific journals, internal report, conference presentation and publication on websites. No identifiable personal data will be published. All anthropometry and personal clinical data will be expressed as mean/ median and spread of the population in the study. All participants will be informed of the results by letter at the conclusion of the study and details of any publications that arise from the study will be disseminated to participants.

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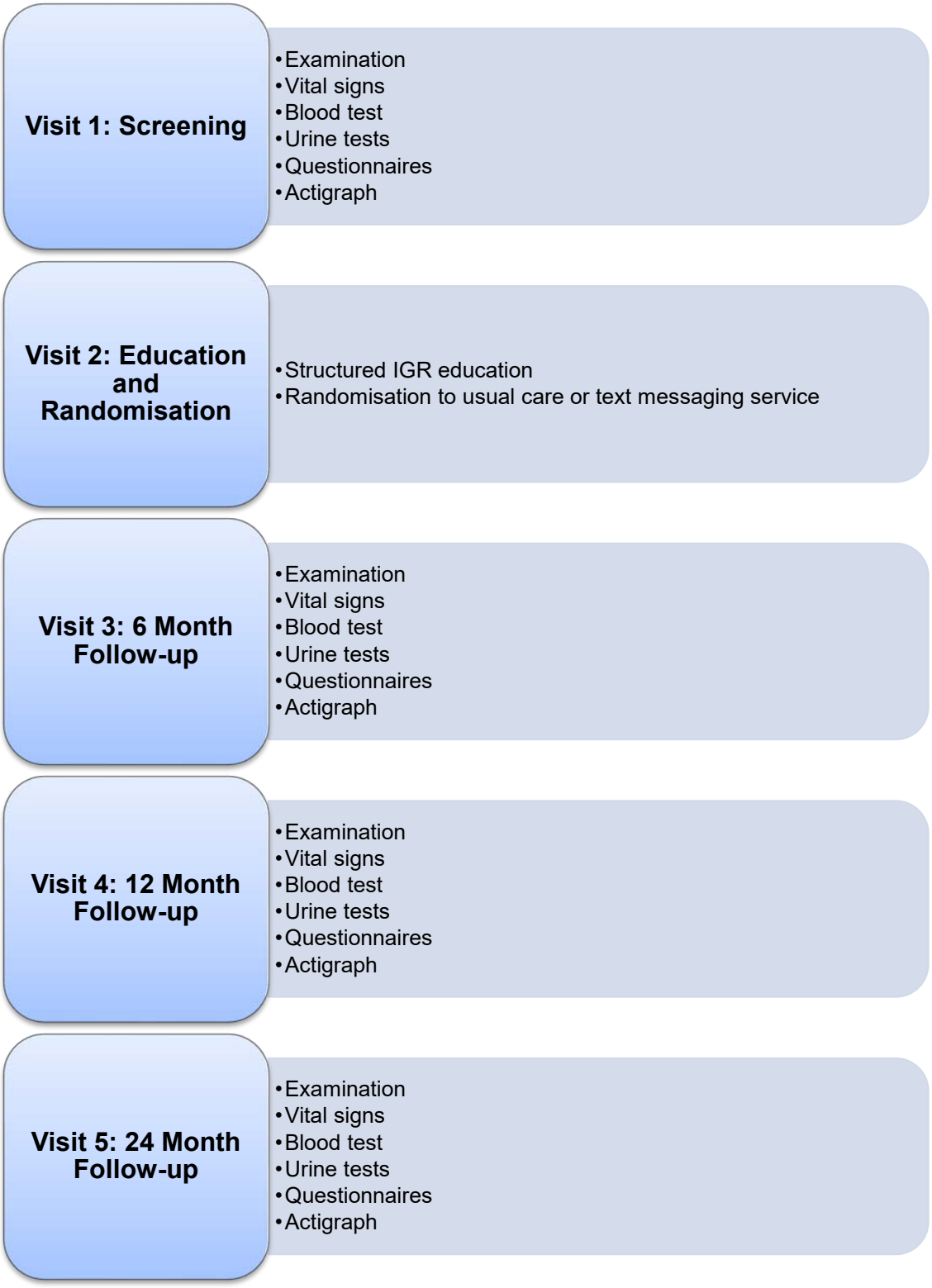
Supplements

i. REC form
ii. RPAQ
iii. Food frequency questionnaire
iv. EQ-5D
v. TTM Questionnaire
vi. TTM Scoring sheet
vii. Written education material
viii. Text message list

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Clinical Examination	✓		✓	✓	✓
Vital signs	✓		✓	✓	✓
Blood test	✓		✓	✓	✓
Urine test	✓		✓	✓	✓
Pregnancy test	✓		✓	✓	✓
RPAQ	✓		✓	✓	✓
FFQ	✓		✓	✓	✓
EQ-5D	✓		✓	✓	✓
Acceptability questionnaire			✓	✓	✓
TTM questionnaire	✓		✓	✓	✓
Randomisation	□	✓			
Education		✓			

RPAQ= Recent physical activity questionnaire
FFQ = Food frequency questionnaire
TTM = Transtheoretical model


Visit 1: Screening
•Examination
•Vital signs
•Blood test
•Urine tests
•Questionnaires
•Actigraph
Visit 2: Education and Randomisation
•Structured IGR education
•Randomisation to usual care or text messaging service
Visit 3: 6 Month Follow-up
•Examination
•Vital signs
•Blood test
•Urine tests
•Questionnaires
•Actigraph
Visit 4: 12 Month Follow-up
•Examination
•Vital signs
•Blood test
•Urine tests
•Questionnaires
•Actigraph
Visit 5: 24 Month Follow-up
•Examination
•Vital signs
•Blood test
•Urine tests
•Questionnaires
•Actigraph