ASPIRE-DNA

Assessment of the Impact of a Personalised Nutrition Intervention in Impaired Glucose Regulation

V1.4 16th March 2020

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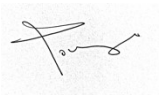
Prof. Christofer Toumazou (Co-Investigator)	16th July 2018	
Dr. Maria Karvela (Co-Investigator)	16th July 2018	
Dr. Caroline Golden (Study Manager)	16th July 2018	

Summary of Changes:

Version Number	Date	Summary of Revisions Made:
V0.19	27/02/2019	Section 4.4 - Substantial amendment submitted to include three other recruitment pathways.
V1.0	18/03/2019	Section 4.4 - Substantial amendment submitted to include the addition of Patient Identification Centres (PICs) Also, overall formatting was adjusted to make the document more readable (no information was changed)
V1.1	28/05/2019	Section 4.1: - Addition of measuring the finger prick blood sample via a lab analyser as a screening method for HbA1c Section 6.1.1: - HbA1c added to hematology procedure Section 6.2.1 - Addition of measuring the finger prick blood sample via a lab analyser as a screening method for HbA1c - Time between Screening and Baseline Clinical Visit was 2 weeks, it is now 3 weeks. - Time between Baseline Clinical Visit and Initial Dietary Consultation was 2 weeks, it is now 3 weeks. - Visit Windows changed as follows: o Visits 2, 3: Window changed from +/-3 to +-10 working days

		○ Visits 4 - 11 : Window changed from +/-3 to +- 6 working days Schematic of Study Design changed to reflect the change of a 3 week interval (old interval: 2 weeks) between screening and the baseline clinical visit, and a change of a 3 week interval (old interval 2 weeks) between the baseline clinical visit and the initial dietary consultation
V1.2	08/08/19	Section 4.4 - Substantial amendment submitted to include two other recruitment pathways. - Community centres added to recruitment pathway (5) The addition of section 6.2.5 Participant Testimonials.
V1.3	13/09/19	Section 6.2.5 - Added more detail on the types of publication that participant testimonials can be used for and the anonymity of testimonials.
V1.4	16/03/20	The section 12. 2 Trial Suspension was added.

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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

Clinical Trial Agreement between DnaNudge Ltd. and Dept. of Medicine, Imperial College London.

This protocol describes the ASPIRE-DNA study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Study Manager.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

RCT	Randomised Control Trial
OGTT	Oral Glucose Tolerance Test
ICMJE	International Committee of Medical Journal Editors
FDA	Federal Drug Administration
CI	Chief Investigator
CRF	Case Report Form
EMEA	European Medicines Agency
HOMA	Homeostasis model assessment
DNA	Deoxyribonucleic acid
ICL	Imperial College London
JRCO	Joint Research Compliance Office
SNP	Single Nucleotide Polymorphism
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
GCP	Good Clinical Practice
IRB	Investigational Review Board
OR	Odds Ratio
PR	Public Relations
POCT	Point-Of-Care Testing
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
FFQ	Food Frequency Questionnaire
PIC	Patient Identification Centre

KEYWORDS

Pre-diabetic, non-diabetic hyperglycemia, genetics, app-based dietary intervention.

STUDY SUMMARY

TITLE Assessment of the Impact of a Personalised Nutrition Intervention in Impaired Glucose Regulation

DESIGN Pilot Study;

Allocation: RCT

Intervention model: Parallel assignment with an active control

Masking: None

Primary purpose: Prevention

AIMS • To compare the impact of a DNA-based diet on glucose regulation in prediabetic individuals with that of standard care.

OUTCOME MEASURES Primary outcome (measured at 6 weeks):

- Difference in 0 minutes glucose on 75g oral glucose tolerance test between the control arm and the intervention arm.

Secondary outcomes:

- Cross-arm and within arm differences (compared to 0 week measurements) between the control arm, intervention arm, and the exploratory arm, in respect of:
  - 120 minutes glucose on 75g oral glucose tolerance test
  - 0 minutes glucose on 75g oral glucose tolerance test
  - HbA1c
  - Weight
  - BMI
  - Lean mass
  - Fat mass
  - Waist circumference
  - Total cholesterol
  - Fasting Triglycerides
  - LDL cholesterol
  - HDL cholesterol
  - HOMA Insulin sensitivity and secretion measurement
  - 120 minute c-peptide following 75g oral glucose tolerance test
  - Systolic blood pressure
  - Diastolic blood pressure
  - Food frequency (by food frequency questionnaire (FFQ) and 24hour recall)
  - Energy intake
  - Carbohydrate intake

- Fat intake
- Saturated fat intake
- Salt intake
- Vitamin D
- Vitamin B6
- Vitamin B12

All of the above secondary outcomes will be measured at 6 and 12 weeks, and a follow-up at 26 weeks (with the exception of HbA1c which will only be measured at 12 and 26 weeks).

- The number of participant withdrawals during the trial.

POPULATION Adults with impaired glucose regulation defined by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) in line with WHO criteria (N = 180).

ELIGIBILITY Inclusion criteria:

- Adults over 18 years of age
- Impaired glucose regulation including IFG and IGT by fasting glucose, OGTT or HbA1c criteria
- Access to smartphone with an operating system of iOS 8.0 or above, or Android 4.0 or above.

Exclusion criteria:

- Diabetes
- Pregnant or planning pregnancy
- Breastfeeding
- Enrolled in other clinical trials
- Have active malignancy or under investigation for malignancy
- Severe visual impairment
- Reduced manual dexterity
- Use of psychiatric, anti-diabetic, and/or weight loss medication, and/or oral steroids
- Bariatric surgery
- History of illnesses that could interfere with the interpretation of the study results (e.g. HIV, Cushing syndrome, chronic kidney disease, chronic liver disease, hyperthyroidism, hereditary fructose intolerance, alcohol or substance abuse)
- Unable to participate due to other factors, as assessed by the Chief Investigator

STUDY DURATION 1 year 11 months

PARTICIPANT DURATION 6 months

NUMBER OF SITES 1

SCHEMATIC OF STUDY DESIGN

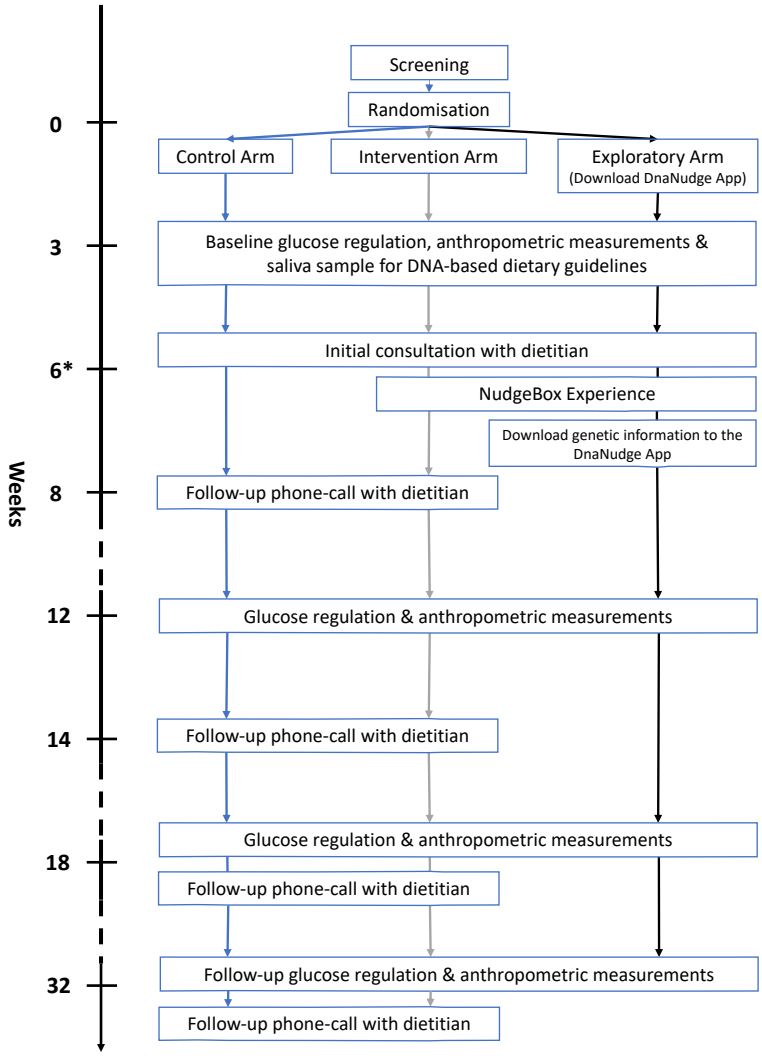

Figure 1: Study design. The asterisk indicates the start of the intervention period.

1 INTRODUCTION

1.1 BACKGROUND

Diabetes is amongst the most common long term conditions, with the number of people affected worldwide quadrupling from 108 million in 1980 to 422 million in 2014 (Mathers & Loncar 2006). Its prevalence in people over 18 years of age has risen from 4.7% in 1980 to a staggering 8.5% in 2014 (Mathers & Loncar 2006). In 2012, there were 1.5 million deaths as a direct result of diabetes, making it the 8th leading cause of death amongst both sexes, and the 5th leading cause of death amongst women. There were a further 2.2 million deaths as a result of complications due to higher-than-optimal glucose levels (WHO 2016). In 2013, 6% of the UK adult population (2.7 million people) were diabetic (Gatineau et al. 2014), 90% of whom had type 2 diabetes (UK 2014). A further 5 million people were estimated to be at high risk of developing type 2 diabetes (NHS n.d.). This has led to a cost of £8 billion per year to the NHS, 80% of which is due to diabetes-related complications such as cardiovascular disease, amputations, renal failure and sight loss (Hex et al. 2012).

The potential for lifestyle interventions to reduce the progression to type 2 diabetes from high risk states has been demonstrated in a number of randomised control trials (RCTs) in different countries, with a meta-analysis of RCTs suggesting that lifestyle intervention in high risk subjects can halve the incidence of diabetes (Neil Thomas et al. 2010). The lifestyle modification RCTs that show reduced progression to diabetes in high risk subjects have given impressive results (Diabetes Prevention Program Research Group 2002; Pan et al. 1997; Kosaka et al. 2005; Tuomilehto et al. 2001; Ramachandran et al. 2006). However, they have been expensive and labour intensive, with multiple personal contacts (including in some instances home visits) for those in the trial who were deemed to be failing to achieve their goals (Diabetes Prevention Program Research Group 2002). 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 (Ramachandran et al. 2013) .

Furthermore, the use of dietary interventions to adjust postprandial glucose levels have indicated the potential benefits of an individualised approach. Traditional approaches of predicting postprandial glucose level such as carbohydrate intake or glycemic index (American Diabetes Association 2015; Bao et al. 2011), have shown mixed results. Carbohydrate intake has been shown to be a poor predictor of postprandial glucose levels (Conn & Newburgh 1936; Zeevi et al. 2015). In fact, individual responses to carbohydrate intake were sufficiently disparate to distinguish two groups of carbohydrate-sensitive and carbohydrate-insensitive individuals, emphasising the need for an individualised intervention (Zeevi et al. 2015). Using the glycemic index of food succumbs to the caveats of examining only a single macronutrient profile, and neglecting the wide range of food combinations at a given meal, and the proximity of the next/previous meal

and/or physical exercise (Dodd et al. 2011). The importance of an individualised approach is most clearly illustrated by the discrepancy in postprandial glucose readings between people who consume identical meals (Vrolix & Mensink 2010; Vega-López et al. 2007; Zeevi et al. 2015), highlighting the need for a personalised treatment plan.

Personalised nutrition enables health interventions by optimising multiple dietary components simultaneously and enhancing motivation to adhere to dietary advice. An innovative approach to personalised nutrition has emerged in the form of DNA-based dietary advice. This intervention provides people with dietary advice that has been tailored to information based on their DNA. In a study in which a DNA-based diet was used to treat obesity, the DNA-based diet had a dramatic effect on the fasting blood glucose levels of participants (Arkadianos et al. 2007). 57% of the intervention group (n = 30, receiving DNA-based recommendations), achieved fasting blood glucose values <5.6mmol/L (100mg/dL), compared to 25% of the control group (n = 16), 90 days following treatment (OR = 1.98). Notably, the DNA-based nutritional advice was not tailored to be a weight loss program, or indeed to improve prediabetic biomarkers. It was targeted to optimise the nutrient profile of a given individual. Another point of interest was the longevity of the effect. The greatest difference between the intervention and control group was found >300 days post treatment; the control cohort showed a slight increase in BMI, compared to the decrease found in the intervention group. This may indicate that there is a greater probability of long-term adherence to nutritional guidelines when tailored, actionable DNA-based advice is provided. A prospective study examined the potential for DNA-based advice to enhance adherence to nutrition protocols (Nielsen & El-Sohemy 2012). Participants received general dietary advice, versus the same advice supplemented with information based on their DNA (n = 149). Those in the intervention group reported a greater understanding of the dietary advice (93% versus 78%), they were more likely view the advice as useful (88% versus 72%), and they were more interested in receiving further recommendations (95% versus 76%).

1.2 RATIONALE

The standard treatment protocol for pre-diabetic individuals in the UK is a brief consultation with their clinician highlighting the dangers of an increased risk of diabetes, and some general information regarding healthy eating and the benefits of regular physical activity. The individual will subsequently be contacted every 3 years to assess the state of their glucose regulation (NICE 2012). Despite the implementation of this system, incidence rates of diabetes have continued to rise over the years. From 1994-2011, the number of women diagnosed with diabetes has risen from 1.9 – 4.9%, and 2.9 – 7.0% for men (England 2016). In response to this, the NHS launched the NHS Diabetes Prevention Program (DPP) in 2016. The aforementioned studies and the predictions of the DPP are in agreement that an intensive lifestyle intervention can radically reduce incidence rates of diabetes. However, these interventions are costly, labour-intensive and require the health system to

pre-identify prediabetic patients. The last point is one of the greatest challenges to any diabetes prevention program, as many at-risk individuals will not self-assess to pre-empt a glucose regulation test (Christensen et al. 2004). Our solution aims to assess the improvement in glucose regulation by following a DNA-based diet in comparison with the standard protocol. Furthermore, our intervention will assess whether a positive change can be implemented by using an app to aid in grocery shopping for a DNA-based diet. If effective, this solution could provide a costeffective, widely-distributed, easily scalable prevention tool for improving glucose regulation in high risk individuals. Moreover, the non-invasive nature of the intervention, paired with the autonomy that it provides the individual in choosing their food choices, enables it to be a lowrisk intervention. Furthermore, as a DNA-based diet is relevant for the general public, it has the potential to perform the preventative measures on individuals who do not self-identify as pre-diabetic.

In this pilot study, we propose to use genetic data to guide personalised nutrition in people with impaired glucose tolerance to demonstrate the impact of personalised nutrition on glucose metabolism, anthropometry, non-glucose metabolism and quality of life.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To compare differences in the impact of a DNA-based diet and standard care in improving glucose regulation in pre-diabetic individuals

2.2 SECONDARY OBJECTIVES

- To assess the ability of a DNA-based diet to improve the macro- and micro-nutrient profile of pre-diabetic participants.
- To assess the impact of a DNA-based diet on clinical markers including cholesterol, body composition and blood pressure, as they relate to diabetes risk.
- Where applicable, to assess changes in anthropometric measurements as a result of following a DNA-based diet, where they relate to diabetic risk reduction.

2.3 EXPLORATORY OBJECTIVES

- To assess the impact of providing DNA-based dietary guidelines via the DnaNudge App, on improving glucose regulation in pre-diabetic individuals
- To assess the impact of providing DNA-based dietary guidelines via the DnaNudge App, on the secondary outcomes outlined in section 2.2.
- To explore the utility of an app as a delivery mechanism for DNA-based dietary advice.
- To examine the changes in leptin measurements via saliva samples during the study.

3 STUDY DESIGN

3.1 TYPE OF STUDY

Physiological; pilot study; RCT, parallel design with an active control.

3.2 DURATION

23 months.

3.3 STUDY POPULATION

Adults with impaired glucose regulation defined by HbA1c, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) in line with WHO criteria (N = 180):

HbA1c:

- < 42 mmol/mol (6.0%): Non-diabetic
- 42 < 47 mmol/mol (6.0–6.4%): IGT – Pre-diabetic
- [3] 48 mmol/mol (6.5%): Type 2 diabetic

IFG (World Health Organization 2006):

- Fasting plasma glucose: 6.1mmol/L (110mg/dL) ≤ IFG ≤ 6.9mmol/L (125mg/dL)
- 2 hr plasma glucose: < 7.8 mmol/L (140mg/dL)

IGT (World Health Organization 2006):

- Fasting plasma glucose: < 7mmol/L (126mg/dL)
- 2 hour plasma glucose: 7.8mmol/L (140mg/dL) ≤ IGT < 11mmol/L (200mg/dL)

3.4 DESCRIPTION OF STUDY DESIGN

Following informed consent, study participants will undergo baseline assessment including assessment of anthropometry, glucose tolerance, metabolism and diet. A trial commencement questionnaire (see Appendix 2) will be completed by each participant upon entry into the trial, and a trial completion questionnaire (see Appendix 4) will be given after 12 weeks of the intervention and after the 26-week follow-up measurement. The questionnaires will address lifestyle factors that may impact the outcomes of the study, and data regarding DnaNudge App utility. DNA will be sampled from saliva from all participants. Two saliva samples will be taken at the baseline assessment (Visit 3 – see Table 1). One sample will be used to create the DNA-based dietary recommendations and the second sample will be used to assess the leptin levels of the participants. Leptin will be measured from saliva samples taken at the 6-, 12-, and 26-week clinical visits to assess the changes in the hunger hormone during the study. Participants will be

assigned to one of three cohorts using stratified blocked randomisation by age and gender (block size = 15):

1. Control arm (n = 60):
    - Participants will receive general health guidelines according to the NICE guidelines, as per standard care.
    - Active control

2. Intervention arm (n = 60):
    - Participants will receive DNA-based health guidelines via a genetic report (see Appendix 13).

3. Exploratory arm (n = 60):
    - Participants will receive DNA-based health guidelines via the DnaNudge App.

The DNA for all arms of the study will be analysed for pre-determined single nucleotide polymorphisms (SNPs) relevant to metabolism. Participants in the intervention arm, will be provided with a hard-copy of a genetic report (for an example report see Appendix 13), which will explain how their SNPs influence their dietary habits. Participants in the exploratory arm, will be given personalised DNA-based dietary advice via the DnaNudge App. Participants in the control arm will be provided with a summary of NICE guidance via a dietitian, as per standard care.

Participants will then be reviewed after 6 and 12 weeks with repeat baseline measures. Participants in the control arm will be offered a personalised nutrition plan on completion of the study. Participants will be asked to complete a food frequency questionnaire (see Appendix 12) before their initial consultation with the dietitian (Visit 4 – see Table 1), and at the 6-, 12- and 26-week follow up clinical visits. Participants will also be asked to perform a 24-hour recall at each follow-up phone call with a dietitian (Visits 5, 7, 9 & 11 – see Table 1). A summary of the activities for each participant is given in Table 1. Data from the App will also be used in exploratory analysis to examine usage patterns and decision making as a result of the DNA-based dietary recommendations.

See Figure 1 for a diagram of the study design and estimated timeframe.

3.5 STUDY OUTCOME MEASURES

Primary outcome:	Difference in 0 minutes glucose on 75g oral glucose tolerance test between the control arm and intervention arm at 6 weeks

Secondary outcomes:	120 minutes glucose on 75g oral glucose tolerance test 0 minutes glucose on 75g oral glucose tolerance test HbA1c Weight BMI Lean mass Fat mass Waist circumference Total cholesterol Fasting Triglycerides LDL cholesterol HDL cholesterol HOMA Insulin sensitivity and secretion measurement 120 minute c-peptide following 75g oral glucose tolerance test Systolic blood pressure Diastolic blood pressure Food frequency (by food frequency questionnaire and interviews) Energy intake Carbohydrate intake Fat intake Saturated fat intake Salt intake Vitamin D Vitamin B6 Vitamin B12

All secondary outcomes will be measured at 6, 12 and 26 weeks (with the exception of HbA1c which will only be measured at 12 and 26 weeks).

4 PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Potential participants will undergo a screening process prior to entry into the study. Potential participants will be invited to the clinical research facility where they will be talked through the consent procedure and allowed to ask any questions they may have. Following consent and verification that they are eligible via the inclusion and exclusion criteria, they will undergo a glucose regulation test via finger prick blood sample that will be analysed either via a point of care (POC) HbA1c test, or a lab analyser, to measure HbA1c. The lab analyser (TOSOH G8 analyser) will be used to assess HbA1c on a capillary sample if the Siemens DCA Vantage Analyser POC device is unavailable or returns values that are out of the acceptable range for accuracy. Both devices will be used in line with manufacturer instructions. If a participant is found to be type 2 diabetic they will be referred to their GP for further care.

The HbA1c test results will be interpreted according to WHO criteria:

- HbA1c below 42 mmol/mol (6.0%): Non-diabetic
- HbA1c between 42 and 47 mmol/mol (6.0–6.4%): IGT – Pre-diabetic
- HbA1c of 48 mmol/mol (6.5%) or over: Type 2 diabetic

4.2 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Provision of signed and dated informed consent form
- Adults over 18 years of age
- Impaired glucose regulation including IFG and IGT by fasting glucose, OGTT or HbA1c criteria
- Access to smartphone with an operating system of iOS 8.0 or above, or Android 4.0 or above.

4.3 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Diabetic
- Pregnant or planning pregnancy
- Breastfeeding
- Enrolled in other clinical trials
- Have active malignancy or under investigation for malignancy
- Severe visual impairment
- Reduced manual dexterity

- Use of psychiatric, anti-diabetic, and/or weight loss medication, and/or oral steroids
- Bariatric surgery
- History of illnesses that could interfere with the interpretation of the study results (e.g. HIV, Cushing syndrome, chronic kidney disease, chronic liver disease, hyperthyroidism, hereditary fructose intolerance, alcohol or substance abuse)
- Unable to participate due to other factors, as assessed by the Chief Investigator

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited through some/all of the following approaches:

1. Communication with Waitrose customers and their partners through Waitrose customer/partner communication platforms
2. Imperial College Healthcare Trust Diabetes Clinics
3. Healthy volunteer database in the Imperial Clinical Research Facility
4. NIHR CRN distribution of text messages to individuals chosen by the NIHR CRN based on study inclusion/exclusion criteria in London Clinical Commissioning Groups (CCGs).
5. Flyers for display in hospitals/Imperial Clinical Research Facility (ICRF), Imperial College London/Community Centre noticeboards.
6. Advertisement in local London newspapers with same information as flyer.
7. The use of Patient Identification Centres (PICs) to identify and contact potential participants through one of the aforementioned approved methods e.g. text messages
8. Advertisement of the study via Diabetes UK through for example, their website, social media.
9. Opportunistic recruitment via either GP staff, Clinic staff, or Trial Team staff providing patients with study information before/during/after their consultation.

If identified through method (1), (3), (5) and (6), the initial information that will be communicated will direct the potential participants to self-assess if they may be pre-diabetic by completing the Leicester Risk Score Assessment (Gray et al. 2010), available on the Diabetes UK website (https://riskscore.diabetes.org.uk/start). Participants will be offered the opportunity to contact the clinical trial team if they would like to partake in the trial. The clinical trial team will then invite the potential participant to the Clinical Research Facility for a screening appointment. If identified through method (2), (5), (7) and (9), the participants will be identified from the current registry of prediabetic individuals who were identified through standard care. They will be provided with contact details for the study should they wish to participate. If identified through method (8), participants will be directed to the clinical trial website and/or the Trial Team contact email address and phone number if they would like to find out more information about the trial. Of note, patients can only be approached by members of the Trial Team if they have

given permission via their direct care team. If the potential participant is considered eligible by any of the above methods, they will be contacted via email or telephone by the clinical trial team to ask them if they would like to undergo a screening test at the clinical research facility to assess their suitability for the trial.

Given the high rate of diagnosis of diabetes and pre-diabetic individuals by the North-West London GP network in 2016, we anticipate the accrual rate for N = 180 pre-diabetic individuals to fulfil our planned recruitment schedule of N = 60 participants every 3 months.

4.5 WITHDRAWAL CRITERIA

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue the participation of a participant from the study at any time, if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of consent
- Loss to follow-up

Following participant withdrawal, no further clinical tests will be performed, and no further information will be obtained from the participant's DnaNudge App for the purposes of the trial. All data recorded prior to withdrawal may be analysed in the context of determining reasons for withdrawal. Participants will have the option of participating in a follow-up interview to ensure patient well-being and to provide reasons for withdrawal if they wish. The reason for withdrawal will be recorded in the CRF. Participants will not be required to provide reasons for withdrawing from the study. Participant withdrawal will result in exclusion from the study if the length of time prior to withdrawal is not sufficient to provide useful data for the study.

4.6 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is a sufficiently reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the principal investigators, the JRCO, ICL and DnaNudge Ltd. If the study is prematurely terminated or suspended, the Trial Manager will promptly inform the JRCO and will provide reason(s) for termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about protocol compliance and data quality are addressed and satisfy the clinical trial team, and ICL.

5 STUDY AGENT(S) AND CONTROL DESCRIPTION

The control arm will receive NICE guidelines for prediabetic individuals via a consultation with a dietitian. The will also receive 2 follow up phone calls from the dietitian during the intervention period, and 2 further follow up phone calls; one to accompany the 12-week clinical measurement, and one to accompany the 26-week final follow up clinical measurement. A further description of the relevant timings of each of the above is given in section 6.2.

The intervention and exploratory arms will receive DNA-based dietary recommendations via consultation with the dietitian. The DNA-based dietary recommendations are determined via the integration of DNA information, scientific nutrigenomic data, and national dietary guidelines. The intervention arm will also have follow-up phone calls with the dietitian as per the control arm, however the exploratory will only receive the app, and no follow-up phone calls.

The DNA of an individual is assessed to determine their genotype for a pre-defined set of SNPs that relate to their metabolism. Their genotype for each SNP is subsequently mapped to the nutrigenetic dietary recommendations in the established database of DnaNudge Ltd., that has intensively reviewed scientific literature to determine the nutrigenomic correlates of each SNP. Furthermore, many of the nutrigenomic links do not act in isolation. Therefore, algorithms have been developed to combine all of the genomic data from the pre-defined set of SNPs to give the optimal, personalised dietary guidelines to each individual.

The genetic analysis will be performed in both the lab in the Centre for Bio-Inspired Technology at Imperial College London, and in a lab-on-chip device called the NudgeBox. The NudgeBox is technology developed by DnaNudge, to miniaturise and improve the speed of genetic analysis techniques such that they can be performed in the NudgeBox, in front of the user, in approximately 15 minutes. It will require the participant to take a buccal cheek swab and insert it into the DNA cartridge provided. The cartridge will contain the primers necessary to analyse metabolism-based SNPs in the saliva sample. The cartridge will then be inserted into the NudgeBox, where the genetic analysis will be performed. This technology will be demonstrated to each participant during their initial consultation with the dietitian.

The exploratory arm will also receive the DnaNudge App to help them with their grocery shopping and food choices. The aforementioned nutrigenetic information for each individual will be supplied in an easy to use electronic format to provide recommendations on demand e.g. via the DnaNudge App or other visual indicator. A summary of the equipment being used is provided in Appendix 3. The user will scan the barcode of a product using the App, which will provide immediate feedback as to whether the food product is good for their health, or is incompatible with one or more of their genetic traits. Furthermore, the App will then link this data to an internal database of food products and produce recommendations of food products that will be very

similar to the first product but more amenable to their genetic traits. Moreover, the App will contain all of the DNA-based dietary recommendations that will have been determined via their DNA in a genetic report. It will also contain educational information on action steps that they can take to improve their health, and how each of their DNA-based guidelines relate to the national dietary guidelines.

6 STUDY PROCEDURES AND SCHEDULE

6.1 STUDY PROCEDURES/EVALUATIONS

6.1.1 STUDY SPECIFIC PROCEDURES

The following list of procedures will be performed on all participants:

- Medical history - Participants will be asked a series of questions by the research nurse to ensure that they do not meet any of the exclusion criteria of the study.
- Genetic testing – saliva samples will be provided.
- Physical examination – Assessment of weight, height, waist circumference, blood pressure, lean mass, fat mass.
- Hematology – blood test to examine total cholesterol, HDL cholesterol, LDL cholesterol, fasting triglycerides, HbA1c
- Biological specimen collection – saliva samples will be obtained via the collection of 2ml of spit per sample. Another saliva sample will be provided by means of a buccal cheek swab, to be used in conjunction with the NudgeBox.
- Insulin sensitivity – 0 minutes on 75g glucose OGTT, 120 minutes on 75g glucose OGTT, 120 minutes c-peptide following 75g glucose OGTT, HOMA insulin sensitivity and secretion measurement
- Pregnancy test
- Food frequency questionnaire
- Trial commencement and completion questionnaires

6.1.2 SPECIMEN PREPARATION, HANDLING AND STORAGE

In line with the Human Tissue Act 2004 and the Imperial College London Retention Schedule, the saliva sample will be anonymised, and stored for up to 5 years after study completion. After this time the sample will be destroyed and the data will be kept for up to 10 years after study completion. Blood samples will be stored for 1 year after study completion, upon which time they will be destroyed and the data will be stored for 10 years after study completion.

6.2 STUDY SCHEDULE

6.2.1 SCREENING

Visit 1: Study preparation

- Send participants a Participant Invitation Letter (Appendix 8), and PIS (Appendix 6).
- Schedule a screening visit for potential participants.

Visit 2: Screening (Day -42 to -0 +/-10 working days)

- Discuss the consent procedure (Appendix 5) and any questions that a potential participant may have regarding the trial.

- If the potential participant would like to participate in the trial, they will be provided with an opportunity to sign the consent form and the PIS. A copy of the consent form will be provided to the participant and a copy will be retained by the clinical trial team.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria. This will include a finger prick blood sample that will be analysed either using a point-of-care HbA1c test using a Siemens DCA Vantage POCT device, or a lab analyser, to measure HbA1c levels.
- Send the GP letter (Appendix 7) to the GP of each confirmed participant in the trial who has consented to informing their GP of their participation in the trial.
- Provide participants with access to online and/or hard-copy food frequency questionnaire that they will need to complete for 1 week of food intake prior to their first clinical appointment in the trial (Visit 3).

Following confirmed enrolment in Visit 2, participants will undergo assignment to one of the three arms of the study.

Visit 3: Baseline clinical measurements (Day -21 +/- 10 working days)

- Verify inclusion/exclusion criteria and consent.
- Perform clinical assessment of glucose regulation and anthropometric measurements.
- Obtain urine pregnancy test (if applicable).
- Collect blood sample (15mL).
- Assess blood pressure, weight, height, waist circumference, lean body mass, and fat body mass.
- Perform 0 minutes on 75g glucose OGTT, 120 minutes on 75g glucose OGTT, 120 minutes c-peptide following 75g glucose OGTT, HOMA insulin sensitivity and secretion measurement.
- Provide two saliva samples (2mL each) via spit.
- Complete trial commencement questionnaire.

6.2.2 FOLLOW-UP

For sample scripts for all interactions with the dietitian for each arm of the study, see Appendices 9 (control arm), 10 (intervention arm), and 11 (exploratory arm).

Visit 4: Initial consultation with a dietitian (Day 0 +/- 6 working days)

- Perform 30-60 minute consultation with the dietitian
- Perform 24-hour recall of food intake for each participant.
- **Intervention and exploratory arms:** Provide NudgeBox experience whereby the participant will provide a buccal cheek swab to perform on-site rapid genotyping. This will provide the participant with a visualisation of how some of their genetic information is analysed

- **Control arm:** Provide NICE guidance by verbal and written communication as per standard care.
- **Intervention arm:** Provide DNA-based dietary information in verbal and written form to participants.
- **Exploratory arm:** Provide DNA-based dietary information via the DnaNudge App.

Visit 5: Follow-up phone-call with the dietitian (Day 14 +/- 6 working days) (Control and intervention arms only)

- Contact participants for a brief phone-call with the dietitian to address any dietary questions/problems.
- Perform 24-hour recall of food intake for each participant.

Visit 6: Glucose regulation review (Day 42 +/- 6 working days)

- Perform clinical assessment of glucose regulation and anthropometric measurements.
    - Obtain urine pregnancy test (if applicable).
    - Collect blood sample (15mL).
    - Assess blood pressure, weight, height, waist circumference, lean body mass, and fat body mass.
    - Perform 0 minutes on 75g glucose OGTT, 120 minutes on 75g glucose OGTT, 120 minutes c-peptide following 75g glucose OGTT, HOMA insulin sensitivity and secretion measurement.
    - Provide saliva sample (2mL) via spit.
- Complete FFQ

Visit 7: Follow-up phone-call with the dietitian (Day 56 +/- 6 working days) (Control and intervention arms only)

- Contact participants for a brief phone-call with the dietitian to address any dietary questions/problems.
- Perform 24-hour recall of food intake for each participant.

Visit 8: Glucose regulation review (Day 84 +/- 6 working days)

- Perform clinical assessment of glucose regulation and anthropometric measurements.
    - Obtain urine pregnancy test (if applicable).
    - Collect blood sample (15mL).
    - Assess blood pressure, weight, height, waist circumference, lean body mass, and fat body mass.
    - Perform 0 minutes on 75g glucose OGTT, 120 minutes on 75g glucose OGTT, 120 minutes c-peptide following 75g glucose OGTT, HOMA insulin sensitivity and secretion measurement.
    - Provide saliva sample (2mL) via spit.
- Complete FFQ.
- Complete trial completion questionnaire.

Visit 9: Follow-up phone-call with the dietitian (Day 84 +/- 6 working days) (Control and intervention arms only)

- Contact participants for a brief phone-call with the dietitian to address any dietary questions/problems.
- Perform 24-hour recall of food intake for each participant.

6.2.3 FINAL STUDY VISIT

Visit 10: Glucose regulation review (follow-up) (Day 182 +/- 6 working days)

- Perform clinical assessment of glucose regulation and anthropometric measurements.
    - Obtain urine pregnancy test (if applicable).
    - Collect blood sample (15mL).
    - Assess blood pressure, weight, height, waist circumference, lean body mass, and fat body mass.
    - Complete a food frequency questionnaire.
    - Perform 0 minutes on 75g glucose OGTT, 120 minutes on 75g glucose OGTT, 120 minutes c-peptide following 75g glucose OGTT, HOMA insulin sensitivity and secretion measurement.
    - Provide saliva sample (2mL) via spit.
- Complete FFQ
- Complete trial completion questionnaire.

Visit 11: Follow-up phone-call with the dietitian (Day 182 +/- 6 working days) (Control and intervention arms only)

- Contact participants for a brief phone-call with the dietitian to address any dietary questions/problems.
- Perform 24-hour recall of food intake for each participant.

6.2.4 EARLY TERMINATION VISIT

In the case of early termination, an interview will be conducted with the participant to determine reasons for termination if appropriate, and/or to determine if the data collected thus far may be useful.

6.2.5 Participant Testimonials

Once participants have completed their participation in the trial, they may be contacted by the Trial Team to see if they would like to provide a testimonial about their experience on the clinical trial. This may cover aspects including their experience using DnaNudge technology, aspects that they may have found useful, what is their opinion on DNA-based dietary guidelines, amongst others. Participants will consent to being contacted to see if they would like to provide a testimonial in the Informed Consent Form. Participant testimonials will allow for potential publication/media release either following the written consent of the participant. This may be in journals, newspapers, radio, interviews, TV, social media, websites, newsletters, marketing in print and online. When being asked to provide a testimonial, participants will be provided with a list of the above media types so that they can provide specific permission for which types of publication can be used. The testimonials will be published anonymously or with the participant's name, provided the participant has provided permission to do so.

6.2.6 SCHEDULE OF EVENTS TABLE

Activity	Trial Visit											Additional information
	1	2	3	4	5	6	7	8	9	10	11	
Send information documents to potential participants	x											All participants
Consent		x										
Screening visit to assess glucose regulation		x										
Randomisation		x										
Fill in food frequency questionnaire		x				x		x		x		
Trial commencement questionnaire			x									
Perform baseline measurements			x									
Take saliva sample for genetic testing (PCR)			x									
Initial consultation with dietitian				x								
Perform NudgeBox genetic test				x								
Provided with the DnaNudge App				x								Exploratory arm only
Follow-up phone-call with dietitian					x		x		x		x	Control and intervention arms
Perform 24-hour food recall				x	x		x		x		x	Control and intervention arms
6-week glucose regulation review						x						All participants
Take saliva sample for leptin testing			x			x		x		x		
12-week glucose regulation review								x				
Trial completion questionnaire								x		x		
26-week glucose regulation review										x		
Weight measurement			x			x		x		x		
Height measurement			x			x		x		x		
Body composition			x			x		x		x		
Waist measurement			x			x		x		x		
Blood pressure			x			x		x		x		
Saliva sample (s)			x			x		x		x		
Venous blood test			x			x		x		x		
OGTT			x			x		x		x		
Pregnancy test (if applicable)			x			x		x		x		
Follow-up clinical visits						x		x		x		

Table 1: Schedule of events table for a trial participant.

7 ADVERSE EVENTS

7.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject 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 hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject, or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

7.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

7.2.1 NON SERIOUS AES

All such events, whether expected or not, should be recorded.

7.2.2 SERIOUS AES

An SAE form should be completed and sent to the Chief Investigator within 24 hours. However, relapse and death, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the North of Scotland REC 1 where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Please send SAE forms to: Prof. Nick Oliver
Tel: +44 (0)20 3313 1593 (Mon to Fri 09.00 – 17.00)

7.3 EXPECTEDNESS

The probability of adverse events is expected to be low given the single-centre nature of the study with a small cohort. The randomisation and diet allocation algorithms have been rigorously tested for misallocation.

8 ASSESSMENT AND FOLLOW-UP

For each participant, follow-up measurements will be taken at 26 weeks. This will include all of the secondary outcomes outlined above. Participants will then complete a questionnaire (see Appendix 4) at the conclusion of the study to collect information regarding their experience of the intervention.

The study will be complete when the 26 week follow-up measurements are taken for the final participant in the trial.

9 STATISTICS AND DATA ANALYSIS

9.1 ANALYSIS DATASETS

Primary analyses will be conducted following the intention to treat (ITT) principle. All participants who are randomised into the study will be included in the ITT analysis. Such participants constitute the Full Analysis Set (FAS) for this study. In addition, the primary endpoint and the main secondary outcomes will also be analysed with the Per Protocol Analysis Set (PPS), which will consist of those subjects in the FAS who complete the study with no significant deviations from the planned protocol procedures.

9.2 THE NUMBER OF PARTICIPANTS

The total number of participants recruited into the study will be 180. All arms of the trial with have 60 participants each.

Participants will be recruited in cohorts of N = 60. Each member of a given cohort will be randomly allocated into one of the three arms of the study, as per the blocked randomisation method outlined below. The subdivision of the recruitment process into cohorts has been implemented in order to:

1. Allow sufficient time to perform the genetic analysis to prepare the DNA-based diet for the participants allocated to the intervention and the exploratory arms.
2. Ensure that the data collected is of sufficient quality. If data in the first cohort of 60 participants is not deemed to be of sufficient quality, appropriate changes will be made to ensure that useful data is obtained from subsequent trial participants.
3. To prevent delayed commencement of the study due to recruitment capacity.

Upon enrolment into the trial, each participant will be assigned to a study arm based on stratified, blocked randomisation. A block size of 15 will be employed, using the stratifications and allocation size according to age and gender shown in Table 2.

	Control arm	**Intervention arm**	**Exploratory arm**
Women (age =< 40)	5	5	5
Women (age > 40)	5	5	5
Men (age =< 40)	5	5	5
Men (age > 40)	5	5	5

Table 2: Allocation categories and size for the stratified blocked randomisation of participants.

9.3 POWER CALCULATION

Using baseline from the peer-reviewed study that examined the effect of a DNA-based diet on obese individuals (Arkadianos et al. 2007), at 90% power with an alpha of 0.05, 50 participants are required in each group to

demonstrate a between-group difference in effect size of -0.5 mmol/L as the primary outcome. This assumes a SD of the baseline to endpoint difference of 0.6 mmol/L. The sample size will be increased by 20% to 60 participants per arm of the study in order to compensate for participants lost to follow up (this includes the 10% risk that a given participant will have of becoming type 2 diabetic within a 12 month period due to their prediabetic state, and a subsequent addition to account for those participants who may be lost to follow up for other reasons).

9.4 ANALYSIS OF PRIMARY AND SECONDARY OUTCOME MEASURES

Data will be analysed after all primary and secondary outcomes have been recorded for the last participant. The primary analysis will be conducted under the ITT principle using modified analysis of covariance (ANCOVA) (Yang & Tsiatis 2001). Raw and adjusted mean differences in PFG at week 6 between the intervention and control arm will be presented with 95% confidence interval (95%CI). The adjusted mean difference will be estimated using a linear regression model of week 6 FPG to baseline PFG and treatment arm adjusted for age and sex. An interaction of baseline FPG with the indicator for treatment arm will be included. PFG will be log transformed and variables will be centred.

The primary null hypothesis is no difference in W6 FPG between the intervention and the control arm. It will be rejected if the adjusted 95%CI of the mean difference does not include 0. The robustness of the results will be tested using PP analysis and two alternative models (repeated measure mixed model and non parametric model). Missing data will be imputed using the multiple imputation with chain equation (MICE) method if there is no evidence against the assumption of data missing at random.

The secondary analysis will be conducted under the ITT principle. The ANCOVA will be used to compare mean difference in FPG, weight, BMI, mass, waist, fasting lipids and blood pressure at the different time points (W6, W12 and W26). In addition, mixed models will be used to compare the overall changes in these outcomes over the all follow up period. Adequacy of the models will be assessed through residual plots and Shapiro-Wilk tests for normality. Non-parametric methods may be used in case of severe departure from normality. In the addition, logistic regression model will be used to compare the proportion of participants with IGR between the two arms. Change in dietary habits will be analysed using polytomous regression.

For each of the primary and secondary outcomes, formal statistical analysis will be based on appropriate linear models. From each linear model, an estimate of the magnitude of the treatment effect i.e. the difference in mean outcomes between the control arm and intervention arm, will be derived, together with adjusted (least squares) means, 95% confidence intervals, and associated p-values. Initial exploratory analyses of these models will include relevant baseline covariates, including baseline values of the endpoint, and

all covariates that are statistically significant will be retained in the model for the purposes of deriving the final treatment effect outcomes. Baseline values of the endpoint will be retained in each model regardless of statistical significance.

All analyses will be conducted using two-sided tests and at a significance level of 5%.

9.5 EXPLORATORY ANALYSIS

Data collected from the exploratory arm will be used to examine exploratory hypotheses. In addition to the data collected from clinical measurements and questionnaires, this arm will also provide data via the App. The App will collect information regarding usage of features, food choice on the App, amongst other App utilisation parameters. This data will be used to explore:

- the efficacy of implementing a DNA-based diet using an App to improve glucose regulation in pre-diabetic patients
- the utility of the App to participants in both practical terms (e.g. saving time on food choices), and aspiration terms (encouragement to pursue a more healthy lifestyle).
- the aspects of the App that were the most/least effective
- how the App influences adherence levels of participants to a healthier lifestyle

Additional exploratory analyses may be performed using this arm, if the data suggest other effects of interest.

10 REGULATORY ISSUES

10.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the North of Scotland REC 1. The study must be submitted for HRA and CCC approval 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.

10.2 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.

Please see Appendix 5 for an example consent form.

10.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study. Following the consent of participants, a participant's GP may be informed of significant findings from physical examination or laboratory tests.

It will be necessary for DnaNudge Ltd to be transferred the following **anonymised** data:

- Genetic results
- Participant ID
- Year of Birth
- Ethnicity
- Sex

This is necessary in order for the algorithms of DnaNudge Ltd to compute the DNA-based dietary guidelines that will be provided to participants in the intervention and exploratory arms. For participants in the exploratory arm, it will also be required to provide participants with an App to provide the DNA-based dietary guidelines and to guide their grocery shopping choices. Of note, DnaNudge Ltd will not receive the names of participants, the only data that will be transferred will be anonymised.

The following is a statement from DnaNudge Ltd. regarding the security of the data which they will hold for the ASPIRE-DNA trial:

> **"How personal information is protected? For the data governance approval** Buccal mucosal cells samples from the inner side of the cheek and the oral cavity of the participant will be processed in a small genetic testing device (NudgeBox). The end-to-end processing of the sample includes inserting the swab sample into the disposable cartridge, placing the cartridge in the NudgeBox and extracting DNA from the swab sample (a process that can be controlled by the participant's mobile device), amplifying DNA, and analysing genetic results. The sample-containing cartridge is single use only and is disposed upon completion of the test. An additional 2ml saliva sample of the participant will be anonymised and processed with conventional DNA analysis methods (e.g. PCR, and RT-PCR analysis) at the Imperial College laboratory facilities. Both genetic analyses, carried out either by the NudgeBox or at the Imperial College laboratories, will not examine the whole genetic sequence of the participant, but will be focuses on isolated partial genetic information (i.e. single-nucleotide polymorphism SNPs) that will give us an insight in how a participant is metabolises food, how different nutrients affect his/her body, and what impact different ingredients have on the participant in the long term. To the best of our knowledge, the genetic results provided by our test will not be informative enough to trace the personal details of an individual; furthermore, we will not perform any test to trace personal details. The genetic results, which are encrypted and protected by the password set by the participant, will be stored in the participant's mobile device App. The genetic results are also anonymised, encrypted, and backed-up in a password-protected and secure cloud service (i.e. AWS) maintained by DnaNudge when the mobile device is connected to the internet. The genetic results are separated from other data in cloud storage and are secured by password-protected mechanism in which only the user can access his/her own results through the App using his/her log-in and participant ID.
>
> **Data deletion**
> If a participant would like to have all his/her data deleted, his/her account will be deleted in the cloud and he/she will not be able to access his/her App. All his/her data (such as genetic results and shopping records) and the back-up will be deleted in the cloud."

10.4 INDEMNITY

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

Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

10.5 SPONSOR

Imperial College London will act as the Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

10.6 FUNDING

This study will be funded via a clinical trial agreement between Imperial College London and DnaNudge Ltd. Participants will be reimbursed for any travel expenses incurred, or greater than normal grocery expenses during the course of the trial.

10.7 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 UK Policy Framework for Health and Social Care Research.

11 DATA HANDLING AND RECORD KEEPING

11.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into password-protected hard-drives. The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Data collected in the study will be stored in the Imperial Clinical Research Facility for the duration of the trial. A back up of the data will be transferred to the Centre for BioInspired Technology at Imperial College London on a weekly basis during the trial via a password-protected hard-drive. The hard-drive will be transported by designated individuals using the Imperial Shuttle Bus. After trial completion, the remainder of the data will be transferred to the Centre for Bio-Inspired Technology at Imperial College London. This includes the Site Files and Participant Notes. Both during and after the trial, anonymised genetic information, sex, ethnicity and year of birth will be transferred to the DnaNudge cloud to compute the DNA-based dietary guidelines.

Trial data, blood samples and saliva samples may be used in future research by research studies in Imperial College London and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. The information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

11.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 10 years after the completion of the trial. These documents should be retained for a longer period, however, if required by local regulations.

11.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, or GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the Trial Manager and the study Sponsor. Protocol deviations must be sent to the local IRB as per their guidelines. The site study staff is responsible for knowing and adhering to their IRB requirements.

12 STUDY MANAGEMENT

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the CI Prof. Nick Oliver, Co-Investigators Prof. Chris Toumazou and Dr. Maria Karvela, and Trial Manager, Dr. Caroline Golden. The Steering Committee will meet in person at least quarterly. The day-to-day management of the study will be co-ordinated by Dr. Caroline Golden.

12.1 TRIAL MONITORING

The monitoring plan has been devised and will be approved by the Sponsor before the trial begins.

12. 2. TRIAL Suspension

In the event of the Imperial College Healthcare NHS Trust issuing a suspension of all non-essential clinical research activity, such as during the outbreak of COVID-19 in early 2020, all clinical visits to the ICRF will be suspended for the duration of the suspension. Phone-call visits will continue to be performed, as advised from the ICRF. For any participants for whom their clinical visits were to fall within the suspension period, their intervention period will be extended by the length of the suspension and their visits will re-commence once clinical research has resumed.

13 PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded via a clinical trial agreement between Imperial College London and DnaNudge Ltd. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

REFERENCES

American Diabetes Association, 2015. (4) Foundations of care: education, nutrition, physical activity, smoking cessation, psychosocial care, and immunization. *Diabetes care*, 38 Suppl(Supplement_1), pp.S20–30.

Arkadianos, I. et al., 2007. Improved weight management using genetic information to personalize a calorie controlled diet. *Nutrition Journal*, 6(1), p.29.

Bao, J. et al., 2011. Improving the estimation of mealtime insulin dose in adults with type 1 diabetes: the Normal Insulin Demand for Dose Adjustment (NIDDA) study. *Diabetes care*, 34(10), pp.2146–2151.

Christensen, J.O. et al., 2004. Population-based stepwise screening for unrecognised Type 2 diabetes is ineffective in general practice despite reliable algorithms. *Diabetologia*, 47(9), pp.1566–1573.

Conn, J.W. & Newburgh, L.H., 1936. THE GLYCEMIC RESPONSE TO ISOGLUCOGENIC
QUANTITIES OF PROTEIN AND CARBOHYDRATE. *The Journal of Clinical Investigation*, 15(6), pp.665–671.

Diabetes Prevention Program Research Group, 2002. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. *The New England journal of medicine*, 346(6), pp.393–403.

Dodd, H. et al., 2011. Calculating meal glycemic index by using measured and published food values compared with directly measured meal glycemic index. *The American Journal of Clinical Nutrition*, 94(4), pp.992–996.

England, N., 2016. *NHS England Impact Analysis of implementing NHS Diabetes*
Prevention Programme, 2016 to 2021,

Gatineau, M. et al., 2014. *Adult obesity and type 2 diabetes*,

Gray, L.J. et al., 2010. The Leicester Risk Assessment score for detecting undiagnosed Type 2 diabetes and impaired glucose regulation for use in a multiethnic UK setting. *Diabetic Medicine*, 27(8), pp.887–895.

Hex, N. et al., 2012. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabetic Medicine*, 29(7), pp.855–862.

Kosaka, K., Noda, M. & Kuzuya, T., 2005. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. *Diabetes Research and Clinical Practice*, 67(2), pp.152–162.

Mathers, C.D. & Loncar, D., 2006. Projections of global mortality and burden of disease from 2002 to 2030. J. Samet, ed. *PLoS medicine*, 3(11), p.e442.

Neil Thomas, G. et al., 2010. A Systematic Review of Lifestyle Modification and Glucose Intolerance in the Prevention of Type 2 Diabetes. *Current diabetes …*, 6(6), pp.378–387.

NHS, Quality and Outcomes Framework (QOF) for April 2013 - March 2014

. *content.digital.nhs.co.uk*. Available at: http://content.digital.nhs.uk/catalogue/PUB15751 [Accessed September 6, 2017].

NICE, 2012. *Type 2 diabetes: prevention in people at high risk*,

Nielsen, D.E. & El-Sohemy, A., 2012. A randomized trial of genetic information for personalized nutrition. *Genes & nutrition*, 7(4), pp.559–566.

Pan, X.R. et al., 1997. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes care*, 20(4), pp.537–544.

Ramachandran, A. et al., 2013. Effectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modification in men in India: a prospective, parallel-group, randomised controlled trial. *The Lancet Diabetes & …*, 1(3), pp.191–198.

Ramachandran, A. et al., 2006. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia*, 49(2), pp.289–297.

Tuomilehto, J. et al., 2001. Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance. *The New England journal of medicine*, 344(18), pp.1343–1350.

UK, D., 2014. *Diabetes: Facts and Stats (v3)*,

Vega-López, S. et al., 2007. Interindividual variability and intra-individual reproducibility of glycemic index values for commercial white bread. *Diabetes care*, 30(6), pp.1412–1417.

Vrolix, R. & Mensink, R.P., 2010. Variability of the glycemic response to single food products in healthy subjects. *Contemporary Clinical Trials*, 31(1), pp.5–11.

WHO, 2016. *Global Report on Diabetes*,

World Health Organization, 2006. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia : report of a WHO/IDF consultation. *World Hearth Org*.

Yang, L. & Tsiatis, A.A., 2001. Efficiency Study of Estimators for a Treatment Effect in a Pretest–Posttest Trial. *The American Statistician*, 55(4), pp.314–321.

Zeevi, D. et al., 2015. Personalized Nutrition by Prediction of Glycemic Responses. *Cell*, 163(5), pp.1079–1094.

Appendix 1

ASPIRE-DNA Gantt Chart

Appendix 2

Commencement questionnaire

Appendix 3

Summary of equipment

Appendix 4

Completion questionnaire

Appendix 5

Consent form

Appendix 6

Participant information sheet

Appendix 7

GP letter

Appendix 8

Participant invitation letter

Appendix 9

Dietary Intervention Protocol CONTROL Arm

Appendix 10

Dietary Intervention Protocol INTERVENTION Arm

Appendix 11

Dietary Intervention Protocol EXPLORATORY Arm

Appendix 12

Food Frequency Questionnaire

Appendix 13

Sample Genetic Report