Post-GDM-DNA

Post delivery intervention in women with previous gestational diabetes mellitus to improve glycaemia

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STUDY COORDINATION CENTRE: Queen Charlotte's and Chelsea Hospital
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Protocol authorised by: **Date** **Signature**
Name
& Role

Study Management Group

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Study Management: Dr Edward Mullins

Study Coordination Centre

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Clinical Queries

Clinical queries should be directed to Edward Mullins who will direct the query to the appropriate person.

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:
Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
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Funder

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

This protocol describes the Post-GDM-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 Controlled Trial
GDM	Gestational Diabetes Mellitus

CI	Chief investigator
TMG	Trial Management Group
GCP	Good clinical practice
HbA1c	Glycated haemoglobin - monitors average blood glucose
HDL	High-density lipoprotein cholesterol
LDL	Low-density lipoprotein cholesterol
BP	Blood pressure

KEYWORDS

Weight, blood pressure, glycaemia, HbA1c, physical activity, wearable, postnatal, post-delivery, DNA, personalised

STUDY SUMMARY

TITLE Post-delivery intervention in women with previous gestational diabetes mellitus for weight loss, glycaemia and cardiovascular health
DESIGN Feasibility study
Allocation: RCT
AIMS To determine the feasibility of a post-delivery intervention to improve glycemia and cardiovascular function and promote weight loss in women who have had gestational diabetes.

OUTCOME MEASURES Primary outcome; Effect of intervention on HbA1c: difference in HbA1c between intervention arm and control arm measured at 12 weeks.
Secondary Outcomes;

- Adherence to intervention;
- Willingness to be randomised to post-delivery intervention;
- Process measures to evaluate patient experience of study and intervention;
- Participants' preferred time to commence the study, within the start date allowance of 6 weeks – 6 month post-delivery.
- Between-arm differences and within-arm differences to evaluate:
    - Effect of intervention on HbA1c at 12 and 24 weeks
    - Effect of intervention on weight and BMI at 12 and 24 weeks
    - Effect of intervention on systolic and diastolic blood pressure at 12 and 24 weeks
    - Effect of intervention on lipid profile (total cholesterol, HDL, LDL) at 12 and 24 weeks
    - Effect of intervention on physical activity at 12 and 24 weeks

POPULATION We will recruit 50 women aged 18-45 with previous gestational diabetes and randomise them to 1 of 2 arms to commence study at 6 weeks – 6 months post-delivery. Women starting the study at 13 weeks post-delivery will have their routine post-delivery HbA1c act as baseline HBA1c.
ELIGIBILITY Pregnant women with gestational diabetes (women will be given the option to start the study between 6 weeks and 6 months post-delivery) or women who have given birth in the last 12 months and had gestational diabetes during that pregnancy; aged 18-45; and access to a smartphone with an operating system of iOS 9.0 or above, or Android 5.0 or above.

DURATION Study duration: 1/4/21-1/9/22. Participant duration: 24 weeks

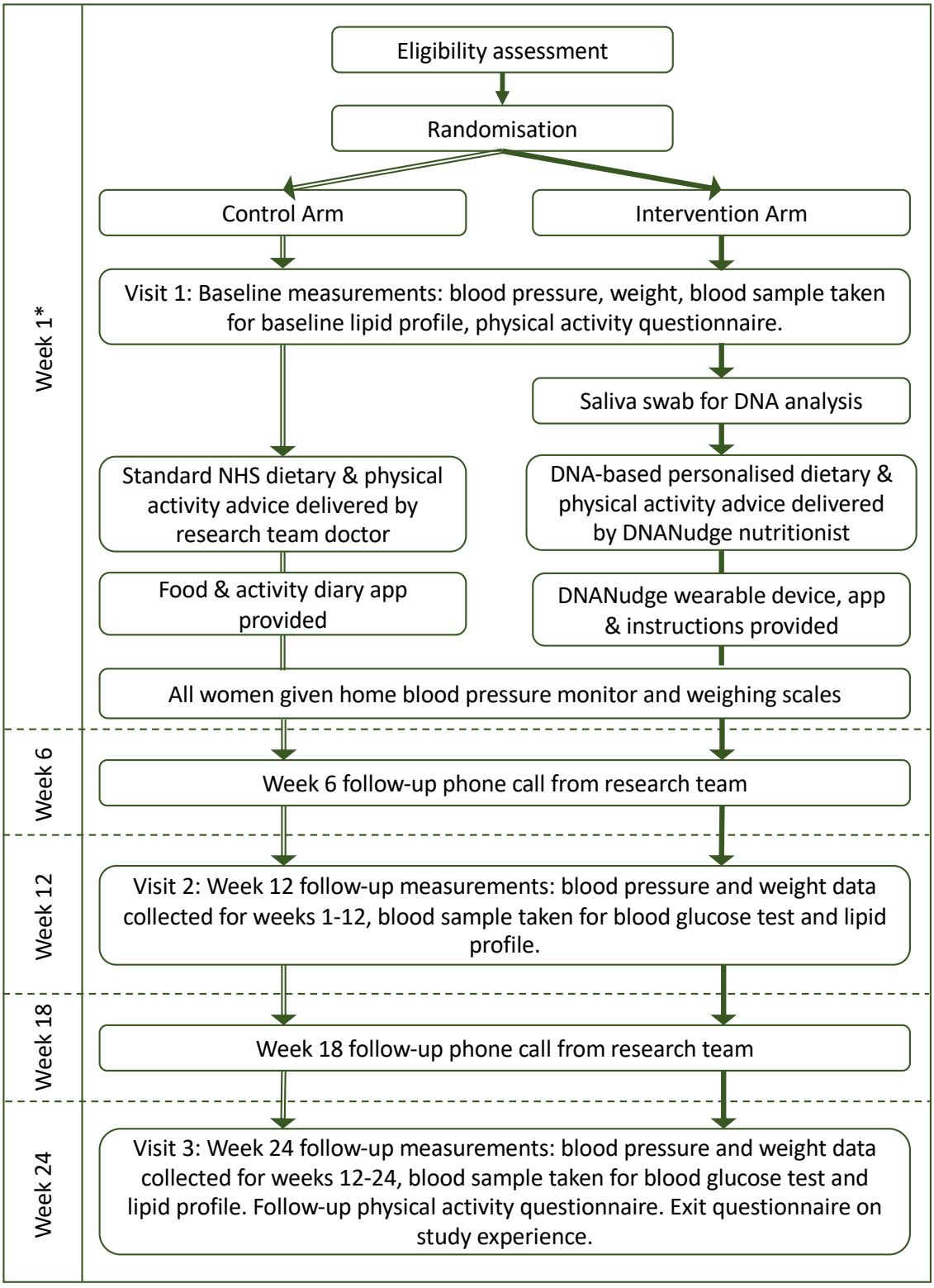

Figure 1: Study design. *Intervention starts at week 1 and coincides with routine NHS postnatal check on blood glucose = baseline blood glucose (at 13 weeks post-delivery).

1. INTRODUCTION

1.1 BACKGROUND

In the UK, 60% of women and 28% of children are overweight or obese, children's overweight and obesity is associated with that of their parents (1). Overweight and obesity are associated with cardiovascular disease, diabetes and cancer, the leading causes of death (prior to the COVID-19 pandemic) for women in the UK and are associated with increased risk of death from the COVID-19 pandemic (2). Overweight and obesity are also associated with nearly all major pregnancy complications, including pre-term birth, stillbirth, gestational hypertension, pre-eclampsia, gestational diabetes and maternal death (3). Pre-conception BMI is also associated with offspring BMI.

Gestational diabetes (GDM) affects 2-18% of pregnancies and is associated with stillbirth, pre-term delivery, macrosomia, birth trauma, neonatal hypoglycaemia and offspring overweight and obesity(4). Women with GDM have 10 times the risk of those not affected by GDM of developing type-2 diabetes in the 10 years after delivery(5). As such, the post-delivery period represents a unique point for secondary prevention – of recurrent GDM- and primary preventions of type-2 diabetes in a high-risk group.

GDM often co-exists with other pregnancy complications, including hypertension in pregnancy.

No major study has yet examined the use of a post-delivery or inter-conception personalised dietary and exercise intervention using DNA-based dietary advice.

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 in participants with ≥2 unsuccessful attempts to lose weight, a personalised, DNA-based diet saw 19/26 (73%) participants maintain weight loss at 300 days compared with 7/22 (32%) of participants who were given standard Mediterranean dietary advice. Additionally, it also had a dramatic effect on the fasting blood glucose levels of participants (10). Notably, the DNA-based nutritional advice was not tailored to be a weight loss program. 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 (11). 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 FOR CURRENT STUDY

General advice for women with previous GDM planning pregnancy exists on the NHS website, which describes the benefits of taking folic acid, smoking and alcohol cessation, keeping to a healthy weight, vaccinations and management of long-term conditions. No specific intervention is recommended for this group of women.
Consulting our Pre-conception PPI group, funded by an Imperial NIHR BRC PPI grant, we have found that women tend to use a variety of pregnancy planning or pre-conception information, the majority of which is obtained from internet searches, social media and their peers. Women planning pregnancy reported they would be willing to engage in a pre-pregnancy intervention using 'natural' interventions rather than medication, small changes to their daily routine dietary advice which do not focus on weight loss *per-se* but rather a personalised approach to nutrition.
Our group has previous conducted a cohort study recruiting women planning pregnancy, recruitment of 530 women who had 356 pregnancies and 218 deliveries at Queen Charlotte's hospital (9).
We propose to evaluate the feasibility of a post-delivery intervention in women who have had GDM using a novel wearable device which uses focussed genetic analysis of the wearer to allow personalised decisions on food and lifestyle improvement to be made by the wearer. We will also evaluate its effect on participants' weight, physical activity and cardiovascular function.

2. STUDY OBJECTIVES

Objectives

To assess:
1. Effect of intervention on HbA1c at 12 and 24 weeks
2. Adherence to intervention
3. Participants' preferred time to commence the study, within the start date allowance of 6 weeks – 6 month post-delivery.
4. Qualitative data on how participants found post-delivery intervention
5. Effect of intervention on weight at 12 and 24 weeks
6. Effect of intervention on systolic and diastolic blood pressure at 12 and 24 weeks
7. Effect of intervention on lipid profile (total cholesterol, HDL, LDL) at 12 and 24 weeks
8. Effect of intervention on physical activity at 12 and 24 weeks

3. STUDY DESIGN

We will conduct a feasibility study for an open-label, randomised, controlled trial of a personalised post-delivery intervention (*DNA Nudge*) to improve weight, glycaemia and cardiovascular function in women with previous GDM.

The study is designed to be remote, to enable the study to begin and continue in the pandemic and minimise barriers to recruitment. Study participants will be provided with equipment and instructions to collect samples and measurements at home. Contact with the research team will be over telephone or Microsoft Teams video call.

We will advertise in diabetes antenatal clinics using word-of-mouth, posters, social media and on departmental emails at Imperial College Healthcare NHS Trust or Imperial College

for women with current/previous GDM aged 18-45. We will recruit via Twitter, email and in-person encounters.

We will randomise women to 1 of 2 arms:
Arm 1: Standard dietary and physical activity advice as per NICE guidelines at week 1 (active control arm; n = 25)
Arm 2: DNA-based personalised dietary and physical advice delivered by DNA Nudge dietician at week 1 and by DNA Nudge wearable and app for weeks 1-24 (intervention arm; n = 25)

Women not randomised to DNA Nudge will be provided with an activity app/wearable device (Fitbit) to monitor daily step count. All women will be provided with a home BP monitor and weighing scales.

Week 1
Eligibility assessment, consent, randomisation, IPAQ questionnaire, baseline BP and weight, blood sample collected for baseline lipid profile.

Some women will begin the study at 13 weeks post-delivery and coincide with the routine postnatal HbA1c for women with GDM. The routine post-delivery HbA1c will be baseline HbA1c for this study. For women who commence the study outside the 13 weeks post-delivery window, a finger prick blood sample will be used for a baseline HbA1c test.

Women in the control arm will be given standard dietary and physical activity advice by the research team, in line with NICE guidelines.

Women in the DNA Nudge arm will provide a cheek swab for DNA analysis, carried out by DNA Nudge. They will be given personalised dietary advice by a DNA Nudge dietician, and be provided with DNA Nudge wearable, app and instructions.

Week 6:
Telephone/video-call follow-up to check ongoing willingness to participate and assess adherence.

Week 12:
Collect weight and BP data from weeks 1-12, collect blood sample for HbA1c and lipid profile. Check ongoing willingness to participate and assess adherence.

Week 18:
Telephone/video-call follow-up to check ongoing willingness to participate and assess adherence.

Week 24:
Collect weight and BP data from weeks 12-24, follow-up IPAQ questionnaire, collect blood sample for HbA1c and lipid profile, return devices and collect usage data from DNA Nudge. Qualitative questionnaire to explore intervention experience.

4. PARTICIPANT ENTRY

4.1 PRE-RANDOMISATION EVALUATIONS Women replying to our adverts will be assessed for eligibility by questionnaire.

4.2 INCLUSION CRITERIA Pregnant women with gestational diabetes (women will be given the option to start the study between 6 weeks and 6 months post-delivery) or women who have given birth in the last 12 months and had gestational diabetes during that pregnancy;, aged 18-45, access to a smartphone with an operating system of iOS 9.0 or above, or Android 5.0 or above [CB: operating systems correct as of 23/03/21]

4.3 EXCLUSION CRITERIA Diabetes outside of pregnancy (diagnosis of type 1 or 2 diabetes; or HbA1c 48 mmol/mol or above). Health contra-indications to moderate-vigorous exercise. Planning pregnancy during the study period or become pregnant during the study period. Cancer, kidney disease, liver disease, or pancreatitis. Have had gastric bypass surgery or similar weight loss surgery.

4.4 WITHDRAWAL CRITERIA If women withdraw consent or become pregnant during the study period, the data collected to that point will be retained, they will be withdrawn from the study and we will request permission to collect safety outcomes from them.

If they agree to participate, consent will be gained and stored in the site file.

5. RANDOMISATION AND ENROLMENT PROCEDURE

This will be an open-label trial. Randomisation will be in a 1:1 ratio by serially numbered, sealed, opaque envelopes, which will be prepared by a member of staff outside the research team.

Randomisation will be stratified by breastfeeding status (yes/no) at the time of recruitment.

5.1 RANDOMISATION OR REGISTRATION PRACTICALITIES Sealed envelopes will kept in a locked filing cabinet in a research office at Queen Charlotte's and Chelsea Hospital. Randomisation will occur in person at the QCCH site.

5.2 UNBLINDING This will be an open-label study. Data analysis will be study-arm blinded, unblinding will occur after completion.

6. TREATMENTS

6.1 TREATMENT ARMS

Arm 1: Control group. Women will be supplied with an app/wearable device (Fitbit) to monitor physical activity, weighing scales and a home blood pressure monitor. They will be asked to record their resting blood pressure, resting heart rate and weight twice a week for 24 weeks.

Arm 2: DNA-based intervention. In addition to the BP and weighing procedures for the control group, women will be supplied with a DNA Nudge wearable device and the accompanying app. They will take a cheek swab for genetic analysis and this will be processed in accordance with the manufacturer's guidelines.

7. ADVERSE EVENTS

No adverse events are anticipated in this study.

7.1 DEFINITIONS

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

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 participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires 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 in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant 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 faxed to the Chief Investigator within 24 hours. However hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

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

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie 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
jrco@imperial.ac.uk
CI email (and contact details below)

Please send SAE forms to: edward.mullins1@nhs.net Tel: 020 759 42104 (Mon to Fri 09.00 – 17.00)

8. ASSESSMENT AND FOLLOW-UP

Participants will be followed-up for the 24 weeks of the study.

8.1 LOSS TO FOLLOW-UP

Participants lost to follow-up will be flagged by the research team and removed from the study.

8.2 TRIAL CLOSURE

This study will be closed after the last patient completes their week 24 visit and data entry is completed.

8. STATISTICS AND DATA ANALYSIS

A study master list with patient identifiable information will be stored on a password-protected NHS computer in a locked research office at Queen Charlotte's and Chelsea Hospital, accessible only to the research team. This will match patient identifiable information with their study identification number. This study identification number will be used for the study database, which will be a cloud-based Excel database, which will be password protected and accessible only by the research team.

If any health conditions are discovered incidentally during the study they would be discussed with the participant immediately and their consent sought to share the information with their GP for the arrangement of their ongoing healthcare.

The study sample is 50 participants, 25 in each arm. The sample size has been based on guidance from the NIHR on pilot/feasibility studies (12) and the literature that it references that concludes that pilot studies should look for a sample size of at least 50 (13).

Data will be analysed after all participants have completed the 24 study weeks and all data is collected. Patient demographics will be presented as median/range or as categorical data where appropriate. We will evaluate primary and secondary outcomes using descriptive statistics. Between group comparison will be made using logistic regression.

Data and all appropriate documentation will be stored for 10 years after the completion of the study in accordance with ICHT guidance.

10. MONITORING

10.1 RISK ASSESSMENT

This study uses a commercially available DNA analysis product used in-keeping with the manufacturer's guidelines. This study recommends exercise in accordance with the UK Chief Medical Officer's recommendations. This study supplies commercially available products for home blood pressure, weight and activity monitoring. As such it is considered low risk.

11. REGULATORY ISSUES

11.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Brent Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. 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.

11.2 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.

As this study follows a remote design, the informed consent process will be either face to face or using an online eConsent platform provided by REDCap.

11.3 CONFIDENTIALITY

Participants' identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Blood and saliva samples will be anonymised. All samples will be destroyed during sample analysis. Research data and consent forms will be kept for 10 years after study completion.]

It will be necessary for DnaNudge Ltd to be transferred the following anonymised data:
• Genetic results
• Participant ID
• Year of Birth
• Sex
This is necessary in order for the algorithms of DnaNudge Ltd to compute the DNA-based dietary guidelines, the app and the wearable device that will be provided to participants in the intervention arm. Of note, DnaNudge Ltd will not receive the names of participants, the only data that will be transferred will be anonymised.

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. The genetic analysis, carried out by the NudgeBox, 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.

If a participant would like to have all their data deleted, their account will be deleted in the cloud and they will not be able to access their App. All their data (such as genetic results and shopping records) and the back-up will be deleted in the cloud.

11.4 INDEMNITY
Imperial College London holds Indemnity and insurance cover which apply to this study
11.5 SPONSOR
Imperial College London will act as the main Sponsor for this study.
11.6 FUNDING
DNA-Nudge are funding this study.
11.7 AUDITS AND INSPECTIONS
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.

12. TRIAL MANAGEMENT

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated through the Queen Charlotte's and Chelsea Study Coordination Centre.

The TMG, the PI, CI and research midwife, will meet monthly to discuss recruitment and issues with the study and as required by telephone.

13. PUBLICATION POLICY

The study will be published in peer review journals and at relevant conferences. It will be made available on Imperial College London's open access Spiral server. Results will be emailed to participants who indicate they would like to receive them.

14. REFERENCES

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