PROTOCOL

Assessing metabolic profiling strategies for nutritional management of cardiovascular disease risk

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Sponsor

Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) 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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PROBLEMS RELATED TO THIS TRIAL SHOULD BE REFERRED TO PROFESSOR GARY FROST
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1. STUDY SUMMARY

TITLE Assessing metabolic profiling strategies for nutritional management of cardiovascular disease risk

AIMS To evaluate the applicability of providing metabolically-informed personalised dietary advice to help free living people at risk of Cardio Vascular Disease (CVD) to change their dietary habits.

Study 1 aims:

- Build a multiplatform mathematical model to establish the level of adherence of individuals to dietary recommendations based on comprehensive molecular phenotyping of urine and blood plasma.
- To investigate variability in response to the same dietary interventions.
- To identify metabolic patterns at baseline that are predictive of an individual's response to diet in terms of changes in metabolism.

Study 2 aims:

- Establish the response of free-living individuals at risk of CVD to dietary interventions by determining the relationship of the metabolic profiles with traditional metrics of CVD risk including cholesterol, BMI and blood pressure.
- Evaluate the clinical benefit of delivering metabolically-driven personalised nutritional advice, to enhance the support given to people at risk of CVD who follow a healthy diet compared to standard dietary advice.
- Assess whether the use of metabolic profiling to tailor healthy eating interventions improves compliance to dietary recommendations.
- Assess if misreporting of dietary habits of individuals at CVD-risk declines when they are aware that the dietitian will receive accurate information on participant's adherence to diet via use of metabolic profiling data.

DESIGN **STUDY 1:** Participants will be asked to attend the NIHR/Wellcome Trust Imperial CRF at Hammersmith Hospital for 5-days, in two occasions, with a minimum of 2 weeks between both visits. Each week, in a randomized order, participants will receive a diet with different levels of compliant with NICE-guidelines for the management of CVD-Risk:

Week 1: 25% compliance to dietary guidelines
Week 2: 100% compliance to dietary guidelines

STUDY 2: Participants will be asked to attend a randomized control trial aiming to change dietary habits during a 12-week period. This will take place at the NIHR/Wellcome Trust Imperial CRF. A target group will received personalised dietary advice based on knowledge of urine and plasma metabolic profiles from samples collected at clinic every 2-weeks in addition to 24-h food diaries. A control group will mirror the intervention group but will receive standard NICE-guideline dietary recommendations for the nutritional management of people at risk of CVD.

POPULATION We will be studying male and female of all ethnicities, at risk of CVD aged between 30 and 65 years.

ELIGIBILITY Men and women with a body mass index of 20-35 BMI of ≥25 and <35kg/m2, systolic BP≥140 or diastolic BP≥90 mmHg or under antihypertensive medication, LDL-cholesterol ≥

4.14 mmol/l and HDL-cholesterol ≤1.03 mmol/l (men) or ≤1.29 mmol/l (women), family history of premature CHD and waist circumference >102cm in men or > 88cm in women, aged between 30 to 65 years will be eligible to this study.

DURATION **STUDY 1:** 38 days (including pre-study visit)
STUDY 2: 14 weeks (including pre-study visit)

2. INTRODUCTION

Cardiovascular diseases (CVD) account for approximately a third of the total deaths worldwide (1). It is universally acknowledged that a major cause of non-communicable diseases (NCD), particularly CVD, is lifestyle, with diet being a major contributing factor.

At present, the main cornerstone of the UK government's policies to reducing CVD-risk is to encourage people to adopt healthier dietary habits on the basis of NICE-guidelines (2-4). However, although the adoption of healthy dietary patterns such as Dietary Approaches to Stop Hypertension (DASH) (5), the Mediterranean (6) has unequivocally been shown to reduce CVD risk (7), the adoption of these diets has not been extensive enough to impact sufficiently on heart disease statistics and CVD remains the leading non-communicable diseases worldwide Even in a controlled environment it has been demonstrated that the response to standardised dietary change varies, suggesting there is individual variability in response to diet (8). Data from both rodent models and humans suggest that this variability in dietary response is partially attributable to gene-diet interactions and indeed, interpersonal variability has been observed in the amount of weight loss induced by caloric restriction (9) and in the postprandial response to identical meals (10). However, other evidence points to modifiable factors such as changes in body weight (11) or compositional variation in the gut microbiota (12) driving the variation in inter-individual differences in dietary response.

This highlights the problem of compliance to one-size-fits-all dietary advice and is further compounded by the fact that the use of self-reported food intake, wherein the prevalence of misreporting is estimated to be between 30-88% (13). This compromises understanding of the impact of dietary changes on disease prevention.

Moreover, efforts to enhance the understanding of the impact of dietary changes by improving strategies to measure changes in population's habits such as The Healthy Eating Index (HEI) are insufficient because they rely on self-reported food intake. For example, with present dietary tools it is difficult to assess if lack of effect of dietary change at a population or individual level is due to there being no physiological effect, poor compliance to the recommended dietary change or high inter-individual variability in response to a particular diet.

Recent data from the "EU Food for Me" project shows that personalised dietary advice has a greater impact on dietary change than general dietary advice. However, individualising dietary advice generally relies on information gained from dietary recall, which is known to be flawed. Significant advances have been made recently in developing a novel methodology based on metabolic profiling, capable to provide an accurate and objective understanding of dietary intake in an individual (14) which can be used to enhance dietary counselling. At the present time it is not possible for an individual to assess dietary change and outcome is based on surrogate biomarkers of disease endpoint that may be relatively insensitive to change in the short term

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STUDY DESIGN

Aims:
Study 1:
1. Build a multiplatform mathematical model to establish the level of adherence of individuals to dietary recommendations based on comprehensive molecular phenotyping of urine and blood plasma.
2. To investigate variability in response to the same dietary interventions.
3.To identify metabolic patterns at baseline that are predictive of an individual's response to diet in terms of changes in metabolism.

Study 2:
1. Establish the response of free-living individuals at risk of CVD to dietary interventions by determining the relationship of the metabolic profiles with traditional metrics of CVD risk including cholesterol, BMI and blood pressure.
2. Evaluate the clinical benefit of delivering metabolically-driven personalised nutritional advice, to enhance the support given to people at risk of CVD who follow a healthy diet compared to standard dietary advice.
3. Assess whether the use of metabolic profiling to tailor healthy eating interventions improves compliance to dietary recommendations.
4. Assess if misreporting of dietary habits of individuals at CVD-risk declines when they are aware that the dietitian will receive accurate information on participant's adherence to diet via use of metabolic profiling data.

Methodology:
Study 1: Participants will attend to undergo two 5-day interventions with a minimum of 2 weeks between both visits, with the administration of healthy dietary intervention, compliant with current dietary guidelines for risk reduction of CVD and a diet associated with high risk of CVD according to current UK dietary intake.
Study 2: Participants will attend a randomized control trial for free-living participants at risk of CVD aiming to change dietary habits during a 12-week period. The control group (n=67) will receive standard advice using NICE-guidelines based on dietary intake recorded by food diaries. The target group (n=67) will mirror the control group but will receive personalised dietary advice based on their metabolic response to the diet measured by NMR and MS-based profiling.

Participants:
Study 1: 20 male and female volunteers of all ethnicities, at risk of CVD aged between 30 and 65 years.
Study 2: 134 male and female volunteers of all ethnicities, at risk of CVD aged between 30 and 65 years.

Pre-randomisation evaluations for study 1 and study 2
All potential participants will have a brief initial telephone interview to assess their suitability for the study.

Health Screening Visit for studies 1 and 2

Participants will be screened by a member of the study tem at the NIHR/Wellcome Trust Imperial CRF at Hammersmith Hospital. Measurements of blood pressure, an electrocardiogram (ECG) and blood samples (for full blood count, HbA1c, urea and electrolytes, liver function tests and lipid profile) will be taken. Height, weight, hip and waist measurements will be recorded. All women of child bearing age will have a urinary pregnancy test.
Participants will have the opportunity to ask any questions they may have about the study and medical history, Family history of medical illness, and drug history will be discussed in order to confirm eligibility for the study.

Study visits

Pre-study 1 visit: 4-weeks before the study, volunteers will attend the NIHR/Wellcome Trust Imperial CRF at Hammersmith Hospital. During this visit, the resting energy expenditure of the individual will be assessed to enable the planning of a eucaloric diet by open loop indirect calorimeter. Volunteers will complete a list of food dislikes.

Randomisation for study 1: An independent researcher (i.e. not linked to the study) will be given the task of randomisation, which will be by sealed envelopes. This researcher will not be directly involved in the study and he will use opaque, sealed, sequentially numbered envelopes that each contained one of the two dietary interventions in a random order. The envelopes will be stored securely, away from the trial site, and opened in sequence by an investigator as each participant is enrolled.

Study 1: Participants will then undergo a 10 days study period. Participants will be asked to attend the NIHR/Wellcome Trust Imperial CRF at Hammersmith Hospital for 5-days (and 4 nights) on two occasions, with a minimum of 2 weeks between both visits and in a randomized order, participants will receive a diet with different levels of compliant with NICE-guidelines for the management of CVD-Risk:

Week 1: 25% compliance to dietary guidelines
Week 2: 100% compliance to dietary guidelines

Volunteers will attend the clinical unit on Monday (5pm) and they will bring one spot sample of feces and a 24 hour urine sample from the previous day. Participants will consume a reference dinner in order to provide some level of dietary standardisation before obtaining fasting urine and serum baseline samples on the 2nd day of the study. **On the 2nd day of the first week, the mixed meal tolerance test will be conducted. At 9 am fasting blood sample will be collected through an intravenous peripheral cannula (-10 and 0 min). Participants will then receive a standardized test drink containing 44.5g carbohydrate, 8.3 g fat and 12 g protein (Ensure Original Vanilla Nutrition Shake). Postprandial blood sample will be taken at 10, 20, 30, 45, 60, 90, 120 and 180 min through an intravenous peripheral cannula. 10ml blood will be taken at each blood sample, amounting to 100ml for the analysis of glucose, insulin, NEFA, GLP-1, PYY and SCFAs profiles.**

Blood pressure, BMI and waist circumference will be measured at the start and end of each diet. 24 hour and spots urine samples and feces will be collected during each 5-day study period. Saliva samples will be collected at the beginning of the first visit. 32 ml of blood will be collected on each study visit (13 ml at the beginning and at the end of each visit and 7ml on the 4th day of each study) via venepuncture. DNA samples will be taken to perform genomics and or metagenomics analysis; however, we will not assess any genes related with any disease or risk of disease. The urine, feces, saliva and blood samples will be subjected to metabolic profiling analysis and other methodologies (e.g. whole genome genetics and epigenetics, transcriptomics, targeted proteomics) for the measurements of blood hormones and metabolites to:

1. Generate a comprehensive metabolic profiles of urine, serum and faecal sample of volunteers at risk of CVD based on an in-patient randomised cross-over clinical trial (CCT) with 100% compliance to a very healthy and a very unhealthy diet.
2. Build a multiplatform mathematical model to establish the level of adherence of individuals at risk of CVD to dietary recommendations based on comprehensive molecular phenotyping of urine and blood serum.
3. Investigate variability of individual's responses to both dietary interventions.
4. Identify metabolic patterns at baseline that are predictive of an individual's response to diet in terms of changes in metabolism.

Pre-study 2 visit: Two weeks before the study, volunteers will attend the NIHR/Wellcome Trust Imperial CRF at Hammersmith Hospital. The aim of this visit will be to collect anthropometric data and the baseline samples: 24-h urine and faecal samples from the day before and blood and saliva samples upon arrival. Moreover, the resting energy expenditure of the individual by open loop indirect calorimeter will be measured. Volunteers will be randomly assigned to either the control or the target group.

Randomisation for study 2: An independent researcher (i.e. not linked to the study) will be given the task of randomisation, which will be by sealed envelopes. This researcher will not be directly involved in the study and he/she will use opaque, sealed, sequentially numbered envelopes that each contained "target group" or "control group". The envelopes will be stored securely, away from the trial site, and opened in sequence by an investigator as each participant is enrolled.

Study 2: Participants will attend a randomized control trial for free-living participants at risk of CVD aiming to change dietary habits during a 12-week period. Participants will be asked to attend the NIHR/Wellcome Trust Imperial CRF at Hammersmith Hospital for a few hours every two weeks during a 12-week period. The control group (n=67) will receive standard advice using NICE-guidelines based on dietary intake recorded by food diaries. The target group (n=67) will mirror the control group but will receive personalised dietary advice based on their metabolic response to the diet measured by NMR and MS-based profiling. Faecal samples and fasting urine and blood samples will be collected at the beginning and at the end of the 12 week period. Moreover, the C-reactive protein (CRP) and the HbA1c will be also measured at the beginning and at the end of the study. To monitor changes over time, all volunteers will attend the Clinical Unit 3-h after lunch, once every two weeks, for 12 weeks. Blood pressure, BMI and waist circumference will be measured at each visit. All the volunteers will provide from the day before 24-h urine, faecal samples and corresponding 24-h food diaries. Finally, spot Urine, and blood samples will be collected at each visit upon arrival at the unit. 65 ml of blood samples will be collected (15 ml at the beginning and at the end of the study and 7ml at each visit), via venepuncture. The urine, feces, saliva and blood samples will be subjected to metabolic profiling analysis and other methodologies (e.g. whole genome genetics and epigenetics, transcriptomics, targeted proteomics) for the measurements of blood hormones and metabolites. DNA samples will be taken to perform genomics and or metagenomics analysis; however, we will not assess any genes related with any disease or risk of disease.

Dietary Counselling: All volunteers will receive the same high quality dietary counselling aimed at supporting good compliance to the diet in both the control and the intervention group. This will include face-to-face meetings at weeks 1, 2, 4 and 8, which will set and review dietary progress. This will be undertaken by Prof Frost's team who have 25 years of experience on clinical dietetic intervention. The methodology will reflect current dietetic counselling using individualised targets based on risk factor profile and dietary assessment. In addition, volunteers from the intervention group will receive enhanced personalised dietary advice using urinary and plasma metabolic profiles taken at each visit after obtaining patient consent. Prior to each visit, the dietitian will receive information on each participant's adherence to

diet and changes in the level of biomarkers according to the "metabotracker" report. For example, if the metabolic profile indicates low prolinebetaine levels, which is related to low citrus fruit intake, then increasing citrus fruit intake will become a key dietary target. At the review visits, in weeks 4 and 8, annotated metabolic profiles from week 2 and 6 will be used to encourage change. The dietitian will also be able to assess adherence to the diet based on the mathematical model and to use this information to engage and educate participants.

4. PARTICIPANT ENTRY

PRE-RANDOMISATION EVALUATIONS

Potential participants will first have a short telephone interview to assess their suitability for the study. Potential participants will then be interviewed and screened by one of the team members at the pre-study visit. They will have blood tests and height, weight, hip and waist measurements. They will have an electrocardiogram (ECG). All women of child bearing age will have a urinary pregnancy test.

INCLUSION CRITERIA

Study 1 & Study 2:

Male and female participants of all ethnicities, at risk of CVD using the following criteria: aged 30-65 years, BMI of ≥25 and <35kg/m2, systolic BP≥140 or diastolic BP≥90 mmHg or under antihypertensive medication, LDL-cholesterol ≥4.14 mmol/l and HDL-cholesterol ≤1.03 mmol/l (men) or ≤1.29 mmol/l (women), current smoker, family history of premature CHD and waist circumference >102cm in men or > 88cm in women.

EXCLUSION CRITERIA

- Have been involved in any other study during the 12 weeks
- Weight change of ≥ 3kg in the preceding 3 months
- Substance abuse
- Excess alcohol intake
- Taken any dietary supplements in the last 6 months
- Pregnancy
- Diabetes
- Cancer
- Gastrointestinal disease e.g. inflammatory bowel disease or irritable bowel syndrome
- Kidney disease
- Liver disease
- Pancreatitis
- Any other chronic illness or being diagnosed with HIV
- Use of medications likely to interfere with energy metabolism, appetite regulation and hormonal balance, including: anti inflammatory drugs or steroids, antibiotics, androgens, phenytoin, erythromycin or thyroid hormones.

Subjects with the above conditions would have an altered pattern of hormones and inflammatory molecules because of their disease process and would therefore give us confounding or misleading results.

WITHDRAWAL CRITERIA

- The safety of the study participants takes priority. Any significant adverse event (as assessed by the researchers) will halt the study and the ethics committee and sponsor will be informed as per standard protocol. All adverse events will be recorded and investigators will review each adverse event as it arises. In addition, participants will be free to withdraw at any time and are not required

to give a reason. Finally, if participant's loose capacity to consent they and their data will be immediately excluded from the study.

5. PHARMACOVIGILANCE

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

Serious Adverse Event (SAE): Any untoward and unexpected medical occurrence 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 was more severe.
- requires hospitalisation, or prolongation of existing inpatients' hospitalisation.
- results in persistent or significant disability or incapacity
- is a congenital abnormality 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

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.

Non-serious AEs

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

Serious AEs (SEAs)

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

All SAEs should be reported to the xxxx Research Ethics Committee 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.

Local investigators should report any SAEs to the sponsor and their Local Research Ethics Committee and/ or Research and Development Office.

Contact details for reporting SAEs
Fax 020 838 33142, attention Dr Isabel Garcia-Perez
Please send SAE forms to Dr Isabel Garcia-Perez
Tel: 07704344683 (Mon to Fri 09.00- 17.00)

6. ASSESSMENT AND FOLLOW-UP:

No follow up visit or monitoring of the participant will be needed once participants complete either study 1 or study 2.

7. STATISTICS AND DATA ANALYSIS

Study 1: The power calculation is based on the mathematical model from my previous fellowship (Garcia-Perez *et al.* (2017) Lancet Diabetes and Endocrinology), using the same dietary methodology also proposed here. In order to calculate the effect size, I used the excretion of a previously identified specific urinary biomarker (hippurate) as a result of increasing fruit and vegetable intake. It was shown that a rise in urine concentration of 3.48 mmol/24-h of hippurate is the result of increasing fruit and vegetable intake, in a highly control environment, from 100g to 300g, with an SD 4.52 mmol/24-h. The resulting effect size is 0.772, and with an alpha of 0.05 and power of 0.90 it requires at least 16 volunteers (based on a one tailed difference between two dependent (paired) means). Allowing for a drop-out of 20%, I aim to recruit 20 volunteers.

Study 2: The use of global profiling data to inform clinical practice has not been done up to this point, therefore I will use the preliminary results from my previous fellowship (Garcia-Perez *et al.* (2017) Lancet Diabetes and Endocrinology) to estimate the number of participants. The outcome of this trial is twofold. The global aim is to make a difference towards changing eating habits. We expect a rise in urine concentration of 1.05 mmol/24-h of previously identified specific urinary biomarkers as a result of increasing fruit and vegetable intake from 100g to 180g and a urinary rise of 3.48 mmol/24-h as a result of increasing fruit and vegetable intake from 100g to 300g. With an SD of 3.48 mmol/24-h for increasing from 100 to 180g and an SD of 4.52 mmol/24-h for the increase from 100 to 300g, the resulting effect size was 0.603. Assuming a power of 0.90 and an alpha of 0.05, a total of 118 participants (n=59 per group) are required (two-tailed difference). Therefore, accounting for a 13% drop-out (based on drop-out rates reported in a recent publication on personalised nutrition interventions (C Celis-Morales et al. (2016) Int J Epidemiol), I aim to recruit a total of 134 participants.

The data will be analysed in the Section of Investigative Medicine and in the section of computational and systems medicine. No personal data will be present on any of the data. Individual anonymous study codes will be used for each volunteer on any samples/documents. All documents will be password protected.

Personal data, including identifiable data (e.g. consent forms), must be stored for 10 years following completion of the study according to the Imperial College London retention schedule.
Research data will be stored for 10 years as per other studies performed within the Section of Investigative Medicine on completion of the study as college policy. It will be archived as per Imperial College Standard operating procedures.

8. REGULATORY ISSUES

ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the 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.

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 such cases, the participants remain within the study for the purposes of follow-up and data analyses. All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment.

CONFIDENTIALITY
The Chief Investigator will preserve the confidentiality of participants taking part in the fulfil transparency requirements under the General Data Protection Regulation for health and care research
All electronic data about participants will be stored on Imperial College departmental database. This is a confidential computer system which requires a specific password for access and can only be viewed by authorised persons. It is a requirement that participants GP is informed of your participation in this study.

All staff involved in the study are aware of the requirements of the Data Protection Act and adherence to Good Clinical Practice (GCP). Subjects will be given a personal study code number which will be used throughout the study and in the analysis of data. The study codes will be kept on our departmental database. All personal data (PID data) will be stored as GCPR Requirements for 10 years after the study has finished. Specifically, PID data will be stored in locked filing cabinets in the Section of Investigative Medicine, Imperial College London. Only members of the Section of Investigative Medicine will have access to this.

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

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

FUNDING
This research project is part of a grant funded by the National Health Research Institute (NIHR).

Participants will be reimbursed for their time and for any inconvenience caused due to study 1 and/or 2.
STUDY 1: £400 will be awarded for completion of the entire study 1. Participants will be paid £200 for each of the 5-day in-patient interventions that they complete.
STUDY 2: £60 will be awarded for completion of the entire study 2. Participants will be paid £10 for each of 6 study visits that they complete.

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 and the NHS Research Governance Framework for Health and Social Care (2nd edition).

8. PUBLICATION POLICY

The findings of the research will be published in an open-access, peer-reviewed journal. In addition we will be collaborating with patient groups and professional groups to disseminate the findings via multiple media channels such as patient association publications, print and broadcast media.