Imperial College London

PROTOCOL

Exploring the Physiological role of propionate in glucose homeostasis in man.

Main Sponsor	Imperial College London
Funders	National Health Institute for Research
IRAS Reference	

Protocol authorised by

Dr. Gavin Bewick
Lecturer
Department of Investigative Medicine,
Hammersmith Hospital Campus, Imperial College,
6th Floor, Commonwealth Building,
Du Cane Road, London,
W12 0NN

Professor Gary Frost,
Professor of Nutrition and Dietetics,
Department of Investigative Medicine,
Hammersmith Hospital Campus, Imperial College,
6th Floor, Commonwealth Building,
Du Cane Road, London,
W12 0NN

Dr. Chong Lim
Department of Investigative Medicine,
Hammersmith Hospital Campus, Imperial College,
6th Floor, Commonwealth Building,
Du Cane Road, London,
W12 0NN

Short title

Oral propionate and glucose homeostasis.

Long title

Exploring the Physiological role of propionate in glucose homeostasis in man.

Study Management Group	
Chief Investigator	Dr. Gavin Bewick
Co-investigators	Prof. Gary Frost, Dr. Ian Godsland, Dr. Cong Lim
Study Management	Dr. Gavin Bewick, Prof Gary Frost, Dr. Chong Lim

Sponsor

Imperial College is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance Manager at:

Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
Room 5L10A
5th Floor, Lab Block
Charing Cross Hospital
Fulham Palace Road
London, W6 8RF
0203 311 0205
www.imperial.ac.uk/clinicalresearchoffice

Clinical Queries

Clinical queries should be directed to Dr. Chong Lim who will direct the query to the appropriate person.

PROBLEMS RELATED TO THIS TRIAL SHOULD BE REFERRED TO Dr. Gavin Bewick
g.bewick@imperial.ac.uk

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1. STUDY SUMMARY

TITLE Exploring the physiological role of propionate in glucose homeostasis in man.

AIMS To investigate the effect of propionate on pancreatic beta cell and determine the impact of diabetes risk on this function.

DESIGN **Study 1 Pharmacokinetic study:** we will determine the pharmacokinetic profile of orally delivered sodium propionate in healthy volunteers in order to determine time to peak plasma concentration of orally administered propionate. Initially a dose ranging study will be conducted followed by a full pharmacokinetic profile.

Study 2 Dose finding study: In an open label study we will determine the most dose dependently determine the role of sodium propionate on beta cell function in healthy volunteers using oral glucose tolerance tests.

Study 3 How does sodium propionate improve glucose tolerance: we will determine the mode of action of propionate on improving glucose tolerance by performing acute intravenous glucose tolerance tests in both healthy volunteers and healthy volunteers at risk of developing diabetes, i.e people with impaired fasting glucose (between 5.5-7mmol/l) and HbA1C between 5.7% and 6.5%.

ELIGIBILITY **Study 1:** Healthy men and women aged between 18 and 70 years with BMI between 20-25 kg/m2 and with normal fasting blood glucose (below5.5mmol/l and HbA1C less than 5.7% will be eligible to volunteer.

Study 2: As for Study 1.

Study 3: Cohort 1: Healthy volunteers aged between 30 to 70 with a BMI between 25-35 kg/m2 who do not have impaired fasting glucose and have HbA1c below 5.7%.

Cohort 2: Healthy volunteers aged between 30 to 70 years with a BMI between 25-35 kg/m2 who have impaired fasting glucose (between 5.5-7mmol/l) and HbA1C between 5.7% and 6.5%,

ENROLMENT **For all studies:** Participants will have an initial telephone interview to assess suitability for the study. If suitable the participant will be sent the study information sheet and a date for their enrolment visit agreed. Provision of the information sheet will be no less than 24 hours before the enrolment visit. At the enrolment visit the following measurements of blood pressure, an ECG and a blood test (for full blood count, urea and electrolytes, liver function tests, lipid profile, fasting glucose, HbA1C) will be taken. In addition, a general medical and social history will be taken. All female volunteers will

undergo a pregnancy test and will be informed that they should not plan to become pregnant whilst participating in the study.

TREATMENT Participants in the Intervention groups will receive enteric coated capsules containing sodium propionate. Participants in the Control group will receive sodium chloride in the same capsule formulation. For each study one dose per visit will be taken.

DURATION **Study 1:** Individuals participating in the dose ranging study will be asked to attend our clinical trials unit on a single day for a total of 8 hours. Volunteers taking part in the full pharmacokinetic study will be asked to attend the clinical trials unit twice for a total of 8h at each visit.

Study 2: Individuals will be asked to attend the clinical trials unit on 5 separate occasions each visit lasting 4 hours during which oral glucose tolerance testing will take place.

Study 3: All participants will be asked to attend the clinical trials unit to undertake an oral glucose tolerance test in order to screen for impaired glucose tolerance. Individuals will be asked to attend the clinical trials unit on two separate occasions each visit lasting 4 hours for the main part of the study.

MEASURES **Study 1:** The primary outcome will be peak plasma concentration of propionate coupled with determination of the elimination profile. Secondary outcomes will aim to understand the acute effects of propionate and will include plasma insulin, glucagon like peptide-1 (GLP-1), peptide yy (PYY), leptin, glucose and free fatty acid concentrations following propionate administration.

Study 2: Our primary outcome will be the insulinogenic index which is the increase in plasma insulin from 0-30mins during an oral glucose tolerance test. Secondary outcomes will be plasma concentrations of insulin, Glp-1, free fatty acids, PYY, leptin, glucose and free fatty acids will be measured during the oral glucose tolerance test.

Study 3: The primary outcome will be measurement of beta cell function as determined by the calculation of acute insulin response to glucose (the incremental area under the insulin profile from 0-10minutes following an intravenous glucose bolus) during an intravenous tolerance test.

Secondary outcomes will be plasma concentrations of insulin, GLP-1, PYY, Leptin glucose and free fatty acids.

2. INTRODUCTION

The NHS is estimated to spend £1million per hour (~ 10% of its yearly budget) treating diabetes and its complications. Despite advances in detection and treatment, the incidence of the disease is spiraling. Some 2.3 million people in the UK are already diagnosed and the estimated number of diagnosed and "hidden" cases of diabetes is expected to top 4 million by 2025. In those with pre-diabetes and high-risk groups, the progression towards diabetes is marked by deterioration in the function of beta-cells, the cells in the pancreas which secrete insulin in response to glucose. Maintaining tight regulation of plasma glucose by supporting beta cell function in diabetics has been shown to prevent the development of complications caused by long term hyperglycaemia. There is an urgent need for well tolerated oral therapies. We have identified a novel neutraceutical target, the short chain fatty acid (SCFA) propionate, for the prevention of diabetes in high risk groups. We aim to develop an enteric capsulation formulation to deliver propionate to the small intestine and determine its efficacy in the treatment of diabetes in man.

Short chain fatty acids.

The majority of ingested nutrients are digested by intestinal enzymes and absorbed in the upper gastrointestinal tract. However, in the colon, non-digestible carbohydrates (NDC's), which are resistant to small intestine enzymes, are digested by the colonic microbiota. Fermentation of these carbohydrates produces short chain fatty acids (SCFA), carboxylic acids with a chain length under six carbon atoms. The most abundant forms of SCFA are acetate, propionate and butyrate. A number of studies have shown that dietary supplementation with the naturally occurring NDC's inulin and oligofructose increases satiety, promotes weight loss and improves glucose homeostasis, in both animals and humans. However, the amount of NDC required to robustly produce this effect in man is associated with adverse gastrointestinal symptoms which lead to poor compliance.

How do SCFA's regulate glucose homeostasis?

Dietary NDC's are fermented by gut microbiota to produce SCFAs in the colon 10. Propionate increases the expression and release of the gut peptide glucagon like peptide-1 (GLP-1) in animals and humans. GLP-1 is a potent incretin, it has therefore been hypothesised that NDC's increase glycaemic control via the production of SCFA's in the colon. Recently, two orphan G-protein coupled receptors (GPCRs), free fatty acid receptors 2 and 3 (FFAR2 and FFAR3) have been shown to bind SCFA's. Localisation data suggests FFAR2 is the receptor which mediates SCFA release of gut hormones. However, our pilot data has suggested that propionate may also have a direct effect on the pancreas and beta cell function.

Propionate improves glucose stimulated insulin release from the beta cell.

Our preliminary data indicates the SCFA propionate augments glucose-stimulated insulin release from perifused mouse and human islets. We have also demonstrated that during intraperitoneal glucose tolerance tests (i.p. GTT) propionate improves glucose tolerance and significantly increases first phase glucose-stimulated insulin release. These findings suggest propionate may act both directly on the islet to increase insulin release and indirectly by

stimulating the release of the incretin GLP-1 from the gut. Propionate is therefore an ideal emerging target for the control of glucose homeostasis. Drugs designed to target FFAR2 are currently in development by a number of pharmaceutical companies but a drug suitable for use in man is likely to be at least ten years from production.

Propionate and glucose control in Man.

One attractive avenue for the treatment of diabetes is the use of dietary modification using existing natural substances, for example SCFA's. This strategy has the potential to be well tolerated, to achieve patient benefit in a shorter timeframe and be more cost effective than traditional pharmaceuticals. Sodium propionate exhibits very low toxicity levels in man. It is widely used in the food industry as a preservative (E281) in bread, cakes, pastries and cheese. In man propionate has been shown to be effective at improving glucose tolerance. Seven weeks of dietary supplementation with 7.5g of sodium propionate, delivered via an orally administered capsule, has been shown to decrease fasting serum glucose and maximum insulin increments during a glucose tolerance test in healthy human volunteers. Additionally, oral sodium propionate (3g/day) delivered in the diet via bread has been shown to improve plasma glucose disposal in a meal tolerance test both acutely and following one week of dietary supplementation. Our group has also demonstrated that the addition of 3g of sodium propionate to the diet decreases post prandial glucose following a high carbohydrate meal. These studies clearly demonstrate sodium propionate is well tolerated and effective at improving glucose handling in man. However, sodium propionate is very unpalatable indicating the only clinically viable route of administration is via capsule formulation. This would avoid the issue of palatability and be economically viable for widespread nutritional usage.

Design of enteric coated capsules for the delivery of propionate to the small intestine.

To overcome the very unpalatable taste of sodium propionate we developed a partnership with the Department of Chemical Engineering (CE) at Imperial College. This resulted in the development of a simple nutritional supplement based on a Hydroxypropylmethyl cellulose capsule (HPMC). HPMC capsules can be coated with enteric films which prevent gastric digestion and deliver drugs to targeted parts of the small or large bowel. For example, the enteric coating Eudragit® L 30 D-55 predominantly dissolves in the small bowel whereas Eudragit® FS 30 D-coated capsules dissolve in the proximal colon. Recently, we designed a simple encapsulation methodology to facilitate the delivery and the absorption of short chain fatty acids to the small intestine. The emulsified fatty acid is contained within an HPMC capsule with a Eudragit® L 30 D-55 coating which is resistant to the low pH's found in the stomach. We will use this delivery system to determine the effect of sodium propionate on beta cell function in man.

3. **STUDY DESIGN**

Consenting and Enrolment, all studies:

Volunteers will be recruited by advertising e.g posters, printed media and by approaching volunteers from previous studies who have given consent to be approached for recruitment to subsequent studies.

Potential participants will have a brief telephone interview to assess their suitability. Subsequently eligible participants will be sent the patient information sheet. Having read the patient information sheet and if they wish to continue with the enrolment process volunteers will be asked to attend the Hammersmith campus for a brief interview where any concerns regarding the study can address and formal consent taken. Participants will then be eligible to begin the screening process for each study.

Study 1

Aim: To calculate the pharmacokinetic profile of orally administered sodium propionate in healthy volunteers in order to determine time to peak plasma concentration.

Study methodology: Participants will first undergo a dose ranging study where they will be given a single dose of encapsulated sodium propionate. The plasma concentration profile of sodium propionate will be used to inform the design of a full pharmacokinetic profiling study. In this study participants will receive a low dose of sodium propionate and a second higher dose a week later.

Participants: 6 male or female volunteers, age 18-70 years, BMI 20-25 kg/m^2, with normal fasting glucose and HbA1C. Screen failures will be replaced.

Health Screening and enrolment Visit

Participants will arrive fasted from 8pm the previous evening. They will be clerked and examined by a research doctor. Measurements of height, weight, body fat content, blood pressure, an ECG and a blood test (for full blood count, urea and electrolytes, liver function tests, lipid profile, fasting glucose, HbA1C) will be taken. Screen failures will be replaced.

Dose ranging Study

Participants will arrive at the St John McMichael Centre (Hammersmith Hospital) on the day of the study having fasted from the previous evening. A canulae will be inserted into a peripheral vein and blood samples (10ml) will be taken at -10, 0, 15, 30, 60, 90, 120, 150, 180, 4h, 6h, 8h post administration of an oral dose of propionate (3g). Total volume of blood removed will be 120mls.

Pharmacokinetic profiling Study

Study Day1: Using the data from the dose ranging study a full pharmacokinetic study will be undertaken. Participants will arrive at the St. John McMichael Centre (Hammersmith

hospital) having fasted from the previous evening and a canulae will be inserted into a peripheral vein. Blood samples (10ml) will be taken at -10 and 0 post oral propionate administration (3g) then 4 samples will be taken during each of the absorption and early elimination phases, followed by further samples post peak for a total of 6 samples in this phase, over three half-lives. In total 120mls of blood will be drawn.

Study Day 2: At least a week following the first study day participants will be asked to attend a repeat visit at the St John Mc Michael Centre which will follow the same protocol as for study day 1 but participants will be given a 6g dose of propionate.

Blood samples will be analysed using the following methods:

- Propionate by Mass spectrometry
- Insulin, GLP-1, PYY, leptin and non-esterified fatty acids will be measured using commercially available kits.
- Glucose will be measured using a glucometer.

Study 2

Aim: To dose dependently determine if propionate augments beta cell function.

Study methodology: Participants will undergo a series of oral glucose tolerance tests (OGTT) following administration of propionate. Each participant will receive all doses of propionate and each study day will be separated by at least 1 week.

Participants: 30 healthy men and women aged 18-70, body mass index (BMI) 20-25 kg/m2, with normal fasting glucose and HbA1C.

Support for number of participants: A previous small study of the effects of propionate on glucose levels in humans identified a 47.4% reduction in glucose AUC over 2 hours following consumption of a standard 50 g carbohydrate load supplemented with propionate. Mean OGTT glucose AUC in a group of 514 healthy subjects was 40.8 mmol.min (SD 7.1 – unpublished data from the study described in Diabetic Medicine 2007;24:1269-1278). A 47.4% reduction in OGTT glucose AUC would result in a mean glucose AUC of 21.5. Using data from the same study, a mean insulinogenic index of 0.99 (SD 0.85) was observed, regression analysis estimated that a 47.4% reduction in glucose AUC would be associated with an increase in insulinogenic index of 0.73 SD. This can be detected as significant at $p<0.05$, with 80% power using 30 in each group. Screen failures will be replaced.

Health Screening and enrolment Visit

Participants will arrive fasted from 8pm the previous evening. They will be clerked and examined by a research doctor. Measurements of height, weight, body fat content, blood pressure , an ECG and a blood test (for full blood count, urea and electrolytes, liver function tests, lipid profile, fasting glucose, HbA1C) will be taken. Screen failures will be replaced.

Study Day 1-5 Participants will undergo a frequently sampled oral glucose tolerance test (OGTT) to detect changes in insulin sensitivity and beta cell function. Participants will be asked to refrain from strenuous exercise and alcohol on the day prior to each study. They will be asked to eat a standard meal of your choice before the study (e.g. ready-made meal) and then be required to fast overnight.
They will be asked to come to the Clinical Investigations Unit at Hammersmith Hospital at 8:30am, having fasted from 8pm the previous day. A small plastic tube (cannula) will be inserted into their arm and a blood sample taken. This will be in place for the duration of the study day. Baseline blood samples will be taken at -30 and -10mins before the participant will take capsules containing either sodium chloride (placebo control) or sodium propionate. They will then consume a 250 ml drink containing 75 g of glucose at a pre-determined time so that the expected peak blood glucose level coincides with the expected peak propionate blood concentration. During the next 3 hours they will have blood samples taken at 0, 10, 20, 30, 60, 90, 120, 180 mins after the glucose drink. A total of 90 ml of blood will be taken (about 6-8 tablespoons of blood). These will be taken through the cannula. After 3 hours the cannula will be removed and the participant will be provided with a light snack and able to go home.
Participants will be asked to attend four repeat visits with a minimum of a week between visits. They will randomly be assigned an oral dose of propionate, either 0, 1, 3, 6, 9g.

Blood samples will be analysed using the following methods:

- Propionate by Mass spectometry
- Insulin, GLP-1, PYY, leptin and non-esterified fatty acids will be measured using commercially available kits.
- Glucose will be measured using a glucometer.

Study 3

Aim: To determine the effect of propionate on beta cell function using the gold standard intravenous glucose tolerance (IVGTT) test in healthy participants and healthy volunteers at risk of developing diabetes.

Study methodology: Participants will undergo intravenous glucose tolerance tests. The effect of propionate on beta cell function will be determined in a randomised double blind placebo controlled crossover study.

Participants:
Cohort 1: 34 healthy men and women aged 30-70, body mass index (BMI) 25-35 kg/m2, normal fasting blood glucose (below5.5mmol/l and HbA1C less than 5.7% will be eligible to volunteer. Screen failures will be replaced.

Cohort 2: 34 men and women at risk of developing diabetes aged 30-70 with a body mass index (BMI) 25-35 kg/m2 with fasting blood glucose between 5.6mmol/l and HbA1C between 5.8 and 6.5% will be eligible to volunteer. Screen failures will be replaced.

Support for number of participants: Our pilot data demonstrates mean Insulin AUC_{10} of 8.1 for saline treated mice versus 11.3 for mice propionate-treated mice, an increase in the acute insulin response to glucose of 40%. Mean IVGTT-AIRg in a group of 306 healthy subjects was 492 mU.min (SD 48.7 - unpublished data from the study described in Diabetologia 2004;47:1157-1166). Using log-transformed data for IVGTT-AIRg, it was estimated that a 40% increase in IVGTT-AIRg would constitute an increase of 0.79 SD, which could be detected as significant at $p<0.05$, with 90% power using 34 in each group. Screen failures will be replaced.

Health Screening and enrolment Visit

Participants will arrive fasted from 8pm the previous evening. They will be clerked and examined by a research doctor. Measurements of height, weight, body fat content, blood pressure, an ECG and a blood test (for full blood count, urea and electrolytes, liver function tests, lipid profile, fasting glucose, HbA1C) will be taken. Screen failures will be replaced.

Visit 1: Oral glucose tolerance test.

The participant will be asked to come to the Clinical Investigations Unit at Hammersmith Hospital at 8:30am, having fasted from 8pm the previous day. A cannula will be inserted into a peripheral vein and two fasting blood samples taken at -30 and -10 mins before the participant consumes a drink containing 75 g of glucose. During the next 3 hours blood samples will be taken at 0, 10, 20, 30, 60, 90, 120, 180 minutes post glucose administration. A total of 100ml of blood will be taken.

Visit 2 and 3: Participants will undergo a frequently sampled intravenous glucose tolerance test (IVGTT) to detect changes in insulin sensitivity and beta cell function. The day prior to the study subjects will be asked to refrain from alcohol and strenuous exercise and fast for 12 hours prior to the study. The study will be carried out at the St. John Mc Michael Centre (Hammersmith hospital). Subjects will have two cannulae placed in separate peripheral veins. Subjects will be given glucose (20% solution-0.3g/kg) directly into a peripheral vein following oral administration of propionate at the most effective dose determined in study 2. Timing of the glucose bolus will be determined from data gathered in study 1 and be given 5mins prior to the expected plasma peak concentrations of sodium propionate. Blood samples (10ml) will be taken at, -5, 0, 2, 4, 6, 8, 10, 19, 22, 30, 40, 50, 70, 100 & 180 where glucose is administered at time 0, in total 150ml of blood will be drawn. Participants will be administered human insulin (0.03units/kg, 'regular human insulin – Novo Nordisk') at 20 mins post glucose. Participants will be asked to attend a repeat visit with a minimum of a week between visits. Participants will be randomly assigned propionate or placebo.

Blood samples will be analysed using the following methods:

- Propionate by Mass spectometry

- Insulin, GLP-1, PYY, leptin and non-esterified fatty acids will be measured using commercially available kits.
- Glucose will be measured using a glucometer.
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4. PARTICIPANT ENTRY

PRE-RANDOMISATION EVALUATIONS

Potential participants will be interviewed and examined by one of the research doctors. They will be asked to complete a medical and lifestyle questionnaire and have blood tests and height, waist and weight measurements to calculate body mass index. They will have an electrocardiogram (ECG) and fasting blood samples will be taken. They will be asked to undergo a glucose tolerance test. All women of child bearing age will have a pregnancy test.

INCLUSION CRITERIA

Study 1: Healthy men and women aged between 18 and 70 years with BMI between 20-25 kg/m2 and with normal fasting blood glucose (below5.5mmol/l and HbA1C less than 5.7% will be eligible to volunteer.
Study 2: As for Study 1.
Study 3:
Cohort 1: Volunteers aged between 30 to 70 with a BMI between 25-35 kg/m2 who do not have impaired fasting glucose and have HbA1c below 5.7%.
Cohort 2: Volunteers aged between 30 to 70 years with a BMI between 25-35 kg/m2 who have impaired fasting glucose (between 5.5-7mmol/l) and HbA1C between 5.7% and 6.5%,

EXCLUSION CRITERIA

- Type 1 or Type 2 Diabetes
- Gained or lost ≥ 3kg weight in the past three months
- Taken prescription medicines having an impact on metabolism, appetite regulation, glucose homeostasis and hormonal regulation
- Taken any dietary supplements in the last 6 months
- Any chronic illness
- Cardiovascular disease
- Excess alcohol intake
- Current smokers
- Any gastrointestinal disorder e.g. Crohn's disease, coeliac disease or irritable bowel syndrome
- A history of drug or alcohol abuse in the last 2 years
- Pregnancy (all women of child bearing age will undergo a pregnancy test).
- Pancreatitis
- Use of medications likely to interfere with glucose metabolism, appetite regulation, hormonal balance.

Any participants with the above conditions would have an altered pattern of glucose homeostasis and would therefore give 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.

5. ADVERSE EVENTS

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 to the Sponsor, the local ethical review committee and the local research and development office. 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, will be recorded.

Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. 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 London – West London 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 for non-IMP studies.

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

AMMENDMENTS

Any amendments to the protocol should be approved by the Sponsor before submission to the local research ethics committee, Subsequent to ethics approval further approval from the Trust research and development office should be sought, unless in the case of an urgent safety measure).

Contact details for reporting SAEs
Fax 020 838 33142, attention Dr. Chong Lim
Please send SAE forms to Dr. Chong Lim
Tel: 020 838 33242 (Mon to Fri 09.00- 17.00)

7. STATISTICS AND DATA ANALYSIS

An independent researcher (i.e. not linked to the study) will be given the task of randomisation, which will be by sealed envelopes.

Although the data handling and statistical methodology can only be confirmed once all the data is collect. Our intention is to us parametric techniques to analyse the data if the it is normally distributed. We will therefore use T-tests for comparisons between two groups and ANOVA for comparisons of three or more groups.

8. REGULATORY ISSUES

ETHICS APPROVAL

This study is awaiting ethical approval from the West London Research Ethics Committee. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

CONSENT

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

CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Results will be stored on our departmental database. This is a confidential computer system which requires a specific password for access. Only authorised members of the Imperial College Healthcare Trust and Department of Investigative Medicine will have this password. The system can only be accessed from within the hospital. Researchers themselves will undertake analysis of data stored on the shared drive. This will take place at the Imperial College Healthcare Trust. Any other data collected from participants will be kept in locked storage in the Department of Investigative Medicine, under the authority of Dr. Gavin Bewick.

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

National Health Institute for Research will be funding this study.

Participants will be reimbursed for their time at the rate of £33 per visit.

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).

9. STUDY MANAGEMENT

The day to day management of the study will be co-ordinated by Dr. Gavin Bewick and Dr. Emma Livingston.

10. 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.