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# Study Protocol
# Comparison of the effects of the long-limb to the standard-limb gastric bypass on type 2 diabetes mellitus
# The LONG LIMB trial

**Background and rationale**

The most effective and durable treatment for both obesity and type 2 diabetes mellitus (T2DM) remains bariatric surgery. Prospective case-controlled studies and randomised controlled clinical trials have shown that bariatric surgery causes a mean body weight loss of 20-40% and a mean absolute reduction in glycated haemoglobin (HbA1c) of ~2% at 1-2 years post-operatively in the context of reduced diabetes medications [1-4]. Despite initial optimism that this operation would cause long term remission for the majority of patients with moderate diabetes, disappointingly, <40% achieve euglycaemia without diabetic medications with the 'gold standard' standard-limb RYGB [5].

Alternative surgical techniques have been sought to improve the rates of T2DM remission. An RCT performed by our co-investigator, Professor Francesco Rubino [1], showed that standard-limb RYGB and biliopancreatic diversion (BPD) performed on obese patients with T2DM led to a matched total body weight loss of 33% at 2 years post-operatively. However, after this weight loss, BPD was superior in its glycaemic improvements, with a clinically meaningful absolute reduction in HbA1c of 3.9% compared to a 2.2% after standard-limb RYGB. Unfortunately, the BPD procedure has the distinct disadvantage of a substantially higher risk of developing severe nutritional complications, and this has limited its use [6]. To improve the glucose-lowering efficacy of standard-limb RYGB, whilst avoiding the high risk of complications with the BPD procedure, the long-limb RYGB has been devised as a hybrid operation that combines the standard design of standard-limb RYGB, but with a longer biliopancreatic limb.

Nora *et al* reported on the results of a prospective study of obese T2DM patients who underwent an long-limb RYGB with a 200 cm biliopancreatic limb and a 120 cm alimentary limb [7]. The cohort of 40 patients that completed the 3 year follow up lost 25% body weight, stopped all of their glucose-lowering medications and reduced their HbA1c by 0.9% (from a baseline of 6.7%). A longer biliopancreatic limb is therefore associated with superior glycaemic control (100% diabetes remission) when compared to that usually achieved by standard-limb RYGB, <40% [5, 8]. The rates of any complications, including nutritional, were not higher than those reported after standard-limb RYGB.

The standard-limb RYGB causes a large release of gut hormones such as GLP-1, oxyntomodulin and peptide YY after eating, leading to reductions in appetite and/or increases in insulin secretion [9-12]. As the long-limb RYGB enables the faster delivery of un-digested nutrients to the distal jejunum, where there is a greater number of gut endocrine L cells [13, 14], we expect that there will be an *even greater* release of gut hormones that will drive a higher secretion of insulin immediately after eating compared to the standard-limb RYGB.

In the long-limb RYGB, the biliopancreatic limb is longer than the standard-limb RYGB (150 vs. 50 cm). We therefore expect that the long-limb RYGB will be similar to the BPD and that both hepatic and peripheral insulin sensitivity will be increased *before* weight loss has taken place. We also expect that the increased insulin sensitivity will persist in the longer term and will be more powerful in reducing glucose levels than standard-limb RYGB.

In this trial, we wish to confirm the superior efficacy on T2DM of the long-limb RYGB over the standard-limb RYGB, and investigate the mechanisms underlying their differences.

**Hypotheses**

The main anatomical difference between long-limb RYGB and standard-limb RYGB is that the segment of the bypassed proximal intestine, the biliopancreatic limb, is longer (150 vs. 50cm respectively). This means that in the long-limb RYGB the common channel is shorter, and as a result nutrients reach the distal small bowel faster and in a less-digested state. The physiological mechanisms through which these changes in anatomy can alter glucose homeostasis are not currently known.

We hypothesize that the long-limb RYGB is better for T2DM because:

1. It increases the immediate post-prandial insulin secretion significantly more than the standard-limb RYGB, by enhancing the post-prandial secretion of gut hormones, and in particular glucagon-like peptide (GLP) -1, over that seen with the standard-limb RYGB.

2. It increases insulin sensitivity significantly more than the standard-limb RYGB, before *and* after weight loss has taken place.

**Objectives**

Our objectives are to compare the standard and the long-limb RYGB in terms of the differences in:

1. Insulin and gut hormone secretion, following a standardised mixed meal tolerance test.
2. Insulin sensitivity (hepatic and peripheral), using the two-step euglycaemic-hyperinsulinaemic clamp method.
3. Changes in plasma bile acid levels.
4. Gut bacterial diversity and their metabolite profile.

**Trial team**

The Chief Investigator is Professor Stephen R. Bloom, Professor of Medicine and Head of Department of Investigative Medicine, Imperial College London. Co-investigators and collaborators are Prof Francesco Rubino (King's College London), Mr Ahmed Ahmed, Dr Tricia Tan, Dr Alexander Miras, Prof Gary Frost, Prof Jeremy Nicholson, Prof Elaine Holmes, Prof Margot Umpleby (University of Surrey), Prof Ameet Patel (Kings College London), Mr Sanjay Purkayastha, Mr Krishna Moorthy, Miss Avril Chang (King's College London), Dr Harvinder Chahal and Dr Julian Marchesi.

**Trial design**

This will be a prospective double-blinded randomised controlled clinical trial. Fifty patients will be recruited from the Imperial Weight Centre and the King's College Obesity Clinic, and randomised to either the long-limb or the standard-limb RYGB surgery.

**Inclusion criteria**

- Male or female participants
- Aged between 18-70 years
- Diagnosed with T2DM according to WHO 2006 and 2011 criteria
- HbA1c ≥7.0% (≥53.0 mmol/mol) on screening
- Body mass index (BMI) ≥ 30 kg/$m^2$ and eligible for bariatric surgery based on NICE guidance
- On glucose-lowering medications
- Willing to comply with study requirements and able to give informed consent

**Exclusion criteria**

- History of any medical, psychological or other condition, or use of any medications, including over-the-counter products, which, in the opinion of the investigators, would either interfere with the study or potentially cause harm to the volunteer.
- Without access at home to a telephone or other factor likely to interfere with ability to participate reliably in the study.
- Specific contraindications to bariatric surgery
- Previous bariatric surgery
- Diagnosed with Type 1 diabetes mellitus
- Donated blood during the preceding 3 months or intention to do so before the end of the study
  Current pregnancy or breastfeeding
- Inability to maintain adequate contraception

**Screening visit**

All participants will be screened to assess whether they meet inclusion criteria and this process will comprise a medical history, routine physical examination, basic investigations (full blood count, urea and electrolytes, liver function tests, thyroid function tests, fasting plasma glucose, fructosamine, HbA1c, lipid profile, iron indices, vitamins, minerals and metabolites, urinalysis for dipstick and albuminuria, and electrocardiogram) and psychological/quality of life questionnaires. All women of child-bearing age will also be asked to undergo a pregnancy test.

**Baseline visit before surgery**

*Day 1: Assessment of insulin sensitivity - euglycaemic hyperinsulinaemic clamp*

On the days prior to the visit patients' glucose-lowering medications will be adjusted by a research nurse or a clinician in order to avoid their interference with the measurements. Patients will also be asked to refrain from alcohol and strenuous physical activity for 48 hours before the study. A non-invasive device (e.g. pedometer) may be used to monitor their physical activity levels. Patients will attend the research facility in the evening before the clamp procedure. Two venous catheters will be inserted. The first cannula will be used for infusions and the other for blood sampling. They will be asked to consume a standardised meal, remain fasted from 10pm onwards, and commenced on an insulin infusion to keep their blood glucose stable between 4.0-6.0 mmol/l. On the morning of the clamp a primed continuous infusion of [6, 6-$^{2}H_{2}$] glucose, a stable isotope tracer, will be started and maintained for 7 hours. Two hours later a two-stage hyperinsulinaemic-euglycaemic clamp procedure will be started and continued for 5 hours. During stage 1 of the clamp procedure, in which hepatic insulin resistance is assessed, insulin will be infused at a low dose (depending on patient's weight/body surface area) for 2 hours. During stage 2 of the clamp procedure, in which peripheral insulin resistance is assessed, insulin will be increased to a higher dose (depending on patient's weight/body surface area) for 3 hours. Euglycaemia will be maintained by infusing 20% dextrose at a variable rate. Blood samples will be taken every 5-10 minutes to measure blood glucose concentration and the dextrose infusion will be adjusted accordingly. The exogenous glucose infusion will be enriched with 6, 6 $^{2}H_{2}$ glucose to prevent a fall in plasma tracer enrichment and underestimation of endogenous glucose production rate. Regular glucose monitoring is necessary to ensure safety and avoid the small risk of hypoglycaemia.

Blood samples will be obtained before the start of the tracer infusions, every 10 min during the final 30 min of the basal period and stages 1 and 2 of the clamp procedure and every 30 minutes between these periods to determine glucose enrichment and concentration, free fatty acid, insulin, c-peptide, glucagon, gut hormones, bile acids and metabolite concentrations. At the same time points participants will be asked to complete appetite visual analogue scales.

At the end of the study, participants will be fed a standardised meal and the glucose infusion continued for a further 20 minutes to prevent hypoglycaemia. The maximum amount of venesected blood will be 180 mls. Patients will be asked to remain fasted and sleep overnight in the Clinical Research facility.

Blood samples will be centrifuged and the separated plasma kept in a -20°C or -80°C freezer. The isotopic enrichment of plasma glucose will be determined by gas chromatography mass spectrometry (GCMS) at the Wolfson Centre for Translational Research, Postgraduate Medical School, University of Surrey.

The stable labelled isotope tracer [6, 6 $^{2}H_{2}$] glucose is not a drug, but a naturally occurring metabolite which has been labelled with a stable and non-radioactive label. Stable isotope tracers are widely and safely used in metabolic research by groups throughout the UK and worldwide. All labelled isotope tracers are ordered from Cambridge Isotopes Ltd through their UK suppliers CK Gases Ltd. They are prepared as sterile solutions suitable for intravenous use by the Pharmacy Production Unit at Guys & St. Thomas' NHS Trust to ensure they are safe for the participants. The products are supplied with the appropriate certificate of analysis and MSDS. We have used the same manufacturer to ensure the quality of the products and the supporting documentation.

*Day 2: Assessment of insulin and gut hormone secretion - mixed meal tolerance test*

On the morning of day 2 the fasted patients will be given a standardized mixed-meal followed by measurements of glucose, insulin, gut hormones, bile acids and metabolites at t= -30, -15, 0, 15, 30, 60, 90, 120 and 180 minutes, where time zero is the time of administration of the meal. At the same time points they will be asked to rate their appetite, and have their BP and pulse measured. They will then be discharged from the clinical research facility.

*Additional assessments*

The following assessments will also take place on or around the baseline visit:

- glycaemia - fasting plasma glucose, glycated haemoglobin (HbA1c) and fructosamine
- body weight and body composition using bioelectrical impedance machines
- plasma lipids - total, low-density and high-density lipoprotein cholesterol, and triglycerides
- 24 hour collection of faeces for bomb calorimetry analysis
- Blood, urine and faecal samples collection for microbiomic and metabolomic analyses
- total caloric intake and macronutrient composition will be assessed through the use of food diaries
- frequency of hypoglycaemic episodes
- adverse events

**Surgery**

The patient, the research and clinical team, except for the operating surgeon, will be blinded to the type of operation that has been performed, unless clinical need and urgency dictates the un-blinding of the clinical team (e.g. development of a surgical complication). The procedures will be filmed in order to allow the data monitoring and ethical committee to audit procedures and ensure the consistency of the surgical technique amongst the operating surgeons. Filming of surgery takes place as part of routine NHS care for clinical governance purposes. In brief, the total length of the small intestine will be measured from the ligament of Treitz to the terminal ileum. A completely isolated proximal gastric pouch 15-30ml in volume will be created using endostaplers. Next the ligament of Treitz will be exposed and a loop of small bowel taken up to the gastric pouch (antecolic) with the alimentary limb on the patient's right and a 50 cm biliopancreatic limb in the standard-limb RYGB or 150 cm biliopancreatic limb in the long-limb RYGB, on patients' left. The alimentary limb will be anastomosed with a stapler to the gastric pouch. A leak test will be performed with the Roux loop occluded; the gastro-jejunal anastomosis will be submerged under saline, distended with oxygen via an orogastric tube and with multiple distensions while submerged. Next the alimentary limb will be measured to 100 cm. Then a side-to-side entero-enterostomy will be performed by stapling the biliopancreatic limb to the 100 cm mark on the alimentary limb making parallel antimesenteric enterotomies and firing the endostapler into the lumen of each. The enterotomy will be closed and the procedure completed. Following surgery patients in both groups will be advised to consume the same standard post-operative low-calorie diet.

**Early post-operative visit**
This will take place 7-14 days after surgery and before substantial weight loss has taken place. The same assessments and procedures as in the baseline visit will be followed.

**Late post-operative visit**
This will take place when patients in both groups achieve a total body weight loss of 20% of their pre-operative weight. The same assessments and procedures as in the baseline visit will be followed.

**Yearly visit**
This will take place 1 year after surgery and will involve clinical assessments including the following:

- Body weight and body fat
- Blood pressure and pulse
- Blood tests: full blood count, urea and electrolytes, liver function tests, thyroid function tests, fasting plasma glucose, HbA1c, lipid profile, iron indices, vitamins, minerals and metabolites, and urinalysis for dipstick and albuminuria
- Psychological/quality of life questionnaires
- Medical, surgical, nutritional and psychological complications, including length of inpatient stay and number of outpatient consultations
- Number of medications

**Clinical assessment and follow-up:** Patients will be assessed clinically as part of routine NHS care. Patients in both groups and both hospitals will receive protocol-driven medical care. After surgery patients will be followed-up at ~10 days, 3, 6, 12 months and yearly thereafter, unless clinical need dictates more frequent consultations. The data obtained from these clinical assessments will be used to compliment the data from the mechanistic studies.

**Primary outcome** change in peak GLP-1 level after the mixed meal tolerance test
**Secondary outcomes** change from baseline in:

- plasma levels of glucose, insulin, c-peptide, gut hormones, bile acids, FGF-19 and 21 after the mixed meal tolerance test
- rate of glucose appearance (Ra) and disposal (Rd) in the euglycaemic hyperinsulinaemic clamp
- faecal caloric content
- blood, urine and faecal microbial diversity and metabolomics
- total caloric intake and macronutrient composition
- HbA1c
- total number of medications
- rates of patients achieving diabetes remission
- body weight
- systolic, diastolic blood pressure and pulse
- serum fasting lipids
- medical, surgical, nutritional and psychological complications
- adverse events

**Sample size calculations**
The majority of published studies have shown that peak active GLP-1 concentrations are ~2-fold greater after standard-limb RYGB (11, 20) compared to pre-operatively. We have estimated that that peak active GLP-1 levels after long-limb RYGB will be tripled at 1-2 weeks after surgery. We have powered this study to detect a statistically significant difference in peak active GLP-1 of 10.0 pmol/L between the group means assuming a SD of 10.8 pmol/L within each group. A power calculation shows that a sample size of 20 completers in each arm will have a statistical power of 80% to detect this difference at $\alpha$=0.05. We plan to recruit 25 patients to each arm, assuming a 20% drop-out rate based on our own experience with our previous patient cohorts undergoing standard-limb RYGB and metabolic testing after surgery.

**Drop-outs**
Subjects will be free to withdraw at any point. If a subject withdraws from the study before they have completed their last visit, they will be replaced.

**Trial Closure**
The end of the clinical trial is defined as the last visit of the last patient.

**Data analysis plan**
The primary outcome will be compared between treatment groups using a linear model, incorporating stratifying factors and adjusting for relevant baseline covariates. Bayesian estimates of the mean difference, with 95% credible intervals, will also be derived. Other data will be summarized using appropriate descriptive statistics, and exploratory linear models may also be used to compare mean values of continuous variables, or to compare categorical outcomes, between the two treatment groups.

**Procedure for emergency un-blinding**
This is a randomised, double-blinded study. The randomisation lists will be created and held by Dr Victoria Salem, Clinical Lecturer in Endocrinology, Imperial College London, in a secure area within the centre (this copy to be held as code-break envelopes)

In the case of a medical emergency or in the event of a serious medical condition, when knowledge of treatment allocation is essential for the clinical management or welfare of the subject, an investigator or other physician managing the subject may decide to un-blind that subject's treatment code. They should therefore request and obtain the relevant code-break envelope.

The investigator must sign and date the open un-blinding envelope, as soon as is reasonably possible, and at the very least within 24 hours of the code break. The reason for the code break must be documented on the envelope. The Investigator will also record the date and reason for revealing the blinded treatment assignment for that subject in the CRF and in the subject's medical notes.

**Patient and public involvement**
Mrs Georgina Hayman runs a very successful support group for obese patients undergoing bariatric surgery (British Obesity Surgery Patient Association West London) and she will help with patient retention by creating a "belonging to a family" environment. Her group have already contributed to the development of this application, starting from its design, undertaking the research, choice of research topic and eventually dissemination of the study findings through her patient support group.

**Definitions of Adverse Events and Reactions**

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 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**
An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to non-obesity or diabetes related causes, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs. All SAEs should be reported to the REC 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, Sponsor and/or Research & Development Office.

**Contact details for reporting SAEs**
SAEs must be reported to the Chief investigator and the Sponsor within 24hrs of becoming aware of the event:
CI details: Fax: 0208 383 8320, attention of: Prof Sir Stephen Bloom
Sponsor details: Fax: 0203 311 0203 or email: jrco.ctimp.team@imperial.ac.uk
Please send SAE forms to: Section of Investigative Medicine, Division of Diabetes, Endocrinology & Metabolism, Imperial College London
Tel: 0208 383 3242 (Mon to Fri 09.00 – 17.00) or 07751236735 (24 hours, 7 days a week).

**Follow-up of AEs and SAEs**
After the initial AE report, the Chief Investigator or appropriately qualified designee will proactively follow the subject at subsequent visits and contacts. Follow up information about a previously reported SAE must be reported to the Trial Management Group and Sponsor within 24 hours of receiving it. AEs and SAEs will be followed until they resolve, stabilise to a level acceptable to the Investigator or delegates even after the reporting period or the subject is lost to follow-up. Additional measures may be carried out by the Investigator to elucidate as fully as possible the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations or consultation with other health care professionals. In the event that a subject becomes pregnant, the follow-up period will be deemed to have ended when the health status of the child has been determined on its birth.

**Monitoring**
A risk assessment will be completed by the Sponsor and the monitoring frequency will ensue from this. The monitoring will be performed by members of the JRCO.

**Regulatory issues**
*Ethics and regulatory approvals:* The study must be submitted for Site Specific Assessment (SSA) and approval by the research and development (R&D) department at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before recruitment of participants from the NHS Trust in question into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

*Consent:* The study will be conducted in accordance with applicable regulatory requirements, with International Conference on Harmonization "Good Clinical Practice" (GCP), with all applicable subject privacy requirements, and with the guiding principles of the Declaration of Helsinki. Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

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

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

*Sponsor:* Imperial College 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:* The National Institute for Health Research (NIHR) and Medical Research Council is funding this study through its Efficacy and Mechanism Evaluation programme.

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

**Study management, data monitoring and ethics**

The trial will be coordinated by a Trial Steering Committee (TSC), which will consist of an independent chair and members, the Principal Investigator, co-investigators, the Project Manager and a patient representative. A Data Monitoring & Ethics Committee will also be established. All its members will be independent of the applicants and of the TSC, while reporting to the TSC. They will meet at least annually and their role will be to monitor the unblinded data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. The committee will consist of Professor Carel W le Roux (Metabolic Physician), Mr Richard Welbourn (Bariatric Surgeon) and Dr Les Huson (statistician). The day-to-day management and coordination of the study will be performed by Dr Alexander Miras.

**Quality Control and Quality Assurance**

The trial will be adopted by the NIHR/Wellcome Trust Clinical Research Facilities at both Imperial and King's College London and will fall under their QC/QA regime.

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