Department of Investigative Medicine
Imperial College London
6th Floor Commonwealth Building
Imperial College London at Hammersmith Campus
Du Cane Road, London W12 0NN, UK
Tel: +44 (0)20 8383 3242 Fax: +44 (0)20 8383 8320

Imperial College London

LONG LIMB-2

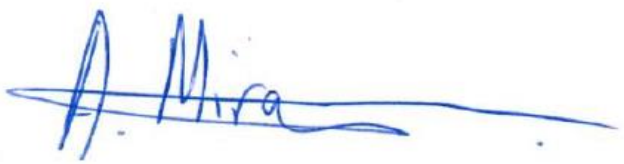
Study Protocol

What is the impact of a modified Roux-en-Y-gastric bypass operation on people with type 2 diabetes mellitus?
The LONG LIMB-2 double-blinded randomised controlled clinical trial

Version 6.0, 26th May 2022

Main Sponsor: Imperial College London
Funder: JP Moulton Charitable Foundation
REC Reference: 20/LO/1071
IRAS Project ID: 279091

Protocol authorised by:

Name & Role	Date	Signature
Dr Alex Miras Chief Investigator	26th May 2022	

Study Management Group
Chief Investigator: Dr Alex Miras
Co-investigators: Mr Sanjay Purkayastha, Mr Ahmed Rashid Ahmed, Mr Krishna Moorthy, Mr Sherif Hakky, Mr Christos Tsironis, Dr Suhaniya Samarasinghe, Mr Brett Johnson, Mr Dimitri Pournaras, Miss Alexis Sudlow, Ms Karen O'Donnell, Dr Georgios K Dimitriadis, Prof Ameet Patel, Mr Shamsi El-Hasani, Mr Chetan Parmar
Statistician: Not appointed
Study Management: Dr Suhaniya Samarasinghe

Clinical Queries
Clinical queries should be directed to Dr Alex Miras 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 (RGIT)
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 9459/ 0207 594 1862**
http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice

Funder
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This protocol describes the LONG LIMB-2 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 Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work 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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STUDY SUMMARY

TITLE: What is the impact of a modified Roux-en-Y-gastric bypass (RYGB) operation on people with type 2 diabetes mellitus? The LONG LIMB-2 double-blinded randomised controlled clinical trial

DESIGN: Double-blind randomised controlled clinical trial

AIMS: To investigate if a "modified" RYGB procedure is equally safe but superior to "standard" RYGB in improving glycaemic control in patients with type 2 diabetes mellitus (T2DM) and obesity.

OUTCOME MEASURES: Change in glycated haemoglobin (HbA1C) from baseline.

POPULATION: Men and women with T2DM and obesity

ELIGIBILITY: Diagnosis of T2DM, body mass index (BMI) >30 kg/m^2, aged between 18 – 65 years, eligible for metabolic/bariatric surgery as per NICE CGI189

DURATION: 3 years

1.1 BACKGROUND AND RATIONALE

The profound improvements in glucose control after RYGB have unexpectedly led to the recognition of the intestine as an organ with a major impact on glucose regulation. Thus, surgeons have experimented with different intestinal limb lengths in an attempt to enhance the clinical effect of RYGB on glucose control. However, the optimal length of each of these limbs remains controversial with substantial variation in practice. The matter is complicated further by the variability in the total length of the human small intestine (range of 3.5–10.5 metres) [8].

The anatomical rearrangements of RYGB result in three intestinal segments or "limbs": the "alimentary limb" through which food enters through the gastric pouch to the small intestine, the "biliopancreatic limb" which includes the bypassed segments of duodenum and proximal jejunum through which the biliopancreatic secretions flow, and the "common limb" (or channel) in which the food and biliopancreatic secretions mix (Figure 1A). More recently, our clinical and mechanistic data, together with other clinical trials and animal experiments [9-11] have shifted the focus from the biliopancreatic limb to the lengths of the alimentary and common limbs. The evidence supports the hypothesis that a "modified" RYGB with a long alimentary limb and short common limb may be the optimal design for glycaemic control (Figure 1C).

It should be noted that this "modified" RYGB (Figure 1C) is not new and indeed currently performed around the world. There is no signal that it is associated with higher morbidity compared to the standard RYGB [12]. However, a formal comparison between the "modified" and "standard" RYGB with glycaemic control as the primary outcome has never taken place.

Hypothesis: A "modified" RYGB procedure with a long alimentary and short common limb (40:60) is equally safe but superior to the "standard" RYGB with a short alimentary and long common limb (20:80) for glycaemic control in patients with T2DM and obesity.

2. STUDY OBJECTIVES

To perform a double-blind RCT to compare safety and efficacy of "modified" RYGB vs. "standard" RYGB in improving glycaemic control in patients with T2DM and obesity. Secondary objectives from baseline to 12 months post operatively are changes in:

- Rate of remissions of T2DM
- Number of glucose-lowering medications
- Body weight
- Arterial blood pressure
- Lipid profile
- Adverse events (including surgical complications, hypoglycaemia and micronutrient deficiencies)

3. STUDY DESIGN

In the LONG LIMB-2 prospective double-blinded RCT we propose to recruit 80 patients with T2DM and obesity who are eligible for metabolic surgery based on NICE guidance 189 who are on the waiting list for bariatric surgery at Imperial College Healthcare NHS Trust, North Bristol NHS Trust, King's College Hospital NHS Foundation Trust and The Whittington Hospital NHS Trust obesity service. Randomisation will take place intra-operatively. The surgeon will measure total intestinal length and decide if the patient can be randomised intraoperatively (only patients with a calculated common channel length of >2.5m will be randomised) and if so will contact the randomiser who will make the allocation at the time to either:

- A "standard" RYGB or
- A "modified" RYGB

The randomisation ratio will be 1:2 i.e. 24 participants for standard RYGB and 48 for modified RYGB.

3.1 STUDY OUTCOME MEASURES

Primary outcomes

- Change in HbA1C from baseline to 12 months

Secondary outcomes

Change from baseline to 12 months for:

- Rate of remission of T2DM
- Number of glucose-lowering medications
- Body weight
- Arterial blood pressure
- Lipid profile
- Adverse events (including surgical complications, hypoglycaemia and micronutrient deficiencies)
- Rate of intestinal absorption of ingested glucose (mechanistic study only)

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Screening will be performed to confirm that patients meet the inclusion criteria for the trial and are safe to undergo treatment for obesity following psychological and dietetic assessments which are part of standard care. Participants will also be invited to take part in the nested mechanistic sub-study (Appendix 2).

4.2 INCLUSION CRITERIA

- Diagnosis of T2DM
- BMI >30 kg/m^2
- Age 18-65 years
- Eligible for metabolic/bariatric surgery as per NICE CG189

4.3 EXCLUSION CRITERIA

- Unacceptably high risk for anaesthesia or surgery
- Pregnancy/breastfeeding

calculated common channel length of <2.5m

4.4 WITHDRAWAL CRITERIA

All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. Should they wish to withdraw their consent, all of their data to date will be held.

5. ADVERSE EVENTS

5.1 DEFINITIONS

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

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

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious 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.

5.3 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.

5.3.1 Non serious AEs

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

5.3.2 Serious AEs

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

All SAEs should be reported to the London-Dulwich Research Ethics Committee 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.

Pregnancy

We ask female participants to use adequate contraception for the duration of the study. Women using the oral contraceptive pill (OCP) will be asked to stop it one month pre- and post-operatively (due to the deep vein thrombosis risk) and use alternative non-hormonal contraception which includes:

- Barrier methods
- intrauterine device (non-hormone releasing)
- vasectomised partner: this is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- sexual abstinence: sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments and when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

One month following surgery they can resume the OCP but there may be a chance of unplanned pregnancy which is not recommended for the first 18 months. This is due to the theoretical risk of malabsorption after RYGB. For this reason, we recommend using alternative contraceptive methods (above).

Contact details for reporting SAEs

jrco@imperial.ac.uk
Dr Alex Miras
Fax: +44 (0)20 8383 8320, attention Dr Alex Miras
Please send SAE forms to:
Department of Investigative Medicine
Imperial College London
6th Floor Commonwealth Building
Imperial College London at Hammersmith Campus
Du Cane Road, London W12 ONN, UK

Tel: +44 (0)20 8383 3242 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

Baseline and randomisation visit: At the baseline visit patients will have routine clinical bloods tests, if not already conducted in the clinical service.

Interventions

The consultant surgeons involved in the trial will perform the two operations using the same standard operating procedure. The limb lengths will be determined as ratios of the entire small intestine length in order to account for variability in total intestinal length in humans and minimise the confounding effect. The biliopancreatic limb length will be fixed at 50 cm. Subjects will be randomized via computer software at a 1:2 to either "standard" RYGB or "modified" RYGB stratified by BMI and duration of T2DM.

- "Standard" RYGB: performed with a 30 ml gastric pouch and an alimentary limb 20% of total length of the remaining intestine with a side-to-side jejuno-jejunal anastomosis. The common limb will be 80% of total length of the remaining intestine.

- "Modified" RYGB: performed with a 30 m gastric pouch and an alimentary limb 40% of total length of the remaining intestine with a side-to-side jejuno-jejunal anastomosis. The common limb will be 60% of total length of the remaining intestine.

Blinding: The patient, research and clinical team and staff conducting the final analyses will be blinded to the type of operation. Unblinding will be done if the clinical need arises e.g. surgical complication.

Clinical trial follow-up

Patients in both groups will be cared for by a multidisciplinary team as part of standard NHS care and assessed on day 10 (post-operatively), 3 months, 6 months and 12 months.

Drop-outs

Subjects will be free to withdraw at any point and only participants with a calculated common channel length of <2.5m will be replaced.

Trial Closure

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

Sample storage

For the clinical trial, blood samples will be sent to NHS labs for processing and handled as per standard NHS care. The additional samples from the sub-study will be stored for up to 10 years in freezers located in the Department of Metabolism, Digestion and Reproduction at Imperial College London.

7. STATISTICS AND DATA ANALYSIS

Justification of sample size

Based on our own data from the LONG LIMB-1 trial and the most relevant RCT in the field [12] we estimated that the absolute HbA1c reduction in the standard RYGB group will be 3.0% and in the modified RYGB group 4.0%. With a standard deviation of 1.2% around both means and using a 1:2 randomisation, we will need 24 participants in the standard RYGB and 48 in the modified RYGB to have a 90% power to detect statistically significant differences between the groups at α of 0.05. We will recruit 80 patients in total to account for an approximate 10% drop-out rate based on rates in similar trials we have conducted in this field (e.g. LONG LIMB-1 trial ISRCTN15283219).

Statistical analysis plan

Analysis of the data will only take place after completion of the trial having written a statistical analysis plan and use the intention-to-treat principle. Analysis will take place by staff blinded to participant disposition. Data will be summarised using descriptive statistics. Differences between treatment groups

will be compared using regression models adjusting for the randomisation stratification variables. For binary outcomes this will be a logistic regression model and for continuous this will be a linear regression model.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the London-Westminster 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.

8.2 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 a minimum of 24hrs 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.

8.3 CONFIDENTIALITY

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

8.4 INDEMNITY

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

8.5 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.

8.6 FUNDING

The J P Moulton Charitable Foundation is funding the trial.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated by Dr Suhaniya Samarasinghe. A Trial Management Group, Trial Steering Committee (TSC) and a Data Monitoring & Ethics Committee will be established. The trial will be conducted at the NIHR Clinical Research Facility at Imperial according to their SOPs and with oversight of their QA team.

10. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Members of the TMG and the Data Monitoring

Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project. The results are likely to be published within the 12 months following the study in peer-reviewed journals and websites, and presented in medical conferences. Participant confidentiality will be ensured at all times and they will not be identified in any publication as these will be anonymised. A lay summary of the key results from the study will be written and sent and/or presented to them.

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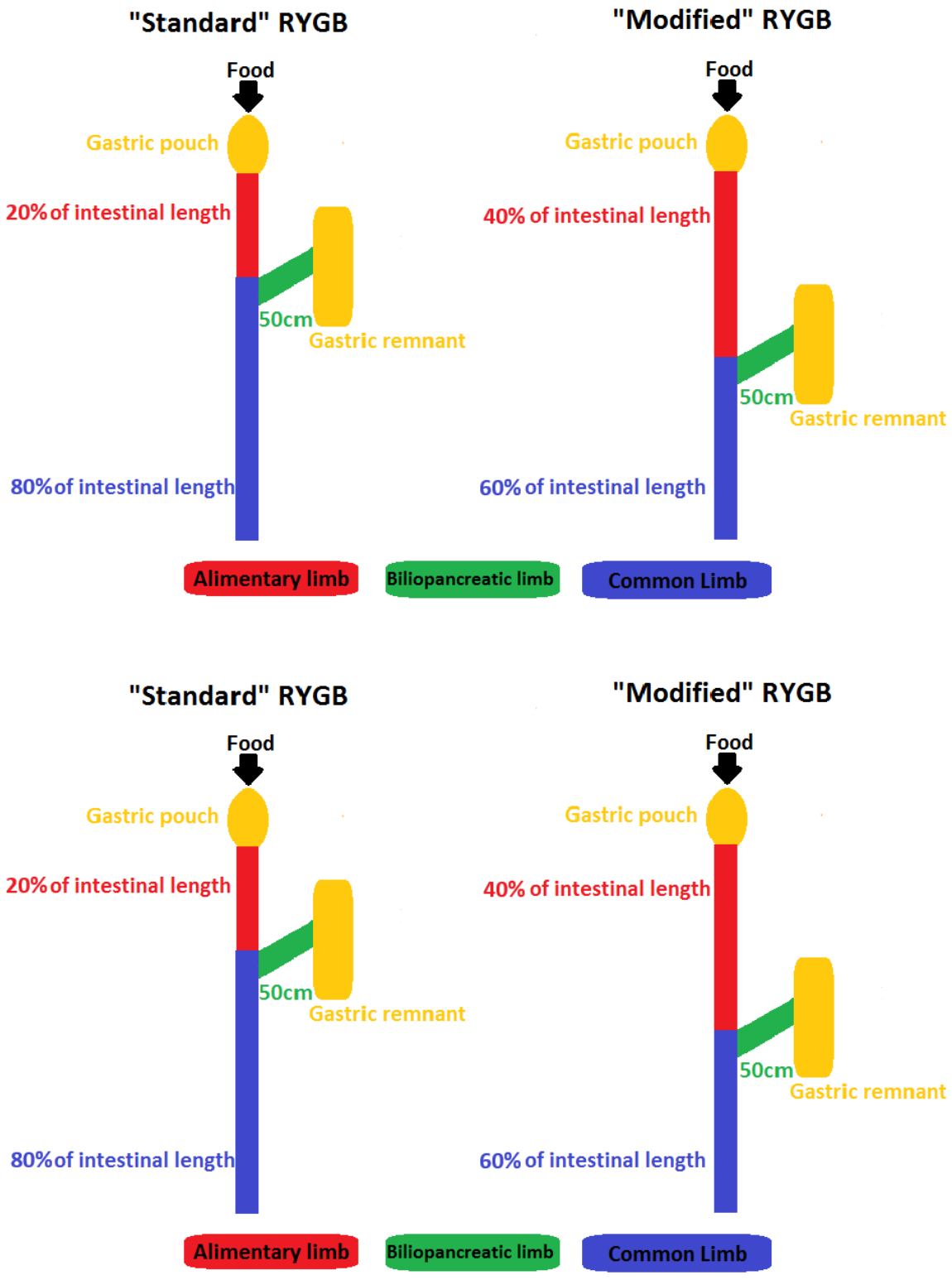
Appendix 1.

Figure 1
Design of the “standard” and “modified” RYGB in the proposed LONG LIMB-2 trial.



Appendix 2

Nested mechanistic sub-study: before and at 20% of weight loss after surgery

In order to evaluate the effect of RYGB on intestinal absorption of ingested glucose, participants will attend the NIHR Imperial Clinical Research Facility (CRF) at Hammersmith Hospital after an overnight fast. Their glucose-lowering medications will be adjusted for 5 days before the visit based on capillary glucose measurements and they will be asked to refrain from alcohol and vigorous exercise for 24 hours before the visit.

An enteral feeding tube which will be placed by a trained medical professional using the CORTRAK system that tracks the position of the tube during placement without the need for X-ray confirmation. The tube will be inserted into the duodenum before the operation and in the alimentary limb (jejunum) after the operation. The position of the tube will be confirmed using a PANPEHA pH strip. A solution containing 30 g glucose and 3 g 3-O-methylglycose (a well-established and used marker of glucose absorption) will be infused through the enteral feeding tube. An intravenous cannula will be inserted for blood sampling for metabolites at time points 0, +30, +60, +90, +120, +150, +180 min. The blood tests will be used to measure intestinal absorption of ingested glucose and 3-omg. Once the last blood sample is taken, both the enteral feeding tube and cannula will be removed and the participant will be free to leave the facility.

Participants who consent to take part in this sub-study will be reimbursed £200.