CLINICAL STUDY PROTOCOL

(ICTU ADOPTED)

Full Study Title:	Left gastric artery embolisation for weight loss in obese patients with BMI 35-50kg/m^2: EMBIO trial
Short Study title / Acronym:	EMBIO
Sponsor:	Imperial College London
Version no:	2.0
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This protocol has regard for the HRA guidance

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ABBREVIATIONS

AE	Adverse Event
AUC	Area Under Curve
BMI	Body Mass Index
BNF	British National Formulary
CCG	Clinical Commissioning Group
CI	Chief Investigator
CRF	Case Report Form
CT	Computer Tomography
DEBQ	Dutch Eating & Behavioural Questionnaire
DMEC	Data Monitoring and Ethical Committee
ECG	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture System
ELISA	Enzyme-Linked Immunosorbent Assay
EME	Efficacy and Mechanism Evaluation
EPIC FFQ	European Prospective Investigation into Cancer and Nutrition Food Frequency Questionnaire
FBC	Full Blood Count
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide 1
GP	General Practitioner
HADS	Hospital anxiety and Depression Scale
HbA1c	Hemoglobin A1c
HH	Hammersmith Hospital
HRA	Health Research Authority
ICF	Informed Consent Form
ICLH	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit

ICRF	Imperial College Research Facility
IR	Interventional Radiologist
IQWOL lite	Impact of Weight on Quality of Life lite
ISRCTN	International Standard Randomised Controlled Trials Number
LFT	Liver Function Test
LGAE	Left Gastric Artery Embolisation
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSAID	NonSteroidal Anti-Inflammatory Drugs
PIS	Patient Information Sheet
PPI	Public Patient Involvement
PYY	Peptide YY
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RYGB	Roux-en-Y Gastric Bypass
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF36-V2	Short Form Health Survey Version 2
SOP	Standard Operating Procedure
TMG	Trial Management Group
TRC	Transradial Catheterization
TSC	Trial Steering Committee
UCLH	University College London Hospitals NHS Trust
U&E	Urea and Electrolytes
UK	United Kingdom
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

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TRIAL SUMMARY

TITLE: Left gastric artery embolisation for weight loss in obese patients with BMI 35-50kg/m^2: EMBIO trial

OBJECTIVES:

- To evaluate the efficacy of left gastric artery (LGA) embolisation on weight loss and obesity related comorbidities at pre-determined times points over a 12 month follow up period.
- To evaluate the mechanism of action of LGA embolisation at pre-determined time points over a 12 month follow up period.
- To evaluate the safety of LGA embolisation by adverse event recording.

DESIGN: This is a multi-centre, double-blinded randomised controlled (left gastric artery embolisation vs. placebo procedure) trial including two participating centres in England (Imperial College Healthcare NHS Trust and University College London Hospitals NHS Trust). Recruitment and Intervention will be carried out at each participating centre. All mechanistic assessments will be completed at Imperial Clinical Research Facility, Hammersmith Hospital.

SAMPLE SIZE: 76 patients

INCLUSION CRITERIA:

- Adults aged 18-70 years
- BMI 35-50Kg/m2
- Ability to lie supine
- Appropriate anatomy of the Left Gastric Artery and coeliac plexus on CT Angiogram
- Willing and able to provide informed consent.

EXCLUSION CRITERIA:

- Haematological, hepatic or renal dysfunction
- Weight >150kg,
- HbA1c > 8.5%
- Known renal, vascular or aortic disease
- Malignancy
- Prior major abdominal surgery, prior gastric or bariatric surgery
- Prior abdominal radiotherapy,
- GI bleeding or bleeding diathesis
- Allergy to iodinated contrast,
- Known gastric ulceration or active H. Pylori infection
- Positive pregnancy test in females of childbearing age
- Chronic NSAID use
- Current use of insulin or sulphonylurea
- Current use of anti-tricyclic anti-depressants or steroids

INTERVENTION: Left gastric artery embolisation versus placebo procedure.

MAIN STUDY PROCEDURES

- Potential participants will be identified through bariatric clinics and invited to attend a screening visit at their hospital. All participants will undergo a CT angiogram to assess left gastric artery anatomy as part of the eligibility checks. All participants will follow the local hospital standard tier 3 program for weight loss after the intervention.

- Planned intervention:

  Patient attends the Interventional Radiology / Angiography suite. Following Barbeau test for left radial artery (via the wrist) access is performed. If Barbeau test precludes radial access, femoral access (via the groin) will be performed. The protocol for either radial or femoral access is exactly the same. An intravenous catheter will be sited and moderate sedation administered. The patient's view of the wrist, x-ray monitors and the local puncture site will be restricted by the use of this erected sterile drape so the patient cannot see the procedure. Auditory isolation of participants with over the ear headphones playing music will be used in all cases.

  A hydrophilic sheath is placed into the radial artery. The operator will then randomise the patient to either LGAE or placebo procedure 1 to 1 using the online OpenClinica database which will be accessed by an online device inside the angiography suite.

  LGAE Arm: Once the sheath is in place, the catheter will be safely navigated through the left arm vasculature and proximal thoracic aorta to achieve super selection of the coeliac axis under fluoroscopic guidance. A contrast injection will be performed to confirm position of the catheter as well as the left gastric artery. Once the position is satisfactory, the procedure may begin. The particle suspension (containing contrast, saline, and Bead Block™ Bland Embolic Bead) is then injected through the micro catheter under fluoroscopy until satisfactory embolisation is achieved. The micro catheter and the catheter are removed, and a closure device is used to aid haemostasis at the puncture site.

  Placebo Arm: Once the sheath is in place, the C arm gantry will move in an equivalent manner to the LGAE procedure without radiation exposure. No further interventions will be performed following sheath insertion, but as far as possible the procedure will mimic the actions and experience of the LGAE arm. The patients will stay in the IR suite the same amount of time as the patients randomised to LGAE. A closure device is used to aid haemostasis at the puncture site.

  LGAE and the Placebo Procedure will usually end after 40 minutes. The patient can then be transferred to the recovery area while auditory isolation with music via headphones is still in place. A standardised handover sheet will be used for all participants when transferring them from angio suite to recovery area.

  Patients in both trial arms will undergo the same recovery procedures. Neurovascular puncture site observations are carried out on the hand or groin in regular intervals. The patient will be discharged at 4 hours.

- At baseline (prior to intervention), and at 3, 6 and 12 months post-procedure, patients will attend a mechanistic visit at the Imperial Clinical Research Facility Hammersmith Hospital. During each mechanistic visit, the following tests will be performed and data collected:
    - Body measurements: weight, height, neck, waist, hip circumference, pulse and blood pressure
    - Mixed Meal Tolerance Test including measurements of clinical markers (e.g. HbA1C, insulin, glucose, FBC, U&E, LFT, lipids), gut hormones (e.g. Ghrelin, PYY, GLP-1) and patients will be asked to complete Eating behaviour and quality of life Questionnaires (SF36-V2, IQWOL lite, HADS, DEBQ, EPIC FFQ and VAS)
    - Gastric Emptying Study (paracetamol test)
    - Food Intake Study (meal and food diaries)

PRIMARY ENDPOINT

- Absolute difference in percent weight loss at 12 months

SECONDARY ENDPOINTS

- Absolute difference in percent weight loss at predetermined time points other than 12 months
- TBL at 12 months, i.e. the absolute change in weight (in kg)
- Proportion of patients with ≥5% %TBL at 12 months
- Changes in:
    - Gut hormones
    - Hunger and satiety scores (Visual Analogue Scales)
    - Food intake (meal test and food diaries)
    - Delay in gastric emptying (paracetamol test)
    - Eating behaviour and quality of life Questionnaires (SF36-V2, IQWOL lite, HADS, DEBQ, EPIC FFQ)
- Improvement in markers of obesity related complications (blood pressure, cholesterol levels, glycaemia as assessed by HbA1c, fasting glucose and insulin)
- Frequency of adverse events
- Preference of treatment arm

1. BACKGROUND

1.1 Rationale for the study

Nearly one quarter of UK adults are obese (BMI greater than 30kg/m^2). By 2050, obesity is predicted to affect 60% of adult men, and 50% of adult women[1]. Obesity is a leading cause of preventable death worldwide and associated with a range of health problems including type 2 diabetes, cardiovascular disease and cancer. The resulting NHS costs attributable to being overweight and obese are projected to reach £9.7 billion by 2050, with wider costs to society estimated to reach £49.9 billion per year[1]. These factors combine to make the prevention of obesity a major public health challenge.

Currently about £6 billion are spent on obesity treatment, with another £10 billion on diabetes which is closely linked to obesity. Current diet and lifestyle therapies produce modest weight loss of 3-5%, and multidisciplinary programs are costly to deliver[2]. Only one drug is currently available in England for treating obesity, Orlistat, and this produces a placebo-subtracted weight loss of about 3-5%. Collectively these non-surgical lifestyle measures are grouped as 'Tier 3' programs and are commissioned by Clinical Commissioning Groups (CCGs).

Bariatric surgery (Tier 4 intervention) is increasingly being undertaken and is highly effective achieving 20-30% weight loss, which is well-maintained and with resolution of many obesity co-morbidities. While it is cost effective (recommended by NICE), provision remains low. Of 2.6 million currently eligible for bariatric surgery in the UK based on NICE criteria, only 5557 underwent bariatric surgery in 2014-15 and even fewer 5184 in 2015-16[3]. The vast majority of eligible patients are not offered, nor choose to undergo surgical treatment. Furthermore, the expense of bariatric surgery (HRG tariffs FZ 84/85) for 2017-18 ranges from £5078-5809 (without MFF) and the cost of these procedures understandably remains of concern to commissioners. Bariatric surgery requires general anaesthesia and usually 1-3 nights in hospital stay which may not be acceptable to all. Complications although rare (National Bariatric Surgery Registry data from 2014 notes an in hospital mortality rate of 0.07% and an overall surgical complication rate of 2.9%) can be devastating.

There is a need for more effective alternatives to tier 3 lifestyle interventions that are cheaper and safer alternatives to tier 4 surgical treatments and deliver sustained weight loss of >5% for those with a BMI >35.

1.2 Existing Research

Animal studies in porcine and canine models have shown that LGAE suppresses ghrelin levels, resulting in weight loss. Arepally[5], Paxton[6] and Bawudun[7] have all described left gastric artery embolisation with resultant significant reduction in plasma ghrelin, body weight, and subcutaneous fat.

Experimental medicine studies: LGAE has developed from observations in patients undergoing embolisation for other reasons, such a gastrointestinal bleeding: A retrospective case-controlled study found a 7.3% average decrease in body weight at 3 months in 19 patients who underwent LGAE for life-threatening haemorrhage compared to 2% in 28 age-matched controls who underwent embolisation other than the left gastric artery for upper gastrointestinal bleeding (P=0.001)[8]. In another retrospective review of patients who

underwent arterial embolisation for acute upper gastrointestinal haemorrhage between January 2002 and January 2014, the left gastric artery embolisation group (N=10) had a significantly greater reduction in body mass index compared with the control group (N=22) at 1 month (-9.8% vs. -4.0%, p=0.042) and 4 months (-11.7% vs. +0.1%, p=0.033). The authors concluded that left gastric artery embolisation provided early post-procedural weight loss that may persist for at least 1 year[9].

In interventional studies in bariatric patients results were encouraging: In a prospective, single-arm study of five patients, Kipshidze[10] showed weight loss of 16% and 17% at 6 and 24 months, respectively, as well as reduced ghrelin levels after LGAE. In the US FDA–supervised investigational device exemption study, Weiss[11] reported 7% total body weight loss at 3 months (maintained at 1 year, N=20 personal communication), and Syed[12] reported a mean 17.2% excess weight loss at 6 months. A recent single arm study with 9 months data in 5 patients (mean BMI 38), published in October 2017, also demonstrated that LGAE is: 1) safe (superficial linear ulceration below the cardia was seen in 1 patient 3 days after LGAE and healed within 30 days); 2) suppresses the production of ghrelin (decreased by 40.83%, 31.94%, and 24.82% at 3, 6, and 9 months after LGAE), and 3) results in weight loss (8.28 ± 7.3 kg, 10.42 ± 8.21 kg, and 12.9 ± 14.66 kg at 3, 6, and 9 months)[13].

1.3 Risk / Benefit Assessment

Benefits:

Compared to bariatric surgery, benefits of the proposed intervention (LGAE) include a minimally invasive percutaneous technique that can be done under local anaesthesia with sedation, taking only 40 minutes, as a day case.

Risks:

Phase 1 safety assessments for LGAE are complete and well established for treating life-threatening gastric hemorrhage over 40 years[4]. Known risks include:

(i) Adverse events related to embolisation:
Phase 1 human studies have already demonstrated the safety of LGAE for weight loss. To date just 6 minor adverse events in total have been recorded in the literature, namely, 5 superficial gastric erosions healing by 30-90 days and 1 case of subclinical pancreatitis out of 65 approximate cases in total.

Other risks and adverse events (all participants) include:

(i) Local anaesthetic: Mild pain may be experienced at the wrist or groin during local anaesthetic infiltration. There is also a very small risk of an allergic reaction (1 in 10,000) during local anaesthetic infiltration.
(ii) Sedation: There is a very small risk (1 in 20) of feeling drowsy that can last for 5-10 minutes after the procedure is over but can be reversed if needed.
(iii) Radiation Exposure (Screening CT Angiogram scan) equivalent to 3.3 years natural background radiation (radiation present in the environment) in the UK and gives a risk of inducing cancer of 1 in 2660.

(iv) Radial artery puncture: Local complications of TRC (transradial catheterization) are rare; including radial occlusion (reported as 7.9% immediate reducing to 5.5% after 7 days in one large series) however this is almost always asymptomatic if the ulnar artery has been demonstrated as patent prior to the procedure. Local haematoma rates are low (1-2 per 1000 major bleeding rate that requires intervention). Adverse events during femoral artery puncture are identical to radial artery puncture.

(v) Contrast injection: Average rates for a contrast allergy are very low. The rate of acute adverse events for low-osmolar contrast agents is approximately 0.2%–0.7% and for severe acute reactions 0.04%. Fatal reactions to contrast media are rare, with an incidence of one in 170,000 injections.

(vi) Blood sampling: This may cause minor discomfort or superficial bruising. In rare cases vessel or nerve injuries can happen.

Additional risks for participants in the LGAE group:

(vii) Radiation Exposure (LGAE procedure) equivalent to 6 years natural background radiation (radiation present in the environment) in the UK and gives a risk of inducing cancer of 1 in 1420.

(viii) Catheter insertion: There is a 1-3% (1-3 in 100) risk of infection when inserting a catheter through the artery in the wrist or groin.

(ix) Harm to the unborn child: LGAE has not yet been studied in pregnant women. Participation in this study requires that women of child-bearing age undergo a pregnancy test before receiving the procedure and agree to use acceptable contraception for the duration of the study. If a patient becomes pregnant during the course of the study than their participation in this trial will end.

(x) Potential complications of the Bead Block™ Bland Embolic Bead are listed in the Manufacturer's (Boston Scientific Corporation) Instructions for Use.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- To evaluate the efficacy of left gastric artery embolisation (LGAE) on weight loss and obesity related comorbidities at pre-determined times points over a 12 month follow up period.

2.2 Secondary Objective

- To evaluate the mechanism of action of LGA embolisation at pre-determined time points over a 12 month follow up period.
- To evaluate the safety of LGA embolisation by adverse event recording.

2.3 Primary Endpoint

- Absolute difference in percent weight loss at 12 months.

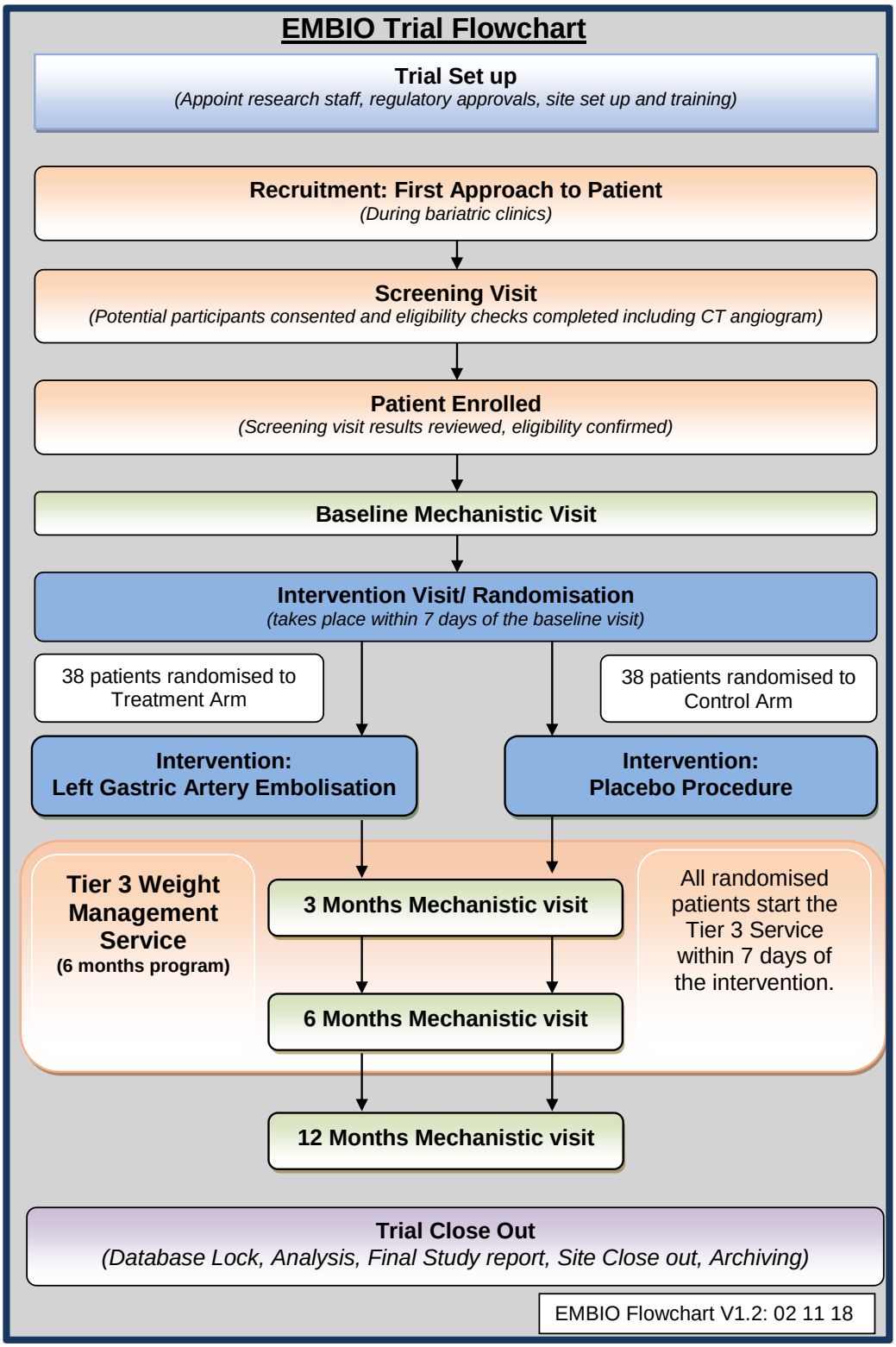
2.4 Secondary Endpoints

- Absolute difference in percent weight loss at predetermined time points other than 12 months
- TBL at 12 months, i.e. the absolute change in weight (in kg)
- Proportion of patients with ≥5% %TBL at 12 months
- Changes in:
    - Gut hormones
    - Hunger and satiety scores (Visual Analogue Scales)
    - Food intake (meal test and food diaries)
    - Delay in gastric emptying (paracetamol test)
    - Eating behaviour and quality of life Questionnaires (SF36-V2, IQWOL lite, HADS, DEBQ, EPIC FFQ)
- Improvement in markers of obesity related complications (blood pressure, cholesterol levels, glycaemia as assessed by HbA1c, fasting glucose and insulin)
- Frequency of adverse events
- Preference of treatment arm

3. STUDY DESIGN

This is a multi-centre, double-blinded randomised controlled trial including two participating centres in England (Imperial College Healthcare NHS Trust and University College London Hospitals NHS Trust). Recruitment and Intervention will be carried out at the participating centres. All mechanistic assessments will be completed at Imperial College London (Imperial Clinical Research Facility, Hammersmith Hospital). Participants will be randomised to LGAE or placebo procedure (see figure 1).

Figure 1: Study flow chart



Mechanistic Visits:

- Body measurements: weight, height, neck, waist, hip circumference, pulse and blood pressure
- Meal test including collection of clinical markers (e.g. HbA1C, insulin, glucose, FBC, U&E, LFT, lipids), gut hormones (Ghrelin PYY, GLP-1, Oxyntomodulin) and collection of appetite questionnaires (Visual Analogue Scales)
- Gastric Emptying Study (Paracetamol test)
- Food Intake Study (meal and food diaries)
- Eating behaviour and quality of life Questionnaires (SF36-V2, IQWOL lite, HADS, DEBQ, EPIC FFQ)

4. PARTICIPANT ENTRY

4.1 Trial setting and population

This trial is open to all Tier 3 patients attending bariatric clinics at two NHS Trusts. A total of 76 patients (50% left gastric artery embolisation vs. 50% placebo procedure) will be recruited into this trial.

(i) Inclusion criteria

1. Adults aged 18-70 years
2. BMI 35-50Kg/m^2
3. Ability to lie supine
4. Appropriate anatomy of the Left Gastric Artery and coeliac plexus on CT Angiogram
5. Willing and able to provide informed consent.

(ii) Exclusion criteria

1. Haematological , hepatic or renal dysfunction
2. Weight >150kg,
3. HbA1c > 8.5%
4. Known renal, vascular or aortic disease
5. Malignancy
6. Prior major abdominal surgery, prior gastric or bariatric surgery
7. Prior abdominal radiotherapy,
8. GI bleeding or bleeding diathesis
9. Allergy to iodinated contrast,
10. Known gastric ulceration or active H. Pylori infection
10. Positive pregnancy test in females of childbearing age
11. Chronic NSAID use
12. Current use of insulin or sulphonylurea
13. Current use of anti-tricyclic anti-depressants or steroids

5. PROCEDURES AND MEASUREMENTS

5.1 Identification and recruitment of patients

Participants will be recruited from bariatric outpatient clinics at both participating sites using the following approaches:

1. Patients will attend the standard bariatric weight loss seminar which is part of their routine care. Here they will receive an information talk about various weight loss treatments and the trial will be presented to them by a member of the bariatrics clinic. In the event that a patient is interested in the trial, they will be given the patient information sheet (PIS). The member of the bariatrics team will also take their details to contact them later and enquire about their interest in attending a screening visit.

2. The bariatric surgeon will flag potentially eligible participants and talk to them about the trial and provide a PIS during their routine visit at the bariatrics clinic. The bariatric surgeon will notify the local bariatrics team about the potential participant so they can contact them later and enquire about their interest in attending a screening visit.

5.2 Screening and pre-randomisation evaluations

Potentially eligible participants will be invited to attend a screening visit. They will be informed about the nature of the trial and given relevant information about the objectives of the research, benefits and possible adverse events, verbally and in writing. Participants will have the opportunity to ask any questions and will be informed of their right to withdraw from the trial at any time, without giving reasons and without prejudicing further treatment. Participants will be given as much time as is required to consider their participation in the trial.

After obtaining informed consent at the screening visit (more details in section 9.9), subject's eligibility will be further assessed and documented (see visit schedule section 5.6 for more details).

Patients will be consented to longitudinal follow-up outside of the EMBIO trial in order to capture information regarding their health service needs. This will be primarily from hospital medical records.

5.3 Interventions and Randomisation

Intervention: Both LGAE and Placebo Procedure

Patient attends the Interventional Radiology / Angiography suite. Following Barbeau test for left radial artery (via the wrist) access is performed. If Barbeau test precludes radial access, femoral access (via the groin) will be performed. The protocol for either radial or femoral access is exactly the same. The patient will be placed in the supine position on imaging table with the arm extended. Next an intravenous catheter will be sited and moderate sedation administered. Prior to radial access, 2mg iv midazolam is given (up to 10mg midazolam may be given in 1mg aliquots according to the level of sedation and patient discomfort). Moderate levels of conscious sedation are to be maintained. This will cause patients to have no recollection of the proceedings. Standard monitoring equipment will be used. The wrist will be exposed and prepared with 2% chlorhexidine. A sterile fenestrated drape - Klass drape (Merit medical) will be placed over the wrist. The patient's view of the x-ray monitors and the local puncture site will also be restricted by the use of this erected sterile drape so the patient cannot see the procedure.

Auditory isolation of participants with over the ear headphones playing music will be used in all cases.

The skin and subcutaneous tissues are infiltrated with 1% lidocaine under ultrasound guidance. "Pre radial cocktail" is given (2.5mg verapamil, 3000u heparin, and 200u GTN) to reduce distal arterial spasm and vessel thrombosis. A hydrophilic sheath is inserted in to the radial artery.

Randomisation: The operator will now randomize the patient to either LGAE or placebo procedure 1 to 1 using the online OpenClinica database which will be accessed on a computer inside the angiography suite. In the event that the OpenClinica database is not accessible then a manual randomisation system will be available.

LGAE Arm: Angled glide wire supported by an angled catheter is placed into radial artery. The catheter will be safely navigated through the left arm vasculature and proximal thoracic aorta to achieve super selection of the coeliac axis under fluoroscopic guidance. A contrast injection will be performed to confirm the position of the catheter as well as the left gastric artery. This will then be cannulated with a microcatheter and contrast injection will be used to confirm the position and to evaluate the territory of supply and anatomy of the branches. Once the position is satisfactory, the procedure may begin.

The Bead Block™ Bland Embolic Bead will be used in line with the Manufacturer's (Boston Scientific Corporation) Instructions for Use. The syringe contains an admixture of contrast and saline with 1-2 vials of Bead Block™. The particle suspension is then injected through the micro catheter in small aliquots under fluoroscopy until satisfactory embolisation is achieved (cessation of forward flow, or flow in both directions for 6 cardiac cycles). A further vial of particles may be required. Once the radiological end point has been achieved, the micro catheter and the catheter are removed from the sheath and a closure device is used to aid haemostasis at the puncture site. Additional manual pressure will be applied to the puncture site if needed as per device recommendations.

Placebo Arm: Once the sheath is in place, the C arm gantry will move in an equivalent manner to the LGAE procedure without radiation exposure. No further interventions will be performed following sheath insertion, but as far as possible the procedure will mimic the actions and experience of the LGAE arm. The patients will stay in the IR suite the same amount of time as the patients randomised to LGAE. A closure device is used to aid haemostasis at the puncture site. Additional manual pressure will be applied to the puncture site if needed.

LGAE and the Placebo Procedure will usually end after 40 minutes. The patient can then be transferred to the recovery area.

A study specific manual will be developed to ensure that the documentation in the IR suites in both centres is managed in a consistent and appropriate manner. During the procedure, the nurses will document that the patient has participated in the EMBIO trial. They will not document treatment allocation or any details of intervention in the medical notes and the local hospital database (e.g. CERNER).

Recovery: Both LGAE and Placebo Procedure

A standardised handover sheet will be used for all participants when transferring from angio suite to recovery area without mentioning details about the embolisation part of the procedure. The handover between the IR suite staff and recovery ward nursing staff will be carefully managed to include only the location of access sites and medication given (which will be identical for the two randomised arms, as all patients will have received sedation). During the handover process patients will continue to have auditory isolation with music via

headphones for the period of handover. The IR suite staff involved in the procedure will have no contact with the patient after handover.

Patients in both trial arms will undergo the same recovery procedures. Patients can mobilise immediately with radial access but should remain in bed until sedation has worn off. Neurovascular puncture site observations are carried out on the hand or groin every 15 minutes for 1 hour and then every 30 minutes thereafter by the recovery nurses using the local SOP for management of an arterial puncture site. Any complications should be managed as per the SOP. The patient will be discharged at 4 hours.

To further assess the fidelity of blinding, patients will be asked just before being discharged home, what procedure they think they underwent and why. Patients and recovery staff will also be asked to guess one of the following: (1) Embolisation (2) Placebo, (3) Don't know and asked to state the certainty of their answers grade 1-5 with 5 being most sure. This will form the basis of the Blinding Index.

Discharge: Both LGAE and Placebo Procedure

Documentation and instructions: A standardised discharge summary (exactly the same for placebo and LGAE arm) will be sent to the GP for all participants. The instructions on this discharge summary will include information on managing the post-procedure arterial puncture site. All participants will be given an emergency contact number to contact a member of the local trial team if there are any post-procedural related issues. This person will be able to advise on further management and on the need to unblind if necessary.

All participants will take Lanzoprazole 30 mg once a day for one week before and continue for 6 weeks after the intervention. Lanzoprazole will be given to patients during visit 2 (baseline mechanistic visit) and visit 3 (during discharge).

5.4 Blinding and Unblinding

Only staff inside the IR suite will be unblinded but will have no future contact with the participant. The unblinded interventionists will not be involved in clinical follow up or data evaluation. All staff outside the IR suite will remain blinded at all times. Medical records will mention that participants have taken part in EMBIO. The interventionist will enter the treatment allocation and other procedure related information in the Intervention Form in the OpenClinica database. To maintain blinding, access to the Intervention Form will be controlled so that only the intervention team can enter and the un-blinded monitor view data in this part of the database.

The patient will have an emergency contact number managed 24/7 by a member of the local trial team. Even if serious adverse events occur from the arterial puncture or later during the trial, at the principal investigator's discretion, trial participation can continue without unblinding.

The trial staff performing the follow up assessments (mechanistic testing) will remain blinded to treatment allocation.

Unblinding procedures will be clearly documented in a trial specific procedure manual for site and sponsor. The site manual will include (a) the reasons that unblinding may be required (b) who is authorised to unblind and (c) the method for provision of 24-hour access to unblinded information in the event of an emergency. The manual will also include details on unblinding arrangements at the end of the trial.

The following activities will be implemented in order to ensure fidelity of blinding:

- A training programme for the interventional radiologists specifically on optimum methodology to maintain blinding. Five dummy runs will be performed before performing the LGAE/ placebo procedure on trial participants.
- After the 1st five trial cases, the DMEC will assess fidelity of blinding through the calculation of the blinding index. If this is <100 %, further training will be undertaken.
- The DMEC will review the fidelity of blinding throughout the trial. The frequency of the review will be set out in the DMEC charter.
- The blinding index for patients and the clinical team will be analysed at the end of the trial and will be published with the primary manuscript.

5.5 Follow-up

5.5.1 Lifestyle program

All participants will follow the hospital's standard tier 3 clinical lifestyle program for weight loss from the time of the intervention (see figure 1 for a detailed outline of all study visits). Clinical follow up of the patients is managed under a specialist Bariatric Lead together with a specialist Bariatric dietician.

5.5.2 Mechanistic assessments

At baseline (prior to intervention), at 3, 6 and 12 months post-procedure, all patients will attend a mechanistic visit at the Imperial Clinical Research Facility (ICRF) at Hammersmith Hospital in London (see section 5.6).

During each mechanistic visit, the following tests will be performed and data collected:

- Body measurements: weight, height, neck, waist, hip circumference, pulse and blood pressure
- Clinical markers for safety and metabolic status (e.g. HbA1C, insulin, glucose, FBC, U&E, LFT, lipids)
- Mixed Meal Tolerance Test including measurements of insulin, glucose, gut hormones (e.g. Ghrelin, peptide YY, GLP-1, Oxyntomodulin) and bile acid. Measurement of subjective sensations of appetite, nausea, hunger, satiety using Visual Analogue Scales.
- Gastric Emptying Test (Paracetamol test – contemporaneous with Mixed Meal Test)
- Food Intake Test (meal and food diaries)

- Eating behaviour and quality of life Questionnaires (SF36-V2, IQWOL lite, HADS, DEBQ, EPIC FFQ)
- Clinical evaluation and changes to medication
- Adverse events
- Preference of treatment arm

Mixed Meal Tolerance Test:

This will involve the administration of a standardized mixed-meal (220 ml Ensure Plus, providing 330 kcal of which 15% is derived from protein, 57% carbohydrate and fat 28%) to fasting participants, followed by measurements of glucose and insulin at -15, 0, 15, 30, 60, 120, 180 minutes, where zero is the time of administration of the meal. Indices of insulin sensitivity that will be calculated include HOMA-IR (an index of hepatic insulin sensitivity) and the Matsuda and DeFronzo whole-body insulin sensitivity index, which has been established in previous studies to estimate changes in insulin sensitivity in patients with obesity and diabetes after RYGB[18, 19]. Gut hormone changes will be measured during this dynamic test. Other clinical markers and appetite scores using Visual Analogue Scales will also be collected[20].

Gastric Emptying Test:

Participants will take 1.5 g paracetamol dissolved in 50 ml water, added to the mixed meal. Paracetamol levels will be measured serially at the same time points noted above, and the time to the peak concentration calculated as a measure of gastric emptying. For further details see Falken et al[21].

Food Intake Test:

An ad libitum meal, provided to excess, will be served and participants will be allowed 20 minutes to eat. The participant will be instructed to eat until they feel comfortably full. Pulse and blood pressure will be taken every 30 minutes, or more often at the discretion of the attending physician. Simultaneously participants will be asked to fill in a VAS to record appetite and nausea levels every 30 mins. Blood samples for glucose, insulin and gut hormones will be taken prior to the meal and 30 and 60 minutes after eating. Three day food diaries will also be collected on the study day.

Eating Behaviour and Quality of Life Questionnaires:

Participants will complete eating and behavioural questionnaires (duration 20-30 minutes) to assess eating behaviour and attitudes and personality measures related to reward sensitivity and mood. If they do not manage to complete all the questionnaires in the time available they will be able to complete them at home using pen and paper or over the internet.

- Short-Form 36 Health Survey Questionnaire (SF36-V2) - to assess quality of life[16]
- Impact of Weight on Quality of Life IQWOL lite – to assess quality of life[14]

- Hospital Anxiety and Depression Scale (HADS) - to assess symptoms of anxiety and depression[22]
- Dutch Eating Behaviour Questionnaire (DEBQ) − to measure restraint, emotional and external influences on eating behaviour[17]
- EPIC Food Frequency Questionnaire (European Prospective Investigation into Cancer and Nutrition) – to quantify changes in food intake[15]

Patients will also be asked to indicate their treatment arm preference meaning that they will need to answer the following question during mechanistic visits 4, 5, and 6: 'Knowing what has happened now - would you have chosen the same procedure?'

5.6 Visit Schedule

A summary of all visits and procedures has been outlined in Table 1.

Table 1. Visit Schedule

	Screening	Baseline Mechanistic	Intervention	Mechanistic Follow-ups		
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Week/Day	Max -3m	- 1w ± 7d	- 0w ± 3d	3m ± 7d +	6m ± 7d	12m ± 7d
Informed consent (section 5.2)	X					
Inclusion & exclusion criteria (section 4.1)	X					
Demography (section 5.2)	X					
Medical history/medication (see section 5.7.1)	X					
Physical examination (see section 5.7.1)	X					
Body measurements: weight, height, pulse and blood pressure (see section 5.7.2)	X	X	X	X	X	X
Body measurements: neck, waist & hip circumference (see section 5.7.2)		X		X	X	X
Routine Blood Test (see section 5.7.3)	X**	X	X	X	X	X
Urine Dipstick and Pregnancy Test (see section 5.7.4)	X	X*	X*	X*	X*	X*
H. Pylori Breath Test (see section 5.7.5)	X					
ECG (see section 5.7.6)	X**					
CT scan angiography of the splanchnic vessel	X					
Randomisation (section 5.3)			X			
LGAE or Placebo Procedure (section 5.3)			X			
Blinding Index			X			
Distribution of Proton Pump Inhibitors (section 5.3)		X	X			
Changes in medical history /medication/ adverse events		X	X	X	X	X
Mixed Meal Tolerance Test (section 5.5.2)		X		X	X	X
Gut hormones (section 5.5.2 and 5.7.8)		X		X	X	X
Appetite Visual Analogues Scales (section 5.5.2 and 5.7.8)		X		X	X	X
Gastric Emptying Test (section 5.5.2)		X		X	X	X
Food Intake Test (section 5.5.2 and 5.7.8)		X		X	X	X
Eating and Behaviour Questionnaires (section 5.5.2)		X		X	X	X
3-day Food Diary (section 5.5.2 and 5.7.8)		X		X	X	X

X= performed in all patients unless otherwise stated; *= pregnancy test only performed if a menstrual period is missed; **= review of results from Tier 3 clinic

5.7 Assessments and Evaluations

5.7.1 Medical history and physical examination

A medical history will be performed at the screening visit to record illnesses, disorders and medications. This information needs to be updated on all follow-up visits and any changes recorded in the eCRF. Any changes as compared to the screening visit which fulfil the criteria of an AE must be recorded as an AE.

Physical examination will be performed at the Screening visit (study visit 1) according to local procedure. During this visit the doctor will perform a cardiology, respiratory and gastrointestinal examination on the patient. They may go on to examine other appropriate systems if clinically indicated. Any abnormal, clinical significant findings must be recorded in the eCRF.

5.7.2 Body measurements

Weight and height will be measured (without shoes) at all visits. The same pair of scales should preferably be used throughout the trial. BMI will be calculated as follows: BMI = weight (kg)/heightx2 (m^2).

Neck, waist and hip circumference will be determined at all mechanistic visits (visits 2, 4-6). Three consecutive measurements will be performed at each visit and recorded in the eCRF. The waist circumference will be measured in the horizontal plane to the nearest 0.5 cm using non-stretchable measuring tape.

Pulse will be recorded at all visits after resting for five minutes in a sitting position. Systolic and diastolic blood pressure will be measured in sitting position at all visits.

5.7.3 Routine Blood Tests

Routine blood samples including HbA1C, insulin, glucose, full blood count, routine biochemistry (including Urea and Electrolytes - U&E's), liver function test (LFT), and lipids will be obtained at study visits 2, 3, 4, 5, and 6 after an 8 hour fast and processed by the local laboratory at Imperial College London NHS Trust or at University College London NHS Trust using standard methods for routine tests. Any remainders of samples will be discarded. During the screening visit, routine blood test results from the Tier 3 clinic will be reviewed to assess eligibility.

The total amount of blood to be taken from each subject during the trial is a maximum of 600 ml.

5.7.4 Urine dipstick and pregnancy test

Urine dipstick tests will be performed at the screening visit to determine pathological changes (e.g. protein in urine and any evidence of infection) in patient's urine. Any abnormal, clinical significant findings must be recorded in the eCRF.

Female urine pregnancy tests will be performed for females of childbearing potential at screening and at any time during the trial if a menstrual period is missed.

Any remainders of samples will be discarded.

Female patients of child bearing potential who agree to take part in the EMBIO trial will be asked to confirm during the informed consent process that they have no intention to get pregnant during the duration of the trial period. The importance of using adequate contraceptive methods will be reinforced to each individual at screening and during each study visit. In the unlikely event that a patient's pregnancy test comes back positive or if a patient is identified as confirmed pregnant, the patient will be withdrawn from the trial.

Pregnancy tests will not be required for females who have undergone a hysterectomy or bilateral tubal ligation, or for females above the age of 50, who have been without a menstrual period for at least one year.

5.7.5 H. Pylori Breath Test

All patients attending the screening visit must be tested for the presence of H. Pylori. Those patients testing positive for H. Pylori will be offered eradication therapy for 1 week following the standard triple therapy guidelines published in the British National Formulary (BNF). H. Pylori treatment will be managed by the patient's GP. Repeat testing will be requested via the GP and if negative and the patient meets all other eligibility criteria, they will be invited for their next study visit (visit 2/ baseline mechanistic visit).

5.7.6 ECG

The ECG results from the Tier 3 clinic will be reviewed at the screening visit. The ECG will be interpreted, signed and dated by the investigator before the next study visit.

The interpretation must follow the categories:
- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

If the ECG is abnormal and clinically significant, then the patient will be sent for further investigations and if necessary treated prior to attending the baseline visit (visit 2). If the abnormality cannot be treated then they will not be able to enter the trial.

5.7.7. CT Angiogram

All trial participants will undergo a CT angiogram to assess left gastric artery anatomy as part of the eligibility checks. A CT angiogram is needed to assess anatomy and to identify patients at the screening visit who will not be suitable (individuals with aberrant anatomy) for fundal embolization i.e. screen failures.

The CT Angiogram will involve a volumetric CT scan being performed of the whole abdominal aorta at an arterial time point after the infusion of intravenous contrast. The whole aorta from the base of scull to the common femoral artery vasculature will be scanned.

In detail, CT Angiography scans will be acquired using multidetectors scanners. The slice thickness will be 0.625mm and will be reconstructed at 0.6mm intervals. Nonionic iodinated contrast medium (350mg/ml) or (400mg/ml) will be injected via large bore antecubital cannula at a rate of 4-6ml/s, tailored to the body weight of the patient. The arterial phase of the scan will be acquired. The scan triggering time will be determined by automated triggering bolus centred over the descending thoracic aorta. The chest (from thoracic inlet) and abdomen parts of the body will be covered.

5.7.8. Mechanistic Assessments

Gut hormones

In addition to the routine biochemistry and haematology, venous blood samples will be taken at intervals by venepuncture through a cannula placed in the antecubital fossa. No more than 100 mls will be taken on each mechanistic visit (2, 4, 5, 6). Serial plasma levels of gut hormones, bile acids and associated peptides will be measured and stored at the Imperial Clinical Research Facility in Hammersmith Hospital and the Department of Investigative Medicine. Assays will be performed using in-house assays, outside contracts and commercial kits for radio-immunoassay and ELISA.

Further details will be defined in study specific guidelines for sample collection and handling and in the lab manual.

Samples will be kept beyond the end of the trial and stored in accordance with the Human Tissue Act. All mechanistic samples will be registered with the Imperial College Healthcare Tissue Bank.

Food diaries

Around each visit participants will be asked to keep a food diary for up to three days in order to determine their dietary intake.

Visual analogue Scales

Visual analogue scales will be used to assess subjective feelings including hunger, nausea, fullness, sleepiness, stress, anxiety, volume of food that can be eaten and food palatability at intervals throughout the study visits (2, 4, 5 and 6). These will be given during fixed/test meal sampling periods.

6. EARLY DISCONTINUATION OF INDIVIDUAL PARTICIPANTS

6.1 Withdrawal from Trial

Withdrawal from the trial refers to discontinuation of trial procedures and can occur for the following reasons:

- At the request of the patient
- If a patient falls pregnant
- Adverse event/ Serious Adverse Event
- If the investigator considers that a subject's health will be compromised due to adverse events or concomitant illness that develops after entering the trial.
- Loss to follow-up

A participant may permanently withdraw from the trial:
EITHER
1. Pre-intervention: this means that they will not attend the follow-up visit at 12 months
OR
2. Post-intervention: this means that they will attend the follow-up visit at 12 months (visit 6)

In the event that the subject is unable to attend their 12 months follow-up visit in person, a telephone appointment can be arranged and the following data should be obtained:

- Body weight in kg (obtained via patients GP Practice)
- Adverse events
- Medical history/medication changes

Participants who have withdrawn from the trial will not be replaced as the sample size allows for a 10% drop-out rate.

7. SAFETY REPORTING

7.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, whether or not considered related to the trial protocol.

7.2 Adverse Event recording

All adverse events, non-serious and serious, occurring after consent has been obtained will be reported for this trial, except for elective medical procedures.

For the purposes of the trial, AEs will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. SAEs will be recorded throughout the trial.

(i) Severity of Adverse Events

Definitions for assessment of severity:

Mild: Awareness of event but easily tolerated
Moderate: Discomfort enough to cause some interference with usual activity
Severe: Inability to carry out usual activity

(ii) Causality of Adverse Events

Definitions for assessment of causality:

Unrelated: No evidence of any causal relationship
Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.3 Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results occurring during the trial will be recorded as adverse events. The trial physician will decide what the best course of action is i.e. referral to GP, hospital, clinic or other. Again, the event will be followed up according to local practice until stabilised, resolved, diagnosed/treated, or the last trial follow-up visit, whichever is sooner.

7.4 Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" 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.

** “Hospitalisation” means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before trial inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a patient, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

7.5 Reporting of AEs

All such AEs, whether expected or not, should be recorded in the adverse event section of the relevant case record form within one month of the form being due.

The trial physician will decide what the best course of action is i.e. referral to GP, hospital, clinic or other. AEs will be followed up according to local practice until stabilised, resolved, diagnosed/ treated or the last trial follow-up visit, whichever is sooner.

7.6 Reporting of SAEs

Rapid reporting of all SAEs i.e. within 24 hours, occurring during the trial must be performed as detailed in the SAE reporting instructions. If the investigator becomes aware of safety information that appears to be related to the trial, involving a subject who participated in the trial, even after an individual subject has completed the trial, this should be reported to the Sponsor.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF).

For trials of medical devices that are non UKCA/CE-marked, such as the EMBIO trial, the following must be reported to the MHRA by the Sponsor or ICTU if delegated using local SOPs:

a) Any SAE (whether initially considered to be device related or not)
b) Any Investigational Medical Device Deficiency that might have led to a SAE if
    1. Suitable action had not been taken or
    2. Intervention had not been made or
    3. If circumstances had been less fortunate
c) New findings/updates in relation to already reported events

The Trial Manager should ensure reportable events are reported to the CI and Sponsor within 24 hours.
All SAE data relating to a patient will be pseudo anonymised and shared with the device manufacturer for safety reporting purposes.

SAEs which indicate an imminent risk of death, serious injury or serious illness and require prompt remedial action for other patients, users or other persons or a new finding to it, must be reported to the MHRA by the Sponsor/ICTU Trial Manager immediately but not later than 2 calendar days following the date the Sponsor is made aware.

Any other reportable events should be reported immediately but not later than 7 calendar days following the date the Sponsor is made aware.

The device manufacturer should also be informed within 24 hours of the SAE or device deficiency if indicated in the trial's communication agreement.

The device manufacturer can request trial data (in accordance with the agreement between the Sponsor and manufacturer) in the event that an unexpected problem with the device or related AE/ SAE occurred. Information will be provided to the manufacturer at the discretion of the chief investigator.

(ii) Reporting of SAEs that are related and unexpected

Related: resulted from administration of the investigational medical device or any of the research procedures.

Unexpected: type of event is not listed in the protocol as an expected occurrence

SAEs that are related and unexpected should be notified to the relevant REC, the Sponsor and the DMEC in accordance with local requirements.

Follow up of patients who have experienced a related and unexpected SAE should continue until recovery is complete or the condition has stabilised. Reports for related and unexpected SAEs should be unblinded prior to submission.

(iii) Reporting of SAEs that are device related and unexpected

If an SAE is determined to be unexpected (not previously described in the IB, or protocol) and related to the trial device then it is considered an USADE (unanticipated serious adverse device effect). For USADEs, in addition to reporting to the MHRA, the sponsor, or ICTU Trial Manager when delegated, must also report the event to the REC within 15 days in line with HRA guidelines. The Trial Manager should also notify the Device Manufacturer and Investigators at all sites of the USADE.

7.7 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

8. STATISTICAL ANALYSES

8.1 Sample Size and power considerations

This will be a two-arm randomised controlled trial, where the control is the placebo procedure and the intervention is embolisation of the left gastric artery. In a previous weight management trial[23], investigating using a drug for weight loss in patients with BMI>27, patients experienced a percentage (%) change in body weight (loss) of -8.0%±6.7% in the intervention arm compared to -2.6%±5.7% in the control arm at 56 weeks. From clinical judgment any treatment that causes >5% weight loss is regarded as clinically important. A large proportion of obese individuals with type 2 diabetes, hypertension, and hyperlipidemia experience positive health benefits with modest weight loss. For patients who are unable to attain and maintain substantial weight reduction, modest weight loss should be recommended; even a small amount of weight loss appears to benefit a substantial subset of obese patients. There are numerous examples of papers supporting the clinical benefits of >5% weight loss[24-27]. Embolisation of the left gastric artery should result in an improvement of at least 5% of the body weight at 12 months compared to placebo. Therefore we have used the same assumptions of effect size and standard deviation for the sample size calculation in this trial.

Assuming that the mean percent of body weight loss in the placebo group is 2.6% (standard deviation=5.7%) at 12 months, and the expected percent of body weight loss in the embolisation group is 8% (standard deviation=6.7%) at 12 months, without considering the dropout rate, it is estimated that a sample size of 68 participants (34 per group) will have 90% power with a two sided alpha = 0.05 to detect the effect size of a 5.4% absolute difference in the mean percent body weight loss from baseline at 12 months between the embolisation and the placebo groups. A sample size of 76 participants in total has been chosen allowing for a 10% drop out rate. The sample size was computed for a two-sample means test using the software Stata 13.2.

8.2 Stratification

Randomisation will be stratified by BMI (strata: 35≤BMI<42 and 42≤BMI≤50) which we anticipate will limit the opportunity for chance baseline imbalances in weight to occur. The choice of 42 is chosen because this is the average BMI in this cohort. We will also adjust for baseline BMI as a covariate in the primary outcome analysis of weight loss in order to obtain more precise estimates of treatment effect and also to further limit any unexpected influence of chance imbalance in baseline weight. This will be incorporated in the statistical analysis plan.

8.3 Data Analysis

(i) General approach to analyses

A detailed Statistical Analysis Plan (SAP) will be developed by the trial statistician under the supervision of the senior statistician and signed off by the Chief Investigator and trial committees. Analyses of the primary and other endpoints will be primarily on an intention-to-treat basis where all participants will be analysed in the groups to which they were allocated regardless of the treatment they received. A two-sided 5% level of significance will be used for the primary 12-month endpoint. Analyses of other outcomes will be interpreted cautiously and refer to the 95% confidence interval.

Any deviations from the SAP will be documented and signed off by the statisticians and CI, and filed in the statistics section of the Trial Master File (TMF) which will be merged with the main TMF at the end of the study.

(ii) Primary Endpoint Analysis

The primary analysis will estimate the difference between the groups in the mean percent weight loss at 12-months with 95% CI using a linear mixed-effects regression model incorporating the outcome at earlier time points of follow up, and adjusted for the stratification variable (baseline BMI).

(iii) Secondary Endpoints Analysis

Weight loss at 3 and 6 months.

The between-arm difference in the mean percent weight loss at earlier time points of follow up (3, 6 months) will be estimated from the primary endpoint analysis model which is specified to involve ‘time’ in interaction with the fixed effect covariates (including arm), and to account for correlation in the outcome over time.

This approach is intended to be taken to estimate other longitudinally measured clinical and mechanistic continuous outcomes (principally at 12 months and secondarily at earlier timepoints of follow-up, and using additional covariate-adjustment for the baseline of the outcome under analysis), such as for anthropometric indices (e.g. waist and hip circumference), QoL questionnaires (e.g. HADS), Visual Analogue Scale measures, Calories consumed from the Food Intake test, and clinical measures (such as from within the mixed meal tolerance test).

We plan to calculate AUC for each analyte (e.g. GLP-1 and PYY) of the mixed meal using the trapezoid method. We intend to use mixed linear models to analyse the analyte of the mixed meal test, the food intake and the visual analogue scale data. This takes into account the repeated measures over time. For the paracetamol absorption test, the mean time to peak concentrations for each group will be compared using two-way ANOVA.

We intend to analyse QoL questionnaires data using non-parametric analyses.

We intend to use regression to investigate the relationship between percent weight loss and the mechanistic parameters, such as the % reduction in ghrelin and change in paracetamol absorption.

Alternative methods may be required, dependent on the assumptions of the methods and the size and distribution of the data. The actual methods to be used will be justified in the approved statistical analysis plan.

(iv) Safety Analysis

Adverse events will be reported in detail to the Data Monitoring Committee. Classifications of adverse events (from drawing on the seriousness, intervention relatedness and unexpectedness of events) will be presented using frequencies by arm with 95% exact confidence intervals.

8.4 Handling Missing Data

An allowance has been made for up to 10% of the trial population to be missing the primary endpoint. An assessment will be made of the sensitivity of the primary endpoint analysis results to the impDatlicit ‘missing at random’ assumption underlying this analysis. The specific approach to be taken will depend on the level of missing data, and so the full strategy will be described in the approved statistical analysis plan.

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The investigator will ensure that this trial is conducted in full conformity with the 7th revision of the 1964 Declaration of Helsinki.

9.2 Good Clinical Practice

The trial will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines and Addendum ICH GCP E6 (R2)).

9.3 Independent Ethics Committee Approval

(i) Initial Approval

Prior to the enrolment of participants, the Research Ethics Committee (REC) must provide written approval of the conduct of the trial at named sites, the protocol and any amendments, the Participants Information Sheet and Consent Form, any other written information that will be provided to the participants, any advertisements that will be used and details of any participant compensation.

The favourable ethical opinion of the London-Central Research Ethics Committee was confirmed on 11 Oct 2019.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

The trial team, in collaboration with the Sponsor will assess whether a proposed amendment is substantial or non-substantial. For each proposed amendment, a revised version of the protocol will be prepared using tracked changes, a new version number assigned and the revised document will be reviewed and approved by Protocol Development Group and Sponsor prior to submission to the REC and Health Research Authority (HRA). The amended protocol will be sent to participating sites for local approval to be granted and the approved version will be shared with all staff involved in the trial.

(iii) Annual Progress Reports

The REC will be sent annual progress reports in accordance with national requirements, on each anniversary of REC approval, until the end of trial.

(iv) End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines.

9.4 Regulatory Authority Approval

The trial will be performed in compliance with UK regulatory requirements. The Medicines and Healthcare Products Regulatory Agency (MHRA) will be notified of the clinical investigation of a class IIb device prior to the start of the trial. In addition, the MHRA will approve amendments prior to their implementation (as instructed by the Sponsor), receive SAE reports and relevant safety updates, and be notified of the end of the trial.

9.5 HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the trial. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

The procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.

9.6 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial subjects; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the DMEC and REC within 7 days of becoming aware of the serious breach.

9.7 Insurance and Indemnity

Imperial College London, the sponsor of the trial has civil liability insurance, which covers this trial in all participating centres. Imperial College London also holds negligent harm and non-negligent harm insurance policies which apply to this trial.

9.8 Trial Registration

The trial is registered on the International Standard Randomised Controlled Trials Number (ISRCTN number 16158402) database in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

9.9 Informed Consent

Informed consent will be obtained from all participants using REC approved Participant Information Sheet(s) (PIS) and Informed Consent Form(s) (ICF).

The participant will be informed about the trial by the responsible clinician or a member of the research team and given a copy of the PIS. Informed subjects will be given an adequate amount of time to consider their participation in the trial. If the subject decides to participate

in the trial they will be asked to sign the ICF which will then be countersigned by the responsible clinician / researcher. The patient will retain one copy of the signed ICF. Another copy will be placed in the patient's medical records whilst the original will be retained in the participant's research record, at site.

After the participant has consented to take part in the trial 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 trial for the purposes of follow-up and data analysis.

The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol intervention without giving reasons and without prejudicing further treatment.

9.10 Contact with General Practitioner

It is the participating site investigator's responsibility to inform the participants' General Practitioner by letter that the participant is taking part in the trial and that they will be given one weeks' supply of Proton Pump Inhibitors prior to the procedure (during visit 2), provided the participant agrees to this, and information to this effect is included in the Participant Information Sheet and Informed Consent Form. A second letter to the GP will be issued after the patient's procedure (visit 3) to inform the GP about an additional 4 weeks supply of Proton Pump Inhibitors through the local research team. The local research team will also request from the GP that they continue the patients Proton Pump Inhibitor prescription for an additional 2 weeks after their initial 4 weeks course will be finished. A copy of the letters to the GP will be filed in the Investigator Site File.

9.11 Data Protection and Patient Confidentiality

The participating site investigator must ensure that the patient's confidentiality is maintained. On the eCRF or other documents submitted to the Sponsor, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the site investigator.

The site investigator will preserve the confidentiality of all participants taking part in the trial, which will be conducted in accordance with the General Data Protection Regulation (GDPR).

Imperial College London is the Sponsor for this study based in the United Kingdom. The Sponsor will be using information from participants and their medical records in order to undertake this study and will act as the data controller for this study. This means that the Sponsor is responsible for looking after participant information and using it properly. Imperial College London will keep unidentifiable information about participants for 25 years (as per the device manufacturer's retention policy) after the study has finished.

Participants' rights to access, change or move their information are limited, as information needs to be managed in specific ways in order for the research to be reliable and accurate. If participants withdraw from the study, the information about them already obtained will be kept. To safeguard participant rights, the minimum personally-identifiable information possible will be used.

When participants agree to take part in a research study, the information about their health and care may be provided to researchers running other research studies in the organisation

and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Their information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

9.12 Monitoring, audits and inspections

The investigator shall permit direct access to participants' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Regulatory Authorities and REC.

9.13 End of Trial

The end of the trial will occur when the final participant has completed the final follow up visit and all trial data have been captured on the trial database. All participants will be informed about their treatment allocation once the trial will be finished.

10. DATA MANAGEMENT

10.1 Source Data

Source documents include original documents related to the trial, to medical treatment and to the history of the participant, and adequate source documentation must be maintained at participating sites to allow reliable verification and validation of the trial data. What constitutes source data for this trial will be outlined in the trial Monitoring Plan.

10.2 Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the participating site.

10.3 Database

Trial data will be collected on an electronic case report form (eCRF). The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the OpenClinica database. Data is entered into the EDC system via site personnel. All data recorded in the eCRF will be signed off by the Investigator or his/her appropriate designee. All changes made following the initial submission of data will have an electronic audit trail with a date. Specific instructions and further details will be outlined in trial specific eCRF manual.

Automated Randomisation and unblinding will be carried out using the OpenClinica system in accordance with ICTU specific SOPs.

Part of the data from the mechanistic assessments (e.g. gut hormone results) will be collected on other databases (e.g. excel).

10.4 Data Collection

Data from all trial visits will be collected and entered on the trial eCRF built in the OpenClinica system. Data will include demographics, vital signs, blood test results, questionnaire data and data arising from the mechanistic evaluations. Some of the data from the mechanistic visits will be collected outside of the eCRF..

Procedures for eCRF completion will be detailed in a study specific manual.

10.5 Data Storage and Archiving

The participating site investigator must retain essential documents until notified by the Sponsor, and for at least 25 years after trial completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the trial) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

11. STUDY MANAGEMENT STRUCTURE

The trial will be managed by the United Kingdom Clinical Research Collaboration (UKCRC) registered Imperial Clinical Trials Unit (ICTU).

The following groups and trial committees will be established:

11.1 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, a lay person, the Chief Investigator and members of ICTU (Trials Manager, Operations Manager and Statisticians). The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate TSC Charter.

11.2 Trial Management Group (TMG)

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, Senior and Trial statisticians, Operations Manager and Trial Manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference.

11.3 Data Monitoring and Ethics Committee (DMEC)

A fully independent Data Monitoring and Ethics Committee (DMEC) will be set up to monitor progress, participant safety, blinding fidelity, operator variability and any ethical issues involved in this trial. They will review trial progress, recruitment rates, safety, and data emerging from other trials and make recommendations to the TSC as to whether there are any reasons why the trial should not continue. The DMEC membership will include independent experts in interventional radiology and bariatric surgery and a clinical trials statistician.

A separate DMEC Charter will be drawn up defining their responsibilities, frequency of meetings and reporting to the TSC.

The DMEC are permitted to have access to the unblinded data for review and any comparisons between groups where appropriate.

11.4 Early Discontinuation of the Trial

The recruitment will be closely monitored by the TMG, potential issues will be discussed with the TSC and remedial actions put in place to ensure that recruitment is delivered to time and target. If within six months of both centres recruiting, the recruitment is below 20 patients, then it is unlikely that recruitment will be completed to time and target. Second, if drop-out after enrolment is >20% this would also be a stopping rule.

The sponsor and/or Ethics Committee and/or government agencies may also request to stop enrolment of additional subjects for the study or an individual site for any reason.

11.5 Risk Assessment

A trial-specific risk assessment will be performed prior to the start of the trial to assign a risk category of ‘low’, ‘medium’ or ‘high’ to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Trial Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the trial and will be updated as required during the course of the trial.

11.6 Monitoring

The trial will be monitored periodically by the trial monitor to assess the progress of the trial, verify adherence to the protocol, ICH GCP E6 (and R2) guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan, in accordance with the risk assessment.

11.7 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The trial may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The trial may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

The Quality Assurance Manager within ICTU will review all documents before submission to the ethics committee.

11.8 Peer review

The trial has undergone independent peer review via the NIHR-EME funding programme. The trial has also been reviewed by senior members of Imperial College and ICTU and representatives from the device manufacturer (BTG - BIOCOMPATIBLES UK LTD - a BTG International group company).

11.9 Patient and Public Involvement

PPI members were involved in reviewing the plain English summary in the grant and the REC application, and will be part of the Trial Steering Committee, supporting the creation of patient facing materials, identifying the most effective ways to share information with potential participants in order to maximise recruitment, promoting the trial during the recruitment phase and disseminating the trial results.

11.10 Publication and Dissemination policy

The EMBIO trial is funded by the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme (EME 17/11/49). EME is a partnership between the Medical Research Council (MRC) and NIHR. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.

Information concerning the trial, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The trial investigator(s) may use this information for the purposes of the trial only.

It is understood by the investigator(s) that the Sponsor will use information developed in this clinical trial and, therefore, may disclose it as required to other clinical investigators. In order to allow the use of the information derived from this clinical trial, the investigator(s)

understand that he/she has an obligation to provide complete test results and all data developed during this trial to the Sponsor.

Verbal or written discussion of results prior to trial completion and full reporting should only be undertaken with written consent from the Sponsor. Therefore all information obtained as a result of the trial will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

Any request by participating site investigators or other collaborators to access the trial dataset must be formally reviewed by the TSC.

The results may be published or presented by the trial investigator(s), but the Funder will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced.

A Clinical Study Report summarising the study results will be prepared and submitted to the MHRA and REC within a year of the end of trial.

Participants will be informed of the trial results upon request once the trial is completed.

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SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Left gastric artery embolisation for weight loss in obese patients with BMI 35-50kg/m2: EMBIO trial

Protocol Number: 19SM4996

Signed: _____

Mr Ahmed Ahmed
Consultant Upper GI and Bariatric Surgeon
Clinical Lead - Bariatric Surgery
Imperial College London

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Left gastric artery embolisation for weight loss in obese patients with BMI 35-50kg/m2: EMBIO trial

Protocol Number: 19SM4996

Signed: _____

Mrs Ruth Nicholson
Research Governance Manager
Imperial College London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Left gastric artery embolisation for weight loss in obese patients with BMI 35-50kg/m2: EMBIO trial

Protocol Number: 19SM4996

Signed: _____

Francesca Fiorentino
Senior Satistician Imperial Clinical Trials Unit
Imperial College London/ Imperial Clinical Trials Unit

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this trial will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Left gastric artery embolisation for weight loss in obese patients with BMI 35-50kg/m2: EMBIO trial

Protocol Number: 19SM4996

Signed: _____

Dr Jowad Raja
Consultant Interventional and Vascular Radiologist
University College London Hospitals NHS Trust

Date: _____