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EMBIO trial study protocol: left gastric artery embolisation for weight loss in patients living with obesity with a BMI 35–50 kg/m^2

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ABSTRACT

Introduction Left gastric artery embolisation (LGAE) is a well-established treatment for major upper gastrointestinal (GI) bleeding when control is not established via upper GI endoscopy and recently has shown promising results for weight loss in small single arm studies. LGAE could be a treatment option in between our current tier-3 and tier-4 services for obesity. EMBIO is a National Institute for Health Research funded trial, a multicentre double-blinded randomised controlled trial between Imperial College National Health Service Trust and University College London Hospital, comparing LGAE versus Placebo procedure. The key aims of the trial is to evaluate LGAE efficacy on weight loss, its mechanism of action, safety profile and obesity-related comorbidities.

Methods and analysis 76 participants will be recruited from the existing tier-3 database after providing informed consent. Key inclusion criteria include adults aged 18–70 with a body mass index 35–50 kg/m^2 and appropriate anatomy of the left gastric artery and coeliac plexus on CT Angiogram. Key exclusion criteria included previous major abdominal and bariatric surgery, weight >150 kg, type 2 diabetes on any medications other than metformin and the use of weight modifying medications. Participants will undergo mechanistic visits 1 week prior to the intervention and 3, 6 and 12 months postintervention. Informed consent will be received from each participant and they will be randomised in a 1:1 ratio to left gastric artery embolisation and placebo treatment. Blinding strategies include the use of moderate doses of sedation, visual and auditory isolation. All participants will enter a tier-3 weight management programme postintervention. The primary analysis will estimate the difference between the groups in the mean per cent weight loss at 12 months.

Ethics and dissemination This trial shall be conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions. Local research ethics approval was granted by London-Central Research Ethics Committee, (Reference 19/LO/0509) on 11 October 2019. The Medicines and Healthcare products Regulatory Agency (MHRA) issued the Letter of No Objection on 8 April 2022 (Reference CI/2022/0008/GB). The trial's development and progress are monitored by an independent trial steering committee and data monitoring and ethics committee. The researchers plan to disseminate results at conferences, in peer- reviewed journals as well as lay media and to patient organisations.

Trial registration number ISRCTN16158402.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study will represent level 1 evidence to support left gastric artery embolisation (LGAE) as a potential treatment for obesity.
- ⇒ This study will provide the safety profile of LGAE.
- ⇒ This study will provide information about the mechanism of action of LGAE.
- ⇒ A long follow-up period introduces the risk of participants withdrawing from the trial.
- ⇒ Participants will not be able to seek other obesity (medical or surgical) treatments during the 12 months follow-up phase.

INTRODUCTION

The rise in obesity (body mass index (BMI) greater than >30 kg/m^2) is worldwide, with it already being a major concern in some countries, such as the USA.[1] In the UK, the prevalence of obesity has doubled over the last 25 years with 29% of men and 27% of women now classified as suffering with obesity.[2–4] The UK government foresight programme has predicted that 50% of UK adults could be obese by 2050.[1 3 4] Without significant intervention, this will have both major health and economic implications. Obesity is already the leading cause of preventable death worldwide and associated with metabolic conditions such as type 2 diabetes (T2DM), cardiovascular disease and hypertension. The resulting National Health Service (NHS) costs

attributable to suffering with being overweight and obese are projected to double to £10 billion per year by 2050, with wider costs to society estimated to reach 49.9 billion per year.[3 4]

Currently, the NHS offers a 1–4 tiered weight management service to treat obesity. Tier-1 services are focused on identification and reinforcement of healthy eating and physical exercise with a tier-2 service including NHS endorsed weight management programmes, for example, weight watchers.[5] A tier-3 service is commissioned by the Clinical Commissioning Groups and are a multidisciplinary programme consisting of a bariatric physician, a dietician, a specialist nurse and a clinical psychologist with access to physical therapy and includes the use of pharmacological agents such as orlistat and liraglutide.[6]

A systematic review by Alkharaiji *et al* revealed a modest 4.8% weight loss from tier-3 interventions at 6 months, but the magnitude of the effect seems to lose momentum thereafter.[7] More recently, Davies *et al* has demonstrated 2.4 mg once a week subcutaneous semaglutide injections (GLP-1 analogue) in patients suffering with both obesity and T2DM produced 6.2% more weight loss in comparison to a placebo group, and is soon to be introduced onto the tier-3 system.[7 8] The multidisciplinary tier-3 service is costly to deliver and the pharmacological agents each have their own risk profile, 30% failure rate and require continuous use. The step 1 trial extension demonstrated 1 year after withdrawal of once-weekly subcutaneous semaglutide 2.4 mg and lifestyle intervention, participants regained two-thirds of their prior weight loss, with similar changes in cardiometabolic variables.[9]

Tier-4 services involve bariatric surgery with the two most common operations being performed involving the Roux-en-Y gastric bypass and sleeve gastrectomy.[10] Bariatric surgery has been demonstrated to be the most effective treatment for morbid obesity, achieving 20%–30% weight loss, which is well maintained and with resolution of many obesity-related comorbidities. While it is cost-effective (recommended by the national institute for health and care excellence (NICE)), provision remains low. Under the current NICE guidelines, 3.62 million people are eligible for Bariatric surgery in the UK,[11] however, only 5341 and 1429 (pandemic-related) operations were recorded in the national bariatric surgery registry in 2019–2020 and 2020–2021, respectively. Furthermore, the expense of bariatric surgery (HRG tariffs FZ 84/85) for 2017–2018 ranges from £5078 to £5809 (without market forces factor (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 2016 to 2019) note an in-hospital mortality rate of 0.0294% and 30-day postoperative mortality of 0.054% which can be devastating.

It is widely accepted that 5% weight loss improves metabolic function in multiple organs simultaneously with improved adipose tissue, liver and muscle insulin sensitivity and β-cell function.[12] 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 kg/m^2. We have particular interest in therapies that can modulate gut peptide hormone levels with the knowledge that it plays a key role in weight loss and the modulation of metabolic derangement (eg, T2DM) following bariatric surgery.[13]

Left gastric artery embolisation

Left gastric artery embolisation (LGAE) is a minimally invasive procedure which has shown promising results for weight loss in recent studies and could play a key role as a treatment option in-between our current tier-3 and tier-4 services.[14] The left gastric artery provides bloody supply to the fundus of the stomach, where the majority of the enteroendocrine cells which produce the appetite stimulating hormone, ghrelin are located. This endovascular procedure performed by interventional radiologist aims to render the fundus of the stomach ischaemic, thereby theoretically reducing Ghrelin levels and resulting in weight loss.[15]

A number of initial studies performing LGAE conducted on porcine and canine models demonstrated significant reduction in plasma ghrelin, body weight and subcutaneous fat levels.[16–18] LGAE is a well-established treatment for major upper gastrointestinal (GI) bleeding when control is not established via upper GI endoscopy. Gunn *et al* in 2014 identified an incidental 7.3% average reduction in total body weight at 3 months in 19 patients who underwent LGAE for life-threatening haemorrhage compared with 2% in 28 patients who underwent Embolisation other than left gastric artery for upper GI bleed (p=0.001).[19] Retrospective weight loss findings following LGAE for upper GI bleeding were further supported by Anton *et al*.[20]

Such observations have stimulated a number of prospective single arm studies to investigate weight loss, metabolic changes and safety profile following LGAE. A prospective single arm 5 patient study by Kipshidze *et al* showed weight loss of 16% and 17% (p<0.05) and a drop-in blood ghrelin levels by 19% and 21% (p<0.05) at 6 and 12 months, respectively, postintervention.[21] A separate 4-patient study by Syed *et al* demonstrated 8.5% weight loss at 6 months, with three superficial gastric ulcerations identified day 3 postprocedure on upper GI endoscopy that had healed by day 30 without hospitalisation.[22 23] The BEAT trial conducted by Weiss *et al* evaluating the safety and efficacy of LGAE involved a single arm 20 patient study reporting 12.8% and 11.5% weight loss at 6 and 12 months postintervention. Supporting previous findings, eight cases of asymptomatic gastric ulcers were identified which resolved 3 months post-LGAE. In addition, there was one case of mild pancreatitis, managed conservatively without surgical intervention.[24]

Reddy *et al*'s study was the first reported single blinded randomised sham-controlled trial of LGAE. It reported

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findings of 6.5% and 9.3% weight loss and 12.2% and 15.5% drop in Ghrelin levels at 6 and 12 months. In addition, five minor asymptomatic gastric ulcers were identified with no serious adverse events.[25] When assessing this study as per the consolidated standards of reporting trials (CONSORT) statement, although the reporting and discussion was well done there are several methodological aspects that we believe could bias the outcome of the results. Specifically, there was no clarity on the blinding of the patients and the reporting group. The control group was not a true placebo as no intervention was undertaken, specifically radial or femoral access, and they spent less time in the intervention suite compared with the treatment group. With the knowledge that arterial access would mean treatment allocation, the subjects would automatically guess which arm they have been allocated to. Consequently, both patients and assessors would be subject to reporting bias.

Although the literature to date supports LGAE as a safe and feasible option for the treatment of obesity, study sizes have been small, with a high degree of heterogenicity and without a true controlled placebo group. Therefore, there is a requirement for a high-quality double-blinded randomised controlled trial (RCT) to validate LGAE as a treatment option for obesity and evaluate its safety profile. In this paper, we describe the methodology for a £1.04m government funded EMBIO trial,[26] which represents the first multicentre double blinded RCT including two participating centres in England (Imperial College Healthcare NHS Trust and University College London Hospitals NHS Trust) evaluating the efficacy of LGAE on weight loss and obesity-related comorbidities. It will involve 76 participants randomised in a 1:1 ratio to LGAE or placebo procedure, performed by 4 experienced interventional radiologists across both sites.

Objectives

Primary objective

- To evaluate the efficacy of LGAE on weight change and obesity-related comorbidities at predetermined times points over a 12-month follow-up period.

Secondary objective

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

METHODS

This is a multicentre, double-blinded RCT 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 in a 1:1 ratio. Patient recruitment started in July 2022 and the final follow-up visit is planned for July 2024.

Primary end point

- Absolute difference in per cent weight change at 12 months.

Secondary end point

- Absolute difference in per cent weight change at 3 and 6 months.
- Total body loss at 3, 6 and 12 months, that is, the absolute change in weight (in kg).
- Proportion of participants with ≥5% TBL at 12 months.
- Changes in:
  - Gut hormones.
  - Hunger and satiety scores (Visual Analogue Scales, VAS).
  - Food intake (meal test and food diaries).
  - Delay in gastric emptying (paracetamol test).
  - Eating behaviour and quality of life Questionnaires (Short-Form 36 Health Survey (SF36)-V2, Impact of Weight on Quality of Life (IQWOL) lite, Hospital Anxiety and Depression Scale (HADS), Dutch Eating Behaviour Questionnaire (DEBQ), European Prospective Investigation into Cancer (EPIC) Food Frequency Questionnaire (FFQ).
- Change in markers of obesity-related complications (blood pressure, cholesterol levels, glycaemia as assessed by Haemoglobin A1C (HbA1c), fasting glucose and insulin).
- Frequency of adverse events.
- Preference of treatment arm.

Power calculation

This will be a two-arm RCT, where the control is the placebo procedure and the intervention is embolisation of the left gastric artery. In a previous weight management trial investigating a drug for weight loss in patients with BMI>27 kg/m^2, patients experienced a percentage (%) change in body weight (loss) of −8.0%±6.7% in the intervention arm compared with −2.6%±5.7% in the control arm at 56 weeks.[27]

From clinical judgement any treatment that causes >5% weight loss is regarded as clinically important. Goldstein reported for patients suffering with obesity and T2DM, hypertension or hyperlipidaemia that modest weight reduction appeared to improve glycaemic control, reduce blood pressure and reduce cholesterol levels, respectively. 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 patients suffering with obesity.[28] There are numerous examples of papers supporting the clinical benefits of >5% weight loss.[12 28–30] Embolisation of the left gastric artery should result in an improvement of at least 5% of the body

weight at 12 months compared with placebo. Therefore, we have used the same assumptions of effect size and SD for the sample size calculation in this trial. Assuming that at 12 months, the mean per cent of body weight loss in the placebo group is 2.6% (SD=6.7%), and the expected per cent of body weight loss in the embolisation group is 8.0% (SD=6.7%), conservatively taking the greater SD for both groups (6.7%), 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 per cent 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 V.13.2.

Participants entry

This trial is open to all tier-3 patients attending bariatric clinics at two NHS Trusts. A total of 76 participants (50% LGAE vs 50% placebo procedure) will be recruited into this trial. A minimum of 25% of participants will be recruited from University College London Hospitals NHS Trust and a maximum of 75% of participants will be recruited from Imperial College Healthcare NHS Trust. The opportunity to participate in the EMBIO trial will be presented to all participants alongside all other weight loss treatments during their tier-3 visits, and if interested they will be provided with a patient information sheet. Participants who wish to proceed with entering the trial will be invited to a screening visit and be assessed against the inclusion/exclusion criteria and a screening CT angiogram equivalent to 3.3 years of natural background radiation in the UK to assess for appropriate anatomy. Figure 1 represents a time line for the EMBIO trial. Study participants will be recruited according to the inclusion and exclusion criteria outlined in tables 1 and 2, respectively. BMI inclusion of 35–50 kg/m^2 was selected as in the UK, a minimum BMI of 35 kg/m^2 is required for referral to a specialist weight management (tier-3) service. All participants on antidiabetic medication excluding metformin or any weight modifying medications including orlistat, liraglutide and semaglutide will be excluded as it would add significant confounding bias to the weight loss results.

Patient and public involvement

One patient as a coinvestigator has been involved from the inception of the study to design and review.

Simulation training

Prior to commencing recruitment, the radiology staff across both sites underwent five simulation training sessions. A professional actor played the role of the participant and was blinded by visual and auditory isolation using noise-cancelling headphones and erect sterile drapes. Two recovery nurses were allocated to be blinded. Interventional radiology (IR) staff members were unblinded and were instructed to simulate a LGAE intervention or placebo case based on open clinical randomisation. Feedback was provided at the end of each session to the IR staff members, particularly focusing on verbal and non-verbal communication and maintaining a consistent methodology to maintain blinding. The IR staff were assessed on their ability to maintain treatment arm concealment from the participant and blinded recovery nurses by using the 'James blinding index' and achieved 100% blinding success by the final session.[31]

Intervention and randomisation

Intervention will be performed at both Imperial College Healthcare NHS Trust and University College London Hospitals NHS Trust by four experienced interventional radiologists (two at each site). All participants will be appropriately informed and consented for a LGAE procedure, with the knowledge that there is a 50% chance of having a 'placebo' procedure. First-line preference for access will be via the radial artery with second line via the femoral route.

Participants in both groups will be given a minimum of 2 mg intravenously (up to 10 mg) midazolam with standard monitoring and will have auditory and visual isolation using over the ear headphones playing music and erected sterile drapes (see figure 2). Moderate levels of conscious sedation will be maintained to ensure the participants have no recollection of the proceedings. This will be followed by skin and subcutaneous tissues infiltrated with 1% lidocaine under ultrasound guidance. 'Preradial cocktail' is given (2.5 mg verapamil, 3000u heparin and 200u GTN) to reduce distal arterial spasm and vessel thrombosis. A hydrophilic sheath is inserted into the radial/femoral artery.

Randomisation

The operator will now randomise the patient to either LGAE or placebo procedure in a 1 to 1 ratio using the online OpenClinica database which will be accessed on a computer inside the angiography suite. Randomisation will be stratified by BMI (35≤BMI≤42 and 42≤BMI≤50) and HbA1c (<48 mmol/mol and 48≤Hb1Ac≤69.4 mmol/mol).

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. We appreciate the arterial supply to the gastric fundus can be variable, with supply from the left gastroepiploic artery. To maintain standardisation of our technique among our four

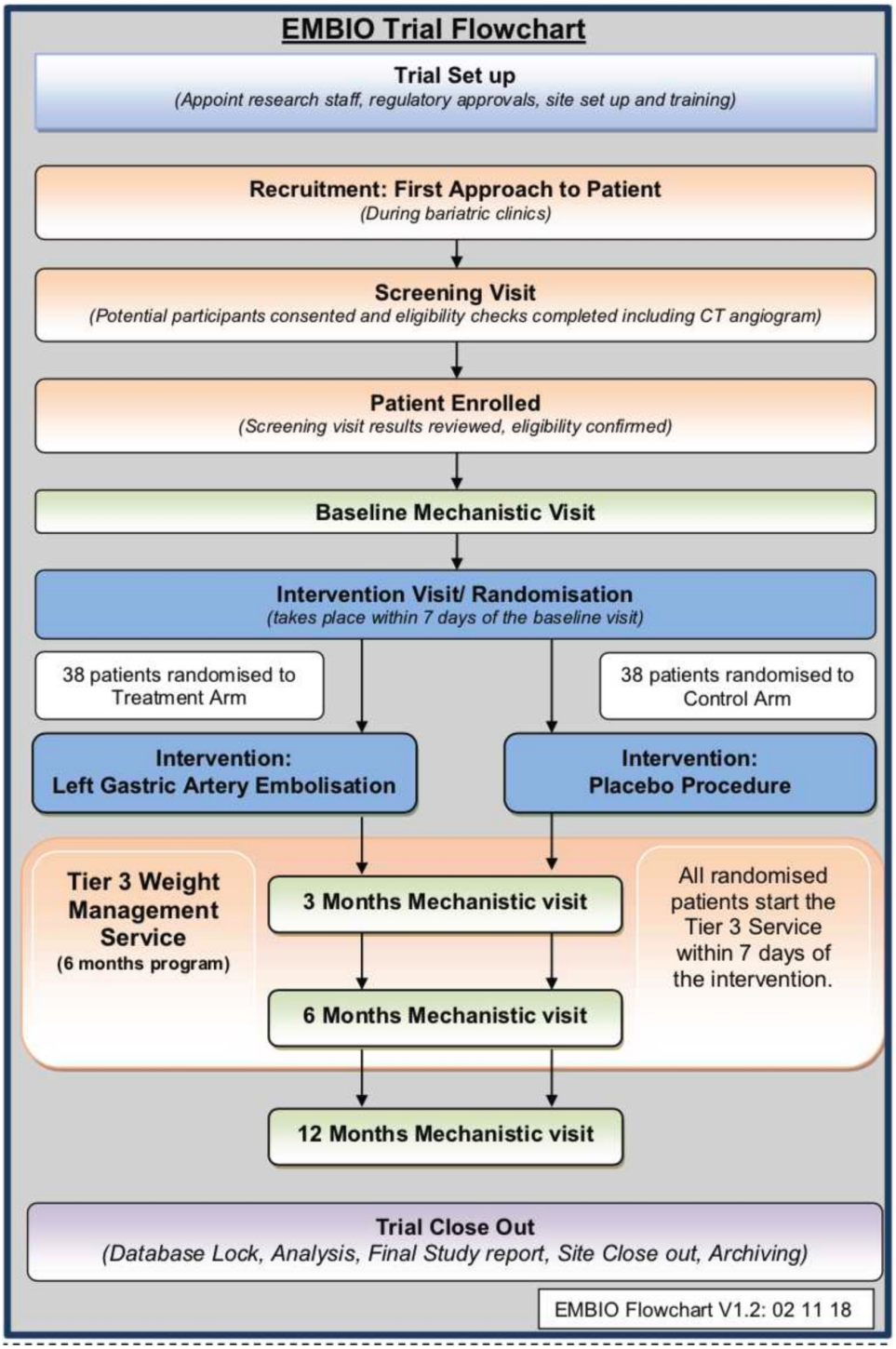

Figure 1 Left Gastric Artery Embolisation Trial (EMBIO) flow chart.

radiologists across both sites, we decided to only embolise the left gastric artery for every participant.

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 microcatheter in small aliquots under fluoroscopy until satisfactory embolisation is achieved (cessation of forward flow or flow in both directions for six cardiac cycles). A further vial of particles may be required. Once the radiological end point has been achieved, the microcatheter 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

Table 1 Inclusion criteria

1	**Adults aged 18–70 years**
2	BMI 35–50 kg/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 (online supplemental file 1)

BMI, body mass index.

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 participants will stay in the IR suite the same amount of time as the participants 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.

Postprocedure for both arms

LGAE and the placebo procedure will usually end after 40 min. The patient can then be transferred to the recovery area. Data collection will be transcribed into the OpenClinica database via the interventional radiologist. A study-specific manual will be developed to ensure

Table 2 Exclusion criteria

1	**Haematological, hepatic or renal dysfunction**
2	Weight >150 kg
3	Haemoglobin A1C (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 *Helicobacter pylori* infection
11	Positive pregnancy test in females of childbearing age
12	Chronic Non-steriodal anti-inflammatory drugs (NSAID) use
13	Current use of insulin, sulphonylurea or any other diabetic medication other than metformin or weight modifying drugs including orlistat, liraglutide and semaglutide
14	Patients on antidepressants <6 months or patients on antidepressants >6 months who are not stable or patients on appetite-stimulatory antipsychotic medications such as risperidone, olanzapine or oral glucocorticoid steroids

GI, gastrointestinal.

Figure 2 (Interventional Radiology) IR suite set up demonstrating erect sterile drapes to conceal vision.

that the documentation in the IR suites in both centres is managed in a consistent and appropriate manner.[32] All staff within the IR suite will have no further involvement with the participants in the study once they leave IR suite. All staff outside the IR suite including those performing mechanistic testing will remain blinded at all times. A standardised handover sheet will be used for all participants when transferring from IR suite to recovery area without mentioning details about the embolisation part of the procedure. Participants in both trial arms will undergo the same recovery procedures and will be discharged at 4 hours. All participants will be given an emergency contact number to contact a member of the local trial team, if there are any postprocedural-related issues, who will be able to advise on further management and on the need to unblind if necessary. A number of cases of minor gastric ulceration were identified from previous studies post-LGAE within the literature which were all managed with proton pump inhibitors and resolved without requiring further intervention. Therefore, all participants within the EMBIO study will take lansoprazole 30 mg once a day for 1 week before and continue for 6 weeks after the intervention for gastric protection. We will not be routinely performing an upper GI endoscopy postprocedure. Lansoprazole will be prescribed to the participants during visit 2 (baseline mechanistic visit).

A postprocedure of 2–4 hours, the participants and a blinded member of the IR recovery nurse will be asked two blinding index questions by an IR staff member according to the 'James blinding index'.[31]

1. In your opinion which study arm are you in?
   - Left gastric artery embolisation.
   - Placebo.
   - I don't know.
2. How certain are you?
   - 1 (least).
   - 2.
   - 3.
   - 4.

Table 3 Summary of participant visits and procedures

Assessment	Screening	Baseline mechanistic	Intervention	3 months mechanistic follow-up	6 months mechanistic follow-up	12 months mechanistic follow-up
Week/day	0–3 months	1 week±7 days	0 week±3 days	3 months±7 days	6 months±7 days	12 months±7 days
Informed consent	+					
Inclusion and exclusion criteria	+					
Demographic	+					
Medical history/medication	+					
Physical examination	+					
Clinical assessment	+	+	+	+	+	+
Routine blood tests	+	+	+	+	+	+
Urine dips and pregnancy test	+	+	+	+	+	+
Helicobacter pylori breath test	+					
ECG	+					
Screening CT angiogram	+					
Randomisation			+			
LGAE or placebo procedure			+			
Blinding index			+			
Prton pump inhibitor (PPI) distribution		+	+			
Changes in medical history/ medication/ adverse events		+	+	+	+	+
Mixed meal tolerance test		+		+	+	+
Gut hormones		+		+	+	+
Appetite Visual Analogue Scales		+		+	+	+
Gastric emptying tests		+		+	+	+
Food intake tests		+		+	+	+
Eating and behaviour questionnaires		+		+	+	+
3 day food diary		+		+	+	+

LAGE, left gastric artery embolisation.

– 5 (most).

Tier-3 programme

Participants from both arms and sites will be entered into a tier-3 weight management programme within 7 days of the intervention. The tier-3 programme will be standardised programme delivered by Imperial College London NHS Trust over a 6-month period led by the bariatric doctors with input from the bariatric multidisciplinary team (MDT).

Mechanistic assessment

Measures are summarised in table 3.

Mechanistic assessments will be carried out on all participants at baseline, 3, 6, 12 months postprocedure at the Imperial Cinical Research Facility at Hammersmith Hospital London. The following assessments will be taken undertaken at each visit.

Clinical assessment

A comprehensive assessment of body measurements will be taken including weight, height, neck, waist, hip circumference, pulse and blood pressure. Routine blood tests and clinical markers for safety and metabolic status will be taken including HbA1C, insulin, glucose, full blood count (FBC), Urea and Electrolytes (U&E), Liver function test (LFT), lipids . The participants will be screened for any changes in medical history or medications and any adverse events since their last appointment. Females of childbearing age will be asked to complete a pregnancy test if they have missed a menstrual cycle.

Mixed meal tolerance test

This will involve the administration of a standardised 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 min, where 0 is the time of administration of the meal. In addition, measurements of gut hormones (eg, Ghrelin, peptide YY, GLP-1) and bile acid. Measurement of subjective sensations of appetite, nausea, hunger, satiety using VAS will also be collected.

Gastric emptying test

Participants will take 1.5 g effervescent 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.

Food intake test

An ad libitum meal, provided to excess, will be served and participants will be allowed 20 min to eat. The participant will be instructed to eat until they feel comfortably full. Pulse and blood pressure will be taken every 30 min, 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 min. Blood samples for glucose, insulin and gut hormones will be taken prior to the meal and 30 and 60 min after eating. Three-day food diaries will also be collected on the study day.

Eating behaviour and quality of life questionnaires

Participants will complete the following questionnaires to assess eating behaviour and attitudes and personality measures related to reward sensitivity and mood.

- SF36-V2—to assess quality of life.
- IQWOL lite—to assess quality of life.
- HADS—to assess symptoms of anxiety and depression.
- DEBQ—to measure restraint, emotional and external influences on eating behaviour.
- EPIC FFQ—to quantify changes in food intake.

Statistical analysis

All statistical analyses will be completed at imperial clinical trials unit (ICTU). Analysis of primary and secondary 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 separate statistical analysis plan (SAP) will be prepared containing information on (not exclusively); the rationale for the methods chosen, assumptions and associated tests, prespecifying the handling of covariates prior to analysis and approaches to missing data.

Primary endpoint analysis

The primary analysis will estimate the difference between the groups in the mean per cent weight loss at 12 months with 95% CI using a linear mixed-effects regression model adjusted for the stratification variables (baseline BMI and HbA1c).

The choice of mean percentage weight loss over absolute weight loss at 12 months was made as a primary outcome after in-depth meetings between senior EMBIO TMG clinicians, ICTU statisticians and EMBIO trial steering committee and data monitoring and ethics committee independent statistician. It was unanimously agreed that mean percentage weight loss at 12 months would provide greater clinical relevance with the study adequately powered.

Secondary endpoint analysis

The between-arm difference in the mean per cent weight loss at earlier time points of follow-up (3, 6 months) will be estimated from a mixed-effects analysis model specified to involve 'time' in interaction with the fixed effect covariates (including arm) and to account for correlation in the outcome over time. The same mixed-effect model will be used to investigate the outcome of absolute weight change at 3, 6 and 12 months.

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 time points of follow-up, and using additional covariate-adjustment for the baseline of the outcome under analysis), such as for anthropometric indices (eg, waist and hip circumference), QoL questionnaires (eg, HADS), VAS measures, calories consumed from the food intake test and clinical measures (such as from within the mixed meal tolerance test).

We plan to calculate area under the curve (AUC) for each analyte (eg, 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 VAS data. This considers 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 analysis of variance. We intend to analyse QoL questionnaires data using non-parametric analyses. Regression analysis will be used to investigate the relationship between per cent weight loss and the mechanistic parameters, such as the per cent reduction in ghrelin and change in paracetamol absorption.

Under circumstances where the above approaches are deemed no longer suitable due to violation of assumptions, an alternate approach will be prespecified and defined within the SAP.

Research approvals and dissemination

This trial shall be conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions. Local research ethics approval was granted by London-Central Research Ethics Committee, (Reference 19/LO/0509) on 11 October 2019. The Medicines and Healthcare products Regulatory Agency (MHRA) issued

the Letter of No Objection on 8 April 2022 (Reference CI/2022/0008/GB).

The trial's development and progress are monitored by an independent trial steering committee (TSC) and data monitoring and ethics committee (DMEC).

Informed consent will be obtained from each participant (online supplemental file 1). All participants have the right to withdraw from the study at any time.

The researchers plan to disseminate results at conferences, in peer-reviewed journals as well as lay media and to patient organisations.

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