Cover Page

BARI-STEP: A double-blinded, randomised, placebo-controlled trial of semaglutide 2.4 mg in patients with poor weight-loss following bariatric surgery.

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BARI-STEP Statistical Analysis Plan

Title of trial	A double-blinded, randomised, placebo-controlled trial of semaglutide 3.0 mg/ml in patients with poor weight-loss following bariatric surgery.
Short title	BARI-STEP
Universal Clinical Trial Number	U1111-1263-5209
Active Treatment	Subcutaneous injection of semaglutide 3.0 mg/ml
Placebo Treatment	Same composition as the Active Treatment, but no active ingredient (semaglutide 3.0 mg/ml)
Sites	Multi-centre (UCLH and Homerton)
Chief Investigator	Dr Janine Makaronidis, Centre for Obesity Research, Division of Medicine UCL
List of Abbreviations	BDI Beck Depression Inventory BIA Bioelectrical Impedance Analysis BMI Body Mass Index BP Blood Pressure eCRF Electronic Case Report Form EQ-5D EuroQol-5D GLP-1 Glucagon-like peptide-1 HbA1c Glycosylated haemoglobin HR Heart Rate HRQoL Health Related Quality of Life IPAQ International Physical Activity Questionnaire IWQOL-LITE Impact of weight in quality of life-lite. JRO Joint Research Office LOCF Last Observation Carried Forward PIS Participant Information Sheet QALY Quality-Adjusted Life Year RCT Randomised Control Trial REC Research Ethics Committee GB Gastric Bypass PYY Peptide YY STS Sit-to-stand test SG Sleeve gastrectomy T2D Type 2 Diabetes Mellitus TMF Trial Master File TMG Trial Management Group TSC Trial Steering Committee UK GDPR UK General Data Protection Regulation WL Weight Loss
	Trial Personnel
Statistician	David Boniface, RSS Chartered Statistician, UCL Honorary Senior Research Fellow
Data Manager	Victoria Jeffs, Centre for Obesity Research, Division of Medicine, UCL
Co-investigators	Dr Sulmaaz Qamar, Dr Ritwika Mallik, Clinical Fellows, Centre for Obesity Research, Division of Medicine, UCL

Objectives	The primary aim of this trial is to determine whether 68 weeks of subcutaneous semaglutide 3.0 mg/ml causes greater percentage weight loss (%WL), reduction in adiposity, improvement in metabolic and inflammatory indices and health-related quality of life (HRQoL) than placebo, in patients with poor weight loss following gastric bypass or sleeve gastrectomy.
Type of Trial	Phase 3b, double-blinded, randomised, parallel group trial in patients with poor weight loss following bariatric surgery.
	Trial Design and Methods
Selection of participants –	The clinical bariatric teams at UCLH and Homerton Hospital will identify patients potentially fulfilling the eligibility criteria either when these attend follow-up clinics, or through search of existing databases. Subjects with poor weight loss response (<20% of their total weight), ≥ 1 year after primary gastric bypass or primary sleeve gastrectomy, will be identified from the trial site (University College London Hospital) and invited to attend a screening visit.
Screening Visit	Trial assessments will be undertaken only upon participants providing informed consent. Information regarding medical history and concomitant medications will be gathered. In addition, a full physical examination and screening blood tests will be performed. All female participants of childbearing potential will be tested for pregnancy. Assurance of adequate use of highly effective contraceptive throughout the trial period will be obtained prior to enrolment in the trial. The following screening procedures will be carried out: • Physical examination. • Vital signs (heart rate (HR) and blood pressure (BP). • Medical history and co-morbidities. • Concomitant medications. • Urine pregnancy test for women of childbearing potential. • Weight and height. • Blood tests: ✓ Haematology: full blood count. ✓ Serum biochemistry: renal, liver and thyroid function, HbA1c. Once all data related to the screening visit has been obtained, the investigator will review the data to ensure that the participant is eligible to take part in the trial. Subjects who are deemed not to be eligible will not be re-screened and enrolled in the trial. All screening procedures will be carried out as specified in the schedule of assessments (Appendix 1). An investigator will call the patient to notify of the outcome of screening, answer their questions and explain possible next steps (depending on outcome). Once all data related to the screening visit have been acquired, the investigator will review the participants' eligibility for the trial. Participants fulfilling the inclusion and exclusion criteria will be invited to enrol in the trial. Participants will then be asked to attend a baseline visit.

Baseline Visit	During the baseline visit, data including body weight, body composition and HRQoL will be collected. The following baseline assessments will be carried out: • Sociodemographic data. • Physical examination. • Vital signs (HR and BP). • Urine pregnancy test for women of childbearing potential. • Weight. • BIA. • ECG • Blood tests: ✓ Haematology: full blood count. ✓ Serum biochemistry: renal, liver and thyroid function, HbA1c (If baseline visit >7 days from screening), glucose, lipids ✓ HsCRP and inflammatory cytokines ✓ Fasted and meal-stimulated GLP-1 levels: Prior to, 15 and 30 minutes after a standardised liquid meal • Questionnaires: ✓ Impact of weight on quality of life-lite (IWQOL-Lite CT) ✓ SF-36 physical functioning score ✓ Power of food questionnaire ✓ EuroQol-5D (EQ-5D) • Counselling on lifestyle modification (500-kcal deficient diet and 150 minute of physical activity/week and resistance exercise). • Distribution of: ✓ Scale ✓ Drug diary ✓ Semaglutide 3.0 mg/ml/placebo pens, injection needles and sharps bins • Subcutaneous injection training. Participants will be contacted by the investigator to assess their injection technique. They will be offered additional injection training by the research investigator as required. A 30-minute meal test will be performed. Upon completion of all the baseline procedures, participants will be randomised to receive either subcutaneous injection of semaglutide 3.0 mg/ml or identical placebo for 68 weeks. Participants will receive diet and physical activity counselling. Participants will also be taught how to self-administer the treatment (by subcutaneous injection) and will be given scales to self-monitor their weight at home.
Randomisation procedure	Following participant screening, consent and baseline measure collection, the randomisation procedure will be remotely carried out through an online randomisation service through Sealed Envelope, with provision to enable unblinding if required. Subjects will be randomly assigned in a 1:1 ratio to receive either semaglutide 3.0 mg/ml or placebo, stratified for sex, type of surgical procedure and T2D status. The investigator will provide

	participant's initials, date of birth and stratification information before a randomisation code can be generated for each participant. Both participants and investigators will be blinded to study-group assignments. Once randomisation has been performed, no group allocation will be disclosed. A randomisation notification email will be sent to the pharmacist reporting the participant randomisation code; this randomisation code will reveal group allocation when identified in the code list. Only the trial pharmacist will have access to the code list.
Blinding	The blinding of the trial will be maintained throughout the trial until all data entry and processing are complete, the database has been locked and data analysis performed.
Follow-up visits	Follow-up trial visits to monitor participants will be carried out at week 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68 weeks. The majority of these visits will be carried out remotely. Data including weight, adverse events and concomitant medication use will be collected at each visit. The visits at weeks 6, 14, 32, 52 and 68 weeks will be carried out in person, to allow a targeted physical examination to be performed and blood samples to be taken for biochemical monitoring and measurement of metabolic and inflammatory indices. Study medication will only be administered once all visit 2 assessments have been completed and the relevant safety reports have been obtained
	Visits 3-5, 7-9, 11-14, 16-19, 21-23: Intervention phase remote visits (Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64) (+/- 3 days, +/- 7 days from visit 16 onwards) The following will be assessed at each of the remote trial visits: • Weight (using the scales provided to the participants). • Concomitant medications. • Compliance with trial treatment. • Nutritional and exercise counselling. • Adverse events (AE) review. **Visits 6, 10, 15, 20: Intervention phase site visits (Weeks 6, 14, 32, 52) (+/- 3 days; +/- 7 days for visit 20)** The following will be assessed at each of the face-to-face trial visits: • Targeted physical examination. • Vital signs (HR and BP). • Weight. • BIA. • Blood tests: ✓ Haematology: full blood count. ✓ Serum biochemistry: renal, liver, HbA1c. ✓ HsCRP and inflammatory cytokines

	• Questionnaires: ✓ Impact of weight on quality of life-lite (IWQOL-Lite CT) ✓ SF-36 physical functioning score ✓ Power of food questionnaire ✓ EuroQol-5D (EQ-5D) • Concomitant medications. • Adverse event (AE) review. • Review of: ✓ Drug diary **Visit 24: End-of-treatment assessment (Week 68 +/- 7 days)** The following assessments will be carried out following the last dose of semaglutide 3.0 mg/ml/placebo: • Physical examination. • Vital signs (HR and BP). • Urine pregnancy test for women of childbearing potential. • Weight. • BIA. • ECG. • Blood tests: ✓ Haematology: full blood count. ✓ Serum biochemistry: renal, liver and thyroid function, glucose, lipids, HbA1c (If baseline visit >7 days previously). ✓ HsCRP and inflammatory cytokines • Questionnaires: ✓ Impact of weight on quality of life-lite (IWQOL-Lite CT) ✓ SF-36 physical functioning score ✓ EuroQol-5D (EQ-5D) ✓ Power of food questionnaire • Concomitant medications. • Adverse event (AE) review. • Collection of: ✓ Drug diary
Primary endpoint assessment	The primary endpoint assessment will be undertaken at 68 weeks (Visit 24)
Wash-out Period	Participants will then enter a 6-week wash-out period with two follow-up visits 25 and 26: at weeks 70 and 74. Wash-out period and end of trial assessment (Week 70 and 74 +/- 7 days) The final trial assessments will be carried out remotely.

	Participants who discontinue treatment will be asked to remain enrolled in the trial and contribute their data and will be invited to continue attending trial visits as scheduled. Participants who withdraw before completion of the trial will be asked to attend for their end-of-trial visit (as soon as possible after withdrawal). Withdrawn participants will not be replaced. The following will be assessed at the end of trial visit: • Weight (using the scales provided to the participants). • Concomitant medications. • Adverse events (AE) review.
Trial duration per participant	Minimum of 18 months, maximum of 20 months
Total Trial Duration	Approximately 26 months from when first participant enrolled to last participant follow-up.
Total number of participants planned	70 subjects (35 subjects in each arm) will be enrolled into the trial.
Main inclusion criteria	1. Patients, ≥1 year primary GB or primary SG, with poor weight-loss (<20% WL) that is not caused by either a surgical or psychological problem. 2. Adults, 18-65 years inclusive. 3. Females of childbearing potential and female partners of male participants must be willing to use highly effective method of contraception (Appendix 2) from the time consent is signed until 6 weeks after treatment discontinuation. 4. Females of childbearing potential must have a negative pregnancy test within 7 days prior to randomisation. NOTE: Subjects are considered not of child bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal. 5. ≤5 % variation in body weight over preceding 3 months. 6. Fluent in English and able to understand and complete questionnaires. 7. Willing and able to provide written informed consent and comply with the trial protocol.
Main exclusion criteria	1. Had a surgical procedure other than GB and SG, or revision bariatric surgery of any operation type. 2. Personal history of type I diabetes or type II diabetes mellitus currently treated with insulin. 3. Concomitant use of GLP-1R agonist or DPPIV-inhibitors. 4. Female who is pregnant, breast-feeding, or intends to become pregnant. 5. Participation in other clinical intervention trial. 6. History of suicidal attempt in the previous 5 years or untreated severe depression or mental health condition assessed by direct questioning. 7. Symptomatic gallstone disease 8. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg). 9. Renal impairment measured as glomerular infiltration rate (eGFR <15 ml/min 1.73 m2 10. Known or suspected hypersensitivity to semaglutide 3.0 mg/ml or any of the excipients involved in their formulation.

	11. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. 12. History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed. 13. Personal history of acute pancreatitis 180 days before screening or chronic pancreatitis. 14. Uncontrolled thyroid disease. 15. History of stroke, unstable angina, acute coronary syndrome, congestive heart failure New York Heart Association class III-IV within the preceding 12 months. 16. Untreated clinically significant arrhythmias. 17. Diabetic gastroparesis. 18. Concomitant usage of medications that cause weight gain or weight loss. 19. Known or suspected abuse of alcohol or recreational drugs. 20.Any additional factor, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the trial protocol.
	Statistical Analysis Plan
Sample size calculation	A sample size calculation was conducted using both the 68-week primary ITT analysis from our trial with Semaglutide 3.0mg/ml versus placebo in people with poor weight loss following bariatric surgery and the results of the Davies et al multi-centre trial of Semaglutide in adults with overweight or obesity, and type 2 diabetes . Assuming SD for %WL of 4.0, dropout rate of 10%, and 1% critical significance level, 62 patients (31 per group) will provide at least 95% power to detect an estimated difference of 10%WL with a 95% CI no wider than 8.0 to 12.0. The recruitment target is set at 35 participants per group. We anticipate screening between 80 and 100 patients with less than 20% weight loss at one year or more post-surgery. We will consent, recruit and randomise the first 70 patients who fulfil the inclusion and exclusion criteria.
Primary Analysis	The mean difference in %WL at 68 weeks (primary outcome) between the groups will be analysed using linear regression, adjusting for stratification variables and any baseline variables which are not balanced between the groups. The main statistical analyses will estimate the difference in mean %WL between patients randomised to semaglutide + lifestyle and placebo + lifestyle.

	Specifically, the following linear regression model will be fitted: $\%WLi=\beta_0+\beta_1 TRTi+\beta_2 Baseline_weighti+ \beta_3 Typei+\beta_4 T2Di+\epsilon i$ where: • $\%WLi$ is the weight loss at 24 weeks for the ith patient • $TRTi$ is an indicator for the allocated treatment for the ith patient (0 = placebo, 1 = semaglutide) • $Baseline_weighti$ is the weight at baseline for the ith patient • $Typei$ is an indicator for the type of surgical treatment the ith patient receives (0 = SG , 1 = GB) and is one of the stratification factors • $T2Di$ is an indicator for diabetes status for the ith patient (0 = no diabetes, 1 = have diabetes) and is one of the stratification factors • $\beta 0$ is the regression intercept • $\beta 1$ is the parameter of interest which quantifies the effect of treatment • $\beta 2$ is the parameter of interest which quantifies the effect of baseline weight • $\beta 3$ is the parameter of interest which quantifies the effect of type of surgical treatment • $\beta 4$ is the parameter of interest which quantifies the effect of diabetes • $\epsilon i \sim N(0,\sigma\epsilon 2)$ are the residuals • The results from this analysis will be presented in terms of a treatment difference (β1), 95% confidence interval and a P-value. All analyses will be carried out comparing the intervention and control groups as randomised using all available data (intention to treat analysis). The assumptions of the model will be checked, and a suitable transformation/non-parametric method will be used where the assumptions are not met.
Model checking	The model for the primary outcome analysis includes an assumption that the model residuals are normally distributed. The normality of the residuals will be assessed through the construction of appropriate histograms and normal quantile-quantile plots. If such plots suggest that the normality assumption is violated, then appropriate transformations of the primary outcome variable will be considered. The homoscedasticity of the residuals will be assessed using a scatter plot. Possible influential observations and outliers will be identified graphically or using summary statistics. Sensitivity to such influential observations and/or outliers (if present) will be considered.
Missing Data	Bias due to missing data will be investigated and dealt with as appropriate. All available data will be analysed as randomised (ie ITT).
6 week wash-out period	Participants will remain in the trial for an additional 6-week wash out period with remote monitoring visits at week 70 and 74, where weight concomitant medication and AEs will be recorded.

Secondary Analysis	The results of the secondary analysis will be treated as exploratory. Continuous outcomes will be analysed using separate linear regression models, adjusting for stratification variables and any baseline variables which are not balanced between the groups. Mean differences in each outcome will be reported with 95% confidence intervals. The assumptions of each model will be checked, and a suitable transformation/non-parametric method will be used where the assumptions are not met.
Hypothesis	In patients with poor weight loss (<20%) following GB or SG, those randomised to receive semaglutide 3.0 mg/ml subcutaneously once-weekly, as an adjunct to diet and exercise counselling, for 68 weeks, will achieve greater %WL, improvement in health, metabolic and inflammatory indices and HRQoL outcomes compared to those randomised to receive matched placebo as an adjunct to diet and exercise counselling.
Primary outcome	The primary outcome of this trial is %WL from the baseline visit to 68 weeks of treatment. Percentage weight loss will be calculated using the following formula: %WL = [(weight at the baseline visit–weight at the end of the 68-week treatment period)/ weight at the baseline visit] x 100, measured at the end of treatment.
Secondary outcomes	The secondary outcomes of this trial are: 1. The percentage of participants receiving subcutaneous semaglutide 3.0 mg/ml versus placebo who after 68 weeks achieve: • A body weight reduction ≥10% • A body weight reduction ≥15% • A body weight reduction ≥20% 2. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml versus placebo administration upon glycaemia, pre-diabetes and T2D by comparing: • Change in circulating HbA1c levels (mmol/mol) • Change in circulating HbA1c levels in participants with pre-diabetes at baseline. (mmol/mol) • Change in circulating HbA1c levels in participants with T2D at baseline. (mmol/mol) • The number of pharmacological agents required for the management of T2D in participants with pre-existing T2D at baseline. 3. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml versus placebo administration upon BP and hypertension by comparing: • Systolic and diastolic BP (mm/Hg) • Systolic and diastolic BP in participants with pre-existing hypertension. (mm/Hg) • The number of pharmacological agents required for the management of hypertension in participants with pre-existing hypertension.

	4. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml versus placebo administration upon: • Change in lipids and inflammatory markers (HsCRP and inflammatory cytokines) (pg/ml) • Change in food cravings. • Change in HRQoL measures. 5. The relationship between GLP-1 levels at baseline and %WL at 68 weeks. (pg/ml)
Consort Diagram	A CONSORT diagram will be presented. Patient characteristics will be described using means (SDs) or medians (interquartile range) for continuous measures and proportions for categorical measures. These values will be presented by randomisation group.
Economic Impact	To evaluate the economic impact of the trial intervention, we will calculate the cost-effectiveness from an NHS and personal social services (PSS) perspective, relative to usual care. The analysis will be based on per-participant intervention costs, and NHS/PSS resource use and HRQoL assessed retrospectively in the trial between baseline and end of the 68-week treatment period. We will calculate the incremental cost per quality-adjusted life year (QALY) gained for the within-trial period. We will run deterministic and probabilistic sensitivity analyses.