BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054313
Article Type:	Protocol
Date Submitted by the Author:	09-Jun-2021
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Keywords:	DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, SURGERY

Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study: rationale and design of a randomised controlled study

Key words: obesity, type 2 diabetes mellitus, bariatric surgery, sleeve gastrectomy, roux en y gastric bypass

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Sources of funding: The authors of this work, Alexis Sudlow and Dimitri Pournaras received funding from the Royal College of Surgeons (England) for this work.
Grant number: PO117623

Main text word count: 3907

Protocol amendment number: 01

Trial Sponsor: Imperial College London
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Abstract

Introduction

Bariatric surgery is an effective method of controlling glycaemia in patients with type 2 diabetes mellitus and obesity. Long-term studies suggest that although glycaemic control remains good, only 20-40% of patients will maintain remission according to the American Diabetes Association (ADA) criteria.

Purpose

This trial aims to examine the safety and efficacy of combining Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) with goal-directed medical therapy to improve long-term glycaemic control of T2DM.

Methods and Analysis

This prospective, open-label multi-centre RCT will recruit 150 patients with obesity and T2DM from tertiary care obesity centres. Patients will be randomised 1:1 to receive either bariatric surgery and standard medical care or bariatric surgery and intensive goal-directed medical therapy, titrated to specific targets for HbA1c, blood pressure (BP), and LDL-cholesterol. The primary endpoints are the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) at one year and the proportion of patients in each arm achieving the composite endpoint of HbA1c <6.5% (48mmol/mol), BP<130/80mmHg and LDL <2.6mmol/L at five years.

Ethics and Dissemination

The local Institutional Review Board approved this study. This study represents the first RCT to examine the safety and efficacy of combining bariatric surgery with intensive medical therapy compared to bariatric surgery and usual care for long-term diabetes control.

Trial registration number

NCT04432025

Full trial registration data set in Appendix 1

Article Summary

Strengths and limitations of this study

- This is a randomised controlled trial designed to compare the efficacy and safety of combining goal directed medical therapy for type 2 diabetes mellitus (T2DM) with bariatric surgery to bariatric surgery and standard medical care.
- The long-term follow up will evaluate whether patients receiving goal directed medical therapy following bariatric surgery improves long term diabetes control according to the ADA criteria.
- The results will help inform how patients with T2DM should be managed following bariatric surgery.
- This study cannot be blinded due to the nature of the interventions.
- This study is not powered to detect differences between the two surgical procedures included in the trial.

Introduction

Obesity and type 2 diabetes mellitus (T2DM) are inherently linked, and patients suffering from both diseases present a particular challenge to clinicians concerning treatment due to their significantly increased risk of cardiovascular events and end-organ complications. Long-term success in treating hyperglycaemia, hypertension, and dyslipidaemia in patients with T2DM prevents the development of diabetes-related complications with conventional best medical treatment alone (anti-hyperglycaemic agents, anti-hypertensives, and statins in combination with lifestyle modification) has proven to be elusive. Bariatric/metabolic surgery has level 1 evidence from 12 randomised controlled trials (RCTs) demonstrating its safety and efficacy as a treatment for obesity and T2DM [1-12]. Given the powerful metabolic effects on glucose homeostasis and subsequent diabetes control, it is now widely recommended that bariatric surgery is considered a key treatment approach for patients with obesity and difficult to control T2DM[13, 14]. Changes in glucose metabolism, independent of weight loss have been observed in the immediate postoperative period, and remission rates according to the ADA criteria (all diabetic medications stopped, HbA1c<6% (42mmol/mol), fasting plasma glucose <5.6mmol/l (100mg/dl) off all hypoglycaemic agents for one year) of 40% have been demonstrated over a median follow up of two years[15-17].

Despite these promising results, emerging evidence suggests that though glycaemic control improves after surgery, only 20-50% of patients who initially experienced remission will maintain remission in the long-term [15, 18, 19]. The Swedish Obesity Surgery Register (SOReg) data also suggests that patients who do not achieve glycaemic remission within one year have more cardiovascular events[20].

Although standard medical therapy alone is inferior to bariatric surgery regarding control of T2DM, a more intensive approach with pharmacotherapy titrated to prespecified targets for hyperglycaemia, hypertension, and dyslipidaemia has been demonstrated to be safe and

effective. Over a 13.3 year follow-up period, the STENO-2 trial showed a 20% absolute risk reduction in death and a 13% reduction in death due to cardiovascular endpoints with intensive, goal-directed medical therapy compared to conventional therapy[21].

Evidence would support improved glycaemic control due to the powerful metabolic changes evoked by bariatric surgery; however, the effects tend to attenuate with time, and a proportion of patients will ultimately experience a relapse of diabetes[22]. What remains to be seen is whether a multimodal approach with surgery and goal-directed medical therapy can be safely utilised to improve diabetes control[23, 24].

Objectives

This study aims to investigate the long-term safety and efficacy of combining bariatric surgery (Roux-en-Y gastric bypass-RYGB or Sleeve gastrectomy- SG) with goal-directed medical therapy versus bariatric surgery and usual medical care on the glycaemic control and the ADA triple endpoint as a marker of good diabetes control and reflected in measures for HbA1c, BP and lipids.

Trial design

The BY PLUS study is a multi-center, open-label randomised controlled trial. The trial will involve two arms with an allocation ratio of 1:1. There are two primary endpoints:

1. the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) over a follow up of one year
2. the proportion of patients in each arm reaching the composite endpoint of HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/l over a follow-up period of five years.

Patient recruitment was commenced in August 2020. The trial was registered on ClinicalTrials.gov (NCT04432025). A planned interim analysis will also be carried out at a prespecified follow-up period of 12 months and then yearly until trial conclusion at five years (60 months follow up).

Several strategies, such as the use of checklists and workflow, have been employed to guarantee the data's quality and completeness. A dedicated monitor will audit the overall quality and completeness of the data entered on the electronic case report form, examine source documents, and compliance of the team with Good Clinical Practice.

The full SPIRIT checklist can be found in appendix 1.

Methods

Study setting

The study will be undertaken in tertiary care centres with expertise in bariatric surgery and the treatment of obesity and T2DM.

Eligibility criteria

Inclusion criteria

- ≥18 years old
- Eligible for bariatric surgery as per NICE CG189 or IFSO guidelines

- Diagnosis of type 2 diabetes mellitus based on an HbA1c of 48mmol/mol or 6.5%
- Body mass index (BMI) > 30kg/m^2

Exclusion criteria

- Specific contraindications to bariatric surgery
- Previous bariatric surgery
- Current pregnancy or breastfeeding
- Recent illness requiring hospitalisation within the previous 30 days
- Recurrent episodes of hypoglycaemia
- Recurrent episodes of hypotension
- History of any medical, psychological, or other condition, or use of any medications, including over-the-counter products, which, in the opinion of the investigators, would either interfere with the study or potentially cause harm to the participant.
- Lack of access to a telephone or other factors likely to interfere with the ability to participate reliably in the study.
- Concurrent or recent participation in another research study

Interventions

After randomisation, patients will be allocated in a 1:1 ratio, stratified by BMI and site to bariatric surgery plus standard medical care or bariatric surgery and intensive medical therapy. Patients in both arms will undergo bariatric surgery, either SG or RYGB, with the decision regarding the specific procedure being made by the patient and multi-disciplinary team (MDT). The individual arms are discussed below:

Bariatric surgery plus standard medical care- two weeks preoperatively, SGLT-2 inhibitors will be stopped due to the risk of euglycaemic acidosis and following bariatric surgery, all remaining oral diabetic medications will be stopped. If on insulin, patients will be monitored as inpatients. If they require insulin to maintain glycaemic control while in hospital, then a basal dose of insulin will be provided on discharge equivalent to their insulin requirement over the previous 24 hours. Rapid-acting insulin will be stopped postoperatively. The basal insulin dose will be titrated every day by the research team to allow fasting glucose values to be maintained between 7 and 9 mmol/L (126-162mg/dl). For any further monitoring or adjustments of diabetic medications, the clinicians caring for the patient will resume their primary care for metabolic control. Prescribing and/or titration of any medications for glycaemic control, BP and lipids will be according to current standard of care.

Bariatric surgery plus intensive medical therapy- following bariatric surgery, patients will modify their preoperative medications for glycaemic control, BP, lipids, and doses of medications reduced to prevent hypoglycaemia episodes or hypotension. If on insulin, patients will be monitored as inpatients. If they require insulin to maintain glycaemic control while inpatients, then a basal dose of insulin will be provided on discharge equivalent to their insulin requirement over the previous 24 hours. Rapid-acting insulin will be stopped postoperatively. The basal insulin dose will be titrated every day by the research team to allow fasting glucose values to be maintained between 6 and 8 mmol/L (106-145mg/dl). Oral medications in the postoperative period will be adjusted as follows:

Glucose lowering agents:

1. Metformin will be continued at the same dose used pre-surgery
2. SGLT-2 inhibitors will be stopped two weeks preoperatively due to the risk of euglycaemic acidosis
3. All sulphonylureas and thiazides will be stopped preoperatively
4. If fasting glucose >7.5mmol/l (135mg/dl) one month postoperatively, a GLP-1 analogue will be added
5. If fasting glucose remains >7.5mmol/l (135mg/dl) despite the addition of GLP-1 analogue, a SGLT-2 inhibitor will be added

Blood pressure medications:

1. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) at half dose (or lowest dose if this is what they are already on) will be continued
2. All diuretics will be stopped
3. All calcium antagonists will be stopped

Statin

1. Continued at preoperative dose

In subsequent follow-up visits, medications will be individually titrated as required by the obesity clinic staff to achieve specific targets- HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/L.

Surgical procedures

All operations will be performed by consultant surgeons with experience in laparoscopic RYGB or SG. Patients will be admitted to the hospital on the day of the procedure after an overnight fast. The procedures are standardised for both RYGB and SG according to previously described techniques and will be performed as follows[25, 26]. Laparoscopic RYGB will be performed under general anaesthesia and with the creation of a 20-30mL pouch, a biliary limb of approximately 80cm, and an alimentary limb of approximately 120cm. A linear stapler will typically be used to form the gastrojejunostomy and side-to-side jejunojejunostomy. Both mesenteric and Petersen's defects will be routinely closed using non-absorbable clips. For patients undergoing SG, the stomach's greater curvature will be mobilised to allow for the stomach's division using the linear stapler, starting 4-6cm from the pylorus, proceeding towards the angle of His. A 32Fr bougie will be used to help guide the division of the stomach. Deep vein thrombosis (DVT) prophylaxis in the form of compression stockings and intermittent pneumatic compression intraoperatively will be given to all patients and subcutaneous enoxaparin administered after the procedure unless contraindicated. Prophylactic antibiotics will be administered at the induction of anaesthesia. Both groups of will receive identical dietary counselling with regards to food consistency and progression to solid as well as long term follow up for micronutrient replacement and biochemical monitoring[27].

Drug titration

For patients in the surgery plus intensive medical treatment arm, follow-up regarding medications in the postoperative period will be coordinated through clinic. Metformin will be continued, but doses may be reduced if HbA1c is <6% (42 mmol/mol) or discontinued if there are recorded hypoglycaemic episodes or severe gastrointestinal side-effects. The parameters for full withdrawal of medications for glycaemic control are an HbA1c<6% (42mmol/mol) and fasting glucose of 5.5 mmol/L (100mg/dl). Medications for blood pressure control, ACEi, and ARB as well as statins for lipid control will be continued, but doses may be reduced to avoid side effects. At subsequent follow-up visits, patients in this cohort will have their HbA1c, BP, and LDL checked with the results used to guide titration of doses towards the prespecified treatment thresholds HbA1c<6.5% (48mmol/mol), BP<130/80mmHg and LDL<2.6mmol/l.

Outcomes

The primary outcomes are:

1. The proportion of patients in each arm who achieve an HbA1c<6.5% (48mmol/mol) at one year
2. The proportion of patients in each arm who reach the composite endpoint for good diabetes control as outlined by the American Diabetes Association (ADA), which is an HbA1c<6.5% (48mmol/mol), BP<130/80mmHg and LDL<2.6mmol/l at five years.

Secondary outcomes

The secondary outcomes are change from baseline to 5 years for each endpoint, temporal changes, mean levels, and peak levels will be analysed as appropriate: body weight, waist circumference, plasma lipid concentration, plasma liver function tests, urinary creatinine: albumin ratio, inflammatory markers including CRP, Multidimensional Health Profile: Health Functioning questionnaire score (MHP-H), Social Functioning Questionnaire score (SFQ) and the number of medications.

Participant timeline

Screening visit

The screening visit will be undertaken by a member of the bariatric and research team. During this visit, patients will be given information on the study design, randomisation process, the two study arms and follow-up procedures. Patients will also have the opportunity to discuss the risks and benefits of participating in the trial and the risks specific to each arm of the trial. A standardised checklist will be used to ensure that prospective patients are eligible to participate, in keeping with the inclusion and exclusion criteria. Written informed consent will be required for all patients' participation in the surgical procedure (RYGB/SG) and subsequent follow-up procedures. Baseline blood and urine tests will be taken along with height, weight, waist circumference, and blood pressure measurements. Medications will be reviewed, and for those on suboptimal treatment for glycaemic control, BP or lipids medications will either be started or titrated as required.

Randomisation visit

All patients will be required to attend a comprehensive clinical evaluation 4-6 weeks following the screening visit to ensure all eligibility requirements are met. Once confirmed, patients will be assigned an identification number to be used for all further documentation. All patients will be required to undergo upper digestive endoscopy. Two weeks after the randomisation visit, all clinical evaluations will be reviewed to ensure patients were eligible to proceed with trial participation. A dietician will review both groups with expertise in managing patients with obesity and following bariatric surgery. The dietician appointment will focus on the importance of adherence to postoperative dietary changes and nutritional supplement intake.

Follow up visits

Irrespective of the allocation, all patients will be followed up in the obesity clinic according to the same timeline with visits at six weeks, 3, 6, 12 months, and then yearly after that until study completion at 60 weeks. At each follow-up visit, all adverse events will be recorded. For patients in the surgery + intensive medical treatment arm, medications will be titrated to the previously discussed treatment thresholds for HbA1c, BP, and LDL. In addition to routine clinical parameters including weight/BMI, waist circumference the following will be measured/performed (Table 1):

- Non-invasive blood pressure monitoring
- HbA1
- Plasma lipids
- Plasma liver function tests
- Inflammatory markers
- Urinary albumin: creatinine ratio

- Every 12 months: Multidimensional Health Profile: Health Functioning questionnaire (MHP-H) and Social Functioning Questionnaire (SF-36).

Table 1 Schedule of visits, examinations and procedures

Assessments	Screen	Random	Surgery	W6	W12	W24	W52	Y2	Y3	Y4	Y5
Informed consent	X										
Medical history	X	x									
Physical examination	X	x									
Medical assessment	X	X	x	X	x	x	x	x	x	x	x
Medication review	X	X		X	x	x	x	x	x	x	x
Inclusion/exclusion criteria	X	X									
Randomisation		X									
Adverse events				X	x	x	x	x	x	x	x
Nutritional assessment		x		X	x	x	x	x	x	x	x

Serum pregnancy test	X										
MPH-H, SF-36	X							x	x	x	x
Urine sample	X			x	x	x	x	x	x	x	x
Fasting plasma glucose	X			x	x	x	x	x	x	x	x
HbA1c	X			x	x	x	x	x	x	x	x
Lipids	X			x	x	x	x	x	x	x	x
Blood pressure	X			x	x	x	x	x	x	x	x
CRP	X			x	x	x	x	x	x	x	x
Height	X										
Weight	X		x	x	x	x	x	x	x	x	x
Waist circumference	X	x	x	x	x	x	x	x	x	x	x
Upper digestive endoscopy		x									
RYGB or SG			x								
Drug titration and dispensing			x	x	x	x	x	x	x	x	x
Glucose monitoring			x	x	x	x	x	x	x	x	x

Sample size

Based on published data comparing the effect size of best medical therapy combined with bariatric surgery vs. best medical therapy alone on glycaemic control, BP and cholesterol levels in patients with T2DM, we estimated that 30% of patients in the control group and 50% of patients in the intensive treatment group would reach the primary endpoint [28]. Based on these data, we calculated that to have 80% power to detect statistically significant differences between the groups at α of 0.05, we would need 55 patients per arm. We will recruit 75 patients in each group to account for a possible 20-25% drop-out rate.

Recruitment strategy

All patients presenting to the obesity clinic within the participating centres who are due to undergo RYGB or SG and meet the eligibility criteria will be given written and verbal information regarding participation in the study. After a minimum period of 24 hours to consider the information, patients can indicate whether they are willing to participate and will be asked to provide written consent.

Assignment of interventions

Sequence generation

Patients will be randomised by an independent researcher not involved in patient recruitment, treatment, or follow-up. A computer-generated sequence will randomise patients 1:1 to either surgery + standard medical care or surgery + intensive goal-directed medical therapy with random block sizes of 4.

Concealment mechanism
Randomisation codes will only be released after patients are formally recruited to the trial. The randomisation sequence will be held by a senior project manager not associated directly with this trial and will not be available to any of the research investigators at any time. Participants, staff members, and researchers will be unable to foresee the assignment because of central randomisation. All participant data will be pseudo anonymised (personal information removed and replaced with a coded identifier), and this list will be supplied to the central allocation, which randomly allocates patients to either arm of the study.

Blinding
Because of the study's nature, neither study investigators nor patients can be blinded regarding their allocation. All investigators in charge of statistical analysis or analysis of samples (laboratory staff) will be blinded to the patient allocation.

Data management

In order to assure data quality, several procedures are in place, including missing data, permitted/non-permitted value ranges, and logic checks. Checklists and standard operating procedures were created and routinely used to ensure data are complete and reliable. As this is a multi-centre trial, training will be done centrally at the host institution with members of all sites present and all data collection forms are standardised to ensure homogeneity in data collection and entry. Each member of the study team requires training before study initiation, and roles are delegated and assigned. Each participant will receive a numerical code to ensure confidentiality and tracking. Source documents (paper) will be stored at each site in a secured location, with all documents being stored according to their numerical code and accessible only to the study team.

A dedicated monitor, which has been designated specifically for this protocol, will be responsible for source data verification and the creation of queries and/or data clarification forms for all participants' source documents. This monitor will assure quality assurance and control, and a statistician will be responsible for final data verification and database analysis throughout the study.

Retention
We anticipate a 20-25% drop-out rate over the 60-month follow-up period. This was reflected in the power calculation to plan the sample size. To mitigate the effects of losing patients to follow up, trial coordinators will make every possible effort to follow up patients for the entire duration of the study. Strategies using multiple contact methods such as email, mail, telephone calls will be employed to achieve the highest possible level of follow-up.

Participant withdrawals

In the case of a participant deciding to withdraw from the study, they will be asked to provide further monitoring and data collection after their withdrawal. For participants who have been lost to follow up despite attempts to contact them, their data will be imputed.

Patient and public involvement

Qualitative research specifically examining patients' expectations and experiences of undergoing bariatric surgery as a treatment for T2DM was undertaken. This information was used to help develop the research question, ensuring that patient priorities were reflected in the design of the study as well as the choice of outcome measures. This study also explored patient perceptions of continued medications following surgery to determine whether the proposed intervention would be acceptable to the target population.

Statistical methods

All data analysis and statistical methods were advised by a statistician and will be performed on an intention to treat principle (ITT). An overview of the methods of analysis is presented in Table 2. We will compare the proportion of participants achieving the primary outcome between bariatric surgery and goal-directed medical therapy versus bariatric surgery and usual care using an unconditional logistic regression model. Continuous outcomes will be analysed by mixed-effects generalised linear models adjusting for the response variable's baseline version. Missing data will be imputed using several different models, assuming data will be missing at random. Participants' demographic data and clinical characteristics will be analysed using an unpaired Student's T-test for continuous variables, whereas dichotomous variables will be analysed using Fischer's exact test. Data will be expressed as mean +/-SD, median, and IQR or counts (percentage) as appropriate. In any circumstances, variables with asymmetric distributions will be transformed using standard mathematical models (logarithm, square root, etc.). Statistical significance will be set at the 1.7% level (two-sided) for the primary outcome and 5% for secondary outcomes. The main conclusions will be based on the ITT principle and on the logistic regression model. All data analysis will be performed using Stata (V.13.0, Stata Corp, College Station, Texas, USA).

Table 2- Variable, measures, and method of analysis

Variable/outcome	Hypothesis	Outcome measure	Method of analysis
Primary outcome HbA1c	The proportion of patients with an HbA1c<6.5%(48mmol/mol) at one year will be higher in the surgery + intensive treatment group compared to control	The proportion of patients in each group with an HbA1c <6.5% (48mmol/mol)	Mixed-effects generalized linear models
Composite end point of HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, LDL<2.6mmol/l	The proportion of participants reaching the composite endpoint will be higher in the surgery+ intensive treatment group compared to the control	The proportion of participants reaching the composite endpoint	Logistic regression

Secondary outcomes			
BMI	The reduction will be higher in the surgery+ intensive treatment group compared to the control	kg/m^2	Student's t-test
Waist circumference	The reduction will be higher in the surgery+ intensive treatment group compared to the control	cm	Student's t-test
Glycaemic control	The reduction will be higher in the surgery+ intensive treatment group compared to the control	HbA1c levels	Mixed-effects generalized linear models
Blood pressure control	The proportion of patients achieving blood pressure control will be higher in the surgery + intensive treatment group compared to the control	Number of participants achieving BP<130/80mmHg	Mixed-effects generalized linear models
Lipid control	The proportion of patients achieving lipid control will be higher in the surgery + intensive treatment group compared to the control	Number of participants with LDL <2.6mmol/L	Logistic regression
Liver function	The proportion of patients achieving normal liver function tests will be higher in the surgery + intensive treatment group compared to the control	ALT (IU/L), GGT (IU/L), AST (IU/L), ALP(IU/L) levels	Mixed-effects generalized linear models
Inflammatory markers	The reduction in CRP will be greater in the surgery + intensive treatment group compared to control	CRP	Mixed-effects generalized linear models
Urine albumin: creatinine ratio	The proportion of patients in the surgery + intensive treatment group with a uACR<30µg will be higher than the control group	Number of participants in each group with a uACR<30µg	Logistic regression
Quality of life	Quality of life is higher in patients in the surgery + intensive medical therapy arm compared to control	SF-36 and MHP-H	Mixed-effects generalized linear models
Clinical and sociodemographic variables			

Age	There is no difference between the two groups	Years	Student's t-test
BMI	There will be a greater reduction in BMI in the intensive medical therapy arm compared to control group	kg/m^2	Student's t-test
Weight	There will be a greater reduction in weight in the intensive medical group compared to control group	Kg	Student's t-test
Gender	There is no difference between the two groups	1= male, 0= female	Fischer's exact test
Waist circumference	There will be a greater reduction in the waist circumference in the intensive medical group compared to the control group	cm	Student's t-test
Fasting blood glucose	There will be a greater reduction in the fasting blood glucose in the intensive medical group compared to the control group	mg/dL, mol/L	Student's t-test
Total HDL and LDL cholesterol	There will be a greater reduction in the total HDL and LDL cholesterol in the intensive medical group compared to the control group	mmol/L	Student's t-test
Triglycerides	There will be a greater reduction in triglycerides in the intensive medical group compared to the control group	Mmol/L	Student's t-test
Diastolic and systolic blood pressure	There will be a greater reduction in diastolic and systolic pressure in the intensive medical group compared to the control group	mmHg	Student's t-test

Additional analysis

All primary analyses will be carried out on an ITT basis, but subsequent studies may be conducted on a per-protocol basis. The primary analysis will also be performed out with multiple imputation methods. We will also provide results from analyses restricted to complete cases to compare results from the multiple imputation processes.

Adjusted analysis
All statistical models will be run with appropriate adjustment for baseline characteristics.

Analysis population and missing data
In the case of missing data, we will perform and report the multiple imputation analysis according to the recommendation of White *et al. [29].* Missing data will be handled using multiple imputation methods, assuming all data are missing at random. We will use a combination of predictive mean matching and regression-based methods to impute missing data. Specifically, we will use a combination of predictive mean matching and regression-based methods to impute missing data. A total of 100 data sets will be created to reduce sampling variability. A burn-in period of 500 iterations will be used. Imputation will be performed in Stata V.14.0 (StataCorp, College Station, Texas, USA).

Monitoring
Adverse events
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical study subject even if it did not directly relate to the medical or surgical intervention. Serious adverse events were defined as any untoward and unexpected medical occurrence or effect that:

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

All AE or SAE are required to be reported within 24h with detailed documentation to the research and ethics committee.

Auditing
Throughout the study, audits will be carried out by a dedicated monitor using several key indicators on all source documents and participants. The key indicators are informed consent form (ICF) and process, eligibility criteria, enrolment, allocation of study groups, scheduled and missed tests and procedures, policies to protect participants, concomitant and prohibited medications, dispensing medication procedures, identification and reporting of A.E.s and SAEs, deviation report, regulatory documents and communication with local research and ethics committee, following International conference on Harmonisation-Good Clinical Practice (ICH-GCP) and regulatory agency guidelines.

Ethics and dissemination
Research ethics approval
Protocol, ICF, and recruitment materials were reviewed and approved by the study sites' local research and ethics committee. Approval was received within Ireland on the 11th of

February 2020 and on the 2nd of December 2020 within the UK. All sites will report back regarding study progress regularly.

Protocol amendments

All changes needed after initial approval will be re-submitted to the research and ethics committee for review. Amendments to the clinical protocol will require formal review, accompanied by an updated, informed consent signed by both the investigators and participants. If any changes are made to the protocol, the history will be available and tracked by version and date changes.

Consent

Patients identified as potential participants will receive verbal and written information from an investigator (medical doctor). A copy of the study materials and ICF will be given, and patients allowed an opportunity to review and discuss with family/friends. After being given a minimum of 24 hours to consider the materials, a formal discussion will be carried out with the patient and an investigator. Patients will be allowed to ask any questions and clarify any areas of uncertainty. If the patient then decides to participate, they will be given an ICF to sign (also signed by the investigator), after which they are considered a study participant. Assent form and ancillary studies consent are not necessary for the study.

Confidentiality

All medical information derived from the study will be confidential, and no third-party access will be allowed. The designated personnel will handle source/data information stored on password-protected computers and in-coded patient notes to protect confidentiality.

Declaration of interests

The author RC has received an honorarium as a member of the Speaker's panel of Johnson & Johnson.
The author ClR has received grants from the Science Foundation Ireland, Health Research Board, Irish Research Council, Johnson & Johnson and AnaBio. Personal fees have been received from Eli Lily, Johnson & Johnson, Sanofi Aventis, Astra Zeneca, Janssen, Bristol-Meyers Squibb and Boehringer-Ingelheim. He is on the advisory board for GI dynamics.
The author DJP has received personal fees from NovoNordisk and Johnson & Johnson.

Study sponsorship and access to data

Data will be available to authorised investigators only. Third parties may have access to data with express written permission from the lead investigator. However, sponsors will not participate in data analysis, nor will they have access to data, either in full or in part.

Ancillary and post-trial care

Participating sites will have insurance policies to cover non-negligent harm associated with the protocol, which covers additional healthcare, compensation, or damages whether awarded voluntarily by the BY PLUS study or by claims pursued through the courts.

Dissemination policy

After the trial protocol publication, the investigators plan to publish all the listed endpoints as this RCT is the first trial to compare intensive goal-directed medical therapy combined with bariatric surgery versus bariatric surgery and standard medical care for patients with T2DM and obesity. The results of this trial will be published in peer-reviewed scientific journals and presented at major conferences, regardless of the magnitude or direction of the observed effect.

Trial organisation and management
The study investigators are responsible for completing all pertinent information using the clinical report forms, data accuracy, and maintaining the confidentiality of patients' data. Only the investigators will have access to the final data set. All documentation will be kept for five years after the study's termination if it has to be monitored, audited, or inspected by the sponsor or regulatory authorities.

Author Contributions

Conceived the trial and were involved in logistical planning- AS, AM, HK, JT, RC, HH, ClR, DJP
Drafted the article- AS, AM, HK, RC, HH, ClR, DJP

Data sharing

The authors shall make data available to the scientific community with as few restrictions as feasible, ensuring anonymisation, while retaining exclusive use until the publication of major outputs.

Funding
The authors of this work, Alexis Sudlow and Dimitri Pournaras received funding from the Royal College of Surgeons (England) for this work.
Grant number: PO117623

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Appendix 1

Consent form

Medications following bariatric surgery for type 2 diabetes mellitus
The BY-PLUS Randomised Controlled Trial

Please initial within each box to indicate you consent/agree

I confirm that I have read and understand the subject information sheet dated ..... version ..... for the above study and have had the opportunity to ask questions which have been answered fully. ☐

I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. ☐

I understand that sections of any of my medical notes may be looked at by responsible individuals from Imperial College London, from NHS Trust or from regulatory authorities where it is relevant to my taking part in this research. ☐

I give permission for these individuals to access my records that are relevant to this research ☐

I consent to my GP being informed of my participation in this study and to them being contacted for information relating to my participation and of any significant incidental findings during the study. ☐

I give / do not give (delete as applicable) consent for information collected about me to be used to support other research in the future, including those outside of the EEA. ☐

I give / do not give (delete as applicable) consent for samples collected during this study to be used in future ethically approved studies. ☐

I give / do not give permission for my samples to be sent to other organisations, including those outside of the EEA. ☐

I consent to take part in the above study. ☐

I give /do not give (delete as applicable) consent to being contacted to potentially taking part in other research studies. ☐

_____	_____	_____
Name of Subject	Signature	Date

_____	_____	_____
Name of Person taking consent	Signature	Date

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Appendix 1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1,16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3,4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4,5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 10-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8,9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	9

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9,10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	20
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study: rationale and design of a randomised controlled study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054313.R1
Article Type:	Protocol
Date Submitted by the Author:	19-Jan-2022
Complete List of Authors:	Sudlow, Alexis; Southmead Hospital, Department of Upper GI and Bariatric Surgery Miras , Alexander ; Imperial College Healthcare NHS Trust, Division of Diabetes, Endocrinology and Metabolic Medicine Cohen, Ricardo; Hospital Alemao Oswaldo Cruz, The Center for Obesity and Diabetes; Hospital Alemao Oswaldo Cruz, Health Research Unit Kahal, Hassan; Southmead Hospital, Department of Diabetes and Endocrinology Townley, Jill; Southmead Hospital, Department of Surgery Heneghan, Helen; St Vincent's University Hospital, Department of Surgery Le Roux, Carel; University College Dublin, Department of Experimental Pathology Pournaras, Dimitri; Southmead Hospital, Department of Upper GI and Bariatric Surgery
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics, Surgery
Keywords:	DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, SURGERY

Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study: rationale and design of a randomised controlled study

Key words: obesity, type 2 diabetes mellitus, bariatric surgery, sleeve gastrectomy, roux en y gastric bypass

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Sources of funding: The authors of this work, Alexis Sudlow and Dimitri Pournaras received funding from the Royal College of Surgeons (England) for this work.
Grant number: PO117623

Main text word count: 3907

Protocol amendment number: 01

Trial Sponsor: Imperial College London
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Abstract

Introduction
Bariatric surgery is an effective method of controlling glycaemia in patients with type 2 diabetes mellitus and obesity. Long-term studies suggest that although glycaemic control remains good, only 20-40% of patients will maintain remission according to the American Diabetes Association (ADA) criteria.

Purpose
This trial aims to examine the safety and efficacy of combining Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) with goal-directed medical therapy to improve long-term glycaemic control of T2DM.

Methods and Analysis
This prospective, open-label multi-centre RCT will recruit 150 patients with obesity and T2DM from tertiary care obesity centres. Patients will be randomised 1:1 to receive either bariatric surgery and standard medical care or bariatric surgery and intensive goal-directed medical therapy, titrated to specific targets for HbA1c, blood pressure (BP), and LDL-cholesterol. The primary endpoints are the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) at one year and the proportion of patients in each arm achieving the composite endpoint of HbA1c <6.5% (48mmol/mol), BP<130/80mmHg and LDL <2.6mmol/L at five years.

Ethics and Dissemination
The local Institutional Review Board approved this study. This study represents the first RCT to examine the safety and efficacy of combining bariatric surgery with intensive medical therapy compared to bariatric surgery and usual care for long-term diabetes control.

Trial registration number
NCT04432025
Full trial registration data set in Appendix 1

Article Summary

Strengths and limitations of this study

- This is a randomised controlled trial designed to compare the efficacy and safety of combining goal directed medical therapy for type 2 diabetes mellitus (T2DM) with bariatric surgery to bariatric surgery and standard medical care.
- The long-term follow up will evaluate whether patients receiving goal directed medical therapy following bariatric surgery improves long term diabetes control according to the ADA criteria.
- The results will help inform how patients with T2DM should be managed following bariatric surgery.
- This study cannot be blinded due to the nature of the interventions.
- This study is not powered to detect differences between the two surgical procedures included in the trial.

Introduction

Obesity and type 2 diabetes mellitus (T2DM) are inherently linked, and patients suffering from both diseases present a particular challenge to clinicians concerning treatment due to their significantly increased risk of cardiovascular events and end-organ complications. Long-term success in treating hyperglycaemia, hypertension, and dyslipidaemia in patients with T2DM prevents the development of diabetes-related complications with conventional best medical treatment alone (anti-hyperglycaemic agents, anti-hypertensives, and statins in combination with lifestyle modification) has proven to be elusive. Bariatric/metabolic surgery has level 1 evidence from 12 randomised controlled trials (RCTs) demonstrating its safety and efficacy as a treatment for obesity and T2DM [1-12]. Given the powerful metabolic effects on glucose homeostasis and subsequent diabetes control, it is now widely recommended that bariatric surgery is considered a key treatment approach for patients with obesity and difficult to control T2DM[13, 14]. Changes in glucose metabolism, independent of weight loss have been observed in the immediate postoperative period, and remission rates according to the ADA criteria (all diabetic medications stopped, HbA1c<6% (42mmol/mol), fasting plasma glucose <5.6mmol/l (100mg/dl) off all hypoglycaemic agents for one year) of 40% have been demonstrated over a median follow up of two years[15-17].

Despite these promising results, emerging evidence suggests that though glycaemic control improves after surgery, only 20-50% of patients who initially experienced remission will maintain remission in the long-term [15, 18, 19]. The Swedish Obesity Surgery Register (SOReg) data also suggests that patients who do not achieve glycaemic remission within one year have more cardiovascular events[20].

Although standard medical therapy alone is inferior to bariatric surgery regarding control of T2DM, a more intensive approach with pharmacotherapy titrated to prespecified targets for hyperglycaemia, hypertension, and dyslipidaemia has been demonstrated to be safe and

effective. Over a 13.3 year follow-up period, the STENO-2 trial showed a 20% absolute risk reduction in death and a 13% reduction in death due to cardiovascular endpoints with intensive, goal-directed medical therapy compared to conventional therapy[21].

Evidence would support improved glycaemic control due to the powerful metabolic changes evoked by bariatric surgery; however, the effects tend to attenuate with time, and a proportion of patients will ultimately experience a relapse of diabetes[22]. What remains to be seen is whether a multimodal approach with surgery and goal-directed medical therapy can be safely utilised to improve diabetes control[23, 24].

Objectives

This study aims to investigate the long-term safety and efficacy of combining bariatric surgery (Roux-en-Y gastric bypass-RYGB or Sleeve gastrectomy- SG) with goal-directed medical therapy versus bariatric surgery and usual medical care on the glycaemic control and the ADA triple endpoint as a marker of good diabetes control and reflected in measures for HbA1c, BP and lipids.

Trial design

The BY PLUS study is a multi-center, open-label randomised controlled trial. The trial will involve two arms with an allocation ratio of 1:1. There are two primary endpoints:

1. the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) over a follow up of one year
2. the proportion of patients in each arm reaching the composite endpoint of HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/l over a follow-up period of five years.

Patient recruitment was commenced in August 2020. The trial was registered on ClinicalTrials.gov (NCT04432025). A planned interim analysis will also be carried out at a prespecified follow-up period of 12 months and then yearly until trial conclusion at five years (60 months follow up).

Several strategies, such as the use of checklists and workflow, have been employed to guarantee the data's quality and completeness. A dedicated monitor will audit the overall quality and completeness of the data entered on the electronic case report form, examine source documents, and compliance of the team with Good Clinical Practice.

The full SPIRIT checklist can be found in appendix 1.

Methods

Study setting

The study will be undertaken in tertiary care centres with expertise in bariatric surgery and the treatment of obesity and T2DM.

Eligibility criteria

Inclusion criteria

- ≥18 years old
- Eligible for bariatric surgery as per NICE CG189 or IFSO guidelines

- Diagnosis of type 2 diabetes mellitus based on an HbA1c of 48mmol/mol or 6.5%
- Body mass index (BMI) > 30kg/m^2

Exclusion criteria

- Specific contraindications to bariatric surgery
- Previous bariatric surgery
- Current pregnancy or breastfeeding
- Recent illness requiring hospitalisation within the previous 30 days
- Recurrent episodes of hypoglycaemia
- Recurrent episodes of hypotension
- History of any medical, psychological, or other condition, or use of any medications, including over-the-counter products, which, in the opinion of the investigators, would either interfere with the study or potentially cause harm to the participant.
- Lack of access to a telephone or other factors likely to interfere with the ability to participate reliably in the study.
- Concurrent or recent participation in another research study

Interventions

After randomisation, patients will be allocated in a 1:1 ratio, stratified by BMI and site to bariatric surgery plus standard medical care or bariatric surgery and intensive medical therapy. Patients in both arms will undergo bariatric surgery, either SG or RYGB, with the decision regarding the specific procedure being made by the patient and multi-disciplinary team (MDT). The individual arms are discussed below:

Bariatric surgery plus standard medical care- two weeks preoperatively, SGLT-2 inhibitors will be stopped due to the risk of euglycaemic acidosis and following bariatric surgery, all remaining oral diabetic medications will be stopped. If on insulin, patients will be monitored as inpatients. If they require insulin to maintain glycaemic control while in hospital, then a basal dose of insulin will be provided on discharge equivalent to their insulin requirement over the previous 24 hours. Rapid-acting insulin will be stopped postoperatively. The basal insulin dose will be titrated every day by the research team to allow fasting glucose values to be maintained between 7 and 9 mmol/L (126-162mg/dl). For any further monitoring or adjustments of diabetic medications, the clinicians caring for the patient will resume their primary care for metabolic control. Prescribing and/or titration of any medications for glycaemic control, BP and lipids will be according to current standard of care.

Bariatric surgery plus intensive medical therapy- following bariatric surgery, patients will modify their preoperative medications for glycaemic control, BP, lipids, and doses of medications reduced to prevent hypoglycaemia episodes or hypotension. If on insulin, patients will be monitored as inpatients. If they require insulin to maintain glycaemic control while inpatients, then a basal dose of insulin will be provided on discharge equivalent to their insulin requirement over the previous 24 hours. Rapid-acting insulin will be stopped postoperatively. The basal insulin dose will be titrated every day by the research team to allow fasting glucose values to be maintained between 6 and 8 mmol/L (106-145mg/dl). Oral medications in the postoperative period will be adjusted as follows:

Glucose lowering agents:

1. Metformin will be continued at the same dose used pre-surgery
2. SGLT-2 inhibitors will be stopped two weeks preoperatively due to the risk of euglycaemic acidosis
3. All sulphonylureas and thiazides will be stopped preoperatively
4. If fasting glucose >7.5mmol/l (135mg/dl) one month postoperatively, a GLP-1 analogue will be added
5. If fasting glucose remains >7.5mmol/l (135mg/dl) despite the addition of GLP-1 analogue, a SGLT-2 inhibitor will be added

Blood pressure medications:

1. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) at half dose (or lowest dose if this is what they are already on) will be continued
2. All diuretics will be stopped
3. All calcium antagonists will be stopped

Statin

1. Continued at preoperative dose

In subsequent follow-up visits, medications will be individually titrated as required by the obesity clinic staff to achieve specific targets- HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/L.

Surgical procedures

All operations will be performed by consultant surgeons with experience in laparoscopic RYGB or SG. Patients will be admitted to the hospital on the day of the procedure after an overnight fast. The procedures are standardised for both RYGB and SG according to previously described techniques and will be performed as follows[25, 26]. Laparoscopic RYGB will be performed under general anaesthesia and with the creation of a 20-30mL pouch, a biliary limb of approximately 80cm, and an alimentary limb of approximately 120cm. A linear stapler will typically be used to form the gastrojejunostomy and side-to-side jejunojejunostomy. Both mesenteric and Petersen's defects will be routinely closed using non-absorbable clips. For patients undergoing SG, the stomach's greater curvature will be mobilised to allow for the stomach's division using the linear stapler, starting 4-6cm from the pylorus, proceeding towards the angle of His. A 32Fr bougie will be used to help guide the division of the stomach. Deep vein thrombosis (DVT) prophylaxis in the form of compression stockings and intermittent pneumatic compression intraoperatively will be given to all patients and subcutaneous enoxaparin administered after the procedure unless contraindicated. Prophylactic antibiotics will be administered at the induction of anaesthesia. Both groups of will receive identical dietary counselling with regards to food consistency and progression to solid as well as long term follow up for micronutrient replacement and biochemical monitoring[27]. Blood results will be checked at baseline, 3, 6, 12 months and then annually thereafter including corrected Ca, vitamin D, ferritin/iron profile, vitamin B12, folate. PTH, copper, zinc and selenium will be checked at 12 months

and yearly thereafter. Magnesium, chromium and fat soluble vitamins will not be routinely checked. (Reviewer 1, Comment 3)

Drug titration and safety monitoring

For patients in the surgery plus intensive medical treatment arm, follow-up regarding medications in the postoperative period will be coordinated through clinic. Metformin will be continued, but doses may be reduced if HbA1c is <6% (42 mmol/mol) or discontinued if there are recorded hypoglycaemic episodes or severe gastrointestinal side-effects. The parameters for full withdrawal of medications for glycaemic control are an HbA1c<6% (42mmol/mol) and fasting glucose of 5.5 mmol/L (100mg/dl). Medications for blood pressure control, ACEi, and ARB as well as statins for lipid control will be continued, but doses may be reduced to avoid side effects. At subsequent follow-up visits, patients in this cohort will have their HbA1c, BP, and LDL checked with the results used to guide titration of doses towards the prespecified treatment thresholds HbA1c<6.5% (48mmol/mol), BP<130/80mmHg and LDL<2.6mmol/l.

Outcomes

The primary outcomes are:

1. The proportion of patients in each arm who achieve an HbA1c<6.5% (48mmol/mol) at one year
2. The proportion of patients in each arm who reach the composite endpoint for good diabetes control as outlined by the American Diabetes Association (ADA), which is an HbA1c<6.5% (48mmol/mol), BP<130/80mmHg and LDL<2.6mmol/l at five years.

Secondary outcomes

The secondary outcomes are change from baseline to 5 years for each endpoint, temporal changes, mean levels, and peak levels will be analysed as appropriate: body weight, BMI, waist circumference, plasma lipid concentration, plasma liver function tests, urinary creatinine: albumin ratio, inflammatory markers including CRP, Multidimensional Health Profile: Health Functioning questionnaire score (MHP-H), Social Functioning Questionnaire score (SFQ) and the number of medications.

The safety of concurrent medication administration following surgery for blood pressure and glycaemic control will also be monitored with standardised reporting procedures for episodes of:

1. Symptomatic or asymptomatic hypoglycaemia deined as a BM of <4mmol/L (70mg/dL)
2. Symptomatic or asymptomatic hypotension defined as systolic BP<90mmHg

Symptoms of either hypoglycaemia or hypotension will be discussed with patients and they will be instructed to contact the study coordinators to arrange clinic review for titration of medication as necessary. (Reviewer 1, Comment 1)

Participant timeline

Screening visit

The screening visit will be undertaken by a member of the bariatric and research team. During this visit, patients will be given information on the study design, randomisation process, the two study arms and follow-up procedures. Patients will also have the opportunity to discuss the risks and benefits of participating in the trial and the risks specific to each arm of the trial. A standardised checklist will be used to ensure that prospective patients are eligible to participate, in keeping with the inclusion and exclusion criteria. Written informed consent will be required for all patients' participation in the surgical procedure (RYGB/SG) and subsequent follow-up procedures. Baseline blood and urine tests will be taken along with height, weight, waist circumference, and blood pressure measurements. Medications will be reviewed, and for those on suboptimal treatment for glycaemic control, BP or lipids medications will either be started or titrated as required.

Randomisation visit

All patients will be required to attend a comprehensive clinical evaluation 4-6 weeks following the screening visit to ensure all eligibility requirements are met. Once confirmed, patients will be assigned an identification number to be used for all further documentation. All patients will be required to undergo upper digestive endoscopy. Two weeks after the randomisation visit, all clinical evaluations will be reviewed to ensure patients were eligible to proceed with trial participation. A dietician will review both groups with expertise in managing patients with obesity and following bariatric surgery. The dietician appointment will focus on the importance of adherence to postoperative dietary changes and nutritional supplement intake.

Follow up visits

Irrespective of the allocation, all patients will be followed up in the obesity clinic according to the same timeline with visits at six weeks, 3, 6, 12 months, and then yearly after that until study completion at 60 months.(Reviewer 1, Comment 4) At each follow-up visit, all adverse events will be recorded. For patients in the surgery + intensive medical treatment arm, medications will be titrated to the previously discussed treatment thresholds for HbA1c, BP, and LDL. In addition to routine clinical parameters including weight/BMI, waist circumference the following will be measured/performed (Table 1):

- Non-invasive blood pressure monitoring
- HbA1
- Plasma lipids
- Plasma liver function tests
- Plasma renal function tests (Reviewer 1, Comment 2)
- Inflammatory markers
- Urinary albumin: creatinine ratio

- Every 12 months: Multidimensional Health Profile: Health Functioning questionnaire (MHP-H) and Social Functioning Questionnaire (SF-36).

Table 1 Schedule of visits, examinations and procedures

Assessments	Screen	Random	Surgery	W6	W12	W24	W52	Y2	Y3	Y4	Y5
Informed consent	X										
Medical history	X	x									
Physical examination	X	x									
Medical assessment	X	X	x	X	x	x	x	x	x	x	x
Medication review	X	X		X	x	x	x	x	x	x	x
Inclusion/exclusion criteria	X	X									
Randomisation		X									
Adverse events				X	x	x	x	x	x	x	x
Nutritional assessment		x		X	x	x	x	x	x	x	x
Serum pregnancy test	X										
MPH-H, SF-36	X							x	x	x	x
Urine sample	X			x	x	x	x	x	x	x	x
Fasting plasma glucose	X			x	x	x	x	x	x	x	x
HbA1c	X			x	x	x	x	x	x	x	x
Lipids	X			x	x	x	x	x	x	x	x
Liver function test	x			x	x	x	x	x	x	x	x
Renal function test	X			X	X	X	X	X	X	X	X
Blood pressure	X			x	x	x	x	x	x	x	x
CRP	X			x	x	x	x	x	x	x	x
Height	X										
Body weight	X		x	x	x	x	x	x	x	x	x
Waist circumference	X	x	x	x	x	x	x	x	x	x	x
Upper digestive endoscopy		x									
RYGB or SG			x								
Drug titration and dispensing			x	x	x	x	x	x	x	x	x
Glucose monitoring			x	x	x	x	x	x	x	x	x

Sample size

Based on published data comparing the effect size of best medical therapy combined with bariatric surgery vs. best medical therapy alone on glycaemic control, BP and cholesterol levels in patients with T2DM, we estimated that 30% of patients in the control group and 50% of patients in the intensive treatment group would reach the primary endpoint [28]. Based on these data, we calculated that to have 80% power to detect statistically significant

differences between the groups at α of 0.05, we would need 55 patients per arm. We will recruit 75 patients in each group to account for a possible 20-25% drop-out rate.

Recruitment strategy

All patients presenting to the obesity clinic within the participating centres who are due to undergo RYGB or SG and meet the eligibility criteria will be given written and verbal information regarding participation in the study. After a minimum period of 24 hours to consider the information, patients can indicate whether they are willing to participate and will be asked to provide written consent.

Assignment of interventions

Sequence generation

Patients will be randomised by an independent researcher not involved in patient recruitment, treatment, or follow-up. A computer-generated sequence will randomise patients 1:1 to either surgery + standard medical care or surgery + intensive goal-directed medical therapy with random block sizes of 4.

Concealment mechanism

Randomisation codes will only be released after patients are formally recruited to the trial. The randomisation sequence will be held by a senior project manager not associated directly with this trial and will not be available to any of the research investigators at any time. Participants, staff members, and researchers will be unable to foresee the assignment because of central randomisation. All participant data will be pseudo anonymised (personal information removed and replaced with a coded identifier), and this list will be supplied to the central allocation, which randomly allocates patients to either arm of the study.

Blinding

Because of the study's nature, neither study investigators nor patients can be blinded regarding their allocation. All investigators in charge of statistical analysis or analysis of samples (laboratory staff) will be blinded to the patient allocation.

Data management

In order to assure data quality, several procedures are in place, including missing data, permitted/non-permitted value ranges, and logic checks. Checklists and standard operating procedures were created and routinely used to ensure data are complete and reliable. As this is a multi-centre trial, training will be done centrally at the host institution with members of all sites present and all data collection forms are standardised to ensure homogeneity in data collection and entry. Each member of the study team requires training before study initiation, and roles are delegated and assigned. Each participant will receive a numerical code to ensure confidentiality and tracking. Source documents (paper) will be stored at each site in a secured location, with all documents being stored according to their numerical code and accessible only to the study team.

A dedicated monitor, which has been designated specifically for this protocol, will be responsible for source data verification and the creation of queries and/or data clarification forms for all participants' source documents. This monitor will assure quality assurance and control, and a statistician will be responsible for final data verification and database analysis throughout the study.

Retention

We anticipate a 20-25% drop-out rate over the 60-month follow-up period. This was reflected in the power calculation to plan the sample size. To mitigate the effects of losing patients to follow up, trial coordinators will make every possible effort to follow up patients for the entire duration of the study. Strategies using multiple contact methods such as email, mail, telephone calls will be employed to achieve the highest possible level of follow-up.

Participant withdrawals

In the case of a participant deciding to withdraw from the study, they will be asked to provide further monitoring and data collection after their withdrawal. For participants who have been lost to follow up despite attempts to contact them, their data will be imputed.

Patient and public involvement

Qualitative research specifically examining patients' expectations and experiences of undergoing bariatric surgery as a treatment for T2DM was undertaken. This information was used to help develop the research question, ensuring that patient priorities were reflected in the design of the study as well as the choice of outcome measures. This study also explored patient perceptions of continued medications following surgery to determine whether the proposed intervention would be acceptable to the target population.

Statistical methods

All data analysis and statistical methods were advised by a statistician and will be performed on an intention to treat principle (ITT). An overview of the methods of analysis is presented in Table 2. We will compare the proportion of participants achieving the primary outcome between bariatric surgery and goal-directed medical therapy versus bariatric surgery and usual care using an unconditional logistic regression model. Continuous outcomes will be analysed by mixed-effects generalised linear models adjusting for the response variable's baseline version. Missing data will be imputed using several different models, assuming data will be missing at random. Participants' demographic data and clinical characteristics will be analysed using an unpaired Student's T-test for continuous variables, whereas dichotomous variables will be analysed using Fischer's exact test. Data will be expressed as mean +/-SD, median, and IQR or counts (percentage) as appropriate. In any circumstances, variables with asymmetric distributions will be transformed using standard mathematical models (logarithm, square root, etc.). Statistical significance will be set at the 1.7% level (two-sided)

for the primary outcome and 5% for secondary outcomes. The main conclusions will be based on the ITT principle and on the logistic regression model. All data analysis will be performed using Stata (V.13.0, Stata Corp, College Station, Texas, USA).

Table 2- Variable, measures, and method of analysis

Variable/outcome	Hypothesis	Outcome measure	Method of analysis
Primary outcome HbA1c	The proportion of patients with an HbA1c<6.5%(48mmol/mol) at one year will be higher in the surgery + intensive treatment group compared to control	The proportion of patients in each group with an HbA1c <6.5% (48mmol/mol)	Mixed-effects generalized linear models
Composite end point of HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, LDL<2.6mmol/l	The proportion of participants reaching the composite endpoint will be higher in the surgery+ intensive treatment group compared to the control	The proportion of participants reaching the composite endpoint	Logistic regression
Secondary outcomes			
Body weight	There will be a greater reduction in weight in the intensive medical group compared to control group	Kg	Student's t-test
BMI	The reduction will be higher in the surgery+ intensive treatment group compared to the control	kg/m^2	Student's t-test
Waist circumference	The reduction will be higher in the surgery+ intensive treatment group compared to the control	cm	Student's t-test
Glycaemic control	The reduction will be higher in the surgery+ intensive treatment group compared to the control	HbA1c levels	Mixed-effects generalized linear models
Blood pressure control	The proportion of patients achieving blood pressure control will be higher in the surgery + intensive treatment group compared to the control	Number of participants achieving BP<130/80mmHg	Mixed-effects generalized linear models
Lipid control	The proportion of patients achieving lipid control will be higher in the surgery +	Number of participants with LDL <2.6mmol/L	Logistic regression

Commented [AS1]: Reviewer 1, comment 2

	intensive treatment group compared to the control		
Liver function	The proportion of patients achieving normal liver function tests will be higher in the surgery + intensive treatment group compared to the control	ALT (IU/L), GGT (IU/L), AST (IU/L), ALP(IU/L) levels	Mixed-effects generalized linear models
Renal function	The proportion of patients achieving normal renal function test will be higher in the surgery + intensive treatment group compared to the control group	Plasma Cr, eGFR	Mixed-effects generalized linear models
Inflammatory markers	The reduction in CRP will be greater in the surgery + intensive treatment group compared to control	CRP	Mixed-effects generalized linear models
Urine albumin: creatinine ratio	The proportion of patients in the surgery + intensive treatment group with a uACR<30µg will be higher than the control group	Number of participants in each group with a uACR<30µg	Logistic regression
Quality of life	Quality of life is higher in patients in the surgery + intensive medical therapy arm compared to control	SF-36 and MHP-H	Mixed-effects generalized linear models
Clinical and sociodemographic variables			
Age	There is no difference between the two groups	Years	Student's t-test
BMI	There will be a greater reduction in BMI in the intensive medical therapy arm compared to control group	kg/m^2	Student's t-test
Body weight	There will be a greater reduction in weight in the intensive medical group compared to control group	Kg	Student's t-test
Gender	There is no difference between the two groups	1= male, 0= female	Fischer's exact test
Waist circumference	There will be a greater reduction in the waist circumference in the	cm	Student's t-test

	intensive medical group compared to the control group		
Fasting blood glucose	There will be a greater reduction in the fasting blood glucose in the intensive medical group compared to the control group	mg/dL, mol/L	Student's t-test
Total HDL and LDL cholesterol	There will be a greater reduction in the total HDL and LDL cholesterol in the intensive medical group compared to the control group	mmol/L	Student's t-test
Triglycerides	There will be a greater reduction in triglycerides in the intensive medical group compared to the control group	Mmol/L	Student's t-test
Diastolic and systolic blood pressure	There will be a greater reduction in diastolic and systolic pressure in the intensive medical group compared to the control group	mmHg	Student's t-test

Additional analysis

All primary analyses will be carried out on an ITT basis, but subsequent studies may be conducted on a per-protocol basis. The primary analysis will also be performed out with multiple imputation methods. We will also provide results from analyses restricted to complete cases to compare results from the multiple imputation processes.

Adjusted analysis

All statistical models will be run with appropriate adjustment for baseline characteristics.

Analysis population and missing data

In the case of missing data, we will perform and report the multiple imputation analysis according to the recommendation of White *et al. [29].* Missing data will be handled using multiple imputation methods, assuming all data are missing at random. We will use a combination of predictive mean matching and regression-based methods to impute missing data. Specifically, we will use a combination of predictive mean matching and regression-based methods to impute missing data. A total of 100 data sets will be created to reduce

sampling variability. A burn-in period of 500 iterations will be used. Imputation will be performed in Stata V.14.0 (StataCorp, College Station, Texas, USA).

Monitoring

Adverse events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical study subject even if it did not directly relate to the medical or surgical intervention. Serious adverse events were defined as any untoward and unexpected medical occurrence or effect that:

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

All AE or SAE are required to be reported within 24h with detailed documentation to the research and ethics committee.

Auditing

Throughout the study, audits will be carried out by a dedicated monitor using several key indicators on all source documents and participants. The key indicators are informed consent form (ICF) and process, eligibility criteria, enrolment, allocation of study groups, scheduled and missed tests and procedures, policies to protect participants, concomitant and prohibited medications, dispensing medication procedures, identification and reporting of A.E.s and SAEs, deviation report, regulatory documents and communication with local research and ethics committee, following International conference on Harmonisation-Good Clinical Practice (ICH-GCP) and regulatory agency guidelines.

Ethics and dissemination

Research ethics approval

Protocol, ICF, and recruitment materials were reviewed and approved by the study sites' local research and ethics committee. Approval was received within Ireland on the 11th of February 2020 and on the 2nd of December 2020 within the UK. All sites will report back regarding study progress regularly.

Protocol amendments

All changes needed after initial approval will be re-submitted to the research and ethics committee for review. Amendments to the clinical protocol will require formal review, accompanied by an updated, informed consent signed by both the investigators and participants. If any changes are made to the protocol, the history will be available and tracked by version and date changes.

Consent

Patients identified as potential participants will receive verbal and written information from an investigator (medical doctor). A copy of the study materials and ICF will be given, and patients allowed an opportunity to review and discuss with family/friends. After being given a minimum of 24 hours to consider the materials, a formal discussion will be carried out

with the patient and an investigator. Patients will be allowed to ask any questions and clarify any areas of uncertainty. If the patient then decides to participate, they will be given an ICF to sign (also signed by the investigator), after which they are considered a study participant. Assent form and ancillary studies consent are not necessary for the study.

Confidentiality

All medical information derived from the study will be confidential, and no third-party access will be allowed. The designated personnel will handle source/data information stored on password-protected computers and in-coded patient notes to protect confidentiality.

Declaration of interests

The author RC has received an honorarium as a member of the Speaker's panel of Johnson & Johnson.
The author ClR has received grants from the Science Foundation Ireland, Health Research Board, Irish Research Council, Johnson & Johnson and AnaBio. Personal fees have been received from Eli Lily, Johnson & Johnson, Sanofi Aventis, Astra Zeneca, Janssen, Bristol-Meyers Squibb and Boehringer-Ingelheim. He is on the advisory board for GI dynamics.
The author DJP has received personal fees from NovoNordisk and Johnson & Johnson.

Study sponsorship and access to data

Data will be available to authorised investigators only. Third parties may have access to data with express written permission from the lead investigator. However, sponsors will not participate in data analysis, nor will they have access to data, either in full or in part.

Ancillary and post-trial care

Participating sites will have insurance policies to cover non-negligent harm associated with the protocol, which covers additional healthcare, compensation, or damages whether awarded voluntarily by the BY PLUS study or by claims pursued through the courts.

Dissemination policy

After the trial protocol publication, the investigators plan to publish all the listed endpoints as this RCT is the first trial to compare intensive goal-directed medical therapy combined with bariatric surgery versus bariatric surgery and standard medical care for patients with T2DM and obesity. The results of this trial will be published in peer-reviewed scientific journals and presented at major conferences, regardless of the magnitude or direction of the observed effect.

Trial organisation and management

The study investigators are responsible for completing all pertinent information using the clinical report forms, data accuracy, and maintaining the confidentiality of patients' data. Only the investigators will have access to the final data set. All documentation will be kept for five years after the study's termination if it has to be monitored, audited, or inspected by the sponsor or regulatory authorities.

Author Contributions

Conceived the trial and were involved in logistical planning- AS, AM, HK, JT, RC, HH, ClR, DJP
Drafted the article- AS, AM, HK, RC, HH, ClR, DJP

Data sharing

The authors shall make data available to the scientific community with as few restrictions as feasible, ensuring anonymisation, while retaining exclusive use until the publication of major outputs.

Funding
The authors of this work, Alexis Sudlow and Dimitri Pournaras received funding from the Royal College of Surgeons (England) for this work.
Grant number: PO117623

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Appendix 1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1,16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3,4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4,5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 10-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8,9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	9

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9,10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	20
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study: rationale and design of a randomised controlled study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054313.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Mar-2022
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics, Surgery
Keywords:	DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, SURGERY

Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study: rationale and design of a randomised controlled study

Key words: obesity, type 2 diabetes mellitus, bariatric surgery, sleeve gastrectomy, roux en y gastric bypass

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Sources of funding: The authors of this work, Alexis Sudlow and Dimitri Pournaras received funding from the Royal College of Surgeons (England) for this work.
Grant number: PO117623

Main text word count: 3907

Protocol amendment number: 02

Trial Sponsor: Imperial College London
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Abstract

Introduction

Bariatric surgery is an effective method of controlling glycaemia in patients with type 2 diabetes mellitus and obesity. Long-term studies suggest that although glycaemic control remains good, only 20-40% of patients will maintain remission according to the American Diabetes Association (ADA) criteria.

Purpose

This trial aims to examine the safety and efficacy of combining Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) with goal-directed medical therapy to improve long-term glycaemic control of T2DM.

Methods and Analysis

This prospective, open-label multi-centre RCT will recruit 150 patients with obesity and T2DM from tertiary care obesity centres. Patients will be randomised 1:1 to receive either bariatric surgery and standard medical care or bariatric surgery and intensive goal-directed medical therapy, titrated to specific targets for HbA1c, blood pressure (BP), and LDL-cholesterol. The primary endpoints are the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) at one year and the proportion of patients in each arm achieving the composite endpoint of HbA1c <6.5% (48mmol/mol), BP<130/80mmHg and LDL <2.6mmol/L at five years.

Ethics and Dissemination

The local Institutional Review Board approved this study. This study represents the first RCT to examine the safety and efficacy of combining bariatric surgery with intensive medical therapy compared to bariatric surgery and usual care for long-term diabetes control.

Trial registration number

NCT04432025

Full trial registration data set in Appendix 1

Article Summary

Strengths and limitations of this study

- This is a randomised controlled trial designed to compare the efficacy and safety of combining goal directed medical therapy for type 2 diabetes mellitus (T2DM) with bariatric surgery to bariatric surgery and standard medical care.
- The long-term follow up will evaluate whether patients receiving goal directed medical therapy following bariatric surgery improves long term diabetes control according to the ADA criteria.
- The results will help inform how patients with T2DM should be managed following bariatric surgery.
- This study cannot be blinded due to the nature of the interventions.
- This study is not powered to detect differences between the two surgical procedures included in the trial.

Introduction

Obesity and type 2 diabetes mellitus (T2DM) are inherently linked, and patients suffering from both diseases present a particular challenge to clinicians concerning treatment due to their significantly increased risk of cardiovascular events and end-organ complications. Long-term success in treating hyperglycaemia, hypertension, and dyslipidaemia in patients with T2DM prevents the development of diabetes-related complications with conventional best medical treatment alone (anti-hyperglycaemic agents, anti-hypertensives, and statins in combination with lifestyle modification) has proven to be elusive. Bariatric/metabolic surgery has level 1 evidence from 12 randomised controlled trials (RCTs) demonstrating its safety and efficacy as a treatment for obesity and T2DM [1-12]. Given the powerful metabolic effects on glucose homeostasis and subsequent diabetes control, it is now widely recommended that bariatric surgery is considered a key treatment approach for patients with obesity and difficult to control T2DM[13, 14]. Changes in glucose metabolism, independent of weight loss have been observed in the immediate postoperative period, and remission rates according to the ADA criteria (all diabetic medications stopped, HbA1c<6% (42mmol/mol), fasting plasma glucose <5.6mmol/l (100mg/dl) off all hypoglycaemic agents for one year) of 40% have been demonstrated over a median follow up of two years[15-17].

Despite these promising results, emerging evidence suggests that though glycaemic control improves after surgery, only 20-50% of patients who initially experienced remission will maintain remission in the long-term [15, 18, 19]. The Swedish Obesity Surgery Register (SOReg) data also suggests that patients who do not achieve glycaemic remission within one year have more cardiovascular events[20].

Although standard medical therapy alone is inferior to bariatric surgery regarding control of T2DM, a more intensive approach with pharmacotherapy titrated to prespecified targets for hyperglycaemia, hypertension, and dyslipidaemia has been demonstrated to be safe and

effective. Over a 13.3 year follow-up period, the STENO-2 trial showed a 20% absolute risk reduction in death and a 13% reduction in death due to cardiovascular endpoints with intensive, goal-directed medical therapy compared to conventional therapy[21].

Evidence would support improved glycaemic control due to the powerful metabolic changes evoked by bariatric surgery; however, the effects tend to attenuate with time, and a proportion of patients will ultimately experience a relapse of diabetes[22]. What remains to be seen is whether a multimodal approach with surgery and goal-directed medical therapy can be safely utilised to improve diabetes control[23, 24].

Objectives

This study aims to investigate the long-term safety and efficacy of combining bariatric surgery (Roux-en-Y gastric bypass-RYGB or Sleeve gastrectomy- SG) with goal-directed medical therapy versus bariatric surgery and usual medical care on the glycaemic control and the ADA triple endpoint as a marker of good diabetes control and reflected in measures for HbA1c, BP and lipids.

Trial design

The BY PLUS study is a multi-center, open-label randomised controlled trial. The trial will involve two arms with an allocation ratio of 1:1. There are two primary endpoints:

1. the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) over a follow up of one year
2. the proportion of patients in each arm reaching the composite endpoint of HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/l over a follow-up period of five years.

Patient recruitment was commenced in August 2020. The trial was registered on ClinicalTrials.gov (NCT04432025). A planned interim analysis will also be carried out at a prespecified follow-up period of 12 months and then yearly until trial conclusion at five years (60 months follow up).

Several strategies, such as the use of checklists and workflow, have been employed to guarantee the data's quality and completeness. A dedicated monitor will audit the overall quality and completeness of the data entered on the electronic case report form, examine source documents, and compliance of the team with Good Clinical Practice.

The full SPIRIT checklist can be found in appendix 1.

Methods

Study setting

The study will be undertaken in tertiary care centres with expertise in bariatric surgery and the treatment of obesity and T2DM.

Eligibility criteria

Inclusion criteria

- ≥18 years old
- Eligible for bariatric surgery as per NICE CG189 or IFSO guidelines

- Diagnosis of type 2 diabetes mellitus based on an HbA1c of 48mmol/mol or 6.5%
- Body mass index (BMI) > 30kg/m^2

Exclusion criteria

- Specific contraindications to bariatric surgery
- Previous bariatric surgery
- Current pregnancy or breastfeeding
- Recent illness requiring hospitalisation within the previous 30 days
- Recurrent episodes of hypoglycaemia
- Recurrent episodes of hypotension
- History of any medical, psychological, or other condition, or use of any medications, including over-the-counter products, which, in the opinion of the investigators, would either interfere with the study or potentially cause harm to the participant.
- Lack of access to a telephone or other factors likely to interfere with the ability to participate reliably in the study.
- Concurrent or recent participation in another research study

Interventions

After randomisation, patients will be allocated in a 1:1 ratio, stratified by BMI and site to bariatric surgery plus standard medical care or bariatric surgery and intensive medical therapy. Patients in both arms will undergo bariatric surgery, either SG or RYGB, with the decision regarding the specific procedure being made by the patient and multi-disciplinary team (MDT). The individual arms are discussed below:

Bariatric surgery plus standard medical care- two weeks preoperatively, SGLT-2 inhibitors will be stopped due to the risk of euglycaemic acidosis and following bariatric surgery, all remaining oral diabetic medications will be stopped. If on insulin, patients will be monitored as inpatients. If they require insulin to maintain glycaemic control while in hospital, then a basal dose of insulin will be provided on discharge equivalent to their insulin requirement over the previous 24 hours. Rapid-acting insulin will be stopped postoperatively. The basal insulin dose will be titrated every day by the research team to allow fasting glucose values to be maintained between 7 and 9 mmol/L (126-162mg/dl). For any further monitoring or adjustments of diabetic medications, the clinicians caring for the patient will resume their primary care for metabolic control. Prescribing and/or titration of any medications for glycaemic control, BP and lipids will be according to current standard of care.

Bariatric surgery plus intensive medical therapy- following bariatric surgery, patients will modify their preoperative medications for glycaemic control, BP, lipids, and doses of medications reduced to prevent hypoglycaemia episodes or hypotension. If on insulin, patients will be monitored as inpatients. If they require insulin to maintain glycaemic control while inpatients, then a basal dose of insulin will be provided on discharge equivalent to their insulin requirement over the previous 24 hours. Rapid-acting insulin will be stopped postoperatively. The basal insulin dose will be titrated every day by the research team to allow fasting glucose values to be maintained between 6 and 8 mmol/L (106-145mg/dl). Oral medications in the postoperative period will be adjusted as follows:

Glucose lowering agents:

1. Metformin will be continued at the same dose used pre-surgery
2. SGLT-2 inhibitors will be stopped two weeks preoperatively due to the risk of euglycaemic acidosis
3. All sulphonylureas and thiazides will be stopped preoperatively
4. If fasting glucose >7.5mmol/l (135mg/dl) one month postoperatively, a GLP-1 analogue will be added
5. If fasting glucose remains >7.5mmol/l (135mg/dl) despite the addition of GLP-1 analogue, a SGLT-2 inhibitor will be added

Blood pressure medications:

1. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) at half dose (or lowest dose if this is what they are already on) will be continued
2. All diuretics will be stopped
3. All calcium antagonists will be stopped

Statin

1. Continued at preoperative dose

In subsequent follow-up visits, medications will be individually titrated as required by the obesity clinic staff to achieve specific targets- HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/L.

Surgical procedures

All operations will be performed by consultant surgeons with experience in laparoscopic RYGB or SG. Patients will be admitted to the hospital on the day of the procedure after an overnight fast. The procedures are standardised for both RYGB and SG according to previously described techniques and will be performed as follows[25, 26]. Laparoscopic RYGB will be performed under general anaesthesia and with the creation of a 20-30mL pouch, a biliary limb of approximately 80cm, and an alimentary limb of approximately 120cm. A linear stapler will typically be used to form the gastrojejunostomy and side-to-side jejunojejunostomy. Both mesenteric and Petersen's defects will be routinely closed using non-absorbable clips. For patients undergoing SG, the stomach's greater curvature will be mobilised to allow for the stomach's division using the linear stapler, starting 4-6cm from the pylorus, proceeding towards the angle of His. A 32Fr bougie will be used to help guide the division of the stomach. Deep vein thrombosis (DVT) prophylaxis in the form of compression stockings and intermittent pneumatic compression intraoperatively will be given to all patients and subcutaneous enoxaparin administered after the procedure unless contraindicated. Prophylactic antibiotics will be administered at the induction of anaesthesia. Both groups of will receive identical dietary counselling with regards to food consistency and progression to solid as well as long term follow up for micronutrient replacement and biochemical monitoring[27]. Blood results will be checked at baseline, 3, 6, 12 months and then annually thereafter including corrected Ca, vitamin D, ferritin/iron profile, vitamin B12, folate. PTH, copper, zinc and selenium will be checked at 12 months

and yearly thereafter. Magnesium, chromium and fat soluble vitamins will not be routinely checked.

Drug titration and safety monitoring

For patients in the surgery plus intensive medical treatment arm, follow-up regarding medications in the postoperative period will be coordinated through clinic. Metformin will be continued, but doses may be reduced if HbA1c is <6% (42 mmol/mol) or discontinued if there are recorded hypoglycaemic episodes or severe gastrointestinal side-effects. The parameters for full withdrawal of medications for glycaemic control are an HbA1c<6% (42mmol/mol) and fasting glucose of 5.5 mmol/L (100mg/dl). Medications for blood pressure control, ACEi, and ARB as well as statins for lipid control will be continued, but doses may be reduced to avoid side effects. At subsequent follow-up visits, patients in this cohort will have their HbA1c, BP, and LDL checked with the results used to guide titration of doses towards the prespecified treatment thresholds HbA1c<6.5% (48mmol/mol), BP<130/80mmHg and LDL<2.6mmol/l.

Outcomes

The primary outcomes are:

1. The proportion of patients in each arm who achieve an HbA1c<6.5% (48mmol/mol) at one year
2. The proportion of patients in each arm who reach the composite endpoint for good diabetes control as outlined by the American Diabetes Association (ADA), which is an HbA1c<6.5% (48mmol/mol), BP<130/80mmHg and LDL<2.6mmol/l at five years.

Secondary outcomes

The secondary outcomes are change from baseline to 5 years for each endpoint, temporal changes, mean levels, and peak levels will be analysed as appropriate: body weight, BMI, waist circumference, plasma lipid concentration, plasma liver function tests, urinary creatinine: albumin ratio, inflammatory markers including CRP, Multidimensional Health Profile: Health Functioning questionnaire score (MHP-H), Social Functioning Questionnaire score (SFQ) and the number of medications.

The safety of concurrent medication administration following surgery for blood pressure and glycaemic control will also be monitored with standardised reporting procedures for episodes of:

1. Symptomatic or asymptomatic hypoglycaemia deined as a BM of <4mmol/L (70mg/dL)
2. Symptomatic or asymptomatic hypotension defined as systolic BP<90mmHg

Symptoms of either hypoglycaemia or hypotension will be discussed with patients and they will be instructed to contact the study coordinators to arrange clinic review for titration of medication as necessary.

Participant timeline

Screening visit

The screening visit will be undertaken by a member of the bariatric and research team. During this visit, patients will be given information on the study design, randomisation process, the two study arms and follow-up procedures. Patients will also have the opportunity to discuss the risks and benefits of participating in the trial and the risks specific to each arm of the trial. A standardised checklist will be used to ensure that prospective patients are eligible to participate, in keeping with the inclusion and exclusion criteria. Written informed consent will be required for all patients' participation in the surgical procedure (RYGB/SG) and subsequent follow-up procedures. Baseline blood and urine tests will be taken along with height, weight, waist circumference, and blood pressure measurements. Medications will be reviewed, and for those on suboptimal treatment for glycaemic control, BP or lipids medications will either be started or titrated as required.

Randomisation visit

All patients will be required to attend a comprehensive clinical evaluation 4-6 weeks following the screening visit to ensure all eligibility requirements are met. Once confirmed, patients will be assigned an identification number to be used for all further documentation. All patients will be required to undergo upper digestive endoscopy. Two weeks after the randomisation visit, all clinical evaluations will be reviewed to ensure patients were eligible to proceed with trial participation. A dietician will review both groups with expertise in managing patients with obesity and following bariatric surgery. The dietician appointment will focus on the importance of adherence to postoperative dietary changes and nutritional supplement intake.

Follow up visits

Irrespective of the allocation, all patients will be followed up in the obesity clinic according to the same timeline with visits at six weeks, 3, 6, 12 months, and then yearly after that until study completion at 60 months. At each follow-up visit, all adverse events will be recorded. For patients in the surgery + intensive medical treatment arm, medications will be titrated to the previously discussed treatment thresholds for HbA1c, BP, and LDL. In addition to routine clinical parameters including weight/BMI, waist circumference the following will be measured/performed (Table 1):

  - Non-invasive blood pressure monitoring
  - HbA1c
  - Plasma lipids
  - Plasma liver function tests
  - Plasma renal function tests
  - Inflammatory markers
  - Urinary albumin: creatinine ratio

- Every 12 months: Multidimensional Health Profile: Health Functioning questionnaire (MHP-H) and Social Functioning Questionnaire (SF-36).

Table 1 Schedule of visits, examinations and procedures

Assessments	Screen	Random	Surgery	W6	W12	W24	W52	Y2	Y3	Y4	Y5
Informed consent	X										
Medical history	X	x									
Physical examination	X	x									
Medical assessment	X	X	x	X	x	x	x	x	x	x	x
Medication review	X	X		X	x	x	x	x	x	x	x
Inclusion/exclusion criteria	X	X									
Randomisation		X									
Adverse events				X	x	x	x	x	x	x	x
Nutritional assessment		x		X	x	x	x	x	x	x	x
Serum pregnancy test	X										
MPH-H, SF-36	X							x	x	x	x
Urine sample	X			x	x	x	x	x	x	x	x
Fasting plasma glucose	X			x	x	x	x	x	x	x	x
HbA1c	X			x	x	x	x	x	x	x	x
Lipids	X			x	x	x	x	x	x	x	x
Liver function test	x			x	x	x	x	x	x	x	x
Renal function test	X			X	X	X	X	X	X	X	X
Blood pressure	X			x	x	x	x	x	x	x	x
CRP	X			x	x	x	x	x	x	x	x
Height	X										
Body weight	X		x	x	x	x	x	x	x	x	x
Waist circumference	X	x	x	x	x	x	x	x	x	x	x
Upper digestive endoscopy		x									
RYGB or SG			x								
Drug titration and dispensing			x	x	x	x	x	x	x	x	x
Glucose monitoring			x	x	x	x	x	x	x	x	x

Sample size

Based on published data comparing the effect size of best medical therapy combined with bariatric surgery vs. best medical therapy alone on glycaemic control, BP and cholesterol levels in patients with T2DM, we estimated that 30% of patients in the control group and 50% of patients in the intensive treatment group would reach the primary endpoint [28]. Based on these data, we calculated that to have 80% power to detect statistically significant

differences between the groups at α of 0.05, we would need 55 patients per arm. We will recruit 75 patients in each group to account for a possible 20-25% drop-out rate.

Recruitment strategy

All patients presenting to the obesity clinic within the participating centres who are due to undergo RYGB or SG and meet the eligibility criteria will be given written and verbal information regarding participation in the study. After a minimum period of 24 hours to consider the information, patients can indicate whether they are willing to participate and will be asked to provide written consent.

Assignment of interventions

Sequence generation

Patients will be randomised by an independent researcher not involved in patient recruitment, treatment, or follow-up. A computer-generated sequence will randomise patients 1:1 to either surgery + standard medical care or surgery + intensive goal-directed medical therapy with random block sizes of 4.

Concealment mechanism

Randomisation codes will only be released after patients are formally recruited to the trial. The randomisation sequence will be held by a senior project manager not associated directly with this trial and will not be available to any of the research investigators at any time. Participants, staff members, and researchers will be unable to foresee the assignment because of central randomisation. All participant data will be pseudo anonymised (personal information removed and replaced with a coded identifier), and this list will be supplied to the central allocation, which randomly allocates patients to either arm of the study.

Blinding

Because of the study's nature, neither study investigators nor patients can be blinded regarding their allocation. All investigators in charge of statistical analysis or analysis of samples (laboratory staff) will be blinded to the patient allocation.

Data management

In order to assure data quality, several procedures are in place, including missing data, permitted/non-permitted value ranges, and logic checks. Checklists and standard operating procedures were created and routinely used to ensure data are complete and reliable. As this is a multi-centre trial, training will be done centrally at the host institution with members of all sites present and all data collection forms are standardised to ensure homogeneity in data collection and entry. Each member of the study team requires training before study initiation, and roles are delegated and assigned. Each participant will receive a numerical code to ensure confidentiality and tracking. Source documents (paper) will be stored at each site in a secured location, with all documents being stored according to their numerical code and accessible only to the study team.

A dedicated monitor, which has been designated specifically for this protocol, will be responsible for source data verification and the creation of queries and/or data clarification forms for all participants' source documents. This monitor will assure quality assurance and control, and a statistician will be responsible for final data verification and database analysis throughout the study.

Retention

We anticipate a 20-25% drop-out rate over the 60-month follow-up period. This was reflected in the power calculation to plan the sample size. To mitigate the effects of losing patients to follow up, trial coordinators will make every possible effort to follow up patients for the entire duration of the study. Strategies using multiple contact methods such as email, mail, telephone calls will be employed to achieve the highest possible level of follow-up.

Participant withdrawals

In the case of a participant deciding to withdraw from the study, they will be asked to provide further monitoring and data collection after their withdrawal. For participants who have been lost to follow up despite attempts to contact them, their data will be imputed.

Patient and public involvement

Qualitative research specifically examining patients' expectations and experiences of undergoing bariatric surgery as a treatment for T2DM was undertaken. This information was used to help develop the research question, ensuring that patient priorities were reflected in the design of the study as well as the choice of outcome measures. This study also explored patient perceptions of continued medications following surgery to determine whether the proposed intervention would be acceptable to the target population.

Statistical methods

All data analysis and statistical methods were advised by a statistician and will be performed on an intention to treat principle (ITT). An overview of the methods of analysis is presented in Table 2. We will compare the proportion of participants achieving the primary outcome between bariatric surgery and goal-directed medical therapy versus bariatric surgery and usual care using an unconditional logistic regression model. Continuous outcomes will be analysed by mixed-effects generalised linear models adjusting for the response variable's baseline version. Missing data will be imputed using several different models, assuming data will be missing at random. Participants' demographic data and clinical characteristics will be analysed using an unpaired Student's T-test for continuous variables, whereas dichotomous variables will be analysed using Fischer's exact test. Data will be expressed as mean +/-SD, median, and IQR or counts (percentage) as appropriate. In any circumstances, variables with asymmetric distributions will be transformed using standard mathematical models (logarithm, square root, etc.). Statistical significance will be set at the 1.7% level (two-sided)

for the primary outcome and 5% for secondary outcomes. The main conclusions will be based on the ITT principle and on the logistic regression model. All data analysis will be performed using Stata (V.13.0, Stata Corp, College Station, Texas, USA).

Table 2- Variable, measures, and method of analysis

Variable/outcome	Hypothesis	Outcome measure	Method of analysis
Primary outcome HbA1c	The proportion of patients with an HbA1c<6.5%(48mmol/mol) at one year will be higher in the surgery + intensive treatment group compared to control	The proportion of patients in each group with an HbA1c <6.5% (48mmol/mol)	Mixed-effects generalized linear models
Composite end point of HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, LDL<2.6mmol/l	The proportion of participants reaching the composite endpoint will be higher in the surgery+ intensive treatment group compared to the control	The proportion of participants reaching the composite endpoint	Logistic regression
Secondary outcomes			
Body weight	There will be a greater reduction in weight in the intensive medical group compared to control group	Kg	Student's t-test
BMI	The reduction will be higher in the surgery+ intensive treatment group compared to the control	kg/m^2	Student's t-test
Waist circumference	The reduction will be higher in the surgery+ intensive treatment group compared to the control	cm	Student's t-test
Glycaemic control	The reduction will be higher in the surgery+ intensive treatment group compared to the control	HbA1c levels	Mixed-effects generalized linear models
Blood pressure control	The proportion of patients achieving blood pressure control will be higher in the surgery + intensive treatment group compared to the control	Number of participants achieving BP<130/80mmHg	Mixed-effects generalized linear models
Lipid control	The proportion of patients achieving lipid control will be higher in the surgery +	Number of participants with LDL <2.6mmol/L	Logistic regression

	intensive treatment group compared to the control		
Liver function	The proportion of patients achieving normal liver function tests will be higher in the surgery + intensive treatment group compared to the control	ALT (IU/L), GGT (IU/L), AST (IU/L), ALP(IU/L) levels	Mixed-effects generalized linear models
Renal function	The proportion of patients achieving normal renal function test will be higher in the surgery + intensive treatment group compared to the control group	Plasma Cr, eGFR	Mixed-effects generalized linear models
Inflammatory markers	The reduction in CRP will be greater in the surgery + intensive treatment group compared to control	CRP	Mixed-effects generalized linear models
Urine albumin: creatinine ratio	The proportion of patients in the surgery + intensive treatment group with a uACR<30µg will be higher than the control group	Number of participants in each group with a uACR<30µg	Logistic regression
Quality of life	Quality of life is higher in patients in the surgery + intensive medical therapy arm compared to control	SF-36 and MHP-H	Mixed-effects generalized linear models
Clinical and sociodemographic variables			
Age	There is no difference between the two groups	Years	Student's t-test
BMI	There will be a greater reduction in BMI in the intensive medical therapy arm compared to control group	kg/m^2	Student's t-test
Body weight	There will be a greater reduction in weight in the intensive medical group compared to control group	Kg	Student's t-test
Gender	There is no difference between the two groups	1= male, 0= female	Fischer's exact test
Waist circumference	There will be a greater reduction in the waist circumference in the	cm	Student's t-test

	intensive medical group compared to the control group		
Fasting blood glucose	There will be a greater reduction in the fasting blood glucose in the intensive medical group compared to the control group	mg/dL, mol/L	Student's t-test
Total HDL and LDL cholesterol	There will be a greater reduction in the total HDL and LDL cholesterol in the intensive medical group compared to the control group	mmol/L	Student's t-test
Triglycerides	There will be a greater reduction in triglycerides in the intensive medical group compared to the control group	Mmol/L	Student's t-test
Diastolic and systolic blood pressure	There will be a greater reduction in diastolic and systolic pressure in the intensive medical group compared to the control group	mmHg	Student's t-test

Additional analysis

All primary analyses will be carried out on an ITT basis, but subsequent studies may be conducted on a per-protocol basis. The primary analysis will also be performed out with multiple imputation methods. We will also provide results from analyses restricted to complete cases to compare results from the multiple imputation processes.

Adjusted analysis

All statistical models will be run with appropriate adjustment for baseline characteristics.

Analysis population and missing data

In the case of missing data, we will perform and report the multiple imputation analysis according to the recommendation of White *et al. [29].* Missing data will be handled using multiple imputation methods, assuming all data are missing at random. We will use a combination of predictive mean matching and regression-based methods to impute missing data. Specifically, we will use a combination of predictive mean matching and regression-based methods to impute missing data. A total of 100 data sets will be created to reduce

sampling variability. A burn-in period of 500 iterations will be used. Imputation will be performed in Stata V.14.0 (StataCorp, College Station, Texas, USA).

Monitoring

Adverse events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical study subject even if it did not directly relate to the medical or surgical intervention. Serious adverse events were defined as any untoward and unexpected medical occurrence or effect that:

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

All AE or SAE are required to be reported within 24h with detailed documentation to the research and ethics committee.

Auditing

Throughout the study, audits will be carried out by a dedicated monitor using several key indicators on all source documents and participants. The key indicators are informed consent form (ICF) and process, eligibility criteria, enrolment, allocation of study groups, scheduled and missed tests and procedures, policies to protect participants, concomitant and prohibited medications, dispensing medication procedures, identification and reporting of A.E.s and SAEs, deviation report, regulatory documents and communication with local research and ethics committee, following International conference on Harmonisation-Good Clinical Practice (ICH-GCP) and regulatory agency guidelines.

Ethics and dissemination

Research ethics approval

Protocol, ICF, and recruitment materials were reviewed and approved by the study sites' local research and ethics committee. Approval was received within Ireland on the 11th of February 2020 and on the 2nd of December 2020 within the UK. All sites will report back regarding study progress regularly.

Protocol amendments

All changes needed after initial approval will be re-submitted to the research and ethics committee for review. Amendments to the clinical protocol will require formal review, accompanied by an updated, informed consent signed by both the investigators and participants. If any changes are made to the protocol, the history will be available and tracked by version and date changes.

Consent

Patients identified as potential participants will receive verbal and written information from an investigator (medical doctor). A copy of the study materials and ICF will be given, and patients allowed an opportunity to review and discuss with family/friends. After being given a minimum of 24 hours to consider the materials, a formal discussion will be carried out

with the patient and an investigator. Patients will be allowed to ask any questions and clarify any areas of uncertainty. If the patient then decides to participate, they will be given an ICF to sign (also signed by the investigator), after which they are considered a study participant. Assent form and ancillary studies consent are not necessary for the study.

Confidentiality

All medical information derived from the study will be confidential, and no third-party access will be allowed. The designated personnel will handle source/data information stored on password-protected computers and in-coded patient notes to protect confidentiality.

Declaration of interests

The author RC has received an honorarium as a member of the Speaker's panel of Johnson & Johnson.

The author ClR has received grants from the Science Foundation Ireland, Health Research Board, Irish Research Council, Johnson & Johnson and AnaBio. Personal fees have been received from Eli Lily, Johnson & Johnson, Sanofi Aventis, Astra Zeneca, Janssen, Bristol-Meyers Squibb and Boehringer-Ingelheim. He is on the advisory board for GI dynamics.

The author DJP has received personal fees from NovoNordisk and Johnson & Johnson.

Study sponsorship and access to data

Data will be available to authorised investigators only. Third parties may have access to data with express written permission from the lead investigator. However, sponsors will not participate in data analysis, nor will they have access to data, either in full or in part.

Ancillary and post-trial care

Participating sites will have insurance policies to cover non-negligent harm associated with the protocol, which covers additional healthcare, compensation, or damages whether awarded voluntarily by the BY PLUS study or by claims pursued through the courts.

Dissemination policy

After the trial protocol publication, the investigators plan to publish all the listed endpoints as this RCT is the first trial to compare intensive goal-directed medical therapy combined with bariatric surgery versus bariatric surgery and standard medical care for patients with T2DM and obesity. The results of this trial will be published in peer-reviewed scientific journals and presented at major conferences, regardless of the magnitude or direction of the observed effect.

Trial organisation and management

The study investigators are responsible for completing all pertinent information using the clinical report forms, data accuracy, and maintaining the confidentiality of patients' data. Only the investigators will have access to the final data set. All documentation will be kept for five years after the study's termination if it has to be monitored, audited, or inspected by the sponsor or regulatory authorities.

Author Contributions

Conceived the trial and were involved in logistical planning- AS, AM, HK, JT, RC, HH, ClR, DJP
Drafted the article- AS, AM, HK, RC, HH, ClR, DJP

Data sharing

The authors shall make data available to the scientific community with as few restrictions as feasible, ensuring anonymisation, while retaining exclusive use until the publication of major outputs.

Funding

The authors of this work, Alexis Sudlow and Dimitri Pournaras received funding from the Royal College of Surgeons (England) for this work.
Grant number: PO117623

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Appendix 1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1,16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3,4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4,5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 10-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8,9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	9

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9,10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	20
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study: rationale and design of a randomised controlled study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054313.R3
Article Type:	Protocol
Date Submitted by the Author:	20-Apr-2022
Complete List of Authors:	Sudlow, Alexis; Southmead Hospital, Department of Upper GI and Bariatric Surgery Miras , Alexander ; Imperial College Healthcare NHS Trust, Division of Diabetes, Endocrinology and Metabolic Medicine Cohen, Ricardo; Hospital Alemao Oswaldo Cruz, The Center for Obesity and Diabetes; Hospital Alemao Oswaldo Cruz, Health Research Unit Kahal, Hassan; Southmead Hospital, Department of Diabetes and Endocrinology Townley, Jill; Southmead Hospital, Department of Surgery Heneghan, Helen; St Vincent's University Hospital, Department of Surgery Le Roux, Carel; University College Dublin, Department of Experimental Pathology Pournaras, Dimitri; Southmead Hospital, Department of Upper GI and Bariatric Surgery
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics, Surgery
Keywords:	DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, SURGERY

Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study: rationale and design of a randomised controlled study

Key words: obesity, type 2 diabetes mellitus, bariatric surgery, sleeve gastrectomy, roux en y gastric bypass

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Sources of funding: The authors of this work, Alexis Sudlow and Dimitri Pournaras received funding from the Royal College of Surgeons (England) for this work.
Grant number: PO117623

Main text word count: 3907

Protocol amendment number: 02

Trial Sponsor: Imperial College London
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Abstract

Introduction

Bariatric surgery is an effective method of controlling glycaemia in patients with type 2 diabetes mellitus and obesity. Long-term studies suggest that although glycaemic control remains good, only 20-40% of patients will maintain remission according to the American Diabetes Association (ADA) criteria.

Purpose

This trial aims to examine the safety and efficacy of combining Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) with goal-directed medical therapy to improve long-term glycaemic control of T2DM.

Methods and Analysis

This prospective, open-label multi-centre RCT will recruit 150 patients with obesity and T2DM from tertiary care obesity centres. Patients will be randomised 1:1 to receive either bariatric surgery and standard medical care or bariatric surgery and intensive goal-directed medical therapy, titrated to specific targets for HbA1c, blood pressure (BP), and LDL-cholesterol. The primary endpoints are the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) at one year and the proportion of patients in each arm achieving the composite endpoint of HbA1c <6.5% (48mmol/mol), BP<130/80mmHg and LDL <2.6mmol/L at five years.

Ethics and Dissemination

The local Institutional Review Board approved this study. This study represents the first RCT to examine the safety and efficacy of combining bariatric surgery with intensive medical therapy compared to bariatric surgery and usual care for long-term diabetes control.

Trial registration number

NCT04432025

Article Summary

Strengths and limitations of this study

- This is a randomised controlled trial designed to compare the efficacy and safety of combining goal directed medical therapy for type 2 diabetes mellitus (T2DM) with bariatric surgery to bariatric surgery and standard medical care.
- The long-term follow up will evaluate whether patients receiving goal directed medical therapy following bariatric surgery improves long term diabetes control according to the ADA criteria.
- The results will help inform how patients with T2DM should be managed following bariatric surgery.
- This study cannot be blinded due to the nature of the interventions.
- This study is not powered to detect differences between the two surgical procedures included in the trial.

Introduction

Obesity and type 2 diabetes mellitus (T2DM) are inherently linked, and patients suffering from both diseases present a particular challenge to clinicians concerning treatment due to their significantly increased risk of cardiovascular events and end-organ complications. Long-term success in treating hyperglycaemia, hypertension, and dyslipidaemia in patients with T2DM prevents the development of diabetes-related complications with conventional best medical treatment alone (anti-hyperglycaemic agents, anti-hypertensives, and statins in combination with lifestyle modification) has proven to be elusive. Bariatric/metabolic surgery has level 1 evidence from 12 randomised controlled trials (RCTs) demonstrating its safety and efficacy as a treatment for obesity and T2DM [1-12]. Given the powerful metabolic effects on glucose homeostasis and subsequent diabetes control, it is now widely recommended that bariatric surgery is considered a key treatment approach for patients with obesity and difficult to control T2DM[13, 14]. Changes in glucose metabolism, independent of weight loss have been observed in the immediate postoperative period, and remission rates according to the ADA criteria (all diabetic medications stopped, HbA1c<6% (42mmol/mol), fasting plasma glucose <5.6mmol/l (100mg/dl) off all hypoglycaemic agents for one year) of 40% have been demonstrated over a median follow up of two years[15-17].

Despite these promising results, emerging evidence suggests that though glycaemic control improves after surgery, only 20-50% of patients who initially experienced remission will maintain remission in the long-term [15, 18, 19]. The Swedish Obesity Surgery Register (SOReg) data also suggests that patients who do not achieve glycaemic remission within one year have more cardiovascular events[20].

Although standard medical therapy alone is inferior to bariatric surgery regarding control of T2DM, a more intensive approach with pharmacotherapy titrated to prespecified targets for hyperglycaemia, hypertension, and dyslipidaemia has been demonstrated to be safe and effective. Over a 13.3 year follow-up period, the STENO-2 trial showed a 20% absolute risk

reduction in death and a 13% reduction in death due to cardiovascular endpoints with intensive, goal-directed medical therapy compared to conventional therapy[21].

Evidence would support improved glycaemic control due to the powerful metabolic changes evoked by bariatric surgery; however, the effects tend to attenuate with time, and a proportion of patients will ultimately experience a relapse of diabetes[22]. What remains to be seen is whether a multimodal approach with surgery and goal-directed medical therapy can be safely utilised to improve diabetes control[23, 24].

Objectives

This study aims to investigate the long-term safety and efficacy of combining bariatric surgery (Roux-en-Y gastric bypass-RYGB or Sleeve gastrectomy- SG) with goal-directed medical therapy versus bariatric surgery and usual medical care on the glycaemic control and the ADA triple endpoint as a marker of good diabetes control and reflected in measures for HbA1c, BP and lipids.

Trial design

The BY PLUS study is a multi-center, open-label randomised controlled trial. The trial will involve two arms with an allocation ratio of 1:1. There are two primary endpoints:

1. the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) over a follow up of one year
2. the proportion of patients in each arm reaching the composite endpoint of HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/l over a follow-up period of five years.

Patient recruitment was commenced in August 2020. The trial was registered on ClinicalTrials.gov (NCT04432025). A planned interim analysis will also be carried out at a prespecified follow-up period of 12 months and then yearly until trial conclusion at five years (60 months follow up).

Several strategies, such as the use of checklists and workflow, have been employed to guarantee the data's quality and completeness. A dedicated monitor will audit the overall quality and completeness of the data entered on the electronic case report form, examine source documents, and compliance of the team with Good Clinical Practice.

The full SPIRIT checklist can be found in appendix 1.

Methods

Study setting

The study will be undertaken in tertiary care centres with expertise in bariatric surgery and the treatment of obesity and T2DM.

Eligibility criteria

Inclusion criteria

- ≥18 years old
- Eligible for bariatric surgery as per NICE CG189 or IFSO guidelines
- Diagnosis of type 2 diabetes mellitus based on an HbA1c of 48mmol/mol or 6.5%

- Body mass index (BMI) > 30kg/m^2

Exclusion criteria

- Specific contraindications to bariatric surgery
- Previous bariatric surgery
- Current pregnancy or breastfeeding
- Recent illness requiring hospitalisation within the previous 30 days
- Recurrent episodes of hypoglycaemia
- Recurrent episodes of hypotension
- History of any medical, psychological, or other condition, or use of any medications, including over-the-counter products, which, in the opinion of the investigators, would either interfere with the study or potentially cause harm to the participant.
- Lack of access to a telephone or other factors likely to interfere with the ability to participate reliably in the study.
- Concurrent or recent participation in another research study

Interventions

After randomisation, patients will be allocated in a 1:1 ratio, stratified by BMI and site to bariatric surgery plus standard medical care or bariatric surgery and intensive medical therapy. Patients in both arms will undergo bariatric surgery, either SG or RYGB, with the decision regarding the specific procedure being made by the patient and multi-disciplinary team (MDT). The individual arms are discussed below:

Bariatric surgery plus standard medical care- two weeks preoperatively, SGLT-2 inhibitors will be stopped due to the risk of euglycaemic acidosis and following bariatric surgery, all remaining oral diabetic medications will be stopped. If on insulin, patients will be monitored as inpatients. If they require insulin to maintain glycaemic control while in hospital, then a basal dose of insulin will be provided on discharge equivalent to their insulin requirement over the previous 24 hours. Rapid-acting insulin will be stopped postoperatively. The basal insulin dose will be titrated every day by the research team to allow fasting glucose values to be maintained between 7 and 9 mmol/L (126-162mg/dl). For any further monitoring or adjustments of diabetic medications, the clinicians caring for the patient will resume their primary care for metabolic control. Prescribing and/or titration of any medications for glycaemic control, BP and lipids will be according to current standard of care.

Bariatric surgery plus intensive medical therapy- following bariatric surgery, patients will modify their preoperative medications for glycaemic control, BP, lipids, and doses of medications reduced to prevent hypoglycaemia episodes or hypotension. If on insulin, patients will be monitored as inpatients. If they require insulin to maintain glycaemic control while inpatients, then a basal dose of insulin will be provided on discharge equivalent to their insulin requirement over the previous 24 hours. Rapid-acting insulin will be stopped postoperatively. The basal insulin dose will be titrated every day by the research team to allow fasting glucose values to be maintained between 6 and 8 mmol/L (106-145mg/dl). Oral medications in the postoperative period will be adjusted as follows:

Glucose lowering agents:

1. Metformin will be continued at the same dose used pre-surgery
2. SGLT-2 inhibitors will be stopped two weeks preoperatively due to the risk of euglycaemic acidosis
3. All sulphonylureas and thiazides will be stopped preoperatively
4. If fasting glucose >7.5mmol/l (135mg/dl) one month postoperatively, a GLP-1 analogue will be added
5. If fasting glucose remains >7.5mmol/l (135mg/dl) despite the addition of GLP-1 analogue, a SGLT-2 inhibitor will be added

Blood pressure medications:

1. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) at half dose (or lowest dose if this is what they are already on) will be continued
2. All diuretics will be stopped
3. All calcium antagonists will be stopped

Statin

1. Continued at preoperative dose

In subsequent follow-up visits, medications will be individually titrated as required by the obesity clinic staff to achieve specific targets- HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/L.

Surgical procedures

All operations will be performed by consultant surgeons with experience in laparoscopic RYGB or SG. Patients will be admitted to the hospital on the day of the procedure after an overnight fast. The procedures are standardised for both RYGB and SG according to previously described techniques and will be performed as follows[25, 26]. Laparoscopic RYGB will be performed under general anaesthesia and with the creation of a 20-30mL pouch, a biliary limb of approximately 80cm, and an alimentary limb of approximately 120cm. A linear stapler will typically be used to form the gastrojejunostomy and side-to-side jejunojejunostomy. Both mesenteric and Petersen's defects will be routinely closed using non-absorbable clips. For patients undergoing SG, the stomach's greater curvature will be mobilised to allow for the stomach's division using the linear stapler, starting 4-6cm from the pylorus, proceeding towards the angle of His. A 32Fr bougie will be used to help guide the division of the stomach. Deep vein thrombosis (DVT) prophylaxis in the form of compression stockings and intermittent pneumatic compression intraoperatively will be given to all patients and subcutaneous enoxaparin administered after the procedure unless contraindicated. Prophylactic antibiotics will be administered at the induction of anaesthesia. Both groups of will receive identical dietary counselling with regards to food consistency and progression to solid as well as long term follow up for micronutrient replacement and biochemical monitoring[27]. Blood results will be checked at baseline, 3, 6, 12 months and then annually thereafter including corrected Ca, vitamin D, ferritin/iron profile, vitamin B12, folate. PTH, copper, zinc and selenium will be checked at 12 months

and yearly thereafter. Magnesium, chromium and fat soluble vitamins will not be routinely checked.

Drug titration and safety monitoring

For patients in the surgery plus intensive medical treatment arm, follow-up regarding medications in the postoperative period will be coordinated through clinic. Metformin will be continued, but doses may be reduced if HbA1c is <6% (42 mmol/mol) or discontinued if there are recorded hypoglycaemic episodes or severe gastrointestinal side-effects. The parameters for full withdrawal of medications for glycaemic control are an HbA1c<6% (42mmol/mol) and fasting glucose of 5.5 mmol/L (100mg/dl). Medications for blood pressure control, ACEi, and ARB as well as statins for lipid control will be continued, but doses may be reduced to avoid side effects. At subsequent follow-up visits, patients in this cohort will have their HbA1c, BP, and LDL checked with the results used to guide titration of doses towards the prespecified treatment thresholds HbA1c<6.5% (48mmol/mol), BP<130/80mmHg and LDL<2.6mmol/l.

Outcomes

The primary outcomes are:

1. The proportion of patients in each arm who achieve an HbA1c<6.5% (48mmol/mol) at one year
2. The proportion of patients in each arm who reach the composite endpoint for good diabetes control as outlined by the American Diabetes Association (ADA), which is an HbA1c<6.5% (48mmol/mol), BP<130/80mmHg and LDL<2.6mmol/l at five years.

Secondary outcomes

The secondary outcomes are change from baseline to 5 years for each endpoint, temporal changes, mean levels, and peak levels will be analysed as appropriate: body weight, BMI, waist circumference, plasma lipid concentration, plasma liver function tests, urinary creatinine: albumin ratio, inflammatory markers including CRP, Multidimensional Health Profile: Health Functioning questionnaire score (MHP-H), Social Functioning Questionnaire score (SFQ) and the number of medications.

The safety of concurrent medication administration following surgery for blood pressure and glycaemic control will also be monitored with standardised reporting procedures for episodes of:

1. Symptomatic or asymptomatic hypoglycaemia defined as a BM of <4mmol/L (70mg/dL)
2. Symptomatic or asymptomatic hypotension defined as systolic BP<90mmHg

Symptoms of either hypoglycaemia or hypotension will be discussed with patients and they will be instructed to contact the study coordinators to arrange clinic review for titration of medication as necessary.

Participant timeline

Screening visit

The screening visit will be undertaken by a member of the bariatric and research team. During this visit, patients will be given information on the study design, randomisation process, the two study arms and follow-up procedures. Patients will also have the opportunity to discuss the risks and benefits of participating in the trial and the risks specific to each arm of the trial. A standardised checklist will be used to ensure that prospective patients are eligible to participate, in keeping with the inclusion and exclusion criteria. Written informed consent will be required for all patients' participation in the surgical procedure (RYGB/SG) and subsequent follow-up procedures. Baseline blood and urine tests will be taken along with height, weight, waist circumference, and blood pressure measurements. Medications will be reviewed, and for those on suboptimal treatment for glycaemic control, BP or lipids medications will either be started or titrated as required.

Randomisation visit

All patients will be required to attend a comprehensive clinical evaluation 4-6 weeks following the screening visit to ensure all eligibility requirements are met. Once confirmed, patients will be assigned an identification number to be used for all further documentation. All patients will be required to undergo upper digestive endoscopy. Two weeks after the randomisation visit, all clinical evaluations will be reviewed to ensure patients were eligible to proceed with trial participation. A dietician will review both groups with expertise in managing patients with obesity and following bariatric surgery. The dietician appointment will focus on the importance of adherence to postoperative dietary changes and nutritional supplement intake.

Follow up visits

Irrespective of the allocation, all patients will be followed up in the obesity clinic according to the same timeline with visits at six weeks, 3, 6, 12 months, and then yearly after that until study completion at 60 months. At each follow-up visit, all adverse events will be recorded. For patients in the surgery + intensive medical treatment arm, medications will be titrated to the previously discussed treatment thresholds for HbA1c, BP, and LDL. In addition to routine clinical parameters including weight/BMI, waist circumference the following will be measured/performed (Table 1):

  - Non-invasive blood pressure monitoring
  - HbA1c
  - Plasma lipids
  - Plasma liver function tests
  - Plasma renal function tests
  - Inflammatory markers
  - Urinary albumin: creatinine ratio

- Every 12 months: Multidimensional Health Profile: Health Functioning questionnaire (MHP-H) and Social Functioning Questionnaire (SF-36).

Table 1 Schedule of visits, examinations and procedures

Assessments	Screen	Random	Surgery	W6	W12	W24	W52	Y2	Y3	Y4	Y5
Informed consent	X										
Medical history	X	x									
Physical examination	X	x									
Medical assessment	X	X	x	X	x	x	x	x	x	x	x
Medication review	X	X		X	x	x	x	x	x	x	x
Inclusion/exclusion criteria	X	X									
Randomisation		X									
Adverse events				X	x	x	x	x	x	x	x
Nutritional assessment		x		X	x	x	x	x	x	x	x
Serum pregnancy test	X										
MPH-H, SF-36	X							x	x	x	x
Urine sample	X			x	x	x	x	x	x	x	x
Fasting plasma glucose	X			x	x	x	x	x	x	x	x
HbA1c	X			x	x	x	x	x	x	x	x
Lipids	X			x	x	x	x	x	x	x	x
Liver function test	x			x	x	x	x	x	x	x	x
Renal function test	X			X	X	X	X	X	X	X	X
Blood pressure	X			x	x	x	x	x	x	x	x
CRP	X			x	x	x	x	x	x	x	x
Height	X										
Body weight	X		x	x	x	x	x	x	x	x	x
Waist circumference	X	x	x	x	x	x	x	x	x	x	x
Upper digestive endoscopy		x									
RYGB or SG			x								
Drug titration and dispensing			x	x	x	x	x	x	x	x	x
Glucose monitoring			x	x	x	x	x	x	x	x	x

Sample size

Based on published data comparing the effect size of best medical therapy combined with bariatric surgery vs. best medical therapy alone on glycaemic control, BP and cholesterol levels in patients with T2DM, we estimated that 30% of patients in the control group and 50% of patients in the intensive treatment group would reach the primary endpoint [28]. Based on these data, we calculated that to have 80% power to detect statistically significant

differences between the groups at α of 0.05, we would need 55 patients per arm. We will recruit 75 patients in each group to account for a possible 20-25% drop-out rate.

Recruitment strategy

All patients presenting to the obesity clinic within the participating centres who are due to undergo RYGB or SG and meet the eligibility criteria will be given written and verbal information regarding participation in the study. After a minimum period of 24 hours to consider the information, patients can indicate whether they are willing to participate and will be asked to provide written consent.

Assignment of interventions

Sequence generation

Patients will be randomised by an independent researcher not involved in patient recruitment, treatment, or follow-up. A computer-generated sequence will randomise patients 1:1 to either surgery + standard medical care or surgery + intensive goal-directed medical therapy with random block sizes of 4.

Concealment mechanism

Randomisation codes will only be released after patients are formally recruited to the trial. The randomisation sequence will be held by a senior project manager not associated directly with this trial and will not be available to any of the research investigators at any time. Participants, staff members, and researchers will be unable to foresee the assignment because of central randomisation. All participant data will be pseudo anonymised (personal information removed and replaced with a coded identifier), and this list will be supplied to the central allocation, which randomly allocates patients to either arm of the study.

Blinding

Because of the study's nature, neither study investigators nor patients can be blinded regarding their allocation. All investigators in charge of statistical analysis or analysis of samples (laboratory staff) will be blinded to the patient allocation.

Data management

In order to assure data quality, several procedures are in place, including missing data, permitted/non-permitted value ranges, and logic checks. Checklists and standard operating procedures were created and routinely used to ensure data are complete and reliable. As this is a multi-centre trial, training will be done centrally at the host institution with members of all sites present and all data collection forms are standardised to ensure homogeneity in data collection and entry. Each member of the study team requires training before study initiation, and roles are delegated and assigned. Each participant will receive a numerical code to ensure confidentiality and tracking. Source documents (paper) will be stored at each site in a secured location, with all documents being stored according to their numerical code and accessible only to the study team.

A dedicated monitor, which has been designated specifically for this protocol, will be responsible for source data verification and the creation of queries and/or data clarification forms for all participants' source documents. This monitor will assure quality assurance and control, and a statistician will be responsible for final data verification and database analysis throughout the study.

Retention

We anticipate a 20-25% drop-out rate over the 60-month follow-up period. This was reflected in the power calculation to plan the sample size. To mitigate the effects of losing patients to follow up, trial coordinators will make every possible effort to follow up patients for the entire duration of the study. Strategies using multiple contact methods such as email, mail, telephone calls will be employed to achieve the highest possible level of follow-up.

Participant withdrawals

In the case of a participant deciding to withdraw from the study, they will be asked to provide further monitoring and data collection after their withdrawal. For participants who have been lost to follow up despite attempts to contact them, their data will be imputed.

Patient and public involvement

Qualitative research specifically examining patients' expectations and experiences of undergoing bariatric surgery as a treatment for T2DM was undertaken. This information was used to help develop the research question, ensuring that patient priorities were reflected in the design of the study as well as the choice of outcome measures. This study also explored patient perceptions of continued medications following surgery to determine whether the proposed intervention would be acceptable to the target population.

Statistical methods

All data analysis and statistical methods were advised by a statistician and will be performed on an intention to treat principle (ITT). An overview of the methods of analysis is presented in Table 2. We will compare the proportion of participants achieving the primary outcome between bariatric surgery and goal-directed medical therapy versus bariatric surgery and usual care using an unconditional logistic regression model. Continuous outcomes will be analysed by mixed-effects generalised linear models adjusting for the response variable's baseline version. Missing data will be imputed using several different models, assuming data will be missing at random. Participants' demographic data and clinical characteristics will be analysed using an unpaired Student's T-test for continuous variables, whereas dichotomous variables will be analysed using Fischer's exact test. Data will be expressed as mean +/-SD, median, and IQR or counts (percentage) as appropriate. In any circumstances, variables with asymmetric distributions will be transformed using standard mathematical models (logarithm, square root, etc.). Statistical significance will be set at the 1.7% level (two-sided)

for the primary outcome and 5% for secondary outcomes. The main conclusions will be based on the ITT principle and on the logistic regression model. All data analysis will be performed using Stata (V.13.0, Stata Corp, College Station, Texas, USA).

Table 2- Variable, measures, and method of analysis

Variable/outcome	Hypothesis	Outcome measure	Method of analysis
Primary outcome HbA1c	The proportion of patients with an HbA1c<6.5%(48mmol/mol) at one year will be higher in the surgery + intensive treatment group compared to control	The proportion of patients in each group with an HbA1c <6.5% (48mmol/mol)	Mixed-effects generalized linear models
Composite end point of HbA1c<6.5% (48mmol/mol), BP<130/80mmHg, LDL<2.6mmol/l	The proportion of participants reaching the composite endpoint will be higher in the surgery+ intensive treatment group compared to the control	The proportion of participants reaching the composite endpoint	Logistic regression
Secondary outcomes			
Body weight	There will be a greater reduction in weight in the intensive medical group compared to control group	Kg	Student's t-test
BMI	The reduction will be higher in the surgery+ intensive treatment group compared to the control	kg/m^2	Student's t-test
Waist circumference	The reduction will be higher in the surgery+ intensive treatment group compared to the control	cm	Student's t-test
Glycaemic control	The reduction will be higher in the surgery+ intensive treatment group compared to the control	HbA1c levels	Mixed-effects generalized linear models
Blood pressure control	The proportion of patients achieving blood pressure control will be higher in the surgery + intensive treatment group compared to the control	Proportion of participants achieving BP<130/80mmHg	Mixed-effects generalized linear models
Lipid control	The proportion of patients achieving lipid control will be higher in the surgery +	Number of participants with LDL <2.6mmol/L	Logistic regression

	intensive treatment group compared to the control		
Liver function	The proportion of patients achieving normal liver function tests will be higher in the surgery + intensive treatment group compared to the control	ALT (IU/L), GGT (IU/L), AST (IU/L), ALP(IU/L) levels	Mixed-effects generalized linear models
Renal function	The proportion of patients achieving normal renal function test will be higher in the surgery + intensive treatment group compared to the control group	Plasma Cr, eGFR	Mixed-effects generalized linear models
Inflammatory markers	The reduction in CRP will be greater in the surgery + intensive treatment group compared to control	CRP	Mixed-effects generalized linear models
Urine albumin: creatinine ratio	The proportion of patients in the surgery + intensive treatment group with a uACR<30µg will be higher than the control group	Number of participants in each group with a uACR<30µg	Logistic regression
Quality of life	Quality of life is higher in patients in the surgery + intensive medical therapy arm compared to control	SF-36 and MHP-H	Mixed-effects generalized linear models
Clinical and sociodemographic variables			
Age	There is no difference between the two groups	Years	Student's t-test
BMI	There will be a greater reduction in BMI in the intensive medical therapy arm compared to control group	kg/m^2	Student's t-test
Body weight	There will be a greater reduction in weight in the intensive medical group compared to control group	Kg	Student's t-test
Gender	There is no difference between the two groups	1= male, 0= female	Fischer's exact test
Waist circumference	There will be a greater reduction in the waist circumference in the	cm	Student's t-test

	intensive medical group compared to the control group		
Fasting blood glucose	There will be a greater reduction in the fasting blood glucose in the intensive medical group compared to the control group	mg/dL, mol/L	Student's t-test
Total HDL and LDL cholesterol	There will be a greater reduction in the total HDL and LDL cholesterol in the intensive medical group compared to the control group	mmol/L	Student's t-test
Triglycerides	There will be a greater reduction in triglycerides in the intensive medical group compared to the control group	Mmol/L	Student's t-test
Diastolic and systolic blood pressure	There will be a greater reduction in diastolic and systolic pressure in the intensive medical group compared to the control group	mmHg	Student's t-test

Additional analysis

All primary analyses will be carried out on an ITT basis, but subsequent studies may be conducted on a per-protocol basis. The primary analysis will also be performed out with multiple imputation methods. We will also provide results from analyses restricted to complete cases to compare results from the multiple imputation processes.

Adjusted analysis

All statistical models will be run with appropriate adjustment for baseline characteristics.

Analysis population and missing data

In the case of missing data, we will perform and report the multiple imputation analysis according to the recommendation of White *et al. [29].* Missing data will be handled using multiple imputation methods, assuming all data are missing at random. We will use a combination of predictive mean matching and regression-based methods to impute missing data. Specifically, we will use a combination of predictive mean matching and regression-based methods to impute missing data. A total of 100 data sets will be created to reduce

sampling variability. A burn-in period of 500 iterations will be used. Imputation will be performed in Stata V.14.0 (StataCorp, College Station, Texas, USA).

Monitoring

Adverse events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical study subject even if it did not directly relate to the medical or surgical intervention. Serious adverse events were defined as any untoward and unexpected medical occurrence or effect that:

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

All AE or SAE are required to be reported within 24h with detailed documentation to the research and ethics committee.

Auditing

Throughout the study, audits will be carried out by a dedicated monitor using several key indicators on all source documents and participants. The key indicators are informed consent form (ICF) and process, eligibility criteria, enrolment, allocation of study groups, scheduled and missed tests and procedures, policies to protect participants, concomitant and prohibited medications, dispensing medication procedures, identification and reporting of A.E.s and SAEs, deviation report, regulatory documents and communication with local research and ethics committee, following International conference on Harmonisation-Good Clinical Practice (ICH-GCP) and regulatory agency guidelines.

Ethics and dissemination

Research ethics approval

Protocol, ICF, and recruitment materials were reviewed and approved by the study sites' local research and ethics committee. Approval was received within Ireland on the 11th of February 2020 (St Vincent's University Hospital) and on the 2nd of December 2020 within the UK (Fulham Research Ethics Committee). The full list of the committee members can be found in the Supplementary file 1. All sites will report back regarding study progress regularly.

Protocol amendments

All changes needed after initial approval will be re-submitted to the research and ethics committee for review. Amendments to the clinical protocol will require formal review, accompanied by an updated, informed consent signed by both the investigators and participants. If any changes are made to the protocol, the history will be available and tracked by version and date changes.

Consent

Patients identified as potential participants will receive verbal and written information from an investigator (medical doctor). A copy of the study materials and ICF will be given, and

patients allowed an opportunity to review and discuss with family/friends. After being given a minimum of 24 hours to consider the materials, a formal discussion will be carried out with the patient and an investigator. Patients will be allowed to ask any questions and clarify any areas of uncertainty. If the patient then decides to participate, they will be given an ICF to sign (also signed by the investigator), after which they are considered a study participant. Assent form and ancillary studies consent are not necessary for the study.

Confidentiality

All medical information derived from the study will be confidential, and no third-party access will be allowed. The designated personnel will handle source/data information stored on password-protected computers and in-coded patient notes to protect confidentiality.

Declaration of interests

The author RC has received an honorarium as a member of the Speaker's panel of Johnson & Johnson.

The author ClR has received grants from the Science Foundation Ireland, Health Research Board, Irish Research Council, Johnson & Johnson and AnaBio. Personal fees have been received from Eli Lily, Johnson & Johnson, Sanofi Aventis, Astra Zeneca, Janssen, Bristol-Meyers Squibb and Boehringer-Ingelheim. He is on the advisory board for GI dynamics.

The author DJP has received personal fees from NovoNordisk and Johnson & Johnson.

Study sponsorship and access to data

Data will be available to authorised investigators only. Third parties may have access to data with express written permission from the lead investigator. However, sponsors will not participate in data analysis, nor will they have access to data, either in full or in part.

Ancillary and post-trial care

Participating sites will have insurance policies to cover non-negligent harm associated with the protocol, which covers additional healthcare, compensation, or damages whether awarded voluntarily by the BY PLUS study or by claims pursued through the courts.

Dissemination policy

After the trial protocol publication, the investigators plan to publish all the listed endpoints as this RCT is the first trial to compare intensive goal-directed medical therapy combined with bariatric surgery versus bariatric surgery and standard medical care for patients with T2DM and obesity. The results of this trial will be published in peer-reviewed scientific journals and presented at major conferences, regardless of the magnitude or direction of the observed effect.

Trial organisation and management

The study investigators are responsible for completing all pertinent information using the clinical report forms, data accuracy, and maintaining the confidentiality of patients' data. Only the investigators will have access to the final data set. All documentation will be kept for five years after the study's termination if it has to be monitored, audited, or inspected by the sponsor or regulatory authorities.

Author Contributions

Conceived the trial and were involved in logistical planning- AS, AM, HK, JT, RC, HH, ClR, DJP
Drafted the article- AS, AM, HK, RC, HH, ClR, DJP

Data sharing

The authors shall make data available to the scientific community with as few restrictions as feasible, ensuring anonymisation, while retaining exclusive use until the publication of major outputs.

Funding

The authors of this work, Alexis Sudlow and Dimitri Pournaras received funding from the Royal College of Surgeons (England) for this work.
Grant number: PO117623

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BMJ Open Supporting Information

Ethics and Dissemination

London Fulham Research Ethics Committee- Rev Nigel Griffin (chairperson) , Ms Diana Barham, Mr Keith Berelowitz, Ms Mabel Cortes, Mr Frank Cross, Professor John Dark, Dr Jan Downer, Dr Peter Richard Hayes, Miss Kate Hazelhurst, Mr Greg Kyle-Langley, Mrs Deborah Morgan, Miss Hayley Noble, Dr Phillipa Jane Rollins, Mr David Parr, Ms Catriona Stirling, Ms Gemma Warren

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Appendix 1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1,16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3,4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	4

		be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4,5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 10-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8,9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9,10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	10

		Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events	14

		and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the	15

		public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	20
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a