BMJ Open

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

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To cite: Sudlow A, Miras AD, Cohen RV, *et al*. Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study: rationale and design of a randomised controlled study. *BMJ Open* 2022;**12**:e054313. doi:10.1136/bmjopen-2021-054313

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-054313).

Received 09 June 2021
Accepted 03 May 2022

Check for updates

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ABSTRACT

Introduction Bariatric surgery is an effective method of controlling glycaemia in patients with type 2 diabetes mellitus (T2DM) 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 criteria.

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

Methods and analysis This prospective, open-label multicentre randomised controlled trial (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 glycated haemoglobin (HbA1c), blood pressure (BP) and low-density lipoproteins (LDL) cholesterol. The primary endpoints are the proportion of patients in each arm with an HbA1c<6.5% (48 mmol/mol) at 1 year and the proportion of patients in each arm achieving the composite endpoint of HbA1c<6.5% (48 mmol/mol), BP<130/80 mm Hg and LDL<2.6 mmol/L at 5 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 with bariatric surgery and usual care for long-term diabetes control.

Trial registration number NCT04432025.

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 American Diabetes Association 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 (antihyperglycaemic agents, antihypertensives 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 American Diabetes Association (ADA) criteria (all diabetic medications stopped, glycated haemoglobin (HbA1c)<6% (42mmol/mol), fasting plasma

glucose<5.6 mmol/L (100 mg/dL) off all hypoglycaemic agents for 1 year) of 40% have been demonstrated over a median follow-up of 2 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 data also suggest that patients who do not achieve glycaemic remission within 1 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 with 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 used 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, blood pressure (BP) and lipids.

TRIAL DESIGN

The BY PLUS study is a multicentre, 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% (48 mmol/mol) over a follow-up of 1 year.
2. The proportion of patients in each arm reaching the composite endpoint of HbA1c<6.5% (48 mmol/mol), BP<130/80 mm Hg and low-density lipoproteins (LDL)<2.6 mmol/L over a follow-up period of 5 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 5 years (60-month 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 (GCP).

The full SPIRIT checklist can be found in online supplemental 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 National Institute for Health and Care Excellence (NICE) CG189 or International Federation for the Surgery of Obesity and Metabolic DIsorders (IFSO) guidelines.
- Diagnosis of T2DM based on an HbA1c of 48 mmol/mol or 6.5%
- Body mass index (BMI)>30 kg/m^2.

Exclusion criteria:

- Specific contraindications to bariatric surgery.
- Previous bariatric surgery.
- Current pregnancy or breast feeding.
- 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 multidisciplinary team. The individual arms are discussed below:

Bariatric surgery plus standard medical care: two weeks preoperatively, Sodium-Glucose Cotransporter-2 (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 (126–162 mg/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 (106–145 mg/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 2 weeks preoperatively due to the risk of euglycaemic acidosis.
3. All sulphonylureas and thiazides will be stopped preoperatively.
4. If fasting glucose>7.5 mmol/L (135 mg/dL) 1-month postoperatively, a Glucagon-like peptide-1 (GLP-1) analogue will be added.
5. If fasting glucose remains >7.5 mmol/L (135 mg/dL) despite the addition of GLP-1 analogue, an SGLT-2 inhibitor will be added.

BP medications:

1. ACE 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% (48 mmol/mol), BP<130/80 mm Hg and LDL<2.6 mmol/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 20–30 mL pouch, a biliary limb of approximately 80 cm and an alimentary limb of approximately 120 cm. 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 4–6 cm 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 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 regard 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. parathyroid hormone (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% (42 mmol/mol) and fasting glucose of 5.5 mmol/L (100 mg/dL). Medications for BP 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% (48 mmol/mol), BP<130/80 mm Hg and LDL<2.6 mmol/L.

Outcomes

The primary outcomes are:

1. The proportion of patients in each arm who achieve an HbA1c<6.5% (48 mmol/mol) at 1 year.
2. The proportion of patients in each arm who reach the composite endpoint for good diabetes control as outlined by the ADA, which is an HbA1c<6.5% (48mmol/mol), BP<130/80 mm Hg and LDL<2.6 mmol/L at 5 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 C reactive protein, 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 BP and glycaemic control will also be monitored with standardised reporting procedures for episodes of:

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

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 BP 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 6 weeks, 3, 6, 12 months, and then yearly after that until study completion at 60 months. At each follow-up visit, all adverse events (AE) 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 BP monitoring.
- HbA1c.
- Plasma lipids.
- Plasma liver function tests.
- Plasma renal function tests.
- Inflammatory markers.
- Urinary albumin: creatinine ratio.
- Every 12 months: MHP-H and Social Functioning Questionnaire (SF-36).

SAMPLE SIZE

Based on published data comparing the effect size of best medical therapy combined with bariatric surgery versus 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

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

CRP, C reactive protein; HbA1c, glycated haemoglobin; MHP-H, Multidimensional Health Profile: Health Functioning questionnaire score; RYGB, Roux-en-Y gastric bypass; SF-36, Social Functioning Questionnaire; SG, sleeve gastrectomy.

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 pseudoanonymised (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 multicentre 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).

Additional analysis

All primary analyses will be carried out on an ITT basis, but subsequent studies may be conducted on a perprotocol 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 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 AEs (SAEs) 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 24 hours with detailed documentation to the research and ethics committee.

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% (48 mmol/mol) at 1 year will be higher in the surgery+intensive treatment group compared with control	The proportion of patients in each group with an HbA1c<6.5% (48 mmol/mol)	Mixed effects generalised linear models
Composite end point of HbA1c<6.5% (48 mmol/mol), BP<130/80 mm Hg, LDL<2.6 mmol/L	The proportion of participants reaching the composite endpoint will be higher in the surgery+intensive treatment group compared with 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 with control group	kg	Student's t-test
BMI	The reduction will be higher in the surgery+intensive treatment group compared with the control	kg/m^2	Student's t-test
Waist circumference	The reduction will be higher in the surgery+intensive treatment group compared with the control	cm	Student's t-test
Glycaemic control	The reduction will be higher in the surgery+intensive treatment group compared with the control	HbA1c levels	Mixed effects generalised linear models
Blood pressure control	The proportion of patients achieving blood pressure control will be higher in the surgery+intensive treatment group compared with the control	Proportion of participants achieving BP<130/80 mmHg	Mixed effects generalised linear models
Lipid control	The proportion of patients achieving lipid control will be higher in the surgery+intensive treatment group compared with the control	Number of participants with LDL<2.6 mmol/L	Logistic regression
Liver function	The proportion of patients achieving normal liver function tests will be higher in the surgery+intensive treatment group compared with the control	ALT (IU/L), GGT (IU/L), AST (IU/L), ALP(IU/L) levels	Mixed effects generalised linear models
Renal function	The proportion of patients achieving normal renal function test will be higher in the surgery+intensive treatment group compared with the control group	Plasma Cr, eGFR	Mixed effects generalised linear models
Inflammatory markers	The reduction in CRP will be greater in the surgery+intensive treatment group compared with control	CRP	Mixed effects generalised linear models
Urine albumin: creatinine ratio	The proportion of patients in the surgery+intensive treatment group with a uACR<30 µg will be higher than the control group	Number of participants in each group with a uACR<30 µg	Logistic regression
Quality of life	Quality of life is higher in patients in the surgery+intensive medical therapy arm compared with control	SF-36 and MHP-H	Mixed effects generalised linear models
Clinical and sociodemographic variables			
Age	There is no difference between the two groups	Years	Student's t-test

Continued

Table 2 Continued

Variable/outcome	Hypothesis	Outcome measure	Method of analysis
BMI	There will be a greater reduction in BMI in the intensive medical therapy arm compared with 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 with 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 with 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 with 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 with the control group	mmol/L	Student's t-test
Triglycerides	There will be a greater reduction in triglycerides in the intensive medical group compared with 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 with the control group	mm Hg	Student's t-test

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CRP, C reactive protein; eGFR, estimated Glomerular Filtration Rate; GGT, gamma-glutamy transferase; HbA1c, glycated haemoglobin; HDL, high-density lipoproteins; LDL, low-density lipoproteins; MHP-H, Multidimensional Health Profile: Health Functioning questionnaire score; SF-36, Social Functioning Questionnaire score; uACR, urine Albumin to Creatinine Ratio.

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 AEs and SAEs, deviation report, regulatory documents and communication with local research and ethics committee, following International conference on Harmonisation-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 11 February 2020 (St Vincent's University Hospital) and on 2 December 2020 within the UK (Fulham Research Ethics Committee). The full list of the committee members can be found in the online supplemental file 1. All sites will report back regarding study progress regularly.

Protocol amendments

All changes needed after initial approval will be resubmitted 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.

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 5 years after the study's termination if it has to be monitored, audited or inspected by the sponsor or regulatory authorities.

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Funding AS and DJP received funding from the Royal College of Surgeons (England) for this work. Grant number: PO117623.

Competing interests RVC has received an honorarium as a member of the Speaker's panel of Johnson & Johnson. 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. DJP has received personal fees from NovoNordisk and Johnson & Johnson.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Mingrone G, Panunzi S, De Gaetano A, *et al*. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012;366:1577–85.
2 Schauer PR, Bhatt DL, Kirwan JP, *et al*. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. *N Engl J Med* 2017;376:641–51.
3 Kashyap SR, Bhatt DL, Wolski K, *et al*. Metabolic effects of bariatric surgery in patients with moderate obesity and type 2 diabetes: analysis of a randomized control trial comparing surgery with intensive medical treatment. *Diabetes Care* 2013;36:2175–82.
4 Halperin F, Ding S-A, Simonson DC, *et al*. Roux-En-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. *JAMA Surg* 2014;149:716–26.
5 Cummings DE, Arterburn DE, Westbrook EO, *et al*. Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the crossroads randomised controlled trial. *Diabetologia* 2016;59:945–53.
6 Dixon JB, O'Brien PE, Playfair J, *et al*. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 2008;299:316–23.
7 Ikramuddin S, Korner J, Lee W-J, *et al*. Roux-En-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the diabetes surgery study randomized clinical trial. *JAMA* 2013;309:2240–9.
8 Courcoulas AP, Goodpaster BH, Eagleton JK, *et al*. Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. *JAMA Surg* 2014;149:707–15.
9 Simonson DC, Halperin F, Foster K, *et al*. Clinical and patient-centered outcomes in obese patients with type 2 diabetes 3 years after randomization to Roux-en-Y gastric bypass surgery versus intensive lifestyle management: the SLIMM-T2D study. *Diabetes Care* 2018;41:670–9.
10 Liang Z, Wu Q, Chen B, *et al*. Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: a randomized controlled trial. *Diabetes Res Clin Pract* 2013;101:50–6.
11 Wentworth JM, Playfair J, Laurie C, *et al*. Multidisciplinary diabetes care with and without bariatric surgery in overweight people: a randomised controlled trial. *Lancet Diabetes Endocrinol* 2014;2:545–52.

12 Ding S-A, Simonson DC, Wewalka M, *et al*. Adjustable gastric band surgery or medical management in patients with type 2 diabetes: a randomized clinical trial. *J Clin Endocrinol Metab* 2015;100:2546–56.
13 Davies MJ, D'Alessio DA, Fradkin J, *et al*. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetes Care* 2018;41:2669–701.
14 Dixon JB, Zimmet P, Alberti KG, *et al*. Bariatric surgery: an IDF statement for obese type 2 diabetes. *Diabet Med* 2011;28:628–42.
15 Pournaras DJ, Aasheim ET, Søvik TT, *et al*. Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. *Br J Surg* 2012;99:100–3.
16 Pournaras DJ, Osborne A, Hawkins SC, *et al*. Remission of type 2 diabetes after gastric bypass and banding: mechanisms and 2 year outcomes. *Ann Surg* 2010;252:966–71.
17 Pournaras DJ, Aasheim ET, Bueter M, *et al*. Effect of bypassing the proximal gut on gut hormones involved with glycemic control and weight loss. *Surg Obes Relat Dis* 2012;8:371–4.
18 Brethauer SA, Aminian A, Romero-Talamás H, *et al*. Can diabetes be surgically cured? long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. *Ann Surg* 2013;258:628–37.
19 Mingrone G, Panunzi S, De Gaetano A, *et al*. Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 2021;397:293–304.
20 le Roux CW, Ottosson J, Näslund E, *et al*. Bariatric surgery: there is a room for improvement to reduce mortality in patients with type 2 diabetes. *Obes Surg* 2021;31:461–3.
21 Gaede P, Lund-Andersen H, Parving H-H, *et al*. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580–91.
22 Schauer PR, Burguera B, Ikramuddin S, *et al*. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. *Ann Surg* 2003;238:467–85.
23 Pournaras DJ, le Roux CW. Can we predict diabetes remission after weight-loss surgery? *Lancet Diabetes Endocrinol* 2014;2:4–6.
24 Pournaras DJ, le Roux CW. Type 2 diabetes: multimodal treatment of a complex disease. *Lancet* 2015;386:936–7.
25 Olbers T, Lönroth H, Fagevik-Olsén M, *et al*. Laparoscopic gastric bypass: development of technique, respiratory function, and long-term outcome. *Obes Surg* 2003;13:364–70.
26 Wiggins T, Pournaras DJ, Priestman E, *et al*. *Effect of Preoperative Weight Loss and Baseline Comorbidity on Short-Term Complications and Reoperations After Laparoscopic Roux-en-Y Gastric Bypass* in *2,067 Patients*. *Obes Surg* 2021;31:2444–52.
27 O'Kane M, Parretti HM, Pinkney J, *et al*. British obesity and metabolic surgery Society guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery—2020 update. *Obesity Reviews* 2020;21:e13087.
28 Cohen RV, Pereira TV, Aboud CM, *et al*. Microvascular outcomes after metabolic surgery (MOMS) in patients with type 2 diabetes mellitus and class I obesity: rationale and design for a randomised controlled trial. *BMJ Open* 2017;7:e013574.
29 White IR, Horton NJ, Carpenter J, *et al*. Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ* 2011;342:d40.