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

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3 Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study:
4 rationale and design of a randomised controlled study
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10

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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

1
2
3 effective. Over a 13.3 year follow-up period, the STENO-2 trial showed a 20% absolute risk
4 reduction in death and a 13% reduction in death due to cardiovascular endpoints with
5 intensive, goal-directed medical therapy compared to conventional therapy[21].
6
7

8 Evidence would support improved glycaemic control due to the powerful metabolic changes
9 evoked by bariatric surgery; however, the effects tend to attenuate with time, and a
10 proportion of patients will ultimately experience a relapse of diabetes[22]. What remains to
11 be seen is whether a multimodal approach with surgery and goal-directed medical therapy
12 can be safely utilised to improve diabetes control[23, 24].
13
14

15 **Objectives**

16 This study aims to investigate the long-term safety and efficacy of combining bariatric
17 surgery (Roux-en-Y gastric bypass-RYGB or Sleeve gastrectomy- SG) with goal-directed
18 medical therapy versus bariatric surgery and usual medical care on the glycaemic control
19 and the ADA triple endpoint as a marker of good diabetes control and reflected in measures
20 for HbA1c, BP and lipids.
21
22

23 **Trial design**

24 The BY PLUS study is a multi-center, open-label randomised controlled trial. The trial will
25 involve two arms with an allocation ratio of 1:1. There are two primary endpoints:
26
27

- 28 1. the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) over a follow
29 up of one year
- 30 2. the proportion of patients in each arm reaching the composite endpoint of HbA1c<6.5%
31 (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/l over a follow-up period of five years.
32
33

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35 Patient recruitment was commenced in August 2020. The trial was registered on
36 ClinicalTrials.gov (NCT04432025). A planned interim analysis will also be carried out at a
37 prespecified follow-up period of 12 months and then yearly until trial conclusion at five
38 years (60 months follow up).
39
40

41 Several strategies, such as the use of checklists and workflow, have been employed to
42 guarantee the data's quality and completeness. A dedicated monitor will audit the overall
43 quality and completeness of the data entered on the electronic case report form, examine
44 source documents, and compliance of the team with Good Clinical Practice.
45
46

47 The full SPIRIT checklist can be found in appendix 1.
48
49

50 **Methods**

51 *Study setting*

52 The study will be undertaken in tertiary care centres with expertise in bariatric surgery and
53 the treatment of obesity and T2DM.
54
55

56 *Eligibility criteria*

57 Inclusion criteria

- 58 • ≥18 years old
- 59 • Eligible for bariatric surgery as per NICE CG189 or IFSO guidelines
60

- Diagnosis of type 2 diabetes mellitus based on an HbA1c of 48mmol/mol or 6.5%
- Body mass index (BMI) > 30kg/m²

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 jejunojunction. 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 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
 - HbA1c
 - 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

	Screen	Random	Surgery	W6	W12	W24	W52	Y2	Y3	Y4	Y5
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

1
2
3 February 2020 and on the 2nd of December 2020 within the UK. All sites will report back
4 regarding study progress regularly.
5

6 7 *Protocol amendments*

8 All changes needed after initial approval will be re-submitted to the research and ethics
9 committee for review. Amendments to the clinical protocol will require formal review,
10 accompanied by an updated, informed consent signed by both the investigators and
11 participants. If any changes are made to the protocol, the history will be available and
12 tracked by version and date changes.
13
14

15 16 *Consent*

17 Patients identified as potential participants will receive verbal and written information from
18 an investigator (medical doctor). A copy of the study materials and ICF will be given, and
19 patients allowed an opportunity to review and discuss with family/friends. After being given
20 a minimum of 24 hours to consider the materials, a formal discussion will be carried out
21 with the patient and an investigator. Patients will be allowed to ask any questions and
22 clarify any areas of uncertainty. If the patient then decides to participate, they will be given
23 an ICF to sign (also signed by the investigator), after which they are considered a study
24 participant. Assent form and ancillary studies consent are not necessary for the study.
25
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27 28 *Confidentiality*

29 All medical information derived from the study will be confidential, and no third-party
30 access will be allowed. The designated personnel will handle source/data information
31 stored on password-protected computers and in-coded patient notes to protect
32 confidentiality.
33
34

35 36 *Declaration of interests*

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

39 The author CIR has received grants from the Science Foundation Ireland, Health Research
40 Board, Irish Research Council, Johnson & Johnson and AnaBio. Personal fees have been
41 received from Eli Lilly, Johnson & Johnson, Sanofi Aventis, Astra Zeneca, Janssen, Bristol-
42 Meyers Squibb and Boehringer-Ingelheim. He is on the advisory board for GI dynamics.
43 The author DJP has received personal fees from NovoNordisk and Johnson & Johnson.
44
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46 47 *Study sponsorship and access to data*

48 Data will be available to authorised investigators only. Third parties may have access to data
49 with express written permission from the lead investigator. However, sponsors will not
50 participate in data analysis, nor will they have access to data, either in full or in part.
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53 54 *Ancillary and post-trial care*

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

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

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

26
27 Conceived the trial and were involved in logistical planning- AS, AM, HK, JT, RC, HH, CIR, DJP
28 Drafted the article- AS, AM, HK, RC, HH, CIR, DJP
29
30

31 **Data sharing**

32
33 The authors shall make data available to the scientific community with as few restrictions as
34 feasible, ensuring anonymisation, while retaining exclusive use until the publication of
35 major outputs.
36
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42 Royal College of Surgeons (England) for this work.
43 Grant number: PO117623
44
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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

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Name of Person taking consent

Signature

Date

For peer review only

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 SPIRIT reporting 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

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	n/a
8	responsibilities:		collection, management, analysis, and interpretation of data;	
9	sponsor and funder		writing of the report; and the decision to submit the report for	
10			publication, including whether they will have ultimate authority	
11			over any of these activities	
12				
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15	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
16	responsibilities:		centre, steering committee, endpoint adjudication committee,	
17	committees		data management team, and other individuals or groups	
18			overseeing the trial, if applicable (see Item 21a for data	
19			monitoring committee)	
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24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for	3,4
27	rationale		undertaking the trial, including summary of relevant studies	
28			(published and unpublished) examining benefits and harms for	
29			each intervention	
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33	Background and	#6b	Explanation for choice of comparators	3,4
34	rationale: choice of			
35	comparators			
36				
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38	Objectives	#7	Specific objectives or hypotheses	4
39				
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41	Trial design	#8	Description of trial design including type of trial (eg, parallel	4
42			group, crossover, factorial, single group), allocation ratio, and	
43			framework (eg, superiority, equivalence, non-inferiority,	
44			exploratory)	
45				
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47				
48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
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54	Study setting	#9	Description of study settings (eg, community clinic, academic	4
55			hospital) and list of countries where data will be collected.	
56			Reference to where list of study sites can be obtained	
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1	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
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6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
7	description			
8				
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10	Interventions:	#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
11	modifications			
12				
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14				
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
16	adherence			
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20	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
21	concomitant care			
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24	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
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34	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
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39	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
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45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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49	Methods: Assignment			
50	of interventions (for			
51	controlled trials)			
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54	Allocation: sequence	#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
55	generation			
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		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

1	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
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6	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
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10	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
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15	Methods: Monitoring			
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18	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
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28	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
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33	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
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38	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
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43	Ethics and dissemination			
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47	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
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51	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
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
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5	Consent or assent:	#26b	Additional consent provisions for collection and use of	14
6	ancillary studies		participant data and biological specimens in ancillary studies, if applicable	
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10	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
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15	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
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19	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
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24	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
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28	Dissemination policy:	#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
29	trial results			
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36	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
37	authorship			
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40	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
41	reproducible research			
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44	Appendices			
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46	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	20
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50	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
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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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Manuscript ID	bmjopen-2021-054313.R1
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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

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Manuscripts

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10 Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study:
11 rationale and design of a randomised controlled study
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14 Key words: obesity, type 2 diabetes mellitus, bariatric surgery, sleeve gastrectomy, roux en y
15 gastric bypass
16

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37

38 Trial Sponsor: Imperial College London
39 Sponsor Contact: Mrs Becky Ward, Research Governance Manager,
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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

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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/m²

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:

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11 *Glucose lowering agents:*

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

20
21 *Blood pressure medications:*

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

27 *Statin*

- 28 1. Continued at preoperative dose

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

34 *Surgical procedures*

35 All operations will be performed by consultant surgeons with experience in laparoscopic
36 RYGB or SG. Patients will be admitted to the hospital on the day of the procedure after an
37 overnight fast. The procedures are standardised for both RYGB and SG according to
38 previously described techniques and will be performed as follows[25, 26]. Laparoscopic
39 RYGB will be performed under general anaesthesia and with the creation of a 20-30mL
40 pouch, a biliary limb of approximately 80cm, and an alimentary limb of approximately
41 120cm. A linear stapler will typically be used to form the gastrojejunostomy and side-to-side
42 jejunojejunostomy. Both mesenteric and Petersen's defects will be routinely closed using
43 non-absorbable clips. For patients undergoing SG, the stomach's greater curvature will be
44 mobilised to allow for the stomach's division using the linear stapler, starting 4-6cm from
45 the pylorus, proceeding towards the angle of His. A 32Fr bougie will be used to help guide
46 the division of the stomach. Deep vein thrombosis (DVT) prophylaxis in the form of
47 compression stockings and intermittent pneumatic compression intraoperatively will be
48 given to all patients and subcutaneous enoxaparin administered after the procedure unless
49 contraindicated. Prophylactic antibiotics will be administered at the induction of
50 anaesthesia. Both groups will receive identical dietary counselling with regards to food
51 consistency and progression to solid as well as long term follow up for micronutrient
52 replacement and biochemical monitoring[27]. Blood results will be checked at baseline, 3, 6,
53 12 months and then annually thereafter including corrected Ca, vitamin D, ferritin/iron
54 profile, vitamin B12, folate. PTH, copper, zinc and selenium will be checked at 12 months

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10 and yearly thereafter. Magnesium, chromium and fat soluble vitamins will not be routinely
11 checked. (Reviewer 1, Comment 3)
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14 *Drug titration and safety monitoring*

15 For patients in the surgery plus intensive medical treatment arm, follow-up regarding
16 medications in the postoperative period will be coordinated through clinic. Metformin will
17 be continued, but doses may be reduced if HbA1c is <6% (42 mmol/mol) or discontinued if
18 there are recorded hypoglycaemic episodes or severe gastrointestinal side-effects. The
19 parameters for full withdrawal of medications for glycaemic control are an HbA1c<6%
20 (42mmol/mol) and fasting glucose of 5.5 mmol/L (100mg/dl). Medications for blood
21 pressure control, ACEi, and ARB as well as statins for lipid control will be continued, but
22 doses may be reduced to avoid side effects. At subsequent follow-up visits, patients in this
23 cohort will have their HbA1c, BP, and LDL checked with the results used to guide titration of
24 doses towards the prespecified treatment thresholds HbA1c<6.5% (48mmol/mol),
25 BP<130/80mmHg and LDL<2.6mmol/l.
26

27 Outcomes

28 The primary outcomes are:

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

34 Secondary outcomes

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

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

- 44 1. Symptomatic or asymptomatic hypoglycaemia defined as a BM of <4mmol/L
45 (70mg/dL)
- 46 2. Symptomatic or asymptomatic hypotension defined as systolic BP<90mmHg
47

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

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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

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

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

20 **Assignment of interventions**

21 *Sequence generation*

22 Patients will be randomised by an independent researcher not involved in patient
23 recruitment, treatment, or follow-up. A computer-generated sequence will randomise
24 patients 1:1 to either surgery + standard medical care or surgery + intensive goal-directed
25 medical therapy with random block sizes of 4.
26

27 *Concealment mechanism*

28 Randomisation codes will only be released after patients are formally recruited to the trial.
29 The randomisation sequence will be held by a senior project manager not associated
30 directly with this trial and will not be available to any of the research investigators at any
31 time. Participants, staff members, and researchers will be unable to foresee the assignment
32 because of central randomisation. All participant data will be pseudo anonymised (personal
33 information removed and replaced with a coded identifier), and this list will be supplied to
34 the central allocation, which randomly allocates patients to either arm of the study.
35

36 *Blinding*

37 Because of the study's nature, neither study investigators nor patients can be blinded
38 regarding their allocation. All investigators in charge of statistical analysis or analysis of
39 samples (laboratory staff) will be blinded to the patient allocation.
40

41 **Data management**

42
43 In order to assure data quality, several procedures are in place, including missing data,
44 permitted/non-permitted value ranges, and logic checks. Checklists and standard operating
45 procedures were created and routinely used to ensure data are complete and reliable. As
46 this is a multi-centre trial, training will be done centrally at the host institution with
47 members of all sites present and all data collection forms are standardised to ensure
48 homogeneity in data collection and entry. Each member of the study team requires training
49 before study initiation, and roles are delegated and assigned. Each participant will receive a
50 numerical code to ensure confidentiality and tracking. Source documents (paper) will be
51 stored at each site in a secured location, with all documents being stored according to their
52 numerical code and accessible only to the study team.
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11 A dedicated monitor, which has been designated specifically for this protocol, will be
12 responsible for source data verification and the creation of queries and/or data clarification
13 forms for all participants' source documents. This monitor will assure quality assurance and
14 control, and a statistician will be responsible for final data verification and database analysis
15 throughout the study.

16 17 *Retention*

18 We anticipate a 20-25% drop-out rate over the 60-month follow-up period. This was
19 reflected in the power calculation to plan the sample size. To mitigate the effects of losing
20 patients to follow up, trial coordinators will make every possible effort to follow up patients
21 for the entire duration of the study. Strategies using multiple contact methods such as
22 email, mail, telephone calls will be employed to achieve the highest possible level of follow-
23 up.
24

25 26 27 *Participant withdrawals*

28 In the case of a participant deciding to withdraw from the study, they will be asked to
29 provide further monitoring and data collection after their withdrawal. For participants who
30 have been lost to follow up despite attempts to contact them, their data will be imputed.
31

32 33 *Patient and public involvement*

34 Qualitative research specifically examining patients' expectations and experiences of
35 undergoing bariatric surgery as a treatment for T2DM was undertaken. This information was
36 used to help develop the research question, ensuring that patient priorities were reflected
37 in the design of the study as well as the choice of outcome measures. This study also
38 explored patient perceptions of continued medications following surgery to determine
39 whether the proposed intervention would be acceptable to the target population.
40

41 **Statistical methods**

42 All data analysis and statistical methods were advised by a statistician and will be performed
43 on an intention to treat principle (ITT). An overview of the methods of analysis is presented
44 in Table 2. We will compare the proportion of participants achieving the primary outcome
45 between bariatric surgery and goal-directed medical therapy versus bariatric surgery and
46 usual care using an unconditional logistic regression model. Continuous outcomes will be
47 analysed by mixed-effects generalised linear models adjusting for the response variable's
48 baseline version. Missing data will be imputed using several different models, assuming data
49 will be missing at random. Participants' demographic data and clinical characteristics will be
50 analysed using an unpaired Student's T-test for continuous variables, whereas dichotomous
51 variables will be analysed using Fischer's exact test. Data will be expressed as mean +/-SD,
52 median, and IQR or counts (percentage) as appropriate. In any circumstances, variables with
53 asymmetric distributions will be transformed using standard mathematical models
54 (logarithm, square root, etc.). Statistical significance will be set at the 1.7% level (two-sided)
55

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

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10 with the patient and an investigator. Patients will be allowed to ask any questions and
11 clarify any areas of uncertainty. If the patient then decides to participate, they will be given
12 an ICF to sign (also signed by the investigator), after which they are considered a study
13 participant. Assent form and ancillary studies consent are not necessary for the study.
14

15 *Confidentiality*

16 All medical information derived from the study will be confidential, and no third-party
17 access will be allowed. The designated personnel will handle source/data information
18 stored on password-protected computers and in-coded patient notes to protect
19 confidentiality.
20

21 *Declaration of interests*

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

24 The author CIR has received grants from the Science Foundation Ireland, Health Research
25 Board, Irish Research Council, Johnson & Johnson and AnaBio. Personal fees have been
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27 Meyers Squibb and Boehringer-Ingelheim. He is on the advisory board for GI dynamics.
28 The author DJP has received personal fees from NovoNordisk and Johnson & Johnson.
29

30 *Study sponsorship and access to data*

31 Data will be available to authorised investigators only. Third parties may have access to data
32 with express written permission from the lead investigator. However, sponsors will not
33 participate in data analysis, nor will they have access to data, either in full or in part.
34

35 *Ancillary and post-trial care*

36 Participating sites will have insurance policies to cover non-negligent harm associated with
37 the protocol, which covers additional healthcare, compensation, or damages whether
38 awarded voluntarily by the BY PLUS study or by claims pursued through the courts.
39

40 *Dissemination policy*

41 After the trial protocol publication, the investigators plan to publish all the listed endpoints
42 as this RCT is the first trial to compare intensive goal-directed medical therapy combined
43 with bariatric surgery versus bariatric surgery and standard medical care for patients with
44 T2DM and obesity. The results of this trial will be published in peer-reviewed scientific
45 journals and presented at major conferences, regardless of the magnitude or direction of
46 the observed effect.
47

48 *Trial organisation and management*

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

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

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For peer review only

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 SPIRIT reporting guidelines, and cite them as:

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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

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	n/a
8	responsibilities:		collection, management, analysis, and interpretation of data;	
9	sponsor and funder		writing of the report; and the decision to submit the report for	
10			publication, including whether they will have ultimate authority	
11			over any of these activities	
12				
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15	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
16	responsibilities:		centre, steering committee, endpoint adjudication committee,	
17	committees		data management team, and other individuals or groups	
18			overseeing the trial, if applicable (see Item 21a for data	
19			monitoring committee)	
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24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for	3,4
27	rationale		undertaking the trial, including summary of relevant studies	
28			(published and unpublished) examining benefits and harms for	
29			each intervention	
30				
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33	Background and	#6b	Explanation for choice of comparators	3,4
34	rationale: choice of			
35	comparators			
36				
37				
38	Objectives	#7	Specific objectives or hypotheses	4
39				
40				
41	Trial design	#8	Description of trial design including type of trial (eg, parallel	4
42			group, crossover, factorial, single group), allocation ratio, and	
43			framework (eg, superiority, equivalence, non-inferiority,	
44			exploratory)	
45				
46				
47				
48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
52				
53				
54	Study setting	#9	Description of study settings (eg, community clinic, academic	4
55			hospital) and list of countries where data will be collected.	
56			Reference to where list of study sites can be obtained	
57				
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1	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
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6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
7	description			
8				
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10	Interventions:	#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
11	modifications			
12				
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14				
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
16	adherence			
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20	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
21	concomitant care			
22				
23				
24	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
25				
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34	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
35				
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40	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
41				
42				
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45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
46				
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49	Methods: Assignment			
50	of interventions (for			
51	controlled trials)			
52				
53				
54	Allocation: sequence	#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
55	generation			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

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4	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, 9,10
5	concealment		central telephone; sequentially numbered, opaque, sealed
6	mechanism		envelopes), describing any steps to conceal the sequence until
7			interventions are assigned
8			
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10			
11	Allocation:	#16c	Who will generate the allocation sequence, who will enrol 10
12	implementation		participants, and who will assign participants to interventions
13			
14			
15	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial 10
16			participants, care providers, outcome assessors, data analysts),
17			and how
18			
19			
20	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is n/a
21	emergency unblinding		permissible, and procedure for revealing a participant's
22			allocated intervention during the trial
23			
24			
25	Methods: Data		
26	collection,		
27	management, and		
28	analysis		
29			
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32	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and 10
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
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43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, 10
44	retention		including list of any outcome data to be collected for
45			participants who discontinue or deviate from intervention
46			protocols
47			
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50	Data management	#19	Plans for data entry, coding, security, and storage, including any 10
51			related processes to promote data quality (eg, double data entry;
52			range checks for data values). Reference to where details of data
53			management procedures can be found, if not in the protocol
54			
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1	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	11
2			outcomes. Reference to where other details of the statistical	
3			analysis plan can be found, if not in the protocol	
4				
5				
6	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	13
7	analyses		analyses)	
8				
9				
10	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	13
11	population and missing		adherence (eg, as randomised analysis), and any statistical	
12	data		methods to handle missing data (eg, multiple imputation)	
13				
14				
15	Methods: Monitoring			
16				
17	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	14
18	formal committee		its role and reporting structure; statement of whether it is	
19			independent from the sponsor and competing interests; and	
20			reference to where further details about its charter can be found,	
21			if not in the protocol. Alternatively, an explanation of why a	
22			DMC is not needed	
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27	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	n/a
28	interim analysis		including who will have access to these interim results and	
29			make the final decision to terminate the trial	
30				
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33	Harms	#22	Plans for collecting, assessing, reporting, and managing	14
34			solicited and spontaneously reported adverse events and other	
35			unintended effects of trial interventions or trial conduct	
36				
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38	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	14
39			whether the process will be independent from investigators and	
40			the sponsor	
41				
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43	Ethics and			
44	dissemination			
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47	Research ethics	#24	Plans for seeking research ethics committee / institutional	15
48	approval		review board (REC / IRB) approval	
49				
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51	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	14
52			changes to eligibility criteria, outcomes, analyses) to relevant	
53			parties (eg, investigators, REC / IRBs, trial participants, trial	
54			registries, journals, regulators)	
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
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5	Consent or assent:	#26b	Additional consent provisions for collection and use of	14
6	ancillary studies		participant data and biological specimens in ancillary studies, if applicable	
7				
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10	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
11				
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15	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
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19	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
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24	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
25				
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28	Dissemination policy:	#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
29	trial results			
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36	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
37	authorship			
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40	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
41	reproducible research			
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44	Appendices			
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46	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	20
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50	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
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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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Manuscript ID	bmjopen-2021-054313.R2
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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

SCHOLARONE™
Manuscripts

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3 Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study:
4 rationale and design of a randomised controlled study
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8 Key words: obesity, type 2 diabetes mellitus, bariatric surgery, sleeve gastrectomy, roux en y
9 gastric bypass
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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

1
2
3 effective. Over a 13.3 year follow-up period, the STENO-2 trial showed a 20% absolute risk
4 reduction in death and a 13% reduction in death due to cardiovascular endpoints with
5 intensive, goal-directed medical therapy compared to conventional therapy[21].
6
7

8 Evidence would support improved glycaemic control due to the powerful metabolic changes
9 evoked by bariatric surgery; however, the effects tend to attenuate with time, and a
10 proportion of patients will ultimately experience a relapse of diabetes[22]. What remains to
11 be seen is whether a multimodal approach with surgery and goal-directed medical therapy
12 can be safely utilised to improve diabetes control[23, 24].
13
14

15 **Objectives**

16 This study aims to investigate the long-term safety and efficacy of combining bariatric
17 surgery (Roux-en-Y gastric bypass-RYGB or Sleeve gastrectomy- SG) with goal-directed
18 medical therapy versus bariatric surgery and usual medical care on the glycaemic control
19 and the ADA triple endpoint as a marker of good diabetes control and reflected in measures
20 for HbA1c, BP and lipids.
21
22

23 **Trial design**

24 The BY PLUS study is a multi-center, open-label randomised controlled trial. The trial will
25 involve two arms with an allocation ratio of 1:1. There are two primary endpoints:
26
27

- 28 1. the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) over a follow
29 up of one year
- 30 2. the proportion of patients in each arm reaching the composite endpoint of HbA1c<6.5%
31 (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/l over a follow-up period of five years.
32
33

34
35 Patient recruitment was commenced in August 2020. The trial was registered on
36 ClinicalTrials.gov (NCT04432025). A planned interim analysis will also be carried out at a
37 prespecified follow-up period of 12 months and then yearly until trial conclusion at five
38 years (60 months follow up).
39
40

41 Several strategies, such as the use of checklists and workflow, have been employed to
42 guarantee the data's quality and completeness. A dedicated monitor will audit the overall
43 quality and completeness of the data entered on the electronic case report form, examine
44 source documents, and compliance of the team with Good Clinical Practice.
45
46

47 The full SPIRIT checklist can be found in appendix 1.
48
49

50 **Methods**

51 *Study setting*

52 The study will be undertaken in tertiary care centres with expertise in bariatric surgery and
53 the treatment of obesity and T2DM.
54
55

56 *Eligibility criteria*

57 Inclusion criteria

- 58 • ≥18 years old
- 59 • Eligible for bariatric surgery as per NICE CG189 or IFSO guidelines
60

- Diagnosis of type 2 diabetes mellitus based on an HbA1c of 48mmol/mol or 6.5%
- Body mass index (BMI) > 30kg/m²

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 jejunojunction. 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

1
2
3 and yearly thereafter. Magnesium, chromium and fat soluble vitamins will not be routinely
4 checked.
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8 *Drug titration and safety monitoring*

9 For patients in the surgery plus intensive medical treatment arm, follow-up regarding
10 medications in the postoperative period will be coordinated through clinic. Metformin will
11 be continued, but doses may be reduced if HbA1c is <6% (42 mmol/mol) or discontinued if
12 there are recorded hypoglycaemic episodes or severe gastrointestinal side-effects. The
13 parameters for full withdrawal of medications for glycaemic control are an HbA1c<6%
14 (42mmol/mol) and fasting glucose of 5.5 mmol/L (100mg/dl). Medications for blood
15 pressure control, ACEi, and ARB as well as statins for lipid control will be continued, but
16 doses may be reduced to avoid side effects. At subsequent follow-up visits, patients in this
17 cohort will have their HbA1c, BP, and LDL checked with the results used to guide titration of
18 doses towards the prespecified treatment thresholds HbA1c<6.5% (48mmol/mol),
19 BP<130/80mmHg and LDL<2.6mmol/l.
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25 Outcomes

26 The primary outcomes are:

- 27 1. The proportion of patients in each arm who achieve an HbA1c<6.5% (48mmol/mol) at
28 one year
- 29 2. The proportion of patients in each arm who reach the composite endpoint for good
30 diabetes control as outlined by the American Diabetes Association (ADA), which is an
31 HbA1c<6.5% (48mmol/mol), BP<130/80mmHg and LDL<2.6mmol/l at five years.
32
33
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35 Secondary outcomes

36 The secondary outcomes are change from baseline to 5 years for each endpoint, temporal
37 changes, mean levels, and peak levels will be analysed as appropriate: body weight, BMI,
38 waist circumference, plasma lipid concentration, plasma liver function tests, urinary
39 creatinine: albumin ratio, inflammatory markers including CRP, Multidimensional Health
40 Profile: Health Functioning questionnaire score (MHP-H), Social Functioning Questionnaire
41 score (SFQ) and the number of medications.
42
43
44

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

- 48 1. Symptomatic or asymptomatic hypoglycaemia defined as a BM of <4mmol/L
49 (70mg/dL)
- 50 2. Symptomatic or asymptomatic hypotension defined as systolic BP<90mmHg
51
52

53 Symptoms of either hypoglycaemia or hypotension will be discussed with patients and they
54 will be instructed to contact the study coordinators to arrange clinic review for titration of
55 medication as necessary.
56
57
58

59 Participant timeline

60

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

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3 differences between the groups at α of 0.05, we would need 55 patients per arm. We will
4 recruit 75 patients in each group to account for a possible 20-25% drop-out rate.
5
6
7

8 **Recruitment strategy**

9 All patients presenting to the obesity clinic within the participating centres who are due to
10 undergo RYGB or SG and meet the eligibility criteria will be given written and verbal
11 information regarding participation in the study. After a minimum period of 24 hours to
12 consider the information, patients can indicate whether they are willing to participate and
13 will be asked to provide written consent.
14
15

16 **Assignment of interventions**

17 *Sequence generation*

18 Patients will be randomised by an independent researcher not involved in patient
19 recruitment, treatment, or follow-up. A computer-generated sequence will randomise
20 patients 1:1 to either surgery + standard medical care or surgery + intensive goal-directed
21 medical therapy with random block sizes of 4.
22
23
24

25 *Concealment mechanism*

26 Randomisation codes will only be released after patients are formally recruited to the trial.
27 The randomisation sequence will be held by a senior project manager not associated
28 directly with this trial and will not be available to any of the research investigators at any
29 time. Participants, staff members, and researchers will be unable to foresee the assignment
30 because of central randomisation. All participant data will be pseudo anonymised (personal
31 information removed and replaced with a coded identifier), and this list will be supplied to
32 the central allocation, which randomly allocates patients to either arm of the study.
33
34
35
36
37

38 *Blinding*

39 Because of the study's nature, neither study investigators nor patients can be blinded
40 regarding their allocation. All investigators in charge of statistical analysis or analysis of
41 samples (laboratory staff) will be blinded to the patient allocation.
42
43
44

45 **Data management**

46
47 In order to assure data quality, several procedures are in place, including missing data,
48 permitted/non-permitted value ranges, and logic checks. Checklists and standard operating
49 procedures were created and routinely used to ensure data are complete and reliable. As
50 this is a multi-centre trial, training will be done centrally at the host institution with
51 members of all sites present and all data collection forms are standardised to ensure
52 homogeneity in data collection and entry. Each member of the study team requires training
53 before study initiation, and roles are delegated and assigned. Each participant will receive a
54 numerical code to ensure confidentiality and tracking. Source documents (paper) will be
55 stored at each site in a secured location, with all documents being stored according to their
56 numerical code and accessible only to the study team.
57
58
59
60

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4 A dedicated monitor, which has been designated specifically for this protocol, will be
5 responsible for source data verification and the creation of queries and/or data clarification
6 forms for all participants' source documents. This monitor will assure quality assurance and
7 control, and a statistician will be responsible for final data verification and database analysis
8 throughout the study.
9
10

11 12 13 *Retention*

14 We anticipate a 20-25% drop-out rate over the 60-month follow-up period. This was
15 reflected in the power calculation to plan the sample size. To mitigate the effects of losing
16 patients to follow up, trial coordinators will make every possible effort to follow up patients
17 for the entire duration of the study. Strategies using multiple contact methods such as
18 email, mail, telephone calls will be employed to achieve the highest possible level of follow-
19 up.
20
21
22
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26 *Participant withdrawals*

27 In the case of a participant deciding to withdraw from the study, they will be asked to
28 provide further monitoring and data collection after their withdrawal. For participants who
29 have been lost to follow up despite attempts to contact them, their data will be imputed.
30
31
32
33

34 *Patient and public involvement*

35 Qualitative research specifically examining patients' expectations and experiences of
36 undergoing bariatric surgery as a treatment for T2DM was undertaken. This information was
37 used to help develop the research question, ensuring that patient priorities were reflected
38 in the design of the study as well as the choice of outcome measures. This study also
39 explored patient perceptions of continued medications following surgery to determine
40 whether the proposed intervention would be acceptable to the target population.
41
42
43

44 **Statistical methods**

45 All data analysis and statistical methods were advised by a statistician and will be performed
46 on an intention to treat principle (ITT). An overview of the methods of analysis is presented
47 in Table 2. We will compare the proportion of participants achieving the primary outcome
48 between bariatric surgery and goal-directed medical therapy versus bariatric surgery and
49 usual care using an unconditional logistic regression model. Continuous outcomes will be
50 analysed by mixed-effects generalised linear models adjusting for the response variable's
51 baseline version. Missing data will be imputed using several different models, assuming data
52 will be missing at random. Participants' demographic data and clinical characteristics will be
53 analysed using an unpaired Student's T-test for continuous variables, whereas dichotomous
54 variables will be analysed using Fischer's exact test. Data will be expressed as mean +/-SD,
55 median, and IQR or counts (percentage) as appropriate. In any circumstances, variables with
56 asymmetric distributions will be transformed using standard mathematical models
57 (logarithm, square root, etc.). Statistical significance will be set at the 1.7% level (two-sided)
58
59
60

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

1
2
3 sampling variability. A burn-in period of 500 iterations will be used. Imputation will be
4 performed in Stata V.14.0 (StataCorp, College Station, Texas, USA).
5
6

7 **Monitoring**

8 *Adverse events*

9 An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical
10 study subject even if it did not directly relate to the medical or surgical intervention. Serious
11 adverse events were defined as any untoward and unexpected medical occurrence or effect
12 that:
13

- 14 • **Results in death**
- 15 • **Is life-threatening** – refers to an event in which the subject was at risk of death at the
16 time of the event; it does not refer to an event that hypothetically might have caused
17 death if it were more severe
- 18 • **Requires hospitalisation, or prolongation of existing inpatient hospitalisation**
- 19 • **Results in persistent or significant disability or incapacity**
20

21 All AE or SAE are required to be reported within 24h with detailed documentation to the research
22 and ethics committee.
23
24

25 **Auditing**

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

39 *Research ethics approval*

40 Protocol, ICF, and recruitment materials were reviewed and approved by the study sites'
41 local research and ethics committee. Approval was received within Ireland on the 11th of
42 February 2020 and on the 2nd of December 2020 within the UK. All sites will report back
43 regarding study progress regularly.
44
45

46 *Protocol amendments*

47 All changes needed after initial approval will be re-submitted to the research and ethics
48 committee for review. Amendments to the clinical protocol will require formal review,
49 accompanied by an updated, informed consent signed by both the investigators and
50 participants. If any changes are made to the protocol, the history will be available and
51 tracked by version and date changes.
52
53

54 *Consent*

55 Patients identified as potential participants will receive verbal and written information from
56 an investigator (medical doctor). A copy of the study materials and ICF will be given, and
57 patients allowed an opportunity to review and discuss with family/friends. After being given
58 a minimum of 24 hours to consider the materials, a formal discussion will be carried out
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3 with the patient and an investigator. Patients will be allowed to ask any questions and
4 clarify any areas of uncertainty. If the patient then decides to participate, they will be given
5 an ICF to sign (also signed by the investigator), after which they are considered a study
6 participant. Assent form and ancillary studies consent are not necessary for the study.
7
8

9 *Confidentiality*

10 All medical information derived from the study will be confidential, and no third-party
11 access will be allowed. The designated personnel will handle source/data information
12 stored on password-protected computers and in-coded patient notes to protect
13 confidentiality.
14
15

16 *Declaration of interests*

17 The author RC has received an honorarium as a member of the Speaker's panel of Johnson
18 & Johnson.
19

20 The author CIR has received grants from the Science Foundation Ireland, Health Research
21 Board, Irish Research Council, Johnson & Johnson and AnaBio. Personal fees have been
22 received from Eli Lilly, Johnson & Johnson, Sanofi Aventis, Astra Zeneca, Janssen, Bristol-
23 Meyers Squibb and Boehringer-Ingelheim. He is on the advisory board for GI dynamics.
24 The author DJP has received personal fees from NovoNordisk and Johnson & Johnson.
25
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28

29 *Study sponsorship and access to data*

30 Data will be available to authorised investigators only. Third parties may have access to data
31 with express written permission from the lead investigator. However, sponsors will not
32 participate in data analysis, nor will they have access to data, either in full or in part.
33
34

35 *Ancillary and post-trial care*

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

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

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

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

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For peer review only

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 SPIRIT reporting guidelines, and cite them as:

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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

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
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6				
7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	n/a
8	responsibilities:		collection, management, analysis, and interpretation of data;	
9	sponsor and funder		writing of the report; and the decision to submit the report for	
10			publication, including whether they will have ultimate authority	
11			over any of these activities	
12				
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15	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
16	responsibilities:		centre, steering committee, endpoint adjudication committee,	
17	committees		data management team, and other individuals or groups	
18			overseeing the trial, if applicable (see Item 21a for data	
19			monitoring committee)	
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24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for	3,4
27	rationale		undertaking the trial, including summary of relevant studies	
28			(published and unpublished) examining benefits and harms for	
29			each intervention	
30				
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33	Background and	#6b	Explanation for choice of comparators	3,4
34	rationale: choice of			
35	comparators			
36				
37				
38	Objectives	#7	Specific objectives or hypotheses	4
39				
40				
41	Trial design	#8	Description of trial design including type of trial (eg, parallel	4
42			group, crossover, factorial, single group), allocation ratio, and	
43			framework (eg, superiority, equivalence, non-inferiority,	
44			exploratory)	
45				
46				
47				
48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
52				
53				
54	Study setting	#9	Description of study settings (eg, community clinic, academic	4
55			hospital) and list of countries where data will be collected.	
56			Reference to where list of study sites can be obtained	
57				
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1	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
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6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
7	description			
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10	Interventions:	#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
11	modifications			
12				
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14				
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
16	adherence			
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20	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
21	concomitant care			
22				
23				
24	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
25				
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34	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
35				
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40	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
41				
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45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
46				
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49	Methods: Assignment			
50	of interventions (for			
51	controlled trials)			
52				
53				
54	Allocation: sequence	#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
55	generation			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

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4	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, 9,10
5	concealment		central telephone; sequentially numbered, opaque, sealed
6	mechanism		envelopes), describing any steps to conceal the sequence until
7			interventions are assigned
8			
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10			
11	Allocation:	#16c	Who will generate the allocation sequence, who will enrol 10
12	implementation		participants, and who will assign participants to interventions
13			
14			
15	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial 10
16			participants, care providers, outcome assessors, data analysts),
17			and how
18			
19			
20	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is n/a
21	emergency unblinding		permissible, and procedure for revealing a participant's
22			allocated intervention during the trial
23			
24			
25	Methods: Data		
26	collection,		
27	management, and		
28	analysis		
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32	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and 10
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
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43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, 10
44	retention		including list of any outcome data to be collected for
45			participants who discontinue or deviate from intervention
46			protocols
47			
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50	Data management	#19	Plans for data entry, coding, security, and storage, including any 10
51			related processes to promote data quality (eg, double data entry;
52			range checks for data values). Reference to where details of data
53			management procedures can be found, if not in the protocol
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1	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	11
2			outcomes. Reference to where other details of the statistical	
3			analysis plan can be found, if not in the protocol	
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6	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	13
7	analyses		analyses)	
8				
9				
10	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	13
11	population and missing		adherence (eg, as randomised analysis), and any statistical	
12	data		methods to handle missing data (eg, multiple imputation)	
13				
14				
15	Methods: Monitoring			
16				
17	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	14
18	formal committee		its role and reporting structure; statement of whether it is	
19			independent from the sponsor and competing interests; and	
20			reference to where further details about its charter can be found,	
21			if not in the protocol. Alternatively, an explanation of why a	
22			DMC is not needed	
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27	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	n/a
28	interim analysis		including who will have access to these interim results and	
29			make the final decision to terminate the trial	
30				
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33	Harms	#22	Plans for collecting, assessing, reporting, and managing	14
34			solicited and spontaneously reported adverse events and other	
35			unintended effects of trial interventions or trial conduct	
36				
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38	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	14
39			whether the process will be independent from investigators and	
40			the sponsor	
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43	Ethics and			
44	dissemination			
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47	Research ethics	#24	Plans for seeking research ethics committee / institutional	15
48	approval		review board (REC / IRB) approval	
49				
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51	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	14
52			changes to eligibility criteria, outcomes, analyses) to relevant	
53			parties (eg, investigators, REC / IRBs, trial participants, trial	
54			registries, journals, regulators)	
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
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5	Consent or assent:	#26b	Additional consent provisions for collection and use of	14
6	ancillary studies		participant data and biological specimens in ancillary studies, if applicable	
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10	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
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15	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
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19	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
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24	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
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28	Dissemination policy:	#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
29	trial results			
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36	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
37	authorship			
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40	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
41	reproducible research			
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44	Appendices			
45				
46	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	20
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50	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
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054313.R3
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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

SCHOLARONE™
Manuscripts

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3 Medication following bariatric surgery for type 2 diabetes mellitus (BY-PLUS) study:
4 rationale and design of a randomised controlled study
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8 Key words: obesity, type 2 diabetes mellitus, bariatric surgery, sleeve gastrectomy, roux en y
9 gastric bypass
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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

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3 reduction in death and a 13% reduction in death due to cardiovascular endpoints with
4 intensive, goal-directed medical therapy compared to conventional therapy[21].
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7 Evidence would support improved glycaemic control due to the powerful metabolic changes
8 evoked by bariatric surgery; however, the effects tend to attenuate with time, and a
9 proportion of patients will ultimately experience a relapse of diabetes[22]. What remains to
10 be seen is whether a multimodal approach with surgery and goal-directed medical therapy
11 can be safely utilised to improve diabetes control[23, 24].
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14 **Objectives**

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

24 The BY PLUS study is a multi-center, open-label randomised controlled trial. The trial will
25 involve two arms with an allocation ratio of 1:1. There are two primary endpoints:
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- 28 1. the proportion of patients in each arm with an HbA1c<6.5% (48mmol/mol) over a follow
29 up of one year
- 30 2. the proportion of patients in each arm reaching the composite endpoint of HbA1c<6.5%
31 (48mmol/mol), BP<130/80mmHg, and LDL<2.6mmol/l over a follow-up period of five years.
32
33

34 Patient recruitment was commenced in August 2020. The trial was registered on
35 ClinicalTrials.gov (NCT04432025). A planned interim analysis will also be carried out at a
36 prespecified follow-up period of 12 months and then yearly until trial conclusion at five
37 years (60 months follow up).
38
39

40 Several strategies, such as the use of checklists and workflow, have been employed to
41 guarantee the data's quality and completeness. A dedicated monitor will audit the overall
42 quality and completeness of the data entered on the electronic case report form, examine
43 source documents, and compliance of the team with Good Clinical Practice.
44
45

46 The full SPIRIT checklist can be found in appendix 1.
47
48

49 **Methods**

50 *Study setting*

51 The study will be undertaken in tertiary care centres with expertise in bariatric surgery and
52 the treatment of obesity and T2DM.
53
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55 *Eligibility criteria*

56 Inclusion criteria

- 57 • ≥18 years old
- 58 • Eligible for bariatric surgery as per NICE CG189 or IFSO guidelines
- 59 • Diagnosis of type 2 diabetes mellitus based on an HbA1c of 48mmol/mol or 6.5%
60

- Body mass index (BMI) > 30kg/m²

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 jejunojunction. 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 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

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3 and yearly thereafter. Magnesium, chromium and fat soluble vitamins will not be routinely
4 checked.
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8 *Drug titration and safety monitoring*

9 For patients in the surgery plus intensive medical treatment arm, follow-up regarding
10 medications in the postoperative period will be coordinated through clinic. Metformin will
11 be continued, but doses may be reduced if HbA1c is <6% (42 mmol/mol) or discontinued if
12 there are recorded hypoglycaemic episodes or severe gastrointestinal side-effects. The
13 parameters for full withdrawal of medications for glycaemic control are an HbA1c<6%
14 (42mmol/mol) and fasting glucose of 5.5 mmol/L (100mg/dl). Medications for blood
15 pressure control, ACEi, and ARB as well as statins for lipid control will be continued, but
16 doses may be reduced to avoid side effects. At subsequent follow-up visits, patients in this
17 cohort will have their HbA1c, BP, and LDL checked with the results used to guide titration of
18 doses towards the prespecified treatment thresholds HbA1c<6.5% (48mmol/mol),
19 BP<130/80mmHg and LDL<2.6mmol/l.
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25 Outcomes

26 The primary outcomes are:

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

36 The secondary outcomes are change from baseline to 5 years for each endpoint, temporal
37 changes, mean levels, and peak levels will be analysed as appropriate: body weight, BMI,
38 waist circumference, plasma lipid concentration, plasma liver function tests, urinary
39 creatinine: albumin ratio, inflammatory markers including CRP, Multidimensional Health
40 Profile: Health Functioning questionnaire score (MHP-H), Social Functioning Questionnaire
41 score (SFQ) and the number of medications.
42
43
44

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

- 48 1. Symptomatic or asymptomatic hypoglycaemia defined as a BM of <4mmol/L
49 (70mg/dL)
- 50 2. Symptomatic or asymptomatic hypotension defined as systolic BP<90mmHg
51
52

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

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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

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

9 All patients presenting to the obesity clinic within the participating centres who are due to
10 undergo RYGB or SG and meet the eligibility criteria will be given written and verbal
11 information regarding participation in the study. After a minimum period of 24 hours to
12 consider the information, patients can indicate whether they are willing to participate and
13 will be asked to provide written consent.
14
15

16 **Assignment of interventions**

17 *Sequence generation*

18 Patients will be randomised by an independent researcher not involved in patient
19 recruitment, treatment, or follow-up. A computer-generated sequence will randomise
20 patients 1:1 to either surgery + standard medical care or surgery + intensive goal-directed
21 medical therapy with random block sizes of 4.
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23
24

25 *Concealment mechanism*

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

39 Because of the study's nature, neither study investigators nor patients can be blinded
40 regarding their allocation. All investigators in charge of statistical analysis or analysis of
41 samples (laboratory staff) will be blinded to the patient allocation.
42
43
44

45 **Data management**

46
47 In order to assure data quality, several procedures are in place, including missing data,
48 permitted/non-permitted value ranges, and logic checks. Checklists and standard operating
49 procedures were created and routinely used to ensure data are complete and reliable. As
50 this is a multi-centre trial, training will be done centrally at the host institution with
51 members of all sites present and all data collection forms are standardised to ensure
52 homogeneity in data collection and entry. Each member of the study team requires training
53 before study initiation, and roles are delegated and assigned. Each participant will receive a
54 numerical code to ensure confidentiality and tracking. Source documents (paper) will be
55 stored at each site in a secured location, with all documents being stored according to their
56 numerical code and accessible only to the study team.
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4 A dedicated monitor, which has been designated specifically for this protocol, will be
5 responsible for source data verification and the creation of queries and/or data clarification
6 forms for all participants' source documents. This monitor will assure quality assurance and
7 control, and a statistician will be responsible for final data verification and database analysis
8 throughout the study.
9
10

11 12 13 *Retention*

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

27 In the case of a participant deciding to withdraw from the study, they will be asked to
28 provide further monitoring and data collection after their withdrawal. For participants who
29 have been lost to follow up despite attempts to contact them, their data will be imputed.
30
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33

34 *Patient and public involvement*

35 Qualitative research specifically examining patients' expectations and experiences of
36 undergoing bariatric surgery as a treatment for T2DM was undertaken. This information was
37 used to help develop the research question, ensuring that patient priorities were reflected
38 in the design of the study as well as the choice of outcome measures. This study also
39 explored patient perceptions of continued medications following surgery to determine
40 whether the proposed intervention would be acceptable to the target population.
41
42
43

44 **Statistical methods**

45 All data analysis and statistical methods were advised by a statistician and will be performed
46 on an intention to treat principle (ITT). An overview of the methods of analysis is presented
47 in Table 2. We will compare the proportion of participants achieving the primary outcome
48 between bariatric surgery and goal-directed medical therapy versus bariatric surgery and
49 usual care using an unconditional logistic regression model. Continuous outcomes will be
50 analysed by mixed-effects generalised linear models adjusting for the response variable's
51 baseline version. Missing data will be imputed using several different models, assuming data
52 will be missing at random. Participants' demographic data and clinical characteristics will be
53 analysed using an unpaired Student's T-test for continuous variables, whereas dichotomous
54 variables will be analysed using Fischer's exact test. Data will be expressed as mean +/-SD,
55 median, and IQR or counts (percentage) as appropriate. In any circumstances, variables with
56 asymmetric distributions will be transformed using standard mathematical models
57 (logarithm, square root, etc.). Statistical significance will be set at the 1.7% level (two-sided)
58
59
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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

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2
3 patients allowed an opportunity to review and discuss with family/friends. After being given
4 a minimum of 24 hours to consider the materials, a formal discussion will be carried out
5 with the patient and an investigator. Patients will be allowed to ask any questions and
6 clarify any areas of uncertainty. If the patient then decides to participate, they will be given
7 an ICF to sign (also signed by the investigator), after which they are considered a study
8 participant. Assent form and ancillary studies consent are not necessary for the study.
9
10

11 *Confidentiality*

12 All medical information derived from the study will be confidential, and no third-party
13 access will be allowed. The designated personnel will handle source/data information
14 stored on password-protected computers and in-coded patient notes to protect
15 confidentiality.
16
17

18 *Declaration of interests*

19 The author RC has received an honorarium as a member of the Speaker's panel of Johnson
20 & Johnson.
21

22 The author CIR has received grants from the Science Foundation Ireland, Health Research
23 Board, Irish Research Council, Johnson & Johnson and AnaBio. Personal fees have been
24 received from Eli Lilly, Johnson & Johnson, Sanofi Aventis, Astra Zeneca, Janssen, Bristol-
25 Meyers Squibb and Boehringer-Ingelheim. He is on the advisory board for GI dynamics.
26 The author DJP has received personal fees from NovoNordisk and Johnson & Johnson.
27
28
29

30 *Study sponsorship and access to data*

31 Data will be available to authorised investigators only. Third parties may have access to data
32 with express written permission from the lead investigator. However, sponsors will not
33 participate in data analysis, nor will they have access to data, either in full or in part.
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37 *Ancillary and post-trial care*

38 Participating sites will have insurance policies to cover non-negligent harm associated with
39 the protocol, which covers additional healthcare, compensation, or damages whether
40 awarded voluntarily by the BY PLUS study or by claims pursued through the courts.
41
42

43 *Dissemination policy*

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

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

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

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3 BMJ Open Supporting Information
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6 Ethics and Dissemination
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8 London Fulham Research Ethics Committee- Rev Nigel Griffin (chairperson) , Ms Diana
9 Barham, Mr Keith Berelowitz, Ms Mabel Cortes, Mr Frank Cross, Professor John Dark, Dr Jan
10 Downer, Dr Peter Richard Hayes, Miss Kate Hazelhurst, Mr Greg Kyle-Langley, Mrs Deborah
11 Morgan, Miss Hayley Noble, Dr Phillipa Jane Rollins, Mr David Parr, Ms Catriona Stirling, Ms
12 Gemma Warren
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15 St Vincent's University Hospital Ethics Committee- Professor Ronan Killeen, Professor
16 Alastair Nichol, Dr Marcus Butler, Dr Eleanor Dunican, Professor Cormac McCarthy,
17 Professor Aurelie Fabre, Ms Jackie McCavana, Professor Chris McGuigan, Dr Susan Brannick,
18 Dr David Murphy, Dr Keith Smart, Mr S Guan Khoo, Ms Martina Fitzpatrick, Mr Paul Tighe,
19 Dr Marie Galligan, Professor Walter Cullen. Lay Committee- Mr Mark Daly, Mr Dermot
20 Cullinan, Mr Sean Gibney, Mr Donal Kelly, Mr Peter Brady
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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 SPIRIT reporting 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

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7	Roles and	#5c	Role of study sponsor and funders, if any, in study	n/a
8	responsibilities:		design; collection, management, analysis, and	
9	sponsor and funder		interpretation of data; writing of the report; and the	
10			decision to submit the report for publication, including	
11			whether they will have ultimate authority over any of	
12			these activities	
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17	Roles and	#5d	Composition, roles, and responsibilities of the	n/a
18	responsibilities:		coordinating centre, steering committee, endpoint	
19	committees		adjudication committee, data management team, and	
20			other individuals or groups overseeing the trial, if	
21			applicable (see Item 21a for data monitoring committee)	
22				
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24				
25				
26	Introduction			
27				
28	Background and	#6a	Description of research question and justification for	3,4
29	rationale		undertaking the trial, including summary of relevant	
30			studies (published and unpublished) examining benefits	
31			and harms for each intervention	
32				
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35	Background and	#6b	Explanation for choice of comparators	3,4
36	rationale: choice of			
37	comparators			
38				
39				
40	Objectives	#7	Specific objectives or hypotheses	4
41				
42				
43	Trial design	#8	Description of trial design including type of trial (eg,	4
44			parallel group, crossover, factorial, single group),	
45			allocation ratio, and framework (eg, superiority,	
46			equivalence, non-inferiority, exploratory)	
47				
48				
49	Methods:			
50	Participants,			
51	interventions, and			
52	outcomes			
53				
54				
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56	Study setting	#9	Description of study settings (eg, community clinic,	4
57			academic hospital) and list of countries where data will	
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be collected. Reference to where list of study sites can be obtained

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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)
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
12	description		
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15			
16	Interventions:	#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)
17	modifications		
18			
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23	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)
24	adherence		
25			
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27			
28	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
29	concomitant care		
30			
31			
32	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
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43	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)
44			
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50	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
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57	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size
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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
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Reference to where data collection forms can be found, if not in the protocol

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4	Data collection plan:	#18b	Plans to promote participant retention and complete
5	retention		follow-up, including list of any outcome data to be
6			collected for participants who discontinue or deviate
7			from intervention protocols
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11	Data management	#19	Plans for data entry, coding, security, and storage,
12			including any related processes to promote data quality
13			(eg, double data entry; range checks for data values).
14			Reference to where details of data management
15			procedures can be found, if not in the protocol
16			
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19	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary
20			outcomes. Reference to where other details of the
21			statistical analysis plan can be found, if not in the
22			protocol
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26	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and
27	analyses		adjusted analyses)
28			
29			
30	Statistics: analysis	#20c	Definition of analysis population relating to protocol
31	population and		non-adherence (eg, as randomised analysis), and any
32	missing data		statistical methods to handle missing data (eg, multiple
33			imputation)
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36	Methods: Monitoring		
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39	Data monitoring:	#21a	Composition of data monitoring committee (DMC);
40	formal committee		summary of its role and reporting structure; statement
41			of whether it is independent from the sponsor and
42			competing interests; and reference to where further
43			details about its charter can be found, if not in the
44			protocol. Alternatively, an explanation of why a DMC is
45			not needed
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50	Data monitoring:	#21b	Description of any interim analyses and stopping
51	interim analysis		guidelines, including who will have access to these
52			interim results and make the final decision to terminate
53			the trial
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57	Harms	#22	Plans for collecting, assessing, reporting, and managing
58			solicited and spontaneously reported adverse events
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1		and other unintended effects of trial interventions or trial	
2		conduct	
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4	Auditing	#23 Frequency and procedures for auditing trial conduct, if	14
5		any, and whether the process will be independent from	
6		investigators and the sponsor	
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9	Ethics and		
10	dissemination		
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13	Research ethics	#24 Plans for seeking research ethics committee /	15
14	approval	institutional review board (REC / IRB) approval	
15			
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17	Protocol amendments	#25 Plans for communicating important protocol	14
18		modifications (eg, changes to eligibility criteria,	
19		outcomes, analyses) to relevant parties (eg,	
20		investigators, REC / IRBs, trial participants, trial	
21		registries, journals, regulators)	
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25	Consent or assent	#26a Who will obtain informed consent or assent from	15
26		potential trial participants or authorised surrogates, and	
27		how (see Item 32)	
28			
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30	Consent or assent:	#26b Additional consent provisions for collection and use of	14
31	ancillary studies	participant data and biological specimens in ancillary	
32		studies, if applicable	
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36	Confidentiality	#27 How personal information about potential and enrolled	15
37		participants will be collected, shared, and maintained in	
38		order to protect confidentiality before, during, and after	
39		the trial	
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43	Declaration of	#28 Financial and other competing interests for principal	15
44	interests	investigators for the overall trial and each study site	
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47	Data access	#29 Statement of who will have access to the final trial	16
48		dataset, and disclosure of contractual agreements that	
49		limit such access for investigators	
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52	Ancillary and post trial	#30 Provisions, if any, for ancillary and post-trial care, and	15
53	care	for compensation to those who suffer harm from trial	
54		participation	
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57	Dissemination policy:	#31a Plans for investigators and sponsor to communicate	15
58	trial results	trial results to participants, healthcare professionals, the	
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public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of professional writers n/a

Dissemination policy: [#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

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