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Title page

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Sleeve gastrectomy versus Roux-en-Y gastric bypass for type 2 diabetes and morbid obesity: double-blind randomized clinical trial protocol

Authors:

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Running title: Sleeve gastrectomy vs Roux-en-Y gastric bypass

Abstract:

Introduction: Type 2 diabetes (T2D) in association with obesity is an increasing disease burden. Bariatric surgery is the only effective therapy for achieving remission of T2D among those with morbid obesity. It is unclear which of the two most commonly performed types of bariatric surgery: laparoscopic sleeve gastrectomy (LSG) or laparoscopic Roux-en-Y gastric bypass (LRYGB), is most effective for obese patients for T2D. The primary objective of this study is to determine whether LSG or LRYGB is more effective in achieving HbA1c < 6% (<42mmol/mol) without the use of diabetes medication at 5 years.

Methods and Analysis: Single-centre, double-blind (assessor and patient), parallel, randomized, clinical trial (RCT) being conducted in New Zealand, targeting 106 patients. Eligibility criteria include age 20-55 years, T2D of at least 6 months duration and BMI 35-65kg/m^2 for at least 5 years. Randomization 1:1 to LSG or LRYGB, is using random number codes disclosed to the operating surgeon after induction of anesthesia. A standard medication adjustment schedule will be used during post-operative metabolic assessments. Secondary outcomes include proportions achieving HbA1c <5.7% (39mmol/mol) or <6.5% (48mmol/mol) without the use of diabetes medication, comparative weight loss, obesity related comorbidity, operative complications, revision rate, mortality, quality of life, anxiety and depression scores. Exploratory outcomes include changes in satiety, gut hormone and gut microbiota to gain underlying mechanistic insights into T2D remission.

Ethics and Dissemination: Ethics approval was obtained from the New Zealand regional ethics committee (NZ93405) who also provided independent safety monitoring of the trial. Study commenced in September 2011. Recruitment

completed in October 2014. Data collection is ongoing. Results will be reported in manuscripts submitted to peer-reviewed journals and presentations at national and international meetings.

Trial registration number: this study was prospectively registered at ANZCTR (ACTRN12611000751976) and retrospectively registered at clinicaltrials.gov (NCT01486680).

Article summary:

Strengths and limitations:

- There is limited evidence from randomized clinical trials comparing the efficacy of laparoscopic sleeve gastrectomy (LSG) vs laparoscopic Roux-en-Y gastric bypass (LRYGB), to guide optimum surgery selection for morbidly obese patients with T2D.
- We describe our double-blind, randomized trial designed to compare efficacy of LSG and LRYGB on remission of T2D at 5 years among morbidly obese patients using a standard metabolic medication adjustment protocol after surgery, which should assist clinicians managing patients following bariatric surgery and researchers planning future bariatric surgery trials, given the thresholds for discontinuing blood pressure, glucose and lipid medications post-operatively is frequently not reported.
- Limitations include the single-centre study design and use of silastic-ring type of LRYGB, which may limit generalizability of the findings.

Funding: We acknowledge the funding support from Waitemata District Health Board, which provides limited publically funded bariatric surgery (approximately 100 cases annually). Additional funding for blood sample storage and a research nurse salary was provided by Johnson and Johnson (NZ), Covidien (NZ), and Obex (NZ). DEXA scanning for body composition was provided by the Diabetes Research Fund (NZ), and Maurice & Phyllis Paykel Trust (NZ). Sample collection for the gut microbiota and gut hormone sub-study was funded by a grant from the Maurice Wilkins Centre, New Zealand. None of these funders had any role in study design or data analysis or interpretation.

Disclosures: We have read and understood BMJ policy on declaration of interests and declare that we have not competing interests.

Author Contributions: MB and RM conceived this study. HH, LP, RC, DK, SG, MC, NE and JC contributed to study design. MB, MC, HH, NE, SR were primarily responsible for the surgical aspects of the protocol. RC, DK and RM were primarily responsible for the medical assessment protocol of participants. LP is primarily responsible for the body composition assessment and energy expenditure protocol. RM is primarily responsible for the gut microbiota and gut hormone sub-study protocol. RM wrote the first draft of this manuscript. All authors read and contributed to the final draft of the paper.

Keywords: type 2 diabetes, obesity, weight loss, bariatric surgery, Roux-en-Y gastric bypass, Sleeve gastrectomy

Introduction

It is unclear which of the two major types of bariatric surgery, laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (LRYGB), achieves the greatest and most durable remission of T2D and weight loss [1]. There are currently only two prospective randomized controlled trials (RCT) comparing these two types of bariatric surgery in patients with T2D, with one demonstrating greater diabetes remission after LRYGB[2] and the other showing similar efficacy of LRYGB compared to SG[3]. However, each used different criteria for defining their primary outcome of diabetes remission. In a double-blinded, single-centre study of 60 Taiwanese patients with T2D (BMI 25-34 kg/m^2), 93% of those randomized to "mini" –(or loop-) bypass achieved diabetes remission at 12 months compared to 47% randomized to SG, using diabetes remission criteria of fasting glucose <7.0mmol/L and HbA1c ≤6.5% (47mmol/mol) in absence of diabetes medications [2]. At 5 years, 60% in the mini-gastric bypass group achieved the primary endpoint, compared to 30% in the SG group (odds ratio 0.3; 95% confidence interval 0.1-0.8%), despite similar percentage weight loss[4]. In a non-blinded, single-centre study of intensive medical therapy alone or combined with either LRYGP or LSG, the primary outcome of diabetes remission was defined by HbA1c of 6% or less, with or without diabetes medications[3]. In this study of 150 American patients with T2D (BMI 27-43kg/m^2), 42% of those randomized to LRYGB, 37% of those randomized to SG and 12% of those in the medical therapy group achieved diabetes remission at 12 months. All of those achieving the glycemic threshold in the LRYGB group did so without medications, compared to only 72% of patients in the SG group, so the recalculated proportions for those achieving HbA1c of ≤6% without diabetes

medication in the two bariatric surgery groups was 42% after LRYGB and 27% after SG. After 3 years, 35% of patients in the LRYGB and 20% in the SG group achieved HbA1c ≤6% without medications, which was not significantly different (p=0.10)[5]. Neither of these two randomized studies reported their medication adjustment protocol after surgery. The assessment of T2D remission may be affected by both participant lifestyle factors and clinician variation in glucose medication withdrawal thresholds used. Further studies evaluating comparative efficacy of LSG and LRYGB are required, particularly using blinding of both patients and investigators assessing for T2D remission utilizing standard protocols for post-operative medical management to minimize bias.

The advantages of LRYGB include being fully reversible, however the irreversible LSG is a faster and simpler procedure with potentially less dumping. There are technical difficulties involved in performing LRYGB in severely obese patients, and such patients may have limited success from LRYGB attributed to pouch dilation and loss of restriction at the gastrojejunal anastomosis over time. The placement of a silastic ring band around the gastric pouch at the time of primary RYGB is considered superior to the non-banded RYGB in the super-obese population[6].

The underlying mechanisms by which SG and RYGB achieve T2D remission are unclear and may involve changes in gut hormones[7], inflammatory markers[8] and gut microbiota[9]. Investigation into the impact of these two types of bariatric surgery on glucose metabolism, body composition and satiety is required.

The primary objective of this trial is to compare the efficacy of silastic ring SR-LRYGB and LSG on remission of T2D, defined by HbA1c <6% (42mmol/mol) without the use of diabetes medications, at 5 years post-surgery among patients with T2D and morbid obesity pre-operatively. Secondary objectives are to examine proportions achieving alternative glycemic thresholds HbA1c <5.7% (39mmol/mol) or <6.5% (48mmol/mol) without the use of diabetes medications, extent of weight loss, change in body composition, resting energy expenditure, operative complications, revision rate, hospitalizations, mortality, microvascular and macrovascular complications, cardiovascular risk factors, quality of life, anxiety and depression scores between the two groups. In addition, underlying mechanisms of T2D remission will be investigated by examining comparative changes in gut hormones, inflammatory markers, gut microbiota, in relation to diabetes remission, changes in body composition, food intake and appetite scores.

Methods

Trial design: This is a parallel (1:1), single-centre, two-arm, randomized, double-blind (patient and assessor), superiority trial (figure 1).

Sample size justification and power calculation: Assuming rates of diabetes remission to be 88% in SR-RYGB and 59% in LSG, a minimum of 42 patients per arm, will provide 80% power to detect a difference between the two groups using a two-sided alpha of 0.05. These estimates were derived from our unpublished audit data. An expected loss to follow up rate of 20% requires at least 53 patients per arm.

Data analysis plan: Study analysis will be by intention-to-treat. Prior to performing analyses, standard data screening and cleaning procedures will be applied to detect possible data-entry errors and to check for outliers, assess the extent and patterns of missing data and check that appropriate assumptions of normality are met whenever necessary. Baseline characteristics will be analyzed by descriptive statistics using means and standard deviations for all continuous variables with a normal distribution, and medians and interquartile ranges for variables with a non-normal distribution. Categorical variables will be summarized with frequencies. For the primary analysis, the difference in proportions achieving T2D remission (HbA1c <6% [42mmol/mol] without diabetes medication) will be compared between LSG and SR-LRYGB at 5 years, adjusting for stratification variables using logistic regression. A two-sided p value of 0.05 will be considered to indicate statistical significance. Missing data will be handled by multiple imputation as appropriate. Analyses will be performed with the use of SAS software, version 9.4 or later (SAS Institute).

Participants: All patients aged 20-55years with T2D of at least 6 months duration, BMI 35-65kg/m^2 for at least 5 years, who were referred for consideration of bariatric surgery at a single centre (North Shore Hospital), were invited to participate and to attend a bariatric surgery study information evening. All participants were given a written informed consent form and understood that on entering the randomized study they would not know their treatment allocation until completion of the study at 5 years. Other inclusion criteria included being suitable for either of the two surgical procedures, able to

give informed consent and committed to follow up. Exclusion criteria included post-prandial C-peptide <350pmol/L, pregnancy, type 1 diabetes or secondary diabetes, chronic pancreatitis, oral steroid therapy, current smokers and those not suitable for general anesthesia. The study commenced in September 2011 and completed recruitment in October 2014. A total of 114 participants were recruited into the study (figure 1). Data collection and follow up is ongoing.

Baseline assessments: All participants were prescribed a very-low-calorie diet (VLCD) with three servings of Optifast ®, (Nestle, Vevey, Switzerland), each containing approximately 152 calories, plus vegetables pre-operatively, for two weeks, designed to reduce liver fat and make laparoscopic abdominal surgery safer. Baseline clinical and anthropometric assessments were conducted before and after the VLCD. Baseline body composition assessment was conducted during the VLCD period, in the week before surgery (figure 2).

Randomization: Computer generated random number codes (Minim, London) managed by an independent study member were used to randomize participants 1:1 to either LSG or SR-LRYGB, stratified by age category (20-29, 30-39 or 40-55), BMI category (35-44.9, 45-54.9, 55-65kg/m^2), ethnicity (Maori, Pacific, NZ European/other), duration of diabetes diagnosis (<5 years, 5-10 years, >10 years) and the presence of insulin therapy.

Allocation concealment and blinding: On the day of surgery, following induction of general anesthesia, allocation to either LSG or SR-RYGB was disclosed only to the operating surgeon using a sealed envelope. Both

operations were performed utilizing a four-port technique (optical entry; two 10-12mm ports and two 5mm ports) with an additional epigastric incision for liver retraction. Participants and all other research and clinical team members remain blinded to surgical allocation.

Intervention: For SG, a sleeve was fashioned starting 2cm proximal to the pylorus using serial applications of an Echelon Flex 45 stapler (Ethicon) over a 36Fr oro-gastric bougie. For SR-RYGB, a lesser curve based gastric pouch was fashioned over a 32Fr oro-gastric tube, with a 50cm bilio-pancreatic limb, 100cm antecolic Roux limb with hand-sewn single layer gastro-jejunostomy over a 32Fr oro-gastric tube. A 6.5cm silastic ring was then secured around the gastric pouch 2cm above the gastro-jejunostomy.

Follow up: Post-operative care and follow up will be identical for both groups. All pharmacological agents for diabetes and hypertension will be stopped at the time of surgery. Glucose lowering therapy will be restarted if mean post-operative capillary glucose exceeds 12mmol/L. All participants will be reviewed by an endocrinologist at 6 weeks, 9 months then annually (table 1) for adjustment of all medications and assessment of micro- and macrovascular complications [10]. The medication adjustment protocol including lipid, blood pressure and glucose lowering therapy is outlined in figure 2.

Assessment of outcomes: HbA1c will be measured by high-performance liquid chromatography (Bio-Rad). Body weight will be recorded to the nearest 0.1kg using digital scales (SECA, Chino, CA). Height will be recorded to the nearest

0.5cm using a stadiometer. Total body fat, left femoral neck bone density and AP lumbar spine bone density will be measured by dual-energy X-ray absorptiometry (DXA, model iDXA, software version 15, GE-Lunar, Madison, WI). Percent body fat will be calculated as 100 x total body fat/body weight. Resting energy expenditure (REE) will be measured using a ventilated canopy connected to an open-circuit indirect calorimeter (Deltatrac Metabolic Monitor MBM-100, Datex instruments, Helsinki, Finland). Hospitalizations, operative complications graded according to the Clavien-Dindo classification [11], mortality, revisional surgery, changes in medications will be recorded. Hospital anxiety and depression scale (HADS)[12] and short form-36 item (SF-36)[13] questionnaires will be used (table 1).

Ancillary mechanistic study: Alongside the primary trial, participants were able to opt in to an exploratory gut hormone and gut bacteria mechanistic sub-study. As part of this study, they were asked to provide additional data and biosamples during the three scheduled visits for body composition assessments at baseline, 1 year and 5 years. The additional data include a 3-day food diary, hunger ratings assessment, fecal samples, and a 75g oral glucose tolerance test. Participants were requested to prospectively record all foods and drinks taken during the 3-day diary period including the amounts taken, and any dietary supplements taken or medications during the period. Visual analog scale (VAS) hunger ratings will be collected upon arrival at the body composition unit in a fasted state at baseline, 1 year and 5 years. Participants will be asked to rate their motivation to eat on a horizontal non-graded line measuring 100mm, anchored on the left by “not at all” and on the right by “very much” next to four

responses: How hungry are you? How full do you feel? How strong is your desire to eat? How much food do you think you could eat? Fecal samples will be self-collected in stool containers, sealed and placed into another sealed container filled with water and frozen immediately at -20°C, before being transported in the frozen state to the laboratory where they will be stored at -80°C. Participants will be asked to attend these body composition/REE visits in a fasted state for a two-hour 75g oral glucose tolerance test, with 30 minute blood sampling. Blood samples will be collected into EDTA, serum separator tubes and BD P800 tubes (BD, Franklin Lakes, NJ), containing protease inhibitors to maximize the stability of gut hormones [14].

Ethics and dissemination: Ethics approval has been granted by the New Zealand regional ethics committee (NZ93405). This study was prospectively registered at clinicaltrials.gov (NCT01486680). The results of this study and ancillary studies will be publicized in the form of presentations at national and international meetings. The study and conclusions regarding the primary and secondary objectives and ancillary studies will be presented as manuscripts submitted for peer-reviewed journal publication.

Discussion:

This is the first double-blind, randomized trial to compare SR-LRYGB and LSG for the treatment of T2D in morbidly obese patients including those with BMI up to 65kg/m^2. The use of a standard metabolic medication adjustment protocol is a strength of the study design, in effort to reduce heterogeneity in management of blood pressure, lipids and T2D post-operatively. The ancillary studies

interrogating comparative changes in gut microbiota and gut hormones may uncover novel mechanistic insights into how diabetes remission is achieved through these two contrasting surgical procedures.

The term "remission" with "partial" and "complete" descriptors have been utilized within the bariatric surgery literature with distinct thresholds of HbA1c and fasting glucose, generally in the absence of glucose lowering therapy, to represent varying degrees of diabetes improvement[15]. However, these are controversial given that the diagnosis of diabetes itself is not dichotomous and rather thresholds of glycaemia have been defined on the basis of the associated risk of micro and macrovascular complications. It is not yet known whether these thresholds remain true in a post-bariatric surgery population, and consequently diagnostic criteria for prediabetes and diabetes validated for a non-surgical population may be misleading when applied in reverse, to those who have undergone bariatric surgery. Similarly, there is a paucity of evidence to guide the development of valid, and reliable protocols for discontinuing cardiovascular risk-modifying medications after bariatric surgery for optimum medical management. Nonetheless, we have selected one of the most commonly accepted HbA1c thresholds for classifying diabetes remission[16], and utilized a standard medical management protocol to reduce complacency in medical therapy after abrupt withdrawal of medications post-operatively.

Limitations of this study include the single-centre design and the use of SR-type of LRYGB, which potentially limit generalizability of the study. Another limitation is the relatively small sample size, although comparable to other

recent studies[2 3]. However, by employing stratification for confounding variables in randomization, this will ensure factors such as duration of T2D, insulin use, ethnicity and age, will be matched across both treatment groups.

Conclusion:

This article presents the protocol and data analysis plan for a single-centre, randomized, double-blinded clinical study comparing LSG and SR-LRYGB in the treatment of T2D in morbidly obese patients, including those who are super-obese. The results of this study, when completed, will assist in decision-making between LSG and LRYGB for the treatment of T2D in morbidly obese patients. In the interim we hope this description of the study design and metabolic medication adjustment protocol will assist clinicians looking after patients following bariatric surgery and researchers in planning future bariatric surgery trials.

Funding acknowledgements: Funding for this project was primarily through Waitemata District Health Board, which provides limited publically funded bariatric surgery (approximately 100 cases annually). Additional funding for blood sample storage and a research nurse salary was provided by Johnson and Johnson (NZ), Covidien (NZ), and Obex (NZ). DEXA scanning for body composition was provided by the Diabetes Research Fund (NZ), and Maurice & Phyllis Paykel Trust (NZ). Sample collection for the gut microbiota and gut hormone sub-study was funded by a grant from the Maurice Wilkins Centre, New Zealand.

Declaration of competing interests: None declared

Table 1: Study timeline and investigations

	Baseline	Week 1	Week 6	3 months	6 months	9 months	12 months	18 months	2 years	3 years	4 years	5 years
Clinical history and medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood pressure	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anthropometrics	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DEXA/REE	✓						✓					✓
Endocrinology review	✓			✓	✓	✓	✓		✓	✓	✓	✓
Hospital Anxiety and Depression Score	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Short Form Health survey instrument (SF-36)	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lab tests*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HbA1c	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓
Stored fasting plasma and serum	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mechanistic substudy												
Food diary	✓						✓					✓
Satiety questionnaire	✓						✓					✓
Fecal sample**	✓						✓					✓
plasma and serum samples from oral glucose tolerance test ***	✓						✓					✓

* full blood count, C-reactive protein, ESR, electrolytes, creatinine, calcium, albumin, bilirubin, liver enzymes, lipids, 25-hydroxy-vitamin D,
** samples immediately frozen
*** samples also stored in BD P800 tubes for gut hormone analysis

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of metabolic control after bariatric surgery. Diabetes, obesity & metabolism 2014;**16**(1):86-9.

CONSORT diagram showing the proposed flow of participants through the sleeve gastrectomy vs gastric bypass trial for type 2 diabetes

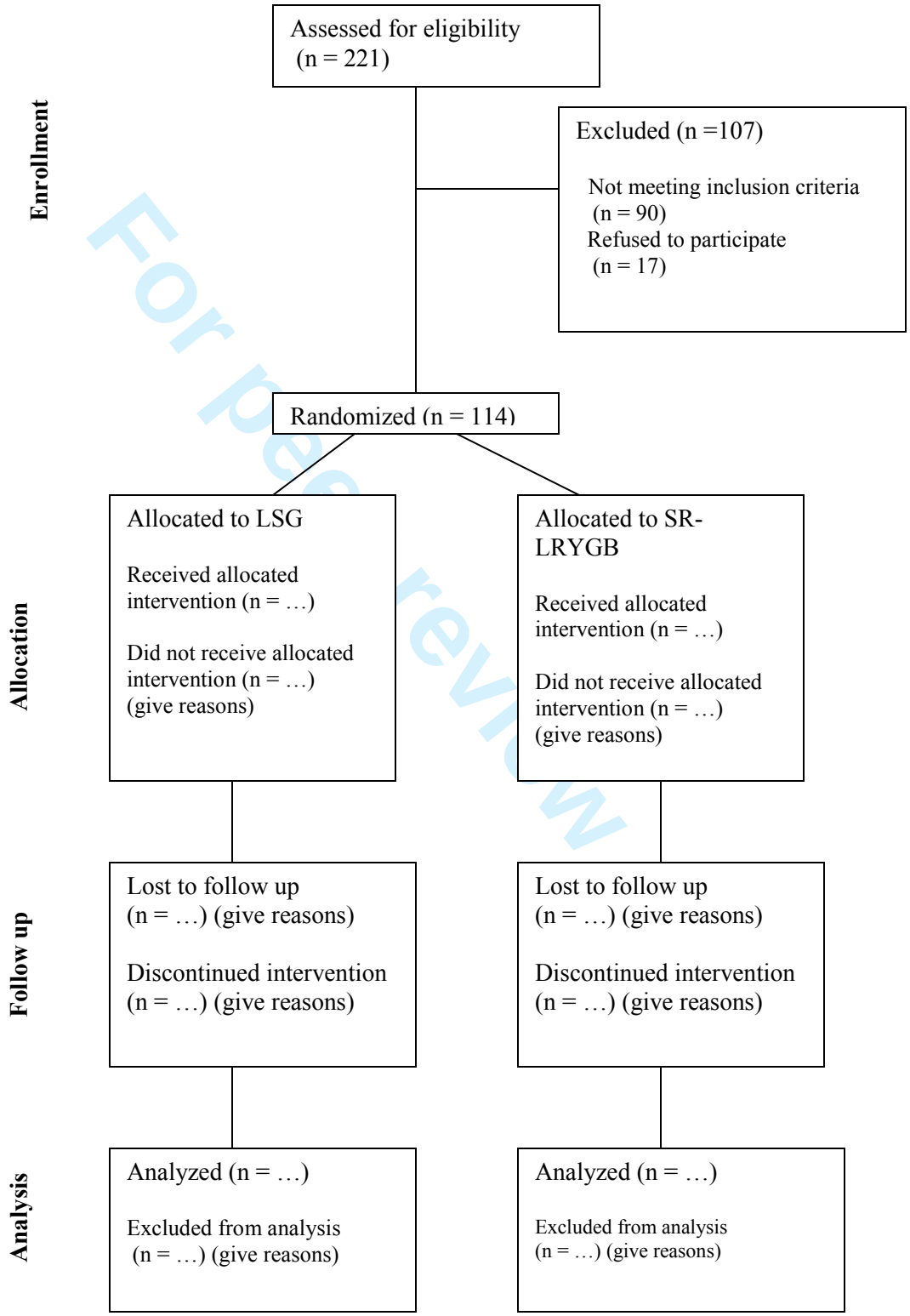

Figure 2: Endocrinology evaluation and treatment protocol for trial patients:

While inpatient at the time of surgery:

- Stop all diabetes, hypertension and lipid lowering therapies (and aspirin) at the time of surgery. *Exceptions* to this are:
  * In those where aspirin and/or lipid lowering therapy is being used for secondary prevention (previous cardiovascular events) – aspirin/ lipid lowering treatment should not be stopped
- * In those with microalbuminuria – Angiotensin Convertase Esterase-inhibitor (ACEI) /Angiotensin Receptor Blocker (ARB) therapy should not be stopped

- Diabetologist to review all trial patients prior to discharge and:
  * Restart antihypertensive therapy in those with post-op mean BP >150/90 mmHg
  * Restart diabetes treatment in those with post-operative mean capillary glucose >12 mmol/L
  (Regimen of antihypertensive and/or diabetes to be decided by the diabetologist reflecting pre-operative treatment, and likely strength of therapy required)

During follow-up visits within the 5 year trial period:

- Those who are *still on any therapy* for diabetes, hypertension or microalbuminuria:
  * Stop/wean diabetes treatment if the latest HbA1c is <53mmol/mol
  * Stop/wean antihypertensive if BP <140/90 (repeat BP +/- 24 hour ambulatory BP monitoring if in doubt)
  * Stop ACE-inhibitor/ARB if latest urinary microalbumin level normal
  * Stop/wean statin/lipid lowering therapy (unless this is for secondary prevention) if 5 year cardiovascular risk has fallen below15% using New Zealand Society for Study of Diabetes CVD risk calculator (nzssd.org.nz/cvd) [9]

- Initiate or augment medical therapy in the following situations:
  *CVD event (CAD/ CVA) mandating appropriate therapy (anti-platelet/aspirin, lipid lowering, BP lowering treatments)
  *2 x latest consecutive HbA1c of 53mmol/mol or above - start diabetes treatment (metformin in almost all instances)
- *Blood pressure >140/90 (repeat if 1x raised, consider 24hr ambulatory BP monitoring) – start BP lowering therapy (an ACE-inhibitor in almost all instances)
  *Newly positive urinary microalbumins – start an ACE-inhibitor (ARB if intolerant)
  *5 year CVD risk >15% using NZSSD CVD risk calculator – start lipid lowering therapy (a statin in almost all instances)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	P7-8
	2b	Specific objectives or hypotheses	p8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	P9, (lines174-5)
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	P10
	4b	Settings and locations where the data were collected	P10, (line 203)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	P11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	P12-13
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	P9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	P11
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	P11
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	P11 (lines 231-3)
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	P11 (line 225)

		interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	P11 (line 236-7)
	11b	If relevant, description of the similarity of interventions	P 11 (Lines 233-6)
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	P10 (lines 212-213
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P14 (lines 314-6)
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	P14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	P4
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	P5

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	5
Authors *	Contact details for the corresponding author	29
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	52
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	53-54
Interventions	Interventions intended for each group	55
Objective	Specific objective or hypothesis	48-50
Outcome	Clearly defined primary outcome for this report	57-59
Randomization	How participants were allocated to interventions	55
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	51
Results		
Numbers randomized	Number of participants randomized to each group	53
Recruitment	Trial status	67-68
Numbers analysed	Number of participants analysed in each group	N/A for protocol
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	N/A
Harms	Important adverse events or side effects	M/A
Conclusions	General interpretation of the results	N/A
Trial registration	Registration number and name of trial register	72
Funding	Source of funding	311-319

**this item is specific to conference abstracts*

BMJ Open

Sleeve gastrectomy versus Roux-en-Y gastric bypass for type 2 diabetes and morbid obesity: double-blind randomized clinical trial protocol

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Secondary Subject Heading:	Diabetes and endocrinology, Research methods
Keywords:	type 2 diabetes, bariatric surgery, morbid obesity, Roux-en-Y gastric bypass, Sleeve gastrectomy

Title page

Title:

Sleeve gastrectomy versus Roux-en-Y gastric bypass for type 2 diabetes and morbid obesity: double-blind randomized clinical trial protocol

Authors:

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Running title: Sleeve gastrectomy vs Roux-en-Y gastric bypass

Abstract:

Introduction: Type 2 diabetes (T2D) in association with obesity is an increasing disease burden. Bariatric surgery is the only effective therapy for achieving remission of T2D among those with morbid obesity. It is unclear which of the two most commonly performed types of bariatric surgery: laparoscopic sleeve gastrectomy (LSG) or laparoscopic Roux-en-Y gastric bypass (LRYGB), is most effective for obese patients with T2D. The primary objective of this study is to determine whether LSG or LRYGB is more effective in achieving HbA_{1c} < 6% [<42mmol/mol] without the use of diabetes medication at 5 years.

Methods and Analysis: Single-centre, double-blind (assessor and patient), parallel, randomized, clinical trial (RCT) conducted in New Zealand, targeting 106 patients. Eligibility criteria include age 20-55 years, T2D of at least 6 months duration and BMI 35-65kg/m^2 for at least 5 years. Randomization 1:1 to LSG or LRYGB, using random number codes disclosed to the operating surgeon after induction of anesthesia. A standard medication adjustment schedule will be used during post-operative metabolic assessments. Secondary outcomes include proportions achieving HbA_{1c} <5.7% [39mmol/mol] or <6.5% [48mmol/mol] without the use of diabetes medication, comparative weight loss, obesity related comorbidity, operative complications, revision rate, mortality, quality of life, anxiety and depression scores. Exploratory outcomes include changes in satiety, gut hormone and gut microbiota to gain underlying mechanistic insights into T2D remission.

Ethics and Dissemination: Ethics approval was obtained from the New Zealand regional ethics committee (NZ93405) who also provided independent safety monitoring of the trial. Study commenced in September 2011. Recruitment

completed in October 2014. Data collection is ongoing. Results will be reported in manuscripts submitted to peer-reviewed journals and presentations at national and international meetings.

Trial registration number: this study was prospectively registered at (ACTRN12611000751976) and retrospectively registered at clinicaltrials.gov (NCT01486680).

Article summary:

Strengths and limitations:

- There is limited evidence from randomized clinical trials comparing the efficacy of laparoscopic sleeve gastrectomy (LSG) vs laparoscopic Roux-en-Y gastric bypass (LRYGB), to guide optimum surgery selection for morbidly obese patients with T2D.
- We describe our double-blind, randomized trial designed to compare efficacy of LSG and silastic-ring LRYGB on remission of T2D at 5 years among morbidly obese patients. We used a standard metabolic medication adjustment protocol after surgery, which should assist clinicians managing patients following bariatric surgery and researchers planning future bariatric surgery trials, given the thresholds for discontinuing and restarting blood pressure, glucose and lipid medications post-operatively is frequently not reported.
- Limitations include the single-centre study design, which may limit generalizability of the findings.

Funding: We acknowledge the funding support from Waitemata District Health Board, which provides limited publically funded bariatric surgery (approximately 100 cases annually). Additional funding for blood sample storage and a research nurse salary was provided by Johnson and Johnson (NZ), Covidien (NZ), and Obex (NZ). DEXA scanning for body composition was provided by the Diabetes Research Fund (NZ), and Maurice & Phyllis Paykel Trust (NZ). Sample collection for the gut microbiota and gut hormone sub-study was funded by a grant from the Maurice Wilkins Centre, New Zealand. None of these funders had any role in study design or data analysis or interpretation.

Disclosures: We have read and understood BMJ policy on declaration of interests and declare that we have not competing interests.

Author Contributions: MB and RM conceived this study. HH, LP, RC, DK, SG, MC, NE and JC contributed to study design. MB, MC, HH, NE, SR were primarily responsible for the surgical aspects of the protocol. RC, DK and RM were primarily responsible for the medical assessment protocol of participants. LP is primarily responsible for the body composition assessment and energy expenditure protocol. RM is primarily responsible for the gut microbiota and gut hormone sub-study protocol. RM wrote the first draft of this manuscript. All authors read and contributed to the final draft of the paper.

Keywords: type 2 diabetes, obesity, weight loss, bariatric surgery, silastic ring, Roux-en-Y gastric bypass, Sleeve gastrectomy

Introduction

It is unclear which of the two major types of bariatric surgery, laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (LRYGB), achieves the greatest and most durable remission of T2D and weight loss [1 2]. There are currently only two prospective, non-blinded, randomized controlled trials (RCT) comparing these two types of bariatric surgery[3 4] in patients with T2D and one blinded study comparing the "mini" –(one anastomosis) gastric bypass with LSG[5]. In one study of 150 American patients with T2D (BMI 27-43kg/m^2) randomized to LRYGB, LSG or medical therapy, 42% after LRYGB, 37% after LSG and 12% after medical therapy achieved diabetes remission at 12 months defined by HbA_{1c} of ≤ 6% [42mmol/mol], with or without diabetes medications. All of those achieving the glycemic threshold in the LRYGB group did so without diabetes medications, compared to only 72% of patients in the SG group, so the recalculated proportions for those achieving HbA_{1c} of ≤6% [42mmol/mol] without diabetes medication in the two bariatric surgery groups was 42% after LRYGB and 27% after SG. In a small study of 41 Israeli patients with T2D (BMI >35kg/m^2), 37 completed 1 year follow up after randomization to LRYGB or SG[4]. There was a similar reduction in HbA_{1c} after LRYGB (by 1.57 ±1.35% or 17 ±15 mmol/mol) and LSG (by 2.37 ±2.22% or 26 ± 24 mmol/mol), p=0.34[4]. In a double-blinded, single-centre study of 60 Taiwanese patients with T2D (BMI 25-34 kg/m^2), 93% of those randomized to "mini" bypass achieved diabetes remission at 12 months compared to 47% randomized to LSG, using diabetes remission criteria of fasting glucose <7.0mmol/L and HbA_{1c} < 6.5% [47mmol/mol] in absence of diabetes medications [5]. None of these studies reported their medication adjustment protocol after surgery. The assessment of

T2D remission may be affected by both participant lifestyle factors and clinician variation in glucose medication withdrawal thresholds used. Further studies evaluating comparative efficacy of LSG and LRYGB are required, particularly using blinding of both patients and investigators assessing for T2D remission utilizing standard protocols for post-operative medical management to minimize bias.

The advantages of LRYGB include being fully reversible, however the irreversible LSG is a faster and simpler procedure with potentially less dumping. There are technical difficulties involved in performing LRYGB in severely obese patients, and such patients may have limited success from LRYGB attributed to pouch dilation and loss of restriction at the gastrojejunal anastomosis over time. The placement of a silastic ring band around the gastric pouch at the time of primary RYGB is considered superior to the non-banded RYGB in the super-obese population[6]. Other modifications to the LRYGB procedure includes variation in pouch size (10-50mL), alimentary limb length (50-250cm), and biliopancreatic limb length (25-150cm)[2].

The underlying mechanisms by which SG and RYGB achieve T2D remission are unclear and may involve changes in gut hormones[7], inflammatory markers[8] and gut microbiota[9]. Investigation into the impact of these two types of bariatric surgery on these mechanisms and resulting glucose metabolism, body composition and satiety is required.

The primary objective of this trial is to compare the efficacy of silastic ring (SR)-LRYGB and LSG on remission of T2D, defined by HbA_{1c} <6% (42mmol/mol) without the use of diabetes medications (as per the consensus definition of complete diabetes remission[10]), at 5 years post-surgery. Secondary objectives are to examine proportions achieving alternative glycemic thresholds HbA_{1c} <5.7% (39mmol/mol) or <6.5% (48mmol/mol) without the use of diabetes medications, extent of weight loss, change in body composition, resting energy expenditure, operative complications, revision rate, hospitalizations, mortality, microvascular and macrovascular complications, cardiovascular risk factors, quality of life, anxiety and depression scores between the two groups. In addition, underlying mechanisms of T2D remission will be investigated by examining comparative changes in gut hormones, inflammatory markers, gut microbiota, in relation to diabetes remission, changes in body composition, food intake and appetite scores.

Methods

Trial design: This is a parallel (1:1), single-centre, two-arm, randomized, double-blind (patient and assessor), superiority trial (figure 1).

Sample size justification and power calculation: Assuming rates of diabetes remission to be 88% in SR-LRYGB and 59% in LSG, a minimum of 42 patients per arm, will provide 80% power to detect a difference between the two groups using a two-sided alpha of 0.05. These estimates were derived from our unpublished audit data. An expected loss to follow up rate of 20%, requires at least 53 patients per arm.

Data analysis plan: Study analysis will be by intention-to-treat. Prior to performing analyses, standard data screening and cleaning procedures will be applied to detect possible data-entry errors and to check for outliers, assess the extent and patterns of missing data and check that appropriate assumptions of normality are met whenever necessary. Baseline characteristics will be analyzed by descriptive statistics using means and standard deviations for all continuous variables with a normal distribution, and medians and interquartile ranges for variables with a non-normal distribution. Categorical variables will be summarized with frequencies. For the primary analysis, the difference in proportions achieving T2D remission (HbA_{1c} <6% [42mmol/mol] without diabetes medication) will be compared between LSG and SR-LRYGB at 5 years, adjusting for stratification variables using logistic regression. A two-sided p value of 0.05 will be considered to indicate statistical significance. Missing data will be handled by multiple imputation as appropriate. Analyses will be performed with the use of SAS software, version 9.4 or later (SAS Institute, Cary, NC).

Participants: All patients aged 20-55years with T2D of at least 6 months duration, BMI 35-65kg/m^2 for at least 5 years, who were referred for consideration of bariatric surgery at a single centre (North Shore Hospital), were invited to participate and to attend a bariatric surgery study information evening. All participants were given a written informed consent form and understood that on entering the randomized study they would not know their treatment allocation until completion of the study at 5 years. Other inclusion

criteria included being suitable for either of the two surgical procedures, able to give informed consent and committed to follow up. Exclusion criteria included post-prandial C-peptide <350pmol/L, pregnancy, type 1 diabetes or secondary diabetes, chronic pancreatitis, oral steroid therapy, current smokers and those not suitable for general anesthesia. The study commenced in September 2011 and completed recruitment in October 2014. A total of 114 participants were recruited into the study (figure 1). Data collection and follow up is ongoing.

Baseline assessments: All participants were prescribed a very-low-calorie diet (VLCD) with three servings of Optifast ®, (Nestle, Vevey, Switzerland), each containing approximately 152 calories, plus vegetables pre-operatively, for two weeks, designed to reduce liver fat and make laparoscopic abdominal surgery safer. Baseline clinical and anthropometric assessments were conducted before and after the VLCD. Baseline body composition assessment was conducted during the VLCD period, in the week before surgery (figure 2).

Randomization: Computer generated random number codes (Minim, London) managed by an independent study member were used to randomize participants 1:1 to either LSG or SR-LRYGB, stratified by age category (20-29, 30-39 or 40-55), BMI category (35-44.9, 45-54.9, 55-65kg/m^2), ethnicity (Maori, Pacific, NZ European/other), duration of diabetes diagnosis (<5 years, 5-10 years, >10 years) and the presence of insulin therapy.

Allocation concealment and blinding: On the day of surgery, following induction of general anesthesia, allocation to either LSG or SR-LRYGB was

disclosed only to the operating surgical team. Both operations were performed utilizing identical incisions with a four-port technique (optical entry; two 10-12mm ports and two 5mm ports) and an additional epigastric incision for liver retraction. Participants and all other research and clinical team members remain blinded to surgical allocation. Only de-identified codes were used to link participants to their data during the study to maintain their confidentiality.

Intervention: For SG, a sleeve was fashioned starting 2cm proximal to the pylorus using serial applications of an Echelon Flex 45 stapler (Ethicon) over a 36Fr oro-gastric bougie. For SR-LRYGB, a lesser curve based gastric pouch was fashioned over a 32Fr oro-gastric tube, with a 50cm bilio-pancreatic limb, 100cm antecolic Roux limb with hand-sewn single layer gastro-jejunostomy over a 32Fr oro-gastric tube. A 6.5cm silastic ring was then secured around the gastric pouch 2cm above the gastro-jejunostomy anastomosis. Mesenteric defects were closed

Follow up: Post-operative care and follow up will be identical for both groups. All pharmacological agents for diabetes and hypertension will be stopped at the time of surgery. Glucose lowering therapy will be restarted if mean post-operative capillary glucose exceeds 12mmol/L. All participants will be reviewed by an endocrinologist at 6 weeks, 9 months then annually (table 1) for adjustment of all medications and assessment of micro- and macrovascular complications [11]. The medication adjustment protocol including lipid, blood pressure and glucose lowering therapy is outlined in figure 2. Microvascular complications will be assessed annually with clinical evaluation for peripheral neuropathy symptoms and signs, retinal photoscreening and measurement of

renal function, urine albumin:creatinine ratio. Macrovascular complications such as incidence of myocardial infarction, stroke, peripheral vascular disease will also be recorded.

Assessment of outcomes: HbA_{1c} will be measured by high-performance liquid chromatography (Bio-Rad). Body weight will be recorded to the nearest 0.1kg using digital scales (SECA, Chino, CA). Height will be recorded to the nearest 0.5cm using a stadiometer. Total body fat, left femoral neck bone density and AP lumbar spine bone density will be measured by dual-energy X-ray absorptiometry (DEXA, model iDXA, software version 15, GE-Lunar, Madison, WI). Percent body fat will be calculated as 100 x total body fat/body weight. Resting energy expenditure (REE) will be measured after overnight fast using a ventilated canopy connected to an open-circuit indirect calorimeter (Deltatrac Metabolic Monitor MBM-100, Datex instruments, Helsinki, Finland). Hospitalizations, operative complications graded according to the Clavien-Dindo classification [12], mortality, revisional surgery, changes in medications will be recorded. Hospital anxiety and depression scale (HADS)[13] and short form-36 item (SF-36)[14] questionnaires will be used (table 1).

Ancillary mechanistic study: Alongside the primary trial, participants were able to opt in to an exploratory gut hormone and gut bacteria mechanistic sub-study. As part of this study, they were asked to provide additional data and biosamples during the three scheduled visits for body composition assessments at baseline, 1 year and 5 years. The additional data include a 3-day food diary, hunger ratings assessment, fecal samples, and a 75g oral glucose tolerance test.

Participants were requested to prospectively record all foods and drinks taken during the 3-day diary period including the amounts taken, and any dietary supplements taken or medications during the period. Visual analog scale (VAS) hunger ratings will be collected upon arrival at the body composition unit in a fasted state at baseline, 1 year and 5 years. Participants will be asked to rate their motivation to eat on a horizontal non-graded line measuring 100mm, anchored on the left by "not at all" and on the right by "very much" next to four responses: How hungry are you? How full do you feel? How strong is your desire to eat? How much food do you think you could eat? Fecal samples will be self-collected in stool containers, sealed and placed into another sealed container filled with water and frozen immediately at -20°C, before being transported in the frozen state to the laboratory where they will be stored at -80°C. Participants will be asked to attend these body composition/REE visits in a fasted state for a two-hour 75g oral glucose tolerance test, with 30 minute blood sampling. Blood samples will be collected into EDTA, serum separator tubes and BD P800 tubes (BD, Franklin Lakes, NJ), containing protease inhibitors to maximize the stability of gut hormones [15].

Ethics and dissemination: Ethics approval has been granted by the New Zealand regional ethics committee (NZ93405). This study was prospectively registered at ANZCTR (ACTRN12611000751976) and retrospectively registered at clinicaltrials.gov (NCT01486680). The results of this study and ancillary studies will be publicized in the form of presentations at national and international meetings. The study and conclusions regarding the primary and

secondary objectives and ancillary studies will be presented as manuscripts submitted for peer-reviewed journal publication.

Discussion:

This is the first double-blind, randomized trial to compare SR-LRYGB and LSG for the treatment of T2D in morbidly obese patients including those with BMI up to 65kg/m^2. The use of a standard metabolic medication adjustment protocol is a strength of the study design, in effort to reduce heterogeneity in management of blood pressure, lipids and T2D post-operatively. The ancillary studies interrogating comparative changes in gut microbiota and gut hormones may uncover novel mechanistic insights into how diabetes remission is achieved through these two contrasting surgical procedures.

The term "remission" with "partial" and "complete" descriptors have been utilized within the bariatric surgery literature with distinct thresholds of HbA_{1c} and fasting glucose, generally in the absence of glucose lowering therapy, to represent varying degrees of diabetes improvement[10]. However, these are controversial given that the diagnosis of diabetes itself is not dichotomous and rather thresholds of glycaemia have been defined on the basis of the associated risk of micro and macrovascular complications. It is not yet known whether these thresholds remain true in a post-bariatric surgery population, and consequently diagnostic criteria for prediabetes and diabetes validated for a non-surgical population may be misleading when applied in reverse, to those who have undergone bariatric surgery. Similarly, there is a paucity of evidence to guide the development of valid, and reliable protocols for discontinuing

cardiovascular risk-modifying medications after bariatric surgery for optimum medical management. Nonetheless, we have selected one of the most commonly accepted HbA_{1c} thresholds for classifying diabetes remission[16], and utilized a standard medical management to reduce complacency in medical therapy after abrupt withdrawal of medications post-operatively.

Limitations of this study include the single-centre design, and the relatively small sample size. However, by employing stratification for confounding variables in randomization, this will ensure these factors (such as duration of T2D, insulin use, ethnicity and age), will be matched across both treatment groups. SR-LRYGB was chosen due to superior long-term weight loss outcomes, largely due to reduction in weight regain when compared to non-banded LRYGB. [17-19] However, this modification of LRYGB is possibly not widely adopted due to unfamiliarity with placing it, and potential issues regarding food intolerance and band-related complications[6]. Some of these concerns are ill conceived and hence currently the use of SR-type of LRYGB may limit generalizability of the study.

Conclusion:

This article presents the protocol and data analysis plan for a single-centre, randomized, double-blinded clinical study comparing LSG and SR-LRYGB in the treatment of T2D in morbidly obese patients, including those who are super-obese. The results of this study, when completed, will assist in decision-making between LSG and LRYGB for the treatment of T2D in morbidly obese patients. In the interim we hope this description of the study design and metabolic medication adjustment protocol will assist clinicians looking after patients

following bariatric surgery and researchers in planning future bariatric surgery trials.

Funding acknowledgements: Funding for this project was primarily through Waitemata District Health Board, which provides limited publically funded bariatric surgery (approximately 100 cases annually). Additional funding for blood sample storage and a research nurse salary was provided by Johnson and Johnson (NZ), Covidien (NZ), and Obex (NZ). DEXA scanning for body composition was provided by the Diabetes Research Fund (NZ), and Maurice & Phyllis Paykel Trust (NZ). Sample collection for the gut microbiota and gut hormone sub-study was funded by a grant from the Maurice Wilkins Centre, New Zealand.

Declaration of competing interests: None declared

Table 1: Study timeline and investigations

	Baseline	Week 1	Week 6	3 months	6 months	9 months	12 months	18 months	2 years	3 years	4 years	5 years
Clinical history and medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood pressure	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anthropometrics	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DEXA/REE#	✓						✓					✓
Endocrinology review	✓		✓			✓		21 months		33 months	45 months	57 months
Hospital Anxiety and Depression Score	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Short Form Health survey instrument (SF-36)	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lab tests*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HbA_{1c}	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓
Stored fasting plasma and serum	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mechanistic substudy												
Food diary	✓						✓					✓
Satiety questionnaire	✓						✓					✓
Fecal sample**	✓						✓					✓
plasma and serum samples from oral glucose tolerance test ***	✓						✓					✓

dual-energy X-ray absorptiometry/resting energy expenditure
* full blood count, C-reactive protein, ESR, electrolytes, creatinine, calcium, albumin, bilirubin, liver enzymes, lipids, 25-hydroxy-vitamin D,
** samples immediately frozen
*** samples also stored in BD P800 tubes for gut hormone analysis

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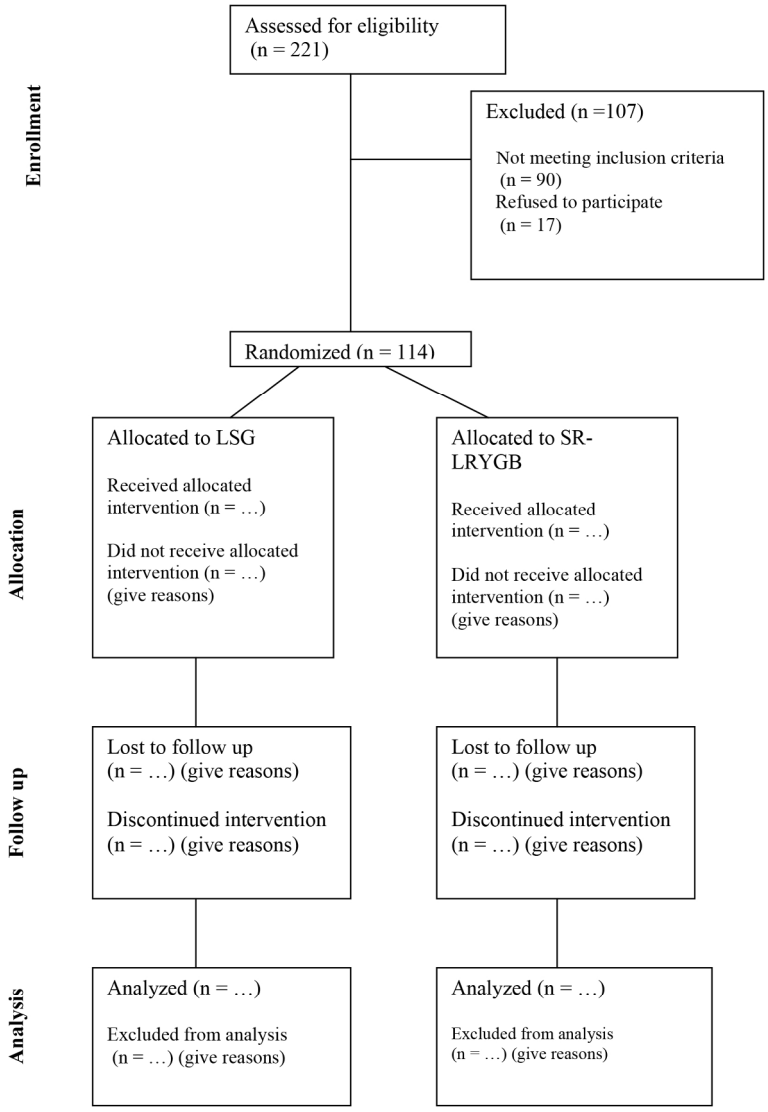
CONSORT diagram showing the proposed flow of participants through the sleeve gastrectomy vs gastric bypass trial for type 2 diabetes



Proposed flow of participants through the trial
157x221mm (300 x 300 DPI)

Figure 2: Endocrinology evaluation and treatment protocol for trial patients:

While inpatient at the time of surgery:

- Stop all diabetes, hypertension and lipid lowering therapies (and aspirin) at the time of surgery. *Exceptions* to this are:
  * In those where aspirin and/or lipid lowering therapy is being used for secondary prevention (previous cardiovascular events) – aspirin/ lipid lowering treatment should not be stopped
- * In those with microalbuminuria – Angiotensin Convertase Esterase-inhibitor (ACEI) /Angiotensin Receptor Blocker (ARB) therapy should not be stopped

- Diabetologist to review all trial patients prior to discharge and:
  * Restart antihypertensive therapy in those with post-op mean BP >150/90 mmHg
  * Restart diabetes treatment in those with post-operative mean capillary glucose >12 mmol/L
  (Regimen of antihypertensive and/or diabetes to be decided by the diabetologist reflecting pre-operative treatment, and likely strength of therapy required)

During follow-up visits within the 5 year trial period:

- Those who are *still on any therapy* for diabetes, hypertension or microalbuminuria:
  * Stop/wean diabetes treatment if the latest HbA1c is <53mmol/mol
  * Stop/wean antihypertensive if BP <140/90 (repeat BP +/- 24 hour ambulatory BP monitoring if in doubt)
  * Stop ACE-inhibitor/ARB if latest urinary microalbumin level normal
  * Stop/wean statin/lipid lowering therapy (unless this is for secondary prevention) if 5 year cardiovascular risk has fallen below15% using New Zealand Society for Study of Diabetes CVD risk calculator (nzssd.org.nz/cvd) [9]

- Initiate or augment medical therapy in the following situations:
  *CVD event (CAD/ CVA) mandating appropriate therapy (anti-platelet/aspirin, lipid lowering, BP lowering treatments)
  *2 x latest consecutive HbA1c of 53mmol/mol or above - start diabetes treatment (metformin in almost all instances)
- *Blood pressure >140/90 (repeat if 1x raised, consider 24hr ambulatory BP monitoring) – start BP lowering therapy (an ACE-inhibitor in almost all instances)
  *Newly positive urinary microalbumins – start an ACE-inhibitor (ARB if intolerant)
  *5 year CVD risk >15% using NZSSD CVD risk calculator – start lipid lowering therapy (a statin in almost all instances)

Endocrinology evaluation and treatment protocol for trial patients
169x205mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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	_____4_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	____ S1_____
Funding	4	Sources and types of financial, material, and other support	_____5_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____5_____
	5b	Name and contact information for the trial sponsor	____ 5_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____ 5_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
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)	9-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
	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)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
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	12
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)	17

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	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
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	10-11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	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	11-13
	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	12-13

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	____9_____
Statistical methods	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	___9_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___9_____
	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)	____9_____
Methods: Monitoring			
Data monitoring	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	_____
	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	_____
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	_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____13_____
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)	_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____9_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____12-13_____
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	____11_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____5_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____
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	_____
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	___ 13_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
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	____12-13_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	5
Authors *	Contact details for the corresponding author	29
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	52
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	53-54
Interventions	Interventions intended for each group	55
Objective	Specific objective or hypothesis	48-50
Outcome	Clearly defined primary outcome for this report	57-59
Randomization	How participants were allocated to interventions	55
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	51
Results		
Numbers randomized	Number of participants randomized to each group	53
Recruitment	Trial status	67-68
Numbers analysed	Number of participants analysed in each group	N/A for protocol
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	N/A
Harms	Important adverse events or side effects	M/A
Conclusions	General interpretation of the results	N/A
Trial registration	Registration number and name of trial register	72
Funding	Source of funding	311-319

**this item is specific to conference abstracts*

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	P7-8
	2b	Specific objectives or hypotheses	p8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	P9, (lines174-5)
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	P10
	4b	Settings and locations where the data were collected	P10, (line 203)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	P11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	P12-13
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	P9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	P11
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	P11
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	P11 (lines 231-3)
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	P11 (line 225)

		interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	P11 (line 236-7)
	11b	If relevant, description of the similarity of interventions	P 11 (Lines 233-6)
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	P10 (lines 212-213
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P14 (lines 314-6)
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	P14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	P4
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	P5

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.