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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

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2 **Title page**

3 **Title:**

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

6
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14 37 **Running title:** Sleeve gastrectomy vs Roux-en-Y gastric bypass
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For peer review only

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3 41 **Abstract:**
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5 42 **Introduction:** Type 2 diabetes (T2D) in association with obesity is an increasing
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7 43 disease burden. Bariatric surgery is the only effective therapy for achieving
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9 44 remission of T2D among those with morbid obesity. It is unclear which of the
10
11 45 two most commonly performed types of bariatric surgery: laparoscopic sleeve
12
13 46 gastrectomy (LSG) or laparoscopic Roux-en-Y gastric bypass (LRYGB), is most
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15 47 effective for obese patients for T2D. The primary objective of this study is to
16
17 48 determine whether LSG or LRYGB is more effective in achieving HbA1c < 6%
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19 49 (<42mmol/mol) without the use of diabetes medication at 5 years.
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22
23 50 **Methods and Analysis:** Single-centre, double-blind (assessor and patient),
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25 51 parallel, randomized, clinical trial (RCT) being conducted in New Zealand,
26
27 52 targeting 106 patients. Eligibility criteria include age 20-55 years, T2D of at least
28
29 53 6 months duration and BMI 35-65kg/m² for at least 5 years. Randomization 1:1
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31 54 to LSG or LRYGB, is using random number codes disclosed to the operating
32
33 55 surgeon after induction of anesthesia. A standard medication adjustment
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35 56 schedule will be used during post-operative metabolic assessments. Secondary
36
37 57 outcomes include proportions achieving HbA1c <5.7% (39mmol/mol) or <6.5%
38
39 58 (48mmol/mol) without the use of diabetes medication, comparative weight loss,
40
41 59 obesity related comorbidity, operative complications, revision rate, mortality,
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43 60 quality of life, anxiety and depression scores. Exploratory outcomes include
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45 61 changes in satiety, gut hormone and gut microbiota to gain underlying
46
47 62 mechanistic insights into T2D remission.
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51 63 **Ethics and Dissemination:** Ethics approval was obtained from the New Zealand
52
53 64 regional ethics committee (NZ93405) who also provided independent safety
54
55 65 monitoring of the trial. Study commenced in September 2011. Recruitment
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3 66 completed in October 2014. Data collection is ongoing. Results will be reported
4
5 67 in manuscripts submitted to peer-reviewed journals and presentations at
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7 68 national and international meetings.
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10 69 **Trial registration number:** this study was prospectively registered at ANZCTR
11
12 70 (ACTRN12611000751976) and retrospectively registered at clinicaltrials.gov
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14 71 (NCT01486680).
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19 73 **Article summary:**

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21 74 **Strengths and limitations:**

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23 75 • There is limited evidence from randomized clinical trials comparing the
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25 76 efficacy of laparoscopic sleeve gastrectomy (LSG) vs laparoscopic Roux-
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27 77 en-Y gastric bypass (LRYGB), to guide optimum surgery selection for
28
29 78 morbidly obese patients with T2D.
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31
32 79 • We describe our double-blind, randomized trial designed to compare
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34 80 efficacy of LSG and LRYGB on remission of T2D at 5 years among
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36 81 morbidly obese patients using a standard metabolic medication
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38 82 adjustment protocol after surgery, which should assist clinicians
39
40 83 managing patients following bariatric surgery and researchers planning
41
42 84 future bariatric surgery trials, given the thresholds for discontinuing
43
44 85 blood pressure, glucose and lipid medications post-operatively is
45
46 86 frequently not reported.
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48 87 • Limitations include the single-centre study design and use of silastic-ring
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50 88 type of LRYGB, which may limit generalizability of the findings.
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3 91 **Funding:** We acknowledge the funding support from Waitemata District Health
4
5 92 Board, which provides limited publically funded bariatric surgery
6
7 93 (approximately 100 cases annually). Additional funding for blood sample
8
9 94 storage and a research nurse salary was provided by Johnson and Johnson (NZ),
10
11 95 Covidien (NZ), and Obex (NZ). DEXA scanning for body composition was
12
13 96 provided by the Diabetes Research Fund (NZ), and Maurice & Phyllis Paykel
14
15 97 Trust (NZ). Sample collection for the gut microbiota and gut hormone sub-study
16
17 98 was funded by a grant from the Maurice Wilkins Centre, New Zealand. None of
18
19 99 these funders had any role in study design or data analysis or interpretation.
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25 101 **Disclosures:** We have read and understood BMJ policy on declaration of
26
27 102 interests and declare that we have not competing interests.
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31 103

32 104 **Author Contributions:** MB and RM conceived this study. HH, LP, RC, DK, SG,
33
34 105 MC, NE and JC contributed to study design. MB, MC, HH, NE, SR were primarily
35
36 106 responsible for the surgical aspects of the protocol. RC, DK and RM were
37
38 107 primarily responsible for the medical assessment protocol of participants. LP is
39
40 108 primarily responsible for the body composition assessment and energy
41
42 109 expenditure protocol. RM is primarily responsible for the gut microbiota and gut
43
44 110 hormone sub-study protocol. RM wrote the first draft of this manuscript. All
45
46 111 authors read and contributed to the final draft of the paper.
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52 113 **Keywords:** type 2 diabetes, obesity, weight loss, bariatric surgery, Roux-en-Y
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54 114 gastric bypass, Sleeve gastrectomy
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116 Introduction

117 It is unclear which of the two major types of bariatric surgery, laparoscopic
118 sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (LRYGB), achieves the
119 greatest and most durable remission of T2D and weight loss¹. There are
120 currently only two prospective randomized controlled trials (RCT) comparing
121 these two types of bariatric surgery in patients with T2D, with one
122 demonstrating greater diabetes remission after LRYGB² and the other showing
123 similar efficacy of LRYGB compared to SG³. However, each used different criteria
124 for defining their primary outcome of diabetes remission. In a double-blinded,
125 single-centre study of 60 Taiwanese patients with T2D (BMI 25-34 kg/m²), 93%
126 of those randomized to “mini” –(or loop-) bypass achieved diabetes remission at
127 12 months compared to 47% randomized to SG, using diabetes remission criteria
128 of fasting glucose <7.0mmol/L and HbA1c ≤6.5% (47mmol/mol) in absence of
129 diabetes medications². At 5 years, 60% in the mini-gastric bypass group
130 achieved the primary endpoint, compared to 30% in the SG group (odds ratio
131 0.3; 95% confidence interval 0.1-0.8%), despite similar percentage weight loss⁴.
132 In a non-blinded, single-centre study of intensive medical therapy alone or
133 combined with either LRYGP or LSG, the primary outcome of diabetes remission
134 was defined by HbA1c of 6% or less, with or without diabetes medications³. In
135 this study of 150 American patients with T2D (BMI 27-43kg/m²), 42% of those
136 randomized to LRYGB, 37% of those randomized to SG and 12% of those in the
137 medical therapy group achieved diabetes remission at 12 months. All of those
138 achieving the glycemic threshold in the LRYGB group did so without
139 medications, compared to only 72% of patients in the SG group, so the
140 recalculated proportions for those achieving HbA1c of ≤6% without diabetes

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3 141 medication in the two bariatric surgery groups was 42% after LRYGB and 27%
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5 142 after SG. After 3 years, 35% of patients in the LRYGB and 20% in the SG group
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7 143 achieved HbA1c \leq 6% without medications, which was not significantly different
8
9 144 ($p=0.10$)⁵. Neither of these two randomized studies reported their medication
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11 145 adjustment protocol after surgery. The assessment of T2D remission may be
12
13 146 affected by both participant lifestyle factors and clinician variation in glucose
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15 147 medication withdrawal thresholds used. Further studies evaluating comparative
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17 148 efficacy of LSG and LRYGB are required, particularly using blinding of both
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19 149 patients and investigators assessing for T2D remission utilizing standard
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21 150 protocols for post-operative medical management to minimize bias.
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28 152 The advantages of LRYGB include being fully reversible, however the irreversible
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30 153 LSG is a faster and simpler procedure with potentially less dumping. There are
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32 154 technical difficulties involved in performing LRYGB in severely obese patients,
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34 155 and such patients may have limited success from LRYGB attributed to pouch
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36 156 dilation and loss of restriction at the gastrojejunal anastomosis over time. The
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38 157 placement of a silastic ring band around the gastric pouch at the time of primary
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40 158 RYGB is considered superior to the non-banded RYGB in the super-obese
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42 159 population⁶.
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48 161 The underlying mechanisms by which SG and RYGB achieve T2D remission are
49
50 162 unclear and may involve changes in gut hormones⁷, inflammatory markers⁸ and
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52 163 gut microbiota⁹. Investigation into the impact of these two types of bariatric
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54 164 surgery on glucose metabolism, body composition and satiety is required.
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3 166 The primary objective of this trial is to compare the efficacy of silastic ring SR-
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5 167 LRYGB and LSG on remission of T2D, defined by HbA1c <6% (42mmol/mol)
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7 168 without the use of diabetes medications, at 5 years post-surgery among patients
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10 169 with T2D and morbid obesity pre-operatively. Secondary objectives are to
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12 170 examine proportions achieving alternative glyceic thresholds HbA1c <5.7%
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14 171 (39mmol/mol) or <6.5% (48mmol/mol) without the use of diabetes
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16 172 medications, extent of weight loss, change in body composition, resting energy
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18 173 expenditure, operative complications, revision rate, hospitalizations, mortality,
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20 174 microvascular and macrovascular complications, cardiovascular risk factors,
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22 175 quality of life, anxiety and depression scores between the two groups. In
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24 176 addition, underlying mechanisms of T2D remission will be investigated by
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26 177 examining comparative changes in gut hormones, inflammatory markers, gut
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28 178 microbiota, in relation to diabetes remission, changes in body composition, food
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30 179 intake and appetite scores.
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181 **Methods**

182 **Trial design:** This is a parallel (1:1), single-centre, two-arm, randomized,
183 double-blind (patient and assessor), superiority trial (figure 1).
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185 **Sample size justification and power calculation:** Assuming rates of diabetes
186 remission to be 88% in SR-RYGB and 59% in LSG, a minimum of 42 patients per
187 arm, will provide 80% power to detect a difference between the two groups
188 using a two-sided alpha of 0.05. These estimates were derived from our
189 unpublished audit data. An expected loss to follow up rate of 20% requires at
190 least 53 patients per arm.

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5 192 **Data analysis plan:** Study analysis will be by intention-to-treat. Prior to
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7 193 performing analyses, standard data screening and cleaning procedures will be
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9 194 applied to detect possible data-entry errors and to check for outliers, assess the
10 195 extent and patterns of missing data and check that appropriate assumptions of
11 196 normality are met whenever necessary. Baseline characteristics will be analyzed
12 197 by descriptive statistics using means and standard deviations for all continuous
13 198 variables with a normal distribution, and medians and interquartile ranges for
14 199 variables with a non-normal distribution. Categorical variables will be
15 200 summarized with frequencies. For the primary analysis, the difference in
16 201 proportions achieving T2D remission (HbA1c <6% [42mmol/mol] without
17 202 diabetes medication) will be compared between LSG and SR-LRYGB at 5 years,
18 203 adjusting for stratification variables using logistic regression. A two-sided p
19 204 value of 0.05 will be considered to indicate statistical significance. Missing data
20 205 will be handled by multiple imputation as appropriate. Analyses will be
21 206 performed with the use of SAS software, version 9.4 or later (SAS Institute).

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41 208 **Participants:** All patients aged 20-55years with T2D of at least 6 months
42 209 duration, BMI 35-65kg/m² for at least 5 years, who were referred for
43 210 consideration of bariatric surgery at a single centre (North Shore Hospital), were
44 211 invited to participate and to attend a bariatric surgery study information
45 212 evening. All participants were given a written informed consent form and
46 213 understood that on entering the randomized study they would not know their
47 214 treatment allocation until completion of the study at 5 years. Other inclusion
48 215 criteria included being suitable for either of the two surgical procedures, able to

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3 216 give informed consent and committed to follow up. Exclusion criteria included
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5 217 post-prandial C-peptide <350pmol/L, pregnancy, type 1 diabetes or secondary
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7 218 diabetes, chronic pancreatitis, oral steroid therapy, current smokers and those
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10 219 not suitable for general anesthesia. The study commenced in September 2011
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12 220 and completed recruitment in October 2014. A total of 114 participants were
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14 221 recruited into the study (figure 1). Data collection and follow up is ongoing.
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19 223 **Baseline assessments:** All participants were prescribed a very-low-calorie diet
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21 224 (VLCD) with three servings of Optifast®, (Nestle, Vevey, Switzerland), each
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23 225 containing approximately 152 calories, plus vegetables pre-operatively, for two
24
25 226 weeks, designed to reduce liver fat and make laparoscopic abdominal surgery
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27 227 safer. Baseline clinical and anthropometric assessments were conducted before
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29 228 and after the VLCD. Baseline body composition assessment was conducted
30
31 229 during the VLCD period, in the week before surgery (figure 2).
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37 231 **Randomization:** Computer generated random number codes (Minim, London)
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39 232 managed by an independent study member were used to randomize participants
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41 233 1:1 to either LSG or SR-LRYGB, stratified by age category (20-29, 30-39 or 40-
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43 234 55), BMI category (35-44.9, 45-54.9, 55-65kg/m²), ethnicity (Maori, Pacific, NZ
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45 235 European/other), duration of diabetes diagnosis (<5 years, 5-10 years, >10
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47 236 years) and the presence of insulin therapy.
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52 238 **Allocation concealment and blinding:** On the day of surgery, following
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54 239 induction of general anesthesia, allocation to either LSG or SR-RYGB was
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56 240 disclosed only to the operating surgeon using a sealed envelope. Both
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3 241 operations were performed utilizing a four-port technique (optical entry; two
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5 242 10-12mm ports and two 5mm ports) with an additional epigastric incision for
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7 243 liver retraction. Participants and all other research and clinical team members
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10 244 remain blinded to surgical allocation.

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14 246 **Intervention:** For SG, a sleeve was fashioned starting 2cm proximal to the
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16 247 pylorus using serial applications of an Echelon Flex 45 stapler (Ethicon) over a
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18 248 36Fr oro-gastric bougie. For SR-RYGB, a lesser curve based gastric pouch was
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20 249 fashioned over a 32Fr oro-gastric tube, with a 50cm bilio-pancreatic limb, 100cm
21
22 250 antecolic Roux limb with hand-sewn single layer gastro-jejunostomy over a 32Fr
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24 251 oro-gastric tube. A 6.5cm silastic ring was then secured around the gastric pouch
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26 252 2cm above the gastro-jejunostomy.

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32 254 **Follow up:** Post-operative care and follow up will be identical for both groups.
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34 255 All pharmacological agents for diabetes and hypertension will be stopped at the
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36 256 time of surgery. Glucose lowering therapy will be restarted if mean post-
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38 257 operative capillary glucose exceeds 12mmol/L. All participants will be reviewed
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40 258 by an endocrinologist at 6 weeks, 9 months then annually (table 1) for
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42 259 adjustment of all medications and assessment of micro- and macrovascular
43
44 260 complications¹⁰. The medication adjustment protocol including lipid, blood
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46 261 pressure and glucose lowering therapy is outlined in figure 2.

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52 263 **Assessment of outcomes:** HbA1c will be measured by high-performance liquid
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54 264 chromatography (Bio-Rad). Body weight will be recorded to the nearest 0.1kg
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56 265 using digital scales (SECA, Chino, CA). Height will be recorded to the nearest
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3 266 0.5cm using a stadiometer. Total body fat, left femoral neck bone density and AP
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5 267 lumbar spine bone density will be measured by dual-energy X-ray
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7 268 absorptiometry (DXA, model iDXA, software version 15, GE-Lunar, Madison, WI).
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10 269 Percent body fat will be calculated as 100 x total body fat/body weight. Resting
11
12 270 energy expenditure (REE) will be measured using a ventilated canopy connected
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14 271 to an open-circuit indirect calorimeter (Deltatrac Metabolic Monitor MBM-100,
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16 272 Datex instruments, Helsinki, Finland). Hospitalizations, operative complications
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18 273 graded according to the Clavien-Dindo classification ¹¹, mortality, revisional
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20 274 surgery, changes in medications will be recorded. Hospital anxiety and
21
22 275 depression scale (HADS)¹² and short form-36 item (SF-36)¹³ questionnaires will
23
24 276 be used (table 1).
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30 278 **Ancillary mechanistic study:** Alongside the primary trial, participants were
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32 279 able to opt in to an exploratory gut hormone and gut bacteria mechanistic sub-
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34 280 study. As part of this study, they were asked to provide additional data and
35
36 281 biosamples during the three scheduled visits for body composition assessments
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38 282 at baseline, 1 year and 5 years. The additional data include a 3-day food diary,
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40 283 hunger ratings assessment, fecal samples, and a 75g oral glucose tolerance test.
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42 284 Participants were requested to prospectively record all foods and drinks taken
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44 285 during the 3-day diary period including the amounts taken, and any dietary
45
46 286 supplements taken or medications during the period. Visual analog scale (VAS)
47
48 287 hunger ratings will be collected upon arrival at the body composition unit in a
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50 288 fasted state at baseline, 1 year and 5 years. Participants will be asked to rate
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52 289 their motivation to eat on a horizontal non-graded line measuring 100mm,
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54 290 anchored on the left by “not at all” and on the right by “very much” next to four
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3 291 responses: How hungry are you? How full do you feel? How strong is your
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5 292 desire to eat? How much food do you think you could eat? Fecal samples will be
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7 293 self-collected in stool containers, sealed and placed into another sealed container
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10 294 filled with water and frozen immediately at -20°C, before being transported in
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12 295 the frozen state to the laboratory where they will be stored at -80°C. Participants
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14 296 will be asked to attend these body composition/REE visits in a fasted state for a
15
16 297 two-hour 75g oral glucose tolerance test, with 30 minute blood sampling. Blood
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18 298 samples will be collected into EDTA, serum separator tubes and BD P800 tubes
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20
21 299 (BD, Franklin Lakes, NJ), containing protease inhibitors to maximize the stability
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23 300 of gut hormones ¹⁴.
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28 302 **Ethics and dissemination:** Ethics approval has been granted by the New
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30 303 Zealand regional ethics committee (NZ93405). This study was prospectively
31
32 304 registered at clinicaltrials.gov (NCT01486680). The results of this study and
33
34 305 ancillary studies will be publicized in the form of presentations at national and
35
36 306 international meetings. The study and conclusions regarding the primary and
37
38 307 secondary objectives and ancillary studies will be presented as manuscripts
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40 308 submitted for peer-reviewed journal publication.
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46 310 **Discussion:**

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48 311 This is the first double-blind, randomized trial to compare SR-LRYGB and LSG for
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50 312 the treatment of T2D in morbidly obese patients including those with BMI up to
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52 313 65kg/m². The use of a standard metabolic medication adjustment protocol is a
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54 314 strength of the study design, in effort to reduce heterogeneity in management of
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56 315 blood pressure, lipids and T2D post-operatively. The ancillary studies
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3 316 interrogating comparative changes in gut microbiota and gut hormones may
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5 317 uncover novel mechanistic insights into how diabetes remission is achieved
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7 318 through these two contrasting surgical procedures.
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11 320 The term “remission” with “partial” and “complete” descriptors have been
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13 321 utilized within the bariatric surgery literature with distinct thresholds of HbA1c
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15 322 and fasting glucose, generally in the absence of glucose lowering therapy, to
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17 323 represent varying degrees of diabetes improvement¹⁵. However, these are
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19 324 controversial given that the diagnosis of diabetes itself is not dichotomous and
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21 325 rather thresholds of glycaemia have been defined on the basis of the associated
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23 326 risk of micro and macrovascular complications. It is not yet known whether
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25 327 these thresholds remain true in a post-bariatric surgery population, and
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27 328 consequently diagnostic criteria for prediabetes and diabetes validated for a
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29 329 non-surgical population may be misleading when applied in reverse, to those
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31 330 who have undergone bariatric surgery. Similarly, there is a paucity of evidence
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33 331 to guide the development of valid, and reliable protocols for discontinuing
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35 332 cardiovascular risk-modifying medications after bariatric surgery for optimum
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37 333 medical management. Nonetheless, we have selected one of the most commonly
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39 334 accepted HbA1c thresholds for classifying diabetes remission¹⁶, and utilized a
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41 335 standard medical management protocol to reduce complacency in medical
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43 336 therapy after abrupt withdrawal of medications post-operatively.
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52 338 Limitations of this study include the single-centre design and the use of SR-type
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54 339 of LRYGB, which potentially limit generalizability of the study. Another
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56 340 limitation is the relatively small sample size, although comparable to other
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3 341 recent studies^{2 3}. However, by employing stratification for confounding variables
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5 342 in randomization, this will ensure factors such as duration of T2D, insulin use,
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7 343 ethnicity and age, will be matched across both treatment groups.
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11
12 345 **Conclusion:**

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14 346 This article presents the protocol and data analysis plan for a single-centre,
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16 347 randomized, double-blinded clinical study comparing LSG and SR-LRYGB in the
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18 348 treatment of T2D in morbidly obese patients, including those who are super-
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20 349 obese. The results of this study, when completed, will assist in decision-making
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22 350 between LSG and LRYGB for the treatment of T2D in morbidly obese patients. In
23
24 351 the interim we hope this description of the study design and metabolic
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26 352 medication adjustment protocol will assist clinicians looking after patients
27
28 353 following bariatric surgery and researchers in planning future bariatric surgery
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30 354 trials.
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37 356 **Funding acknowledgements:** Funding for this project was primarily through
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39 357 Waitemata District Health Board, which provides limited publically funded
40
41 358 bariatric surgery (approximately 100 cases annually). Additional funding for
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43 359 blood sample storage and a research nurse salary was provided by Johnson and
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45 360 Johnson (NZ), Covidien (NZ), and Obex (NZ). DEXA scanning for body
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47 361 composition was provided by the Diabetes Research Fund (NZ), and Maurice &
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49 362 Phyllis Paykel Trust (NZ). Sample collection for the gut microbiota and gut
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51 363 hormone sub-study was funded by a grant from the Maurice Wilkins Centre, New
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3 366 **Declaration of competing interests:** None declared
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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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CONSORT diagram showing the proposed flow of participants through the sleeve gastrectomy vs gastric bypass trial for type 2 diabetes

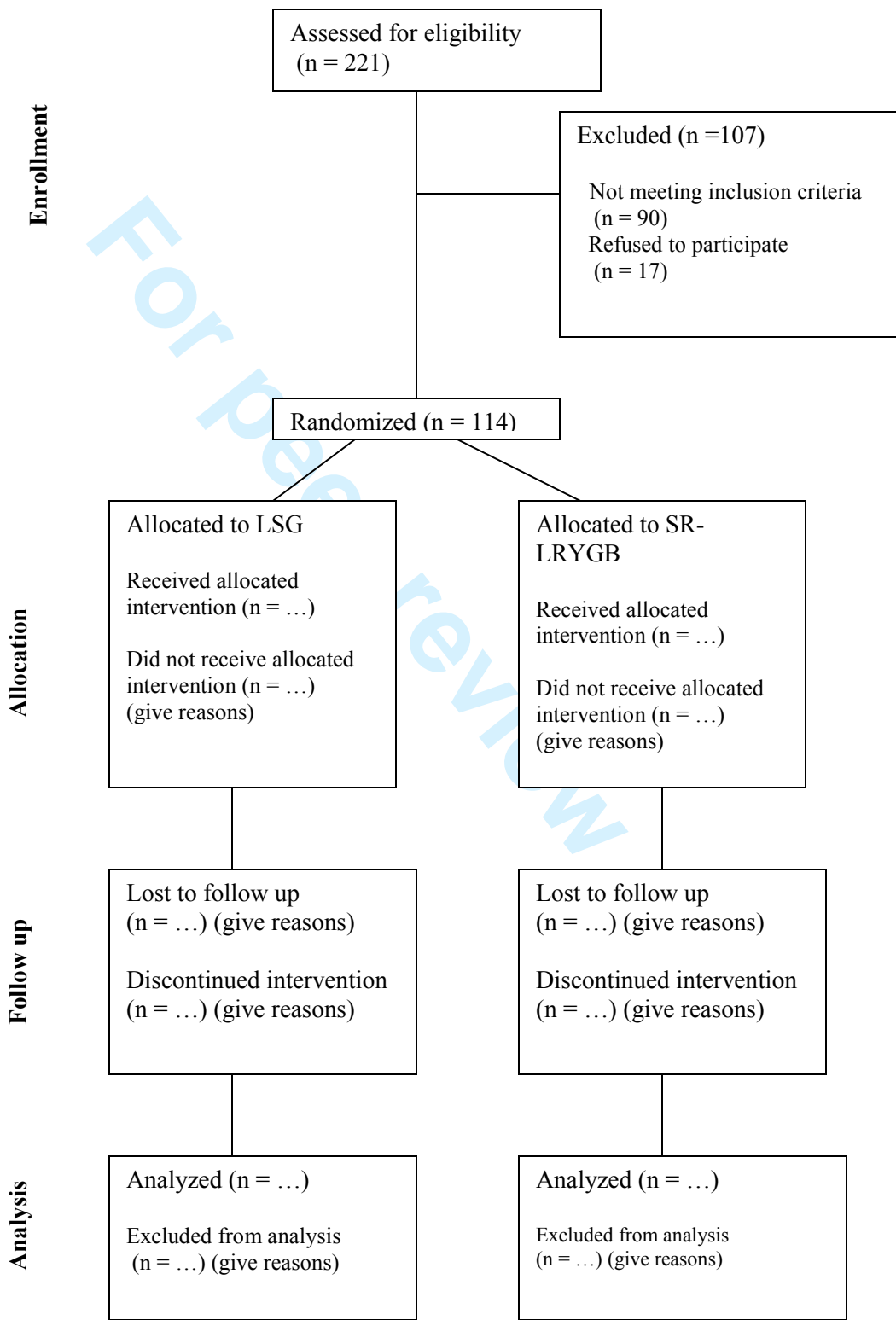


Figure 2: Endocrinology evaluation and treatment protocol for trial patients:

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 below 15% 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)

1				
2			interventions	
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4	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)
5				
6		11b	If relevant, description of the similarity of interventions	P 11 (Lines 233-6)
7				
8				
9	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P9
10		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
11	Results			
12	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
13				
14		13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
15	Recruitment	14a	Dates defining the periods of recruitment and follow-up	P10 (lines 212-213)
16				
17		14b	Why the trial ended or was stopped	N/A
18				
19	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
20	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
21				
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23	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
24				
25		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
26	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
27				
28				
29	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
30				
31	Discussion			
32	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P14 (lines 314-6)
33				
34	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	P14
35	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
36				
37	Other information			
38	Registration	23	Registration number and name of trial registry	P4
39	Protocol	24	Where the full trial protocol can be accessed, if available	N/A
40	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	P5
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4 *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
5 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.
6 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-011416.R1
Article Type:	Protocol
Date Submitted by the Author:	13-May-2016
Complete List of Authors:	Murphy, Rinki; Greenlane Clinical Center, Auckland Diabetes Centre; FMHS, Medicine Evennett, Nicholas; North Shore Hospital, Department of Surgery Clarke, Michael; North Shore Hospital, Surgery Robinson, S; North Shore Hospital, Surgery Jones, Bronwen; North Shore Hospital, Surgery Kim, David; North Shore Hospital, Endocrinology Cutfield, Rick; North Shore Hospital, Endocrinology Plank, Lindsay; University of Auckland, Surgery Hammodat, Hisham; North Shore Hospital, Surgery Booth, Michael; North Shore Hospital, Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Diabetes and endocrinology, Research methods
Keywords:	type 2 diabetes, bariatric surgery, morbid obesity, Roux-en-Y gastric bypass, Sleeve gastrectomy

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2 **Title page**

3 **Title:**

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

6
7 **Authors:**

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14 37 **Running title:** Sleeve gastrectomy vs Roux-en-Y gastric bypass

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3 **41 Abstract:**
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5 **42 Introduction:** Type 2 diabetes (T2D) in association with obesity is an increasing
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50 **Methods and Analysis:** Single-centre, double-blind (assessor and patient),
51 parallel, randomized, clinical trial (RCT) conducted in New Zealand, targeting
52 106 patients. Eligibility criteria include age 20-55 years, T2D of at least 6
53 months duration and BMI 35-65kg/m² for at least 5 years. Randomization 1:1 to
54 LSG or LRYGB, using random number codes disclosed to the operating surgeon
55 after induction of anesthesia. A standard medication adjustment schedule will
56 be used during post-operative metabolic assessments. Secondary outcomes
57 include proportions achieving HbA_{1c} <5.7% [39mmol/mol] or <6.5%
58 [48mmol/mol] without the use of diabetes medication, comparative weight loss,
59 obesity related comorbidity, operative complications, revision rate, mortality,
60 quality of life, anxiety and depression scores. Exploratory outcomes include
61 changes in satiety, gut hormone and gut microbiota to gain underlying
62 mechanistic insights into T2D remission.

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

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3 66 completed in October 2014. Data collection is ongoing. Results will be reported
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5 67 in manuscripts submitted to peer-reviewed journals and presentations at
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7 68 national and international meetings.
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10 69 **Trial registration number:** this study was prospectively registered at
11
12 70 (ACTRN12611000751976) and retrospectively registered at clinicaltrials.gov
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14 71 ([NCT01486680](http://clinicaltrials.gov)).
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19 73 **Article summary:**

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21 74 **Strengths and limitations:**

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24 75 • There is limited evidence from randomized clinical trials comparing the
25
26 76 efficacy of laparoscopic sleeve gastrectomy (LSG) vs laparoscopic Roux-
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28 77 en-Y gastric bypass (LRYGB), to guide optimum surgery selection for
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30 78 morbidly obese patients with T2D.
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32 79 • We describe our double-blind, randomized trial designed to compare
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34 80 efficacy of LSG and silastic-ring LRYGB on remission of T2D at 5 years
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36 81 among morbidly obese patients. We used a standard metabolic
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38 82 medication adjustment protocol after surgery, which should assist
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40 83 clinicians managing patients following bariatric surgery and researchers
41
42 84 planning future bariatric surgery trials, given the thresholds for
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44 85 discontinuing and restarting blood pressure, glucose and lipid
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46 86 medications post-operatively is frequently not reported.
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48 87 • Limitations include the single-centre study design, which may limit
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50 88 generalizability of the findings.
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2
3 91 **Funding:** We acknowledge the funding support from Waitemata District Health
4
5 92 Board, which provides limited publically funded bariatric surgery
6
7 93 (approximately 100 cases annually). Additional funding for blood sample
8
9 94 storage and a research nurse salary was provided by Johnson and Johnson (NZ),
10
11 95 Covidien (NZ), and Obex (NZ). DEXA scanning for body composition was
12
13 96 provided by the Diabetes Research Fund (NZ), and Maurice & Phyllis Paykel
14
15 97 Trust (NZ). Sample collection for the gut microbiota and gut hormone sub-study
16
17 98 was funded by a grant from the Maurice Wilkins Centre, New Zealand. None of
18
19 99 these funders had any role in study design or data analysis or interpretation.
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25 101 **Disclosures:** We have read and understood BMJ policy on declaration of
26
27 102 interests and declare that we have not competing interests.
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31 103

32 104 **Author Contributions:** MB and RM conceived this study. HH, LP, RC, DK, SG,
33
34 105 MC, NE and JC contributed to study design. MB, MC, HH, NE, SR were primarily
35
36 106 responsible for the surgical aspects of the protocol. RC, DK and RM were
37
38 107 primarily responsible for the medical assessment protocol of participants. LP is
39
40 108 primarily responsible for the body composition assessment and energy
41
42 109 expenditure protocol. RM is primarily responsible for the gut microbiota and gut
43
44 110 hormone sub-study protocol. RM wrote the first draft of this manuscript. All
45
46 111 authors read and contributed to the final draft of the paper.
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52 113 **Keywords:** type 2 diabetes, obesity, weight loss, bariatric surgery, silastic ring,
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54 114 Roux-en-Y gastric bypass, Sleeve gastrectomy
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116 Introduction

117 It is unclear which of the two major types of bariatric surgery, laparoscopic
118 sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (LRYGB), achieves the
119 greatest and most durable remission of T2D and weight loss^{1 2}. There are
120 currently only two prospective, non-blinded, randomized controlled trials (RCT)
121 comparing these two types of bariatric surgery^{3 4} in patients with T2D and one
122 blinded study comparing the “mini” –(one anastomosis) gastric bypass with
123 LSG⁵. In one study of 150 American patients with T2D (BMI 27-43kg/m²)
124 randomized to LRYGB, LSG or medical therapy, 42% after LRYGB, 37% after LSG
125 and 12% after medical therapy achieved diabetes remission at 12 months
126 defined by HbA_{1c} of ≤ 6% [42mmol/mol], with or without diabetes medications.
127 All of those achieving the glycemic threshold in the LRYGB group did so without
128 diabetes medications, compared to only 72% of patients in the SG group, so the
129 recalculated proportions for those achieving HbA_{1c} of ≤6% [42mmol/mol]
130 without diabetes medication in the two bariatric surgery groups was 42% after
131 LRYGB and 27% after SG. In a small study of 41 Israeli patients with T2D (BMI
132 >35kg/m²), 37 completed 1 year follow up after randomization to LRYGB or SG⁴.
133 There was a similar reduction in HbA_{1c} after LRYGB (by 1.57 ±1.35% or 17 ±15
134 mmol/mol) and LSG (by 2.37 ±2.22% or 26 ± 24 mmol/mol), p=0.34⁴. In a
135 double-blinded, single-centre study of 60 Taiwanese patients with T2D (BMI 25-
136 34 kg/m²), 93% of those randomized to “mini” bypass achieved diabetes
137 remission at 12 months compared to 47% randomized to LSG, using diabetes
138 remission criteria of fasting glucose <7.0mmol/L and HbA_{1c} < 6.5%
139 [47mmol/mol] in absence of diabetes medications⁵. None of these studies
140 reported their medication adjustment protocol after surgery. The assessment of

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3 141 T2D remission may be affected by both participant lifestyle factors and clinician
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5 142 variation in glucose medication withdrawal thresholds used. Further studies
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7 143 evaluating comparative efficacy of LSG and LRYGB are required, particularly
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9 144 using blinding of both patients and investigators assessing for T2D remission
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11 145 utilizing standard protocols for post-operative medical management to minimize
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14 146 bias.

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19 148 The advantages of LRYGB include being fully reversible, however the irreversible
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21 149 LSG is a faster and simpler procedure with potentially less dumping. There are
22
23 150 technical difficulties involved in performing LRYGB in severely obese patients,
24
25 151 and such patients may have limited success from LRYGB attributed to pouch
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27 152 dilation and loss of restriction at the gastrojejunal anastomosis over time. The
28
29 153 placement of a silastic ring band around the gastric pouch at the time of primary
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31 154 RYGB is considered superior to the non-banded RYGB in the super-obese
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33 155 population⁶. Other modifications to the LRYGB procedure includes variation in
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35 156 pouch size (10-50mL), alimentary limb length (50-250cm), and biliopancreatic
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37 157 limb length (25-150cm)².

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44 159 The underlying mechanisms by which SG and RYGB achieve T2D remission are
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46 160 unclear and may involve changes in gut hormones⁷, inflammatory markers⁸ and
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48 161 gut microbiota⁹. Investigation into the impact of these two types of bariatric
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50 162 surgery on these mechanisms and resulting glucose metabolism, body
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52 163 composition and satiety is required.

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3 165 The primary objective of this trial is to compare the efficacy of silastic ring (SR)-
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5 166 LRYGB and LSG on remission of T2D, defined by HbA_{1c} <6% (42mmol/mol)
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7 167 without the use of diabetes medications (as per the consensus definition of
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10 168 complete diabetes remission¹⁰), at 5 years post-surgery. Secondary objectives
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12 169 are to examine proportions achieving alternative glyceic thresholds HbA_{1c}
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14 170 <5.7% (39mmol/mol) or <6.5% (48mmol/mol) without the use of diabetes
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16 171 medications, extent of weight loss, change in body composition, resting energy
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18 172 expenditure, operative complications, revision rate, hospitalizations, mortality,
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20 173 microvascular and macrovascular complications, cardiovascular risk factors,
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22 174 quality of life, anxiety and depression scores between the two groups. In
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24 175 addition, underlying mechanisms of T2D remission will be investigated by
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26 176 examining comparative changes in gut hormones, inflammatory markers, gut
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28 177 microbiota, in relation to diabetes remission, changes in body composition, food
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30 178 intake and appetite scores.
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180 **Methods**

181 **Trial design:** This is a parallel (1:1), single-centre, two-arm, randomized,
182 double-blind (patient and assessor), superiority trial (figure 1).
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184 **Sample size justification and power calculation:** Assuming rates of diabetes
185 remission to be 88% in SR-LRYGB and 59% in LSG, a minimum of 42 patients per
186 arm, will provide 80% power to detect a difference between the two groups
187 using a two-sided alpha of 0.05. These estimates were derived from our
188 unpublished audit data. An expected loss to follow up rate of 20%, requires at
189 least 53 patients per arm.

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5 191 **Data analysis plan:** Study analysis will be by intention-to-treat. Prior to
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7 192 performing analyses, standard data screening and cleaning procedures will be
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9 193 applied to detect possible data-entry errors and to check for outliers, assess the
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11 194 extent and patterns of missing data and check that appropriate assumptions of
12
13 195 normality are met whenever necessary. Baseline characteristics will be analyzed
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15 196 by descriptive statistics using means and standard deviations for all continuous
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17 197 variables with a normal distribution, and medians and interquartile ranges for
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19 198 variables with a non-normal distribution. Categorical variables will be
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21 199 summarized with frequencies. For the primary analysis, the difference in
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23 200 proportions achieving T2D remission (HbA_{1c} <6% [42mmol/mol] without
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25 201 diabetes medication) will be compared between LSG and SR-LRYGB at 5 years,
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27 202 adjusting for stratification variables using logistic regression. A two-sided p
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29 203 value of 0.05 will be considered to indicate statistical significance. Missing data
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31 204 will be handled by multiple imputation as appropriate. Analyses will be
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33 205 performed with the use of SAS software, version 9.4 or later (SAS Institute, Cary,
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35 206 NC).

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43 208 **Participants:** All patients aged 20-55years with T2D of at least 6 months
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45 209 duration, BMI 35-65kg/m² for at least 5 years, who were referred for
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47 210 consideration of bariatric surgery at a single centre (North Shore Hospital), were
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49 211 invited to participate and to attend a bariatric surgery study information
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51 212 evening. All participants were given a written informed consent form and
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53 213 understood that on entering the randomized study they would not know their
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55 214 treatment allocation until completion of the study at 5 years. Other inclusion
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3 215 criteria included being suitable for either of the two surgical procedures, able to
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5 216 give informed consent and committed to follow up. Exclusion criteria included
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7 217 post-prandial C-peptide <350pmol/L, pregnancy, type 1 diabetes or secondary
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9 218 diabetes, chronic pancreatitis, oral steroid therapy, current smokers and those
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11 219 not suitable for general anesthesia. The study commenced in September 2011
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13 220 and completed recruitment in October 2014. A total of 114 participants were
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15 221 recruited into the study (figure 1). Data collection and follow up is ongoing.
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21 223 **Baseline assessments:** All participants were prescribed a very-low-calorie diet
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23 224 (VLCD) with three servings of Optifast ®, (Nestle, Vevey, Switzerland), each
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25 225 containing approximately 152 calories, plus vegetables pre-operatively, for two
26
27 226 weeks, designed to reduce liver fat and make laparoscopic abdominal surgery
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29 227 safer. Baseline clinical and anthropometric assessments were conducted before
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31 228 and after the VLCD. Baseline body composition assessment was conducted
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33 229 during the VLCD period, in the week before surgery (figure 2).
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39 231 **Randomization:** Computer generated random number codes (Minim, London)
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41 232 managed by an independent study member were used to randomize participants
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43 233 1:1 to either LSG or SR-LRYGB, stratified by age category (20-29, 30-39 or 40-
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45 234 55), BMI category (35-44.9, 45-54.9, 55-65kg/m²), ethnicity (Maori, Pacific, NZ
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47 235 European/other), duration of diabetes diagnosis (<5 years, 5-10 years, >10
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49 236 years) and the presence of insulin therapy.
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55 238 **Allocation concealment and blinding:** On the day of surgery, following
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57 239 induction of general anesthesia, allocation to either LSG or SR-LRYGB was
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3 240 disclosed only to the operating surgical team. Both operations were performed
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5 241 utilizing identical incisions with a four-port technique (optical entry; two 10-
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7 242 12mm ports and two 5mm ports) and an additional epigastric incision for liver
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9 243 retraction. Participants and all other research and clinical team members
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11 244 remain blinded to surgical allocation. Only de-identified codes were used to link
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13 245 participants to their data during the study to maintain their confidentiality.
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19 247 **Intervention:** For SG, a sleeve was fashioned starting 2cm proximal to the
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21 248 pylorus using serial applications of an Echelon Flex 45 stapler (Ethicon) over a
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23 249 36Fr oro-gastric bougie. For SR-LRYGB, a lesser curve based gastric pouch was
24
25 250 fashioned over a 32Fr oro-gastric tube, with a 50cm bilio-pancreatic limb, 100cm
26
27 251 antecolic Roux limb with hand-sewn single layer gastro-jejunostomy over a 32Fr
28
29 252 oro-gastric tube. A 6.5cm silastic ring was then secured around the gastric pouch
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31 253 2cm above the gastro-jejunostomy anastomosis. Mesenteric defects were closed
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37 255 **Follow up:** Post-operative care and follow up will be identical for both groups.
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39 256 All pharmacological agents for diabetes and hypertension will be stopped at the
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41 257 time of surgery. Glucose lowering therapy will be restarted if mean post-
42
43 258 operative capillary glucose exceeds 12mmol/L. All participants will be reviewed
44
45 259 by an endocrinologist at 6 weeks, 9 months then annually (table 1) for
46
47 260 adjustment of all medications and assessment of micro- and macrovascular
48
49 261 complications ¹¹. The medication adjustment protocol including lipid, blood
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51 262 pressure and glucose lowering therapy is outlined in figure 2. Microvascular
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53 263 complications will be assessed annually with clinical evaluation for peripheral
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55 264 neuropathy symptoms and signs, retinal photoscreening and measurement of
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3 265 renal function, urine albumin:creatinine ratio. Macrovascular complications
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5 266 such as incidence of myocardial infarction, stroke, peripheral vascular disease
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7 267 will also be recorded.
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11 269 **Assessment of outcomes:** HbA_{1c} will be measured by high-performance liquid
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13 chromatography (Bio-Rad). Body weight will be recorded to the nearest 0.1kg
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15 270 using digital scales (SECA, Chino, CA). Height will be recorded to the nearest
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17 271 0.5cm using a stadiometer. Total body fat, left femoral neck bone density and AP
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19 272 lumbar spine bone density will be measured by dual-energy X-ray
20
21 273 absorptiometry (DEXA, model iDXA, software version 15, GE-Lunar, Madison,
22
23 274 WI). Percent body fat will be calculated as 100 x total body fat/body weight.
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25 275 Resting energy expenditure (REE) will be measured after overnight fast using a
26
27 276 ventilated canopy connected to an open-circuit indirect calorimeter (Deltatrac
28
29 277 Metabolic Monitor MBM-100, Datex instruments, Helsinki, Finland).
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31 278 Hospitalizations, operative complications graded according to the Clavien-Dindo
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33 279 classification ¹², mortality, revisional surgery, changes in medications will be
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35 280 recorded. Hospital anxiety and depression scale (HADS)¹³ and short form-36
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37 281 item (SF-36)¹⁴ questionnaires will be used (table 1).
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44 284 **Ancillary mechanistic study:** Alongside the primary trial, participants were
45
46 285 able to opt in to an exploratory gut hormone and gut bacteria mechanistic sub-
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48 286 study. As part of this study, they were asked to provide additional data and
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50 287 biosamples during the three scheduled visits for body composition assessments
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52 288 at baseline, 1 year and 5 years. The additional data include a 3-day food diary,
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54 289 hunger ratings assessment, fecal samples, and a 75g oral glucose tolerance test.
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3 290 Participants were requested to prospectively record all foods and drinks taken
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5 291 during the 3-day diary period including the amounts taken, and any dietary
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7 292 supplements taken or medications during the period. Visual analog scale (VAS)
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10 293 hunger ratings will be collected upon arrival at the body composition unit in a
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12 294 fasted state at baseline, 1 year and 5 years. Participants will be asked to rate
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14 295 their motivation to eat on a horizontal non-graded line measuring 100mm,
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16 296 anchored on the left by “not at all” and on the right by “very much” next to four
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18 297 responses: How hungry are you? How full do you feel? How strong is your
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20 298 desire to eat? How much food do you think you could eat? Fecal samples will be
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22 299 self-collected in stool containers, sealed and placed into another sealed container
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24 300 filled with water and frozen immediately at -20°C, before being transported in
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26 301 the frozen state to the laboratory where they will be stored at -80°C. Participants
27
28 302 will be asked to attend these body composition/REE visits in a fasted state for a
29
30 303 two-hour 75g oral glucose tolerance test, with 30 minute blood sampling. Blood
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32 304 samples will be collected into EDTA, serum separator tubes and BD P800 tubes
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34 305 (BD, Franklin Lakes, NJ), containing protease inhibitors to maximize the stability
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36 306 of gut hormones ¹⁵.

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43 308 **Ethics and dissemination:** Ethics approval has been granted by the New
44
45 309 Zealand regional ethics committee (NZ93405). This study was prospectively
46
47 310 registered at ANZCTR (ACTRN12611000751976) and retrospectively registered
48
49 311 at clinicaltrials.gov (NCT01486680). The results of this study and ancillary
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51 312 studies will be publicized in the form of presentations at national and
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53 313 international meetings. The study and conclusions regarding the primary and
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3 314 secondary objectives and ancillary studies will be presented as manuscripts
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5 315 submitted for peer-reviewed journal publication.
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10 317 **Discussion:**

11 318 This is the first double-blind, randomized trial to compare SR-LRYGB and LSG for
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13 319 the treatment of T2D in morbidly obese patients including those with BMI up to
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15 320 65kg/m². The use of a standard metabolic medication adjustment protocol is a
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17 321 strength of the study design, in effort to reduce heterogeneity in management of
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19 322 blood pressure, lipids and T2D post-operatively. The ancillary studies
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21 323 interrogating comparative changes in gut microbiota and gut hormones may
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23 324 uncover novel mechanistic insights into how diabetes remission is achieved
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25 325 through these two contrasting surgical procedures.
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32 327 The term “remission” with “partial” and “complete” descriptors have been
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34 328 utilized within the bariatric surgery literature with distinct thresholds of HbA_{1c}
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36 329 and fasting glucose, generally in the absence of glucose lowering therapy, to
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38 330 represent varying degrees of diabetes improvement¹⁰. However, these are
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40 331 controversial given that the diagnosis of diabetes itself is not dichotomous and
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42 332 rather thresholds of glycaemia have been defined on the basis of the associated
43
44 333 risk of micro and macrovascular complications. It is not yet known whether
45
46 334 these thresholds remain true in a post-bariatric surgery population, and
47
48 335 consequently diagnostic criteria for prediabetes and diabetes validated for a
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50 336 non-surgical population may be misleading when applied in reverse, to those
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52 337 who have undergone bariatric surgery. Similarly, there is a paucity of evidence
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54 338 to guide the development of valid, and reliable protocols for discontinuing
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3 339 cardiovascular risk-modifying medications after bariatric surgery for optimum
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5 340 medical management. Nonetheless, we have selected one of the most commonly
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7 341 accepted HbA_{1c} thresholds for classifying diabetes remission¹⁶, and utilized a
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9
10 342 standard medical management to reduce complacency in medical therapy after
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12 343 abrupt withdrawal of medications post-operatively.

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16 345 Limitations of this study include the single-centre design, and the relatively small
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18 346 sample size. However, by employing stratification for confounding variables in
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20 347 randomization, this will ensure these factors (such as duration of T2D, insulin
21
22 348 use, ethnicity and age), will be matched across both treatment groups. SR-LRYGB
23
24 349 was chosen due to superior long-term weight loss outcomes, largely due to
25
26 350 reduction in weight regain when compared to non-banded LRYGB.¹⁷⁻¹⁹ However,
27
28 351 this modification of LRYGB is possibly not widely adopted due to unfamiliarity
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30 352 with placing it, and potential issues regarding food intolerance and band-related
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32 353 complications⁶. Some of these concerns are ill conceived and hence currently the
33
34 354 use of SR-type of LRYGB may limit generalizability of the study.

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41 356 **Conclusion:**

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43 357 This article presents the protocol and data analysis plan for a single-centre,
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45 358 randomized, double-blinded clinical study comparing LSG and SR-LRYGB in the
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47 359 treatment of T2D in morbidly obese patients, including those who are super-
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49 360 obese. The results of this study, when completed, will assist in decision-making
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51 361 between LSG and LRYGB for the treatment of T2D in morbidly obese patients. In
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53 362 the interim we hope this description of the study design and metabolic
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55 363 medication adjustment protocol will assist clinicians looking after patients
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3 364 following bariatric surgery and researchers in planning future bariatric surgery
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5 365 trials.
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10 367 **Funding acknowledgements:** Funding for this project was primarily through
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12 368 Waitemata District Health Board, which provides limited publically funded
13
14 369 bariatric surgery (approximately 100 cases annually). Additional funding for
15
16 370 blood sample storage and a research nurse salary was provided by Johnson and
17
18 371 Johnson (NZ), Covidien (NZ), and Obex (NZ). DEXA scanning for body
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20 372 composition was provided by the Diabetes Research Fund (NZ), and Maurice &
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22 373 Phyllis Paykel Trust (NZ). Sample collection for the gut microbiota and gut
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24 374 hormone sub-study was funded by a grant from the Maurice Wilkins Centre, New
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26 375 Zealand.
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32 377 **Declaration of competing interests:** None declared
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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 ***	✓						✓					✓

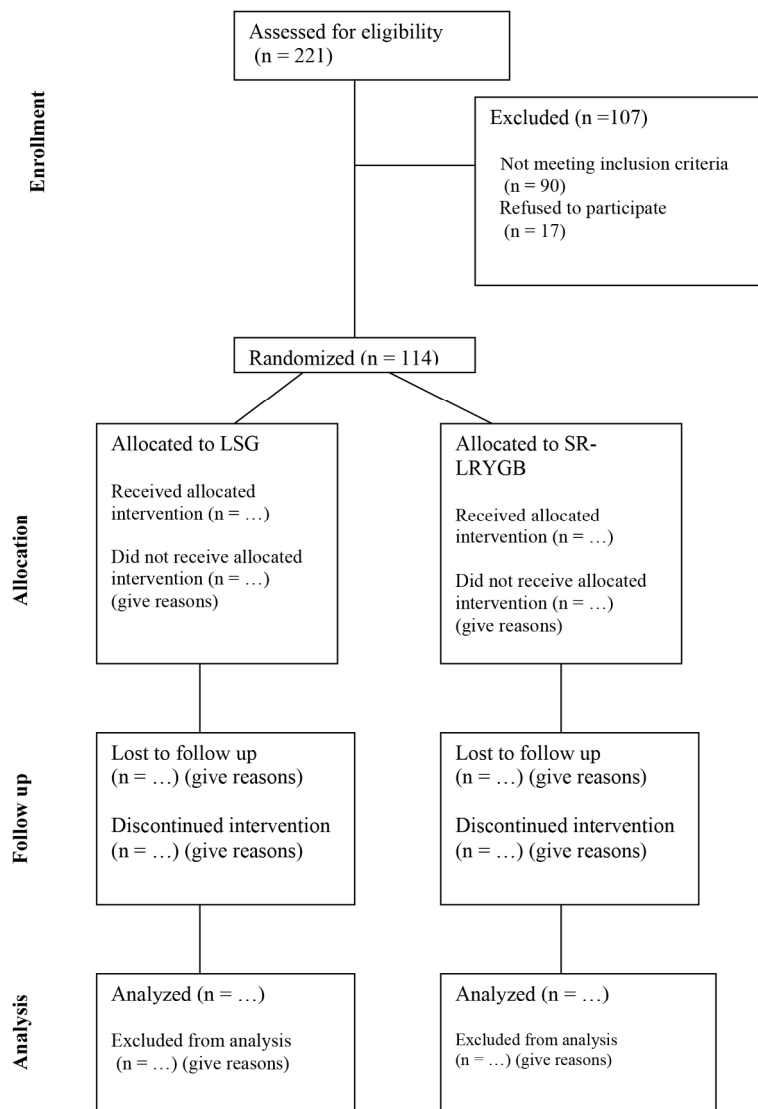
dual-energy X-ray absorptiometry/resting energy expenditure
 * full blood count, C-reactive protein, ESR, electrolytes, creatinine, calcium, albumin, bilirubin, liver enzymes, lipids, 25-hydroxy-vitamin D,
 ** samples immediately frozen
 *** samples also stored in BD P800 tubes for gut hormone analysis

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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 below 15% 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)	_____

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3 **Introduction**
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5	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	_____ 6 _____
6	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
7				
8		6b	Explanation for choice of comparators	_____ 6 _____
9				
10	Objectives	7	Specific objectives or hypotheses	_____ 8 _____
11				
12	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
13			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____ 8 _____
14				
15				
16	Methods: Participants, interventions, and outcomes			
17				
18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	_____ 9 _____
19			be collected. Reference to where list of study sites can be obtained	
20				
21	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	_____ 9-11 _____
22			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
23				
24	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	_____ 11 _____
25			administered	
26				
27		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	_____
28			change in response to harms, participant request, or improving/worsening disease)	
29				
30		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	_____ 11 _____
31			(eg, drug tablet return, laboratory tests)	
32				
33		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____ 11 _____
34				
35	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	_____ 12 _____
36			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
37			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
38			efficacy and harm outcomes is strongly recommended	
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41	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	_____ 17 _____
42			participants. A schematic diagram is highly recommended (see Figure)	
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3	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_____
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6	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____9_____
7				

8 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

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12	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_____
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18	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_____
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22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___10-11_____
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25	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___11_____
26				
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28		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
29				
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32 **Methods: Data collection, management, and analysis**

33				
34	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_____
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39		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_____
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3	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___
4				
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7	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___
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___9___
11				
12		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___
13				
14				
15				

16 **Methods: Monitoring**

17				
18	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	_____
19				
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23		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	_____
24				
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26	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	_____
27				
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29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
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33 **Ethics and dissemination**

34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___13___
36				
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38	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)	_____
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___ 9 ___
4				
5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___ 12-13 ___
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9	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 ___
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___ 5 ___
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15	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	_____
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18	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	_____
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21	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 ___
22				
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	_____
27				
28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
29				
30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
33				
34				
35	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 ___
36				
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*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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)

1				
2			interventions	
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4	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)
5				
6		11b	If relevant, description of the similarity of interventions	P 11 (Lines 233-6)
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9	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P9
10		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
11	Results			
12	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
13				
14		13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
15	Recruitment	14a	Dates defining the periods of recruitment and follow-up	P10 (lines 212-213)
16				
17		14b	Why the trial ended or was stopped	N/A
18				
19	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
20	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
21				
22				
23	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
24				
25		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
26	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
27				
28				
29	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
30				
31	Discussion			
32	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P14 (lines 314-6)
33				
34	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	P14
35	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
36				
37	Other information			
38	Registration	23	Registration number and name of trial registry	P4
39	Protocol	24	Where the full trial protocol can be accessed, if available	N/A
40	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	P5
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4 *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
5 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.
6 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
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For peer review only