Gastric Bypass, adjustable gastric Banding or Sleeve gastrectomy surgery to treat severe and complex obesity: a multi-centre randomised controlled trial

The By-Band-Sleeve Study

REC No: 11/SW/0248

ISRCTN No: 00786323

Clinical Trials No: TBA

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Glossary / abbreviations

AE	Adverse event - any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.
Band	Laparoscopic adjustable gastric banding surgery
Bypass	Laparoscopic gastric bypass surgery
BMI	Body mass index
CA	Conversation analysis
CI	Confidence interval
CRF	Case report form
CPAP	Continuous positive airways pressure
CTEU	Clinical Trials and Evaluation Unit
DMSC	Data monitoring and safety committee
DVT	Deep vein thrombosis
EQ-5D-5L	EuroQol health status questionnaire (5 level version)
ELF	Enhanced liver fibrosis test
GI	Gastro-intestinal
GIQLI	Gastro-intestinal quality of life index
GP	General practitioner
HA	Hyaluronic acid
HADS	Hospital anxiety and depression scale
HRQOL	Health related quality of life
HTA	Health Technology Assessment
ICH-GCP	International conference for harmonisation of good clinical practice
IQS	Integrated qualitative study
IWQOL-Lite	Impact of weight of quality of life-Lite
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PIIINP	Aminoterminal peptide of procollagen type III
PCT	Primary care trust
PI	Principal investigator
PIL	Patient information leaflet
QALY	Quality adjusted life years
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.
SAR	Serious adverse reaction
SF-12	Short-form 12 question HRQOL questionnaire
Sleeve	Sleeve gastrectomy surgery
SMS	Standard message service
SOP	Standard operating procedure
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction - an untoward medical occurrence suspected to be related to a medicinal product that is not consistent with the applicable product information and is serious.
TIMP-1	Tissue inhibitor of matrix metalloproteinase
TMG	Trial management group
TPN	Total parenteral nutrition
TSC	Trial steering committee

1. Trial summary

Obesity is an increasing health problem in the UK and is predicted to worsen. There are many health problems associated with obesity including risk of diabetes, gallbladder disease, sleep problems, heart disease and arthritis. These health issues can shorten a person's life expectancy, impair quality of life and increase the use of expensive health services. Current national guidelines to treat obesity recommend management of life-style changes as the initial treatment for people who are overweight. However, surgery is considered for the very overweight (severe and complex obesity) or for those remaining obese after trying other options. The three recognised operations in bariatric surgery are laparoscopic adjustable gastric banding ('Band'), laparoscopic gastric bypass ('Bypass') and Sleeve gastrectomy ('Sleeve'). When By-Band was conceived, the two most commonly performed operations in the UK and worldwide were laparoscopic adjustable gastric banding ('Band surgery') and laparoscopic gastric bypass ('Bypass surgery'). Together these accounted for over 80% of all operations carried out to treat severe and complex obesity. At that time Sleeve gastrectomy ('Sleeve surgery') accounted for 8% of procedures and was considered to be insufficiently established to warrant full evaluation in a pragmatic randomised controlled trial (RCT). However, over the past five years the number of Sleeve gastrectomies undertaken in the UK has increased from 8% to 29% and this pattern is mirrored worldwide. At the same time there has been a gradual decrease in gastric Band surgery, although it still accounts for over 40% of operations carried out in the private sector.

Bypass surgery alters the food passage so food spends less time in the stomach and avoids some of the small bowel. Band surgery involves inserting an adjustable plastic band around the top of the stomach to reduce its capacity, and Sleeve gastrectomy involves removing a large part of the stomach to reduce it to about 25% of its original size. All three operations lead to weight loss by reducing appetite and inducing satiety, but they are associated with different problems. In the short term there are varying complications and inconvenience relating to the operation. In the longer term there are different outcomes relating to weight regain, symptoms and side effects of the gastric Bypass, Sleeve gastrectomy or problems with the band. Estimates of initial surgical costs of Band is about 3K, Sleeve about 5K and more complex Bypass procedure (about 6K), however Band surgery requires more intensive follow-up clinic visits with adjustment of fluid in the band. At present only rough estimates of overall costs can be therefore given because of the variation between tariffs for the procedures in the NHS and variable provision of follow up visits. The tariffs may also change over the next few years due to changes in the commissioning of bariatric surgery in the UK.

There is a lack of well-designed research comparing Band, Bypass and Sleeve and current decisions in the UK to undergo one of the three operations rely upon guidance from general practitioners (GPs), or local surgeons (not informed by good evidence) and patients' preferences. Head to head comparisons of the three surgical procedures has previously been considered too difficult to undertake because surgeons have tended to favour one type of procedure more than another. However, it is widely acknowledged that studies are urgently required to compare the effectiveness, cost effectiveness and acceptability of Band, Bypass and Sleeve. The most suitable study design is a trial in which patients could be allocated to one of the three procedures by a process of randomisation. This means they have an equal chance of having one of the procedures and so a fair comparison of the outcomes of each of them can be made.

We propose a three phase study in twelve hospitals. The first phase (in two hospitals) will test the feasibility of recruitment, randomisation and develop ways to optimise information for patients to maximise trial recruitment to either Band or Bypass. Phase 1 will also establish a core set of clinical outcomes to use to evaluate the surgery for severe and complex obesity. The second phase (in all 12 hospitals) will be adapted to include Sleeve. The third phase will

complete the recruitment and follow-up. The three group trial will recruit a total of 1341 patients and will follow-up all participants for at least three years after randomisation.

We will compare the effects of Band, Bypass and Sleeve surgery three years after randomisation on weight loss, a wide range of symptoms and aspects of quality of life. We will also examine patients' experiences during follow-up, nutritional outcomes, short and long term surgical complications and NHS value for money.

2. Background

2.1 Existing research evidence

Adult obesity prevalence is increasing around the world, and in the UK rates have trebled during the past 25 years to around 24% [1]. If trends persist, 36% of men and 28% of women aged 21 to 60 will be obese in 2015, and worldwide approximately 700 million adults will be living with the condition [1, 2]. The prevalence of severe and complex obesity (clinically defined as a body mass index (BMI) ≥ 35kg/m^2 with co-morbidity or a BMI > 40 kg/m^2 without co-morbidity) is also on the increase, and UK prevalence has been estimated at around 2.1% [3, 4].

Obesity is associated with a number of health problems, including type 2 diabetes, cardiovascular disease, musculoskeletal disorders, infertility, and psychiatric disorders. The mortality rate for those with severe and complex obesity is approximately double that for the general population. Additionally, obesity is a major contributor to social inequalities in health [5] and places a huge financial burden on the NHS. The direct costs of treating diseases associated with overweight and obesity were estimated at £3.2 billion in 2002, or nearly 5% of total NHS expenditure [6]. On an individual level, living with obesity has been associated with psychological distress and social stigma, both of which may have a significant impact on individuals' quality of life [7, 8]. The prevention and treatment of obesity is thus a key priority for the NHS, and the provision of weight management services for adults is now firmly established as a core policy objective.

Reversal of obesity is uncommon without intervention [9], and National Institute for Health and Care Excellence (NICE) guidance states that health authorities should establish comprehensive care pathways for addressing overweight and obesity within their populations, which should include access to diet and exercise interventions, anti-obesity drugs, and, in some circumstances, weight reduction surgery [10]. However, it is known that many interventions for obesity fail, and bariatric surgery is increasingly being viewed as a solution to weight loss, particularly for those who have severe and complex obesity. Although surgery is usually considered after patients have attempted other forms of weight loss without success, the exception to this is for adults with a BMI > 50. NICE guidelines recommend surgery as a first-line option for this group of patients (instead of lifestyle interventions or drug treatment) if surgical intervention is considered appropriate.

2.2 Surgery for severe and complex obesity

Surgical procedures for those with obesity aim to reduce weight and maintain weight loss through restriction of intake and/or malabsorption of food. There are several different operations in use including laparoscopic gastric bypass (Bypass), laparoscopic adjustable gastric band (Band), biliopancreatic diversion and its duodenal switch variant, vertical banded gastroplasty and sleeve gastrectomy (Sleeve). Despite the variety of different surgical procedures available, the three most commonly performed operations worldwide are Bypass, Band and Sleeve. Together these account for about 80% of all obesity operations in the UK and the USA [11-13].

2.2.1 Laparoscopic gastric bypass (Bypass)

Bypass achieves weight loss by altering the flow of food through the gut and combining restrictive, hormonal and some malabsorptive principles. The surgical procedure alters physiology and anatomy in such a way as to achieve rapid weight loss, although it is not adjustable. Observational studies show that significant early weight loss occurs within 12 months of Bypass and this is associated with improvements in generic aspects of health related quality of life (HRQOL) (physical, social and role function) [5, 14]. There is a lack of

medium or longer term outcome data after Bypass and studies suffer from loss to follow up and lack of generic and disease specific long term HRQOL data [15]. Surgical risks of Bypass include serious morbidity and death. In a study of 2975 patients undergoing Bypass the risk of death at 30 days was 0.2% (6 deaths), and 94 patients (3.2%) required re-operation [16, 17]. Longer term complications of Bypass may include the need for re-operation because of internal hernias or intestinal obstruction, symptoms of flatulence and regurgitation and nutritional deficiencies. Long term follow up is therefore required and may also provide an opportunity for dietary education and support.

2.2.2 Laparoscopic adjustable gastric banding (Band)

Band achieves weight loss by three processes, (i) placement of a band surgically around the top of the stomach to restrict the stomach, (ii) post-operative adjustment of the band (at out-patient visits) to regulate the degree of gastric restriction (by injection or removal of fluid from the band via a subcutaneous access port) and to help control the appetite and iii) education and support of patients at band adjustment appointments. Observational studies show that after Band patients experience gradual weight loss and that it may take 12 to 24 months to achieve optimal weight loss [17]. The number and nature of visits for band adjustment are important [18, 19], however there are currently no UK nationally agreed standards for post-operative visits after Band to assist either service providers or commissioners. The literature suggests that up to 7 visits are required in the first year and that three monthly visits are required in the second year to achieve and maintain optimal weight loss. There is also evidence that on-going visits (six monthly thereafter) are needed [18, 19]. Centres which achieve the greatest weight loss with Band ensure that the follow up care is at least three monthly at first and that it is maintained [3, 18, 19]. After Band patients may have symptoms of dysphagia and regurgitation and, although weight loss after Band is associated with improvements in HRQOL [20], medium and long term HRQOL data are lacking. Short term surgical risks of Band are uncommon; in a prospective cohort of 1198 patients undergoing Band, there were no deaths and 9 re-operations [16]. Longer term complications of Band include band erosion or migration, pouch dilatation, leakage from the circuit or infection which may require revision surgery or band removal [17, 21].

2.2.3 Laparoscopic sleeve Gastrectomy (Sleeve)

Sleeve gastrectomy achieves weight loss by reducing the stomach to about 25% of its original size. A large portion of the stomach is removed along the greater curvature. The result is a sleeve or tube like structure. The pyloric valve at the bottom of the stomach is left intact which means that the stomach function and digestion are unaltered. Surgical risks of Sleeve include leakage and vomiting due to damage to the vagus nerve. Registry data to 2 years shows that after Sleeve patients experience gradual weight loss over the first 12 months, which tends to plateau thereafter [12]. Weight loss in the first year after Sleeve is associated with improvements in HRQOL [22], but medium and long term HRQOL data are lacking.

2.3 Systematic review evidence

Evidence for the different types of surgery for severe and complex obesity (and comparison with non-surgical treatment) was summarised in an HTA systematic review [9], which has recently been updated [23]. Of the 22 randomised controlled trials (RCTs) in the updated review, fifteen compared different types of bariatric surgery, three comparing Band with Bypass, six comparing Bypass with Sleeve, and one is comparing Band with Sleeve.

The three trials comparing Band and Bypass were all single centre studies conducted outside the UK. The Italian trial included 51 participants, excluded some after

randomisation, did not perform analyses by 'intention- to treat', did not blind outcome assessors and did not assess HRQOL [24]. The second US-based study randomised 250 patients [25]. Patients, however, were differentially excluded after randomisation creating imbalance in the numbers in each group and an imbalance in key patient characteristics at baseline (age and BMI) and the analysis was not by 'intention-to-treat'. The generation of the allocation sequence was unclear; there was incomplete outcome data in the two groups at follow up and no details of the number of participants completing HRQOL questionnaires were presented. The third trial, conducted in Egypt, randomised 34 patients and did not assess HRQOL [26]. The evidence of the effectiveness of Band and Bypass is therefore inadequate with just three single centre trials that have an uncertain risk of bias and an inadequate HRQOL analysis.

The six trials comparing Bypass and Sleeve were all conducted outside the UK and had relatively small sample sizes ranging from 15 to 217 patients. Except for the largest trial conducted in four centres in Switzerland, all were single centre studies. The Swiss trial was at high risk of bias as the outcomes reported were from an interim analysis that did not include all patients randomised [27]. The other trials also have methodological weaknesses due to risk of bias, they are underpowered with optimistic effect sizes and many have short term primary outcomes (12 months).

The one trial to compare Band and Sleeve was conducted in a single centre in Belgium. Eighty patients were recruited and at 3-years there was a significantly greater weight loss with Sleeve compared to Band (mean 29.5kg vs. 17kg). However, the study has uncertain risk of bias and HRQOL was not assessed.

Bariatric surgical practice continues to be based on the preferences of local commissioners, surgeons and patients. The need for a well-designed RCT of Band, Bypass and Sleeve, with clinically relevant comparisons, measures of generic and disease specific HRQOL, cost effectiveness evaluations and at least medium term follow up and documentation of longer term adverse events remains.

This need was highlighted in both the original and updated HTA systematic reviews, but it was also stated in the original review that a trial may be too difficult to conduct and recruit into because of strong preferences amongst surgeons that influence patient selection for surgery [9]. This RCT will therefore compare Band versus Bypass versus Sleeve in three phases; the first phase (Band versus Bypass only) will establish optimal methods to recruit into the trial and ensure that the main trial is feasible. The second and third phases, which will include Sleeve as a third group, will continue recruitment in multiple centres.

3. Aims and objectives

The By-Band-Sleeve study will compare the effectiveness, cost-effectiveness and acceptability of Band versus Bypass versus Sleeve surgery for treatment of severe and complex obesity.

We will test the following joint hypotheses:

i) Bypass is non-inferior to Band with respect to excess weight loss of more than 50% at three years and that Bypass is superior to Band with respect to HRQOL at three years.

ii) Sleeve is non-inferior to Band with respect to excess weight loss of more than 50% at three years and that Sleeve is superior to Band with respect to HRQOL at three years.

iii) Sleeve is non-inferior to Bypass with respect to excess weight loss of more than 50% at three years and that Sleeve is superior to Bypass with respect to HRQOL at three years.

In the primary analysis both outcomes will be considered collectively, i.e. both hypotheses must be supported to conclude that Bypass is more effective than Band, or that Sleeve is more effective than Band or Sleeve is more effective than Bypass.

Specific objectives are to estimate:

A. The difference between groups in the proportion of patients achieving >50% excess weight loss at three years;

B. The difference between groups in their average EQ-5D-5L health state score at three years;

C. The difference between groups with respect to a range of secondary outcomes including generic, disease specific and gastro-intestinal symptom specific measures of HRQOL, adverse events, and resolution of co-morbidities; to explore, in a sub-sample, patients' experiences of management, outcome and eating behaviour change.

D. The cost effectiveness of Band, Bypass and Sleeve.

4. Plan of Investigation

4.1 Study design

By-Band-Sleeve is a pragmatic RCT with three phases. Phase 1 will establish the feasibility of the trial by undertaking the RCT of Band versus Bypass (By-Band) in two centres. During this time a core outcome set for bariatric surgery will be developed. At the end of phase 1, the progression criteria for undertaking a main trial will be reviewed and discussed with the Trial Steering Committee (TSC) and the funder, NIHR-HTA. This will include a review of the current practice and evidence for sleeve gastrectomy to determine whether in phase 2 the trial should be adapted to include Sleeve. If appropriate and there is agreement the full trial will proceed. Phase 2 is a multi-centre RCT. At the end of phase 2, progression criteria for continuing with a three-group trial will be reviewed and discussed with the TSC and the NIHR-HTA. If appropriate and there is agreement phase 3 will proceed unchanged,

Phase 1: This will take place in two centres, integrating qualitative research to establish optimum methods of recruitment and informed consent. A core outcome set for measuring adverse outcomes and benefits of severe and complex obesity surgery will be developed.

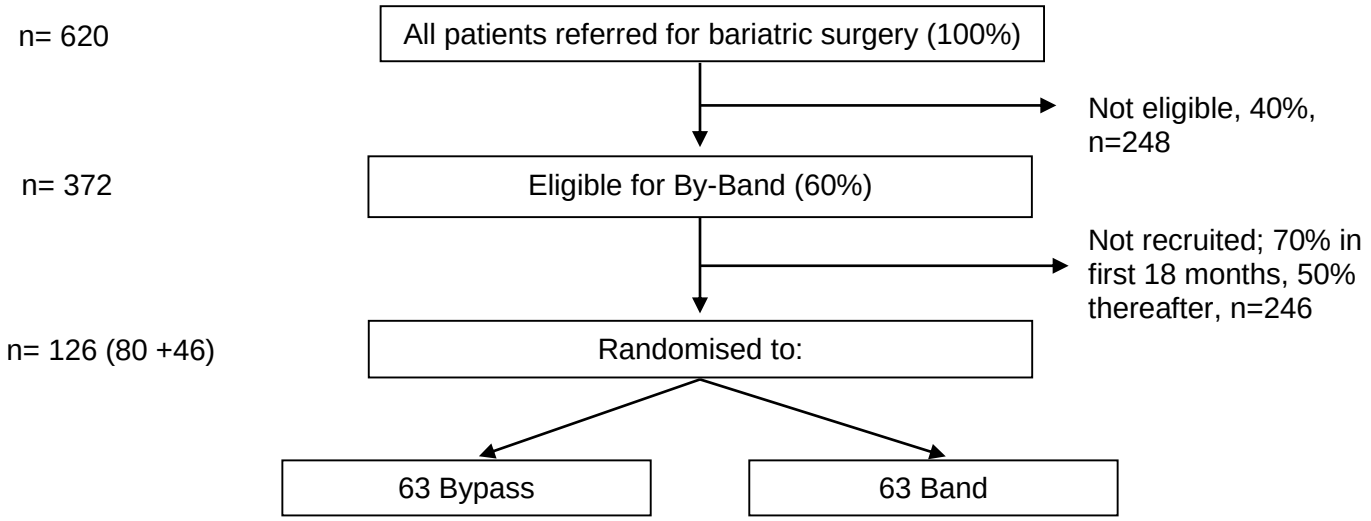
Phase 2: This will extend recruitment to ten additional centres, using the optimum methods of recruitment established in phase 1. Participants will be followed up for at least three years.

Phase 3: This will continue recruitment in the twelve centres. Participants will be followed up for at least three years.

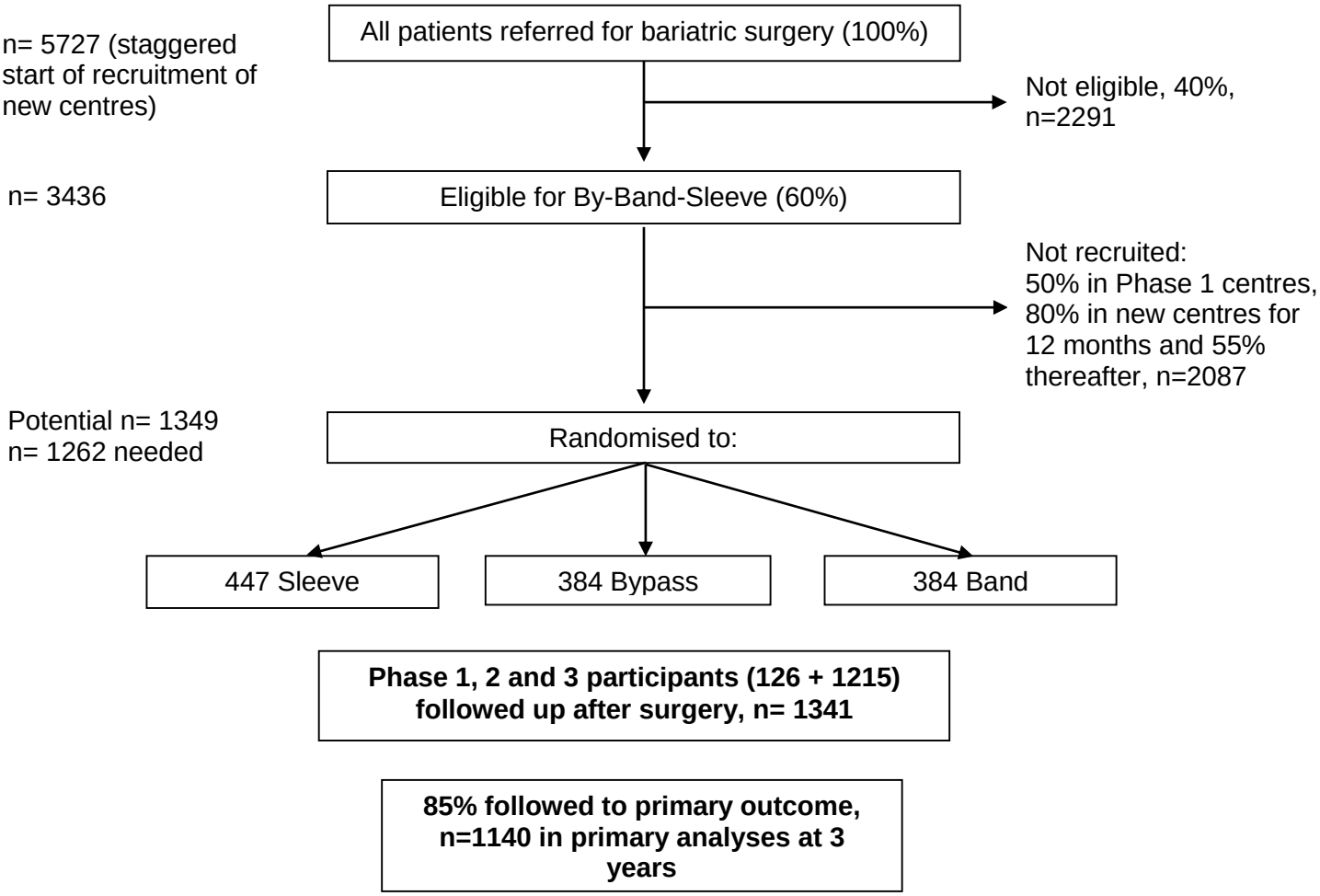
The overall schema for the trial is detailed overleaf.

4.2 Trial schema

Phase 1: By-Band, in 2 centres (24 months)



Phases 2 and 3: By-Band-Sleeve, in 12 centres (48 months)



In **Phase 1** a core set of adverse and beneficial outcomes of obesity surgery will be developed.

4.3 Trial population

4.3.1 Eligibility criteria - participating centres

All centres will be NHS Trusts, with surgical units carrying out at least 50 bariatric surgery operations per year. Participating surgeons will work within a specialist multi-disciplinary bariatric team with at least two surgeons. All centres will have carried out a minimum of 200 Band, 250 Bypass and 200 Sleeve procedures before entering patients into the trial. Phase 1 will take place in two UK centres (Taunton and Southampton). In Phase 2 recruitment will be extended to include a further ten centres (total twelve centres).

4.3.2 Eligibility criteria - participating surgeons

Participating surgeons will have performed more than 100 laparoscopic Bypass procedures, more than 50 laparoscopic Band procedures and more than 50 laparoscopic Sleeve procedures for severe and complex obesity. With the agreement of the Chief Investigator and study team, a surgeon with experience in some but not all three procedures *may* be permitted to participate, but the number of operations this surgeon may contribute will be capped and closely monitored. All other participating surgeons at the centre must have the pre-requisite experience in all three surgical procedures and be willing to carry out all three procedures within the trial according to the randomised allocation.

4.3.3 Eligibility criteria – patients

All patients referred for bariatric surgery will form the target population. Each site will maintain a trial screening log. This will record the details of patients who are or are not screened for trial entry, reasons for ineligibility and it will record details of eligible participants who do not consent for participation (and reasons for this choice).

This information will be reviewed on a monthly basis to provide feedback to recruiters and it will help in understanding surgeons' and patients' preferences for types of surgery. It will also allow the trial results to be reported in accordance with CONSORT guidelines. Patients declining randomisation within the study will be asked for written consent to access clinical records, complete the EQ-5D-5L questionnaire at recruitment and at three years and participate in a telephone follow up at three years.

Eligible patients will be informed about the trial and given the patient information leaflet (PIL) and an appointment for a 'recruitment consultation.' At that consultation they will be given the opportunity to ask questions about the trial and treatments, and asked to give written informed consent to the trial. These consultations will be routinely audio-recorded and available for qualitative investigation.

Inclusion criteria

Participants may enter study if ALL of the following apply

1. Male or female patients
2. Over 18 years of age
3. Referred for bariatric surgery according to NICE guidelines - BMI of 40kg/m^2 or more, OR BMI of 35 kg/m^2 to 40 kg/m^2 and other significant disease (e.g. type 2 diabetes or high blood pressure) OR BMI of 30 kg/m^2 or more and recent onset diabetes OR Asian family origin with lower BMI and recent onset diabetes, that could improve with weight loss
4. Has been or is willing to receive intensive management in a specialist tier 3 obesity service

5. Fit for anaesthesia and surgery
6. Committed to follow-up and able to complete quality of life questionnaires
7. Able to provide written informed consent.

Exclusion criteria

Participants may not enter study if ANY of the following apply (assessed by patient history and clinical examination)

1. Previous gastric surgery or surgery for severe and complex obesity
2. Previous abdominal surgery or gastro-intestinal (GI) condition that precludes one or more of Band, Bypass or Sleeve
3. Large abdominal ventral hernia
4. Pregnancy (women who have given birth and women planning pregnancy will NOT be excluded)
5. Crohn's disease
6. Liver cirrhosis and portal hypertension
7. Systemic lupus erythematosis
8. Known silicone allergy
9. Hiatus hernia >5cm
10. Other clinical/psychological reason, to be specified
11. Active participation in another interventional research study which might interfere with By-Band-Sleeve

4.4 Trial interventions

Participants will be listed for surgery optimally within 2 weeks. The time between randomisation and surgery will be recorded and it is recommended that this is less than 10 weeks.

For the purposes of this pragmatic trial the operations are to be carried out in accordance with the protocol. This protocol classifies each component of the surgery, and the concomitant interventions as mandatory, optional or prohibited. Where surgeons do not undertake mandated components of the surgery or the concomitant interventions, and, when they perform prohibited ones it will form a protocol deviation. Annual review of the individual surgeon adherence to these criteria will be conducted and confidential and team meetings will be organised to provide feedback. Fidelity to the mandated components of the surgical interventions (and prohibited components) will be monitored by completion of the operative case report forms.

4.4.1 All three operations

All three surgical procedures (Band, Bypass and Sleeve) will be carried out laparoscopically. The methods used to create a pneumoperitoneum, the placement of the laparoscopic ports, and retractors are at the discretion of the surgeon. The type of instruments used is also at the surgeon's discretion. Undertaking a hiatal hernia (<5cm) repair and cholecystectomy are permitted but not compulsory. An apronectomy is prohibited at the time of surgery. Placement of drains is optional.

4.4.2 Laparoscopic adjustable gastric banding (Band surgery)

The type and size of adjustable gastric band is at the discretion of the surgeon. It is mandatory to i) dissect the lesser curve using the 'Pars flaccida' technique, ii) to fix the Band

(any fixation method is allowed) and iii) to fix the adjustable port to the anterior abdominal wall.

4.4.3 Laparoscopic gastric bypass surgery (Bypass surgery)

Methods used to create the biliary and gastric limbs are flexible, although upper limits of 75cm and 150 cm are recommended for the biliary and gastric limbs respectively. Routing of the Roux limb (antecolic or retrocolic) is flexible. The pouch can be created according to the surgeon's usual practice, except that a horizontal gastric pouch that includes fundus is prohibited. Use of a bougie is optional. Anastomoses can be performed as the surgeon chooses (e.g. stapled or sutured, single or double layer). Testing integrity of the anastomoses, and the closure of the mesenteric defects, is optional.

4.4.4 Laparoscopic sleeve gastrectomy surgery (Sleeve surgery)

It is mandated to visualise the left crus after dissection of the fundus. The type of bougie used is flexible although should be between 32 and 40Fr. The type of stapler used is flexible and the use of additional sutures, clips, reinforcement of the staple line is at the discretion of the surgeon. Testing the integrity of the staple line is optional.

4.4.5 Concomitant interventions

Procedures will be carried out under general anaesthesia. All patients will receive peri-operative antibiotics and thromboprophylaxis in accordance with local policy. The use of nasogastric tubes, central and arterial lines, and urinary catheters is optional. After surgery, oral intake will be commenced according to local policy. The day of discharge will be chosen at the surgeon's discretion. The use of post-operative contrast swallows is optional.

4.5 Primary and secondary outcomes

4.5.1 Primary outcome

There are two primary endpoints:

i) the proportion achieving loss of greater than 50% of excess weight at three years (calculated as 100×[BMI at 3 years – BMI at randomisation[1]] / [BMI at randomisation – 25])
ii) HRQOL at three years (EQ-5D-5Lhealth state score)

[1] Calculated using the participant weight recorded at baseline, after consent and before randomisation

Procedures for measuring height and weight are described in section 5.2

4.5.2 Secondary outcomes

These will include:

- Change in BMI over time adjusted for BMI at randomisation
- % weight loss at 3 years
- Waist circumference at 3 years
- Time taken from randomisation to reach first loss of at least 50% of excess BMI

- Time taken from first losing 50% excess BMI to first relapse (defined as weight re-gain such that the target of at least 50% of excess weight loss is no longer met)

- Generic and symptom specific (i.e. obesity and GI specific) HRQOL: SF12, EQ5D, IWQOL-Lite, and GIQLI to three years

- Resource use to three years

- Standard NHS nutritional blood tests will be performed at each assessment including; full blood count, electrolytes, creatinine, glucose, HbA1c, liver function tests, iron, ferritin, vitamin B12, folate/red cell folate, lipid profile, 25-hydroxyvitamin D, calcium, parathyroid hormone

- Measures of 24 hour recall eating using a standardised and validated interview process

- Binge eating behaviour using a validated questionnaire

- Adverse health events including the need for re-operation and cross over between interventions
-
- Resolution of co-morbidities at 3 years, including sleep apnoea, non alcoholic fatty liver disease, type-2 diabetes, hypertension and hyperlipidaemia

- Time to resolution of sleep apnoea, type-2 diabetes, hypertension and hyperlipidaemia

Details of methods used to define the above are described below (section 5.2).

A 20ml blood sample will also be taken at baseline and at 3 years for future investigations. These blood samples (serum/plasma/whole blood) will be transferred from each recruiting site to the Clinical Trials and Evaluation Unit, University of Bristol for long-term storage and subsequent analysis. The trial manager/coordinator will organise an approved courier and liaise with the By-Band-Sleeve lead research nurse from each centre to ensure that the samples are ready for collection on dry ice. Once the samples arrive at the CTEU an email will be sent to the recruiting site confirming receipt. Sample logs will be kept at each recruiting site, and copies of these sample logs will be kept in Bristol.
All samples will be used, stored and disposed of in accordance with the Human Tissue Act 2004.

4.6 Sample size calculation

We hypothesise that (a) Bypass/Sleeve/Sleeve will be non-inferior to Band/Band/Bypass in terms of the proportion of participants achieving an excess weight loss of at least 50% at three years, and that (b) the HRQOL at three years for participants receiving a Bypass/Sleeve/Sleeve will be superior to the HRQOL for participants with a Band/Band/Bypass, as measured using the EQ-5D-5L health state score. The sample size has been chosen to test both these hypotheses. Data from the literature [28, 29] and from a registry of patients treated with Bypass or Band at the Taunton centre were used to inform the power calculation. These estimates are unchanged for the adaptation to a three group trial.

The expected proportion of participants losing at least 50% of their excess weight at three years was estimated from the Taunton registry; for the sub-group with a BMI at surgery of between 40 and 60 (the target weight range for trial participants), 73% of Band and 75% of Bypass patients had lost at least 50% of their excess weight at three years. The non-inferiority margin was chosen on the basis of the opinions of the clinical applicants and patient representatives. The power calculation for hypothesis (a) requires the estimation of two parameters, i.e. the total proportion of participants that are expected to have lost at least 50% of their excess weight at three years and the difference in proportions achieving this target that would be considered clinically important (the non-inferiority margin). **Table 1** shows the sample size needed for a one-sided test of non-inferiority at the 2.5% level, for different parameter estimates and power.

The power calculation for hypothesis (b) requires the estimation of six parameters, i.e. the within group standard deviation, the difference in mean HRQOL that would be considered clinically important, the number of pre and post randomisation measures, and the correlations between pre and post randomisation scores and between repeated post randomisation scores. The estimates used were chosen on the basis of the published literature [30, 31] and, in order to estimate correlations between different time points, on data from a surgical trial in spine injury. **Table 2** shows the sample size needed for a 2-sided test of superiority at the 5% level, for different parameter estimates and power.

Table 1 Proportion achieving 50% excess weight loss

Overall, proportion achieving 50% excess weight loss	Smallest difference considered clinically important (margin)	Sample size (total)	
		90% power	80% power
0.75	0.12	548	410
0.70	0.15	394	294
0.70	0.12	**614**	458
0.70	0.10	884	660
0.65	0.12	666	498

Table 2 EQ-5D score

Correlation between pre & post-surgery measures	Correlation between post-surgery repeated measures	No. of post surgery measures	Effect size	Mean difference in EQ5D state score	SD	Sample size (total)	
						Power	
						90%	80%
0.5	0.65	3	0.2	0.06	0.3	544	406
0.5	0.70	3	0.2	0.06	0.3	578	432
0.5	0.75	3	0.2	0.06	0.3	**614**	458
0.5	n/a	1	0.2	0.06	0.3	790	**590**

The study size for a two group trial (Band versus Bypass) has been set at 614; which allowing for a 15% dropout at three years gives a target sample size of 724. Adapting the trial to include a third group, Sleeve, increases the sample size to 1140 (adjusting the significance levels from the conventional 2.5% and 5% levels for non-inferiority and superiority to 1% and 2% respectively to account for the three hypotheses); which allowing for a 15% dropout at three years gives a target sample size of 1341 patients (447 per group). This will provide 90% power to test both hypotheses, assuming that 70% of patients will have lost ≥50% of their excess weight at three years, that a difference of ≥12% between the groups would be clinically important and that a small effect size of 0.2 standard deviations in HRQOL would be clinically important. For the HRQOL score, a conservative estimate of the

correlation between repeated measures has been assumed. The calculation based on three post-surgery measures assumes the treatment difference is similar at the three time points. However, it is anticipated that the difference in HRQOL may change over time. The calculation based on a single measure shows that the study will have 80% power to detect differences at individual time points.

5. Trial methods

5.1 Description of randomisation

Randomisation will be carried out after trial eligibility has been confirmed and consent given, usually within 2 weeks of recruitment. Patients will be informed about their randomisation arm after they have agreed and consented to participate in the trial. This will allow patients time to make arrangements for support at home after discharge from hospital (which is different between the three procedures) and it will allow surgeons time to efficiently plan an operating list (because of the time difference required in theatre for each procedure). Randomisation will be performed by an authorised member of the local research team using a secure internet-based randomisation system ensuring allocation concealment. Patients will be allocated 1:1 to Band or Bypass in phase 1. In phases 2 and 3 patients will be allocated 1:1:1.16 (adjusted to give a 1:1:1 allocation ratio at the end of the trial) into the following treatment strategies:

i) adjustable gastric banding (Band surgery) with follow up appointments (in the first 24 post-surgical months) to include follow up at 4 weeks, 3, 6, 9, 12 and 24 months (expected to be up to 10 appointments) and annual follow up thereafter. Research data collection will not be required at the 3 and 9 months visit.

ii) gastric bypass (Bypass surgery) with standard 4 week, 3, 6, 9 and 12 month follow up and annual follow up thereafter. Research data collection will not be required at the 3 and 9 month visits.

iii) sleeve gastrectomy (Sleeve surgery) with standard 4 week, 3, 6, 9 and 12 month follow up and annual follow up thereafter. Research data collection will not be required at the 3 and 9 month visits.

Allocation will be computer-generated. Cohort minimisation (with a random element incorporated) will be used to ensure balance across the groups, by diabetes status (any type/none), and BMI more than 50 (yes/no). Allocation will also be stratified by centre. Other baseline data to be assessed will include socio-demographic information and prior weight loss methods attempted.

5.2 Research procedures

5.2.1 Measurement of weight and height

At randomisation, on the day of surgery and at each study visit, participants' weight in kilograms (kg) will be measured on calibrated electronic clinic scales. Participants will be weighed fully clothed after removal of shoes. Participants will stand with weight evenly balanced on both feet and they will be asked to remove jackets and heavy items from pockets. The arms should hang loosely at the sides. Participants' heaviest weight ever (both self-reported and heaviest recorded in the participants' medical records) will also be collected.

At randomisation participants' height in centimetres (cm) will be measured after removal of shoes with a calibrated stadiometer.

5.2.2 Assessment of patient reported outcomes

Questionnaires administered at baseline **before** randomisation will be given to patients to complete themselves when they attend hospital (see **Table 3** for details). Participants may elect to complete the questionnaires at home and return them by post in a stamp-addressed envelope which will be provided. Questionnaires completed after randomisation will be posted to participants by the coordinating centre (Bristol CTEU) to ensure that the follow-up time points are met. If the questionnaires are not returned within 3 weeks, participants will be contacted by letter, telephone, email or standard message service (SMS) text as preferred (if appropriate the questionnaires can be read to the participant over the telephone or a second set posted for completion). An option to log in to a secure web-site and complete the questionnaires on-line will also be provided. A 24 hour recall eating assessment will be measured by the research nurses (trained by JT) using repeat 24-hour recalls at baseline and single 24-hour recalls at the 6, 12, 24 and 36 month follow-up assessments.

Reasons for the non-completion of questionnaires will be recorded. Missing or erroneous items on questionnaire measures will be handled according to the questionnaire developers' scoring manuals. Reasons for withdrawal from the study, loss to follow up or death (and cause of death) will be recorded.

Patient reported outcome measures

The SF12 and the EQ-5D-5L will assess generic aspects of health and the EQ-5D-5L data will be used in the analysis of QALYs [32]. A validated obesity specific measure, the Impact of Weight of Quality of Life-Lite (IWQOL-Lite) will assess HRQOL issues perceived by patients that are related to their weight including physical function, self-esteem, sexual life, public distress and work [33, 34]. The IWQOL-Lite is a 31 item self-completed questionnaire developed directly from commonly expressed concerns of obese patients as well as from clinicians' experience. It has five quality of life scales: physical function (11 items), self-esteem (7 items), sexual life (4 items), public distress (5 items) and work (4 items). Respondents are asked to rate their experiences for the previous week. Each item has five options for response and is scored from 1 ("never true") to 5 ("always true"), hence a higher score is less favourable. An increase in score of 8 to 12 points has been shown to indicate a meaningful change in score using anchor-based and distribution-based methods from weight loss studies that have employed the questionnaire [33, 34].

A gastro intestinal specific measure, the GIQLI (Gastrointestinal Quality of Life Index, 36 items), will assess the impact of specific symptoms associated with bariatric surgery and obesity [35]. This measure captures the impact of symptom-specific gastrointestinal disorders on a patient's quality of life. There are four gastrointestinal symptom scales and three generic scales (physical, social and emotional function). Each item is scored on a five point scale (0-4) to denote the burden of the specific symptom; a lower score indicates more burden (less favourable). The majority of items ask about frequency of occurrences from the previous two weeks.

The Hospital Anxiety and Depression Scale (HADS) will be used to assess the participant's levels of anxiety and depression [36]. The HADS is a 14 item scale; 7 of the items relate to anxiety and 7 relate to depression. Each item on the questionnaire is scored from 0-3 giving a total score between 0 and 21 for either anxiety or depression. A score of 8/21 or more indicates anxiety or depression [37].

5.2.3 Assessment of co-morbidities

Sleep apnoea

The STOPBANG questionnaire and Epworth Sleepiness Scale will be completed at baseline. The Epworth Sleepiness Scale, but not STOPBANG, will be completed at each research follow-up appointment (see Table 3) [38]. Patients will be selected for sleep studies on the basis of history or a score of 5 or more using the STOPBANG questionnaire [38]. A variety of techniques for further investigating sleep apnoea are currently available and used in clinical and research practice, although there is no gold standard clinical modality. Polysomnography is the gold standard for research purposes, and currently used techniques range from video plus pulse oximetry plus recording snoring, which generally requires an overnight stay in hospital, to simple pulse oximetry alone that can be performed at home.

Overnight pulse oximetry, where a pulse oximeter and recorder are attached during a period of sleep is the minimum investigation required for patients in the By-Band-Sleeve study being investigated for sleep apnoea. However, if patients are symptomatic for sleep apnoea and pulse oximetry is negative, then further specialist assessment in a sleep clinic is required.

Resolution of obstructive sleep apnoea: remission will be confirmed after repetition of sleep studies. Participants with sleep apnoea at recruitment will be invited to undergo a repeat sleep study at 3 years. The standard definition is less than 5 apnoea episodes per hour as assessed by polysomnography (sleep study).

Non alcoholic fatty liver disease

A non-invasive assessment will be performed at baseline and at three years (timing of the primary end point) with the enhanced liver fibrosis test (ELF). This is an algorithm that combines age, hyaluronic acid (HA), aminoterminal peptide of procollagen type III (PIIINP) and tissue inhibitor of matrix metalloproteinase (TIMP-1) [39].

Type-2 diabetes

Remission of diabetes will be defined by criteria set out from a consensus meeting in Diabetes Care for remission after surgery [40] and HbA1c, fasting glucose and number of diabetes medications taken will be recorded at follow up appointments. Remission is defined as achieving glycaemia below the diabetic range in the absence of active pharmacologic (anti-hyperglycaemic medications, immunosuppressive medications) or surgical (ongoing procedures such as repeated replacements of endoluminal devices) therapy. A remission can be characterized as partial or complete. Partial remission is sub-diabetic hyperglycaemia (A1c not diagnostic of diabetes [<6.5%], fasting glucose 100–125 mg/dl [5.6–6.9 mmol/l]) of at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures. Complete remission is a return to “normal” measures of glucose metabolism (A1c) in the normal range, fasting glucose<100 mg/dl [5.6 > mmol/l]) of at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures.

Hypertension

Remission will be based on the international definition described in the metabolic syndrome, systolic blood pressure < 130mmHg and diastolic < 85 mmHg without treatment.

Hyperlipidaemia

Standard remission of hyperlipidaemia will be defined as total cholesterol ≤5.0 mmol without cholesterol lowering treatments.

5.2.4 Measurement of waist circumference

This will be performed with outer layers of clothing removed. The researcher will be positioned to the right of the participant and will locate the right ilium. Just above the uppermost lateral border of the right ilium, a piece of tape is placed and then crossed with a vertical mark on the mid-axillary line. The researcher places the measuring tape around the trunk at the level of the mark on the right side, and then inspects all sides to make sure the measuring tape is at a level horizontal plane. The tape is then tightened slightly, but without compressing the skin and underlying subcutaneous tissues. The measure is made at minimal respiration and is recorded to the nearest millimetre (0.1cm) asking the participant to look straight ahead, be relaxed, and not to pull the tummy in.

The waist circumference (to the nearest 0.1 cm) will be recorded twice. If the measures differ by more than 0.5 cm, the technique will be checked and a third and fourth measurement taken. All readings will be recorded.

5.3 Integrated qualitative research: recruitment

The By-Band-Sleeve trial compares three different surgical procedures that are in common use, and is likely to face a number of recruitment challenges. Based on previous work by Donovan et al [41], By-Band-Sleeve will include an integrated qualitative study (IQS) in two phases:

5.3.1 Phase I

The aim of the IQS is to work with RCT staff to understand the recruitment process in the early stages, so that any difficulties related to design or conduct can be raised and changes put in place. The IQS will also be used to determine any staff training that needs to be developed or feedback given to staff. There are several distinct parts to Phase I that are intended to provide information about recruitment as it happens, and to provide the basis for the plan of action to improve it. The parts listed below are not necessarily employed sequentially and some may not be required. The ethnographic nature of the IQS means that the research moulds itself around the needs of the research and is completed when theoretical saturation is reached (that is, new data collection does not materially add to the findings).

Patient pathway through eligibility and recruitment

A comprehensive process of logging of potential RCT participants through screening and eligibility phases will be used to monitor recruitment (see section 5.3 for further details). The screening logs and flow charts will be assessed for complexity and compliance with the protocol as well as variation between centres. They will provide data on the numbers of eligible patients and particular points where patients are ‘lost’ from the RCT. They will also indicate levels of equipoise – as evidenced by the numbers rejecting participation in the RCT and the selection of particular treatments. Flow charts will indicate the degree of complexity of participation and any variations between centres.

In-depth interviews and investigator meetings

In-depth, semi-structured interviews will be conducted with three groups:

(a) Members of the trial management group (TMG), including the chief investigator and those most closely involved in the design, management, leadership and coordination of the trial

(b) Clinical and recruitment staff at the centres involved in the RCT

(c) Participants eligible for recruitment to the RCT, including those who agree or decline to take part

Interview topic guides will be used to ensure similar areas are covered in each interview within each group, based on those used in previous studies, but also encouraging the informants to express their own views about the RCT and any recruitment challenges expected or experienced.

Informants in group (a) will be asked about the background, development and purpose of the RCT, including their knowledge of the evidence and equipoise; their role in the trial and recruitment, including their expectation of the pathway through eligibility and recruitment. They will also be asked to provide a short verbal summary of the RCT for the interviewer, as if s/he were a patient.

Informants in group (b) who directly recruit to the trial will also be asked the questions about their knowledge of the evidence and personal views about equipoise; the recruitment pathway, how they feel the protocol fits their clinical setting and any adjustments they think are needed. They will also be asked how they explain the RCT, the two interventions to patients, and the randomisation process. They will be asked to audio-record their appointments with patients, with a view to discussing any discomfort or perceived difficulty with this.

Informants in group (c) will include those who have agreed to randomisation and those who have rejected it but are willing to discuss their views. The following will be explored: perspectives of living with severe and complex obesity, previous experiences with treatments, views about surgery, and the acceptability of randomisation between the procedures. Attempts will be made to obtain a variation sample that includes those who are male and female, younger/older, choosing band or bypass, and employed/unemployed.

In the early stages of the feasibility/pilot phase 1 of the RCT the TMG and clinical investigators will meet several times. The IQS team will ask to observe these meetings and to audio-record them with permission. The IQS researchers will discuss the agenda with the chief investigator, with the aim of fostering discussion, particularly about issues of eligibility and equipoise if these have emerged from the early findings. The meetings will also be a forum to discuss the findings of the IQS, and to deliver training or advice about recruitment.

Interviews and meetings will be audio-recorded and transcribed with consent. Recordings may be transcribed verbatim whole or in selected parts, as necessary for comprehensive or targeted analysis. Transcripts and notes will be analysed thematically by the IQS researcher, using techniques of constant comparison and case-study approaches. Interviews and meetings will provide data about: the perspectives of eligible patients, the evidence underlying the RCT, including the importance of the question and the commitment of staff to it, as well as individual clinical equipoise; the application of the protocol in clinical

centres and any logistical issues; and suggestions about reasons for recruitment difficulties and potential solutions from those working closely within the RCT.

Audio-recording of recruitment appointments

The importance of audio recording discussions about RCT recruitment will be emphasised to the TMG, and methods of communicating this with recruiters will be explored. It has been shown previously that recruiters tend to be unfamiliar with audio-recording and, even if they agree to it, often resist making successful recordings. It will be emphasised that the feedback to them will be confidential and positive (not critical). The TMG will be asked to discuss this with recruiters and attempt to identify a 'recruitment appointment' suitable for recording.

One main point of contact (usually the lead research nurse) will be identified at each centre and digital audio-recorders will be provided; the number of recorders required for the RCT will depend on the number of actively recruiting staff in the centre and the logistics and geographic location of recruiters. Recruitment staff will be requested to audio-record all appointments where they provide information to patients and attempt to recruit them to the RCT. Documents explaining the ethical requirements of audio-recording of patient appointments (Patient and Recruiter Information Sheets and consent forms for audio-recording) and Standard Operating Procedures (SOPs) to help with the operation of the recorder, dictation of patient/recruiter /recording identifiers, naming and transferring of the recording to the computer and then to the IQS team will be provided to centres in 'Recruiter Packs'.

Audio-recordings of appointments will be analysed as described above for interviews, with the addition of some of the techniques of focussed conversation analysis (CA) – pioneered in previous studies. CA techniques will be used to identify and document aspects of informed consent and information provision that is unclear, disrupted or hinders recruitment. Recordings will be listened to by the researcher and notes made about the content of the appointment. An assessment will be made as to whether the appointment is recruiter- or participant-led, and also the degree to which there is evidence that the participant has understood the key issues of equipoise, randomisation, participation in the RCT, the option to choose their treatment, and the option to withdraw from the research at any time.

The IQS researcher will document these details. When at least three recordings have been analysed, the IQS researcher and Principal Investigator (PI) will decide what confidential feedback will be given to the recruiter. Issues to be fed back to the RCT TMG, or to be used anonymously in training programmes will be discussed and defined.

These data will form the basis for feedback to individuals and to determine the content of the information, and training programmes to be implemented in Phase II of the RCT.

Non-participant observation of staff-patient interactions

While the routine audio-recording of all discussions about the trial will be promoted, non-participant observation of a selection of these discussions will be carried out. Appointments to be observed will be purposively selected to include a) discussions by recruiting staff such as surgeons and b) discussions by staff members such as dieticians, nurses and anaesthetists, who may not actively recruit patients to By-Band but whose roles involve providing important information about the two operations. This will mean that some discussions may only be audio-recorded, some audio-recorded and observed and others only observed. Observations of clinics such as the "one-stop" and pre-assessment clinics will be performed. Non-participant observation will involve the qualitative researcher sitting

in the room that the discussions take place and taking notes on the interaction without contributing to the discussion. Prior to undertaking any observation, informed consent will be obtained from the patient and staff member involved. The aim of the observations is to provide data in the form of extensive field notes that can be qualitatively analysed to inform the recruitment process.

Evidence base

The TMG will be asked for the main systematic reviews or published research evidence justifying the need for the RCT (this is also likely to be contained within the protocol and original research proposal). They will be asked about any recent evidence that supports or threatens the RCT. If, during the interviews and recorded appointments, it becomes clear that equipoise is an issue in the RCT or clinicians report other evidence as influential, this will be fed back to the TMG and it may be necessary to undertake a new literature review or to discuss the quality and reliability of the evidence identified.

5.3.2 Phases II and III: Feedback to TMG

The QRS researcher and PI will present summaries of anonymised findings emerging from phase I of the IQS to the RCT TMG, identifying any aspects of RCT design and conduct that could be hindering recruitment with the supporting evidence. A plan of action to try to improve recruitment, if this proves necessary, will be agreed by the RCT TMG and IQS PI and team. No activities will be undertaken by the IQS team without the prior approval of, and collaboration with, the RCT TMG.

The plan for phases 2 and 3 of the RCT will be focussed on the issues emerging from the IQS of phase 1 of the RCT and how it has been applied in the two centres. It is likely that some aspects will be generic, such as difficulties with the application of eligibility criteria or explaining randomisation. The plan is likely to include some or all of: reconsideration of study information, advice about presenting the study, discussions about equipoise or evidence, issues with patient pathways, and logistical issues in particular centres. These may be addressed by a new PIL, documents, changes to the protocol, or training for recruiters in the presentation of RCTs in general or the By-Band-Sleeve RCT.

Numbers of eligible patients, and the percentages of these that are approached about the RCT, consent to be randomised and immediately accept or reject the allocation will be assessed before the plan of action is implemented, and regularly afterwards to check whether rates are improving. Interviews with recruiters will ask about the acceptability of the IQS and any changes that occur.

It is expected that the qualitative research will permit between 40% and 60% of eligible patients to be enrolled into the trial. See section 5.10 for projected recruitment figures with the integrated qualitative research.

5.4 Integrated qualitative research: process evaluation

The aims of the process evaluation are as follows:

1. To describe and refine the intervention (if required), identify key components (of the surgical intervention and concomitant components) and context

2. To establish which components (and/or their individual steps) are a) mandatory, b) optional and c) prohibited

3. To establish the level of standardisation required for each component and set limits concerning fidelity and quality control.

5.4.1 Phases I and II

The process evaluation to be performed in the phase 1 (Band and Bypass) and phase 2 (Band, Bypass and Sleeve) of the trial will be a mixed methods study comprising three parts:

Non-participant observation in the operating theatre

Non-participant observation of a purposively selected sample (n=10-20) of operations will be performed by one or two researchers to supplement and triangulate information obtained from a) video and audio recordings and b) interviews of surgeons and team members (below). Observations will focus on the surgical interventions, concomitant interventions occurring in the operating theatre, and also contextual factors (e.g. noise, interruptions, team working and communication). Observations will either be recorded by hand or using the Observer XT 10.5 PDA. Dual observation will increase the study validity and ensure that both clinical and non-clinical interactions will be recorded. Patients will provide written consent for the recording of their surgery.

Video and audio recording of surgical procedures

Digital video recordings of the operations will be performed using standard techniques. Data will be collected directly from the laparoscopy 'stack' already in routine use for the procedures. Recording will start from when the surgeon has placed the camera port and will end when the camera is removed after the procedure. Recordings will be stored in a secure USB hard drive and then transferred to a secure server held at the University of Bristol. These will be anonymised with study ID, patient initials and date of birth. Audio recordings will be made using a digital recorder and start at the beginning of the procedure (where the patient is anaesthetised and the equipment prepared and checked), continuing through all of the operation itself, including the end of the procedure, patient recovery and clearing up of the theatre and equipment, when the patient has left the operating theatre.

Interviews with surgeons, anaesthetists and nurses

A purposefully selected sample of surgeons and other team members (n=20-30) will be interviewed after the operation (within 3 days) and also 1-2 weeks later. Interviews will be guided by a topic guide which will be a list of open-ended questions to ensure that all topics are covered in each interview but will be sufficiently flexible to enable topics of importance to the informant to emerge. The topic guide is likely to be adapted as interviews and analyses proceed but proposed topics include:

- Exploration of knowledge of the trial and trial protocol, the intervention and if/how they plan to modify it for the particular patient/disease state
- Views of the impact of variations from the surgical (or anaesthetic) protocol
- Reasons for advocating or not advocating surgery and any particular surgical approach
- Questions about which parts of the operation and protocol are considered to be difficult and how patient factors influence this

- Hospital, team or equipment factors that influence carrying out surgery and in what ways this may differ if they are training others to do the procedure

- What advice surgeons give to patients about the surgical intervention in a trial (if any)

- What they think are the most important elements of the surgical (or anaesthetic or nursing) intervention that influence outcomes (and how these might change in light of complications)

- Self-reported expertise

It is anticipated that the process evaluation will result in development of a manual, which will provide details of the surgical interventions, concomitant components and context as well as defining the mandatory, flexible and prohibited aspects of each of the components and/or steps. The manual will be developed and designed in conjunction with the surgeons participating in By-Band-Sleeve.

5.4.2 Phases II and III

During Phases 2 and 3 of the trial, fidelity to the surgical interventions will be monitored by completion of the operative case report forms (see section 4.4).

5.5 Development of a core clinical outcome set for obesity surgery

Systematic literature reviews will identify all the current reported clinical and patient reported outcomes of bariatric surgery (and their definitions) and the National Bariatric Surgery Registry will be included. Data from the qualitative interviews performed in this trial will identify additional potential outcomes of importance to surgeons and patients that are not identified from literature searches. Delphi methodology surveying relevant health care professionals and patients will reduce the potential list to a shorter list of outcomes to be discussed at the consensus meetings. In the Delphi survey, stakeholders (professionals and patients) will be asked to rate the importance of inclusion of each potential outcome in the core outcome set and three rounds will be undertaken to reduce the list according to pre-specified criteria. Each Delphi round will be analysed to identify key or redundant items from the list. Two consensus meetings will be convened with key stakeholders. One will be with health professionals. The meeting will discuss the survey results and further anonymised rating of the importance of retained items. The other will be with patients. It is anticipated that 100 health professionals and 100 patients will participate in the Delphi survey. Participants will be asked if they wish to attend the meeting. We anticipate that up to 30 participants will attend the meeting, which will last between two and three hours and be held at the University of Bristol. This work will link with 'COMET' (http://www.comet-initiative.org/), funded by the MRC ConDuCT and North West Hubs for trials methodology research. The final core set of outcomes of bariatric surgery is expected to be less than 10 items.

5.6 Duration of treatment period

The surgical procedures last between 45 and 120 minutes. The hospital stay varies between one and three days, on average. The on-going band fills for patients randomised to Band surgery take place on 10 follow up visits in the first two years.

5.7 Definition of end of trial

Each participant will have completed follow up at the 36 months post randomisation assessment. The whole trial will have completed follow up when the final randomised participant has reached the 36 months post randomisation assessment.

5.8 Data collection

A unique file identified by the study number will be maintained for participants. All data recorded on paper relating to the participant will be located in these files. A list will be maintained at each centre of staff with authorisation to make alteration to the study records, including the study database (see section 11.2 for information on the database architecture and data handling). Data collection will include the following elements:

(a) A screening log of all patients referred for bariatric surgery and those who are approached for the trial (including the date when they are given the PIL).

(b) Patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility.

(c) Eligible patients approached and refused randomisation and reasons for this.

(d) Consent and baseline information (e.g. history and planned operation and response to health status questionnaires) collected prior to randomisation in participating patients.

(e) Anthropometric and nutritional data, participant responses to health status questionnaires, and co-morbidity assessment collected at follow-up as indicated in Table 3.

(f) Audio-recording of consultations and interviews as outlined in section 5.3.

Table 3 Data collection at the standard assessments

Measurement	**Pre randomisation**	**Day of surgery**	**4 weeks post surgery**	**Post randomisation**			
				Months			
				6	**12**	**24**	**36**
Weight	X	X	X	X	X	X	X
Height	X						
Blood pressure	X		X	X	X	X	X
Waist circumference	X		X	X	X	X	X
Patient questionnaires							
SF12	X		X	X	X	X	X
EQ-5D-5L	X	X[+]	X	X	X	X	X
IWQOL-Lite	X		X	X	X	X	X
GIQLI	X		X	X	X	X	X
HADS	X		X	X	X	X	X
Eating Habits	X			X	X	X	X
Resource use (including medications, use of medical services and other economic information)	X		X	X	X	X	X
Nutritional blood tests ***							
Full blood count	X		X	X	X	X	X
Electrolytes	X		X	X	X	X	X
Creatinine	X		X	X	X	X	X

Measurement	Pre randomisation	Day of surgery	4 weeks post surgery	Post randomisation Months			
				6	12	24	36
Fasting glucose	X		X	X	X	X	X
Lipids	X		X	X	X	X	X
HbA1c	X		X	X	X	X	X
Liver function tests	X		X	X	X	X	X
Iron, ferritin, vitamin B12	X		X	X	X	X	X
Folate/red cell folate	X		X	X	X	X	X
Lipid profile	X		X	X	X	X	X
25-hydroxyvitamin D	X		X	X	X	X	X
Calcium	X		X	X	X	X	X
Parathyroid hormone	X		X	X	X	X	X
Blood sample for future research	X						X
24 hour recall eating questionnaire	X			X	X	X	X
Other co-morbidity							
Sleep apnoea							
STOPBANG	X						
Epworth sleepiness scale	X			X	X	X	X
Non-alcoholic fatty liver disease**	X						X
In-depth interviews*	X		X	X	X	X	X

*undertaken in a purposeful sample of participants, **enhanced liver fibrosis test
***for the assessment of co-morbidities, + posted to participants 2 weeks before surgery

5.9 Source data

The primary data source will be the participant's medical notes. The laboratory reports will be the primary data source for the results of the blood analyses. The CRFs will be the source data for the resource use data and the completed patient questionnaires will be the primary data source for these measures. The audio and video recordings will be the primary data source for the qualitative aspects of the study.

5.10 Planned recruitment rate

Recruitment will be closely monitored throughout the trial. Expected numbers are shown in Table 4 below.

Table 4 Estimated recruitment rates, assuming 60% of patients undergoing bariatric surgery are eligible for the trial

Phase 1 sites (PI)	No. of referrals/yr	No./yr if 30% recruited	No./yr if 50% recruited	No./yr if 60% recruited	Total no. if 30% of eligible patients recruited up to 18 months & 50% thereafter
Taunton (Welbourn)	250	45	75	90	105
Southampton (Byrne)	60	10	18	22	25
Phase 1 (2 yrs)	**620**	**110**	**186**	**224**	**130**
Phase 2 (2 yrs)	**620**	**110**	**186**	**224**	**186**
Phase 3 (2 yrs)	**620**	**110**	**186**	**224**	**186**
Phase 2 sites (PI)	**No. of referrals/yr**	**No./yr if 20% recruited**	**No./yr if 45% recruited**	**No./yr if 50% recruited**	**Total no. if 20% of eligible patients recruited up to 12**

					months & 45% thereafter
Sunderland (Jennings)	180	21	48	54	69
Imperial (Ahmed)	180	21	48	54	69
Luton & Dunstable (Barreca)	180	21	48	54	69
Homerton (Agrawal)	180	21	48	54	69
Whittington (Sufi)	180	21	48	54	69
Derby (Leeder)	160	19	43	48	62
Leeds (Hayden)	130	15	35	39	50
Birmingham (Super)	130	15	35	39	50
Truro (Finlay)	80	9	21	24	30
Bournemouth (Davies)	80	9	21	24	30
10 new centres	1480	172	395	444	
Phase 2 (2 yrs)	**2960**	**344**	**790**	**888**	**567**
Phase 3 (2 yrs)	**2960**	**344**	**790**	**888**	**790**
Total in all centres in 6 yrs	**7780**				**1859***

*allows for some flexibility for recruitment targets

5.11 Participant recruitment

Eligible patients referred for bariatric surgery will be invited to participate in By-Band-Sleeve. Potential trial participants will be identified from the multi-disciplinary team meetings and all surgical clinics. All potential participants will be sent or given an invitation letter and PIL (approved by the local Research Ethics Committee (REC)) describing the study. The patient will have time to read the PIL and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wish. Most patients will have at least 48 hours to consider whether to participate. Following a consultation with the surgical team, patients will be asked if they wish to participate in the trial. If they remain uncertain they will be telephoned the following week to find out their decision and answer further questions that may have arisen.

The baseline data will be collected at the pre-operative assessment clinic where consenting patients will be seen by an authorised member of the local research team (study clinician/research nurse/trial co-ordinator) who will answer any questions, confirm the patient's eligibility and take written informed consent if the patient decides to participate.

5.12 Discontinuation/withdrawal of participants

Each participant has the right to withdraw at any time. In addition, the investigator may withdraw the participant from their allocated treatment arm if subsequent to randomisation a clinical reason for not performing the surgical intervention is discovered. If this occurs this will be documented.

If a participant wishes to withdraw, data collected up until this point will be included in the analyses, unless the participant expresses a wish for their data to be destroyed. Withdrawing patients will be asked at this point if they can be contacted for an assessment of weight and HRQOL three years after surgery (the timing of the primary end point).

5.13 Frequency and duration of follow up

Band patients will have band visits and adjustments in the first two years (expected to be up to 10 visits) and annual visits thereafter. Initial visits will be held at 4 weeks and 3 months post-surgery, and visits at 6, 12, 24 and 36 months post-randomisation will be standard. Additional visits will be scheduled to the participants' requirements.

Bypass and Sleeve patients will be seen at 4 weeks post-surgery, and at 6, 12, 24 and 36 months post-randomisation and annually thereafter. At each visit the patients will be seen by the standard NHS bariatric team (depending upon the local centre practice).

Active participation in the trial ends at 36 months post-randomisation. Thereafter patients will be followed through the NHS Information Centre's 'Medical Research Information Service' for mortality and the patient's weight will be requested on an annual basis.

5.13.1 Band consultations

Participants in the Band arm will undergo follow-up consultations according to a specific Band protocol**.** This will be performed by the trained research nurse or surgeon.

The patient will be interviewed by the research nurse to assess the amount of food they are able to eat, their appetite and whether they feel satisfied between meals. If a fill is indicated, it will be carried out according the local protocol and the patient will be tested for restriction. If there is too much restriction, fluid is withdrawn.

The band is filled progressively to reach the so-called 'sweet spot' of optimal restriction. Care is taken to try to avoid over-filling the band at any one time to avoid the disappointment of needing urgent band defill. Occasionally the port may not be accessible in the clinic and the band fill may need to be done under X-Ray control, and where this occurs it will be separately documented. However, fixing the port to the rectus sheath usually avoids this.

5.14 Likely rate of loss to follow-up

Until discharge from hospital, the only losses to follow-up will be due to death or participant withdrawal; these losses are expected to be very few. We expect loss to follow-up after discharge over the first three years to be less than 15%.

5.15 Expenses

Participant travel expenses will not be reimbursed for the follow up visits which would be expected to occur as part of normal surgical follow up. Exceptions to these can be considered on a case by case basis. Expenses will be available for research-specific visits that would not be expected to occur as part of normal surgical follow up.

5.16 Measures taken to avoid bias

Concealed randomisation will protect against selection bias. Participants, clinicians and other hospital staff caring for participants and participants themselves will not be ‘blind’ to their allocation, because of the need for adjustment of gastric bands with injection of saline into the subcutaneous port after discharge for participants given Band.

Standard protocols for follow-up after all procedures will be used to minimise the risk of performance bias arising from carers differentially providing co-interventions. We will monitor adherence to protocols and explore views of staff and participants with in-depth interviews about the follow up. We cannot prevent participants taking up co-interventions or adopting differential eating or other health behaviours contingent on their knowledge of their allocation. Indeed, such behaviours represent pragmatic aspects of the respective interventions since in routine practice patients will always know what operation they have had (although the uptake of various behaviours after completion of the trial might be modified by the findings of the trial).

With respect to detection bias, the assessor undertaking measurements of all outcomes at the primary endpoint (three years) will be blinded to the treatment allocation. We will assess the success of blinding, and reasons for unblinding, for example by disclosure of allocation by participants. Self-completion HRQOL measures will inevitably be susceptible to bias although we believe that expectations about the effects of the different procedures prior to surgery are likely to wane with follow-up, so participants will not have strong differential expectations of the treatments after three years.

We estimate up to 15% loss to follow-up. However, we aim to keep in touch with participants (through annual assessment; checking on change of address etc.), especially if a participant misses an annual follow-up assessment and we will investigate the sensitivity of the primary analyses to attrition bias.

To further minimise bias, outcome measures are defined as far as possible on the basis of objective criteria. Biochemical markers will be measured by an independent laboratory technician at the local hospital, without knowledge of treatment allocation.

The trial will be analysed on an intention-to-treat basis, i.e. outcomes will be analysed according to the treatment allocation, irrespective of future management and events, and every effort will be made to include all randomised participants. Follow-up for the outcome measures during the participant's stay in hospital should be complete for all participants.

5.17 Criteria for the termination of the trial

The trial may be terminated early on the instruction of the DMSC or if the results of another study supersede the necessity for completion of this study.

5.18 Economic issues

The economic evaluation will follow established guidelines [42, 43]. The main outcome measure will be quality adjusted life years (QALYs) using EQ-5D-5L[40], to be administered at baseline, before surgery, 4 weeks after surgery, 6,12, 24 and 36 months post-randomisation. Respondents will be assigned valuations derived from published UK population tariffs [44] and the mean number of QALYs per trial arm and incremental QALYs will be calculated. Data on percentage weight loss will act as an additional outcome measure. Data will be collected from the trial centres on health care resource use for surgery, follow-up appointments and treatments for any side effects. The costs for short term surgical complications such as peri-operative injury to adjacent organs and early post-operative morbidities such as staple leak or bleed will be estimated. Longer term complications such as wound hernias, or the need for re-intervention or for cosmetic plastic surgery will also be costed.

Resource use will be measured in naturally occurring units; for example, staff time will be measured in terms of length of times for treatments and unit costs will be derived from nationally published sources where available and from trial centres. Collection of these details will allow micro-costing of the two surgical strategies. This is important information that we have identified as lacking, which can feed into NHS tariffs. Costs for contact with additional health care professionals as a result of surgery such as GP visits will be estimated.

The analysis will calculate the average cost and outcome on a per patient basis and, from this the incremental cost-effectiveness ratios for the different trial arms will be derived, producing an incremental cost per QALY and cost per % weight loss achieved. Probabilistic sensitivity analysis will be used to demonstrate the impact of the variation around the key parameters in the analysis on the baseline cost-effectiveness results. Results will be expressed in terms of a cost-effectiveness acceptability curve, which indicates the likelihood that the results fall below a given cost-effectiveness ceiling.

Decision modelling will be used to explore longer terms costs and effects for at least 20 years post-surgery. This will enable us to consider for instance longer term costs such as vitamin B12 replacement, calcium and vitamin D replacement for Bypass and follow-up for post gastric surgery bone disease. Also cost savings as a result of a potential reduction or resolution in co-morbidities (e.g. diabetes) will be explored.

6. Statistical analyses

6.1 Analyses of quantitative data

The analyses will be based on intention to treat and will include all randomised patients. Analyses will be adjusted for design factors included in the cohort minimisation. The proportion of patients with at least 50% excess weight loss at three years will be compared using logistic regression. HRQOL scores (and other continuous outcomes measured at multiple time points) will be compared using a mixed regression model with baseline and post-surgery measures modelled jointly. Changes in treatment effect with time will be assessed by adding a treatment by time interaction to the model and comparing models using a likelihood ratio test. Time to event outcomes will be compared using survival methods for interval censored data. Model fit will be assessed and alternative models and/or transformations (e.g. to induce normality) will be explored where appropriate. Frequencies of adverse events will be described. Treatment differences will be reported with 95% confidence intervals (CIs). A detailed analysis plan will be prepared during the feasibility phase 1. Interim analyses will be decided in discussion with the Data Monitoring and Safety Committee (DMSC). There is no intention to compare any outcomes between groups after phase 1; the only analyses will be descriptive statistics to summarise recruitment to decide whether the trial satisfies the progression criteria.

We will monitor the trial to ensure that each surgeon does approximately equal numbers of operations of each type. In this situation, in contrast to expertise-based randomisation where each surgeon only performs one type of operation (and hence forms a cluster), clustering by surgeon is less relevant to the sample size and is usually ignored (on the basis that intraclass correlation is negligible, personal communication Prof D Altman). However, we will take the data structure into account, i.e. nesting of patients by surgeon and centre, in the primary analyses.

6.2 Analyses of qualitative data

In-depth interviews and recruitment appointments will be audio-recorded. Interviews will be fully transcribed, and the data will be analysed using the methods of constant comparison to elicit themes that will be written up into descriptive accounts that will be shared with the study team [45]. In the recruitment study, the aspects of most interest will be issues of equipoise among surgeons/recruiters, and the acceptability of the procedures and the information provided to patients. The data from recruitment appointments will be documented through summaries of the content, with thematic analyses of areas of the appointments where information is articulated by recruiters and interpreted by patients. This will be supplemented by targeted conversation analysis focussing on areas of appointments where communication appears problematic [45]. Data will be transcribed as required, and then incorporated into training programmes and materials or used in individual confidential feedback for recruiters. In-depth interviews with a sample of trial participants in each arm will focus on experiences of management following surgery and outcome, and will be analysed thematically.

For the process evaluation interview, audio and observational data will initially be coded separately, resulting in two separate coding frames. Relevant themes will then be considered together, with the interview data being used to confirm, challenge, or clarify the observation findings. The intention is to take an inductive approach to the data analysis, enabling theories to be derived from the data. Additionally, negative cases will actively be sought; patients, surgeons or other team members with contrasting views or attitudes, as this will help gain deeper understanding of the data.

It will be possible to synchronise video and observation recordings using the Observer XT 10.5 software, as well as audio recordings, as all equipment can be activated simultaneously.

6.3 Subgroup analyses

One subgroup analysis is planned; outcomes will be described for patients with and without diabetes mellitus at baseline. Differences in treatment effect between the two subgroups will be tested by including interaction terms to the analysis model. This is a secondary analysis as the study is not powered to detect subgroup differences.

6.4 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants. No formal interim analysis is planned. Safety data will be reported to the DMSC at a frequency agreed with DMSC members, together with any additional analyses the committee request.

7. Trial management

The trial will be managed by the Clinical Trials and Evaluation Unit (CTEU Bristol) of the Bristol Heart Institute. The CTEU Bristol is an UK Clinical Research Collaboration registered Clinical Trials Unit. The CTEU Bristol will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators.

7.1 Day-to-day management

The trial will be managed by a TMG, which will meet face to face or by teleconference monthly during the feasibility phase 1 and bi-monthly thereafter. The TMG will be chaired by the Chief Investigator and will include all members of the named research team (see *Chief Investigators & Research Team Contact Details above)*.

A research nurse/coordinator in each centre will be responsible for identifying potential trial participants, seeking informed participant consent, randomising participants, liaising with the theatre planning manager, collecting trial data and ensuring the trial protocol is adhered to.

7.2 Monitoring of sites

7.2.1 Initiation visit

Before the study commences training session(s) will be organised by CTEU Bristol. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study.

7.2.2 Site monitoring

The trial coordinating centre (CTEU) will carry out regular monitoring and audit of compliance of centres with GCP and data collection procedures described in section 5 above.

7.3 Trial Steering Committee and Data Monitoring and Safety Committee

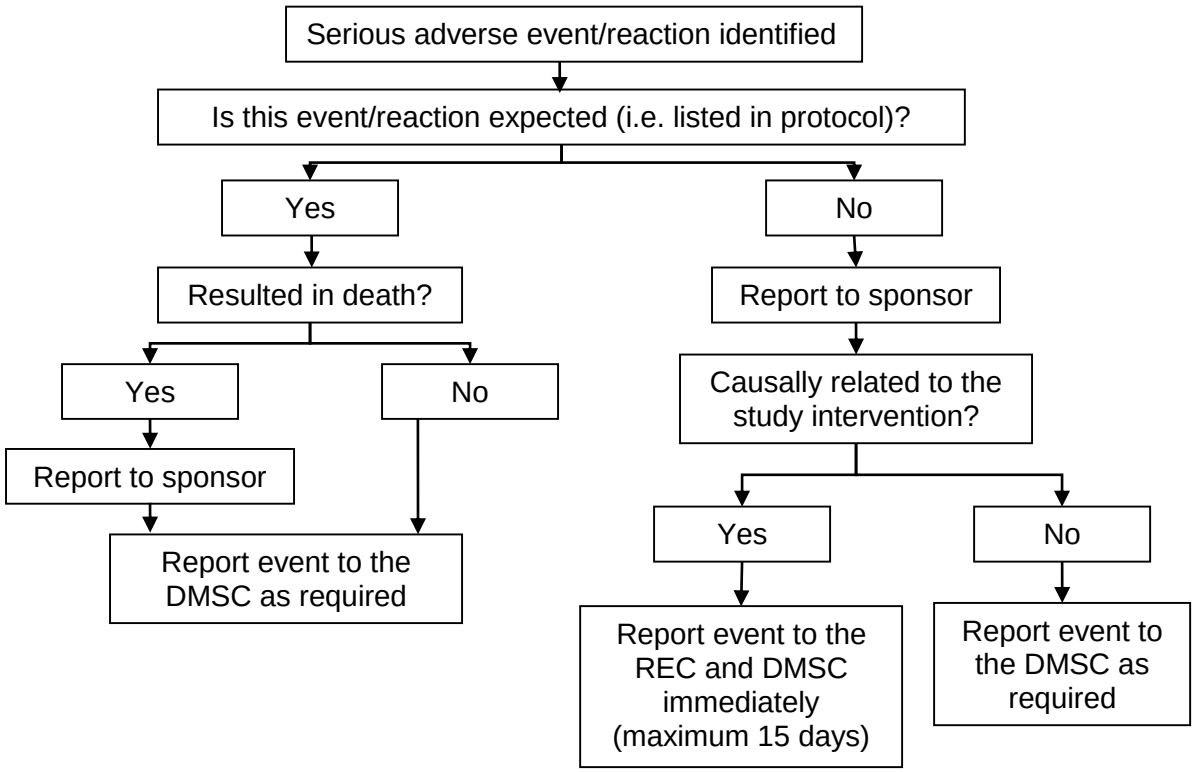
The TSC is made up of representatives of By-Band-Sleeve TMG and independent members. The HTA will appoint members of this committee and the DMSC.

8. Safety reporting

Serious and other adverse events will be recorded and reported in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the Sponsor's Research Related Adverse Event Reporting Policy (see **Figure 2**).

In this population all three interventions are low risk but some SAEs will be 'expected'. These will be reported to the CTEU and data on these adverse events collected during the trial will be reported regularly by the CTEU to the trial DMSC for review and to the Sponsor and the UK Research Ethics Committee (REC) when required.

Figure 2 Serious adverse event reporting flow chart



8.1 Expected adverse events

The following adverse events are 'expected' in the period from surgery to discharge from hospital after the operation:

Peri-operative events
Cardiovascular including,

- Acute myocardial infarction
- Dysrrythmia
- Cardiac arrest

Bleeding requiring blood transfusion
Bleeding requiring acute endoscopy +/- possible injection for bleeding
Bleeding not requiring intervention

Iatrogenic injury to any organ requiring intervention, including

- Spleen
- Liver
- Bowel
- Major blood vessels in abdomen

Anaphylaxis to anaesthetic agent or drug given during surgery or during recovery prior to discharge

Post-operative events
Pulmonary complications, including:

- Intubation and ventilation for any reason
- Initiation of mask continuous positive airway pressure ventilation after weaning from ventilation
- Pneumonia

Thromboembolic complications, including:

- Deep vein thrombosis
- Pulmonary embolus

Renal complications, including:

- Urinary tract infection
- Acute renal failure
- New haemofiltration/dialysis
- Urinary retention

Infective complications, including:

- Wound infection/breakdown
- Gastric band or port site infection
- Urinary tract infection

GI complications, including:

- Oesophagitis
- Leak from gastric staple line at angle of his, or elsewhere
- Leak from gastro-jejunal anastomosis
- Leak from jejuno-jejunal anastomosis
- Upper GI bleed
- Stomach ulcer
- Small bowel obstruction
- Acute gastric dilatation
- Fistula
- Port site hernia
- Internal hernia
- Gastric stricture
- Infective intra-abdominal collection

Neurological complications

- Permanent stroke
- Transient ischaemic attack (TIA)

Bleeding requiring reoperation or blood transfusion
Bleeding requiring acute endoscopy +/- possible injection for bleeding

Band complications, including,

- Band slippage – proximal or distal
- Flipped port
- Gastric band infection
- Port site infection
- Leakage from tubing
- Leakage – damage to port or tubing

Re-operation for any reason, including,

- Band repositioning
- Removal of band for any reason, including intolerance
- Removal of port (under general anaesthetic)
- Re-siting of port (general anaesthetic)
- Small bowel obstruction or perforation
- Division of adhesions
- Closure of internal hernia defects
- Diagnostic laparoscopy alone
- Placement of feeding jejunostomy
- Placement of T-tube into gastric staple line

Re-interventions for any reason, including,

- Upper GI endoscopy
- Endoscopic clipping
- Upper GI dilation
- Radiological drain placement
- Radiological stent placement for leak from gastric staple line
- Enteral feeding
- Total parenteral nutrition (TPN) feeding
- Placement of chest drain
- Removal of port (under local anaesthetic)
- Re-siting of port (under local anaesthetic)

Investigations for any reason, including,

- Chest X-ray
- Abdominal X-ray
- Barium swallow
- CT scan

Other complications

- Rhabdomyolysis
- Fluid/electrolyte problems
- Acute cholecystitis/biliary colic
- Cholangitis/common bile duct stones
- Other abscess/infection/fever
- Unplanned admission to ITU/HDU
- Hypoglycaemia
- Hyperglycaemia
- Iron deficiency/anaemia

Death in hospital

The following adverse events are ‘expected’ <u>after discharge from hospital</u>:

Infective complications, including:

- Wound infection/breakdown

- Gastric band or port site infection

GI complications, including:
- Oesophagitis
- Leak from gastric staple line at angle of his, or elsewhere
- Leak from gastro-jejunal anastomosis
- Leak from jejuno-jejunal anastomosis
- Upper GI bleed
- Stomach ulcer
- Acute gastric dilatation
- Gastric stricture
- Fistula
- Port site hernia
- Internal hernia
- Infective intra-abdominal collection

Thromboembolic complications, including:
- Deep vein thrombosis
- Pulmonary embolus

Neurological complications
- Permanent stroke
- Transient ischaemic attack (TIA)

Re-operation for any reason, including,
- Repositioning of the band
- Removal of band for any reason including band intolerance
- Removal of port (under general anaesthetic)
- Re-siting port under general anaesthetic)
- Division of adhesions
- Small bowel resection
- Closure of internal hernia defects
- Diagnostic laparoscopy alone
- Laparoscopic drain placement
- Placement of feeding jejunostomy
- Placement of T-tube into gastric staple line
- Placement of chest drain
- Joint replacement or repair (e.g. knee replacement)
- Cosmetic surgery (e.g. removal of excess skin)

Re-intervention for any reason, including,
- Upper GI endoscopy
- Endoscopic clipping
- Upper GI dilatation
- Enteral feeding
- TPN feeding
- Radiological drain placement
- Removal of port (under local anaesthetic)
- Re-siting of port (under local anaesthetic)

Investigations for any reason, including,
- Chest X-ray
- Abdominal X-ray
- Barium swallow

- CT scan

Other complications
- Fluid/electrolyte problems
- Acute cholecystitis/biliary colic
- Cholangitis/common bile duct stones
- Iron deficiency/anaemia

8.2 Period for recording serious adverse events

Data on adverse events will be collected from consent for participation for the duration of the participant's 3 year follow-up period.

9. Ethical considerations

9.1 Review by an NHS Research Ethics Committee

Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL and consent forms) will be carried out by a UK Research Ethics Committee (REC). Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC for approval prior to implementation.

9.2 Risks and anticipated benefits for trial participants and society

All participants will undergo one of the three standard operations currently carried out for severe and complex obesity in the NHS. They may expect to experience the weight loss benefits of surgery and experience the side effects of each procedure.

9.3 Information to potential trial participants of possible benefits and known risks

The risks and benefits of the three treatment options will be fully explained. In particular, the uncertain medium to long-term results after the three procedures will be communicated.

9.4 Obtaining informed consent from participants

All participants will be required to give written informed consent. This process, including the information about the trial given to patients in advance of recruitment, is described above in section 5.11. The research nurse/trial coordinator/PI/clinical research fellow will be responsible for the consent process, which will be described in detail in the Trial Manual.

10. Research governance

This study will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- Research Governance Framework for Health and Social Care

10.1 Sponsor approval

Any amendments to the trial documents will be approved by the sponsor prior to submission to the REC.

10.2 NHS approval

Any amendments to the trial documents approved by the REC will be submitted to the Trust R & D departments for information and approval.

10.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or CTEU Bristol or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved by the REC that they receive and ensure that the changes are complied with.

10.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework. All study related documents will be made available on request for monitoring and audit by the sponsor and the relevant REC.

10.5 Indemnity

This study is sponsored by the University of Bristol.

10.6 Clinical Trial Authorisation

Band, Bypass and Sleeve are not classed as investigational medicinal products and therefore a Clinical Trial Authorisation from the MHRA is not required.

11. Data protection and participant confidentiality

11.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 1998.

11.2 Data handling, storage and sharing

11.2.1 Data handling

Data will also be entered into a purpose-designed SQL server database. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to By-Band-Sleeve study staff. Information capable of identifying participants will not be removed from the CTEU or clinical centres or made available in any form to those outside the study.

Access to the database will be via a secure password-protected web-interface (NHS clinical portal). Study data transferred electronically between the University of Bristol and the NHS will only be transferred via a secure NHSnet network in an encrypted form.

Data will be entered promptly and data validation and cleaning will be carried out throughout the trial. Standard operating procedures (SOPs) for database use, data validation and data cleaning will be available and regularly maintained.

11.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 10 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Prior to destruction, paper records will be scanned and stored on the University server with limited password controlled access. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial in accordance to policy of the sponsor. In compliance with the MRC Policy on Data Preservation, relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). A secure electronic 'key' with a unique participant identifier, and key personal identifiers (.e.g. name, date of birth and NHS number) will also be held indefinitely, but in a separate file and in a physically different location (NHS hospital server). These will be retained because of the potential for the raw data to be used subsequently for secondary research.

11.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be made available for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body.

12. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available. A full report for the HTA will be written after each phase of the trial.

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14. Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
1	1	31 August 2011	2	6 August 2012	Removed hiatus hernia >5cm from exclusion criteria Clarified when baseline weight will be measured Changed post-discharge follow-up from 6 weeks to 4 weeks Added • maximum weight recorded in medical records • Epworth sleepiness scale and HADS questionnaire • assessment at 3 months for both groups • participant contact by email or SMS and the option to complete questionnaires on-line • timing of expected events added • qualitative research – process evaluation and development of surgical manual • qualitative research – non-participant observation of consultations Updated expected adverse events to and distinguished	8 October 2012

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					between events expected before and after discharge following surgery	
3	2	6 August 2012	4 (version 3 submitted but not approved)	3 March 2014	Biliary and gastric limbs changed from 100cm and 200cm to 75cm and 150cm respectively Clarified when randomisation takes place and when baseline weight will be measured Revised follow-up schedule so that with the exception of the 4 week post-surgery follow-up all follow-up is timed to be post randomisation Removed • discontinuation of CPAP as a criterion for resolution of sleep apnoea • follow-up at 3 months Added • not suitable for bypass for medical reasons to the exclusion criteria • sleep study at 3 years for participants with sleep apnoea at recruitment	25 March 2014

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					• patient reported outcomes, consensus meeting and Delphi survey of patients for core outcome set • EQ-5D-5L questionnaire 2 weeks before surgery	
4	4	3 March 2014	5	8 August 2014	Addition of EQ-5D-5L at recruitment for patients agreeing to follow-up at 3 years but not randomisation	2 October 2014
5	5	8 August 2014	7 (version 6 submitted but not approved)	6 May 2015	Adaptation of protocol to include a third group, Sleeve Updated • background literature • eligibility criteria to reflect updated NICE guidance • expected recruitment figures Reinstated hiatus hernia >5cm as an exclusion criteria Clarified mandatory and optional components of surgery and concomitant interventions. Removed National Bariatric Surgery Registry	8 May 2015

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					from data collection table Removed minimisation by surgeon as in many centres a pooled operating list is used Period of data storage changed to 10 years	
6	7	06 May 2015	8	29 May 2015	Removal of "surgeon unwilling" as an exclusion criteria. Addition of exclusion criteria reflecting main reasons why surgeons are unwilling to randomise. Clarification of trial interventions. Paragraph explaining the transfer of samples from sites to University of Bristol added. Section on expected adverse revised following review by study team.	29 June 2015
7	8	29 May 2015	9	02 Nov 2015	Changes in the section describing surgical interventions. Added two expected adverse events after discharge from hospital: joint replacement or repair and	2nd December 2015

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					cosmetic surgery.	