

# BMJ Open Protocol for a pilot randomised controlled trial of zoledronic acid to prevent bone loss following sleeve gastrectomy surgery

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## ABSTRACT

**Introduction** Sleeve gastrectomy (SG) is an increasingly used and effective treatment for obesity; however, the rapid weight loss associated with SG adversely affects bone metabolism predisposing patients to skeletal fragility. Bisphosphonate medications have been evaluated for safety and efficacy in combating bone loss in patients with osteoporosis, but their use in SG-induced bone loss is limited. The goal of this study is to investigate how a one-time infusion of zoledronic acid compares to placebo, in its ability to combat SG-associated bone loss.

**Methods and analysis** This research protocol is a 9-month, pilot randomized controlled trial (RCT) involving 30 adult SG patients randomised to receive an infusion of either 5 mg of zoledronic acid or placebo, 6 weeks following surgery. To be included participants must be <350 lbs/158.8 kg, free of bone-impacting pathologies or medications, and must have adequate serum calcium and vitamin D levels at baseline. The primary outcome is change in areal bone mineral density (aBMD) at the total hip. Secondary outcomes include change in aBMD of the femoral neck, and lumbar spine, and change in volumetric BMD at the lumbar spine. The primary aim will be tested using a linear mixed model fit with total hip aBMD at 9 months as the outcome. Treatment, participant sex and menopausal status will be considered in analysis. Groups will be compared using contrast statements at 9 months, with change over 9 months being the primary comparison.

**Ethics and dissemination** This study was approved by the Institutional Review Board of the University of Nebraska Medical Center (IRB820-19). Written consent will be obtained from participants at enrolment by trained staff. Careful and thorough explanation are used in obtainment of consent and voluntariness is emphasised throughout the trial. The findings of this study will be presented locally, nationally, and published in peer-reviewed journals. Additional details will be reported on ClinicalTrials.gov.

**Trial registration number** NCT04279392

## INTRODUCTION

Surgical weight loss procedures, including Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), have emerged as the most effective treatments for obesity and the resolution of obesity-related comorbid conditions.<sup>1</sup>

## Strengths and limitations of this study

- This study uses a comprehensive, quadruple-blinded, randomised controlled trial design to investigate the use of zoledronic acid to prevent bone loss 9 months following sleeve gastrectomy (SG), with additional information including physical activity status, physical function testing, dietary intake and body composition collected preoperatively and postoperatively.
- The inclusion of validated and innovative bone health measures including strength, areal density, volumetric density and bone turnover, will generate high-quality data.
- The use of intravenous zoledronic acid ensures high adherence to the bisphosphonate medication, without the oesophageal risk of oral alternatives.
- The pilot nature of this study implies a relatively small sample size, however, this number is adequate to provide insights into bone health following SG, and the use of zoledronic acid to potentially mitigate that loss.
- Due to the exclusion of women of childbearing capacity, a potential sample bias may occur, limiting the findings to select populations undergoing SG; however, the inclusion of adults across the lifespan is a strength of our study.

Compared with medication alone, surgical procedures are superior in long-term weight loss and resolution of type 2 diabetes.<sup>2</sup> Thus, it is not surprising that over 152 000 SG and 46 000 RYGB procedures were performed in the USA alone in 2019.<sup>3</sup> Despite well-recognised improvements in cardiovascular health, blood pressure, and diabetes, bariatric procedures are also associated with negative skeletal health outcomes.<sup>4 5</sup> RYGB, which is the older of the two most commonly performed procedures, is associated with significant bone loss at both the axial and appendicular skeleton given its malabsorptive and restrictive nature.<sup>6 7</sup> However, SG is emerging as a

potential threat to long-term bone health. Prospective data investigating SG estimates a 3%–7% decrease in areal bone mineral density (aBMD) at the hip and 3%–10% decrease at the femoral neck, within 1 year of surgery.<sup>5</sup> This loss is comparable to the aBMD lost in approximately 5 years following menopause<sup>8</sup> and may predispose persons undergoing SG to premature fracture.

Many Federal Drug Administration-approved treatments exist to maintain bone in periods of rapid loss. Bisphosphonate therapy is the first-line medication used to treat osteoporosis and has been shown to reduce fracture risk at all major fracture sites.<sup>9,10</sup> Similarly, two recent manuscripts addressing the efficacy for bisphosphonate use for bone loss following bariatric surgery have been published, suggesting they may be a useful intervention.<sup>11,12</sup> Oral bisphosphonates, including alendronate and risedronate, are the most commonly prescribed option, while zoledronic acid, which is an intravenous fluid preparation, is emerging in popularity.<sup>13</sup> Although the risk of severe oesophagitis is low with oral dosing in the general population, caution should be used in patients after bariatric surgery due to the risk of ulceration.<sup>14</sup> Intravenous zoledronic acid, which is the most potent osteoclast inhibitor available,<sup>15</sup> may be more appropriate for those with altered stomach anatomy, as it is not associated with oesophagitis, gastritis or ulceration. Likewise, its preparation as a one-time intravenous infusion is preferable to many patient populations.<sup>16</sup> A single dose of zoledronic acid has been shown to suppress bone turnover for 5 years and has repeatedly displayed efficacy in fracture prevention in populations with high bone turnover.<sup>15</sup> We predict that intravenous zoledronic acid is safe, and has the potential to combat the bone turnover and subsequent reduction in aBMD associated with SG, while minimising gastrointestinal risk.

## Objectives

### Specific aim 1

To determine the efficacy of zoledronic acid in preventing bone loss associated with SG. Imaging (BMD, bone strength), bone turnover markers, and physical function measures will be measured at baseline and 9 months. The primary outcome is change in aBMD at the total hip as measured by dual energy X-ray absorptiometry (DXA). Secondary outcomes include change in aBMD of the femoral neck, and lumbar spine by DXA, and change in volumetric BMD and bone strength at the lumbar spine as measured by quantitative CT (QCT) and finite element analysis, respectively. Change in the serum bone turnover markers, serum type 1 procollagen N-terminal (PINP; bone formation marker) and urinary collagen type 1 cross-linked N-telopeptide (NTX; bone resorption marker) will also be assessed.

### Specific aim 2

To evaluate the feasibility of this trial in those who have undergone SG. The feasibility will be assessed by

documenting adverse events, side effects and compliance rates at each study time point.

## METHODS AND ANALYSIS

### Setting and patient population

Adults ( $\geq 19$  years of age) pursuing SG at the University of Nebraska Medical Center Bariatric Center (Omaha, Nebraska, USA) will be recruited and enrolled in this study. Participants will be recruited from the centre's mandated preoperative nutrition courses, whereby study dietitians will provide information about the study and collect contact information from persons who express interest in participation. Participants will be scheduled for consent and enrolment after meeting all requirements for surgery, as recommended by the American Society for Metabolic and Bariatric Surgery (ASMBS).<sup>17</sup> This study was approved by the academic medical centre's Institutional Review Board (IRB). Full inclusion and exclusion criteria are described in [table 1](#). Briefly, study personnel with ethical access will complete an electronic medical record will screen for basic eligibility requirements (weight  $< 350$  lbs/158.8 kg, pursuing SG). Study personnel will contact those who express interest via phone to thoroughly assess all eligibility parameters, describe the study timeline, and schedule eligible and interested participants to read and sign an IRB-approved informed consent form prior to enrolment. Adverse events, incidental findings and changes in health status that may limit or prohibit participation, will be assessed by the study surgeon, endocrinologist and IRB.

### Study design and randomisation

This pilot quadruple-blinded (participant, care provider, investigator and outcomes assessor are blinded to the treatment group) RCT anticipates 30 participants (15 per group) assigned (via computer-generated 1:1 block randomisation, with stratification by sex) to receive a one-time 100 mL infusion of 5 mg zoledronic acid or saline 6–8 weeks following SG. Study assessments will occur at baseline (prior to surgery) and at 9 months postoperatively. A complete study timeline is detailed in [figure 1](#) and [table 2](#). Compensation in the form of gift cards will be given at each assessment and infusion visit.

### Consent/enrolment

The consent and enrolment visit will occur no more than 6 weeks prior to SG. At the consent and enrolment visit, persons will provide informed consent for participation. Participants will confirm relevant medical history and demographic characteristics, including age, race, menopausal status and birth control method, and then complete self-report surveys including the Human Activity Profile (HAP)<sup>18</sup> and Knee Injury and Osteoarthritis Outcomes Score (KOOS).<sup>19</sup> They will also complete the 'National Osteoporosis Foundation Calcium Intake Survey' (NOF), detailing their calcium and vitamin D intake.<sup>20</sup> Following surveys, participants will undergo blood draw for serum

**Table 1** Healthy body, healthy bones inclusion and exclusion criteria

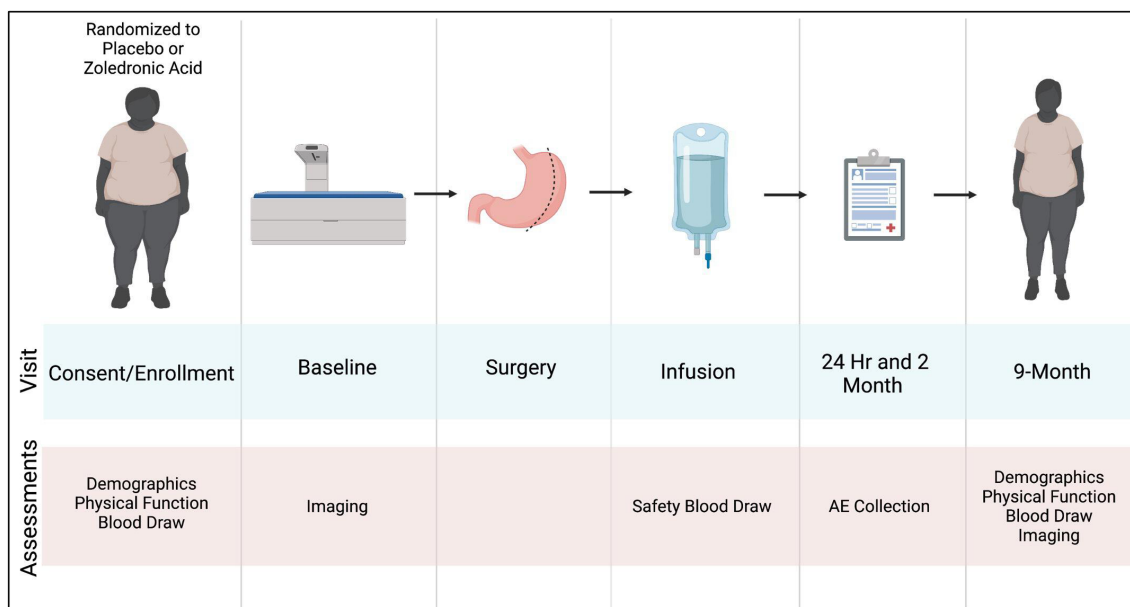
Inclusion criteria	Exclusion criteria
1. Subjects planning a sleeve gastrectomy procedure at the study bariatric surgery centre. 2. Agreement to all study procedures and assessments. 3. Women must be postmenopausal (Follicle-stimulating hormone blood level >30 mIU/m), or incapable of childbearing (non-hormonal long-term birth control*).	1. Prior bariatric surgery. 2. <19 years of age. 3. Weight ≥350 lbs. 4. Liver or renal disease. 5. Hypercalcaemia, hypocalcaemia or hypomagnesaemia. 6. Serum 25-OH vitamin D <20 ng/mL. 7. History of bone-modifying disorders. 8. Use of bone-active medications. 9. Known sensitivity to bisphosphonates. 10. Extensive dental work involving extraction or dental implant within the past 2 months or planned in the upcoming 6 months. 11. Current diagnosis of type 1 diabetes. 12. Current malignancy. 13. Autoimmune disease impacting bone (eg, rheumatoid arthritis).

\*Given the risks of zoledronic acid on fetal development, there are risks to including women of childbearing capacity. However, premenopausal women with documented non-hormonal intrauterine devices in the study population will mitigate this risk. Although there is consensus that pregnancy should be avoided for 12–24 months following bariatric surgery, many women in this population regain fertility and become pregnant following surgery. Research has shown that hormonal contraceptives may not be as efficacious in women with obesity, and bariatric surgery has been shown to impact absorption and efficacy of oral contraception methods. For safety purposes, only premenopausal women with documented intrauterine devices will be eligible for this research study.

bone turnover markers. For those unsure of menopause status, an additional blood draw will be performed to confirm postmenopausal status (follicle stimulating hormone blood level >30 mIU/m). Due to constraints in scheduling, blood will be drawn at approximately the same time for each individual participant, and draw time will be recorded for future processing to minimise the effects of diurnal variation. Fasting conditions for blood draw were not required. Participants will then complete physical function testing, which includes 5 times sit to stand testing,<sup>21</sup> hand grip strength testing<sup>22</sup> and the 4-metre walk test.<sup>23</sup>

### Baseline visit

The baseline visit will take place no more than 6 weeks preoperatively. The first series of DXA scans (total body, hip, femoral neck, lumbar spine) and QCT of the lumbar spine will be completed. Calcium, vitamin D and ProCare Bariatric vitamins will be dispensed at this visit, and participants will be instructed on how to take their supplements as per ASMBS guidelines.<sup>17</sup> Each participant will receive 1200 mg of calcium daily for the duration of the study. Vitamin D will be dosed and prescribed based on baseline 25(OH) D blood levels as follows: participants with serum


**Figure 1** Healthy body, healthy bones study design. AE, Adverse event.

**Table 2** Study variables, collection instruments, rationale for use and timeline

Measure	Purpose	Consent/ enrolment	Baseline	Infusion	24 hours/2 months	9 months
<b>Demographic and survey data</b>						
Anthropometric measures, medical and surgical history, menopause status	Demographic data and medical history to describe sample and identify potential covariates	X				X
Human Activity Profile (HAP)	Self-report 94-item survey to assess habitual physical activity	X				X
Knee Injury and Osteoarthritis Outcomes Score (KOOS)	Self-report survey used to assess the patient's opinion of their short-term and long-term knee function	X				X
National Osteoporosis Foundation (NOF) Calcium Intake Estimate	Calculates dietary intake of calcium based on servings of calcium-rich food per day	X				X
<b>Functional assessments</b>						
5 times sit to stand	Lower extremity strength and function	X				X
Hand grip	Static upper body extremity strength	X				X
4-Metre walk	Functional mobility, gait and vestibular function	X				X
<b>Imaging</b>						
Dual-energy X-ray absorptiometry (DXA)	Areal BMD at total hip, femoral neck and spine; body composition		X			X
Quantitative CT (QCT)	Volumetric BMD and finite element-estimated bone strength at the lumbar spine		X			X
<b>Blood draw</b>						
Serum biomarkers of bone turnover	P1NP (pg/mL) and serum NTX (nmol BCE/L), assesses rate of bone formation and resorption		X			X
Comprehensive metabolic panel (CMP)	Safety, assess kidney function via calculated glomerular filtration rate (GFR)			X		
<b>Adverse events collection</b>						
Adverse events, side effects	Safety, tolerance, feasibility			X	X	X

BMD, bone mineral density; NTX, N-telopeptide; P1NP, procollagen type 1 N-terminal propeptide.

D levels at 30 ng/mL or greater will be prescribed 1000 IU daily, and participants with levels of 20–29 ng/mL will be prescribed 2000 IU daily.

### Surgery

There are no study requirements related to surgery. SG will be performed according to a standard procedure. On postoperative day 1, study personnel will review the electronic health record to document any surgical complications that may have occurred. Participants will then be contacted via phone to schedule their infusion visit.

### Zoledronic acid or placebo infusion

The infusion visit will take place 6–8 weeks following surgery. At the infusion visit, participants will undergo a comprehensive metabolic panel to assess kidney function. For safety of infusion, adequate kidney function will

be confirmed (calculated eGFR of  $\geq 35$  mL/min). If estimated glomerular filtration rate (eGFR) is  $< 35$  mL/min, the infusion will not occur due to safety reasons, and the staff will consult with the study endocrinologist to discuss withdraw criteria. If eGFR is  $\geq 35$  mL/min, research nursing staff will place a peripheral intravenous line, and collect vitals including temperature, blood pressure and heart rate. Participants will receive either placebo or active medication in the form of a 100 mL infusion, delivered over 30 min (200 mL/hour). Following infusion, participants will be monitored for 15 min for adverse events including anaphylaxis. Vitals will be repeated and recorded following the monitoring period, and study personnel will complete the Side Effects Questionnaire. Twenty-four hours and 2 months following the infusion



**Table 3** Outcome measurements for healthy body, healthy bones trial. change measures are over 9 months

Primary outcome(s)	Measurement tool
<b>Areal BMD:</b> change in total hip (g/cm <sup>2</sup> ) areal BMD (g/cm <sup>2</sup> )	DXA
<b>Secondary outcome(s)</b>	
<b>Areal BMD:</b> change in femoral neck (g/cm <sup>2</sup> ) and lumbar spine (L1-L4) areal BMD (g/cm <sup>2</sup> )	DXA
<b>Volumetric BMD:</b> change in lumbar spine (L1-L4) volumetric BMD (mg/cm <sup>3</sup> )	QCT
<b>Finite element analysis (FEA):</b> change in bone strength of the L2 vertebra (Newtons)	QCT
<b>Serum bone turnover markers:</b> change in P1NP (bone formation) and NTX (bone resorption)	Serum bioassay
<b>Body composition:</b> change in total lean mass (kg, %), total fat mass (kg, %) and appendicular lean mass (kg, %)	Whole body DXA
<b>Functional status:</b> change in chair stands (s), handgrip strength (kg) and gait speed (s)	Sit to stand, hand grip, 4-metre walk
<b>Feasibility:</b> proportion of participants completing 9-month study visit requirements (N, %)	Study retention; attendance
<b>Feasibility:</b> proportion of participants experiencing adverse effects or events associated with the study intervention or placebo (N, %)	Side Effects Questionnaire; vitals; monitoring/observation

BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; NTX, N-telopeptide; P1NP, procollagen type 1 N-terminal propeptide; QCT, quantitative CT.

visit, study personnel will call the participants to repeat the Side Effects Questionnaire.

### 9-month follow-up visit

The 9-month follow-up visit will take place 9±1 months following surgery. At this visit, demographic and anthropometric evaluations will be repeated. Study participants will repeat all surveys (HAP, KOOS, NOF), functional assessments, blood draw and imaging (DXA and QCT). Participants will be counselled on maintenance of bone health with resources from the National Osteoporosis Foundation and advised to continue nutritional supplementation.

### Outcome measurements

The primary outcome for this 9-month pilot RCT is defined as change in total hip aBMD (g/cm<sup>2</sup>). Secondary outcomes include change in femoral neck aBMD (g/cm<sup>2</sup>), and change in lumbar spine (L1-L4) aBMD (g/cm<sup>2</sup>). Primary and secondary outcomes are listed in table 3. Details surrounding acquisition of each outcome are provided in more detail below.

### DXA-acquired measures

All DXA-acquired measures will be assessed at baseline and at the 9-month follow-up visit. Areal BMD of the total hip, femoral neck and lumbar spine will be determined using DXA (GE Lunar Prodigy; Model 8743; enCore V.18 software). Likewise, body composition information including total fat mass, total lean mass, and appendicular lean mass (which represents the sum of lean mass of the arms and legs) will be collected using DXA. If the participant exceeds the field of view, a full-view scan of the right side of the participant's body will be acquired, and total body values will be determined using a mirroring protocol.<sup>24</sup> All participants will be scanned on the same scanner by certified DXA technicians. Participants will be

categorised as osteopenic or osteoporotic using the WHO classification system.<sup>25</sup>

### QCT-acquired measures

Helical QCT scans of the L1-L5 vertebrae (top of T11-coccyx) will be acquired at baseline and 9 months. A GE Revolution CT scanner (20MW06.41 SP01) will be used to acquire all scans. The scan parameters will be set at 120 kV, 50 cm scan field of view, automatic exposure with a target noise index of 20 HU, and a 0.625 mm slice thickness. The Mindways Model 3 CT calibration phantom and bolus bag (Mindways Software, Austin, Texas, USA) will be positioned under each participant and imaged in every scan to calibrate volumetric BMD. Quality assurance scans will be performed monthly to monitor operational characteristics of the CT scanner. To evaluate bone strength and fracture risk, subject-specific finite element models of the L2 vertebra from the QCT scans will be developed at baseline and 9-month follow-up.<sup>26 27</sup>

### Physical function testing outcome measures

Functional testing will be completed at baseline and 9 months. The 5 Times Sit to Stand test, used as a measure of lower extremity strength and function, has been validated in populations undergoing bariatric surgery.<sup>21 28</sup> Handgrip strength will be used to estimate static upper body extremity strength.<sup>22</sup> The 4-metre walk test will be used to assess functional mobility, gait, and vestibular function.<sup>23</sup>

### Biomarkers of bone turnover

Blood samples will be collected at baseline and 9 months via venipuncture. After centrifugation for 20 min at 4°C, aliquots of serum will be collected and stored at -80°C. Analysis of bone formation markers including P1NP and bone resorption marker NTX of type 1 collagen will be

performed via commercially available ELISA by our laboratory in batch testing at the conclusion of the study.<sup>29</sup>

### Statistical analysis

A sample size of 10 per group achieves 80% power to detect a difference in mean total hip BMD of 0.11 g/cm<sup>2</sup> between the active and placebo groups using a two-sided Wilcoxon test assuming an estimated SD of 0.07 g/cm<sup>2</sup> and that the distribution is normal. The sample size of 10 per group is also sufficient to detect a paired mean difference in total hip BMD of 0.07 g/cm<sup>2</sup> between baseline and 9 months using a two-sided Wilcoxon signed-rank test assuming an SD of 0.07 g/cm<sup>2</sup> and a correlation of 0.7. A significance level of 0.05 was used in each sample size calculation. To account for attrition of 33%, 15 participants will be recruited for each group (N=30 total).

Baseline characteristics will be summarised overall and by randomised treatment group as means and SDs (mean±SD) for continuous variables or counts and percentages (n (%)) for discrete variables. Because the anticipated sample size is small, medians and ranges will also be provided. Baseline characteristics of participants will be compared between groups using t-tests to establish if there are any between-group differences. The primary aim (comparisons of total hip aBMD) will be tested using a linear mixed model fit with total hip aBMD at 9 months as the outcome. The following independent variables will be considered in the analysis plan: treatment (0 for placebo; 1 for zoledronic acid), participant sex (0 for female; 1 for male) and menopausal status (0 for premenopausal; 1 for postmenopausal). Groups will be compared using contrast statements at 9 months, with change over 9 months being the primary comparison, using a 0.05 level of significance. Because the study was designed as a pilot to determine feasibility and gather evidence for future work, analyses will not be adjusted for multiple comparisons and findings will not be considered confirmatory. Bias due to missing data will be evaluated at baseline and follow-up to ensure there are no significant differences between those with and without complete data. As of 5 November 2021, 78 persons have been screened, 9 persons have enrolled, 5 have received their infusion and 2 have completed the trial. We anticipate completion in December 2022.

### Data storage and retention

All data will be handled securely and only by trained study personnel. Physical data files will be stored in a locked cabinet with limited access, and all other data will be stored on a secure server. The secure server will be password protected. All subjects will be assigned a study identification number, and subject identifiers linking the subject ID to the participant will be stored separately in a secure location. This study is registered with ClinicalTrials.gov. At the conclusion of the study, essential documentation will be stored securely for a minimum of 7 years.

### Patient and public involvement

This research was designed with the participant's existing bariatric surgery requirements and clinical responsibilities in mind. All study visits were made to coincide with existing clinic visits when possible, and provided vitamins were selected based on surgical requirements. Otherwise, patients were not involved in the design, recruitment or conduct of the study. However, patients will be sent details of the results in a study newsletter suitable for a non-specialist audience. All pertinent details will be reported on ClinicalTrials.gov in accordance with reporting rules and regulations.

### Ethics and dissemination

This study was approved by the IRB of the University of Nebraska Medical Center (IRB820-19). Written consent will be obtained from participants at the time of enrolment by study staff trained in Good Clinical Practice (see online supplemental file A for consent form). Careful and thorough explanation are used in obtainment of consent at enrolment to ensure participant comprehension, and voluntariness is emphasised throughout the trial duration. The findings of this study will be presented locally and nationally, and published in peer-reviewed medical journals.

### DISCUSSION

The strengths of this study include the use of clinical and research outcomes to garner a full picture of bone health following SG. Another strength is the comprehensive nutritional supplementation provided to our patients to ensure all participants are calcium and vitamin D replete throughout the study period. The supplementation protocol was created with comprehensive guidelines in mind.<sup>17</sup> The collection of important covariates, including sex, menopause status, habitual physical activity, body composition and physical function contributes to a comprehensive analysis plan. Finally, the use of zoledronic acid is a strength because a single dose has been shown to suppress bone turnover in various disease states (osteoporosis,<sup>30</sup> Paget's disease,<sup>31</sup> HIV<sup>32</sup> and androgen deprivation therapy<sup>33</sup>) for between 12 months and 6.5 years.<sup>11</sup> Considering SG results in increased bone turnover for anywhere between 1 and 5 years following surgery,<sup>34 35</sup> zoledronic acid, with its robust bone turnover suppression, is an ideal treatment option in this population to combat skeletal fragility.

Our study protocol was designed to mitigate concerns about the safety of zoledronic acid. For example, zoledronic acid is associated with a higher risk of hypocalcaemia than oral bisphosphonate preparations.<sup>15</sup> This risk may be exacerbated in bariatric populations given their potential for poor calcium and vitamin D absorption.<sup>36 37</sup> To address this, we will begin robust vitamin D and calcium supplementation at least 6 weeks preoperatively in all patients, and provide free supplementation with ProCare bariatric vitamins throughout the duration

of the study. Risk of acute kidney injury is similarly heightened with zoledronic acid use, and theoretically may be higher in surgical patients given the high incidence of postoperative dehydration.<sup>38</sup> To mitigate the risk of kidney damage associated with zoledronic acid infusion, all participants will undergo a comprehensive metabolic panel to assess kidney function immediately prior to their infusion. Notably, Liu *et al* recently emphasised the safety of zoledronic acid in post-RYGB patients, reporting no evidence of hypocalcemia or significant adverse effects in their population of postmenopausal women undergoing RYGB, which has alleviated some of these concerns.<sup>11</sup>

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**Contributors** LEF, LDB and VK were responsible for the overall study design and manuscript drafting. LEF and LDB oversaw IRB and ClinicalTrials.gov approval and drafted all regulatory paperwork. LM, AAW and CW provided input for outcomes measurements, statistical analysis and nutritional supplementation. LM and VK provided clinical expertise on design and recruitment, as well as safety metrics. VK and LDB are the primary grant holders and LDB, VK and LEF are the primary investigators of the study. All authors have contributed to the final manuscript and approval of its final form.

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