



# BMJ Open Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for type 2 diabetes remission (ORDER): protocol of a multicentre, randomised controlled, open-label, superiority trial

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## ABSTRACT

**Introduction** Previous studies have demonstrated that one anastomosis gastric bypass (OAGB) is not inferior to Roux-en-Y gastric bypass (RYGB) in treating obesity. However, high level evidence comparing the efficacy and safety of both procedures in type 2 diabetes (T2D) treatment is still lacking, which is another main aim of bariatric surgery. The presented trial has been designed to aim at investigating the superiority of OAGB over the reference procedure RYGB in treating T2D as primary endpoint. And diabetes-related microvascular and macrovascular complications, cardiovascular comorbidities, weight loss, postoperative nutritional status, quality of life and overall complications will be followed up for 5 years as secondary endpoints.

**Methods and analysis** This prospective, multicentre, randomised superiority open-label trial will be conducted in patients of Asian descent. A total of 248 patients (BMI ≥ 27.5 kg/m<sup>2</sup>) who are diagnosed with T2D will be randomly assigned (1:1) to OAGB or RYGB with blocks of four. The primary endpoint is the complete diabetes remission rate defined as HbA1c ≤ 6.0% and fasting plasma glucose ≤ 5.6 mmol/L without any antidiabetic medications at 1 year after surgery. All secondary endpoints will be measured at different follow-up visit points, which will start at least 3 months after enrolment, with a continuous annual follow-up for five postoperative years in order to provide solid evidence on the efficacy and safety of OAGB in patients with T2D.

**Ethics and dissemination** The study has been approved by the ethics committee of leading centre (Beijing Friendship Hospital, Capital Medical University, no. 2021-P2-037-03). The results generated from this work will be disseminated to academic audiences and the public via publications in international peer-reviewed journals and conferences. The data presented will be imported into a national data registry. Findings are expected to be available in 2025, which will facilitate clinical decision-making in the field.

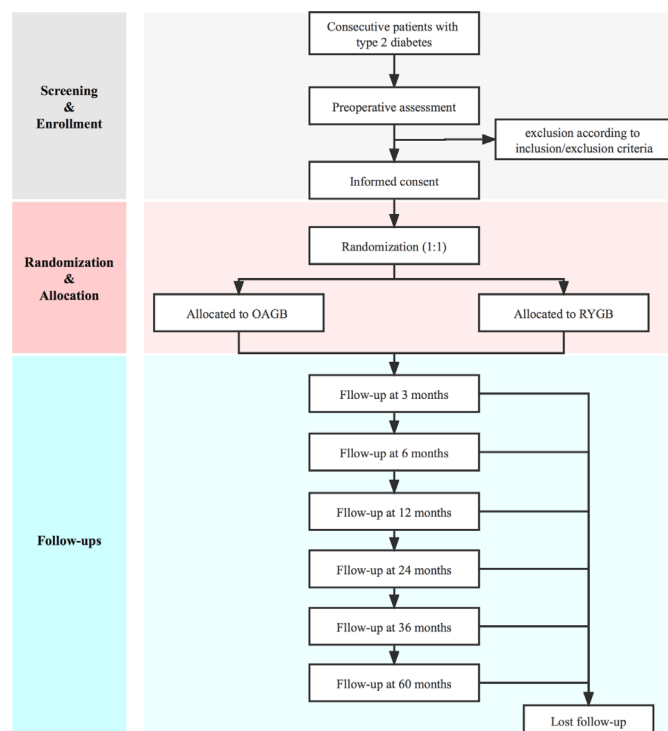
## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This multicentre, open-label, superiority randomised controlled trial (RCT) compares one anastomosis gastric bypass versus the reference procedure Roux-en-Y gastric bypass in diabetes remission.
- ⇒ Primary endpoint is the rate of diabetes remission as defined normalised fasting plasma glucose and HbA1c without any antidiabetic medications at 1 year after surgery.
- ⇒ Secondary endpoints include diabetes complications, cardiovascular comorbidities, weight loss, quality of life and surgery-related complications.
- ⇒ The findings based on this RCT will be from Asian patients and might not be reproducible due to potential variation of metabolic biology among different descents.

**Trial registration number** NCT05015283.

## INTRODUCTION

Considering its role in the treatment algorithm for type 2 diabetes (T2D), some metabolic and bariatric surgical procedures have been demonstrated to induce drastic improvement in glycaemic regulation and reduction of cardiovascular risk factors in patients with obesity and T2D,<sup>1</sup> as evidenced by a substantial body of studies including numerous randomised controlled trials (RCTs).<sup>2–4</sup> Further studies on optimal choice of metabolic and bariatric procedures have corroborated evidence in an important role of the Roux-en-Y gastric bypass (RYGB) in weight loss, diabetes remission, as well



**Figure 1** The ORDER trial flowchart. ORDER, One anastomosis gastric bypass versus Roux-en-Y gastric bypass for type 2 Diabetes Remission; OAGB, one anastomosis gastric bypass; RYGB, Roux-en-Y gastric bypass.

as cost-effectiveness.<sup>5</sup> Therefore, RYGB has long been adopted as a reference procedure in the field of metabolic and bariatric surgery.

As a modified version of conventional RYGB, one anastomosis gastric bypass (OAGB) has gained growing popularity during the past few years owing to its advantages of being less technically demanding and achieving non-inferior or even superior weight loss.<sup>6–9</sup> Using weight loss as the primary endpoint, Lee demonstrated that both RYGB and OAGB were effective for morbid obesity and improvement of quality of life.<sup>6</sup> In addition, Robert and colleagues confirmed that OAGB was not inferior to RYGB in the patients with morbid obesity in the well-designed YOMEGA trial.<sup>9</sup> Published data from observational studies<sup>7 8 10</sup> and meta-analysis<sup>11 12</sup> were in line with the findings. Despite the data from both the above-mentioned RCTs demonstrated that OAGB led to non-inferior, or even better outcome in T2D remission,<sup>13</sup> unfortunately, neither study was designed for T2D treatment comparison, which resulted in the statistical power being insufficient to draw a fair conclusion. Most diabetes care providers and patients are still inadequately informed and convinced about the efficacy and safety of OAGB versus RYGB in diabetes treatment. Thus, the choice of OAGB/RYGB continues to be biased by body weight-centric criteria and the surgeons' technical capacity and cognitive preferences. Furthermore, generally regarded as a malabsorptive procedure, OAGB has a trend towards induction of higher incidences of diarrhoea, steatorrhea and nutritional adverse events as shown in the YOMEGA

trial,<sup>9</sup> which made the utilisation of OAGB controversial, whereas theoretically and practically, considering its growing popularity, superiority of OAGB in T2D remission is able to leverage,<sup>14 15</sup> and potentially offset the concern of higher incidence of adverse events caused by OAGB when compared with RYGB.

Therefore, we proposed this prospective multicentre randomised superiority trial to elaborate the safety and efficacy of OAGB in T2D treatment as referenced by RYGB. Additional relevant outcomes, including weight loss, diabetes-related microvascular and macrovascular risk factors, signs of acid and bile reflux, health-related quality of life, nutritional deficiencies and surgical side effects will also be examined.

## METHODS AND ANALYSIS

### Study design, protocol registration and reporting

This study is a multicentre, open-label, two-armed superiority trial randomising patients with T2D in a 1:1 allocation ratio to either OAGB or RYGB group. Patients will be recruited from tier-3 hospitals with high-volume metabolic and bariatric surgery centres, each performing over 150 surgical procedures per year. Figure 1 illustrates the flowchart of patient recruitment. The study design and protocol adhere to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines.<sup>16</sup>

### Recruitment and eligibility criteria

#### Recruitment

Patients undergoing RYGB or OAGB at participating centres from 1 January 2022 will be screened for competitive recruitment. Data, including sex, body mass index (BMI) and HbA1c involved in the eligibility criteria, will be centrally reviewed before randomisation. Randomisation and allocation will be automatically conducted by an electronic data capture (EDC) system.

#### Eligibility criteria

##### Inclusion criteria

1. Age 21–65 years (both sexes).
2. BMI 27.5–50 kg/m<sup>2</sup>.
3. Previously diagnosed T2D duration ≥6 months.
4. HbA1c ≥7.0%.
5. Currently receiving oral/injectable antidiabetic medications (insulin/glucagon-like peptide-1 receptor agonists).
6. OAGB/RYGB recommended by a multidisciplinary team.

##### Exclusion criteria

1. Active gastrointestinal ulcer.
2. Latent autoimmune diabetes in the adult or type 1 diabetes.
3. Current *Helicobacter pylori* infection.
4. Currently diagnosed with severe gastro-oesophageal reflux disease by esophagogastroduodenoscopy

(EGD) defined as Los Angeles classification grade  $\geq$ B or Barrett's oesophagus.

5. History of major abdominal surgery including bariatric surgery (except appendectomy and gynaecological procedures).
6. History of serious cardiovascular/cerebrovascular diseases.
7. History of liver cirrhosis (Child-Pugh  $\geq$ A).
8. History of chronic kidney disease (estimated glomerular filtration rate) ( $<60$  mL/min/ $1.73$  m<sup>2</sup>).
9. History of inflammatory bowel disease (including ulcerative colitis and Crohn's disease).
10. History of chronic anaemia (Hb level  $<100$  g/L in men and  $<90$  g/L in women).
11. Concomitant surgery for cholecystectomy.
12. Pregnancy or desire for conception during the first year of the study period.
13. Uncontrolled mental and psychological disorders.
14. Expected survival  $<5$  years due to end-stage disease or malignant tumour.
15. Participation in clinical studies/trials with conflicting interest with this study.
16. Unwilling or unable to provide informed consent.

### Sample size

The Power Analysis and Sample Size software (PASS, V.15.0 by NCSS, LLC, Kaysville, Utah, USA) was used for sample size calculation, which was based on the estimate of the complete remission rate as reported by high-quality RCT studies<sup>9 17</sup> and preliminary clinical results from the Greater China Metabolic and Bariatric Surgery Database (GC-MBD), which is a national bariatric database in China. Considering mean complete diabetes remission rates of 37.5% and 60% in the RYGB and OAGB groups at 1 year, respectively, we hypothesised that OAGB would be superior to RYGB if the difference of complete remission rate was significantly superior to the margin of 5%. We assumed a 20% loss to follow-up and another 5% exclusion due to other unpredictable factors, such as pregnancy, consent withdrawal; thus, 124 patients per group (248 in total) were required to conclude OAGB superiority with a statistical power of 80% and an  $\alpha$  of 5%.

### Randomisation and masking

Randomisation of patients will be performed the day before surgery via a web-based programme in random permuted blocks of four, assuming equal allocation between treatment groups. Owing to procedural differences, the study is open-label, and patients or surgeons were not masked.

### Endpoints

#### Primary endpoint

The only primary endpoint is the rate of complete diabetes remission which is defined as HbA1c  $\leq 6.0\%$  (42 mmol/mol) and fasting plasma glucose (FPG)  $\leq 5.6$  mmol/L without any antidiabetic medications at 1 year after surgery.

### Secondary endpoints

Secondary endpoints are listed below. Outcome measures include changes at 3 months, 6 months, 1 year and annually for four more years from baseline, with mean/median and proportions as appropriate. Postprandial plasma glucose, insulin and C-peptide levels will be measured after a standardised test meal provided by our study group.

#### Glycaemic metabolism

- ▶ HbA1c.
- ▶ Fasting and stimulated levels of plasma glucose, insulin and C-peptide.
- ▶ Use of antidiabetic medication.
- ▶ The remission rate of microalbuminuria, defined as the urinary albumin-to-creatinine ratio (ACR)  $<30$  mg/g.
- ▶ The progression rate of diabetic retinopathy (DR), defined as a scale from no retinopathy, mild background DR (BDR), observable BDR to severe non-proliferative/proliferative DR (non-PDR/PDR).

#### Body weight

- ▶ Body weight, BMI, waist and hip circumference.
- ▶ Excess and total BMI loss percentage, excess and total weight loss percentage and absolute weight loss (kg). The above outcome measures are calculated based on the optimal BMI (25 kg/m<sup>2</sup>).

#### Obesity-related cardiovascular comorbidities

- ▶ Resting systolic and diastolic blood pressure.
- ▶ Use of antihypertensive medication.
- ▶ Fasting plasma lipid profile.
- ▶ Use of lipid-lowering drugs.
- ▶ Echocardiography.
- ▶ Cervical vessels and lower extremity vascular ultrasound.
- ▶ Major adverse cardiovascular events.
- ▶ The American Diabetes Association composite triple end point: HbA1c  $<7.0\%$ , low-density lipoprotein cholesterol  $<100$  mg/dL (to convert to millimoles per litre, multiply by 0.0259) and systolic blood pressure  $<130$  mm Hg.

#### Gastrointestinal tract

- ▶ Gastro-oesophageal reflux disease
- ▶ Self-reported gastrointestinal symptoms
- ▶ Gastric and oesophageal mucosa modifications as demonstrate by EGD and the following biopsy pathology

#### Nutritional status

- ▶ Haemoglobin
- ▶ Albumin, prealbumin.
- ▶ Folic acid, ferritin, saturation coefficient, vitamin B<sub>12</sub>.
- ▶ Parathyroid hormone, vitamin D.

#### Quality of life

- ▶ 36-Item Short Form health survey (SF-36)



- ▶ Bariatric Analysis and Reporting Outcome System (BAROS) Questionnaire and Impact Weight Quality Of Life (IWQOL-Lite).
- ▶ Gastrointestinal Symptom Rating Scale (GSRS) and Gastro-oesophageal Reflux Disease Questionnaire (GERDQ).

### Safety

- ▶ Surgical and medical complications (Dindo-Clavien classification)
- ▶ Hypoglycaemic episodes and dumping syndrome (Sigstad questionnaire)
- ▶ Length of hospitalisation
- ▶ Readmissions

### Intervention

Patients will receive standard preoperative assessment, including comorbidities (endocrine, metabolic, nutritional, cardiovascular and psychological assessment), gastroscopy with *H. pylori* testing and abdominal ultrasound. All procedures will be performed laparoscopically by experienced bariatric surgeons. It is recommended that the small bowel is measured from the ligament of Treitz to the ileocecal valve in all patients by using a sterile, flexible 10 cm strip along the antimesenteric aspect of the small bowel after entering the abdominal cavity. The surgical procedures are standardised by all participating centres.

### Roux-en-Y gastric bypass (RYGB)

After gastro-oesophageal junction identification, the stomach is transected with a linear stapler entering the lesser sac 5 cm below the junction, creating a small gastric pouch with of approximately 30 mL volume. A 50-cm biliopancreatic limb is measured and brought up via anti-colic fashion to where small gastric pouch is. Then, gastrojejunal anastomosis is made on the posterior wall of the gastric pouch using a linear cutting stapler at 2.5 cm. After closing the gastroenterostomic opening with a running absorbable suture, the afferent jejunum is transected proximal to the gastroenterostomy. Then, a stapled side-to-side jejunojejunostomy is formed to create 150 cm alimentary limb with a linear cutting stapler. Mesenteric defects and Petersen spaces are closed with non-absorbable sutures.

### One anastomosis gastric bypass (OAGB)

A transverse stapled division of the stomach at 2 cm below the angular incisure starting from lesser curvature side is undertaken. Then, a long gastric tube is divided vertically upward by linear cutting staplers as calibrated with a 36 French bougie. Thus, the bypassed stomach lies on the left, and the narrow lesser-curvature gastric pouch lies on the right. At 200 cm distal to the ligament of Treitz, the jejunal loop is brought up to the distal end of the narrow gastric pouch via ante-colic fashion, where a gastrojejunal anastomosis is created on the posterior wall of the gastric pouch with a linear cutting stapler at 3 cm. Then, the gastroenterostomic opening is closed with a running

absorbable bard suture. Closure of Petersen's space is not needed.

### Postoperative medication

Systematic supplementation of multivitamins, iron, calcium and vitamin D was prescribed with 40 mg proton-pump inhibitor daily for 2 months and 500 mg ursodeoxycholic acid daily for 3 months after surgery to prevent marginal ulcer and gallstones. All these postoperative medications will be provided by our centralised pharmacy.

### Patient follow-ups

According to the guidelines for the follow-up of patients undergoing bariatric surgery,<sup>18</sup> all follow-up visits are recommended at 3 and 6 months, then annually until 5 years after surgery. Follow-up visits have been designed to acquire data corresponding to a case report form (table 1). Data will be obtained through in-hospital visits or over telephone or online platform by a multidisciplinary study team in each participating centre. Questionnaires will be also assessed at corresponding visit points. Safety data on morbidity (surgical and non-surgical short-term and long-term complications) and mortality will be collected and confirmed by all the researchers through a comprehensive review of involved medical records and follow-up details.

### Data collection

A standardised case report form is designed before study and transferred to an EDC system (<https://order-trial.com>). It has a validation component for cross-checking data and a reporting tool for descriptive analysis. Well-trained clinical research coordinators will retrieve all required data from medical records and upload them into the system. Clinical research associates are responsible for monitoring, providing feedback and data quality control.

### Statistical analysis

SPSS V.20.0 (SPSS, Chicago, IL, USA) and R software (R V.3.6.3; R Foundation for Statistical Computing, Vienna, Austria) will be used to perform all statistical analyses. Continuous data will be presented as mean (SD) or median (minimum, maximum), and categorical data will be presented as numbers (proportions/frequencies/percentages). For the comparison between preoperative and postoperative parameters of paired continuous data, paired t-test (normally distributed variables) or Wilcoxon's signed-rank (skewed variables) test will be performed. For categorical paired data,  $\chi^2$  or Fisher's exact test will be used. For quantitative normal endpoints, bilateral 95% CIs for the mean difference (two-sided 5%  $\alpha$  level) will be employed. P-values of <0.05 will be considered statistically significant.

Primary and secondary outcomes will be analysed in the per-protocol population, which include all patients randomly assigned to surgery whose data are used; major deviations from the protocol will be excluded (pregnancy, death, consent withdrawal and switching surgical

**Table 1** Checklist of baseline and follow-up visits of patients enrolled in the ORDER trial

	Visit 1 (baseline)	Visit 2 (30-day intervals)	Visit 2 (3-month intervals)	Visit 3 (6-month intervals)	Visit 4 (1-year intervals)	Visit 5 (2-year intervals)	Visit 6 (3-year intervals)	Visit 7 (5-year intervals)
Demographic data	●	x	●	●	●	●	●	●
Medication usage	●	x	●	●	●	●	●	●
Surgical information	●	x	x	x	x	x	x	x
Weight loss	x	x	●	●	●	●	●	●
Routine blood tests	●	x	●	●	●	●	●	●
HbA1c	●	x	●	●	●	●	●	●
FPG	●	x	●	●	●	●	●	●
Fasting insulin and C-peptide	●	x	●	●	●	●	●	●
OGTT (0.5 hour, 1 hour, 2 hour and 3 hour)	○	x	x	x	○	○	○	○
Diabetes complications (ACR and diabetic retinopathy)	●	x	○	○	●	●	●	●
Biochemical examinations	●	x	●	●	●	●	●	●
Plasma iron profile	●	x	●	○	●	●	●	●
Folate and vitamin B <sub>12</sub>	●	x	●	○	●	●	●	●
Vitamin D <sub>3</sub>	●	x	x	x	●	●	●	●
Thyroid function	○	x	○	○	○	○	○	○
Gastroscopy	●	x	x	x	●	●	●	●
C13 breath tests	●	x	x	x	●	●	●	●
Echocardiography	●	x	x	x	●	●	●	●
Abdominal ultrasonography	○	x	○	○	○	○	○	○
Ultrasound (cervical vessels, lower extremity vascular, gynaecological)	○	x	x	x	○	○	○	○
ASA grade	●	x	x	x	x	x	x	x
Adverse events (MACE)	x	●	●	●	●	●	●	●
QOL	x	x	●	●	●	●	●	●

●: Mandatory.

○: Optional.

x: Not required.

ACR, urinary albumin-to-creatinine ratio; ASA, American Society of Anesthesiologists; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; MACE, major adverse cardiovascular events; OGTT, oral glucose tolerance test; QOL, quality of life.

procedure). We determine a 90% CI of the difference for the primary outcome (one-sided 5%  $\alpha$  value) to confirm superiority if the lower bound of this interval exceeded the superior limit (5 percentage points).

We will impute missing data in the primary outcome analysis using multiple imputation techniques with prediction based on FPG levels, HbA1c levels and anti-diabetic medication use. We will perform sensitivity analyses for the primary outcome on the basis of three scenarios: (1) full per-protocol population data set, (2) all included patients according to their randomly assigned surgery, irrespective of the actual surgery performed, with multiple imputation and (3) per-protocol population with multiple imputation.

We will assess safety endpoints in all patients (safety population) and compare the incidence of serious adverse events per patient in both groups using  $\chi^2$  or Fisher's exact test.

### Quality control

Prior to the study, all participants and study personnel will receive training. Significantly, each participating surgeon should complete his learning curve, performing RYGB or OAGB independently with minimum of 50 cases. The technical performance of RYGB and OAGB will be standardised, including mandatory surgical steps and quality. A standard operating procedure video will be distributed to each centre. Before entering the trial, unedited

videos of two consecutive cases (1 RYGB and 1 OAGB) of all participating centres will be peer-reviewed for their procedure competence. All surgical procedural videos will be maintained in an electronic database of patient records.

For the primary outcome measure, HbA1c and FPG serum samples will be collected at baseline and 1 year after surgery for central review. Throughout the study period, every reasonable effort is made to prevent attrition. Patients will be provided a standardised glucose-monitoring device to assess glycaemia and risks of hypoglycaemia, which will be monitored by our diabetes care team. In addition to the planned visits, all patients will receive letters in connection with milestones and holidays during the study period in order to improve the compliance. Clinical research associates will check and verify the authenticity, accuracy and integrity of all information based on the source data. Data modification traces will be recorded in the EDC system. After verification, data will be locked for final statistical analysis. Study files will be kept in storage for a period of at least 10 years after study completion.

To ensure proper data safety monitoring and relevance, an appropriate board will be installed to promote patient safety, advise on study continuation on superiority of either treatment, ensure the methodological quality of the study, and monitor serious adverse events.

### Patient and public involvement

Patients and public were not involved in the design, the recruitment or conduct of the study.

### ETHICS AND DISSEMINATION

A brief structured summary of the study (WHO Trial Registration Data Set) is shown in online supplemental file 1. The study design and protocol (issue date: 25 January 2022, V1.0) adhere to the SPIRIT reporting guidelines. Significant amendments to the protocol will only be made after ethical approval by ethics committees of all participating centres. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Participation in this trial is strictly voluntary, and patients are allowed to withdraw informed consent at any point without explanation. Patients will be covered by medical insurance during this trial. The results will be disseminated to academic audiences and the public via publications in international peer-reviewed journals and conferences. The data obtained in China will be imported into a national data registry, the GC-MBD. Findings are expected to be available in 2025, which will facilitate clinical decision-making in the field.

### DISCUSSION

As an IFSO recognised metabolic and bariatric procedure and recently approved procedure by American Society for Metabolic and Bariatric Surgery (ASMBS), OAGB has either been approved, or is being under consideration by majority of national academic associations and/or regulatory authorities in the world.<sup>19</sup> Besides obesity treatment, only nine studies with >1-year follow-up periods reported on diabetes remission as a comorbidity of interest after OAGB;<sup>6,9,20–26</sup> in fact, no existing RCT on OAGB, compared with RYGB, has included diabetes remission as the primary outcome endpoint. In Robert and colleagues' YOMEGA trial, only 58 (27%) of 211 patients with available data had T2D. However, the decrease in HbA1c at 2 years was significant in the subgroup of participants with T2D. In the OAGB group, the complete diabetes remission rate was 60%, whereas in the RYGB group that was 38%.<sup>9</sup> As stated by the IFSO Position Statement, early results from OAGB are promising in terms of weight and T2D management; however, bile reflux remains a theoretical risk.<sup>27</sup> Nevertheless, in the ASMBS Clinical Issue Committee's review article, OAGB reportedly has a relatively short operative time, low complication rate and excellent weight loss outcomes. Nonetheless, the evidence level is low because most case series were retrospective and long-term (>5 years) follow-up were lacking. Concerns of OAGB remain due to long-term nutritional deficiencies and potential carcinogenic effect of bile reflux. It is suggested that only prospective studies with long-term follow-up can alleviate these concerns.<sup>28</sup> Therefore, although current data and statements have noted OAGB to be promising in terms of diabetes remission, determining the efficacy and safety of OAGB over RYGB in patients with T2DM is urgently warranted.

In the YOMEGA trial, higher incidences of diarrhoea, steatorrhea and nutritional adverse events were observed with a 200 cm biliopancreatic limb OAGB. However, in Lee's study, both OAGB and RYGB were effective in improving the quality of life in which 200 cm biliopancreatic limb was created in the OAGB procedure. In addition, OAGB has no disadvantage compared with RYGB at 2 years follow-up except a lower haemoglobin level was observed. Considered as a strong factor in malnutrition, Mahawae and colleagues have advocated a biliopancreatic limb length of 150 cm, or even shorter, for OAGB.<sup>29</sup> This advancement in controversy has generated renewed interest in the importance of the length of the small bowel in patient population. In Lee and colleagues' study, the mean small bowel length was 739.8 (115.7) cm in 620 Chinese patients from Asia ethnic, which indicated a longer length than those ethnicities who consume more meat or protein.<sup>30</sup> Since 200 cm biliopancreatic limb is the most common practice in OAGB in the world, and the length of the biliopancreatic limb was 200 cm for OAGB in two RCTs,<sup>6,9</sup> our ORDER study protocol also adopted the 200 cm biliopancreatic limb in OAGB procedure. Thus, the results from this study will be comparable with previously published studies. Nevertheless, since



12% small bowel length less than 6m was reported, the measurement of the small bowel between the ligament of Treitz and the ileocecal valve was adopted in our protocol. In order to avoid the malnutrition caused by this study to patients, patients with small bowel length of <5m will be excluded in this trial.

There is inadequate evidence on long-time follow-up of OAGB, especially on long-term nutritional deficiencies and oesophageal or gastric cancer potentially caused by bile reflux. The strict postoperative follow-ups, regular endoscopic examinations and moderate multivitamin and mineral supplementation are highly recommended during our 5-year trial. Especially, emergency plan for severe nutritional deficiencies, including but not limited to oral medication, intravenous administration or conversion to RYGB, should be established before study. Moreover, each case involving serious adverse event will be reviewed and evaluated by the established data and safety monitoring board to decide treatment plan.

Complications using the Dindo-Clavien system, as well as quality of life, are warranted to address these important safety issues. This trial will potentially be extended beyond 5 years if funding sources allow in order to achieve even longer time outcome measures and better assessment of OAGB vs RYGB.

By communicating with experts in metabolic and bariatric surgery from different countries and represented patient population, a superiority margin of 5% in addition to RYGB's complete diabetes remission rate will convince surgeons and patients with T2D considering OAGB. In this study, we adopted 5% as the superiority margin for this trial. In order to overcome the limitations of surgical procedure bias and the inadequacy of data recording to ensure a high-quality study process, in this multicentre RCT, only tier-3 hospitals with minimum of 150 surgical procedures annually and extensive research experience in metabolic and bariatric surgery are invited to join this trial. Each involved researcher needs to receive Good Clinical Practice certificates issued by the China Food and Drug Administration before study initiation to ensure protocol adherence. Third-party monitoring and regular project meetings will also be conducted throughout the study to coordinate with investigators and ensure data authenticity and integrity.

The proposed ORDER trial is a prospective multicentre randomised controlled open-label superiority trial that compares OAGB versus the reference procedure RYGB in diabetes remission, in order to provide solid evidence on the efficacy and safety of OAGB in patients with T2D. This is the first RCT that compares OAGB versus RYGB with T2D remission rate as the only primary endpoint.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

**Patient consent for publication** Consent obtained directly from patient(s).

**Ethics approval** This study involves human participants and was approved by the ethics committee of Beijing Friendship Hospital (no. 2021-P2-037-03). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. All data will be available for other research groups interested in conducting systematic reviews. Requests for data should be directed to the principle investigator, Zhongtao Zhang, zhangzht@cmmu.edu.cn.

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## World Health Organization Trial Registration Data Set

Data category	Information
1. Primary Registry and Trial Identifying Number	ClinicalTrials.gov Identifier: NCT05015283
2. Date of Registration in Primary Registry	27 February 2022
3. Secondary Identifying Numbers	None
4. Source(s) of Monetary or Material Support	Beijing Municipal Science & Technology Commission (Z211100002921029), National Key Technologies R&D Program (2015BAI13B09), Beithune Charitable Foundation (DXWKYJ001), and Beijing Excellent Talents Training Funding Program (2018000021469G195)
5. Primary Sponsor	Beijing Friendship Hospital, Capital Medical University
6. Secondary Sponsor(s)	None
7. Contact for Public Queries	Peng Zhang
8. Contact for Scientific Queries	Peng Zhang
9. Public Title	Diabetes remission in obese subjects with type 2 diabetes after one anastomosis gastric bypass or Roux-en-Y gastric bypass: a multicenter, randomized controlled, open-label, superiority trial-ORDER trial
10. Scientific Title	Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for type 2 diabetes Remission (ORDER): protocol of a multicenter, randomized controlled, open-label, superiority trial
11. Countries of Recruitment	China, or and Singapore
12. Health Condition(s) or Problem(s) Studied	Type 2 diabetes and obesity
13. Intervention(s)	one anastomosis gastric bypass and Roux-en-Y gastric bypass
14. Key Inclusion and Exclusion Criteria	<p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>① Age 21–65 years (both sexes)</li> <li>② BMI 27.5–50 kg/m<sup>2</sup></li> <li>③ Previously diagnosed T2D duration ≥6 months</li> <li>④ HbA1c ≥7.0%.</li> <li>⑤ Currently receiving oral/injectable antidiabetic medications [insulin/ Glucagon-like peptide-1 (GLP-1) receptor agonists]</li> <li>⑥ OAGB/RYGB recommended by a multidisciplinary team</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>① Active gastrointestinal ulcer</li> <li>② Latent autoimmune diabetes in the adult or type 1 diabetes (Reviewer #1, comment #2)</li> <li>③ Current Helicobacter pylori infection</li> <li>④ Currently diagnosed with severe gastroesophageal</li> </ul>

	<p>reflux disease by esophagogastroduodenoscopy (EGD) defined as Los Angeles classification grade &gt;B or Barrett's esophagus</p> <p>⑤ History of major abdominal surgery including bariatric surgery (except appendectomy and gynecological procedures)</p> <p>⑥ History of serious cardiovascular/cerebrovascular diseases</p> <p>⑦ History of liver cirrhosis (Child-Pugh <math>\geq</math>A)</p> <p>⑧ History of chronic kidney disease (estimated glomerular filtration rate) &lt;60 mL/min/1.73 m<sup>2</sup>)</p> <p>⑨ History of inflammatory bowel disease (including ulcerative colitis and Crohn's disease)</p> <p>⑩ History of chronic anemia (Hgb level &lt;100 g/L in men and &lt;90 g/L in women)</p> <p>⑪ Simultaneous surgery for cholecystectomy</p> <p>⑫ Pregnancy or desire for conception during the first year of the study period</p> <p>⑬ Uncontrolled mental and psychological disorders</p> <p>⑭ Expected survival &lt;5 years due to end-stage disease or malignant tumor</p> <p>⑮ Participation in clinical studies/trials with conflicting interest with this study</p> <p>⑯ Unwilling or unable to provide informed consent</p>
15. Study Type	<p>Interventional</p> <p>Allocation: randomised</p> <p>Intervention model: Parallel assignment</p> <p>Masking: none</p> <p>Primary purpose: treatment</p>
16. Date of First Enrollment	6 May, 2022
17. Sample Size	248
18. Recruitment Status	Recruiting: participants are currently being recruited and enrolled
19. Primary Outcome(s)	The only primary endpoint is the rate of complete diabetes remission which is defined as HbA1c $\leq$ 6.0% (42 mmol/mol) and fasting plasma glucose $\leq$ 5.6 mmol/l without any antidiabetic medications at 1 year after surgery.
20. Key Secondary Outcomes	<ul style="list-style-type: none"> <li>● HbA1c</li> <li>● Fasting and stimulated levels of plasma glucose, insulin, and C-peptide</li> <li>● Use of antidiabetic medication</li> <li>● The remission rate of microalbuminuria,</li> <li>● The progression rate of diabetic retinopathy (DR)</li> <li>● Body weight, BMI, waist and hip circumference</li> </ul>

	<ul style="list-style-type: none"> <li>● Excess and total BMI loss percentage, excess and total weight loss percentage, and absolute weight loss (kg). The above outcome measures are calculated based on the optimal BMI (25 kg/m<sup>2</sup>).</li> <li>● Resting systolic and diastolic blood pressure</li> <li>● Use of anti-hypertensive medication</li> <li>● Fasting plasma lipid profile</li> <li>● Use of lipid-lowering drugs</li> <li>● Echocardiography</li> <li>● Cervical vessels and lower extremity vascular ultrasound</li> <li>● Major Adverse Cardiovascular Events (MACE) events</li> <li>● The American Diabetes Association composite triple end point</li> <li>● Gastro-oesophageal reflux disease</li> <li>● Self-reported gastrointestinal symptoms</li> <li>● Gastric and esophageal mucosa modifications as demonstrate by EGD and the following biopsy pathology</li> <li>● Hemoglobin</li> <li>● Albumin, prealbumin</li> <li>● Folic acid, ferritin, saturation coefficient, vitamin B12</li> <li>● Parathyroid hormone (PTH), vitamin D</li> <li>● Quality of life</li> <li>● Surgical and medical complications (Dindo-Clavien classification)</li> <li>● Hypoglycaemic episodes and dumping syndrome (Sigstad questionnaire)</li> <li>● Length of hospitalization</li> <li>● Readmissions</li> </ul>
21. Ethics Review	<p>Status:Approved</p> <p>Date of approval:25 January 2022</p> <p>Name and contact details of Ethics committee(s): Beijing Friendship Hospital, Capital Medical University (2021-P2-037-03)</p>
22. Completion date	Not yet
23. Summary Results	Not yet
24. IPD sharing statement	<p>1. Will individual deidentified participant data (including data dictionaries) will be shared: Yes</p> <p>2. what data in particular will be shared: Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).</p> <p>3. what other documents will be available: study protocol</p>



	<p>4. when will data be available (start and end dates): Beginning 6 months and ending 24 months following article publication.</p> <p>5. With whom: Investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose.</p> <p>6. For what types of analysis: For individual participant data meta-analysis.</p> <p>7. By what mechanism will data be made available: Proposals should be directed to zhangzht@ccmu.edu.cn to gain access, data requestors will need to sign a data access agreement.</p>
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