DISCOURSE.trial

DIStal gastriC bypass OUtcome in Revision SurgEry after roux-en-y gastric bypass

A multicentre randomised controlled trial

(March, the first of 2021)

NL75322.100.20/R20.093

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AL	Alimentary limb
BMI	Body mass index
%BMIL	Percentage body mass index loss
BPL	Biliopancreatic limb
DGB	Distalisation of RYGB
DSMBS	Dutch Society of Metabolic and Bariatric Surgery
%EWL	Percentage excess weight loss
GERD	Gastroesophageal reflux disease
IC	Informed Consent
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
NOK	Dutch Obesity Clinic; in Dutch: Nederlandse Obesitas Kliniek
OSAS	Obstructive sleep apnoea syndrome
PCM	Protein calorie malnutrition
RCT	Randomised controlled trial
RYGB	Roux-en-Y gastric bypass
(S)AE	(Serious) Adverse Event
SPSS	Statistical package for social sciences
TALL	Total alimentary limb length
TPN	Total parenteral nutrition
%TWL	Percentage total weight loss
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen
QoL	Quality of life

1. SUMMARY

Rationale:
Up to 35% of morbidly obese patients undergoing Roux-en-Y gastric bypass (RYGB) fail to lose sufficient weight or regain excessive weight after initial weight loss. Currently, there is no standardized approach to revisional surgery after failed RYGB. Distalisation of the RYGB limbs (DGB), with shortening of the common channel and extending either the alimentary limb (AL) or biliopancreatic limb (BPL), can be performed as revisional surgery to induce additional weight loss. To date, there is no general consensus as to optimal surgical technique or limb lengths to be used in distalisation of RYGB in both literature as well as clinical practice.

Objective:
The aim of this study is to investigate the effect of two distalisation techniques of a gastric bypass in revisional surgery with standardised limb lengths in total weight loss (TWL) and the need for treatment for protein calorie malnutrition (PCM). In this randomised controlled trial DGB with lengthening of the BPL (DGB type I) will be compared to DGB with extended AL (DGB type II) in order to conclude which surgical technique is the optimal therapeutic strategy as revision surgery following Roux-en-Y gastric bypass.

Study design:
A multicentre randomised controlled trial.

Study population:
Morbidly obese patients with insufficient weight loss or weight regain following primary RYGB, who are eligible for distalisation surgery.

Intervention:
A total of 150 participants will be randomised over two treatment groups: group A will undergo DGB type I and group B will undergo DGB type II.

Main study endpoints:
Primary endpoints: %TWL 1 year after treatment and need for treatment of PCM.
Secondary endpoints: weight loss, co-morbidity remission, PCM grading (debilitating defecation patterns, temporary total parenteral nutrition treatment, revision, mortality), morbidity, nutritional deficiencies, quality of life and patient satisfaction.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
Participants will undergo either DGB type I or DGB type II. The treatment and pre- and postoperative care will not differ from the regular DGB revisional treatment for failed RYGB. Therefore, there are no additional risks associated to this treatment.
Additionally, participants will be asked to fill out written questionnaires regarding defecation patterns and QoL preoperatively as well as 3, 12 and 36 months after treatment.

2. INTRODUCTION AND RATIONALE

Obesity is a public health problem with an increasing prevalence worldwide. Morbid obesity is associated with several medical and psychological conditions, resulting in reduced quality of life (QoL) and a higher mortality risk. Currently, bariatric surgery is considered the most effective treatment for morbid obesity. Compared with non-surgical interventions, it results in greater improvement in weight loss outcomes and remission of obesity-related comorbidities.[1,2]

The Roux-en-Y gastric bypass (RYGB) is one of the most commonly performed bariatric procedures.[3] It provides substantial and sustained weight loss in morbidly obese patients. However, there is a long term failure rate up to 35%, depending on how failure is defined. RYGB failure includes the group of non-responsive patients, with an inability to achieve adequate weight loss, or excessive weight regain after initial adequate weight loss after RYGB. Due to altered anatomy, adhesive disease and no standardised approach to revisional surgery, treatment of these patients can be very challenging. With the growing number of RYGB performed annually, the requirement for revisional surgery is increasing accordingly.[4,5]

One of the revisional options to induce additional weight loss is conversion of RYGB to distal gastric bypass (DGB) by adding a more malabsorptive component by shorting the common channel (CC) - where the food arriving through the alimentary limb AL is introduced to the gastric, biliary and pancreatic fluids coming from the biliopancreatic limb BPL, and most of the nutrients is absorbed (Figure 1).

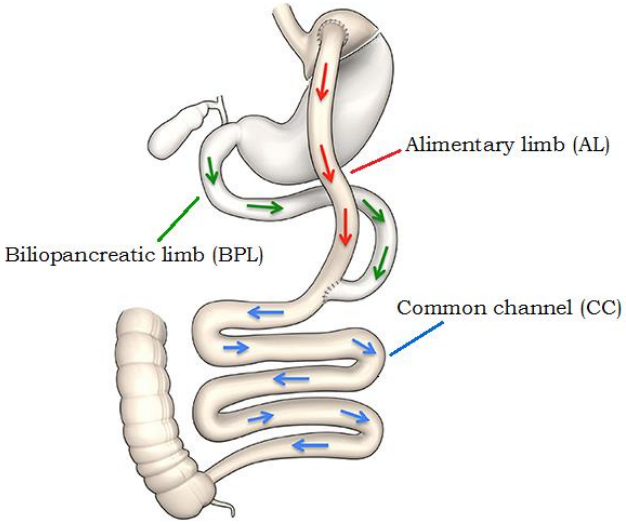


Figure 1: Schematic overview of the limbs in RYGB

Two different approaches are known.[4] DGB type I is a variation in which the AL is divided at the jejuno-jenunostomy and transposed distally, creating a long BPL and a short CC.[6–12] In DGB type II the BPL is transposed distally, creating a long AL and a short CC.[13]

Several authors have reported accelerated weight loss, but with potential for adverse consequences. One of the important complications is protein calorie malnutrition (PCM) due to malabsorption, resulting in debilitating defecation patterns with diarrhea (grade I), the need for temporary total parenteral nutrition treatment (grade II), reoperation to increase the absorptive area by proximal relocation of the enetero-enterostomy (grade III), or mortality (grade IV). Complications associated with DGB are mostly due to a too short CC and a too short total alimentary limb length (TALL; combination of CC and AL lengths).[6–14]

To date, there is no general consensus as to optimal intestinal limb lengths and surgical technique to be used in DGB for failed RYGB in both literature as well as clinical practice. A review of the literature shows that a CC of ≥ 200 cm and a TALL of ≥ 300 cm should be safe to reduce major nutritional deficiencies, while inducing sufficient additional weight loss.[4,11] Limitations of the available literature include the heterogeneity of studies, small study populations and lack of standardisation.

In a short survey on experience of distalisation of the RYGB of 17 bariatric surgeons in the Netherlands, members of the Dutch Society of Metabolic and Bariatric Surgery (DSMBS), a CC of 200 cm is considered as an acceptable length to be used in DGB.

Although most of the nutrient is absorbed in the CC, some absorption occurs in the AL as well. It is hypothesised that DGB type II with a long AL may result in less weight loss, but with lower and more acceptable rates of (metabolic) complications such as PCM compared to DGB type II, and thus a better QoL.

To the best of our knowledge, no randomised controlled trial (RCT) has compared weight loss outcomes, complications and QoL of the distalisation techniques in failed RYGB.

3. OBJECTIVES

Hypothesis
The hypothesis is that both DGB type I and II will provide for sufficient weight loss (EWL>40%), and that DGB type II procedure will be superior to DGB type I in terms of development of PCM.

Primary Objective
- To evaluate the effect of DGB type I and II in terms of percentage excess weight loss (%EWL);
- To investigate the prevalence of PCM after DGB type I compared to DGB type II.

Secondary Objective(s)
- To compare weight loss in percentage total weight loss (%TWL) and percentage body mass index loss (%BMIL) following DGB type I and II;
- To compare co-morbidity remission following DGB type I and II;
- To compare PCM grading (debilitating defecation patterns, temporary total parenteral nutrition treatment, revision, mortality) following DGB type I and II;
- To compare complication rates following DGB type I and II;
- To assess the factors that influence the complication rates;
- To compare QoL and patient satisfaction following DGB type I and II.

4. STUDY DESIGN

4.1 Study design
This study will be a multicentre randomised controlled clinical trial.

4.2 Duration
The duration of inclusion of the participants in the study will be three years, with a total follow-up period of three years.

4.3 Setting
The study will be performed in a clinical and outpatient setting in most of the bariatric centres in the Netherlands. The treatment program is similar in all locations.

4.4 Flow-chart
In total, 150 morbidly obese patients are eligible for distalisation surgery following RYGB. The participants will be randomised into DGB type I (group a) or DGB type II (group b).

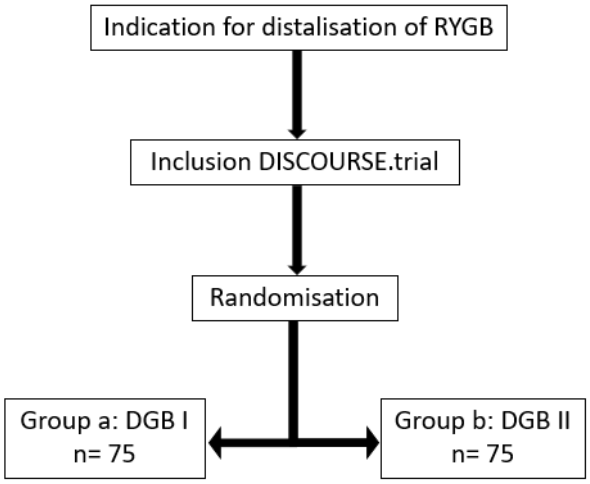


Figure 2: Flowchart

5. STUDY POPULATION

5.1 Population (base)

The study population consists of morbidly obese patients with insufficient weight loss or weight regain following primary Roux-en-Y gastric bypass, who are eligible for distalisation surgery.

5.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age 18-65 years;
- BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with obesity related comorbidity;
- Weight regain or insufficient weight loss (EWL<50% or TWL<20%)[15,16] following RYGB;
- Multidisciplinary team screening at one of the bariatric centres;
- Informed consent and willing to enter the follow-up program.

5.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Failed Roux-en-Y gastric bypass due to anatomic, surgical reasons (gastric pouch dilatation >50 mL, gastro-gastric fistula, gastro-jejunostomy);
- Distalisation of RYGB is technical infeasible (judgment by surgeon);
- Inflammatory bowel disease, celiac disease, irritable bowel syndrome and other causes of chronic diarrhea;
- Severe concomitant disease (such as carcinomas and neurodegenerative disorders);
- Pregnant women;
- Noncompliance in follow-up or unwilling to undergo surgery;
- Inability of reading/understanding and filling out questionnaires.

5.4 Sample size calculation

Based on the experience of bariatric surgeons in the Netherlands and the results of the published studies concerning conversion of RYGB to DGB with a short common channel and the potential risk of protein malnutrition, debilitating defecation patterns and reoperations, this study is designed to reduce the complication and reoperation rate by creating a DGB with only one anastomosis, using a CC length of 200 cm and a TALL of 300 cm. Also, the defecation pattern should be acceptable (no steatorrhea). Realising that a longer CC will induce less weight less, an additional EWL of 40% is considered acceptable to consider the surgery successful.

The sample size calculation is based on two primary aims. Both aims must be fulfilled to declare DGB II superior to DGB I.

The first aim is the superiority of DGB II compared to DGB I with regard to PCM (superiority test, alfa 5%, power 80%). Based on an expected mean PCM of 30%[11,14] in group A (DGB I) and 10%[13] in group B (DGB II), at least 2x 62 patients should be included in the analysis. The other aim is that DGB II achieves no less than a mean of 35% EWL (one sample t-test, s.d.= 5% points, alfa 2,5%). Considering a dropout rate of maximum 20%, a total number of 150 patients is needed for the analysis: 75 in group A and 75 in group B.

6. TREATMENT OF SUBJECTS

6.1 Type I Distal gastric bypass (DGB I)

Distalisation of the RYGB will be performed laparoscopically. After introduction of the trocars and camera, the surgical procedure will start by adhesiolysis and the identification of the gastrojejunostomy. The AL, BPL and CC are identified and measured. Each limb is marked at the jejunojejunostomy, using three different coloured stitches to identify the AL, BPL and CC.

The CC is measured 200 cm from the ileocecal valve and marked with a temporary suture. The RYGB is then modified by dividing the Roux limb at the jejuno-jejunal anastomosis and re-anastomosed distally to 200 cm from the ileocecal valve using linear staplers, creating a long BPL. In cases of initial AL lengths shorter than 100 cm, the CC lengths should be adjusted to create a TALL of at least 300 cm.

After final stapling the new AL, BPL and CC lengths are measured. If necessary, a mesenteric defect is closed with a non-absorbable suture.

6.2 Type II Distal gastric bypass (DGB II)

Most steps are the same as mentioned for DGB I. The only difference is that the BPL will be transposed distally to 200 cm from the ileocecal valve, creating a long AL.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The primary outcome measures of this study will be:

- Development of protein calorie malnutrition (PCM)
- Percentage total weight loss (%TWL) 1 year after treatment

7.1.2 Secondary study parameters/endpoints

- *Weight and co-morbidities*
  - Weight loss (measured 3, 6, 12, 18, 24 and 36 months after treatment)
    - %TWL
    - Excess weight loss (%EWL)
    - BMI loss (%BMIL)
  - Co-morbidity remission[17] (measured 6, 12, 24 and 36 months after treatment)
    - Type II diabetes mellitus
      - Improvement: reduction in glycosylated haemoglobin (HbA1c) and fasting blood glucose (FBG), or decrease in antidiabetic medications requirement;
      - Partial remission: HbA1c 6-6.4%, FBG 100-125 mg/dL in the absence of antidiabetic medications;
      - Complete remission: HbA1c <6%, FBG <100 mg/dL in the absence of antidiabetic medications.
    - Hypertension
      - Improvement: decrease in dosage or number of antihypertensive medication, or decrease in systolic or diastolic blood pressure on the same medication (better control);
      - Partial remission: blood pressure 120-140/80-89 mmHg in the absence of antihypertensive medication;
      - Complete remission: blood pressure <120/80 mmHg in the absence of antihypertensive medication.
    - Dyslipidaemia
      - Improvement: decrease in number or dose of lipid lowering agents with equivalent control of dyslipidaemia, or improved control of lipids on equivalent medication;
      - Remission: normal lipid panel (LDL <100mg/dL, HDL <40 mg/dL, total cholesterol <200 mg/dL, triglycerides <150 mg/dL) in absence of medication.
    - Obstructive sleep apnoea syndrome (OSAS)
      - Improvement: reduced pressure settings on CPAP/BIPAP, improved repeat score on screening tool as compared to preoperative;
      - Remission: AHI<5 off CPAP/BIPAP on repeat objective testing with polysomnography.

- *Deficiencies*
  - PCM grading:
    I. Debilitating defecation patterns with diarrhea (>6 times/day)
       a) Conservative therapy (protein rich diet)
       b) Medical treatment (loperamide, pancreatic enzyme replacement therapy)[18]
    II. Temporary total parenteral nutrition (TPN) treatment
    III. Revision

a) Proximalisation: lengthening of the common channel
b) Revision to standard RYGB
c) Revision to original anatomy

IV. Mortality

- Nutritional deficiencies
  - Blood samples to identify nutritional deficiencies (measured preoperative, as well as 6, 12, 24 and 36 months after treatment):
    - Ferritin, vitamin B1, vitamin B6, vitamin B12, 25-OH vitamin D and folic acid.

- *Complications*
  According to Clavien Dindo classification[19–21]
  Subdivided into peri- and postoperative complications
  - Perioperative complications
    - Conversion to open procedure
    - Major perioperative blood loss
    - Mortality
  - Postoperative complications (<30 days and >30 days)
    - (Intra-abdominal) hematoma
    - Thrombotic event
    - Anastomotic leakage
    - Anastomotic stenosis
    - Intra-abdominal abscess
    - Wound infection
    - Reoperation
    - Re-intervention
    - Readmission
    - Mortality

- *Quality of life*
  Preoperative compared with 3, 12 and 36 months after treatment
  - BODY-Q:
    A patient-reported outcome instrument, designed for weight loss and/or body contouring treatment. The BODY-Q QoL scales measures body image, physical function, physical problems, psychological function and social function.
  - Defecation patterns
    - Faecal score: defecation frequency
      A self-designed questionnaire to measure defecation frequency and consistency.
    - Impact on QoL
      The impact of altered defecation pattern due to PCM following DGB will be measured by the questionnaire FIQL[22]. The questionnaire has good reliability and validity and is condition-specific for faecal incontinence. Since there are no validated questionnaires condition-specific for diarrhea due to PCM following DGB and PCM-related defecation alteration are similar to symptoms of faecal incontinence, the FIQL will be used to measure the impact of DGB-related diarrhea.
      - FIQL: fecal incontinence quality of life scale[22]
        The FIQL consists of 29 items, subdivided into four scales: lifestyle, coping/behavior, depression/self-perception and embarrassment.
        Each item is scored from 1 (strongly agree) to 4 (strongly disagree). An average is calculated for each scale.

- *Patient satisfaction*
  1 year post-operative
  - Instrument: scale 0-5
    A self-designed 5-point scale measuring instrument for patient satisfaction, scored from 0 (no satisfaction) to 5 (excellent satisfaction).

7.1.3 Other study parameters

Baseline characteristics:
- Gender
- Age
- Weight and BMI: prior to RYGB, lowest after RYGB, and prior to DGB
- Comorbidity
- Indication for revision surgery:
  - Insufficient weight loss
  - Weight regain
- Time between RYGB en DGB
- Medication use
- Eating behaviour
  - TFEQ-R21: Three factor eating questionnaire
    A self-assessment scale, designed to assess three cognitive and behavioural domains: cognitive restraint (6 items), uncontrolled eating (9 items) and emotional eating (6 items). The TFEQ consists of 21 questions on a four-point likert scale for items 1-20 and on an eight-point numerical rating scale for item 21.

Other outcomes:
- Operating time
- Mean hospital stay
- Total small bowel, AL, BPL and CC lengths

7.2 Randomisation, blinding and treatment allocation

Patients will be included at the outpatient clinic of the participating hospitals and clinics after IC is obtained. The participating patients will be randomised into one of the surgical techniques. Randomisation will take place in the operating room through an internet-based randomisation system in REDCap. The randomisation table will be created by an independent epidemiologist in the St. Antonius hospital. Patients and the postoperative physicians will be blinded to the treatment.

7.3 Study procedures

Like current practice, bariatric patients with weight regain or insufficient weight loss following Roux-en-Y gastric bypass (>1 year postoperative) follow a multidisciplinary group program involving a dietician, psychologist, physical therapist, and medical doctor. The program is focussed on patients selection, preoperative education, operative risk, medical evaluation, nutritional counselling and postoperative care. After multidisciplinary screening, the indication for revision surgery will be made by the surgeon and/or team.

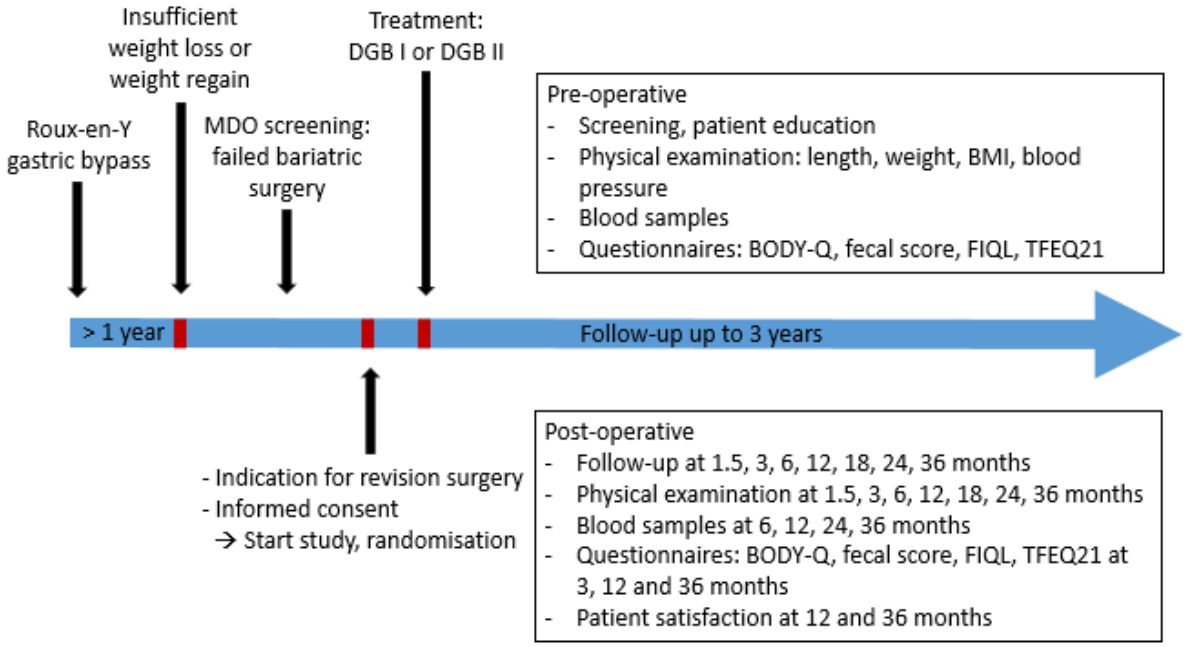
Once the indication for revision surgery is made, patients will be informed of the study. After informed consent, patients will be randomised into one of the following treatment procedures:

DGB I: BPL lengthening	n= 75
DGB II: AL lengthening	n= 75

All patients will follow standard preoperative logistics. Preoperative evaluation of the anatomy will be included by oesophagogastro-duodenoscopy and/or upper gastrointestinal contrast study to evaluate the gastro-gastric pouch and gastrojejunostomy size and to rule out gastric

fistula. Also the nutritional status will be assessed. Treatment of nutritional deficiencies will be according to treatment protocols.
After distalisation, patients start with a clear liquid diet. They are discharged from the hospital with a protein-rich diet. All patients are advised to take a multivitamin, developed for patients who underwent with more malabsorptive bariatric procedures, and calcium carbonate/cholecalciferol.

Pre-treatment, as well as 1.5, 3, 6, 12, 18, 24 and 36 months after treatment, participants will undergo physical examination at the outpatient clinic. Data including demographics, weight status, blood pressure, nutritional status, comorbidities and medications will be registered. Blood samples will be obtained to discover any nutritional deficiencies (chapter 7.1.2) preoperatively, as well as 6, 12, 24 and 36 months after treatment. Patients will be treated according to treatment protocols. Also, patients will be asked to fill out written questionnaires for assessment of diarrhea, eating behaviour and quality of life (faecal score, FIQL, TFEQ, BODY-Q) before and 3, 12 and 36 months after treatment. Lastly, patient satisfaction will be determined at the follow-up of 1 and 3 year. The following schedule of assessments will be used.



Blood samples

Haematology:	haemoglobin, haematocrit, mean corpuscular volume, leukocytes, thrombocytes
Chemistry:	sodium, potassium, calcium, albumin, creatinine, glomerular filtration rate GFR, bilirubin, ferritin,
Glucose:	fasting glucose, HbA1C
Lipid:	total cholesterol, HDL, LDL, triglycerides
Endocrinology:	thyroid stimulating hormone TSH, free thyroxine FT4, parathyroid hormone PTH
Vitamins:	vitamin B1, vitamin B6, vitamin B12, 25-OH vitamin D, folic acid

Figure 3: Timeline and examinations

7.4 Withdrawal of individual subjects
Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal
Study participants will be replaced by newly recruited and randomised subjects in case of withdrawal before surgery, in order to meet the sample size requirement. Patients who withdraw after surgery will not be replaced.

7.6 Follow-up of subjects withdrawn from treatment
All included patients will be analysed according to the intention to treat principle.

7.7 Premature termination of the study
Not applicable.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the surgical treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death
- is life threatening (at the time of the event)
- requires hospitalisation or prolongation of existing inpatients' hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs:

- (Intra-abdominal) hematoma/haemorrhage and the need for blood transfusion, re-operation or endoscopic intervention
- Thrombotic event <30 days post-treatment
- Anastomotic leakage or anastomotic stenosis
- Protein calorie malnutrition with the requirement for medical treatment, TPN or revisional surgery
- Intra-abdominal abscess and (wound) infection
- Chole(docho)lithiasis
- Gastric ulcer
- Internal hernia and small bowel obstruction
- Micro-nutritional complications

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report.

8.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9. STATISTICAL ANALYSIS

The co-primary endpoints will be analyzed using, for the first endpoint, occurrence of PCM in both groups in a 2x2 table with two-sided Chi-square test with alpha set at 5% and for the second endpoint we will use a one sided t-test to assess the mean EWL in the DGB II group compared to the absolute value of 35% EWL with one-sided alpha set at 2.5%. Both claims must come out positive for the DGB II group to declare this trial positive for DGB II.

Descriptive statistics will be used to summarize baseline characteristics and weight change of the studied patient population. Continuous measures will be summarized with sample size, mean, standard deviation, and t-test. Categorical measures will be presented with the counts and percentages of subjects in each category and tested with x2 or Fisher's exact methods. Data will be inspected for normal distribution and presented as mean ± standard deviation for normally distributed data and median [interquartile range] for non-normally distributed data. Multivariable regression analysis will be performed using logistic regression models in order to investigate the factors that influence weight loss, the occurrence of PCM and the complication rate.

Findings will be considered statistically significant if the p-value is <0.05. All analyses will be performed using the statistical package for social sciences (SPSS). The parameters that will be registered are summarised in chapter 7 (page 14,15 and 16).

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 64, October 2016) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and acts.

10.2 Recruitment and consent

Patients will be recruited at the outpatient clinic of the participating hospitals. They will be informed about the study by means of a patient information letter and explanation by the investigator, and asked for their consent. Potential participants can contact the coordinating investigator or the independent expert for questions concerning the trial. After a reasonable time of consideration, the IC form will be signed by both the participant and the investigator.

10.3 Benefits and risks assessment

Participants will undergo either DGB type I or DGB type II. The treatment and pre- and postoperative care will not differ from the regular DGB revisional treatment for failed RYGB. Therefore, there are no additional risks associated to this treatment.

Additionally, participants will fill out written questionnaires regarding defecation patterns and QoL preoperatively as well as 3, 12 and 36 months after treatment.

10.4 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7 of the WMO.

The investigator (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Data will be stored in Redcap. This data management system will contain coded patient information and will be accessible to the principal investigator, the coordinating investigator and the data monitor. The key to the code will be safeguarded by the coordination investigator. The data will be stored and kept for 15 years according to standard guidelines in concordance with the Dutch Personal Data Protection Act (Wet Bescherming Persoonsgegevens, WBP).

11.2 Monitoring and Quality Assurance

Monitoring of the conduct of the study takes once a year place by an independent data monitor.

11.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

11.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The study protocol of this trial will be registered in the Netherlands National Trial Register (NTR). The outcomes of this study will be offered for publication to scientific journals and (inter)national congresses presentations.

12. REFERENCES

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