Laparoscopic Roux-en-Y Gastric Bypass Equipoise Laparoscopic Sleeve Gastrectomy for Severe Obesity in Teenagers: a Randomized Controlled Trial

TEEN-BEST

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PROTOCOL SIGNATURE SHEET

The undersigned confirm that the following protocol has been agreed and accepted and that the Principle Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard Operating Procedure (SOP) and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AGB	Adjustable Gastric Band
ALP	Alkaline Phosphatase
ALT	Alanine-aminotransferase
AST	Aspartate-aminotransferase
BMI	Body Mass Index
CKD	Chronic Kidney Disease
cm	Centimeter
CRP	C-reactive Protein
CTCM	Clinical Trial Center Maastricht
DBP	Diastolic Blood Pressure
DEXA	Dual-energy X-ray Absorptiometry
DSMC	Data Safety and Monitoring Committee
EDE-Q	Eating Disorder Examination Questionnaire
%EWL	Percentage Excess Weight Loss
GFR	Glomerular Filtration Rate
FSH	Follicle-stimulating Hormone
fT4	Free Thyroxine
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
Hb	Hemoglobin
HDL	High-density Lipoprotein
Ht	Hematocrit
IBD	Inflammatory Bowel Disease
IFSO	International Federation for the Surgery of Obesity and Metabolic disorders
IGF-1	Insulin-like Growth Factor-1
IOTF	International Obesity Task Force
IWQOL-Lite	Impact of Weight on Quality of Life Lite
kg	Kilogram
Kg/m^2	Kilogram per square meter
LDL	Low-density Lipoprotein
LH	Luteinizing Hormone
m	Meter
MCV	Mean cell volume
mSv	milliSieverts
NAFLD	Non-Alcoholic Fatty Liver Disease
OSA	Obstructive Sleep Apnea
PedsQl	Pediatric Quality of Life Inventory
PI	Principal Investigator
PIS	Participant Information Sheet
PTH	Parathyroid Hormone
RCT	Randomized Control Trial
RYGB	Roux-en-Y Gastric Bypass
REC	Research Ethics Committee
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SHBG	Sex Hormone Binding Globulin
T2DM	Type II Diabetes Mellitus
TBW	Total Body Weight
TBWL	Total Body Weight Loss
TFEQ	Three-factor Eating Questionnaire
TSH	Thyroid-stimulating Hormone
SDQ	Strengths and Difficulties Questionnaire
SG	Sleeve Gastrectomy

SUMMARY

Trial Title	Laparoscopic Roux-en-Y Gastric Bypass Equipoise Laparoscopic Sleeve Gastrectomy for Severe Obesity in teenagers: a Randomized Controlled Trial.
Short Title	TEEN-BEST (TEENagers Bypass Equipoise Sleeve Trial).
Clinical Phase	III
Trial Design	Multicenter randomized controlled non-inferiority trial. A historical cohort of adolescents who participated in conventional treatment (COACH – Maastricht UMC) will be used to compare with both study arms.
Trial Participants	Adolescents aged 13-17 (Tanner stage IV or more) with severe obesity meeting International Federation for the Surgery of Obesity and Metabolic disorders (IFSO) criteria for bariatric surgery corrected for age and sex based on the International Task Force (IOTF) criteria.
Inclusion criteria	(i) Completed a minimum of twelve months in formal lifestyle intervention +/- pharmacotherapy weight loss program; (ii) Consensus in the multidisciplinary child obesity team, during the multidisciplinary meeting, on a strongly motivated participation of the participant during the lifestyle intervention program so far and in the future (after the bariatric surgery); the participant must have been fully committed to be successful in this program and is expected to continue with this effort after bariatric surgery; (iii) Consensus in the multidisciplinary child obesity team on the diagnosis of non-responding to multidisciplinary lifestyle interventions for now and the near future.
Exclusion criteria	(i) Unable to consent as appropriate; (ii) Illiteracy (disability to read and understand questionnaires); (iii) Secondary obesity (obesity caused by a medical condition for example hypothyroidism); (iv) Known syndrome or genetic disorder (such as Prader-Willi syndrome); (v) Skeletal immaturity (Tanner stage ≤III) – pre-menarche – bone age < 15 years in boys; (vi) Ongoing addiction (alcohol, drugs, medication); (vii) Previous bariatric, gastro-esophageal reflux or gastric surgery; (viii) Psychiatric disorders; (ix) Inflammatory Bowel Disease (IBD); (x) Non-support / non-consent of both parents / caretakers of adolescents aged 13-15 years.
Treatment duration	3 years (recruitment)
Follow up duration	5 years
Planned Trial Period	8 years

	Objectives	*Outcome Measures*
Primary	To determine whether sleeve gastrectomy (SG) is non-inferior to Roux-en-Y Gastric Bypass (RYGB) over 3 years.	Proportion achieving a 20% total body weight loss (TBWL).
Secondary	To compare outcomes between SG and RYGB over 1, 3 and 5 years.	(i) Change in body weight and body mass index (BMI); (ii) Incidence of adverse health events and additional surgical intervention; (iii) Prevalence and remission of obesity-related comorbidities; (iv) Prevalence of cardio metabolic risk factor measures; (v) Bone health measures; (vi) Quality of life, psychosocial health measures, patient satisfaction and educational attainment; (vii) Body composition.

Procedures	(i) Laparoscopic Roux-en-Y gastric bypass (ii) Laparoscopic sleeve gastrectomy

Standardization	Standardized surgical techniques will be used across participating centers.

Rationale: Bariatric surgery is currently the only evidence-based treatment for severe obesity in adults. Recent data also support the use of bariatric surgery in selected adolescents suffering from severe obesity who don't show successful weight reduction and remission of comorbidities in the multimodal lifestyle intervention programs. Although both the SG and the RYGB showed successful weight loss and reduction of obesity related comorbidities in adolescents thus far, long-term outcome data of SG in adolescents has been limited and, to date, no randomized controlled trials have been performed in adolescents with direct comparison of these two bariatric procedures. This clear knowledge gap hampers optimal procedure selection for adolescents and thus prevents evidence-based recommendation to eligible adolescents. Therefore, we propose a Randomized Controlled Trial (RCT) comparing SG with RYGB in untreatable adolescents with severe obesity. In addition, both bariatric procedures will be compared to a historical cohort of patients in a lifestyle intervention program, to determine the effect of bariatric surgery in adolescents compared to only lifestyle intervention program.
Objective: To determine whether SG is non-inferior to RYGB across three years in terms of achieving a 20% TBWL.
Study design: A partial blinded multicenter international randomized controlled non-inferiority trial. *Sample size*: allowing a 15% drop-out, power of 90% and using a non-inferiority margin of -20% a sample size of 264 patients is needed, 132 patients per arm. These study-arms will be compared to a historical matched-cohort of adolescents who participated only in a lifestyle intervention program (COACH – Maastricht UMC).**Study population:** The trial participants are adolescents aged 13-17 (Tanner stage ≥IV) with severe obesity meeting IFSO criteria for bariatric surgery corrected for age and sex based on the IOTF criteria. The exclusion criteria are as follows: (i) inability to consent as appropriate, (ii) illiteracy (disability to read and understand questionnaires), (iii) secondary obesity (obesity caused by a medical condition for example hypothyroidism), (iv) known syndrome or genetic disorder (such as Prader-Willi syndrome), (v) skeletal immaturity (Tanner stage ≤III) – pre-menarche – bone age <15 years in boys, (vi) ongoing addiction (alcohol, drugs, medication), (vii) previous bariatric, gastro-esophageal reflux or gastric surgery, (viii) psychiatric disorders, (iv) IBD and (v) non-support / non-consent of both parents / caretakers of adolescents aged 13-15 years.
Intervention: The adolescents will be randomized for receiving a RYGB or a SG.
Main study parameters/endpoints: The primary outcome is the proportion of participants achieving 20% TBWL at three years follow-up. The secondary outcomes are (i) Body weight and BMI change, (ii) incidence of adverse health events and additional surgical intervention, (iii) resolution of obesity-related comorbidities, (iv) prevalence of cardio metabolic risk factor measures, (v) bone health measures, (vi) quality of life, psychosocial health measures, patient satisfaction and educational attainment and (vii) body composition.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: All patients are at risk for the complications associated with a surgery in general, for the specific complications associated with the bariatric procedures (including anastomotic leak, internal herniation, gall stone formation, gastric ulcer, reflux, transient loss of hair, deficiencies of several vitamins and minerals, dyspepsia, dumping syndrome and food intolerance).).
Regarding the burden; participants need to attend eight follow-up visits in total. In the first year after surgery there will be three follow-up visits; two months, six months and twelve months post-surgery. The other five follow-up visits will be at eighteen months and at two, three, four and five years post-surgery (this follow-up is based on the standard care for adults after bariatric surgery). Blood samples will be taken at baseline, at six and twelve months after surgery and thereafter yearly. Patients who are included in this study will be asked to fill out multiple questionnaires at several visits; at baseline and at one, three and five years postoperatively. The time estimated to fill out these questionnaires is in total 60 minutes. Furthermore, a bariatric intervention requires life changing lifestyle adjustments, especially in the way of eating.
The benefits of participating in this study include that untreatable patients receive a bariatric intervention as being an evidence based successful treatment to lose weight and experience remission of comorbidities. Furthermore, other positive effects may occur, such as improvement of quality of life, improvement in school performance and improvement in social contact, as reported in previous studies.

1. INTRODUCTION AND RATIONALE

The prevalence of overweight and obesity in adults is still increasing worldwide. Parallel to this, the prevalence of overweight and obesity in children has increased by almost 50% between 1980 and 2013 [1]. Alongside increases in developed countries, a growing trend has also been noted in low- and middle-income countries [1]. In the United States, almost thirteen million children and adolescents have obesity, with a reported prevalence in 2014 of 8.9% among children aged two to five, 17.5% among children aged six to eleven and 20.5% among adolescents aged twelve to nineteen [12]. In Western Europe, six to seven percent of the children have obesity, with marked regional variation; ranging from 12.5% in Malta to 4.1% in the Netherlands [1].
The majority of children with obesity will continue to have obesity into their adult life [13]. Especially post-pubertal adolescents with severe obesity have a very high risk of maintaining the severe obesity in adult life [14].

Obesity is a serious disease associated with several chronic diseases, including type II diabetes (T2DM), hypertension, non-alcoholic fatty liver disease (NAFLD), cancer, cardio-vascular disease, obstructive sleep apnea (OSA) and dyslipidemia. Correlated to the increase in prevalence of childhood obesity, an alarming shift in the onset of these obesity associated chronic diseases towards childhood has been noted, especially for T2DM [1-4, 18-19]. Regarding T2DM in adolescents, the timeframe between the onset of T2DM and the requirement of insulin therapy is reduced, with medical treatments failing earlier [4,18]. Additionally, other comorbidities including metabolic and endocrine changes, cardiovascular abnormalities, non-alcoholic fatty liver disease and impaired quality of life also develop earlier in life. As a result, all these factors contribute to a poor prognosis in this population with approximately a twenty-year decline in life expectancy [2, 20-21].

The standard treatment for obesity in children consists of multimodal lifestyle intervention programs, delivered by an expert multidisciplinary team. In these programs focus is specifically on eating patterns, exercise and behavior. In the short term, significant weight loss and improvement of obesity related health hazards are described. An updated Cochrane review, concluded from a meta-analysis of 37 studies, including a total of 27,946 children, that there is strong evidence for the beneficial effects of conservative multimodal lifestyle intervention programs for obesity in childhood. They showed results of reducing adiposity with a mean reduction of 0.15 kilogram per square meter (kg/m^2) in BMI. However, the reduction in the adolescent group (aged thirteen to eighteen years) was only 0.09 kg/m2 [16]. A study performed in the Netherlands showed that a multimodal lifestyle program resulted in significant weight loss and improvement of cardiovascular risk parameters in children with overweight, obesity and morbid obesity, all to a similar degree. In children with morbid obesity a decrease in BMI z-score of -0.23 ± 0.32 ($p=0.01$) was observed after two years of follow-up. In addition, 25% of these children transitioned in weight status from morbid obesity to obesity. Overall, 68% percent of the participants achieved a successful weight reduction, defined as a 10% weight loss at 24 months follow-up [17]. However, despite these promising results of these pediatric obesity expert centers, still as much as one quarter (Rijks et al.) of the adolescents unfortunately did not show any weight reduction [17,22]. Nevertheless, these untreatable adolescents still need treatment for their morbid obesity and concomitant co-morbidities. For this group of adolescents, bariatric surgery might be an option.

In adults, surgical interventions are well-established for the treatment of severe obesity and are considered the standard treatment [5-6]. In the Netherlands, the laparoscopic RYGB is the standard bariatric surgical intervention for severe adult obesity [10]. The outcome after RYGB is well characterized in terms of weight loss and resolution of comorbidities. Two studies published about the laparoscopic RYGB with a follow-up of at least ten years showed a mean percentage excess weight loss (%EWL) of 56% and 59% ten years after surgery [23-24]. Obeid et al. reported rates of remission of comorbidities ten-years after surgery as: 46% for hypertension, 58% for T2DM and 46% for hyperlipidemia [24]. Kothari et al. also showed their results of improvement (including total remission) of comorbidities eight years after the primary bariatric procedure: improvement occurred in 49%, 38% and 46% for dyslipidemia, hypertension and T2DM respectively [23]. However, after RYGB, a limited group of patients suffers from significant morbidity, like internal hernia (2%), gastric

ulcer (1%) and chronic abdominal pain (3%) [29]. Due to the bypass of the duodenum and proximal jejunum there is also a concern for long-term deficiencies of certain vitamins and minerals. The most common deficiencies described after RYGB are iron (49%), vitamin B12 (26-70%), folic acid (35%) and vitamin D (33-50%) [27-28].

The SG has emerged as a stand-alone bariatric technique much more recently compared to RYGB but is being performed increasingly and has recently become the most commonly performed bariatric operation in adults worldwide [10]. Although data reported so far suggests good results regarding weight reduction and resolution of comorbidities up to a few years after SG, long-term results with follow-up beyond ten years are lacking in the literature. A recently published review showed a mean %EWL after one, two, three and five years of 83.0%, 77.8%, 66.3% and 65.1% respectively. No significant difference in %EWL was found between RYGB and SG two years after surgery. However, a slight statistically significant difference was seen at three-year follow-up, favoring the RYGB, which was confirmed at five-year follow-up (p=0.045) [25]. A randomized controlled trial (RCT) performed in four centers in Switzerland comparing SG and RYGB showed no difference in weight loss between the two procedures at one-, two- and three-year follow-up. Mean %EWL at three years was 70.9% and 73.8% for SG and RYGB respectively. Additionally, they noted that the comorbidities were significantly reduced and comparable after both procedures. After three years, complete remission of T2DM after SG and RYGB was reported in 60% and 77%, respectively (p=0.23). Only remission of gastro-esophageal reflux disease and dyslipidemia were significantly more successfully treated after RYGB [26].

A small but increasing number of bariatric procedures is being performed in adolescents. As expected, the number of studies being published in this field is increasing in parallel. A recent systematic review on medium- and long-term outcomes (minimum three-year follow-up) of bariatric surgery in 950 morbidly obese adolescents, aged twelve to nineteen years, showed an average decrease in BMI of 13.3 kg/m^2. In terms of co-morbidities, resolution of T2DM/insulin resistance was seen in 69.9%, resolution of hypertension in 61.6% and resolution of dyslipidemia in 57.1% of the patients. The most commonly performed bariatric surgery was the RYGB followed by the adjustable gastric band. The rate of reoperation was 9.6%, mostly because of postoperative complications and weight loss failure. No long-term data were obtained on nutritional deficiency or growth status [11]. Olbers et al. reported similar weight loss results over five-years among adolescents and adults who received a RYGB. Substantial weight loss was observed, with a mean reduction of 13.1 kg/m^2 in BMI in the adolescent intervention group. Notably, the control group of adolescents, who attended multimodal lifestyle programs, experienced a mean increase in BMI of 3.3 kg/m^2 across the five-year study period. Frequent resolution of cardio metabolic comorbidities and improvement in quality of life over the five-year period was also noted after RYGB in adolescence. Regarding comorbidities among adolescents who received the RYGB, resolution of hypertension was seen in 100%, resolution of dyslipidemia in 82.7%, complete resolution of T2DM and disturbed glucose homeostasis in 100% (n=3) and 85.7%, respectively [7]. This study showed that the RYGB is an efficient and safe bariatric procedure in adolescents into the long-term, just as several other reviews stated [2-3,6,8]. Also, in recent years, Inge et al. have published three-year outcomes from a prospective non-randomized study including adolescents undergoing SG and RYGB. This study has demonstrated comparable results in terms of weight loss, with a mean three-year BMI reduction of 15 kg/m^2 after RYGB and 13 kg/m^2 after SG. Furthermore, significant improvements were observed in cardio metabolic health (95% remission of T2DM, 86% remission of abnormal kidney function, 74% remission of elevated blood pressure, 76% remission of prediabetes and 66% remission of dyslipidemia) and weight-related quality of life three years after surgery. The study also suggested that risks associated with the procedures may be more prevalent after RYGB and included specific micronutrient deficiencies and the need for additional abdominal procedures [15].

As mentioned before, morbid obesity in adolescents is associated with several comorbidities, increased cardiovascular risk, cardiovascular changes and reduction in quality of life. The metabolic syndrome is a strong risk factor for developing cardiovascular diseases later in life [30-32]. Without intervention, the obesity and the comorbidities will continue into adulthood and new comorbidities may occur. This all might result in premature death [33-35]. The Harvard Growth study showed that

overweight in adolescence predicted a broad range of adverse health effects that were independent of adult's weight after 55 years of follow-up. Overweight in adolescence was associated with a doubled risk of mortality from all causes and mortality from coronary heath disease compared with normal weight in adolescence [36]. Bariatric surgery is the most effective treatment for obesity and related comorbidities. This intervention should take place at an early stage, when safe and effective, instead of waiting until adulthood. The rates of remission of comorbidities after bariatric surgery observed in each of the previous mentioned studies were higher than those reported in adults, suggesting that adolescents may have a greater potential than adults for reversal of the cardio metabolic consequences of obesity [7,15]. In addition, Sjöstrom et al. showed in the Swedish Obese Subjects study of adult patients that when T2DM diagnosis was new (<1 year) bariatric surgery resulted in >90% remission, whereas a diagnosis of T2DM >4 years ago resulted in less than 40% remission. In addition, bariatric surgery in adolescents is proven effective in improving renal outcomes and NAFLD/NASH (Non-Alcoholic Steatohepatitis) [37-38]. Furthermore, left ventricular mass as well as thickness of the posterior wall and septum are reduced in adolescents after RYGB, while in adults only ventricular mass is improved The thickness of neither the posterior wall nor the septum is reduced [40]. Thus; delay for surgical treatment until adulthood is therefore negatively associated with the reduction of several comorbidities and therefore cardiovascular risk profile and premature dead.

In short, a small proportion of the morbid obese adolescents do not respond on extensive multimodal lifestyle interventions. For this group of adolescents, bariatric surgery might be a possible therapy. Although both the SG and the RYGB showed successful weight loss and reduction of obesity related comorbidities in adolescents thus far, long-term outcome data of SG in adolescents has been limited and, to date, no RCT's have been performed in adolescents with direct comparison of these two bariatric procedures. This clear knowledge gap hampers optimal procedure selection for adolescents and thus prevents evidence-based recommendation to eligible adolescents. Therefore, we propose an RCT comparing SG with RYGB in untreated adolescents with severe obesity.

Rationale

The RYGB has been the dominating surgical technique during the beginning of the 21st century. Since then, the SG has been introduced and has been increasingly used with substantial regional and local variation. This ongoing shift is driven by surgeon and patient preferences rather than high-quality evidence. While RYGB has the longest track record in bariatric surgery, with reports of outcomes up to twenty years after surgery, there is currently insufficient evidence to recommend one procedure over the other. Systematic reviews have documented a lack of both short- and long-term high-quality comparative data, although there are several ongoing trials in adults.

There is a strong international trend within adolescent bariatric surgery to prefer the SG over RYGB, yet data are largely lacking to support this preference. One factor possibly supporting this trend is the relative technical simplicity of performing SG in comparison to RYGB. Scientific data regarding long-term outcome in adolescents is predominantly from series using RYGB.

The overall aim of this trial is to obtain level one evidence regarding differences in clinical outcomes between RYGB and SG in untreatable morbidly obese adolescents, in a multicenter randomized clinical trial. By assessing safety and efficacy, we aim to provide guidance regarding procedure choice based on reliable risk/benefit data overall as well as in subgroups. In addition, we will compare the clinical outcomes of a historical cohort of patients participating in a lifestyle intervention program with both study arms of the RCT.

2. OBJECTIVES

2.1 Primary objective

Research question
Is the laparoscopic SG non-inferior to the laparoscopic RYGB over three years in terms of achieving a 20% TBWL in untreatable adolescents with severe obesity?

Null hypotheses
(i) The proportion of SG participants achieving 20% or greater TBWL over three years will be 20% less than the proportion of RYGB participants achieving 20% or greater TBWL.

Alternative hypotheses
(i) The proportion of SG participants achieving 20% or greater TBWL over three years will not be 20% less than the proportion of RYGB participants achieving 20% or greater TBWL.

2.2 Secondary objectives

To compare outcomes between SG and RYGB across one, three and five years. In addition, a historical cohort of adolescents who participated in a lifestyle intervention program will be compared to both study arms on these secondary objectives (except for ii and vii).
(i) Change in BMI and body weight;
(ii) Incidence of adverse health events including the need for re-operation;
(iii) Resolution of co-morbidities, including OSA, T2DM, hypertension and hyperlipidemia;
(iv) Time to resolution of OSA, T2DM, hypertension and hyperlipidemia;
(v) Prevalence of cardio metabolic risk factor measures;
(vi) Routine post-bariatric surgery nutritional blood tests at each assessment, including: full blood count, electrolytes, creatinine, fasting glucose, fasting insulin, HbA1c, liver parameters and function tests, iron, ferritin, vitamin B12, thiamine, folate/red cell folate, lipid profile, 25-hydroxyvitamin D, calcium and parathyroid hormone;
(vii) Bone health measures;
(viii) Generic and obesity-specific health-related quality of life;
(ix) Psychosocial health measures and educational attainment;
(x) Patient satisfaction;
(xi) Body composition.

3. STUDY DESIGN

3.1 Trial design

3.1.1 Trial Design - RCT

This trial is designed as a non-inferiority parallel randomized controlled multicenter trial to investigate the primary and secondary objectives as mentioned in the previous section.

There will be two phases during this trial. Phase 1 will be an internal pilot of twenty patients at the two initiating surgical sites (20 SG and 20 RYGB in total) to establish the recruitment rate of the trial. During this phase, the methods of recruitment and informed consent will be refined. At the end of phase 1, the progression criteria for undertaking the main trial will be reviewed and discussed with the Data and Safety Monitoring Committee (DSMC). Phase 2 will be the full multicenter RCT. During this phase, we will extend to the additional sites using the optimized methods of recruitment established during phase 1.

Patients will be recruited for this study from May 2018 until May 2021. The follow-up will be five years for all randomized patients.

3.1.2 Trial Design – Historical cohort

Based on experience from previous studies with adolescents and bariatric surgery (i.e. BASIC trial), a randomized conservative group was not chosen because of the high risk of not achieving the needed inclusion due to the negative psychological impact on the adolescent when randomized to the conservative treatment, a treatment that had already failed. Furthermore, compliance in the conservative group has been limited and bariatric surgery in adolescents is proven more effective compared to the lifestyle intervention programs.

In order to compare the effects of the conservative lifestyle intervention programs with the two operative procedures as describe above, a historical cohort will be used. The historic data of participants in the COACH cohort of the Maastricht UMC+ will be used. COACH offers a long term multidisciplinary outpatient life style intervention. Children in the COACH program are monitored for several years.
COACH participants that started the COACH intervention between 2010 and 2018 aged 13-17 years old will be selected from the COACH cohort and used for analysis. Exclusion criteria are (i) unable to consent as appropriate, (ii) illiteracy, (iii) secondary obesity, (iv) known syndrome of genetic disorder, (v) ongoing addiction, (vi) active psychiatric disorders as described in this protocol, (vii) previous bariatric, gastro-esophageal reflux or gastric surgery. We will include 264 adolescents, matched on BMI z-score.
Baseline and yearly measurements as performed in the TEEN-Best study are also performed in participants in the COACH program (as TEEN-BEST is based on the COACH program). Therefore long term development of anthropometric parameters, cardiovascular risk markers, comorbidities and quality of life can be compared between the intervention groups of the TEEN-Best study and conventional treatment in COACH. The primary and secondary endpoints stated in paragraph 2.1 and 2.2 will be used for this historical cohort as well, except for the incidence of adverse health events including the need for re-operation and bone health measures.
Informed consent is obtained from all participants in COACH for use of their data for scientific research (REC number 13-4-130).

3.2 Trial setting

This is an international multicenter trial, which will initially be conducted at two surgical sites, with the potential to recruit additional sites after successful initiation. Surgical sites are required to have (i) a bariatric center with a specialized bariatric team performing at least 300 adult bariatric procedures yearly, (ii) an existing child obesity management program or a close link with such a program in another institute and (iii) an intensive care unit that treats adolescents or access to such a facility nearby.

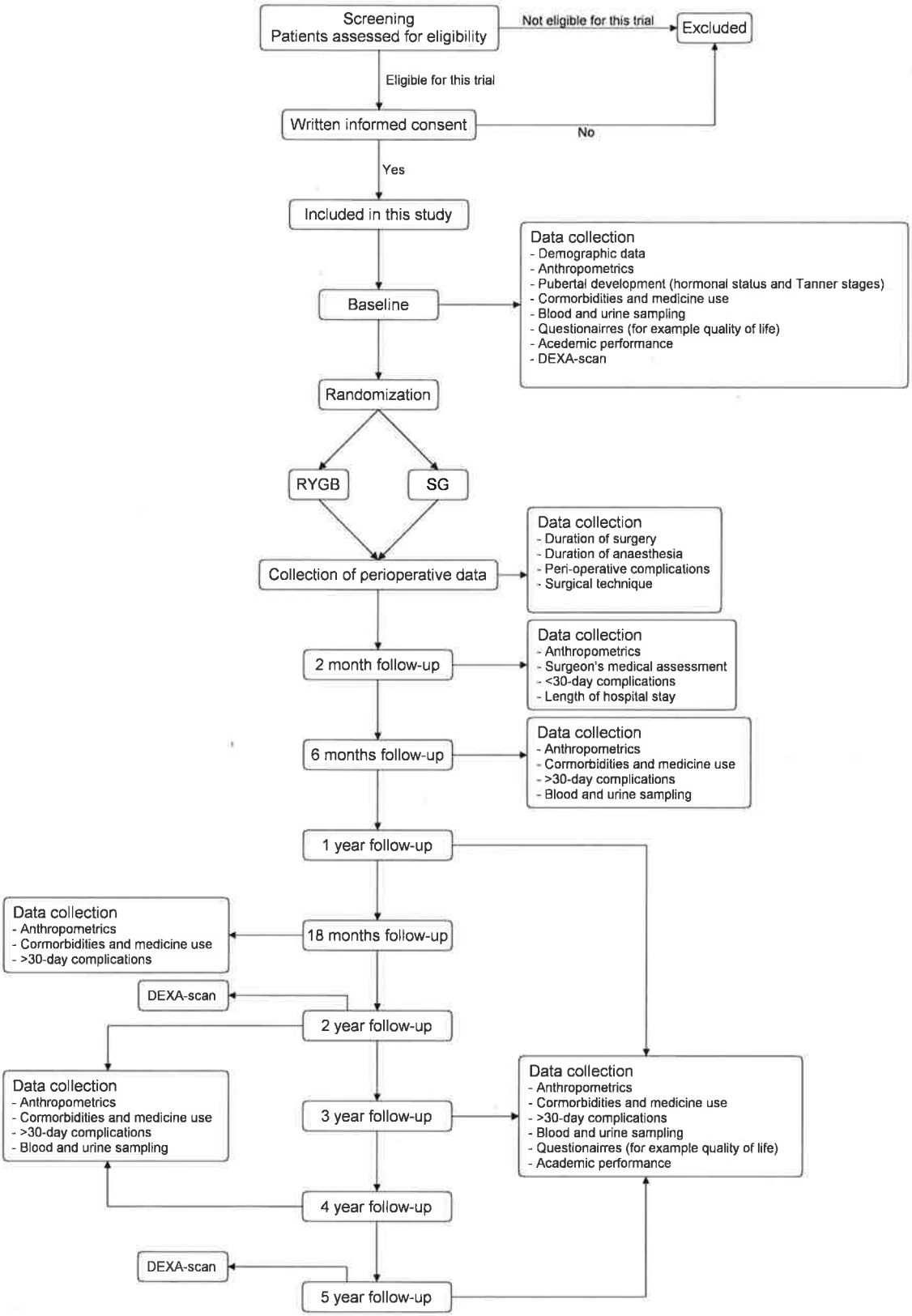
The two initiating surgical sites will be:
(i) Máxima Medical Center, Veldhoven, The Netherlands;
(ii) Queen Silvia's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden.

Additional surgical sites will be:
(i) Rijnstate, Arnhem, The Netherlands;

The child obesity expertise centers will be:
(i) Maastricht University Medical Center, Maastricht, The Netherlands (initiating child obesity expertise center);
(ii) Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands;
(iii) Rijnstate, Arnhem, The Netherlands.

Participants will be identified by named collaborators and existing staff members in the child obesity lifestyle programs at the participating expertise centers or by pediatricians outside of the expertise centers. Participants will be identified by screening the health records of existing patients who have already participated twelve months in the child obesity life style program or by prospective identification of new patients (who have participated a minimum of twelve months in a formal lifestyle program) with potential to meet eligibility criteria.
During a multidisciplinary meeting, with a multidisciplinary team, the participant will be accessed for eligibility. This multidisciplinary team will consist of the pediatrician, the clinical psychologist and the dietician who have treated the participant in the lifestyle intervention program. In addition, a bariatric surgeon will also be part of this multidisciplinary meeting to assess eligibility of the participant. First of all, the members of the multidisciplinary team all need to agree that the participant has been strongly motivated and fully committed to be successful in the lifestyle intervention program so far. Furthermore, all members of the multidisciplinary meeting also need to agree that they expect that the participant will stay strongly motivated during the lifestyle management program after the bariatric surgery and will comply with the adjustments necessary and the follow-up. If the participant met these two inclusion criteria, further assessment of the eligibility of the participant for this trial will follow. If the participant does not meet both of these criteria, the patient will not be eligible for this study and no further assessment of the other eligibility criteria will take place. If eligibility is confirmed, the adolescent will be informed about the trial by the pediatrician.
If an adolescent expresses his/her interest for the TEEN-BEST study, the members of the multidisciplinary team will communicate with the participant that every member of the multidisciplinary team must agree that the adolescent was fully committed during the lifestyle intervention program to be successful and that this effort is expected to continue after the bariatric surgery. And thus if not all members agree, the participant won't be eligible for this study.
The bariatric surgical team will be integrated into the multidisciplinary child obesity teams at participating centers for the screening. Educational sessions will be delivered to staff members treating adolescents within the specialist child obesity programs, outlining the trial objectives and eligibility criteria.
After the bariatric surgery, the follow-up of the participant will include a lifestyle intervention coach, a dietician and a sport plan, which is similar to the preoperative lifestyle intervention program the adolescent participated in. This care will be provided to the adolescent by the child obesity expertise center in collaboration with the regional network of paramedics of the adolescent. Furthermore, the follow-up will include several appointments with the pediatrician and the surgeon.

3.3 Flow Chart



4. STUDY POPULATION

4.1 Population

Adolescents aged 13-17 (Tanner stage IV or more) with severe obesity meeting IFSO criteria for bariatric surgery (BMI ≥40 kg/m^2 or ≥35 kg/m^2 combined with an associated obesity related comorbidity) corrected for age and sex according to the IOTF criteria.
All willing patients, who meet age and BMI criteria and have participated for at least twelve months in a lifestyle intervention program, will be offered formal assessment for study inclusion. Patients who continue to meet eligibility criteria, will be invited to participate in the trial.

4.2 Inclusion criteria

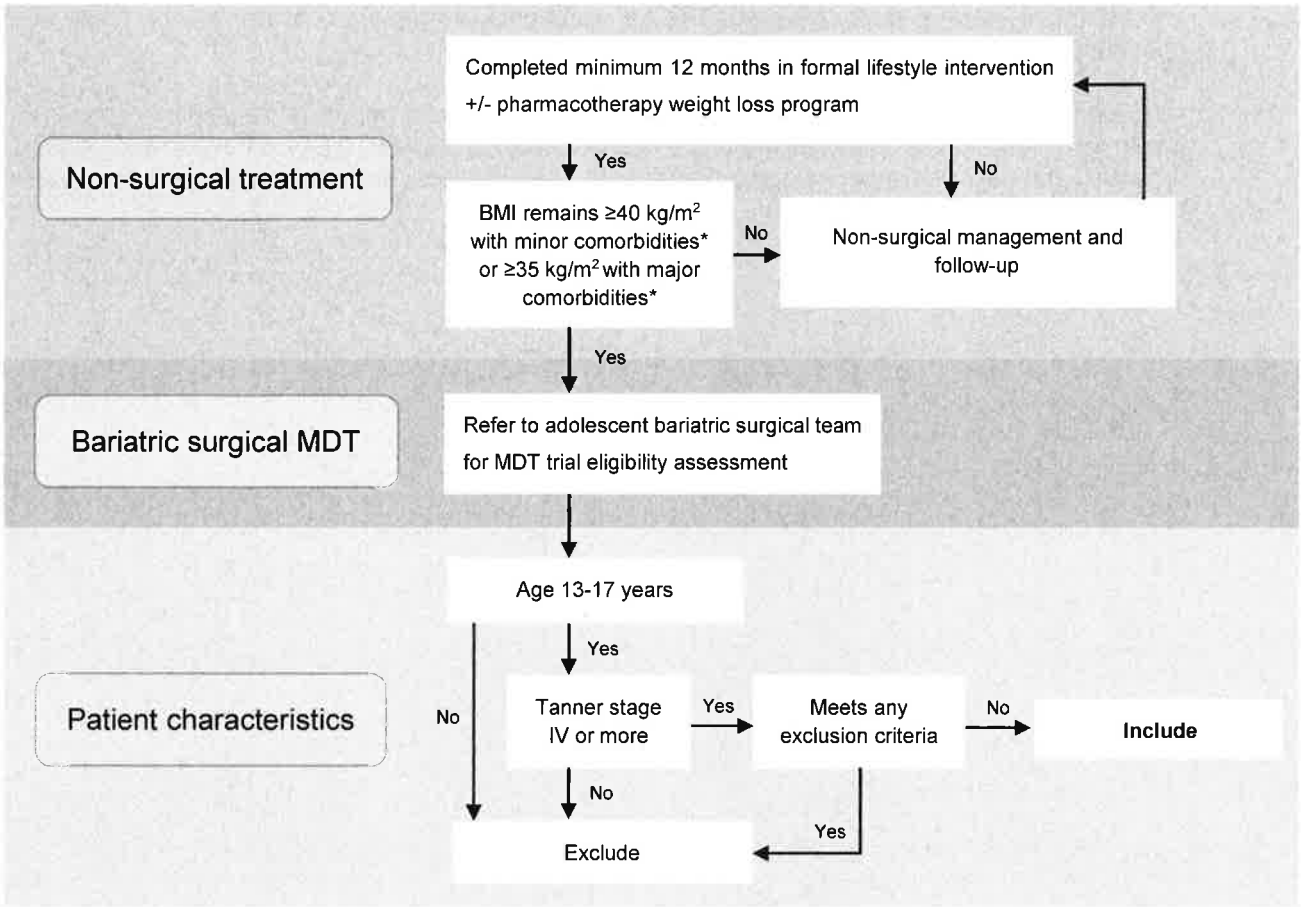
In order to be eligible to participate in this study, a subject must meet all of the following criteria (see figure 4.2.2):

(i) Completed a minimum of twelve months in formal lifestyle intervention and/or pharmacotherapy weight loss program;
(ii) Consensus in the multidisciplinary child obesity team, during the multidisciplinary meeting, on a strongly motivated participation of the participant during the lifestyle intervention program so far and in the future (after the bariatric surgery); the participant must have been fully committed to be successful in this program and is expected to continue with this effort after the bariatric surgery;
(iii) Consensus in the multidisciplinary child obesity team on the diagnosis of non-responding to multidisciplinary lifestyle interventions for now and the near future;
(iv) Age 13-17;
(v) Tanner stage ≥IV;
(vi) Severe obesity meeting IFSO criteria for bariatric surgery, BMI ≥40 kg/m^2 with minor comorbidities or BMI ≥35 kg/m^2 with at least one major comorbidity (see table 4.2.1), corrected for age and sex according to the IOTF criteria.

Table 4.2.1. - Major and minor comorbidities

Category	Comorbidity
Major comorbidity	- Type II diabetes mellitus - Severe hypertension due to obesity - Severe obstructive sleep apnea syndrome - Severe psychosocial morbidity - Liver fibrosis
Minor comorbidity	- Impaired fasting glucose - Impaired glucose tolerance - Dyslipidemia - Steatohepatitis - Panniculitis - Venous stasis - Urinary incontinence - Weight-related joint disease - Body size precluding ambulation - Impaired activities of daily living - Benign intracranial hypertension

Figure 4.2.2. - Eligibility pathway



* Table 4.2.1. BMI will be corrected for age and sex based on the IOTF criteria.

4.3 Exclusion criteria

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

- Unable to consent as appropriate;
- Illiteracy (disability to read and understand questionnaires);
- Secondary obesity, obesity caused by a medical condition (for example hypothyroidism);
- Known syndrome or genetic disorder (such as Prader-Willi syndrome);
- Skeletal immaturity (Tanner stage ≤III) – pre-menarche – bone age < 15 years in boys;
- Ongoing addiction (alcohol, drugs, medication);
- Previous bariatric, gastro-esophageal reflux or gastric surgery;
- Psychiatric disorders;
- IBD;
- Non-support / non-consent of both parents / caretakers of adolescents aged 13-15 years.

4.4 Sample size calculation

The clinical applicants set the definition for a clinical successful weight loss in this study as a TBWL of ≥20%. The sample size has been chosen to test the hypothesis that SG will be non-inferior to RYGB in terms of the proportion of participants achieving a TBWL of at least 20% at three years. We obtained unpublished summary statistics from the Teen-LABS study group, which were used to inform the power calculation. The proportion of participants losing at least 20% of their total body weight (TBW) at three years in the Teen-LABS study was as following: 63% of SG and 72% of RYGB patients had lost at least 20% of their TBW at three years. The following hypotheses was set by the clinical applicants; 70% of the participants will achieve a TBWL of 20%.

The power calculation requires the estimation of two parameters, i.e. the mean TBWL of participants at three years and the difference in mean TWBL that would be considered clinically important (the non-inferiority margin). The non-inferiority margin was chosen on the basis of the opinions of the clinical applicants and was set at 20%.

A group sample size of 132 patients/arm, allowing for a 15% dropout, is needed to achieve 90% power to detect non-inferiority using a one-sides Z-test (unpooled). The non-inferiority margin is -0,20000. The true difference between the means is assumed to be 0. The significance level (alpha) of the test is 0,02500.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The evolution of bariatric surgery across more than half a century has resulted in a range of available procedures, three of which dominate in adults and have been used in most reports of adolescent bariatric surgery. These are the RYGB, the SG and the adjustable gastric band (AGB). The SG, having emerged more recently, and AGB are understandably underpinned by a thinner literature base than the RYGB [40]. Currently, the SG is the most performed bariatric procedure worldwide, followed by the RYGB [10].

The surgical interventions will be performed by an experienced bariatric surgeon. The bariatric surgeon will be required to have a minimum experience of at least fifty of each bariatric procedure (SG and RYGB) in adults with severe obesity.

5.1.1 Laparoscopic Roux-en-Y Gastric bypass

The surgical procedure has been described earlier by Dillemans et al. In short, after induction of pneumoperitoneum and placement of five trocars the majority of the stomach is disconnected from the normal digestive route using a linear stapler to leave a small (20-25 ml) gastric pouch in continuity with the esophagus. The jejunum is transected approximately 50-100 centimeter (cm) from the ligament of Treitz and the distal end (Roux limb) is anastomosed to the gastric pouch, as a gastrojejunal anastomosis, using a 25 mm circular stapler or a 30 mm linear stapler. Thereafter, the proximal end (the biliary limb) is attached approximately 100-150 cm distally along the jejunum, as a jejuno-jejunal anastomosis. Furthermore, the mesenteric defects beneath the jejunojejunostomy and at Petersen's space will be closed. Before closure of the skin incisions, the gastrojejunostomy is tested for leakage using methylene blue.

5.1.2 Laparoscopic Sleeve Gastrectomy

The procedure was described by Garnier et al. SG involves the excision of the majority of the stomach on its greater curvature side, using a stapling device. In short, induction of pneumoperitoneum with the Verres needle and placement of five trocars as with the laparoscopic RYGB. Afterwards the resection line begins from approximately five cm proximal to the pylorus, proceeding to the angle of His to result in a tube or sleeve-shaped remnant stomach of approximately 25% its original capacity. A calibration 34-Fr bougie is used to standardize the sleeve size. Before closure, the stomach remnant will first be removed and the gastric tube will be tested for leakage.

5.2 Use of co-intervention

All patients included in the study will have a protein diet (Modifast or Weight care) two weeks prior the surgery, with a standard number of calories per day (approximately 600 calories). This very low-calorie diet is given in order to decrease liver volume and increase laparoscopic workspace. It is proven that this very low-calorie diet reduces the postoperative complication rate in patients who underwent a laparoscopic RYGB [41].

Based on the implemented standard care for adults after bariatric surgery the following restrictions during the trial will be valid.

Anti-thrombosis precautions

- Preoperatively, perioperative and postoperatively during the hospital stay patients are required to wear anti-embolism stockings (T.E.D.™).
- During hospital stay, patients will receive 5000 IU Fragmin subcutaneously daily, starting from the first day after surgery. After discharge from the hospital, patients are required to continue with injecting 5000 IU Fragmin subcutaneously daily for 28 days.

Medication

- Patients are required to take vitamins daily for the rest of their life. Because of the difference in tolerance between vitamins, we primary advice two vitamins; the vitamins of WLS vital or FitForMe (compass/forte for RYGB and believe/optimum for SG).
- Patients are required to take Calcichew-D3 1000 mg/800 IU ones daily for the rest of their life.
- Patients are required to take Pantoprazole 40mg daily for the first year after the bariatric surgery.
- Patients are advised not to use any non-steroidal anti-inflammatory drugs during their lifetime, because of higher risk for gastric ulcer formation.

General dietary restriction
After the bariatric procedures, strict dietary restrictions are required. Most of these restrictions will be communicated by the dietician and are adjusted to the person.
In general, during the first two weeks patients are required to comply with a liquid diet with biscuits (no other crackers or bread). A timeframe of at least thirty minutes between eating and drinking must be taken account of to reduce the risk of dumping and if patients feel satisfied they have to stop eating directly. The products have to be low fat products without added sugars as much as possible. Furthermore, patients are advised to drink 1.5 liters a day, to eat three meals and three snacks a day and are not allowed to drink carbonated drinks.

Dietary restrictions during hospital stay
Based on the protocol as implemented in adults undergoing bariatric surgery.

Day in hospital	Time	Diet
Day 0 (day of surgery)		After the surgery patients are allowed to drink a sip of water every hour
Day 1 (first postoperative day)	08.00 a.m.	Some sips of water
	10.00 a.m.	Cup of thee (no sugar)
	12.00 a.m.	100-150 cc of yoghurt
	13.00 p.m.	A choice of water, tea, coffee (no sugar), sugar free syrup, bright broth, crystal clear, semi-skimmed milk or buttermilk.
	17.00 p.m.	One biscuit with cream cheese spread low fat or pate.
	20.00 p.m.	A choice of water, tea, coffee (no sugar), sugar free syrup, bright broth, crystal clear, semi-skimmed milk or buttermilk.
Day 2 (second postoperative day) and 3 (day of discharge from hospital)	08.00 a.m.	One biscuit with cream cheese spread low fat or pate.
	10.00 a.m.	Cup of thee (no sugar)
	12.00 a.m.	100-150 cc of yoghurt
	13.00 p.m.	A choice of water, tea, coffee (no sugar), sugar free syrup, bright broth, crystal clear, semi-skimmed milk or buttermilk.
	17.00 p.m.	One biscuit with cream cheese spread low fat or pate
	20.00 p.m.	A choice of water, tea, coffee (no sugar), sugar free syrup, bright broth, crystal clear, semi-skimmed milk or buttermilk.

Table 6.2.1 – Co-medication

NIMP	Dosage	Treatment duration	Administration
Pantoprazole	40mg One tablet daily	First year post surgery	Oral
Calcichew-D3	1000 mg/800 IU One tablet daily	Lifelong	Oral
Multivitamin	One tablet daily	Lifelong	Oral

5.3 Escape medication

Not applicable.

6. INVESTIGATIONAL PRODUCT

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Proportion of patients achieving a 20% total body weight loss at three years follow-up.

8.1.2 Secondary study parameters/endpoints

(i) Change in BMI and bodyweight;
(ii) Incidence of adverse health events including the need for re-operation;
(iii) Resolution of co-morbidities, including OSA, T2DM, hypertension and hyperlipidemia;
(iv) Time to resolution of OSA, T2DM, hypertension and hyperlipidemia;
(v) Prevalence of cardio metabolic risk factor measures;
(vi) Routine post-bariatric surgery nutritional blood tests at each assessment, including: full blood count, electrolytes, creatinine, glucose, HbA1c, liver parameters and function tests, iron, ferritin, vitamin B12, thiamine, folate/red cell folate, lipid profile, 25-hydroxyvitamin D, calcium and parathyroid hormone;
(vii) Bone health measures;
(viii) Generic and obesity-specific health-related quality of life;
(ix) Psychosocial health measures and educational attainment;
(x) Patient satisfaction;
(xi) Body composition.

8.1.3 Study parameters

De following parameters will be collected during the whole study period:

Data	Parameter
Pre-operative	Medical history and use of medication Gender, race Age to closest month at time of surgery High school education / academic performance Smoking, use of alcohol Physical examination - Anthropometry; body height in meter (m), bodyweight in kilogram (kg), BMI, waist circumference - Signs of comorbidity (e.g. pulse rate, blood pressure, acanthosis nigricans) - Signs of syndromes - Tanner stage - Growth; evaluation of growth charts Psychological disorder - Quality of life analysis - Evaluation by a psychologist Food intake - Eating questionnaire (TFEQ) - Evaluation by a dietician Biochemical blood analysis (see detailed description in table 8.3.2.) 24-hour urine collection Dual-energy X-ray Absorptiometry (DEXA) scan
Intra-operative	Duration of surgery Duration of anesthesia Specified data per intervention - RYGB: length of biliopancreatic and alimentary limp, - SG: bougie size, start of transection of the great curvature Complications

	ASA-score
Direct postoperative	Length of hospital stay Postoperative pain (visual analog scale), measured every day during hospitalization <30-day complications (including number of re-interventions)
Long-term follow-up	Comorbidities and medication use, including cardio metabolic risk factor measures >30 days complications - E.g. internal herniation, extreme dumping, food intolerance - Re-interventions - Mortality - Serious Adverse Events Physical examination - Anthropometry; bodyweight (kg), body height (m), BMI, TBWL, waist circumference - Signs of comorbidity (e.g. pulse rate, blood pressure, acanthosis nigricans) - Growth; evaluation of growth charts Questionnaires - Quality of life - Psychological disorder - Food intake - General health Patient satisfaction - Scale from one to ten - Net promotor score High school education / academic performance Biochemical blood analysis (see detailed description in table 8.3.2.) 24-hour urine collection DEXA scan (two and five years follow-up)

8.2 Randomization, blinding and treatment allocation

8.2.1 Randomization

Randomization will be stratified according to hospital/centers in order to ensure balanced groups. This also creates stratification by country, taking account of known disparities in the prevalence and extremity of severe obesity between participating countries.
Randomization will be on a 1:1 basis, with equal allocation to RYGB and SG, using block sizes of 6-8 participants.

Randomization will be performed on the day of surgery after trial eligibility and informed consent to participate in the trial has been confirmed. Randomization will be performed by the surgeon, or an authorized local research team member, using a secure internet-based randomization system ensuring allocation concealment. An identical treatment strategy, appropriate to both procedures, will be employed for all patients, as outlined in section 5.1: Investigational product/treatment.

8.2.2 Blinding

Blinding in this study is possible and we see obvious advantages in terms of bias to apply blinding. Randomization will be on the day of the surgery. Patients and caregivers will be blinded to the procedure until the two-month follow-up visit, which gives us unbiased data regarding the 30-day complications. For safety reasons, patients will not be blinded more than two months as they and potentially emergency health care providers need to know the gastro-intestinal anatomy in case of SAEs as well as to determine the need for supplementation. The bariatric nurse or researcher

measuring, testing or sampling from patients will be blinded during at least the first two months postoperatively.
Standardized management, appropriate to both SG and RYGB, will be conducted during the blinded period and dietary advice and supplementation appropriate to both procedures will be administered to all patients.

8.2.3 Emergency unblinding

Within the first two months, the trial code will only be broken in exceptional circumstances when knowledge of the surgical technique is absolutely essential for the safety of the patient, for example, in case of a Serious Adverse Event (SAE). This is to maintain the overall quality of the trial.
If unblinding is required, the investigator or treating health care professional will make a formal request for this unblinding. The Principal Investigator (PI) will use a help line system for unblinding and will contact the holder of the code break list as a back-up. The chief investigator, PI or coordinating investigator will notify the Sponsor in writing as soon as possible following the code break including the reason(s) for the code break. All emergency unblinding will be reported, including the reason(s).

8.3 Study procedures

Follow-up visits
For a detailed schedule of the follow-up visits and the tests that will be performed during the follow-visits see Table 8.3.1. The bariatric surgeon and the pediatrician will meet the patient together at all follow-up visits over the first ten cases. In this way, pediatricians will get a feeling for the 'normal course' following surgery. After these first ten patients, the bariatric surgeon will meet the patient at two months and at one year postoperatively. The pediatrician will meet the patient at all the other follow-up moments, according to Table 8.3.1. The follow-up schedule is based on the follow-up for adult patients after bariatric surgery.

Table 8.3.1. – Study visits and schedule of assessments

Study Visit	Consent	Anthro-pometry	Blood and urine sample	DEXA -scan	Questionnaires	Visit window
Initial meeting	☐					N/A
Baseline	☐	☐	☐	☐	☐	N/A
2 months	☐	☐				+/- 4 weeks
6 months	☐	☐	☐			+/- 6 weeks
12 months	☐	☐	☐		☐	+/- 2 months
18 months	☐	☐				+/- 3 months
24 months	☐	☐	☐	☐		+/- 3 months
36 months	☐	☐	☐		☐	+/- 3 months
48 months	☐	☐	☐			+/- 3 months
60 months	☐	☐	☐	☐	☐	+/- 3 months

Assessment of anthropometrics

At the preoperative visit, the day of surgery and all follow-up moments (according to Table 8.3.1) participant's weight will be measured in kg on electronic clinic scales, participants balanced on both feet with their arms loosely hanging at their sites. Participants will be fully clothed, but shoes and jackets will be removed.
During the same visits, participant's height will be measured in cm with a stadiometer (after removal of the shoes) and participant's waist circumference (cm) will be measured according to the standard procedure.
TBWL is calculated using the following formula; TWBL (%) = (nadir weight (kg) - current weight (kg)) / nadir weight (kg) * 100%. For this study, a TBWL of 20% at three years is defined as successful weight loss.
BMI is calculated using the following formula: BMI (kg/m^2) = body weight (kg) / (length (m) * length (m)).

Assessment of comorbidities
During every visit (preoperatively and during follow-up) participants will be asked about their medication use and other treatments regarding the obesity related comorbidities.

Impaired glucose tolerance and type II diabetes
At set visits, blood samples regarding fasting blood glucose level, fasting insulin and HbA1c will be taken. HOMA-IR (homeostatic model assessment to quantify insulin resistance) will be determined. Impaired glucose tolerance is defined as a non-fasting glucose of 7.8 – 11.1 mmol/L measured by an oral glucose tolerance test after two hours [42].
T2DM is defined as the use of blood glucose lowering medication or insulin or a fasting (no caloric intake for at least eight hours) blood glucose > 7.0 mmol/l (twice at two different days) or a two-hour blood glucose >11.1 mmol/L in an oral glucose tolerance test [42]. If participants use metformin for weight management without a prior diagnosis of T2DM and no laboratory findings consistent with the diagnosis of T2DM, the participants are not considered to have T2DM.
Remission is defined as a HbA1c <6.5% in the absence of medication use or a fasting serum glucose in normal range in the absence of medication use [42].

Hypertension
During every follow-up visit, the blood pressure will be measured using an aneroid sphygmomanometer.
Hypertension is defined as the use of blood pressure lowering medication or a systolic blood pressure (SBP) or a diastolic blood pressure (DBP) during a 24 hours measurement ≥ 95th percentile (for age, height and sex) based on the reference values by Wühl et al if under eighteen years of age; or a systolic blood pressure > 140 mmHg or a DBP > 90 mmHg if ≥ eighteen years of age [43].
Remission of hypertension is defined as a normal SBP and DPB for age in the absence of blood pressure lowering medication.

Dyslipidemia
At most follow-up visits serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides will be determined.
Dyslipidemia is defined as the use of lipid lowering medication or total cholesterol >5.2 mmol/L or HDL cholesterol < 1.03 mmol/L or LDL cholesterol >3.4 mmol/L or triglycerides >1.46 mmol/L [44].
Remission is defined as total cholesterol <5.2 mmol/L, HDL cholesterol > 1.03 mmol/L, LDL cholesterol <3.4 mmol/L and triglycerides <1.46 mmol/L in the absence of any lipid lowering medication [44].

Kidney function
At most follow-up visits the glomerular filtration rate (GFR) will be determined and a urine sample will be taken to excess the presence of albuminuria. The GFR is calculated using the following formula; (eGFR; ml/min/1.73m2) = 36,5 x height (cm) / plasma creatinine (µmol/L). An abnormal kidney function will be based on the stages of chronic kidney disease (CKD) according to the K/DOQI CKD classification [45]. Microalbuminuria was defined as a urine albumin to creatinine ratio > 0.03 [45]. Stage 1 is defined as a GFR ≥ 90 ml/min/1.7 with microalbuminuria. Stage 2 is defined

as a GRF of 60-89 ml/min/1.7 with microalbuminuria. Stage 3 is defined as a GFR of 30-59 ml/min/1.7, stage 4 is defined as a GFR of 15-29 ml/min/1.7 and stage 5 of CKD is defined as a GFR < 15 ml/min/1.7 [45].
Remission of abnormal kidney function is defined as attaining a GFR > 60 ml/min/1.7 in the absence of micro and macro albuminuria [45].

Obstructive Sleep Apnea
Based on the Epworth Sleepiness scale, participants will be referred to the pulmonologist for a sleep study, a polysomnography, which is the gold standard for the diagnosis of sleep apnea.
Sleep apnea is defined based on the Apnea–Hypopnea Index (AHI) [46].
- Mild sleep apnea: AHI > 1
- Moderate sleep apnea: AHI > 5
- Severe sleep apnea: AHI > 10

Remission of obstructive sleep apnea will be based on another sleeping study with an AHI ≤1 [46].

Blood sampling
Fasting blood sampling will be performed during the visits as stated in Table 8.3.1, for metabolic risk markers and organ damage. Table 8.3.2 lists the blood parameters to be determined at each follow-up visit. The frequency of the blood sampling is based on the standard care for adults receiving bariatric surgery and the parameters are conform the blood sampling during the lifestyle management programs in the expertise centers (standard care).
In addition, a 20ml blood sample will be taken at baseline and at one, three and five years post-surgery. Buffy coat specimens will be frozen for future DNA isolation and stored in Maastricht university hospital at -80 degrees Celsius. This test is part of the standard screening of the child obesity expertise center. Sample logs will be kept at Maastricht university Hospital and copies of these sample logs will be kept as a complete log in the principal site within The Netherlands. All samples will be used, stored and disposed of in accordance with the Human Tissue Act 2004.

Table 8.3.2 – Blood sampling

Clinical visit	Test
Preoperatively	Hematology - Hemoglobin (Hb), hematocrit (Ht), mean cell volume (MCV), white cell count, red cell count, thrombocytes, leukocytes, leukocytes differentiation. Chemistry - Sodium, potassium, creatinine, urea, uric acid; - Alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), bilirubin; - Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, free fatty acids. Protein - C-reactive protein (CRP), albumin, ferritin, transferrin Carbohydrate metabolism - Fasting glucose, HbA1c, fasting insulin Hormones - Thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), free thyroxine (fT4), luteinizing hormone (LH), Follicle-Stimulating hormone (FSH), prolactin, sex hormone binding globulin (SHBG), testosterone, androstenedione, cortisol, insulin-like growth factor-1 (IGF-1) Vitamins - Folic acid, vitamin B1-B6-B12 and 25-hydroxyvitamin D Spare serum/plasma
Two months	Only if indicated
Six months	Hematology - Hb, Ht, MCV, white cell count, red cell count, thrombocytes, leukocytes, leukocytes differentiation. Chemistry

	- Sodium, potassium, creatinine, urea, uric acid; - ALP, GGT, AST, ALT, bilirubin; - Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, free fatty acids. Protein - CRP, albumin, ferritin, transferrin Carbohydrate metabolism - Fasting glucose, HbA1c, fasting insulin Hormones - TSH, PTH, fT4, LH, FSH, prolactin, SHBG, testosterone, androstenedione, cortisol, IGF-1 Vitamins - Folic acid, vitamin B1-B6-B12 and 25-hydroxyvitamin D Spare serum/plasma Additional tests as indicated clinically
Twelve months	Hematology - Hb, Ht, MCV, white cell count, red cell count, thrombocytes, leukocytes, leukocytes differentiation. Chemistry - Sodium, potassium, creatinine, urea, uric acid; - ALP, GGT, AST, ALT, bilirubin; - Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, free fatty acids. Protein - CRP, albumin, ferritin, transferrin Carbohydrate metabolism - Fasting glucose, HbA1c, fasting insulin Hormones - TSH, PTH, fT4, LH, FSH, prolactin, SHBG, testosterone, androstenedione, cortisol, IGF-1 Vitamins - Folic acid, vitamin B1-B6-B12 and 25-hydroxyvitamin D Spare serum/plasma Additional tests as indicated clinically
Eighteen months	Only if indicated
24 months and then yearly	Hematology - Hb, Ht, MCV, white cell count, red cell count, thrombocytes, leukocytes, leukocytes differentiation. Chemistry - Sodium, potassium, creatinine, urea, uric acid; - ALP, GGT, AST, ALT, bilirubin; - Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, free fatty acids. Protein - CRP, albumin, ferritin, transferrin Carbohydrate metabolism - Fasting glucose, HbA1c, fasting insulin Hormones - TSH, PTH, fT4, LH, FSH, prolactin, SHBG, testosterone, androstenedione, cortisol, IGF-1 Vitamins - Folic acid, vitamin B1-B6-B12 and 25-hydroxyvitamin D Spare serum/plasma Additional tests as indicated clinically

Urine sample
A spot urine sample will be collected. The urine will be tested on the following parameters: micro-albuminuria, glucose, ketones, uric acid and creatinine. Information about the kidney function and about the presence of T2DM will be obtained. This is also according to the standard screening of the child obesity expertise centers. There are no additional tests for this study.

DEXA-scan – assessment of bone health
Preoperatively, at two and at five years postoperatively patients will receive a whole body DEXA-scan to measure bone mineral density. Scores will be interpreted following the Z- and T-scores for adolescents and adults in Maastricht University Medical Hospital, as appropriate according to age at follow-up.
It is known that ionizing radiation causes more damage in children. As a result of the fast development, especially in young children, many cells are in mitoses. Those cells are prone to changes in DNA by the ionizing radiation.
The dose of ionizing radiation for a whole body DEXA-scan is very low, even for children and adolescents. The average global background dose of ionizing radiation is 2.4 mSv (milliSieverts). The effective doses for a whole body DEXA-scan is less than 0.01 mSv in 5- and 10-year-old children and even lower in adolescents and adults. This is approximately 0.4% of the average worldwide annual dose of background radiation, or the equivalent of 1.5 days of additional background radiation. The effective dose of 0.01 mSv equates to 50% of the radiation dose associated with a plain film chest radiograph, and just 0.125% of the dose of a plain film abdominal radiograph [47].
So, the amount of ionizing radiation due to the DEXA-scan is very low. Next to this, these adolescents will all be pubertal advanced according to their Tanner stage, which will characterize them as similar to adults developmentally. For these reasons, the risk of ionizing radiation damage after DEXA scanning in the adolescents will be very low.

Assessment of quality of life and health and other questionnaires
Participants will have to fill out the following questionnaires specific for this study at baseline and at one, three and five years post-surgery (table 8.3.1.): RAND-36, Impact of Weight on Quality of Life Lite (IWQOL-Lite), Beck depression Inventory, Back Anxiety Inventory, Three-Factor Eating Questionnaire (TFEQ) and the Epworth Sleepiness Scale. All these questionnaires are validated.
Patient satisfaction will be scored by using a single question satisfaction survey where patients will score using a scale from one to ten. In addition, a net promotor score, what is the probability that you will advise friends and family in the same situation to undergo this surgery, will be obtained [48].
Furthermore, patients have to fill out questionnaires as part of the treatment in the lifestyle intervention programs of the child obesity expertise centers (see section 8.4), including kidscreen-27 (regarding quality of life), AVL-Z (regarding attention deficit hyperactivity disorder) and Pediatric Quality of Life Inventory (PedsQL).
We intend to make these questionnaires available through an application (app) that we aim to develop for this study.
Reasons for not completing the questionnaires will be recorded. Handling/scoring of the questionnaire will be according to the manuals from the questionnaire developers.

Body composition
Body composition will be measured by using a bioelectric impedance analysis. With this technique, the impedance of the body is measured by using a small electric current. Electrodes will be placed on the wrist and ankle [49]. By controlling for changes in body composition, effects on growth by the bariatric surgery can be addressed. This is a standard test performed in the lifestyle management programs and thus is not additional for this study.

8.4 Procedures child obesity expertise centers

In this section, we describe, in short, the standard care regarding the psychological, dietary and physical assessment of the lifestyle intervention programs in the child obesity expertise centers. Data regarding these assessments that will be collected for TEEN-BEST are described in section

8.3 Study procedures. Data that are not mentioned in section 8.3, but are part of the assessments described below, will thus not be collected for TEEN-BEST.

8.4.1 Psychological assessment

In the child obesity expertise centers pediatric clinical psychologists and psychotherapists are involved in the psychological assessment and treatment of all children and adolescents in the lifestyle intervention program. They are all part of the multidisciplinary team for the treatment of the obese children and adolescents.

The psychological assessment of the adolescents in the lifestyle intervention program is based on several questionnaires and one or more interviews.

The questionnaires include, among others, questions regarding quality of life, psychologic disorders or problems, competences, physical activity and eating disorders. The questionnaires have to be filled out by the adolescents and some questionnaires are specific for the parents of the adolescent. The following questionnaires have to be filled out by either the adolescent or his/her parents:

- Kidscreen-27 for children aged eight to eighteen years old
- Kidscreen-27 for parents
- PedsQl for children aged thirteen to eighteen years old
- PedsQl for parents of children aged thirteen to eighteen years old
- Strengths and Difficulties Questionnaire (SDQ) for children
- SDQ for parents
- Children's Depression Inventory (CDI)
- AVL-Z questionnaire for children (for attention deficit hyperactivity disorder)
- AVL-Z questionnaire for parents
- Competence Experience scale for adolescents (in Dutch: Competentie Belevingsschaal voor Adolescenten).
- Three-factor Eating Questionnaire (TFEQ)
- Eating Disorder Examination Questionnaire (EDE-Q)
- Behavioural Regulation in Exercise Questionnaire (BREQ)

All the above questionnaires are of course validated for the use in adolescents, children, parents and teachers.

During the interview, clinical relevant outcomes of the above described questionnaires will be discussed through further assessment of the problem. The clinical psychologist will diagnose any active psychological disorder and will decide whether treatment of the adolescent is necessary. This treatment will take place in a mental healthcare facility (in Dutch; geestelijke gezondheidzorg – GGZ) outside of the lifestyle intervention program. In case there is any doubt about a possible active psychological disorder, more interviews will take place between the adolescent, the family and the clinical psychologist.
In the interview, the clinical physiologist will also assess the social system of the adolescent. The family will be actively involved and questioned about their way of living, caring, relationships, etc. In case there are active problems in the social system of the adolescents which is an indication for treatment, de adolescent and her/his family will be referred for family system therapy.

If treatment of a psychological disorder or a social system problem is necessary, the lifestyle intervention program has not been optimal and the adolescent might achieve success with this treatment in optimal form (after treatment of the psychological and/or social system problem(s)). So, the patient will continue with the lifestyle management program after successful treatment. If after twelve months no success is achieved by the adolescent, the adolescent will be discussed in the multidisciplinary meeting for eligibility for the TEEN-BEST study.

The clinical psychologist is part of the multidisciplinary team and is also a member in the multidisciplinary meeting to discuss the adolescent that is not successful in the lifestyle intervention program. The clinical psychologist will discuss in the multidisciplinary team if there is a contraindication for surgery, based on an active psychological disorder or a problem in the social

system. The assessment of whether the patient will comply with follow-up after the surgery and whether the lifestyle intervention program will be continued are essential.

8.4.2 Dietary assessment

The dietician is also part of the multidisciplinary team and is a member in the multidisciplinary meeting to decide whether the adolescent is eligible or not for TEEN-BEST.

De dietician will assess the dietary pattern of the adolescent by using several questionnaires, a food diary and an interview. The dietician uses the following questionnaires:
- Food Frequency questionnaire
- TFEQ
- EDE-Q

During the lifestyle intervention program, the dietician will teach the adolescent and the social system about all the aspects of a normal dietary intake.

8.4.3 Physical assessment

The psychical activity is assessed by the pediatrician and/or nurse by using two questionnaires and an interview. The following questionnaires for physical activity are used:
- Behavioural Regulation in Exercise Questionnaire (BREQ)
- BAECKE questionnaire (adjusted for adolescents)

During the interview, the adolescent will be questioned about the motivation and commitment for physical activity and about the physical activity program he/she followed. The adolescent is not required to have participated in a physical activity program with a physical therapist. There are many programs that stimulate physical activity without a physical therapist, like real fit and slim kids.

If there is an indication for the help of a physical therapist the pediatrician will consult the physical therapist to treat the adolescent. At that moment, the psychical therapist will become part of the multidisciplinary team and will also be a member of the multidisciplinary meeting to decide if the adolescent is eligible for TEEN-BEST or not.

In case the adolescent hasn't followed a physical activity program the adolescent will not be eligible for TEEN-BEST.

8.5 Withdrawal of individual subjects

The right of a participant to refuse participation without giving reasons will be respected throughout. The participant will be provided with a contact point where he/she may obtain further information about the trial. The participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment. The PI will be responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.
In addition, the investigator may also withdraw a participant. This might be because of a (urgent) medical reason, subsequent to randomization, if the allocated surgical intervention is not performed. This will be documented in the main data sheet.

Data and samples collected up to the point of withdrawal will be used for analysis, unless the participant expresses a wish for removal of the data. No data will be collected after withdrawal.

Taking the primary objective and one of the main secondary objectives into account, participants who withdraw will be asked if they can be contacted for an assessment of weight and possibly IWQOL-Lite three and five years after the surgery.

8.5.1 Specific criteria for withdrawal

There are no specific criteria for withdrawal defined.

8.6 Replacement of individual subjects after withdrawal

Patients will not be replaced after withdrawal. In the power analysis we allowed a 15% dropout rate. If the withdrawal rate exceeds this number we will add more participant to the trial, exceeding the initial 264 participants.

8.7 Follow-up of subjects withdrawn from treatment

The follow-up of patients that withdrawn from the study will continue according to the implemented standard care for adults who underwent bariatric surgery. This actually means that the follow-up just continues according to the follow-up schedule of the study, because the follow-up in the study is according to the standard care for adults.

8.8 Premature termination of the study

The Data Monitoring and Safety Committee will perform interim analyses and can decide to end the study prematurely. No specific criteria are defined for premature termination of the study.

9. SAFETY REPORTING

9.1 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 jeopardize subject health or safety. The sponsor will notify the accredited Research Ethics Committee (REC) 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 REC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 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 investigational product / trial procedure/ the experimental intervention. Only AEs, related to the bariatric surgery, reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 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 inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- any other important medical event that did not result in any of the above listed outcomes due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator. Other 'important medical events' may also be considered serious if they jeopardize the participant or require an intervention to prevent one of the above consequences.

An elective hospital admission is not considered a SAE.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 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.

9.5 Reporting of AEs and SAEs

SAEs and laboratory abnormalities that are critical to the safety evaluation of the participant need to be reported directly (within 24 hours) to the main coordinating investigator by the local coordinating investigator from each participating site, when first knowledge of the event is obtained. Postoperative complications associated with surgery in general, e.g. wound infection, bleeding/hematoma, pneumonia and urinary tract infection will be recorded in the medical health record of the participant but are only reported to the main coordinating investigator every six months. For clarification, these general postoperative complications are complications without a major impact on the patients. Thus, if a patient has a bleeding leading to a re-intervention, a major impact, this has to be reported directly (within 24 hours).

All the AEs and SAEs, occurring from the time point of informed consent until the end of the study (as defined in the protocol), will be recorded and reported to the sponsor by the main coordinating investigator in accordance with the International Conference for Harmonization of Good Clinical Practice guidelines and the Sponsor's Research Related Adverse Event Reporting Policy. If a participant is a non-responder, a drop-out, or withdraws consent for further processing of data, AEs and SAEs will still be reported. This will be stated in the Participant Information Sheet (PIS).

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited REC that approved the protocol. For SAEs that result in death or are life threatening, the sponsor must report these within seven days after first knowledge of the event was obtained. This will be followed by a period of maximum eight days to complete the initial preliminary report. All other SAEs must be reported within a period of maximum fifteen days.

For each AE and SAE, the following information will be collected:
- full details in medical terms and case description;
- event duration (start and end dates);
- action taken;
- outcome;
- seriousness criteria;
- causality in the opinion of the investigator;
- whether the event would be considered anticipated.

9.6 Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the data periodically regarding the safety and efficacy of the trial procedures and advise the sponsor on the future management of the trial. They will review any expected adverse event and may ask to review outcomes or other data that may have an impact on the trial. The will perform interim analyses and can decide to end the study prematurely. The DSMC will send their advice to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMC, the sponsor will send the advice to the reviewing REC, including a note to substantiate why (part of) the advice of the DSMC will not be followed.
Independence is a key characteristic of this committee, where the committee members are completely uninvolved in the running of the trial and the committee members cannot be unfairly influenced by people or institutions involved in the trial.
The members of the DSMC will reflect the disciplines specialties necessary to interpret the data from the trial. This committee exists of an epidemiologist/statistician, a surgeon, a pediatrician and a bariatric surgeon with experience in bariatric surgery in adolescents.

10. STATISTICAL ANALYSIS

The primary analyses will be based on intention to treat and will include all randomized patients. In addition, a per protocol analysis will be performed to explore the influence of protocol deviations and compare the results with the primary analysis. Furthermore, to explore the influence of contamination (switching between study arms) we will perform an as treated analysis, of which the results will be compared with the results of the primary analysis.

Descriptive statistics
Continuous variables, in case of a symmetrical distribution, will be stated as mean with standard deviation and an independent-sample T test (student's T-test) will be performed to calculate the statistical significance. In case of a skewed distribution a Mann-Whitney U test will be performed and the variables will be stated using the median. Categorical variables will be stated as number or percentage and a chi-square test will be performed to calculate the statistical significance.
A p value less than 0.05 will be considered statistically significant. The statistical analysis will be performed using SPSS version 22 for Windows (SPSS, Inc).

Handling of missing values and dropouts
Missing data will be excluded and will not be imputed. To address possible bias of the missing values, the baseline characteristics of patients with and without missing values will be compared. We will do our utmost to collect outcome measures wherever possible to minimize the number of missing values. This means we will also accept patient reported weight in case of missing weight data. In addition, we will retrieve the reason for the missing value to check for informed missing, such as missing because of weight gain.

10.1 Primary study parameter

The proportion of patients achieving at least 20% TBWL at three years will be compared using descriptive statistics and a logistic regression analysis.

10.2 Secondary study parameters

Quality of life questionnaire scores (and other continuous outcomes measured at multiple time points) will be compared using a mixed regression model with baseline and post-surgery measures modeled jointly. Changes in treatment effect with time will be assessed by adding a treatment by time interaction to the model and comparing models using a likelihood ratio test. Time to event outcomes will be compared using survival methods for interval censored data. Frequencies of adverse events will be described. Treatment differences will be reported with 95% confidence intervals (CIs). A detailed analysis plan will be prepared during the feasibility phase 1.

10.3 Other study parameters

Not applicable.

10.4 Interim analysis

Interim analyses will be decided in discussion with the DMSC. There is no intention to compare any outcomes between groups at the end of phase 1; the only analyses will be descriptive statistics to summarize recruitment to decide whether the trial satisfies the progression criteria.

10.5 Subgroup analysis

One subgroup analysis is planned; outcomes will be described for male and female participants. Differences in treatment effect between the two subgroups will be tested by including interaction terms to the analysis model. This is a secondary analysis as the study is not powered to detect subgroup differences.

10.6 Planned recruitment rate

Recruitment is planned to commence in March 2018 and is projected to complete within three years. The rate of recruitment is projected to rise from one participant per country per month, during

the months one to six, to seven participants per country per month during months 30 to 36 (See figure 10.2).

Figure 10.4.1 – Projected recruitment

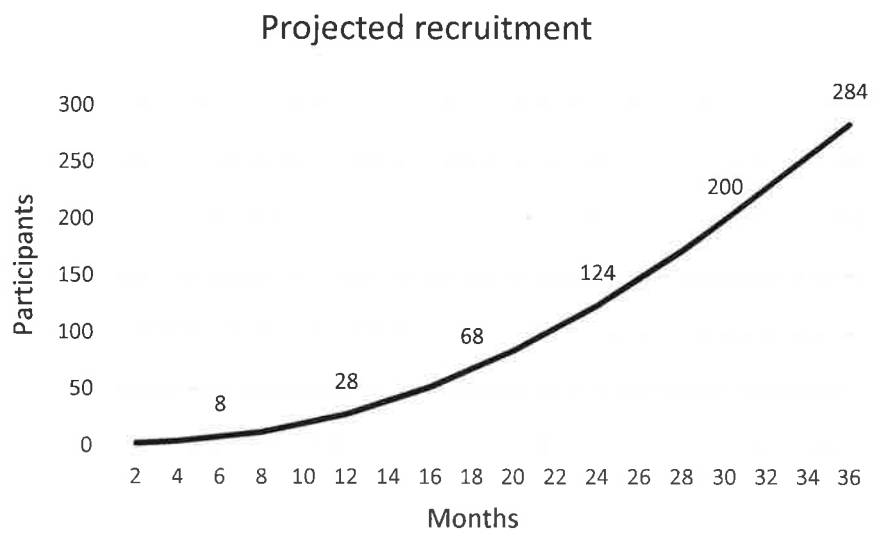


Table 10.4.2 – Projected recruitment

Month	Participants per month	Total
2	0.5	2
4	0.5	4
6	1	8
8	1	12
10	2	20
12	2	28
14	3	40
16	3	52
18	4	68
20	4	84
22	5	104
24	5	124
26	6	148
28	6	172
30	7	200
32	7	228
34	7	256
36	7	284

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).
The trial will not commence until a favorable REC opinion is obtained. Before any site can enroll patients into the study, the chief investigator will ensure that appropriate approvals from participating sites are in place. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

11.2 Recruitment and consent

The PI retains overall responsibility for the conduct of research at his site, including obtaining informed consent of participants at his site. The PI will ensure that any person delegated responsibility to participate in the informed consent process is authorized, trained and competent to participate according to the ethically approved protocol, the principles of Good Clinical Practice (GCP), the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and in accordance with all the laws and regulations regarding medical research involving human subjects. If delegation of consent is acceptable then details should be provided. The PI will be responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

All patients eligible for this study will be informed by their pediatrician about the trial. All patients will receive a written information leaflet and informed consent document, which are approved by the ethical committee and are in compliance with GCP. In case the adolescent is interested in participating in this trial, the pediatrician will ask the adolescent if the coordinating researcher is allowed to contact the adolescent for more information about the trial and the informed consent. If the adolescent agrees, the pediatrician will make a note in the electronic patient file and will inform the coordinating researching about the adolescent.
Informed consent will be obtained prior to the participant undergoing any procedure that is specifically performed for the purposes of the trial at the participating site, including the collection of identifiable participant data. This informed consent conversation will be performed with the coordinating researcher after the patients received the first information about the trial by their pediatrician. Patients will be given one week to consider their decision before entering this study.

As mentioned above, the right of a participant to refuse participation without giving reasons will be respected and the participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment.

The participant will be provided with a contact point where he/she may obtain further information about the trial. PISs will be provided in a format easily understood by the young participant population and their adult caregivers alike. Independent telephone or verbal translation services will be made available when required.

11.3 Objection by minors or incapacitated subjects

Objection by minors (which will be all of our patients) will be handled according to the guideline of the Dutch central commission of human research (CCMO) (see appendix A).

11.4 Benefits and risks assessment, group relatedness

Risk of participation
Every surgery has his risks, i.e. complications. Complications associated with a surgery in general include, for example, pneumonia, thrombosis, wound infection, bleeding and incisional hernia. Complications specifically associated with the bariatric procedures include anastomotic leak, internal herniation, gall stone formation, gastric ulcer, reflux, transient hair loss, deficiencies of several vitamins and minerals, dyspepsia, dumping syndrome and food intolerance. Furthermore,

distension of the gastric pouch can occur, which might lead to weight regain in the long term. Depending on the complication, additional intervention might be necessary.
Specific for patients that consent for a liver biopsy; this can potentially lead to a bleeding and/or liver hematoma at the place where the biopsy is taken. However, the biopsy will be taken under direct visualization of the liver using the laparoscope which reduces the risk of puncturing any other structures and if there is a bleeding, electrocoagulation can by performed directly. Furthermore, previous research has shown that these complications are very rare [32].

Burden of participation
Patients who will be included in this study will have to attend nine follow-up visits in total (based on the protocol for adults after bariatric surgery). In the first year after surgery there will be four follow-up visits; two months, six months and twelve months post-surgery. After the first year, patients need to attend the follow-up visit at eighteen months and at two, three, four and five years postoperatively.
Blood samples will be taken at baseline and at six and twelve months after surgery and thereafter yearly.
Included patients will be asked to fill out multiple questionnaires. This will be asked at baseline and at one, two, three and five years postoperatively. These questionnaires will be available through an application (app) that will be designed for this study. Patients will be able to fill out these questionnaires at a time convenient to them, prior to the control visit. The time estimated to fill out these questionnaires is approximately ten minutes per questionnaire.
Receiving a bariatric intervention requires some life changing adjustments from the patients. Firstly, they are required to take a multivitamin supplement daily for the rest of their life. Second, they have to alter their eating behavior for the rest of their life; they will be unable to consume as much per sitting and in total as they could before the surgery, will need to eat more frequently, eating will take more time, and eating and drinking together will be less feasible. In order to learn this new way of eating they will be assisted actively by a dietician.
Regarding female patients, pregnancy is discouraged the first year after bariatric surgery. In the first year after the surgery patients lose a lot of weight and can develop mineral and vitamin deficiencies. Both of these factors can have a negative impact on the developing fetus, which is why pregnancy is discouraged.

Benefits of participation
Patients will receive a bariatric intervention after unsuccessful multimodal lifestyle treatment. This means that there is actually a therapeutic treatment option for this group of untreatable adolescents. They are expected to be successful in losing weight, regardless of procedure allocation, and might experience remission of their comorbidities. Furthermore, other positive effects on their life can occur, such as improvement of quality of life, improved of school performance and better social contact, as was reported in other trials [7,15].

11.5 Compensation for injury

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

The sponsor 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.

11.6 Incentives

No incentives will be provided to participant of the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All data will be handled confidentially, anonymously and in accordance with the international accepted Personal Data Protection Act. Data will be inserted into a computerized database, Research Manager Software, by local investigators. Registration will be monitored and is in line with GCP guidelines.
After randomization participant will be assigned a study number and a subject identification list will be drafted. This list will be password protected. The subject identification list and the password will be administered by the coordinating and principal investigator.

Access to Data
Access to the data will be limited to the research team (local investigators, coordinating investigator and PI), Inspection for Healthcare/audits, monitors and auditors in line with participant consent.
In case the app will be developed, the organization providing the app will handle the data confidentially and anonymity. The developer of the app will be required to sign a Data Processing Agreement.

Archiving
Archiving of the trial documentation will be authorized by the sponsor following submission of the end of trial report. Data and samples from this study will be stored for a period of fifteen years after completion of the trial. Destruction of essential documents will require authorization from the sponsor.

12.2 Monitoring and Quality Assurance

The Clinical Trial Center Maastricht (CTCM) will perform the external monitoring audit of this study. The monitoring will be done in the first year and at the end of the study in all the participating centers through exploring the trial dataset and/or performing a site visit. Between the first year and the end of the study, the monitoring will be conducted using a risk-based approach that focuses on sites that have for example the highest enrolment rates, largest numbers of withdrawals and/or the highest numbers of reported AEs or SAEs. Specific attention will be payed to SAE's, informed consent, data monitoring and completeness of case record form.
Prior the start of this study the monitoring plan will be developed and agreed by the PI and the DSMC.

12.3 Amendments

The chief investigator/PI will be responsible for deciding whether an amendment is substantial or non-substantial. A 'substantial amendment' is defined as an amendment to the terms of the REC application, to the protocol or any other supporting documentation, that is likely to affect to a significant degree:
- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial;
- the quality or safety of any intervention used in the trial.

The accredited REC will be informed of all substantial amendments. They will be responsible for approval of the amendment prior to implementation in the protocol. Non-substantial amendments will not be notified to the accredited REC but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited REC 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.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited REC of the end of the study within a period of eight weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the REC 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 REC within fifteen 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, to the accredited REC.

12.6 Public disclosure and publication policy

This protocol will be registered at the NTR register and published. Research data can only be presented and/or published in agreement with the PI. The research data will be reported following the Consolidated Standards of Reporting Trials guidelines.

13. STRUCTURED RISK ANALYSIS

Not applicable.

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15. APPENDICIES

15.1 Appendix A – Codes of Conduct Minors

Code of conduct relating to expressions of objection by minors participating in medical research

Netherlands Association for Paediatric Medicine

Introduction

The *Medical Research Involving Human Subjects Act* (WMO) came into force on 1 December 1999. Medical research involving human subjects — both healthy subjects and patients — is permitted in the Netherlands only with the approval of an accredited medical ethics review committee. The approval of such a committee depends upon the research meeting certain criteria set out in the act. The WMO pays particular attention to research involving subjects who are not themselves competent to consent to participation: incapacitated adults and minors. With regard to research involving incapacitated subjects or otherwise dependent, such as minors, the act imposes a prohibition with exceptions. The Central Committee on Research Involving Human Subjects (CCMO) is responsible for reviewing protocols for certain forms of research with minors and incapacitated adults. Non-therapeutic medical research (i.e. research in which participation brings no direct benefit to the patient or healthy subject) is permissible only if the risks associated with participation are negligible and the burden is minimal. Furthermore, approval will be forthcoming only for research that cannot be carried out without the participation of people of the category to which the proposed subjects belong (section 4, subsection 1, of the WMO).

If in the context of such research a (prospective) subject objects to a procedure or to behaving in a particular way, that subject's participation in the research must be discontinued (section 4, subsection 2, of the WMO). During parliamentary consideration of the bill enacting the WMO, questions were raised regarding the implications of section 4, subsection 2. What in practice should be deemed to constitute objection and how should an investigator respond to possible expressions of objection? In response to these questions, the Minister of Health, Welfare and Sports (VWS) promised the House that a code of conduct covering such issues would be developed in consultation with the relevant professional associations.

The Netherlands Association for Paediatric Medicine (NVK) has accordingly drawn up the following code of conduct for use in the context of medical research with minors.

Code of conduct

1 Individual children respond differently to diagnostic and treatment procedures and to participation in medical research. Various factors help to determine the nature of the response: the way the child is prepared for what is going to happen, the parent-child relationship, the doctor-patient relationship, the child-friendliness of the environment in which the procedure takes place and so on.
One child will not be unduly disturbed by having an injection (even if he or she winces or makes some other display of pain), while another will find the experience distressing. Although responses vary considerably from child to child, there is a general correlation between the degree of 'invasiveness' of a procedure and the strength of the response. In some cases, fear regarding participation or a particular procedure will prompt a child to object. Patient and understanding explanation and reassurance will generally be sufficient to enable the research or the procedure to proceed without problems. Where a newborn child or infant is concerned, it is much harder to ascertain whether objection has been expressed. As a general rule, however, it is reasonable to suggest that a child may be deemed to object if its behaviour clearly differs in nature or degree from that normally displayed by the child when confronted with situations not encountered in everyday life. In this context, situations not encountered in everyday life may be considered to include diagnostic or therapeutic procedures.

2 Before seeking consent for a child's participation in medical research, an investigator must fully inform the child's custodial parent(s) or guardian about what is proposed. Information should be provided orally and in writing. The nature of the procedures involved in the research should be discussed with the parents and their views sought on the child's likely response. The possibility of the child objecting to participation and the type of behaviour that should be regarded as an expression of objection should also be discussed. The investigator should also explain what is to happen in the event of the child objecting. The consent obtained from the parents should include agreement to the proposed procedure for dealing with expressions of objection by the child.

3 The consent statement signed by parents should stipulate that, if the child should object to participation in the research, consent for its further participation will be invalidated.

4 If prior to the research there is doubt as to whether a child should participate, consideration may be given to involving the patient in the research for an agreed pilot period.

5 While the research is in progress, the behaviour of the child should be continually assessed at the research location to determine whether the child's behaviour is within the bounds normally associated with the child when confronted with situations not encountered in everyday life. If a child's behaviour is not within these bounds, he or she should be deemed to have expressed an objection in the sense of the WMO.

6 The parents, the investigator(s) and possibly a behavioural scientist should be involved in assessment of a child subject's behaviour. Assessment of a child subject's behaviour should not be a one-off exercise but should continue through all phases of the research.

7 The parents of a child subject should be able to withdraw their consent at any point during the research. If a child subject expresses an objection, the child's participation should be discontinued.

8 In all medical research involving child subjects, the burden associated with participation should be minimised; where non-therapeutic research is concerned, the law stipulates that it must be negligible. Medical studies often involve the combination of research procedures with diagnostic procedures necessary in connection with the subject's treatment. Where research involves an invasive procedure, such as a finger prick or venapunction, this should if possible be combined with a procedure necessary for diagnostic or treatment purposes, such as blood sampling. If possible, a needle or line that has already been inserted should be utilised, so that the number of 'jabs' is kept to the minimum. The burden can also be reduced by the use of plasters with local anaesthetic. The various steps to be taken with a view to minimising the burden should be detailed in the research protocol and in the information given to the parents and subjects.

9 The following should be noted in the research file or the medical (status) report, as appropriate:

a the outcome of any trial participation;

b the consent of the custodial parent(s) or guardian, including the procedure to be followed in the event of a possible expression of objection;

c an account of the subject's participation in the research, stating whether objection was expressed;

d an assessment as to whether the subject's behaviour constitutes objection, as referred to above;

e the names of the people responsible for assessing the subject's behaviour, as described above;

f an assessment as to whether the subject's behaviour in the course of the study constitutes objection;

g the steps taken to minimise the burden associated with participation.

10 The protocol for a medical research project in which minors are to be used as subjects should state that the NVK's code of conduct for dealing with subjects' expressions of objection in the course of the research will be adhered to.

11 This code of conduct will be evaluated in consultation with the research community two years after its initial publication and amended as necessary.

This code of conduct was approved by the Board of the Netherlands Association for Paediatric Medicine (NVK) on 21 May 2001 and published in NVK Newsletter no. 3, June 2001.

15.2 Appendix B – Trial Monitoring Plan

CTCM will perform the external monitoring of this study. Prior the start of this study the monitoring plan will be developed and agreed by the principle investigator and the DSMC.

15.3 Appendix C – Local Investigators

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