JAMA 17-7574: Laparoscopic Sleeve Gastrectomy versus Roux-Y-Gastric Bypass for Morbid Obesity: 5-Year-Results of a Multicentre Randomized Trial (SM-BOSS)

This supplement contains the following items:

1. Final research protocol accepted by the Swiss National Science Foundation (2007), summary of changes to original protocol
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

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Principle investigator of the
SWISS MULTICENTRE - BYPASS OR SLEEVE STUDY (SM-BOSS):

Basle, 11th September, 2017

Final research plan (accepted version by the Swiss National Science Foundation of the investigator initiated clinical trial)

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Proposal form

Project Funding : individual projects (Divisions I-III)
Deadlines : March 1 and October 1

Part 1 : General Information

1. Basic data

Type of proposal	☒ New proposal or ☐ Follow-on proposal No
Continuation foreseen	☐ yes ☒ no
Project title in English	SWISS MULTICENTRE - BYPASS OR SLEEVE STUDY (SM-BOSS): Laparoscopic proximal Roux-Y-gastric bypass (LRYGB) or laparoscopic sleeve-gastrectomy (LSG) in the treatment of morbid obesity
Research field(s)	☐ Human sciences ☐ Engineering sciences ☐ Social sciences ☐ Life sciences ☐ Mathematics, natural sciences ☒ Medical sciences
Amount requested CHF	236'281
Starting date	1 April 2008
Duration	36 months
Institutional declaration	Prof. Dr.med. Peter Meier-Abt, Vice Rector, University of Basel
Main applicant Surname, First name Academic degree Institution	**Dr. med. Ralph Peterli** **Surgical Clinic** **St. Claraspital Basel**
Attachments	☒ Curriculum vitae of applicants Total items: 2 ☒ List of publications by applicants Total items: 2 ☒ List of experts Total items: 1 ☒ Publications Total items: 6 ☐ Offers Total items: ☒ Ethical Committee Total items: 1 ☒ Manuscripts Total items: 1 ☒ Collaboration confirmation Total items: 3

The main applicant confirms hereby the veracity of all the details given in both parts of this proposal including the attachments. They were prepared in agreement with the persons involved.

Place, date:
Basel, 30 September 2007

Signature:

Final Research Plan (2007)

SWISS MULTICENTRE - BYPASS OR SLEEVE STUDY (SM-BOSS):
Laparoscopic proximal Roux-Y-gastric bypass (LRYGB) or laparoscopic sleeve-gastrectomy (LSG) in the treatment of morbid obesity

1. Summary

1.1. Background

Obesity is reaching epidemic proportions in the developed world. In morbidly obese patients only surgical treatment (bariatric operations) leads to a sustained weight loss and cure of co-morbidities in the majority of patients. There exist a number of different operations resulting in either a restrictive and/or malabsorptive effect, accompanied by a humoral effect which is caused by changes of the different gastrointestinal peptides. It is still unknown which patients needs which operation.

1.2. Working Hypothesis

The laparoscopic sleeve-gastrectomy (LSG) is as successful as laparoscopic proximal Roux-Y-gastric bypass (LRYGB) in the treatment of morbid obesity in the majority of patients. In case of insufficient weight loss malabsorption can be added by performing laparoscopic bilio-pancreatic diversion duodenal switch (BPD). The resection of the gastric fundus (LSG) leads to changes in gastrointestinal peptides that are possibly different to bypassing the fundus (LRYGB).

1.3. Specific Aims

We plan to compare the LSG and LRYGB in a prospective randomized Swiss multicentre study. The primary outcome measure is effectiveness in terms of weight loss, reduction in co-morbidity, and quality of life; secondary outcome measures are postoperative changes in gastrointestinal peptides, early morbidity, duration and cost of the operation, late morbidity, and re-operations (for complications, for insufficient weight loss).

1.4. Experimental Design/Methods

Each of the 4 Swiss bariatric centers evaluates with an interdisciplinary team morbidly obese patients for bariatric surgery. After informed consent, eligible patients will be randomly selected for LSG or LRYGB, a total number of 100 per group. Preoperative examination consists of: quantification of comorbidity, eating behavior, indirect calorimetry, body composition by DEXA*, routine blood chemistry, gastrointestinal peptides before and after test meal*, gastroscopy, manometry of the esophagus, upper GI series*, abdominal ultrasound, quality of life. Perioperative investigations: operative time, fat tissue samples* (omental and subcutaneous), early morbidity, gastrointestinal peptides before and after test meal*, duration of

hospital stay, costs*; Follow-up data will be obtained once a year until 5 years postop: weight, reduction in comorbidities, quality of life, complications, re-operations, (gastrointestinal peptides before and after test meal*, DEXA*).
(* only at one center)

1.5. Expected Value of the Proposed Project

With this study we intend to show that LSG has the potential to be a dependable bariatric operation in a staged therapy concept, with equivalent effectiveness in the majority of patients compared to LRYGB. In case of failure of LSG, it can be turned into the more invasive but more effective BPD only in patients who fail restriction alone, thus avoiding over-treatment in a number of patients. This study will add important information regarding which operation technique or which therapy concept has to be applied to morbidly obese patients. In the near future, more operations will have to be performed to treat the growing number of morbidly obese patients; thus, more surgeons will have to be trained. It will add to the safety of bariatric surgery if an operation that is easier to learn, such as the LSG, can be proven to be as effective compared to the more difficult and more expensive LRYGB. Bariatric surgery adds to the basic understanding of the pathophysiology of obesity. In this study we expect to determine whether bypass of the fundus and its resection are equivalent in changes of gastrointestinal peptides and whether a specific preoperative peptide profile or postoperative changes of the peptides may help determining which patient will sufficiently lose weight by restriction alone or will need a malabsorptive procedure.

RESEARCH PLAN

2.1. State of Research/General Introduction

Obesity is reaching epidemic proportions in the developed world. According to the third National Health and Nutrition Examination Survey the prevalence of obesity (body mass index (BMI) > 30 kg/m^2) in the U.S. is more than 30%; five percent of this obese population segment are morbidly so, with a BMI >40 kg/m^2.[1] The prevalence of clinically severe obesity is increasing at a much faster rate among adults in the USA than is the prevalence of moderate obesity.[2] After smoking, it is the second leading cause of preventable premature death in the U.S.[3] Obesity is associated with multiple complications and comorbidities, such as hypertension, coronary heart disease, diabetes, hyperlipidemia, osteoarthrosis, and an increase in cancer risk. [4-7] This has an important impact on the quality and expectancy of life of these patients, with tremendous socio-economic consequences.[8] In morbidly obese patients, conservative treatment (i.e. diet, lifestyle changes, or drugs) leads to sufficient weight loss with reduction of comorbidities in less than 4%.[9] Only surgical treatment (bariatric operations) leads to a sustained weight loss and cure of comorbidities in the majority of patients[9-14] and to a reduction of mortality.[15-18] In

evidence-based medicine, the “gold standard” for strength of evidence is the randomized controlled trial, an important method in pharmacotherapy but having serious limitations when applied to invasive treatments, such as bariatric surgery. It is inappropriate to randomize conservative treatment of morbid obesity when it is acknowledged to have little effect as well as lower safety and quality of life compared to bariatric surgery. Flawed practice guidelines emanating from evidence-based medicine contribute to the underutilization of the most effective and durable therapy for morbid obesity.[19] Bariatric surgery is a rapidly growing discipline throughout the western world, with increasing number of interventions performed every year in spite of lacking consensus on which operation type is the best for which patient.

There exist various types of operations developed in the past 50 years. Purely restrictive operations lead to a reduction of food intake by a small gastric pouch (gastroplasty, gastric banding, sleeve-gastrectomy). Other interventions combine this effect with a malabsorption of micronutrients (proximal gastric bypass) and/or macronutrients (distal gastric bypass, bilio-pancreatic diversion). Purely malabsorptive procedures, such as the jejuno-ileal bypass, have been abandoned due to severe side effects.[20]

Besides restriction and/or malabsorption, these operations appear to induce also humoral mechanisms affecting weight loss and especially diabetes by changing the secretion of gastrointestinal peptides. That this may depend on the type of operation is demonstrated by the observation that diabetes is better cured in bypass procedures than in purely restrictive operations, even before weight loss begins.[23] Bypassing the duodenum seems to have a direct effect on glucose metabolism via these gastrointestinal peptides (e.g. GLP-1). [24,25] Although the past few years have witnessed considerable progress in our understanding of how the brain regulates energy homeostasis in response to hormonal signals from the adipose tissue and the gastrointestinal tract (recently reviewed by Stanley et al [26]), there is only scattered knowledge of the role of the different gastrointestinal peptides known to affect food intake (Table 1)[27-29] in pathophysiological situations in general and after bariatric surgery in particular. For example, reports on changes of PYY and ghrelin levels after Roux-Y gastric bypass surgery, vertical banded gastroplasty, or gastric banding demonstrate differences between the different types of surgery, but the published observations from different studies are contradictory and controversial.[30] At present, there is no detailed study simultaneously analyzing all the different gastrointestinal peptides before and after bariatric surgery in a systematic way and with the same patient group.

Table 1: Gastrointestinal peptides which influence food-intake [27-29]

Gastrointestinal peptide	Location	Cell type	Food- intake
CCK	Duodenum, Jejunum	I-cells	⇩
Amylin	Pancreas	P-cells	⇩
GLP-1	Ileum, Colon	L-cells	⇩
PYY (3-26)	Ileum, Colon	L-cells	⇩
PP	Pancreas	P-cells	⇩
APO-AIV	Jejunum, Ileum	Villus epithels	⇩
Enterostatin	Exocrine pancreas		⇩
Bombesin/GRP	Pancreas, Ileum	A-cells	⇩
Oxyntomodulin	Ileum	L-cells	⇩
Stomach-Leptin	Fundus of stomach	P-cells	⇩
Ghrelin	Fundus of stomach	XA-cells	⇧

Today, all these operations can be performed by laparoscopy. Developments in minimal invasive surgery since 1990 have, after a certain learning curve, led to lower perioperative morbidity and mortality, with an increase in the number of interventions performed.[31-35] All these patients need a very good follow-up postoperatively to detect complications and change the treatment in cases of failure. It is still unknown which patient needs which operation. The advantages of the less invasive, reversible restrictive operations are contrasted by less weight loss and lower effect on comorbidities. On the other hand, more aggressive operations have more severe side effects. In "super super" obese patients (BMI > 60) only malabsorptive procedures are thought to be sufficiently successful in the long run, but these complex operations have a high morbidity and mortality, especially in these high-risk patients.[20-22,36] A two-stage therapy concept was proposed to first perform a restrictive laparoscopic operation for initial weight loss followed by the malabsorptive part 1-2 years later.[37-43] In some patients the initial weight loss was sufficient, and the second part could be abandoned.[39,42-44] The ideal therapy concept for all morbidly obese patients has not yet been found. A sequential, staged therapy concept might be ideal: to begin with a less aggressive operation and continue to a more invasive one only if necessary. One might argue that a patient should obtain the most effective therapy at the beginning. However, there are patients who are satisfactorily treated with a weaker therapy option alone, so otherwise, they would be over-treated.

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2.2. Research Plan

2.2.1. Background

As described in paragraphs 2.1 and 2.2.1, the ideal bariatric operation has not yet been found, that is, one with good weight loss, effective reduction of co-morbidity, little long-term morbidity including few re-operations. A sequential therapeutic concept consisting of a restrictive first operation and a second operation adding malabsorption (applied only to those patients who really need it) has the potential to be a solid therapeutic concept. Laparoscopic gastric banding, as yet the safest bariatric operation, has failed to be sufficiently successful as first stage procedure. Laparoscopic sleeve-gastrectomy (LSG) has been used recently as first-stage operation,[32-38] followed by either laparoscopic Roux-Y-gastric bypass (LRYGB) or bilio-pancreatic diversion (BPD) as second operation. Both LSG and LRYGB are mostly restrictive procedures. The two interventions have the following differences according to published and personal preliminary data (Table 4):

Table 4: Differences between the two operations

	Laparoscopic sleeve-gastrectomy	Laparoscopic Roux-Y-gastric bypass
Method:		
o well established	as isolated operation -	+++
o reversible	-	++
o innervation of stomach intact	++	+
o long-term results known	-	+++
o endoscopy of gastric remnant	+++	(+)
o endoscopic treatment of bile-duct stones postoperatively	+++	-
Operation:		
o performed laparoscopically	+++	+++
o technical difficulty	+	+++
o anastomosis	0	2
o time	1 - 3h	1.5 - 4h
o costs	++	+++
early morbidity	5-10%	5-15%
mortality	?	0.5%
weight loss (excessive weight loss)		
o after 2 years	50-70%*	72%
o after 5 years	?	50-60%
long-term morbidity:		
o dumping	0%	80%
o reflux	20-?%	<2%
o staple line disruption	0%	1%
o ulcer	?	2-4%
o stenosis	?	5%
o bowel obstruction	<1%	1-8%
o hernia	1%	1%
o deficiency of micronutrients	?	5-40%
effect on gastro-intestinal peptides	+ (?)	++ (?)
alternative operation in case of failure (second stage) or symptoms (reflux)	completion into BPD-DS LRYGB	conversion into "distal" gastric bypass or BPD type Scopinaro
Quality of life		
o food-intake	+++	++
o overall	?	++

*depending on the initial BMI

As already mentioned in paragraph 2.1, the published data on hormonal gastrointestinal peptide markers before and after different types of bariatric surgery are not yet convincing enough to be used as (a) outcome parameters after surgery or (b) a help for identifying patients who will need a malabsorptive procedure to lose sufficient weight. We intend to examine the effect of those two operations (resection or bypass of the gastric fundus) on various gastrointestinal peptides. In addition, we should be able to better understand the basic physiological mechanisms that are responsible for appetite regulation, food intake and for specific symptoms (delayed fullness, disturbed satiety) in the obese patients.

2.2.2. Outcome measures:

We propose to compare the laparoscopic Roux-Y-gastric bypass with laparoscopic sleeve-gastrectomy in the treatment of morbid obesity in a prospective randomized study with the following outcome measures:

Primary:

Success of treatment in terms of:

- weight loss (expressed by % excessive BMI loss)

Secondary:

- reduction in co-morbidity
- quality of life
- changes in gastrointestinal peptides comparing resection of fundus (LG) to bypassing the fundus (LGB) *
- duration and cost* of operation
- safety (early and late morbidity)
- quality of food intake
- rate of secondary intervention (adding malabsorption by performing BPD)

* only at St.Claraspital

2.2.3. Methods

2.2.3.1. Participating bariatric centers

1. St. Claraspital, Basel
2. University hospital Zürich
3. Adipositaszentrum St.Gallen
4. University hospital, Bern

2.2.3.2. Patient recruitment and randomization

Morbidly obese patients referred to each interdisciplinary center will be evaluated by a team of dieticians, endocrinologists, obesity specialists, and psychiatrists. Patients who meet the legal criteria for bariatric surgery and are deemed eligible by all members of the team receive a written documentary about all the operations

offered. After having received approval by their health insurance, they are referred to the surgeon's outpatient practice for a first meeting. The different surgical procedures are explained in detail, and, if desired, contact with already operated patients is organized. If a patient meets the criteria for randomization (see below), the purpose of the study is explained, and the patient is asked to participate. If he/she agrees and has signed the informed consent, randomization is performed immediately by closed envelope, and the drawn operation type explained to him/her in detail again. The patient is given time to re-consider and the possibility not to participate or to come back a second time. Afterwards, the preoperative examinations will be organized.

2.2.3.3. Inclusion criteria

1. the interdisciplinary team accepts the indication for a bariatric operation
2. a laparoscopic gastric banding or primary lapasoscopic bilio-pancreatic diversion are not the operations most likely indicated
3. according to the Swiss Health Insurance Regulation (KLV Anhang 1, dated January 2005)
    a. positive decision of the health insurance physician
    b. age 18-60 years
    c. BMI > 40 kg/m^2
    d. BMI > 35 kg/m^2 and one of the following co-morbidities (hypertension, diabetes, sleep apnea syndrome, dyslipidemia, osteoarthritis, coronary heart disease, secondary infertility in females)
    e. after 2 years of unsuccessful conservative treatment
4. the patient signs the informed consent.

2.2.3.4. Study size

In each investigative group a number of 100 patients is needed to have enough statistical power for primary outcome measures. Center 1 has already randomized a number of 35 patients and will add another 45 to a total of 80 patients, the other centers will each add 40 patients. Thus, we estimate a duration of two years to collect the total number of 200 patients for randomization. For power-analysis we estimated minimal differences to be relevant and standard deviations according to the results of our own previous bariatric cohorts, according to our own preliminary results of LSG and LRYGB as well as the literature.

Power-analysis for primary outcome measures:

- weight loss (1, 2, 3, 4, and 5 years postop):
    - If a difference of excessive BMI loss of 10% has to be detected, a total study size of 130 patients would be sufficient (with a standard deviation $\sigma < 20\%$), with a total of 200 patients a power of 94% could be reached.

- to detect a minimal difference of 3 BMI-points lost (standard deviation σ = 5 BMI points) with a power of 80% by two-sample t-test (at a significance level α = 5%) a number of 45 patients in each arm would be sufficient. With a total of 200 patients a power of 99% could be reached, or with a power of 80% a difference in BMI-points of 2 could be detected.

Comments: to compare weight loss between two groups, either an absolute measure (BMI-points lost) or a relative one (excessive weight loss) can be taken depending on initial BMI.

Power-analysis for secondary outcome measures:

- reduction in co-morbidity (12 months postop): to detect a minimal difference of 0.5 co-morbidity-BAROS-points (range: -1 - +3, σ = 0.5) with a power of 80% by two-sample t-test (at a significance level α = 5%) a number of 17 patients in each arm would be sufficient. With a total of 200 patients a power of 100% is reached, or with a power of 80% a minimal difference of 0.2 points could be detected.
- quality of life:
  1. QOL-BAROS-points (range: -3 - +3, σ = 0.5) to detect a minimal difference of 0.5 QOL-BAROS-point with a power of 80% by two-sample t-test (at a significance level α = 5%) a number of 17 patients in each arm would be sufficient. With a total of 200 patients a power of 100% is reached, or with a power of 80% a minimal difference of 0.2 points could be detected.
  2. GIQLI-Score (maximum possible points = 144, σ = 25): to detect a minimal difference of 15 GIQLI-Score-points with a power of 80% by two-sample t-test (at a significance level α = 5%) a number of 45 patients in each arm would be sufficient.
- total BAROS-Score (maximum possible points = 9, σ = 1.6): to detect a minimal difference of 1 total BAROS-point with a power of 80% by two-sample t-test (at a significance level α = 5%) a number of 41 patients in each arm would be sufficient; with a total of 200 patients a power of 99% is reached.
- duration of operation: to detect a minimal difference of 35 minutes (σ = 40 minutes) with a power of 80% by two-sample t-test (at a significance level α = 5%) a number of 22 patients in each arm would be sufficient. With a total of 200 patients a power of 100% is reached, or with a power of 80% a minimal difference of 16 minutes could be detected.
- costs of operation: to detect a minimal difference of 1000 Fr. (σ = 1500) with a power of 80% by two-sample t-test (at a significance level α = 5%) a number of 36 patients in each arm would be sufficient. With a total of 200 patients a power of 99% is reached or with a power of 80% a minimal difference of 600 Fr. could be detected.

- early morbidity: to detect a minimal difference of 15% prevalence in both arms, the power calculated by fisher exact test (at a significance level $\alpha = 5\%$) with a sample size of 200 reaches 80%. If a lower difference is estimated between the two arms, a power of 80% can only be reached with bigger sample sizes.
  comments: for comparisons of proportions the sample sizes usually have to be bigger. As we hypothesize no relevant difference in early morbidity between the two arms and early morbidity being a secondary outcome measure, we refrained from increasing the study population.
- rate of secondary intervention (within 2 years postop due to insufficient weight loss): to detect a minimal difference of 15% failure rate (estimated 5% LRYGB and 20% after LSG) the power calculated by Fisher exact test (at a significance level $\alpha = 5\%$) with a sample size of 200 is 86%.

2.2.3.5. Preoperative examinations

1. quantification of comorbidity
2. eating behavior: detection of binge-eating disorder, eater of fats, gluttonous eater, nocturnal eater, eater of sweets, snacker, made by the dietician and endocrinologist
3. indirect calorimetry: resting energy expenditure, fat and carbohydrate burning capacity †
4. body composition*: body fat and lean body mass determined by dual-energy x-ray absorbitometry (DEXA, QDR 4500A, Hologic, Bedford MA)
5. routine blood chemistry after 12-h overnight fasting: total cholesterol, HDL, LDL, triglycerides, albumin, HbA1c, vitamins B1, 6, 12, D; PTH
6. gastrointestinal peptides* after a 12-h overnight fasting and 30, 60, 120 and 180 minutes following a standard test meal: PYY3-36, ghrelin, GLP1, leptin and CCK will be measured at the clinical research centre of the Department of Gastroenterology, University of Basel. We also plan to determine additional peptides listed in Table 1, such as PP, amylin, oxyntomodulin, and GRP as a second priority. All hormonal assays will be carried out using commercial kits.
7. gastroscopy in ambulatory, in case of H.P.- positive gastritis, an eradication therapy is performed
8. manometry of the esophagus
9. upper GI series*
10. abdominal ultrasound: if gallstones are detected, common bile-duct stones are searched for either by MR-cholangiogram or iv-choangiogram, if patients >170 kg, waist diameter >75cm or claustrophobic
11. quality of life, according to modified GIQLI-Score and BAROS-QoL-questionnaire, quality of food intake according to Suter et al (Obes Surg. 2007 Jan;17(1):2-8)

†: only in center 1 & 3
*: only in center 1

2.2.3.6. Operations

All operations will be performed by experienced bariatric surgeons.

2.2.3.7. Perioperative investigations

1. operative time
2. intraoperative complications
3. costs of material used*
4. fat tissue samples* approximately 5g omental and subcutaneous fat, immediately placed into liquid nitrogen and stored at -75° C
5. result of GI-series postop day 5
6. time until full oral alimentation
7. duration of hospital stay
8. early morbidity (until postop day 30)
9. costs of total hospitalization*
10. gastrointestinal peptides after a 12-h overnight fasting and 30, 60, 120, and 180 minutes following a standard test meal on postop day 8*

*: only in center 1

2.2.3.8. Follow-up examinations

1. Scheme:

time	(years)	1				1.5	2	additional follow-up (beyond this study)	3	4	5
	(months)	3	6	9	12						
•	clinical (including weight)	X	X	X	X	X	X		X	X	X
•	reduction of				X		X		X	X	X
•	standard blood tests				X		X		X	X	X
•	gastrointestinal peptides*	X			X						
•	densitometry				X		X			X	
•	quality of life (GIQLI, BAROS) and food intake				X		X		X	X	X

2. Registration of all complications, re-operations, and re-hospitalizations.

2.2.3.9. Criteria for second stage procedure

The goal of this study is to prove that LSG is a acceptable isolated operation in the majority of patients treated. A second stage procedure is not routinely added. In general, a minimal follow-up of 2 years will have to be fulfilled until patients are considered for re-operation due to insufficient weight loss (<50% EWL) or

insufficient resolution of comorbidities. Patient's wish and quality of life will also be taken into account. For any complication or severe side effects (such as medication refractive reflux) earlier re-operation will be possible. According to our experience and other large series [44] the rate of necessary second stage procedure after LSG is low (10-20%).

Primary operation	*Complication*	*Second stage procedure*
LSG	insuff. weight loss and/or insufficient resolution of comorbidities	Bilio-pancreatic diversion duodenal switch
	reflux	LRYGB
LRYGB	insuff. weight loss and/or insufficient resolution of comorbidities	adding malabsorption by bypassing more small intestine or bilio-pancreatic diversion type Scopinaro

2.2.3.10. Data collection

All data are collected at each center according to a standardized protocol and will be delivered to a central database at St.Claraspital. For cost analysis the hospital accounting software "HOSPIS" is used.

2.2.3.11. Duties of study nurse (see 2.3.3.5-8)

1. at center 1: preoperative: the following points 1, 2 (together with dietician), 3, 4, blood samples (5, 6), 11; perioperative: 1, 2, 3, 5-10; follow-up: organization of follow-up investigation including test meal
2. data management of all Swiss centers: data collection and analysis

2.2.3.11. Duties of lab technician

1. hormone assays
2. management of fat samples for future analysis

2.3. Time-Table

Acquiring sufficient patients (N=200) will take app. 2-3 years. Intensive follow-up data will be collected within the first year after the operation. Thus, 3-4 years after the multicentre study begins, most data should have been gathered but a total of 5 years follow-up will be continued for final analysis.

2.4. Significance of the Proposed Research

Morbid obesity is a growing health problem. Surgery is the only effective treatment. Laparoscopic Roux-Y-gastric bypass is the most frequently performed operation. Only recently, laparoscopic sleeve-gastrectomy, an easier to perform alternative operation, has shown to be as efficient in early weight loss.

With this study we want to prove that the laparoscopic sleeve-gastrectomy in a staged therapy concept is as effective in the majority of patients as is the "gold standard", the laparoscopic gastric bypass. In case of failure following sleeve gastrectomy, the more invasive but more effective bilio-pancreatic diversion duodenal switch will be performed only in patients who fail restriction alone, thus avoiding over-treatment in a number of patients.

In spite of the limitations of evidence-based medicine applied to bariatric surgery when compared to conservative treatment (see paragraph 2.1.), this study will add important information as to which operation technique or which therapy concept should be applied to morbidly obese patients.

In the near future, more operations will have to be performed to treat the growing number of morbidly obese patients; thus, more surgeons will have to be trained. It will add to the safety of bariatric surgery if an operation that is easier to learn, such as the laparoscopic sleeve-gastrectomy, can be proven to be as effective as the more difficult and more expensive laparoscopic Roux-Y-gastric bypass.

Bariatric surgery adds to the basic understanding of the pathophysiology of obesity. In this study we expect to determine whether bypass of the fundus or its resection is equivalent in changes of gastro-intestinal peptides and if a specific preoperative peptide profile or postoperative changes of the peptides may help determining which patient will sufficiently lose weight by restriction alone or will need a malabsorptive procedure.

Summary of changes: original research protocol/final protocol

1. Change from a single center study to a multicenter study
2. Increase of study size
3. Change of bariatric centres participating: instead of Tiefenau Hospital in Berne, the University Hospital of Berne was the fourth bariatric unit participating
4. Primary outcome measure: only one instead of three, weight loss expressed as “excessive BMI loss”

3. Statistical analysis plan

3.1. Original statistical analysis plan

To detect a 10% difference in excessive BMI loss (EBMIL) between the two procedures, we calculated a study size of 200 patients to reach 94% power at 5 years. Values are reported as means ± SD. Descriptive statistics are used for demographic variables such as age, weight, and BMI. Analysis is performed on the intention-to-treat population using the Last observation carry forward (LOCF) imputational approach to deal with missing follow-up values. Student t, Chi square and Fisher's exact 2-sided tests are used where appropriate. A P-value of less than 0.05 is considered as statistically significant.

3.2. Final statistical analysis plan

A study size of 200 patients was calculated to detect a 10% difference in EBMIL between the two procedures with a power of 94% at five years. IBM SPSS for Windows (version 24; IBM, Armonk, NY) was used for data analysis. Values are reported as means ± SEM. Analysis was performed on the intention-to-treat population. Missing follow-up data were imputed by a multiple imputation technique using the fully conditional specification method based on Markov chain Monte Carlo simulation using SPSS, i.e. ten simulated datasets were generated. For sensitivity analysis, statistical tests were performed on original data, the ten imputed datasets and pooled dataset. Derived data (such as BMI, EBMIL and %WL) were calculated from the pooled dataset only. Fasting blood glucose and HbA1c were measure in diabetic patients over the whole study period or until values normalized. The latter values were imputed for the rest of study period by last-observation-carry-forward approach. Longitudinal data were analyzed by repeated measure analysis of variance using OP type as between-factor and gender as covariate. For pairwise comparisons between longitudinal data, the Šidak multicomparison test was used. In addition, on each time point, pairwise comparisons between treatments were performed with multiple t-tests with step-down Šidak correction for p-value adjustment for multiplicity of testing. Student t, Chi square and Fisher's exact 2-sided tests were used where appropriate. A P-value of less than 0.05 was considered statistically significant.

Summary of changes from original statistical analysis plan

1. More details are given on how the statistical analysis was done:

- Multiple imputation technique using fully conditional specification method based on Markov chain Monte Carlo simulation

- Longitudinal data were analyzed by repeated measure analysis of variance; for pairwise comparisons between longitudinal data, the Šidak multicomparison test was used.

2. IBM SPSS for Windows (version 24; IBM, Armonk, NY) was used for data analysis.