Author’s response to reviews

Title: The Sleeve Bypass Trial: a multicentre randomized controlled trial comparing the long term outcome of laparoscopic sleeve gastrectomy and gastric bypass for morbid obesity in terms of excess weight loss percentage and quality of life.

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Author’s response to reviews: see over
Dear editor and reviewers,

Many thanks for the critical review of our paper entitled; “The Sleeve Bypass Trial: a multicentre randomized controlled trial comparing the long term outcome of laparoscopic sleeve gastrectomy and gastric bypass for morbid obesity in terms of excess weight loss percentage and quality of life”.

Enclosed please find our revised version of the manuscript based on the excellent comments by the reviewers. A detailed description with the reply to the reviewers’ comments is also enclosed. We truly hope that the paper in its present form will be accepted for publication in your journal,

With kind regards, also on behalf of the co-authors,

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**Reviewer 1**

Simply nothing exciting.
I'm perplexed by the design of the study, because literature has already studies on this topic in particular for sleeve and bypass which effects are already known. I think that is reductive to base this study on weight loss as objective of the study for these procedures. Research in this field is moving towards more interesting aspects that need to be investigated. However, the merit of the authors is to have organized a randomized trial and for the purpose of a long follow-up.

**Response:**

We can understand your first impression on this matter because there is a lot published regarding the sleeve gastrectomy and the gastric bypass. However, there is in our opinion still a lot unknown about the long term effects of the sleeve gastrectomy versus the gastric bypass, especially regarding quality of life. Our study is not only focussing on EWL but also on the QOL effects after a period of 5 years and the effects on comorbidity in these patients. There are cohort studies showing big amount of patient data but not in an randomized multicentre setting. The amount of randomized controlled trails focussing on these important matters is really low. We think that this study, being a multicentre randomized controlled trial with 620 patients focussing not only on EWL but also on QOL (with all the appropriate questionnaires) deserves publication in an excellent journal like BMC obesity. Thank you again for your comments.
Reviewer 2

General comments
The authors describe a PRT comparing today's two most frequently performed bariatric procedures, sleeve gastrectomy (LSG) and gastric bypass (LRYGB) regarding effectiveness in terms of excessive weight loss as primary endpoint and efficacy regarding remission/improvement of comorbidity and QoL as secondary endpoints.

Response: thank you for your comment.

Specific comments

Background:

1. 3rd paragraph: LRYGB is considered the best surgical option... in what respect? It is the most frequently performed operation worldwide (but challenged by LSG, in 2013 almost as frequently performed, Angrisani et al, paper submitted). What does “best” mean? BPD is more potent in terms of weight loss and remission rates f.ex. T2diabetes. There exist a list of advantages of LRYGB not mentioned here: it is fully reversible, it is well documented in terms of early morbidity and long term results, often regarded as the gold standard in bariatric an/or metabolic surgery, known for more than 50 years.

Response: Indeed the reviewer is correct that the term best surgical option should be clarified. At page 3 we have changed the text in the manuscript as suggested by the reviewer.

2. LSG: describe how the idea of isolated LSG evolved (staged concept in pts with very high BMI (Regan, Obes Surg 2003)). Potential advantages: faster, safer (early and late i.e. no internal hernias), duodenum accessible (endoscopy), less dumping due to pylorus, second stage procedure (LRYGB or BPD-duodenal switch) are standard procedures, BUT one major disadvantage: LSG is irreversible.

Response: We have changed the text in the manuscript at page 3 as suggested by the reviewer.


Response: We have added the comments and the reference of the concerning trial.

Response: We have added the reference of the concerning trials and publications.

Study design:

1. Study has started already 2 years ago (what is the purpose of publishing the design now?)

Response: Indeed the reviewer is correct that an as early as possible publication the design is even better. In our opinion the study is still in the inclusion period without any data analysis so far and therefore still in time for publication of the design. This publication will add more value to our future results, by showing that the study design and analysis is not changed after the inclusion period and therefore more reliable.

2. 3 years for 620 pts to be randomized: how well do Dutch pts accept to be randomized, Scandinavians accept much faster to be randomized for a type of surgery than other Europeans

Response: It is difficult to compare our patients with the Scandinavian population. Because both the cooperating centres in this multicentre RCT have more than 500 procedures a year we think that this inclusion should be possible.

3. with the experience of two years of recruiting is this recruitment period of 3 years still realistic?

Response: Indeed the reviewer is correct that the inclusion started slow. The reason is that inclusion in the second centre started much later than in the first centre. At this moment the inclusion is much faster and therefore we expect that the delay will be limited at the end.

Patient selection:

1. Exclusion criteria: GERD, 40% of morbidly obese pts suffer from GERD, give more precise definition on what criteria pts will be excluded, how to deal with hiatal hernias
Response: both clinics use the same exclusion criteria like cited from page 5 “diagnosed gastro oesophageal reflux disease (GERD)” for exclusion. This means that patients with symptoms of GERD with the use of chronic medication like proton pump inhibitors or a diagnosed hiatal hernia with symptoms are excluded from this study. There is no routine gastroscopy prior to surgery in asymptomatic patients. This is added in the manuscript on page 5 as suggested by the reviewer.

Hypothesis:

2. Apparently they measure not %EWL but % excessive BMI loss

Response: the weight loss is redefined as suggested by the reviewer in the manuscript.

3. Why QoL should be superior in LSG compared to LRYGB is based on one study, I doubt this very much.

Response: There is indeed little hard evidence on this subject. The existing limited data shows that QOL is similar or better. The LSG has some potential advantages like mentioned on page 3 of the manuscript and seen in the daily practice. We think and hope that the data provided by this study in the future, will help answering this important question.

Surgical Intervention:

1. How do you measure 30 day morbidity in the fast track concept, when, by whom in what rhythm are the pts being followed up, give precise CRF’s of each time point or at least an overview table on follow-up appointments and what is being measured

Response: To show the follow up a table and explanation is added to the manuscript on page 6. Not only the study patients but all our patients have 24/7 access to the bariatric surgery department. They are well instructed to call immediately in case of complaints or possible complications. There is a checklist for all our patients with alarm symptoms like fever, excessive pain of a high pulse. Extra visits and investigations are planned customized. Besides scoring the complication the “Clavien Dindo classification” is used to score the severity, making it possible to compare with other studies.

2. Both operations described in detail
Response: thank you for your nice comment.
3. How many surgeons will perform the operations after what personal experience?

Response: This question is partially answered on page 6 “All participating surgeons are experienced bariatric surgeons that have performed at least 150 LSG and 150 LRYGB and work in bariatric centres of excellence that perform over 500 cases per year”. The total amount of participating surgeons is six so far.

4. Escape surgery: you plan an intention to treat analysis, please, include also a per protocol analysis

Response: this is added to the manuscript on page 8.

Outcome measures

Primary endpoint:

1. Your primary endpoint is EBMIL not %EWL

Response: Indeed the reviewer is correct this is changed in the various parts of the manuscript.

Secondary endpoints:

1. How are the co-morbidities defined preop and how will remission or improvement be measured and expressed?, give more details

Response: to give more details about the co-morbidity assessment and the definitions the text is much more detailed in the manuscript on page 8 like suggested.

2. What is the follow-up setting?

Response: To show the follow up a table (table 1) and explanation is added to the manuscript on page 6.

3. How is the database organized?, Which CTU is responsible? How is it organized?

Response: An independent data and safety monitoring committee will evaluate the progress of the trial and will examine safety parameters at regular intervals (every 100 patients). All involved physicians will repetitively be asked to report any potential adverse events caused by the study protocol. These adverse events will be listed and discussed with the monitoring committee. The monitoring committee can ask for a full report in order to discuss a specific
adverse event. A copy of this report will be sent to the central ethics board and to the involved physicians. All deceased patients will be evaluated by the safety committee for cause of death and possible trial related serious adverse effects. Every death will be reported to the central ethics board and the local ethics board. The DSMB will consist of an epidemiologist/statistician who is the chairman, an independent surgeon and an independent endocrinologist.

**Power calculation:**
1. High number if pts for this trial, congratulate

   *Response: thank you for your nice comment.*

**Discussion:**
1. Marceau and Hess described sleeve gastrectomy as part of the BPD duodenal switch, they did not describe the LSG, this was done by Regan and Gagner as part of a staged concept

   *Response: this comment is added to the manuscript.*

2. LSG long term results do exist (Sieber et al, SOARD 2014 etc)

   *Response: the text is due to recent papers changed in to “However, currently long term results of LSG are limited compared to LRYGB”*

3. In case of insufficient weight loss LSG can be converted not only to LRYGB (this makes sense in pts with sever GERD after LSG or hiatal herniation of the sleeve), conversion to BPD-DS would be the standard procedure if pts are adherent to the follow-up, other option could be SADI, or mini-bypass. Please, discuss on these options

   *Response: the reviewer is correct other centres can choose different revisional options therefore the text is changed on page 10 of the manuscript to “Furthermore, LSG can easily be converted to LRYGB, BPD-DS or an omega loop bypass depending the patient characteristics and the preferences of the surgeon in case of insufficient weight reduction”.*

4. Do you have a definition of failure, on what basis will you decide to go for a second stage procedure

   *Response: Insufficient weight loss is defined with the Reinhold criteria (modified by Christou and Biron) this is added to page 9 and 10.*

5. How do you treat gallstones at first and in the follow up?
Response: There is no routine preoperative assessment for gallstones. If a patient has symptoms suggesting gallstone disease an ultrasound is performed. To keep the risk of the bariatric procedure as low as possible preferably the cholecystectomy is not combined with the bariatric procedure. In the follow up a cholecystectomy is performed as soon as possible after the symptoms start. In case of an LRYGB there is also attention for a internal herniation during cholecystectomy.

6. In general: it is difficult to judge with the existing protocol how well the authors will be able to measure all possible long-term complications and reoperations (vitamin deficiencies, internal hernias etc)

Response: At every visit all these data are collected in a digital patient form. If a patient does not show up the patient is called repetitively and/or the GP of the patient is consulted to motivate the patient to show up. During every visit to the endocrinologist extensive laboratory testing is performed including vitamin levels (table 1). Therefore we expect to collect the required data.

Finally, we would like to thank the reviewers for the critical appraisal of the current manuscript.