# Effect of the EndoBarrier Gastrointestinal Liner on obesity and type 2 diabetes: protocol for systematic review and meta-analysis of clinical studies

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID: | bmjopen-2013-003417 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 14-Jun-2013 |
| Complete List of Authors: | Rohde, Ulrich; Copenhagen University Hospital Gentofte, Diabetes Research Division, Department of Medicine<br>Hedbäck, Nora; Copenhagen University Hospital Gentofte, Diabetes Research Division, Department of Medicine<br>Gluud, Lise; Copenhagen University Hospital Gentofte, Diabetes Research Division, Department of Medicine<br>Vilsbøll, Tina; Copenhagen University Hospital Gentofte, Diabetes Research Division, Department of Medicine<br>Knop, Filip; Copenhagen University Hospital Gentofte, Diabetes Research Division, Department of Medicine |
| Primary Subject Heading: | Diabetes and endocrinology |
| Secondary Subject Heading: | Global health |
| Keywords: | DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE |
| | |

# Effect of the EndoBarrier Gastrointestinal Liner on obesity and type 2 diabetes: protocol for systematic review and meta-analysis of clinical studies

*Ulrich Rohde*[1], *Nora Hedbäck*[1,2], *Lise L. Gluud*[1] , *Tina Vilsbøll*[1], *and Filip K. Knop*[1,2]

[1]Diabetes Research Division, Department of Medicine, Copenhagen University Hospital Gentofte, Hellerup, Denmark; [2]Department of Biomedical Sciences, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Correspondence to:
Assoc. Prof. Filip K. Knop, MD PhD
Diabetes Research Division, Department of Medicine
Copenhagen University Hospital Gentofte
Niels Andersens Vej 65
DK-2900 Hellerup
Denmark
Phone: +45 3997 8132; Fax: +45 3977 7661; e-mail: filipknop@dadlnet.dk

Keywords: Duodenal-jejunal bypass sleeve (DJBS), glycaemic control, weight loss, type 2 diabetes, meta-analysis

Word count (excluding title page, abstract, article summary and references): 2,555.

## ABSTRACT

*Introduction:* Obese patients with type 2 diabetes undergoing bariatric surgery experience significant and lasting weight loss and improved glycaemic control. However bariatric surgical procedures such as Roux-en-Y gastric bypass are irreversible and associated with considerable short and long term risks. The EndoBarrier Gastrointestinal Liner or duodenal-jejunal bypass sleeve (DJBS) is a fully reversible procedure that has been developed to treat obesity and type 2 diabetes. We aim to perform a systematic review and meta-analysis of safety and efficacy of the DJBS.

*Methods and analyses:* A systematic review with meta-analysis (as per the preferred reporting items for systematic reviews and meta-analyses – PRISMA) of randomised controlled trials of the device (vs. no intervention, sham and/or low-calorie diet) will be performed. Primary endpoints include change in body weight and glycated haemoglobin A1c and safety. Secondary endpoints constitute changes in other glycaemic parameters and blood lipids and proportion of patients discontinuing anti-diabetic medication. Medline, EMBASE, The Cochrane Library and Science Citation Index will be sought electronically along with manual searches. The primary meta-analysis will use random effects models due to an expected intertrial heterogeneity. Fixed effect meta-analysis will be executed to assess the impact of small trials. Dichotomous data will be analyzed using risk difference and continuous data using weighted mean differences both with 95% confidence intervals.

*Ethics and dissemination:* The study will describe the impact of the DJBS on obesity and type 2 diabetes and possibly contribute to clinical decision making. The results of this study will be disseminated by peer-reviewed publication and scientific presentations.

*Registration:* PROSPERO CRD42013004819

## ARTICLE SUMMARY

### *Article focus*

Impact of EndoBarrier Gastrointestinal Liner/duodenal-jejunal bypass sleeve (DJBS) on weight loss (percent excess weight loss or weight loss in kilogram), glycaemic control (HbA1c and fasting plasma glucose), safety, lipids and proportion of subjects discontinuing anti-diabetic medication in patients treated with the device.

### *Key messages*

There does not exist a systematic review with meta-analysis on the weight and glucose-lowering effect or safety of the DJBS. The current bariatric surgical procedures are effective but associated with short and long-term complications. The need for less invasive and safer but yet effective bariatric treatment modalities are wanted.

### *Strength and limitations of this study*

Despite our groups experience in conducting a systematic review with meta-analysis, small studies with high heterogeneity and varying quality may be this study's limitation.

## INTRODUCTION

Lack of physical exercise and excess nutrient intake constitute important factors leading to obesity and overweight. Worldwide, more than 1.4 billion adults (≥20 years old) are overweight with a body mass index (BMI) ≥25 kg/m$^2$. Of these approximately 500 million adults are obese (BMI ≥30 kg/m$^2$). World Health Organization (WHO) estimates that the number of obese subjects has doubled since 1980[1]. Overweight and obesity are risk factors that increase the risk of cardiovascular disease, musculoskeletal disorders, cancer, type 2 diabetes and premature death. Dietary treatments are ineffective in the long-term treatment of overweight and obesity and current anti-obesity medications are few and largely ineffective[2]. In contrast, bariatric surgery has proven effective - also on the longer term - and leads to an improved glucose homeostasis. Patients with type 2 diabetes undergoing bariatric surgery experience improved glycaemic control or remission of diabetes reducing or even eliminating their need for medication[3].

### *Current clinical practice - the bariatric surgical procedure Roux-en-Y gastric bypass*

Interestingly, rerouting of nutrient flow through the gastrointestinal tract (bypassing the proximal small intestine) following the surgical bariatric procedure Roux-en-Y gastric bypass (RYGB) has been shown to dramatically improve glucose metabolism within few days - prior to any weight loss has occurred - among obese type 2 diabetic patients. Depending on the definition of remission, remission rates of 40[4] to 80%[2] have been reported. The predominant hypotheses on the physiological background for the metabolic advantages after bariatric surgery include changed release of gastrointestinal hormones (increased secretion of hormones with anti-diabetic and/or anti-obesity properties, e.g. glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), and reduced secretion of 'diabetogenic' hormones e.g. glucose-dependent insulinotropic peptide (GIP)) combined with surgery-induced restriction of food intake. Despite the short and long-term benefits RYGB provides for obese patients with type 2 diabetes, the procedure - like most other bariatric surgical procedures - is invasive, irreversible and potentially lethal. In a meta-analysis from 2004 Buchwald et al. report a 30-day mortality after gastric banding, RYGB and biliopancreatic diversion of 0.1%, 0.5% and 1.1% respectively[2]. The most frequent short-term causes of mortality after RYGB are venous thromboembolism and cardiorespiratory disease[5]. Additionally several short and long-term complications are associated with the procedures including anastomotic leaks, bleeding, infections, small bowel obstruction, hernias, dumping syndrome and malabsorption of micro and macronutrients[5,6]. Finding a less invasive bariatric procedure to treat obesity and type 2 diabetes would be of great interest not only for the patients but also for the society in general. The minimal invasive and fully reversible DJBS may represent an alternative to the most commonly used bariatric techniques. With this protocol we intend to investigate the efficacy and safety of DJBS.

### *Description of the intervention*

The EndoBarrier Gastrointestinal Liner (a polymer DJBS) consists of a nickel-titanium anchor and a 60 cm impermeable sleeve made of fluoropolymer (Fig. 1). The device, which is open at both ends, is endoscopically placed in the duodenum via an over-the-wire system. The anchor is fixed to the intestinal wall within the duodenal bulb by small barbs grasping the intestinal mucosa[7]. Ingested nutrients pass down to the stomach and onwards directly and mostly undigested into the sleeve. Pancreatic and bile juice passes naturally into the intestinal tract, flowing down between the sleeve and the intestinal wall. It mixes together with

undigested nutrients at the distal end of the DJBS i.e. in the jejunum[8]. Placing the DJBS endoscopically makes the procedure minimal invasive. Furthermore, the DJBS has the advantage of being fully reversible; the device can easily be removed using an endoscope[9]. The producer of the device (GI Dynamics Inc.) recommends that treatment with DJBS is accompanied with dietetic counselling to optimise the effect and to prevent device malfunction. Currently the device is approved for a maximal treatment period of 12 month. In 2010 the DJBS received European CE marking and achieved conditional approval by the US Food and Drug Administration in August 2012.

***How the intervention might work***

The mechanisms behind the body-weight lowering and the anti-diabetic effects of DJBS are unknown, but are thought to involve less absorption of nutrients and have been speculated to encompass changes in gut hormone secretion. Up to now several human studies with duration from 12 to 52 weeks report that implanted subjects lose weight and achieve improvements in their diabetic state after treatment with the device. Tarnoff et al. reported in their 12 week open-label prospective randomized controlled trial an excess weight loss (EWL) of 22.1% and 5.3% for implanted subjects and subjects treated with a low-calorie diet, respectively[10]. Another randomised sham-controlled trial showed EWL of 11.9% and 2.7% for the device group and the sham group, respectively[8]. Regarding changes in glycaemic parameters both Rodriquez et al. and Schouten et al. have reported improved glycaemic control (greater reduction in glycated haemoglobin A1c (HbA1c)) when treated with DJBS compared to controls[11,12]. de Jonge et al[13] report in their study of 17 obese subjects with type 2 diabetes that DJBS changes the gut hormone secretion favouring postprandial release of GLP-1 and lowering secretion of GIP within one week after implantation before any significant weight loss occurred. This emphasises that changes in gut hormones may constitute one of the mechanisms by which DJBS exerts anti-diabetic anti-obesity effects.

***Why it is important to do this review***

As mentioned above, overweight and obesity represent major concerns for the individual and the society. The growing number of obese people has also lead to a worrying increase in the incidence of people with type 2 diabetes. Worldwide nearly 350 million people suffer from this disease[14]. Bariatic surgery has proven to be effective as a method of reducing body weight and improving type 2 diabetes. However, the potentially serious complications during and following the invasive and irreversible surgical procedures are incontrovertible. Thus, there is currently a strong need for new and less invasive, safer and preferably reversible alternatives to bariatric surgical procedures. The DJBS may provide a modality fulfilling these conditions. Current data on the effects of DJBS stem from rather small studies. Therefore it seems of major importance to compile and analyse current evidence of the effect of the DJBS on obesity and/or type 2 diabetes. Such evidence may help guide clinical decision-making and procure better treatment of obesity and type 2 diabetes.

## OBJECTIVES

The primary objectives of the present protocol is to evaluate the effect of the DJBS on weight loss as assessed by change from baseline or percent of excess weight lost (%EWL), glycaemic control as assessed by HbA1c, and safety. Secondary objectives include evaluation of the proportion of type 2 diabetic patients being able to reduce or discontinue anti-diabetic

medication and changes in glycaemic parameters other than HbA1c (fasting plasma glucose or fasting blood glucose), and total cholesterol.

## METHODS AND ANALYSES

The systematic review will be performed according to the recommendations specified in the Cochrane Handbook for Intervention Reviews[15]. The reporting of the review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16].

### *Criteria for considering studies for review*

*Types of studies*

The review will include randomised clinical trials, prospective non-randomised trials, case-control studies and case series investigating the effects of the DJBS, irrespective of blinding and publication status. Unpublished trials will be included if data and methodology is accessible in written form.

*Types of participants*

Adult overweight or obese patients (age 18 years or older) with or without type 2 diabetes treated with the DJBS will be included. Preferably the definition of overweight, obesity and type 2 diabetes should follow the criteria from WHO, the European Association for the Study of Diabetes (EASD) or the American Diabetes Association (ADA)[17], but if necessary, trials will be included using the author's definition of obesity and type 2 diabetes.

*Types of interventions*

The comparisons will assess implantation of DJBS versus no intervention, sham-endoscopy and/or low-calorie diet.

### *Types of outcome measures*

The outcome measures will be assessed based on analysis of individual patient data from included trials or from published reports when available.

*Primary outcomes*

- Mean weight loss in kilograms at end of intervention
- Change in HbA1c
- Safety

*Secondary outcomes*

- Proportion of type 2 diabetic patients reducing or discontinuing anti-diabetic medication after end of intervention
- Change in fasting plasma glucose or fasting blood glucose
- Change in total cholesterol

### *Search methods for identification of studies*

*Electronic searches*

Electronic searches will be performed in The Cochrane Library, Medline, EMBASE and Web of Science using the strategy below. Only English literature will be included.

- *The Cochrane Library*: djb OR djbs OR djbl OR endobarrier OR duodenal-jejunal OR duodenal jejunal AND diabetes.
- *Medline (PubMed):* (djb[All Fields] OR djbs[All Fields] OR djbl[All Fields] OR endobarrier[All Fields] OR duodenal-jejunal[All Fields] OR (("duodenum"[MeSH Terms] OR "duodenum"[All Fields] OR "duodenal"[All Fields]) AND ("jejunum"[MeSH Terms] OR "jejunum"[All Fields] OR "jejunal"[All Fields]))) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]).
- *EMBASE:* djb or djbs or djbl or endobarrier or duodenal-jejunal or duodenal jejunal and diabetes.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
- *Web of Science:* duodenal-jejunal bypass sleeve (#1); endobarrier gastrointestinal liner (#2); diabetes mellitus (#3); diabetes (#4), duodenal-jejunal (#5); weight loss (#6); #6 AND #5 AND #4 AND #3 AND #2 AND #1

*Searching other resources*

Manual searches will include scanning of reference lists in relevant papers, specialist journals and conference proceedings. Additional trials will be sought via the WHO Trial Register[18] and through correspondence with experts. The website of the producer of the DJBS device (GI Dynamics Inc.) will be sought for available material[19].

### *Data collection and analysis*

Two authors (UR and NH) will independently extract data and resolve disagreements through discussion before analysis. In case of unresolved matters, a third party will be involved. If necessary data are not included in the published trial reports, the authors of the included trial will be contacted for further information.

### *Selection of studies*

The trials identified via electronic and manual searches will be listed. Included trials will be selected using the above mentioned criteria. Trials that are excluded will be listed with the reason for exclusion. All authors participate in the selection of trials.

### *Data extraction and management*

The following data will be extracted from the included trials:

- Patient characteristics: inclusion criteria, proportion of patients with type 2 diabetes, mean age, mean BMI, proportion of men/women, mean HbA1c and mean body weight
- Characteristics of interventions: type and duration of interventions
- Characteristics of trial: number of clinical sites, country of origin and funding

### *Assessment of reporting bias*

We aim to compare trial protocols with subsequent publications when available and will extract whether clinically relevant outcomes are reported

### *Assessment of risk of bias in included trials*

Due to expected inclusion of different types of studies, the following assessment of risk of bias will be used. For *randomised studies* randomization methods will be extracted as the primary measure of bias control. The randomization methods will be assessed on the allocation sequence generation (classified as adequate if based on computer-generated random numbers, a table of random numbers or similar), allocation concealment (classified as adequate if randomization was performed through a independent central unit, identically appearing treatments, serially numbered opaque sealed envelopes or similar) and incomplete data outcome (whether all patients were accounted for). With regard to blinding (detection and performance bias) data will be extracted in order to assess whether single or double blinding were performed. Blinding methods will be evaluated (e.g. use of placebo). Persons who were blinded with regard to the intervention will be assessed (i.e. patients, health care providers or other persons involved in the trial). For *other types of studies* incomplete outcome data (attrition bias), e.g. patients lost to follow up, will be evaluated as a measure of attrition bias. Outcome reporting (reporting bias) - the extent to which clinically relevant outcome measures are reported and differences between trial protocols and subsequent reports - will be evaluated and reported as a marker of reporting bias. Other biases will include sample size calculations and the extent to which the planned sample size was achieved. All non-randomized studies will be classified as high risk of bias.

### *Measures of treatment effect*

Dichotomous data will be analysed using risk differences and continuous data using weighted mean differences, both with 95% confidence intervals. Relative risk will be calculated.

### *Assessment of heterogeneity*

The intertrial heterogeneity will be expressed as $I^2$ values. The general interpretation of the $I^2$ values is:

- 0 to 40%: might not be important
- 30 to 60%: may represent moderate heterogeneity
- 50 to 90%: may represent substantial heterogeneity
- 75 to 100%: considerable heterogeneity

Intertrial heterogeneity, small study effects and risk of bias will be evaluated via regression analysis (Egger's test).

### *Dealing with missing data*

Intention-to-treat analyses including all patients randomized will be performed. In the case of patients with missing outcome data, the last observation carried forward will be used. Individual patient data will be sought from the original source or from the published trial reports where individual patient data are unavailable.

***Data analysis***

STATA (Stata Corp, Texas, USA, version 12) will be used for analyses. The primary meta-analyses will be performed using random effects models due to an expected intertrial heterogeneity.

*Subgroup analysis and investigation of heterogeneity*

Subgroup analyses will be performed to assess the impact of patient, intervention, trial characteristics and intertrial heterogeneity. The test for subgroup differences will be calculated for all subgroups and the results presented as $P$ and $I^2$ values, respectively.

*Sensitivity analysis*

To assess the impact of small trials, fixed effect meta-analyses will be executed. Additional sensitivity analyses with exclusion of trials classified as having unclear adequate randomization will also be performed.

***Unit-of-analysis issues***

In the analysis each patient will be counted for only once. If necessary the same follow-up time point will be chosen to have as much data as possible to do the analysis even though the follow-up period may be longer for the individual trial. This will increase heterogeneity with regards to follow-up time, but may increase the possibility of reporting bias. Otherwise the longest follow-up will be used.

## ETHICS AND DISSEMINATION

This study will evaluate the impact of the DJBS on weight loss, type 2 diabetes (HbA1c) and safety. Furthermore, the effect on fasting plasma or blood glucose, reduction in anti-diabetic medication and changes in blood lipids will be investigated. The study will hopefully shed light on the novel minimally invasive and reversible technique of DJBS and, thus, provide knowledge about the use of it in the treatment of obesity and type 2 diabetes. The study will be disseminated by peer-review publication and conference presentation.

## HISTORY

Protocol first published: xx.xx.xxxx

## CONTRIBUTION OF AUTHORS

Ulrich Rohde and Nora Hedbäck have prepared this protocol in collaboration with Tina Vilsbøll, Lise L. Gluud and Filip K. Knop. All authors have participated in search strategy development. Ulrich Rohde and Nora Hedbäck will extract data and draft a paper describing the systematic review. The remaining authors will critically review the manuscript.

## FUNDING

Ulrich Rohde and Filip K. Knop are supported by The Danish Council for Independent Research Medical Sciences. Otherwise this study did not receive funding from any funding agency in the public, commercial or not-for-profit sectors.

## DECLARATION OF INTEREST

The authors declare no conflict of interests.

## Figure legend

Figure 1. The Endobarrier Gastrointestinal Liner (left) – and in situ (right, animated)

## REFERENCES


1 WHO | 10 facts on obesity. WHO. http://www.who.int/features/factfiles/obesity/en/index.html (accessed 29 Apr2013).

2 Buchwald H, Avidor Y, Braunwald E, *et al.* Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004;**292**:1724–37.

3 Knop FK. Resolution of type 2 diabetes following gastric bypass surgery: involvement of gut-derived glucagon and glucagonotropic signalling? *Diabetologia* 2009;**52**:2270–6.

4 Dirksen C, Jørgensen NB, Bojsen-Møller KN, *et al.* Mechanisms of improved glycaemic control after Roux-en-Y gastric bypass. *Diabetologia* 2012;**55**:1890–901.

5 Buchwald H, Estok R, Fahrbach K, *et al.* Trends in mortality in bariatric surgery: a systematic review and meta-analysis. *Surgery* 2007;**142**:621–632; discussion 632–635.

6 Bal BS, Finelli FC, Shope TR, *et al.* Nutritional deficiencies after bariatric surgery. *Nature reviews Endocrinology* Published Online First: 24 April 2012. doi:10.1038/nrendo.2012.48

7 Fishman E, Melanson D, Lamport R, *et al.* A novel endoscopic delivery system for placement of a duodenal-jejunal implant for the treatment of obesity and type 2 diabetes. *Conf Proc IEEE Eng Med Biol Soc* 2008;**2008**:2501–3.

8 Gersin KS, Rothstein RI, Rosenthal RJ, *et al.* Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. *Gastrointest Endosc* 2010;**71**:976–82.

9 Tarnoff M, Shikora S, Lembo A. Acute technical feasibility of an endoscopic duodenal-jejunal bypass sleeve in a porcine model: a potentially novel treatment for obesity and type 2 diabetes. *Surg Endosc* 2008;**22**:772–6.

10 Tarnoff M, Rodriguez L, Escalona A, *et al.* Open label, prospective, randomized controlled trial of an endoscopic duodenal-jejunal bypass sleeve versus low calorie diet for pre-operative weight loss in bariatric surgery. *Surg Endosc* 2009;**23**:650–6.

11 Rodriguez L, Reyes E, Fagalde P, *et al.* Pilot clinical study of an endoscopic, removable duodenal-jejunal bypass liner for the treatment of type 2 diabetes. *Diabetes Technol Ther* 2009;**11**:725–32.

12 Schouten R, Rijs CS, Bouvy ND, *et al.* A multicenter, randomized efficacy study of the EndoBarrier Gastrointestinal Liner for presurgical weight loss prior to bariatric surgery. *Ann Surg* 2010;**251**:236–43.

13 De Jonge C, Rensen SS, Verdam FJ, *et al.* Endoscopic Duodenal-Jejunal Bypass Liner Rapidly Improves Type 2 Diabetes. *Obes Surg* Published Online First: 23 March 2013. doi:10.1007/s11695-013-0921-3

14 WHO | Diabetes. http://www.who.int/mediacentre/factsheets/fs312/en/index.html (accessed 20 Sep2012).

15 Cochrane Handbook for Systematic Reviews of Interventions | The Cochrane Collaboration. http://www.cochrane.org/training/cochrane-handbook (accessed 20 Sep2012).

16 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–269, W64.

17 Inzucchi SE, Bergenstal RM, Buse JB, *et al.* Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012;**55**:1577–96.

18 WHO | About the ICTRP Search Portal. WHO. http://who.int/ictrp/search/en/ (accessed 20 Sep2012).

19 GI Dynamics. http://www.gidynamics.com/index.php (accessed 20 Sep2012).

Figure 1. The Endobarrier Gastrointestinal Liner (left) – and in situ (right, animated)

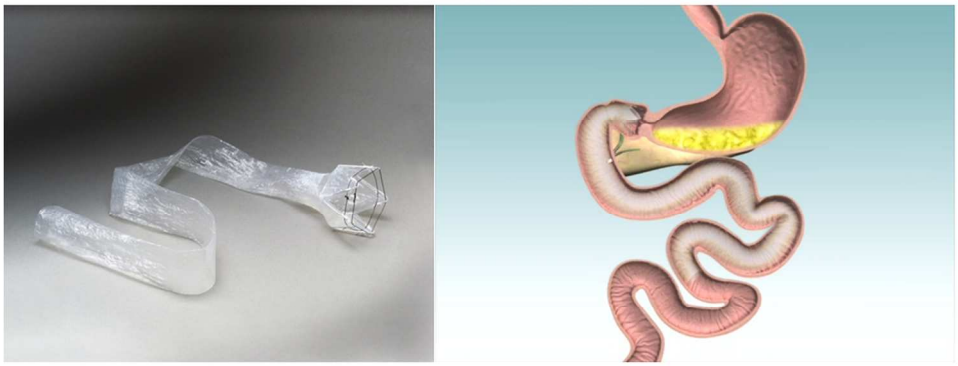

Figure 1. The Endobarrier Gastrointestinal Liner (DJBS) (left) – and in situ (right, animated)
192x90mm (300 x 300 DPI)