
Application 1367

Final Protocol to
guide the assessment
of a duodenal jejunal
bypass liner for the
treatment of clinically
severe obesity

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft protocol that will be used to guide the assessment of an intervention for a particular population of patients. The draft protocol that will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

- P**atients – specification of the characteristics of the patients in whom the intervention is to be considered for use;
- I**ntervention – specification of the proposed intervention
- C**omparator – specification of the therapy most likely to be replaced by the proposed intervention
- O**utcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Purpose of application

A proposal for an application requesting the Medicare Benefits Schedule (MBS) listing of a duodenal jejunal bypass liner (EndoBarrier[®]) was received from GI Dynamics by the Department of Health in September 2013. The proposal relates to a new intervention for the treatment of patients with clinically severe obesity.

It is proposed that this protocol should guide the assessment of the safety, effectiveness and cost-effectiveness of EndoBarrier in the requested populations to inform MSACs decision-making regarding public funding of the procedure.

Although GI Dynamics is not seeking branded MBS listing, the protocol frequently refers to the EndoBarrier brand name for clarity and simplicity. If implemented, the proposed MBS item descriptors would apply to all duodenal jejunal bypass liners registered for use in Australia; however, to the Sponsor's knowledge, the EndoBarrier is the only currently available product that fits this description.

Background

This Protocol for EndoBarrier requests reimbursement for a duodenal jejunal bypass liner that is temporarily implanted in patients to treat clinically severe obesity. For implantation, it is proposed by the applicant that the service will be available to patients with clinically severe obesity. Within this broad population, the following subpopulations will be examined separately:

- a) Patients with uncontrolled type 2 diabetes mellitus;
- b) Patients who are not suitable for bariatric surgery (including patients who are contra-indicated for surgery and "bridge" patients); and
- c) Patients who are eligible for bariatric surgery but have a preference for EndoBarrier.

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health and result in reduced life expectancy. Excess weight is a risk factor for a range of serious diseases, including type 2 diabetes, osteoarthritis, cardiovascular disease, and a variety of cancers (Preventative Health Taskforce, 2009). Direct benefits of weight loss include an increase in insulin sensitivity, improvement in glycaemic control, improved lipid profiles, decreased triglycerides and LDL cholesterol and improved blood pressure, mental health and quality of life (Wing et al., 1991; Maggio and Pi-Sunyer, 1997; Pi-Sunyer, 2000).

Current arrangements for public reimbursement

Currently, the implantation of EndoBarrier is not reimbursed through Medicare or subject to public funding by any other means. Patients who would like access to treatment must currently pay for the device, implantation and removal of the device out of their own pocket. In most cases, EndoBarrier is delivered in private hospitals and obesity clinics, with the service provided by a physician trained in endoscopy.

GI Dynamics has initiated an application to have the EndoBarrier device included on the Prostheses List. If the current MSAC application is successful, it is expected the gastrointestinal liner and the associated delivery and removal systems for EndoBarrier will be included on the Prostheses list and funded by private health insurance companies.

In Australia, EndoBarrier is available at a number of medical centres and has been used in over 100 patients.

Regulatory status

EndoBarrier was approved by the Therapeutic Goods Administration (TGA) in July 2011. The TGA-approved indication for the liner is as follows:

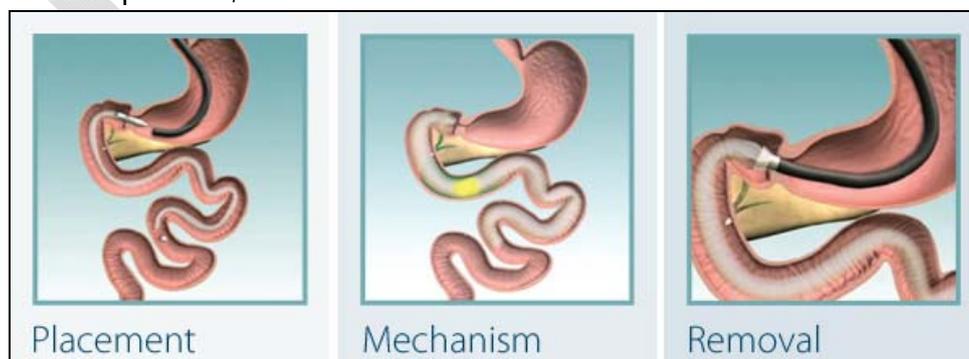
"The gastrointestinal liner system is used for the treatment of type 2 diabetes and obesity. It is provided sterile and consists of an implant (anchor and liner), preloaded in a catheter that delivers the implant to the proximal intestine".

Intervention

Description

EndoBarrier is a duodenal jejunal bypass liner that achieves the metabolic effects of a surgical gastric bypass, with the potential for reduced risk. EndoBarrier has been implanted in more than 1300 patients worldwide as of March 2014. The system consists of two components: the EndoBarrier delivery system and the EndoBarrier retrieval system. The EndoBarrier delivery system includes the gastrointestinal liner preloaded on a custom delivery catheter, while the EndoBarrier retrieval system consists of a Grasper and Retrieval Hood, used with an endoscope to remove the liner upon completion of therapy. The role of each component in the placement, mechanism and removal of the GI liner is illustrated in Figure 1 below.

Figure 1: EndoBarrier placement, mechanism and removal



Source: Schouten et al 2010

This EndoBarrier gastrointestinal liner is a fluoropolymer sheath which is placed in the duodenum just beyond the stomach and stretches into the first part of the small bowel. Its mechanism of action most closely resembles surgical duodenal jejunal gastric bypass. Both procedures produce an effect

on weight-loss and glucose metabolism through preventing nutrient contact with the proximal intestinal mucosa. With EndoBarrier, bile and pancreatic secretions pass along the outer wall of the impermeable 60-cm liner and mix with the chyme as it exits distal to the liner in the jejunum. By creating a physical barrier to food absorption, EndoBarrier reduces the uptake of nutrients from the first part of the small bowel and may also have an effect on key metabolic hormones, including incretin. By modifying normal processes of nutrient absorption, EndoBarrier may result in substantial clinical benefits in terms of weight loss and glycaemic status.

Clinical data suggest that EndoBarrier therapy improves glycaemic levels by affecting key hormones involved in insulin sensitivity, glucose metabolism, satiety and food intake. EndoBarrier therapy has also been shown to produce rapid and sustained weight loss, and may improve cardiometabolic risks, including blood pressure, LDL and triglycerides. A summary of the effects of EndoBarrier on metabolic control is provided in Attachment A.

Delivery of the intervention

The EndoBarrier delivery system is provided sterile, and consists of a gastrointestinal liner (anchor and liner), preloaded in a catheter that delivers the liner to the proximal intestine. The catheter is inserted through the mouth and guides the gastrointestinal liner through the stomach, and into the duodenum. A small anchoring device on the liner keeps the liner in place.

Patients require anaesthesia before the device is implanted with endoscopy used to guide its placement. The endoscopy also serves a diagnostic purpose to determine if a patient is anatomically suitable for implantation with the EndoBarrier device. If a patient is found to be suitable, implantation of the EndoBarrier can take place immediately. X-ray is used during the procedure to ensure that the liner is in the correct position.

An experienced physician with training for endoscopy can perform the implantation, usually with the assistance of a nurse or assistant. In Australia EndoBarrier insertion is typically a (hospital inpatient) day procedure centre; however in some cases hospitalisation may be required. The EndoBarrier device is approved for implantation for up to 12 months; however it may be removed earlier at the patient's request or if it is clinically warranted. Removal of the device is undertaken through another endoscopic procedure, using the EndoBarrier Liner Retrieval System, consisting of a Grasper and a Retrieval Hood, which are compatible with standard endoscopes.

The training protocol for EndoBarrier strongly emphasises that the device is indicated for a placement period of up to 12 months. Any use beyond this duration is unsupported by clinical evidence. Furthermore, to be eligible for implantation, patients should be screened to ensure they are not considered at high risk of loss to follow-up.

The "Instructions for Use" for the delivery and removal of EndoBarrier are provided in Attachment B and Attachment C, respectively.

Prerequisites

It is expected that EndoBarrier will be delivered by a physician with training for endoscopy that is recognised by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy. GI Dynamics currently provides specialists with training on how to implant and remove the device; however this training is not associated with any formal accreditation.

The insertion of the liner will require the attendance of at least one trained specialist in bariatric surgery and/or gastroenterology and the assistance of a nurse or assistant. The main infrastructure needs for the procedure are associated with administering anaesthesia and performing x-ray and endoscopy. This equipment is already available at most hospitals. Therefore, the use of EndoBarrier will not require additional resources in terms of capital equipment or infrastructure. Removal of the device is also not associated with any specific infrastructure requirements other than anaesthesia and x-ray equipment.

As an elective procedure, patients who do not have close access to a centre with endoscopy facilities and an appropriate specialist have the option to travel in order to receive EndoBarrier therapy. As EndoBarrier can be implanted in any centre that currently performs bariatric surgery, access to treatment will be at least as broad.

Co-administered and associated interventions

To minimise the risk of bleeding, patients receiving treatment with EndoBarrier are required to take a proton pump inhibitor (PPI) for the duration of therapy (e.g. omeprazole). The recommendation to use a PPI with EndoBarrier was developed in response to bleeding events observed in early clinical trials using the first generation device; however improvements in the bleeding rate have been observed in recent trials.

The submission will present evidence from clinical trials of EndoBarrier to assess the risk of bleeding, including the use of PPIs to prevent bleeding, as part of its evaluation of clinical safety. The costs of PPI therapy will be included in the economic evaluation. Aside from this, patients implanted with EndoBarrier do not require any co-administered interventions other than anti-diabetic medications already being taken.

The implantation of EndoBarrier will require an endoscopy to determine if a patient is physiologically suitable for treatment; however, this procedure is included in the proposed MBS item for the insertion of the duodenal-jejunal liner. If no issues are identified during endoscopy, the EndoBarrier will be implanted in the same visit. A small minority of patients will be excluded from treatment with EndoBarrier based on the results of endoscopic imaging. These patients will incur an MBS item fee for diagnostic endoscopy only (MBS item 30473) or the MBS item for discontinued operative procedures (MBS item 30001).

Listing proposed and options for MSAC consideration

Proposed MBS listing

The proposed MBS item descriptors for the insertion and removal of EndoBarrier are provided in Table 1. Two separate item descriptors are proposed: for the implantation of EndoBarrier and the removal of the device.

For implantation, it is proposed that the service will be available to patients with clinically severe obesity either in those who are not suitable for bariatric surgery (in patients who are contra-indicated for surgery and “bridge” patients); and in patients who are eligible for bariatric surgery but have a preference for EndoBarrier.

The EndoBarrier will be delivered to patients once, and will remain implanted for up to a year. At this stage, patients will be eligible for implantation once per lifetime; however, there is an emerging body of evidence to support the clinical benefits of re-implantation. It is proposed this emerging body of evidence be reviewed in a future MSAC submission and/or review at which point the words “to be claimed once in the patient’s lifetime” could be removed from the item descriptor should the evidence support this.

Table 1: Proposed MBS item descriptor for insertion and removal of EndoBarrier

MBS [TBD] (Insertion of device)	Category [category number] – [Category description]
DUODENAL-JEJUNAL BYPASS LINER, implantation of, including diagnostic endoscopy in a patient who has clinically severe obesity. Claimed once per patient’s lifetime. The service is performed by a specialist with endoscopic training that is recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy. (Anaes.) (Assist.) Fee: \$[TBD] Note: The term clinically severe obesity generally refers to a patient with a Body Mass Index (BMI) of 40kg/m ² or more, or a patient with a BMI of 35kg/m ² or more with other major medical co-morbidities (such as diabetes, cardiovascular disease, cancer). The BMI values in different population groups may vary due, in part, to different body proportions which affect the percentage of body fat and body fat distribution. Consequently, different ethnic groups may experience major health risks at a BMI that is below the 35-40 kg/m ² provided for in the definition. The decision to undertake obesity surgery remains a matter for the clinical judgment of the surgeon.	

MBS [TBD] (Removal of device)	Category [category number] – [Category description]
DUODENAL-JEJUNAL BYPASS LINER, removal of within 12 months of placement or prior due to medical reasons, including endoscopy. (Anaes.) (Assist.) Fee: \$[TBD]	

Current MBS item descriptors for the surgical treatment of clinically severe obesity (MBS items 31569 to 31581) define clinically severe obesity as BMI ≥ 40 or between 35 and 40 where there are other major medical conditions such as high blood pressure and diabetes. However, due to some variability in the health risks between individuals of the same BMI (especially on the basis of ethnicity), the definition of clinically severe obesity is accompanied by a note stating that "the decision to undertake obesity surgery remains a matter for the clinical judgment of the surgeon" (MBS note T8.30).

It is proposed that the item descriptor for the implantation of EndoBarrier should include a note to define "clinically severe obesity", similar or identical to the note (MBS note T8.30) currently associated with bariatric procedures on the MBS (Items 31569 to 31581). This is consistent with the clinical trial evidence for EndoBarrier in obese patients, which mostly consists of patients with BMI ≥ 40 kg/m² or 35 kg/m² with significant co-morbidities. Patients with clinically severe obesity, but who are unsuitable for treatment with bariatric surgery, have limited treatment options. It is proposed that this population should be eligible for treatment with EndoBarrier.

Clinical place for proposed intervention

It is proposed that the population eligible for treatment with EndoBarrier will consist of patients with clinically severe obesity. Most obesity guidelines agree that all patients should initially attempt behavioural, lifestyle and dietary modifications to lose weight. Despite these interventions, it is generally agreed that obesity is a chronic disorder with a high likelihood of recurrence. This is especially true of severely obese patients, who generally require more intensive care strategies to produce sustainable weight loss (NHMRC, 2013). Table 2 summarises recommendations from some key evidence-based clinical practice guidelines. Only recommendations relating specifically to the management of clinically severely obese patients are listed. The guidelines are generally consistent in their advice that for severely obese patients (i.e. patients with a BMI ≥ 40 kg/m², or between 35 kg/m² and 40 kg/m² and other significant disease), consideration of some form of bariatric surgery is strongly recommended if behavioural modifications have been unsuccessful. In addition to producing weight-loss, bariatric surgery can be effective in achieving glycaemic control. This outcome is especially relevant for patients with clinically severe obesity who also have type 2 diabetes mellitus as a co-morbidity.

Table 2 Clinical practice guideline recommendations for morbid (severe) obesity

Guideline	Recommendations for clinically severe obesity
<p>NHMRC (2013) Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults. Canberra: National Health and Medical Research Council.</p>	<p>For adults with BMI > 40 kg/m², or adults with BMI > 35 kg/m² and comorbidities that may improve with weight loss, bariatric surgery may be considered, taking into account the individual situation (Grade A).</p> <p>For adults with BMI ≥ 30 kg/m², or adults with BMI ≥ 27 kg/m² and comorbidities, orlistat may be considered as an adjunct to lifestyle interventions, taking into account the individual situation (Grade A).</p>
<p>NICE (2006) Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children: National Institute for Health and Clinical Excellence</p>	<p>Bariatric surgery is recommended as a treatment option for adults with obesity if all of the following criteria are fulfilled:</p> <ul style="list-style-type: none"> - they have a BMI of 40 kg/m² or more, or between 35 kg/m² and 40 kg/m² and other significant disease (for example, type 2 diabetes or high blood pressure) that could be improved if they lost weight - all appropriate non-surgical measures have been tried but have failed to achieve or maintain adequate, clinically beneficial weight loss for at least 6 months - the person has been receiving or will receive intensive management in a specialist obesity service - the person is generally fit for anaesthesia and surgery - the person commits to the need for long-term follow-up <p>Bariatric surgery is also recommended as a first-line option (instead of lifestyle interventions or drug treatment) for adults with a BMI of more than 50 kg/m² in whom surgical intervention is considered appropriate.</p> <p>Orlistat should be prescribed only as part of an overall plan for managing obesity in adults who meet one of the following criteria:</p> <ul style="list-style-type: none"> - a BMI of 28.0 kg/m² or more with associated risk factors - a BMI of 30.0 kg/m² or more
<p>Lau DCW, Douketis JD, Morrison KM, et al., for the Obesity Canada Clinical Practice Guidelines Expert Panel 2006. Canadian clinical practice guidelines on the management and prevention of obesity in adults and children. CMAJ 2007;176(8 Suppl): online 1-117</p>	<p>Adults with clinically severe obesity (BMI ≥ 40 kg/m² or ≥ 35 kg/m² with severe comorbid disease) may be considered for bariatric surgery when lifestyle intervention is inadequate to achieve healthy weight goals (Grade B).</p>
<p>SIGN (2010) Management of obesity. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network</p>	<p>Bariatric surgery should be considered on an individual case basis following assessment of risk/benefit in patients who fulfil the following criteria:</p> <ul style="list-style-type: none"> - BMI ≥35 kg/m² - presence of one or more severe comorbidities which are expected to improve significantly with weight reduction (e.g. severe mobility problems, arthritis, type 2 diabetes) <p>Orlistat should be considered as an adjunct to lifestyle interventions in the management of weight loss. Patients with BMI ≥28 kg/m² (with comorbidities) or BMI ≥30 kg/m² should be considered on an individual case basis following assessment of risk and benefit.</p>

Despite these recommendations, only a small proportion of obese patients in Australia eventually resort to surgery. Table 3 summarises the various types of bariatric surgery and provides the number of MBS services provided for each procedure based on Medicare statistics. Until July 2013, the MBS items under which bariatric surgery procedures were billed included a range of bariatric procedures. On the basis of recommendations made in the recent MBS review of items for the surgical treatment of obesity (MBS Review 3), a number of surgical items numbers have been created so that each specific surgery procedure is associated with an individual item. Therefore, data on the utilisation of different surgical procedures is only available from the period between July 2013 and December 2013. Based on these data, it appears that currently, the two most common bariatric procedures are gastric banding and sleeve gastrectomy. Other surgical procedures such as gastroplasty and gastric bypass surgery are declining due to the advent of less invasive procedures. Relative to the total number of patients with clinically severe obesity, it is apparent that only a small proportion of patients receive bariatric surgery, and the vast majority of patients are likely to persist with standard of care. The NHMRC guideline (2013) observes that in Australia, access to surgery under the public health system is limited and services for bariatric surgery and necessary follow-up may be even more limited in rural and remote areas. In addition, it is noted that while bariatric surgery can achieve long-term weight-loss, the surgery is not always successful and revision is frequently required.

Table 3 Summary of different types of bariatric surgery

Surgical procedure	Current MBS item	Description	Fee	Number of MBS items processed July-Dec 2013	Eligible population
<i>Gastric reduction/gastroplasty</i>					
Adjustable gastric banding (AGB)/Laparoscopic adjustable gastric banding (LAGB)	31569	A surgical procedure in which a small silicone band is placed around the top of the stomach to produce a small pouch about the size of a thumb, thereby limiting food intake.	\$849.55	1,871	Clinically severe obesity ^a
Sleeve gastrectomy (SG)	31575	Involves removing the lateral 2/3 of the stomach with a stapling device. It leaves a stomach tube instead of a stomach sack.	\$849.55	3,654	Clinically severe obesity ^a
Vertical banded gastroplasty (stomach stapling) (VGB)	31578	The upper stomach near the oesophagus is stapled vertically to create a small pouch along the inner curve of the stomach. The outlet from the pouch to the rest of the stomach is restricted by a band.	\$849.55	15	Clinically severe obesity ^a
<i>Gastric bypass</i>					
Biliopancreatic diversion (BPD) Biliopancreatic diversion with duodenal switch (BPD-DS)	31581	The first two segments of the small intestine, the duodenum and jejunum, are bypassed and the stomach pouch is attached to the ileum. BPD in conjunction with DS is an additional adaptation where a proportion of the duodenum remains attached to the stomach.	\$1,045.40	7	Clinically severe obesity ^a

Surgical procedure	Current MBS item	Description	Fee	Number of MBS items processed July-Dec 2013	Eligible population
Roux-en-Y gastric bypass (RYGB)	31572	A small stomach pouch is created to restrict food intake. Next, a Y-shaped section of the small intestine is attached to the pouch to allow food to bypass the lower stomach, the duodenum (the first segment of the small intestine), and the first portion of the jejunum (the second segment of the small intestine).	\$1,045.40	355	Clinically severe obesity ^a

Sources: Schouten R., RijsBegg S, Vos T, Barker B, Stevenson C, Stanley L, Lopez AD (2007) The burden of disease and injury in Australia in 2003, AIHW Preventative Health Taskforce (2009) Australia: the healthiest country by 2020, [http://www.health.gov.au/internet/preventativehealth/publishing.nsf/Content/E233F8695823F16CCA2574DD00818E64/\\$File/obesity-jul09.pdf](http://www.health.gov.au/internet/preventativehealth/publishing.nsf/Content/E233F8695823F16CCA2574DD00818E64/$File/obesity-jul09.pdf), accessed 12 April 2013.

^a The term clinically severe obesity generally refers to a patient with a Body Mass Index (BMI) of 40kg/m² or more, or a patient with a BMI of 35kg/m² or more with other major medical co-morbidities (such as diabetes, cardiovascular disease, cancer). The BMI values in different population groups may vary due, in part, to different body proportions which affect the percentage of body fat and body fat distribution. Consequently, different ethnic groups may experience major health risks at a BMI that is below the 35-40 kg/m² provided for in the definition. The decision to undertake obesity surgery remains a matter for the clinical judgment of the surgeon.

On this basis, the clinical place for EndoBarrier in patients with clinically severe obesity is likely to be used as an addition to behavioural, lifestyle and dietary modifications (standard of care; SOC) in the majority of patients, and as a substitute for bariatric surgery in a small proportion of patients.

In patients with clinically severe obesity who are not suitable for bariatric surgery, there are two relevant subpopulations:

- a. Patients with contra-indications for bariatric surgery
- b. "Bridge" patients who are currently not suitable for bariatric surgery due to excess weight and co-morbidities, but may become eligible through significant weight-loss or improvement of other metabolic outcomes using EndoBarrier

The first group of patients is difficult to define as there are no absolute contraindications to bariatric surgery. Relative medical contraindications to surgery may include severe gastrointestinal disease, uncontrolled obstructive sleep apnoea with portal hypertension, and serious blood or autoimmune disorders, severe heart failure, unstable coronary artery disease, end-stage lung disease, active cancer diagnosis/treatment or cirrhosis with portal hypertension. Laparoscopic surgery may be difficult or impossible in patients with giant ventral hernias, severe intra-abdominal adhesions, large liver, high BMI with central obesity or physiological intolerance of pneumoperitoneum (SAGES, 2008). In addition, patients must be able to give fully informed consent to bariatric surgery and commit to post-operative care plans. Therefore, bariatric surgery should not be performed on patients who have serious psychological or psychiatric disorders such as drug/alcohol dependency, significant intellectual

impairment or active psychosis. These contraindications are supported by a range of international guidelines (Fried et al., 2008; Dixon et al., 2011).

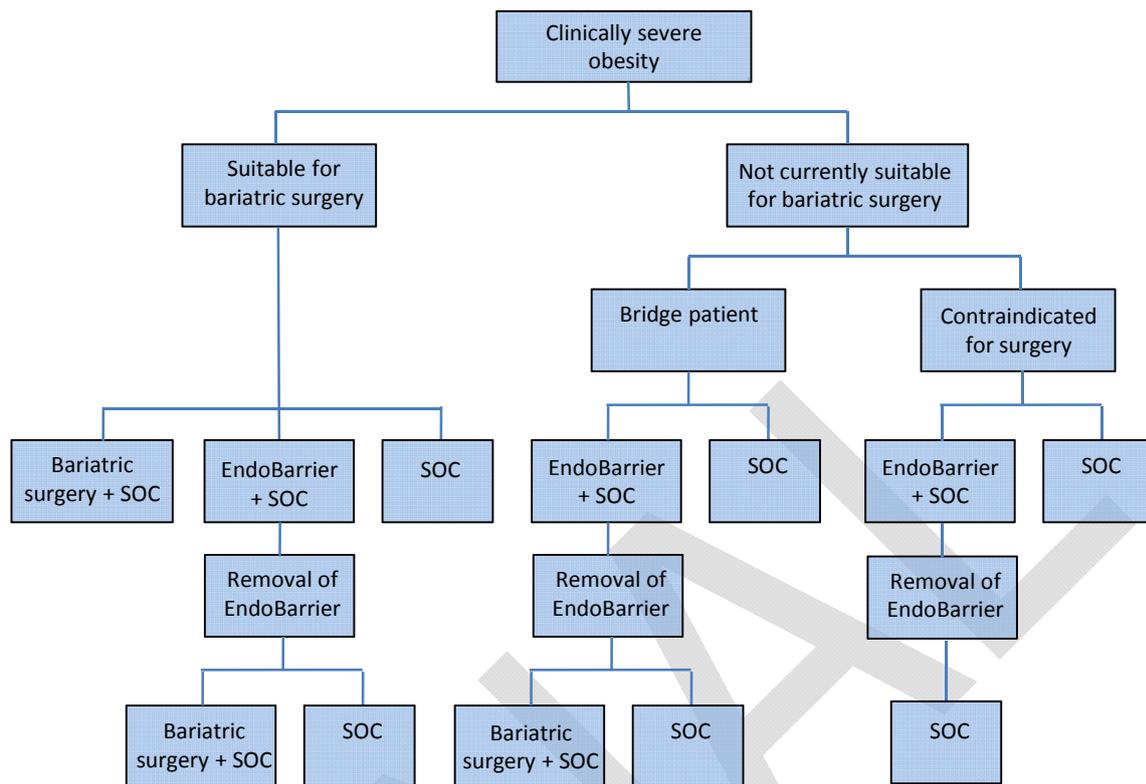
While most patients with the aforementioned contraindications will never be eligible for bariatric surgery, another group ("bridge" patients) may become eligible for bariatric surgery after a successful weight-loss intervention. The intent of this approach is to promote weight loss specifically to reduce the risk from a subsequent intervention, including bariatric surgery. The American Society for Gastrointestinal Endoscopy (ASGE) and the American Society for Metabolic & Bariatric Surgery (ASMBS) Task Force on Endoscopic Bariatric Therapy states in a white paper on the topic that patients with Class III (BMI >50) obesity and those with metabolic co-morbidities present greater technical challenges and surgical risk than less obese, healthier patients. Furthermore, these effects are more pronounced in patients with BMI >60 where there is a greater risk of morbidity or mortality than patients with BMI 45-60 (ASGE/ASMBS, 2011).

Both groups of patients follow the same clinical algorithm for weight-loss as outlined in Table 2, that is to say patients should initially attempt behavioural, lifestyle and dietary modifications to lose weight. If these initial strategies are unsuccessful, bariatric surgery is not an option (by definition). In these patients, EndoBarrier will provide a treatment option where few alternatives currently exist, and will prevent many from experiencing substantial deterioration in health outcomes over time.

In the proposed clinical algorithm patients with clinically severe obesity, but for whom bariatric surgery is not considered suitable, EndoBarrier will be used in addition to SOC. For "bridge" patients, subsequent bariatric surgery may be considered as a downstream option after successful weight-loss using EndoBarrier.

Figure 2 presents the proposed clinical management algorithm for EndoBarrier in the treatment of patients with clinically severe obesity.

Figure 2 Clinical management algorithm for clinically severe obesity



Clinically severely obese: BMI $\geq 40\text{kg/m}^2$ or BMI $\geq 35\text{kg/m}^2$ with co-morbidities

Notes:

Patients are eligible for one EndoBarrier procedure per lifetime

Patients receiving anti-platelet or anti-coagulant therapy are excluded

Abbreviations: SOC, standard of care

Comparator

As discussed above, it is expected that in patients with clinically severe obesity, EndoBarrier will be an add-on to SOC (including behavioural, lifestyle and dietary modifications) or bariatric surgery.

SOC consists of behavioural, lifestyle and dietary modifications, as well as pharmacological therapy with anti-diabetic medications in the subgroup of patients with comorbid type 2 diabetes mellitus.

Bariatric surgery includes a variety of procedures that aim to reduce the size of the stomach with a gastric band (gastric reduction), removal of a portion of the stomach (gastroplasty) or by resecting and re-routing the small intestines to a small stomach pouch (gastric bypass surgery). The choice of procedure will depend on a patient's weight-loss goals, resources, and current health. Of the different types of bariatric surgery, it is expected that gastric banding is the most likely to be replaced by EndoBarrier if it were approved for reimbursement in patients with clinically severe obesity. Like gastric banding, EndoBarrier has the advantages of no alteration to gastrointestinal tract or anastomosisreversibility, and lower operative mortality and morbidity compared with other bariatric

procedures. Although sleeve gastrectomy appears to be widely used, it is relatively radical procedure that involves dividing the stomach vertically to reduce its size to about 25%. The operation is non-reversible and is usually performed laparoscopically. The mechanism of action of EndoBarrier most closely mimics surgical duodenal jejunal gastric bypass (Roux-en-Y gastric bypass); however the number of these procedures performed is relatively low due to an increasing reluctance for procedures that involve extreme and permanent modification of the anatomy. The MBS item descriptor for gastric banding is presented in Table 4 below. It should be noted that patients who undergo gastric banding often require gastric band adjustments (MBS item 31587), and some patients choose to eventually have the procedure reversed (MBS item 31584).

Table 4: MBS item descriptor for gastric banding

Category 3 – THERAPEUTIC PROCEDURES
<p><u>MBS 31569</u></p> <p>Adjustable gastric band, placement of, with or without crural repair taking 45 minutes or less, for a patient with clinically severe obesity</p> <p>Multiple Services Rule (Anaes.) (Assist.)</p> <p>Fee: \$849.55 Benefit: 75% = \$637.20</p>

This submission proposes that the main comparator for EndoBarrier in patients with clinically severe obesity will be a weighted comparator comprising SOC and bariatric surgery. The final weighting given to each intervention included in the comparator (SOC and bariatric surgery) will be determined on the basis of the relative use of these two approaches in the Australian population. As discussed previously, the uptake of bariatric surgery is small relative to the size of the eligible population.

In clinically obese patients who are unsuitable for bariatric surgery, EndoBarrier is an alternative to SOC (consisting of behavioural and lifestyle interventions for weight-loss). This submission proposes that in the subgroup of patients with clinically severe obesity who are not suitable for bariatric surgery, the main comparator will be SOC alone.

Clinical claim

As described above, the MSAC submission for EndoBarrier will seek reimbursement for the procedure in patients with clinically severe obesity. The main comparator will be a weighted comparator comprising SOC and bariatric surgery. In patients who are not suitable for bariatric surgery, the main comparator will be SOC alone. Thus the submission will be based on different clinical claims for each population and comparator.

In patients for whom bariatric surgery is the main comparator:

- EndoBarrier is non-inferior to bariatric surgery in terms of clinical efficacy
- EndoBarrier is superior to bariatric surgery in terms of clinical safety

In patients for whom SOC is the main comparator

- EndoBarrier plus SOC is superior to SOC alone in terms of clinical efficacy

Note that in the absence of a full analysis of clinical data (to be completed in the final submission) the Sponsor is pre-empting the results that would form the basis of the economic evaluation. If the clinical data did not support any of these conclusions, the claims in the final application would be adjusted to reflect this.

As shown in Table 5, for all populations and comparisons, the most appropriate form of economic evaluation is a cost-utility analysis; however as discussed previously the comparators for the various subpopulations will differ. For patients with uncontrolled T2DM and clinically severe obesity, the analysis includes a weighted comparator of bariatric surgery and SOC. The weighting applied to each comparator will be determined in the final submission on the basis of the relative use of bariatric surgery and SOC in the proposed population. A similar approach will be applied to patients with clinically severe obesity who are suitable for bariatric surgery. Depending on the safety data for EndoBarrier and bariatric surgery, there is a possibility that the submission could claim a net clinical benefit for EndoBarrier due to non-inferior clinical efficacy but superior safety.

In patients with clinically severe obesity who are not considered suitable for bariatric surgery, the main comparator will be SOC alone. The comparison with SOC will be a cost-utility analysis based on superior clinical efficacy. For patients who are using EndoBarrier as a bridge to bariatric surgery, patients will proceed to surgery if the intervention is successful. These downstream consequences will be considered in the economic model.

Table 5: Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator				
		Superior		Non-inferior	Inferior	
Comparative safety versus comparator	Superior	CEA/CUA		Comparison with bariatric surgery CUA	Net clinical benefit	CEA/CUA
					Neutral benefit	CEA/CUA*
					Net harms	None^
	Non-inferior	Comparison with SOC CEA/CUA			None^	
	Inferior	Net clinical benefit	CEA/CUA	None^	None^	
		Neutral benefit	CEA/CUA*			
Net harms		None^				

Abbreviations: CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes

The clinical trials for EndoBarrier selected a range of patient relevant clinical efficacy endpoints; however the most important outcomes for the purpose of this evaluation were considered to be: weight loss, HbA1c levels and procedure-related adverse events. These outcomes are discussed in detail in the sections below.

Weight loss

Weight loss is a particularly important clinical outcome for patients with clinically severe obesity (including patients who are suitable and not suitable for surgery) and is therefore considered the primary outcome for this group.

As described previously, there is a vast body of literature to support the relationship between excess weight and the development of long-term health complications including type 2 diabetes, hypertension, dyslipidaemia, and cardiovascular disease. Although weight gain has been demonstrated to increase health risks in paediatric and adult populations, it does not necessarily follow that weight loss can reverse these impacts. The NHMRC systematic review underlying the current obesity guidelines (NHMRC, 2013) addressed this question and concluded that surgically-induced weight loss in adults (gastric banding and gastric bypass) is associated with a reduced risk of cardiovascular disease, all-cause and global mortality in patients with morbid obesity. Gastric bypass was reported to be associated with greater reductions in cardiovascular mortality than gastric banding. The results of this review validate the importance of weight loss as a clinical endpoint. Furthermore, there is clinical evidence to show that only a modest amount of weight loss is required to achieve substantial clinical benefits (Klein et al., 2004).

HbA1c levels

In the subgroup of patients with co-morbid type 2 diabetes mellitus, patient-relevant clinical endpoints such as blindness and amputations are the best measure of disease control. However, the effectiveness of diabetes management strategies is consistently improving and clinical endpoints such as amputation occur much less frequently and later in the course of the disease. Therefore, clinical trials rely on surrogate markers such as HbA1c to establish the effectiveness of diabetes treatment strategies.

The risk of developing microvascular, macrovascular and other complications is closely associated with glycaemic control, as measured by HbA1c levels. The United Kingdom Prospective Diabetes Study (UKPDS) prospective study reported that each 1% reduction in mean HbA1c was associated with a 14% reduction in the relative risk of myocardial infarction, a 37% reduction in the relative risk of microvascular complications and a 21% reduction in the relative risk of death (Stratton et al 2000). The Diabetes Control and Complications Trial (DCCT) study randomised patients to intensive or

conventional therapy, who were followed for a mean of 17 years. A decrease HbA1c was significantly associated with most of the positive effects of intensive treatment on the risk of cardiovascular disease (DCCT, 2005). A 10% reduction in HbA1c was associated with a 20% reduction in the relative risk of a cardiovascular event (95 CI 9%, 30% $p < 0.001$). The vast majority (96%) of the reduction in the risk of retinopathy was explained by the reduction in mean HbA1c level. Similar results were found for microalbuminuria (99.2% of the risk reduction explained by a reduction in HbA1c) and albuminuria (96.7% of the risk reduction explained by a reduction in HbA1c).

The validity of HbA1c is thus well established, and this outcome has been accepted by regulatory authorities worldwide as an appropriate surrogate marker of clinical effectiveness in clinical trials of new treatments. The change in HbA1c will be used in this submission as the primary measure of clinical effectiveness in the subgroup of patients with type 2 diabetes mellitus.

Adverse events

To ensure that EndoBarrier is non-inferior to its comparators in terms of safety, a comparison of safety in terms of intervention-related adverse events will be undertaken. Clinical trial evidence suggests that adverse events are generally infrequent, and of low severity. The following symptoms and adverse effects have been reported from EndoBarrier implantation in some patients:

- Nausea
- Vomiting
- Upper abdominal pain
- Bleeding
- Device migration
- Transient fever
- Obstruction with vomiting

Other outcomes

In addition to the outcomes discussed above, clinical trials of EndoBarrier evaluated a range of other efficacy endpoints associated with safety, resource-use or the risk of diabetes or cardiovascular disease. These outcomes include, but are not limited to, the following:

- Change in fasting plasma glucose (FPG) concentration
- Postprandial seven-point blood glucose profile
- Meal tolerance test (MTT)
- Percentage of subjects achieving 10% excess weight loss (EWL)
- Change in total body weight
- Change in insulin dosage
- Oral anti-diabetic drug (OAD) use
- Blood lipid levels
- Blood pressure
- Waist circumference
- Metabolic syndrome

In addition to the trial-based outcomes, the economic model will also consider some downstream health impacts such as cardiovascular events, microvascular events, quality of life and mortality.

Health care resources

Resources to deliver proposed intervention

The cost of the EndoBarrier device, including the liner, insertion and removal systems, is expected to be reimbursed on the Prostheses List and will be included in the economic evaluation. In addition to the prostheses costs, patients using EndoBarrier will incur a range of additional professional/clinic costs while the implantation and removal procedures are being undertaken all of which will be included in the economic evaluation.

As mentioned previously, an experienced physician with training for endoscopy can complete the implantation process as a (hospital) day-case procedure; however in some cases hospitalisation may be required. The insertion of the liner will require the attendance of at least one trained specialist and the assistance of a nurse or assistant. Removal of the device is undertaken through another endoscopic procedure that is less complex and time-consuming than the implantation procedure. Insertion and removal of the device will also require anaesthesia.

The MBS item fees for EndoBarrier implantation and removal will be determined in the final submission with reference to MBS-listed procedures of similar complexity. A full justification of MBS item fees for the implantation and removal of EndoBarrier in terms of resource-use will be presented in the submission-based assessment.

Resources provided in association with the proposed intervention

To minimise the risk of bleeding, all patients receiving treatment with EndoBarrier are required to take a proton pump inhibitor for the duration of therapy (e.g. omeprazole).

As part of SOC, patients with co-morbid type 2 diabetes mellitus are assumed to receive conventional anti-diabetic medications including metformin, sulfonylurea and third-line treatments such as acarbose, a DPP-4 inhibitor, a glitazone or insulin, depending on a patient's disease severity and treatment history. Although EndoBarrier will be used in addition to anti-diabetic medications there will be some reduction in their use based on a patient's response to treatment.

Resources provided to deliver comparator

As discussed previously, a proportion of patients with clinically severe obesity currently receive gastric banding. Both procedures have the advantages of no alteration to gastrointestinal tract or anastomosis, reversibility, and lower operative mortality and morbidity compared with other bariatric procedures. The costs associated with gastric banding include the MBS item fee for gastric banding (MBS item 31569) plus associated expenses such as hospitalisation and anaesthesia. Hospitalisation costs and average length of stay associated with AR-DRGs K07Z K04A and K04B.

It should be noted that patients who undergo gastric banding often require gastric band adjustments (MBS item 31587), and some patients choose to eventually have the procedure reversed (MBS item 31584). The costs of these procedures will be considered in the economic evaluation.

Resources provided in association with the comparator (SOC)

As is the case for patients implanted with EndoBarrier, patients with comorbid type 2 diabetes mellitus are assumed to receive SOC consisting of conventional anti-diabetic medications including metformin, sulfonylurea and third-line treatments such as acarbose, a DPP-4 inhibitor, a glitazone or insulin, depending on a patient's disease severity and treatment history.

Resources used in the delivery of EndoBarrier and the main comparators are summarised in Table 6. The costs of these resources will take a societal perspective incorporating government and private out of pocket costs (data permitting).

Table 6: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
No additional testing required										
Resources provided to deliver proposed intervention										
Insertion of EndoBarrier	Surgeon/specialist	Private hospital	100%	1	TBD					TBD
Acquisition of liner and removal system	Manufacturers	Private hospital	100%	1				TBD		TBD
Anaesthesia	Specialist	Private hospital	100%	1	TBD					TBD
Hospital stay or day procedure centre	Private hospital	Private hospital	100%	TBD	TBD					TBD
Removal of device	Surgeon/specialist	Private hospital	100%	1	TBD					TBD
Resources provided in association with proposed intervention										
Proton pump inhibitor	PBS	Private hospital	100%	1 (twice daily)			TBD			TBD
Anti-diabetic medications	PBS	Private hospital	TBD	TBD			TBD			TBD
Other cardiovascular medications	PBS and out of pocket	Private hospital	TBD	TBD			TBD		TBD	TBD

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to deliver comparator										
Insertion of gastric band	Surgeon/specialist	Private hospital	100%	1	\$637.20				\$212.35	\$849.55
Acquisition of gastric band	Manufacturers	Private hospital	100%	1				\$3,300		\$3,300
Anaesthesia	Specialist	Private hospital	100%	1	TBD					TBD
Hospital stay	Private hospital	Private hospital	100%	AR-DRGs K07Z K04A and K04B	TBD					TBD
Gastric Band adjustment	Private hospital	Private hospital	TBD	TBD	\$83.50				\$14.65	\$97.95
Reversal of gastric banding	Surgeon/specialist	Private hospital	TBD	TBD	\$1,154.35				\$384.75	\$1,539.10
Resources provided in association with comparator										
Anti-diabetic medications	PBS	Private hospital	TBD	TBD				TBD		TBD
Other cardiovascular medications	PBS and out of pocket	Private hospital	TBD	TBD				TBD	TBD	TBD

Abbreviations: PBS, Pharmaceutical Benefits Scheme; TBD, to be determined

* Include costs relating to both the standard and extended safety net.

Proposed structure of economic evaluation (decision-analytic)

Table 7 summarises the population, intervention, comparator and outcomes of EndoBarrier, for treatment of patients with clinically severe obesity.

Table 7: Summary of extended PICO to define research question that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
Patients with clinically severe obesity GID will present a sensitivity analysis modelling cost-effectiveness in patients with BMI>30 kg/m ² (i.e. obesity and uncontrolled type 2 diabetes).	duodenal jejunal bypass liner (EndoBarrier®)	Comparator 1: Bariatric surgery	HbA1c Weight loss Adverse events/complications Quality of life Mortality Early removal of device	EndoBarrier device (including liner) Insertion and removal of EndoBarrier Professional/clinic visits Anaesthesia Hospital stay Gastric banding device Gastric banding adjustment and removal Management of adverse events/complications
		Comparator 2: Standard of care	HbA1c Weight loss Adverse events/complications	EndoBarrier device (including liner) Insertion and removal of EndoBarrier Professional/clinic visits Anaesthesia Hospital stay

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
			Quality of life Mortality Early removal of device	Management of adverse events/complications Anti-diabetic medication Costs associated with CV, macrovascular and microvascular events Subsequent bariatric surgery
Patients with clinically severe obesity who are not suitable for bariatric surgery (including "bridge" patients and patients with contraindications for surgery)	duodenal jejunal bypass liner (EndoBarrier®)	Standard of care	Weight loss Adverse events/complications Quality of life Mortality Early removal of device	EndoBarrier device (including liner) Insertion and removal of EndoBarrier Professional/clinic visits Anaesthesia Hospital stay or day bed Management of adverse events/complications Anti-diabetic medication Costs associated with CV, macrovascular and microvascular events Subsequent bariatric surgery

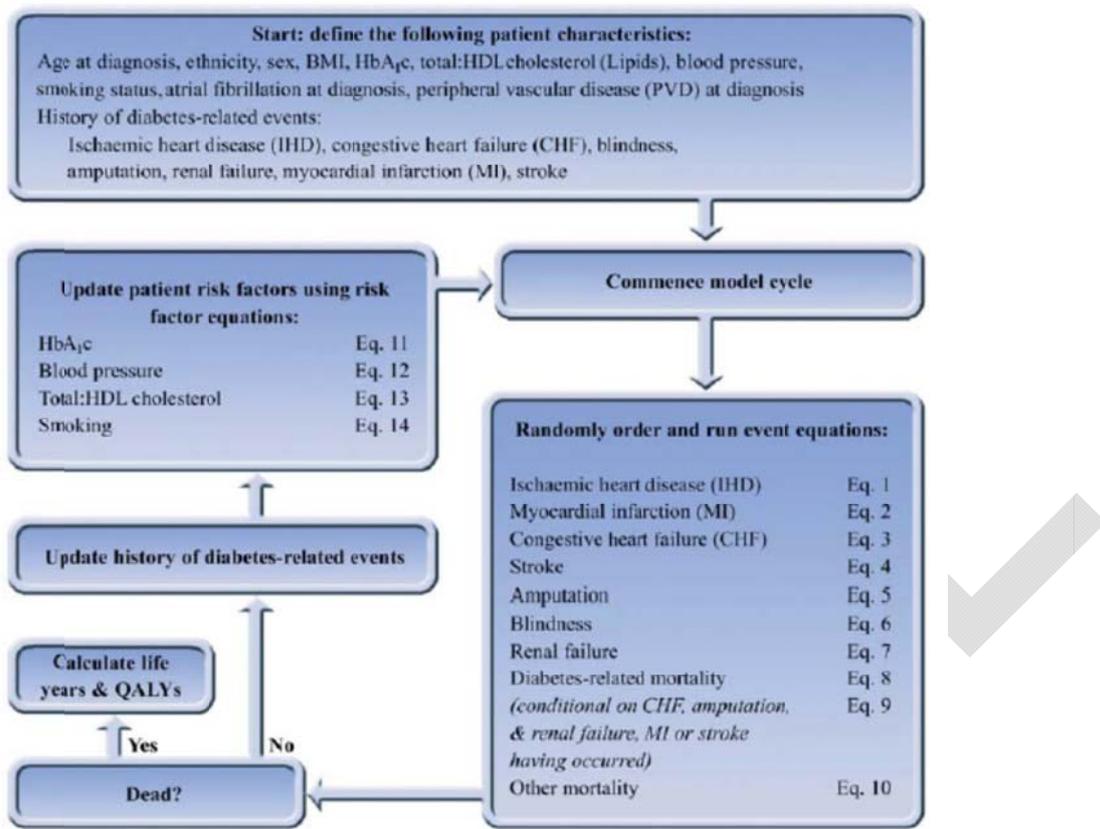
Abbreviations: AEs, adverse events; SOC, standard of care

^a In diabetic patients, SOC consists of anti-diabetic medications including metformin, sulfonylurea and third-line treatments such as acarbose, a DPP-4 inhibitor, a glitazone or insulin, depending on a patient's disease severity and treatment history.

The comparisons of EndoBarrier plus SOC versus SOC alone will require an economic model to calculate the cost-effectiveness of the addition of EndoBarrier to the treatment algorithm for patients with comorbid type 2 diabetes mellitus. The economic model is to be based on the UKPDS outcomes model (Clark et al., 2002). The UKPDS outcomes model is a simulation model for type 2 diabetes that estimates the incidence of 7 major diabetes-related complications. Risk equations used to estimate the probabilities of these complications are derived from the UKPDS dataset, and are a function of patient characteristics and prior complications. The long-term costs and effects of Endobarrier compared to its comparator(s) will be modelled via changes in weight loss and/or Hb1AC and/or other cardiovascular risk factors. The model predicts the risk of the occurrence of a range of microvascular and macrovascular events. The incidence of these events will decrease with EndoBarrier treatment, leading to a reduction in costs and an increase in quality of life. A summary of the UKPDS risk model is provided in Figure 3.

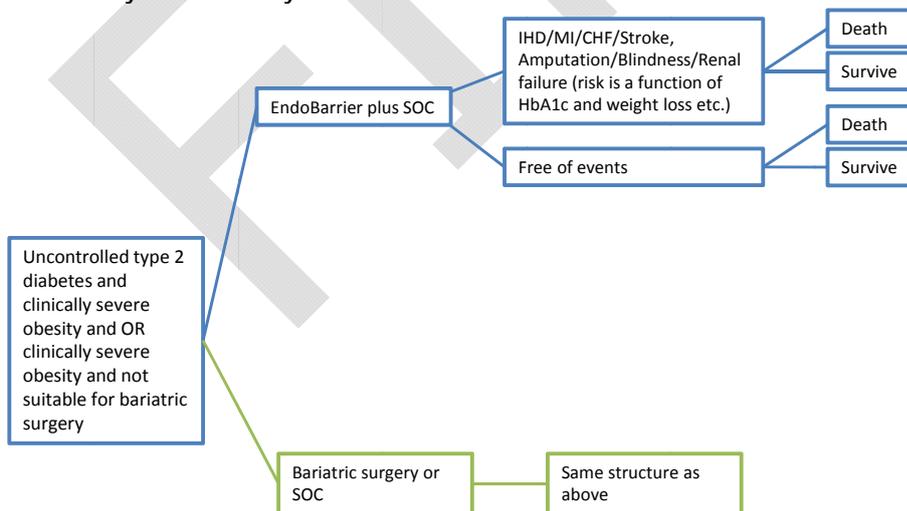
An updated UKPDS outcomes model has recently been published (Hayes et al. 2013). However, these new equations alone are not sufficient to populate an updated economic model for EndoBarrier. Specifically, the derivation of new QALY weights is required for events including ulcer and second events. The estimation of costs associated with complications is also needed to align with the new equations. This point has been acknowledged on the publication of the OM2 itself: "the use of this new outcomes model for cost-effectiveness analysis will require derivation of QALY weights for events including ulcer and second events, and estimation of costs associated with complications."

Figure 3 Summary of UKPDS risk model



The structure of the proposed decision analytic model is presented in Figure 4

Figure 4 Simplified decision analytic model structure for EndoBarrier in patients with uncontrolled diabetes and clinically severe obesity



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