EUnetHTA WP5 Joint Action 2 (2012-2015) Strand B, Rapid assessment of other health technologies such as medical devices, surgical interventions or diagnostics

DUODENAL-JEJUNAL BYPASS SLEEVE FOR THE TREATMENT OF OBESITY WITH OR WITHOUT TYPE II DIABETES MELLITUS

Pilot rapid assessment on other health technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment

Assessment and Appendices

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2. Standing Committee of European Doctors (CPME)
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SUMMARY OF RELATIVE EFFECTIVENESS OF THE DUODENAL-JEJUNAL BYPASS SLEEVE (DJBS)

The assessment element ID codes in brackets (e.g. A0001) refer to the result cards in Appendix 1, which give details of the relevant results.

Scope

Population	Men and women (≥18 years), with: - Obesity: grade III (body mass index [BMI] ≥40) or grade II (BMI 35.0–39.9) with comorbidities* - Type 2 diabetes mellitus (DM) who are not adequately controlled with medication (oral and/or insulin) and lifestyle intervention (haemoglobin A1c [HbA1c] ≥7.5%) + obesity ≥grade I (BMI ≥30)**
Intervention	Duodenal-jejunal bypass sleeve (DJBS)/EndoBarrier® (all generations)
Comparators	- Primary comparator for indication 'obesity': bariatric surgery and endoscopic techniques (gastric band, gastric balloon, gastric bypass, etc.) - Primary comparator for indication 'Type 2 DM + obesity ≥grade I': anti-diabetes pharmacotherapy and lifestyle changes - Further comparators: sham procedures
Outcomes	<u>Efficacy</u>: - Weight loss (temporary, long-term >12 months to 36 months) - Reduction in drug use (e.g. diabetic medication, antihypertensive medication) - Health-related quality of life - Reduction in cardiovascular events (myocardial infarction, stroke, etc.) - Reduction in diabetes-associated microangiopathic complications (diabetic nephropathy, retinopathy) - Reduction in further obesity-related morbidity (e.g. musculoskeletal morbidity) - Overall mortality - Surrogate parameters: Primary surrogate parameters: HbA1c, fasting blood glucose, insulin levels (short-term and long-term after 12 to 36 months) Secondary surrogate parameters: Blood pressure, further markers of metabolic function: C-peptide, low-density lipoprotein (LDL) cholesterol, triglyceride (TG) levels (short-term and long-term after 12 to 36 months) <u>Safety:</u> - Adverse events (AEs) and serious AEs (short-term, long-term) during and after implantation, after explantation (e.g. device removal, abdominal pain, procedure-related mortality, etc.)

* In this subpopulation, some but not necessarily all patients may also suffer from Type 2 DM.

** In this subpopulation, Type 2 DM is required as an inclusion criterion and thus is present in 100% of the patients.

Introduction

Health problem

This assessment addresses two subpopulations of interest:

1) adult obese patients (grade III obesity/BMI ≥40 or grade II obesity/BMI 35.0–39.9 with comorbidities)
2) patients with Type 2 DM and obesity ≥ grade I.

Both obesity and Type 2 DM have developed into a worldwide health problem. Prevalence data from European countries have shown that between 5% and 30% of the population is obese [Branca 2007] and up to 8% of people suffer from DM, of which the majority is related to Type 2 DM [International Diabetes Federation (IDF) 2013] (A0006).

The major cause of obesity is energy imbalance that occurs due to a number of interrelated factors (environment, genes, stress, psychological factors, life stage, life events, etc.) (A0003). Apart from being considered a disease itself, obesity is a risk factor for many other diseases, most importantly Type 2 DM 2006 [Elmadfa 2012, Hauner 2007, National Institute for Health and Clinical Excellence 2006a, Scottish Intercollegiate Guidelines Network 2010a] (A0004a). In addition to adverse physical health consequences, obesity is associated with psychological and social burden, often resulting in social stigma and generally a poor quality of life [National Institute for Health and Clinical Excellence 2007] (A0005).

Type 2 DM results from a progressive insulin secretory defect with a variable degree of insulin resistance in the background [American Diabetes Association 2013, Fauci 2013, Gale 2012] (A0002a). The main risk factor for Type 2 DM is obesity [Gale 2012] (A0003). Apart from acute metabolic disturbance and hyperglycaemia, Type 2 DM is associated with considerable long-term morbidity due to micro- and macrovascular complications (e.g. ischaemic heart disease, retinopathy, nephropathy) and premature mortality (A0004a). People suffer from several symptoms such as fatigue, weakness, poor wound healing or blurred vision and overall diminished health-related quality of life [Fauci 2013, Gale 2012, Inzucchi 2012] (A0005).

Obesity is diagnosed by measuring the BMI and waist circumference (A0024). Diabetes is diagnosed by measuring fasting plasma glucose (FPG; ≥7.0 mmol/l), by the oral glucose tolerance test (OGTT; Plasma glucose ≥11.1 mmol/l at two hours after 75 g oral glucose load), by measuring random blood glucose concentration (≥11.1 mmol/l) or by measuring HbA1c (>6.5%) (A0024).

Both obesity and Type 2 DM are managed in a stepwise approach that starts with education and lifestyle changes, followed by pharmacological interventions if unsuccessful: lipase inhibitors for the management of obesity; biguanides, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonist or insulins for the management of Type 2 DM [American Diabetes Association 2013, Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]. In severely obese patients in whom non-surgical measures have failed, bariatric surgery may be indicated [ECRI Institute 2012, National Institute for Health and Clinical Excellence 2007] (A0025).

Description of technology

The DJBS is a 60 cm long impermeable sleeve-like device (fluoropolymer), placed endoscopically under general anaesthesia into the small intestine for up to 12 months. The device is removed endoscopically [Australian Government: Department of Health and Ageing 2010, ECRI Institute 2012, National Institute for Health and Clinical Excellence 2012] (B0001).

The provider of the device is GI Dynamics (GI Dynamics, Inc., Lexington, Massachusetts, USA) (B0001). The currently available commercialised version of the device has been developed from a prototype. The commercialised version (EndoBarrier®) for the treatment of patients with Type 2 DM and/or obesity for up to 12 months has Conformité Eu-

ropéenne (CE)-mark approval in Europe and is clinically used in Austria, the Czech Republic, Denmark, Germany, the Netherlands, Spain, Switzerland and the UK. Outside Europe, it is available in Chile, Qatar and Israel and it has a Therapeutic Goods Administration (TGA) approval in Australia. In the USA, EndoBarrier® is considered investigational and has not as yet been approved for sale [GI Dynamics 2012] (A0020).

As demonstrated by a number of studies [Gersin 2010, Schouten 2010, Tarnoff 2009] and a recent UK HTA report [National Institute for Health and Clinical Excellence 2012], the DJBS was originally indicated for obese people (grade III or grade II with comorbidities) in whom conservative measures of weight control had failed. The manufacturer has shifted the indication to patients with Type 2 DM and/or obesity (A0001, B0002). The claimed benefit is that the DJBS stimulates the secretion of metabolic agents that improve glycaemic control with the additional benefit of significant weight loss [GI Dynamics 2013] (B0002).

If the primary indication is Type 2 DM, the alternative to the DJBS is optimal non-pharmacological and pharmacological management of DM. If the primary target group is obese patients in whom non-surgical measures of weight control have failed, the most likely alternative to the DJBS would be bariatric surgery, although concerns have been raised whether permanent bariatric procedures would be acceptable comparators (A0025, B0002).

The device is implanted by a surgeon in a hospital setting. Endoscopic facilities are required in addition to equipment for administering the anaesthetic and for managing hygiene. Increased endoscopic capability is required if the device is used in patients with Type 2 DM who are treated pharmacologically and who would not be considered otherwise for bariatric surgery (B0005, B0008, B0009).

Methods

Domains 'Health problem' and 'Description of technology'

The HTA Core Model for Rapid Relative Effectiveness was the main source for selecting relevant assessment elements. A basic search was used to compile the domains 'Health problem' and 'Description of technology'. The following primary sources were used: clinical guidelines, health technology assessment (HTA) reports, textbooks and reports from international organisations. The documents were not assessed in terms of study quality.

Domains 'Safety' and 'Clinical effectiveness'

The HTA Core Model for Rapid Relative Effectiveness was the main source for selecting relevant assessment elements. A systematic literature search (without restriction on publication date) of bibliographic databases, in the Cochrane Library and in the database of the Centre for Reviews and Dissemination, complemented by a SCOPUS handsearch, was used for compiling the domains 'Safety' and 'Clinical effectiveness'.

Selection of relevant documents (in English, German and the Croatian language) was done by two persons independently (see appendix for study selection). In terms of study design for analysing 'Safety', any prospective study was included, provided that safety outcomes were reported. For analysing 'Clinical effectiveness', prospective *controlled* studies were included, provided that the defined outcomes were reported.

Quality of studies was assessed using the Cochrane risk of bias checklist (Table 9). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used for qualitatively summarising the results for the domains: 'Safety' and 'Clinical effectiveness'.

Results

Available evidence

In the evaluation of clinical effectiveness, three randomised controlled trials (RCTs) [Gersin 2010, Rodriguez 2009, Schouten 2010] and one non-RCT [Tarnoff 2009] fulfilled our inclusion criteria, with a total of 155 study participants. They investigated the prototype version of the device primarily in patients with obesity ≥grade II (+ comorbidities). In the studies, a DJBS had been implanted in 95 patients in contrast to 60 patients who received diet only or sham procedure.

For evaluating safety, six non-randomised single-arm studies [Cohen 2013, de Moura 2011, de Moura 2012, Escalona 2012, Escalona 2010, Rodriguez-Grunert 2008] were analysed in addition to the RCTs, resulting in 282 patients overall who received the DJBS. Three of the single-arm studies evaluated the prototype of the device and three investigated the commercialised type.

In half of the studies, follow-up was 12 weeks. The remainder investigated the outcomes for up to 1 year.

Upcoming evidence

Three registered RCTs (two manufacturer-sponsored) are currently ongoing or have recently been completed (Dutch Diabetes Study, US ENDO-Trial, Italy) (Table 8). They evaluate the commercialised type of DJBS in patients with Type 2 DM and obesity ≥grade I (BMI ≥30) for a maximum follow-up of 12 months. The primary outcome parameter is improvement in HbA1c. Three publicly financed RCTs are planned but have not been registered yet: UK/EME MRC Study, France/ENDOMETAB Study, and the ABCD Study.

Furthermore, three uncontrolled trials (in Chile, Israel, and the UK) and one case-control study (in the UK) are registered as ongoing and will be completed between 2013 and 2016. They either evaluate the DJBS in patients with obesity ≥grade II (BMI >35) or in patients with Type 2 DM and obesity ≥grade I (BMI ≥30). The primary outcome parameters are % change in HBA1c level, % of excess weight loss (EWL) or change in energy intake and malnutrition composition at 12 months, except for one study that will have a follow-up at 12 and 24 months.

Safety

AEs (predominately mild) occurred in 64–100% of patients who received the DJBS compared with 0–27% in patients who received diet only [Cohen 2013, de Moura 2012, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009] (C0008).

Serious AEs in the form of gastrointestinal (GI) bleeding occurred in six out of 162 DJBS patients (4%) [de Moura 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009] and in none of the patients in the diet only groups [Schouten 2010, Tarnoff 2009] (C0008).

The frequencies of AEs in the studies that primarily included obese patients were not different from those that primarily included patients with Type 2 DM.

No reports were identified comparing the safety of the DJBS to either sham procedure, pharmacotherapy or to bariatric surgery (in the management of Type 2 DM or obesity).

Unexpected device explantation was required in 67 (24%) of the study participants in the intervention groups [Cohen 2013, de Moura 2012, de Moura 2011, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009] (C0008).

Clinical effectiveness

1) Patients with obesity ≥grade II (and comorbidities)

Mortality

The effect of the DJBS on mortality (overall mortality, disease-specific mortality, mortality due to other causes than the disease) compared with standard care has not been analysed in the included studies (C0008, D0001, D0002, D0003, D0004).

Morbidity

Weight loss

Compared with diet only or sham procedure, the DJBS was associated with a statistically significant and clinically relevant reduction in excess weight (12–22%) up to 12 weeks after implantation. The benefit in terms of absolute weight loss (in kg) compared with diet only or sham procedure was inconsistent. EWL and absolute weight loss compared with standard care (bariatric surgery) as well as long-term weight loss are unknown because these have not been investigated in the studies analysed (D0005).

Function

The effect of the DJBS on the reduction in cardiovascular events, in diabetes-associated microangiopathic complications and on daily living is unknown because no studies that investigated these outcomes have been identified (D0011, D0016).

Surrogate endpoints

The effect on metabolic function expressed in terms of HbA1c and FPG change in comparison with diet only is unclear because between-group differences have either not been statistically analysed or parameters have been presented for <five patients. The effect of DJBS on HbA1c and on FPG compared with usual care (bariatric surgery, pharmacological treatment) is unknown, as it has not been analysed in the included studies (D0005).

Quality of life

The effect on quality of life and patient satisfaction has not been analysed in the studies (D0012, D0013, D0017, D0018).

2) Patients with Type 2 DM and obesity ≥grade I

Mortality

The effect of the DJBS on mortality (overall mortality, disease-specific mortality, mortality due to other causes than the disease) compared with standard care in patients with Type 2 DM and obesity has not been analysed in the included studies (C0008, D0001, D0002, D0003, D0004).

Morbidity

Weight loss

The effect of the DJBS on EWL (in % terms) in patients with Type 2 DM compared with diet or sham procedure has not been analysed. The marginally greater reduction in absolute weight in the DJBS-group (8 kg) compared with sham procedure (7 kg) after 12 weeks is not statistically significant and the difference in weight loss at 20 weeks is of unknown significance. EWL and absolute weight loss compared with standard care (education, lifestyle changes and pharmacological treatment) is unknown as it has not been analysed in the included studies (D0005).

Function

The effect of the DJBS on the reduction in cardiovascular events, in diabetes-associated microangiopathic complications and on daily living is unknown because no studies that investigated these outcomes have been identified (D0011, D0016).

Surrogate endpoints

The effect on metabolic function expressed in terms of HbA1c and FPG change in comparison with sham procedure is not statistically significant. Whether the reduction in oral antidiabetic drug use is lower than in sham procedure is unclear because the difference has not been statistically analysed (D0005).

Quality of life

The effect on quality of life and patient satisfaction has not been analysed in the studies (D0012, D0013, D0017, D0018).

Reimbursement

The reimbursement status differs markedly between European countries. In some countries, the DJBS is not on the market yet (e.g. Croatia); in others, it is authorised for use and reimbursed in selected hospitals (e.g. Spain). In some countries, it is paid by achieving statutory independent grants (e.g. France, the UK, Italy, the Czech Republic), in others by achieving the status of innovative procedure (the Netherlands) or by using existing diagnosis-related group (DRG) codes (e.g. Germany).

Summary table of relative effectiveness of the DJBS/Part 1

Obesity ≥grade II (with comorbidities) *The assessment element ID codes (e.g. D0001) refer to the result cards in Appendix 2, which give details of the relevant results.*						
	Health benefit (12 weeks)			**Harm (12 weeks)**		
	EWL (%)	**Weight loss absolute (kg)**	**HbA1c (% points)**	**Serious AEs (absolute)**	**Other AEs**	**Frequency of AEs (%)**
DJBS [Schouten 2010]	19 (±11) vs. 7 (±6) *p<0.02*	N/A	-1.1 vs.-0.4 *p=N/A*	0 vs. 0	N/A	100 vs. 27 *p=N/A*
[Tarnoff 2009] **Diet only**	22 (±8) vs. 5 (±7) *P=0.02* D0005	10 (5 to 18) vs. 3 (0 to 8) *p=N/A* D0005	*N/A‡* D0005	*3* vs. 0* *p=N/A* C0008		64 vs. 0 *p=N/A* C0008
Quality of body of evidence	low	low	low	very low	N/A	very low
DJBS [Gersin 2010] **Sham procedure**	12 (9 to 15) vs. 3 (-1.4 to 6.7) *p<0.001* D0005	8 (11 to 6) vs. 2 (4 to -0.3) *p=0.002* D0005	N/A	intervention: 3* control: N/A C0008	N/A	N/A
Quality of body of evidence	low	low	N/A	very low	N/A	N/A

Abbreviations: AE=adverse event; N/A=not data available; vs=versus; *GI bleeding; ‡ measured in four patients only.

Summary table of relative effectiveness of the DJBS/Part 2

Type 2 DM + obesity ≥grade I *The assessment element ID codes (e.g. D0001) refer to the result cards in Appendix 2, which give details of the relevant results.*						
	Health benefit (12 to 24 weeks)			**Harm (12 to 24 weeks)**		
	EWL (%)	**Weight loss absolute (kg)**	**HbA1c (% points)**	**Serious AEs**	**Other AEs**	**Frequency of AEs (%)**
DJBS [Rodriguez 2009] **Sham procedure**	N/A	12 weeks: 8 vs.7 *p=NS* 20 weeks: 10 (±1.3) vs. 7 (±4.3) *p=N/A* D0005	12 weeks: -1.3 (±0.9) vs. -0.8 (±0.3) *p >0.05* 24 weeks: -2.4 (±0.7) vs. -0.8 (±0.4) *p >0.05* D0005	intervention: 0; control: N/A C0008	N/A	intervention: 100; control: N/A C0008
Quality of body of evidence	N/A	low	low	very low	N/A	very low

AE=adverse event; N/A=no data available; NS=not significant.

Discussion

A major limitation is that a number of relevant outcome parameters have not been analysed in the studies to date; also, for the effect of the DJBS on the management of Type 2 DM, only surrogate parameters have been investigated. It is of particular concern that none of the studies has evaluated the patients' point of view (e.g. health-related quality of life, dietary compliance, satisfaction).

Another limitation in those RCTs that address obesity as the primary indication is that the comparator does not reflect standard or usual care. If the DJBS is intended for patients for whom conservative measures of weight reduction have failed, diet or doing nothing does not represent standard or usual care, as bariatric surgery would have to be considered. This is of even greater importance, as systematic reviews have shown that bariatric surgery is an effective weight loss intervention in selected patients [Scottish Intercollegiate Guidelines Network 2010a]. If the DJBS is intended for patients with manifest Type 2 DM, the intervention needs to be compared with optimal pharmacotherapy, whereas patients in the according study received a sham procedure combined with limited pharmacotherapeutic management. While a sham procedure increases the validity of the study results compared with an unblinded trial, we do not know to date whether the DJBS results in a net benefit compared with optimal standard care.

Furthermore, the follow-up period has been too short for analysing whether effects of the DJBS are sustainable. This is problematic for both indications because the aim of obesity management is a moderate yet sustainable reduction of weight and similarly, for successful management of Type 2 DM diabetes, long-term benefits are required. Since the majority of published studies investigated a prototype rather than the commercialised product, the benefit-risk relation in the commercialised product is unknown to date. It is of particular relevance that the prototype has been implanted for 3 months, whereas the commercialised version is implanted for up to 12 months and differs in some technical features.

Finally, the mean BMI in the controlled studies ranges between 39 and 49 kg/m². This is considerably higher than the manufacturer's concept of offering the treatment to patients with a BMI ≥30 kg/m². It may be possible that the effect size is larger in patients with a BMI >40, resulting in an overestimation of DJBS's benefit.

The overall quality of evidence is low because of unclear allocation concealment, lack of blinding of study participants and outcome assessors, high and unexplained drop-out rates in some studies, different drop-out rates between intervention and control groups, lack of or unclear intention-to-treat analysis and a small number of study participants in most of the studies.

The manufacturer has shifted the primary indication for the DJBS to patients with Type 2 DM because of signals that the DJBS may be able to elicit glycaemic control independent of weight loss in obese Type 2 diabetes patients. However, consequences for the Type 2 DM metabolism have mostly been analysed as a secondary outcome for a very short follow-up period only and the outcome has not been compared with standard care in Type 2 DM.

Ongoing RCTs will add information on the commercialised version of the DJBS and they will address the current lack of high quality RCTs on patients with Type 2 DM + obesity ≥grade I. Yet, the primary outcomes addressed are again surrogate parameters (HbA1c) rather than final endpoints. Furthermore, only one upcoming study addresses the patients' point of view (health-related quality of life) and in only one registered trial the follow-up will be >12 months, thus adding little information on the long-term benefit for patients.

Conclusion

From the current evidence that is largely based on a prototype, the DJBS has little effect on weight management in obese patients (obesity ≥grade II). Evidence is insufficient or lacking on whether the relative reduction of excess weight is sustained beyond 3 months and on whether the DJBS is more successful than established surgical methods. Additionally, current evidence is insufficient on the effectiveness of the DJBS in the management of Type 2 DM +obesity ≥ grade I.

There is insufficient evidence to determine the safety profile of the DJBS compared with standard care.

Despite this lack of evidence to date, the device is available and in clinical use in a number of European countries. Results from interventional studies on the commercialised version in patients with Type 2 DM are to be expected from 2013 onwards. Studies are required with a long-term follow-up of at least 1.5 years that compare the DJBS to standard care and address relevant clinical endpoints.

LIST OF ABBREVIATIONS

AE	Adverse events
AESGP	Association of the European Self-Medication Industry
AHRQ	Agency for Healthcare Research and Quality
ASGB	Adjustable silicone gastric banding
BMI	Body mass index
BPD	Biliopancreatic diversion
BR	Brazil
CE-mark	Conformité Européenne
CL	Chile
CPME	The Standing Committee of European Doctors
CVD	Cardiovascular disease
DJBS	Duodenal-jejunal bypass sleeve
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
DRG	Diagnosis-related group
Element ID	Individual code for each element
ESIP	European Social Insurance Platform
EU	European Union
EWL	Excess weight loss
FPG	Fasting plasma glucose
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GYEMSZI	The National Institute for Quality and Organizational Development in Healthcare and Medicines (Hungary)
HbA1c	Haemoglobin A1c
HDL	High density lipoprotein
HIQA	Health Information and Quality Authority (Ireland)
HTA	Health technology assessment
HVB	Main Association of the Austrian Social Security Institutions (Austria)
IASO	[International Association for the Study of Obesity 2008]
ICD	International classification of diseases
IDF	International Diabetes Federation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; Institute for Quality and Efficiency in Healthcare (Germany)
ISCIII	Instituto de Salud Carlos III; National Public Health Research Institute and the National Funding Agency for Health Research in Spain
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment (Austria)
LDL	low-density lipoprotein
MoH	Ministry of Health
N/A	Data not available
NL	The Netherlands
NOKC	Nasjonalt kunnskapssenter for helsetjenesten; Norwegian Knowledge Centre for the Health Services
NPH	Neutral protamine Hagedorn
NS	Not significant
OGTT	Oral glucose tolerance test
PYY	Peptide YY
RCT	Randomised Controlled Trial
RR	Relative risk
RYGB	Roux-en-Y gastric bypass
SD	Standard deviation
TG	Triglyceride
TGA	Therapeutic Goods Administration
VBG	Vertical banded gastroplasty
WHO	World Health Organization
WP	Work package

1. SCOPE

Description	Project scope
Population	Men and women (≥18 years), with: - obesity grade III (BMI ≥40) or grade II (BMI 35.0–39.9) with comorbidities* - Type 2 DM who are not adequately controlled with medication (oral and/or insulin) and lifestyle intervention (HbA1c ≥7.5%) + obesity ≥grade I (BMI ≥30)** Mesh-terms: Obesity; Obesity, Morbid; Diabetes Mellitus, Type 2; International classification of diseases-10 (ICD-10) code: E 66, E 11 Intended use: treatment
Intervention	DJBS/EndoBarrier® (all generations): impermeable fluoropolymer sleeve that is placed endoscopically via the mouth and anchored in the first part of the small bowel in a procedure that takes about 30 minutes. The commercialised device remains in the bowel up to 12 months and is removed thereafter. The uptake of nutrients and calories from the first part of the small bowel (duodenum and first section of jejunum) are reduced. The presumed effects of the DJBS are based on gut hormonal signalling changes, which lead to normalization of glycaemic control. Mesh-terms: Jejunum/su [Surgery]; Duodenum/su [Surgery]; Bariatric Surgery
Comparison	- Primary comparator for indication 'obesity': bariatric surgery and endoscopic techniques (gastric band, gastric balloon, gastric bypass, etc.) - Primary comparator for indication 'Type 2 DM + obesity ≥grade I': anti-diabetes pharmacotherapy and lifestyle changes - Further comparators: sham procedures Mesh-terms: N/A* Rationale for choosing the comparators: a) Evidence-based clinical guidelines and HTA-reports [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, Hauner 2007, National Institute for Health and Clinical Excellence 2006a, National Institute for Health and Clinical Excellence 2007, National Institute for Health and Clinical Excellence 2011, National Institute for Health and Clinical Excellence 2012, National Institutes of Health 2009, Rieder 2004, Shekelle 2004, The Royal College of Physicians 2008, World Health Organization 2006] b) Manufacturer comment
Outcomes	Efficacy: - Weight loss (temporary, long-term >12 months to 36 months) - Reduction in drug use (e.g. diabetic medication, antihypertensive medication) - Health-related quality of life - Reduction in cardiovascular events (myocardial infarction, stroke, etc.) - Reduction in diabetes-associated microangiopathic complications (diabetic nephropathy, retinopathy) - Reduction in further obesity-related morbidity (e.g. musculoskeletal morbidity) - Overall mortality - Surrogate parameters: Primary surrogate parameters: HbA1c, fasting blood glucose, insulin levels (short-term and long-term after 12 to 36 months) Secondary surrogate parameters: Blood pressure, further markers of metabolic function: C-peptide, LDL cholesterol, TG levels (short-term and long-term after 12 to 36 months) Safety: - AEs and serious AEs (short-term, long-term) during and after implantation, after explantation (e.g. device removal, abdominal pain, procedure related mortality, etc.) Rationale: of primary interest are patient-relevant endpoints including objective (mortality) and subjective endpoints. Surrogate markers (e.g. for metabolic function) will be extracted but they will have little weight for assessing benefit-harm relations. The selection of endpoints is based on recommendations from the EUnetHTA methods guideline on clinical endpoints [European Network for Health Technology Assessment (EUnetHTA) 2013a] General: long-term outcomes (>1 year) are preferred to short-term outcomes

* In this subpopulation, some but not necessarily all patients may also suffer from Type 2 DM.
** In this subpopulation, Type 2 DM is required as an inclusion criterion and thus is present in 100% of the patients.

Deviations from project plan

The following deviations from the final version of the project plan (Appendix 5) were made:

1) In contrast to the project plan, the 'obese (+comorbid) subpopulation' in the project scope was changed to 'obesity grade III (BMI ≥40) or grade II (BMI 35.0–39.9) with comorbidities' (project plan: obesity grade III only) to better represent a morbidly obese population.
2) According to the manufacturer's comments, the definition of the second subpopulation 'Type 2 DM and/or obesity' was changed to patients with 'Type 2 DM who are not adequately controlled with medication (oral and/or insulin) and lifestyle intervention (HbA1c ≥7.5%) + obesity ≥grade I (BMI ≥ 30)'. (project plan: Type 2 DM + obesity ≥grade II [BMI ≥35-40]).
3) In the project scope the field 'intervention' was changed to 'DJBS/EndoBarrier® (all generations)' to reflect the manufacturer's comment that different versions of the device have been available and investigated in studies.
4) In the field 'outcome' in the project scope, the outcome parameter 'transition to bariatric surgery' was excluded. This was done firstly because of a reviewer's comment that transition to bariatric surgery may also be considered as an AE and, secondly, because the therapeutic aim of the DJBS changed from weight loss to improvement of glycaemic control.
5) The project duration has been extended by one month.

2. HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

Methods

Domain framing

No deviation was required from the general scope of the project, according to the final project plan.

Research questions

Element ID	Research question
A0001	For which indication/for what purposes is the duodenal-jejunal bypass sleeve (DJBS) used and are there any contraindications?
A0002a	What is the precise definition of obesity and Type 2 DM and which diagnosis is given to obesity and Type 2 DM according to ICD-10?
A0002b	What are the main features of obesity and Type 2 DM?
A0003	What are the known risk factors for obesity and Type 2 DM?
A0004a	What is the natural course of obesity and Type 2 DM?
A0005	What are the main symptoms and consequences for the patients?
A0006	What is the burden of obesity and Type 2 DM for society (prevalence, incidence, costs)?
A0007	What is the target population in this assessment?
A0011	What is the expected annual utilisation of the DJBS?
A0020	What is the market authorization status of the DJBS (Endobarrier®) in Europe?
A0021	What is the reimbursement status of DJBS in Europe?
A0024	How are obesity and Type 2 DM currently diagnosed according to published guidelines and in practice?
A0025	How is obesity and Type 2 DM currently managed according to published guidelines and in practice?

Sources

For answering the research question on the definition and features of obesity and Type 2 DM and on the natural history of obesity and Type 2 DM (A0002a, A0002b, A003, A0004a), we used the following information:

- Clinical guidelines from the UK [National Institute for Health and Clinical Excellence 2006a, National Institute for Health and Clinical Excellence 2007, National Institute for Health and Clinical Excellence 2011, National Institute for Health and Clinical Excellence 2006b, Scottish Intercollegiate Guidelines Network 2010a, Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]
- Clinical guidelines from Germany [Hauner 2007]
- Documents from international health organisations [Branca 2007, World Health Organization 2006, World Health Organization 2011]
- An Austrian report on nutrition [Elmadfa 2012]
- Textbooks [Fauci 2013, Gale 2012]

- Recommendations from disease-specific associations [American Diabetes Association 2013]
- International horizon scanning documents [ECRI Institute 2012].

Questions on epidemiology (A006) were answered:

- By deriving international data from the World Health Organization (WHO) [Branca 2007, World Health Organization 2006]
- From the IDF [IDF Clinical Guidelines Task Force 2005, International Diabetes Federation (IDF) 2013]
- From Austrian and Croatian health reports [Croatian National Institute of Public Health 2012, Croatian National Institute of Public Health 2013, Elmadfa 2012, Metelko 2008, Ministarstvo zdravstva i socijalne skrbi Republike Hrvatske 2010, Rathmanner 2006, Rieder 2004].

For questions related to the indication and purpose of the DJBS (A0001, A0007), we used:

- National horizon scanning documents [Australian Government: Department of Health and Ageing 2010, National Horizon Scanning Centre 2011]
- Information from the manufacturer [GI Dynamics 2010, GI Dynamics 2013]
- Recent evidence analyses [ECRI Institute 2012, National Institute for Health and Clinical Excellence 2012].

The current diagnosis and management of obesity and Type 2 DM (A0024, A0025) is based on

- clinical guidelines and HTA reports [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, ECRI Institute 2012, Hauner 2007, IDF Clinical Guidelines Task Force 2005, Inzucchi 2012, National Health & Medical Research Council 2003, National Institute for Health and Clinical Excellence 2006a, National Institute for Health and Clinical Excellence 2006b, Scottish Intercollegiate Guidelines Network 2010a, Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]
- WHO documents [World Health Organization 2006, World Health Organization 2011].

Data on the market authorisation status (A0020) were derived from the manufacturer [GI Dynamics 2010, GI Dynamics 2012, GI Dynamics 2013], while information on the expected utilisation (A0011) came from medical experts and information on the reimbursement status (A0021) came from the manufacturer and HTA institutions.

References were identified by handsearch and from the systematic search results on safety and effectiveness.

Analysis

The sources were sufficient to answer the questions. We did not perform additional data analysis. No quality assessment was performed of the sources used.

Synthesis

The results are presented in plain text format, supplemented by overview tables (e.g. on epidemiological data in different countries).

Main results

Target population in this assessment

In this assessment, the target populations are:

1) Adult obese patients (grade III obesity or grade II obesity with comorbidities)
2) Patients with Type 2 DM who are not adequately controlled with medication (oral and/or insulin) and lifestyle intervention (HbA1c ≥7.5%) + obesity ≥grade I (BMI ≥30).

1) Obesity

Definition

Obesity is a state of excess adipose tissue mass [Fauci 2013, Gale 2012]. It is measured using BMI, which is defined as the individual's body weight (in kg) divided by the square of their height [Branca 2007, Scottish Intercollegiate Guidelines Network 2010a].

$$\text{BMI}=\frac{\text{kg}}{\text{m}^2}$$

People of Caucasian origin are considered as being overweight if their BMI exceeds 25 kg/m² and obese if their BMI exceeds 30 kg/m² (Table 1) [Branca 2007, National Institute for Health and Clinical Excellence 2006a, Scottish Intercollegiate Guidelines Network 2010a]. Patients with BMI >35 kg/m^2 are called severely obese and those with BMI >40 kg/m^2 morbidly obese [ECRI Institute 2012].

Additionally, in adults, central adiposity is frequently measured by waist circumference, with raised waist circumference defined as ≥102 cm in men and ≥88 cm in women [National Institute for Health and Clinical Excellence 2006a]. Waist circumference may also be used, in addition to BMI, in people with a BMI less than 35 kg/m^2 [National Institute for Health and Clinical Excellence 2006a]. Finally, waist-to-hip ratio may be a useful predictor of diabetes and cardiovascular disease (CVD) risk in adults, but it is more difficult to measure than waist circumference [Scottish Intercollegiate Guidelines Network 2010a].

Table 1: Grading of overweight and obesity

Categories	BMI (kg/m²)
Healthy weight	18.5–24.9
Overweight (Pre-obesity)	25.0–29.9
Obesity grade I	30.0–34.9
Obesity grade II	35.0–39.9
Obesity grade III (Obesity permagna or morbid obesity)	≥40.0

According to the ICD-10 classification, five different codes for obesity exist, which are summarised in Table 2.

Table 2: Coding of obesity according to ICD-10

ICD-10 Code	Description
E66.0	Obesity due to excess calories
E66.1	Drug-induced obesity
E66.2	Morbid (severe) obesity with alveolar hypoventilation
E66.8	Other obesity
E66.9	Obesity, unspecified

Source: [International Statistical Classification of Diseases and Related Health Problems 2013a]

Risk factors for and natural course of obesity

The fundamental cause of overweight and obesity is 'energy imbalance'; however, the causes of this imbalance remain unclear. In adults, reasons for energy imbalance are environment, genes, stress and psychological factors, current medication, life stage (early childhood and adolescence, pregnancy and childbirth, menopause) and life events (quitting smoking, marriage, giving up sport, holidays) [Elmadfa 2012, Hauner 2007, National Institute for Health and Clinical Excellence 2006a, Scottish Intercollegiate Guidelines Network 2010a].

It has been observed that the prevalence of obesity increases with age, that obesity is more prevalent among lower socioeconomic and lower-income groups, with a particularly strong social class gradient among women, that obesity is more prevalent among certain ethnic groups, and that it shows regional variations [National Institute for Health and Clinical Excellence 2006a, Scottish Intercollegiate Guidelines Network 2010a].

Obesity can be considered as a disease itself and as a risk factor for other diseases, most importantly Type 2 DM [Branca 2007, Elmadfa 2012, Hauner 2007, National Institute for Health and Clinical Excellence 2006b, Scottish Intercollegiate Guidelines Network 2010a] which in 80% of people is caused by obesity [Branca 2007]. Table 3 presents the relative risks of other diseases in obese adult and Table 4 presents relative risks for the most common diseases stratified by gender.

Table 3: Diseases and conditions associated with obesity

Relative risk (RR)	Associated with metabolic consequences	Associated with excess weight
Greatly increased RR >3	Type 2 diabetes Gall bladder disease Hypertension Dyslipidaemia Insulin resistance Non-alcoholic fatty liver	Sleep apnoea Breathlessness Asthma Social isolation and depression Daytime sleepiness and fatique
Moderately increased RR 2-3	Coronary heart disease Stroke Gout and hyperuricaemia	Osteoarthritis Respiratory disease Hernia Psychological problems
Slightly increased RR 1-2	Cancer* Reproductive	Varicose veins Musculoskeletal problems

Relative risk (RR)	Associated with metabolic consequences	Associated with excess weight
	abnormalities and impaired fertility Polycystic ovaries Skin complications Cataract	Bad back Stress incontinence Oedema and cellulitis

* Breast, endometrial, colon and others; Source: [National Health & Medical Research Council 2003]

Table 4: Gender-specific relative risk of other diseases in obese adults

Disease	Relative Risk	
	Women	Men
Type 2 diabetes	12.7	5.2
Hypertension	4.2	2.6
Heart attack	3.2	1.5
Colon cancer	2.7	3.0
Angina	1.8	1.8
Gall bladder disease	1.8	1.8
Ovarian cancer	1.7	Not applicable
Osteoarthritis	1.4	1.9
Stroke	1.3	1.3

Source: National Audit Office, 2001, cited in [National Institute for Health and Clinical Excellence 2006b].

Additionally, a high BMI is associated with premature mortality [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, Hauner 2007].

Apart from adverse physical health consequences, obesity is considered a psychosocial and social burden, often resulting in social stigma, low self-esteem, reduced mobility and a generally poorer quality of life [National Institute for Health and Clinical Excellence 2007].

Epidemiology

According to the WHO, obesity has developed into a worldwide health problem [Branca 2007, World Health Organization 2000]. According to the International Association for the Study of Obesity (IASO) [International Association for the Study of Obesity 2008] that summarises reported data from 27 countries, 16.2% of the male and 18.5% of the female population is obese in the European Union (EU) (Table 5). In a WHO report from 2007, the prevalence of obesity in those European countries that reported figures ranged from 5%– 23% in males and from 7% – 36% in females [Branca 2007]. Furthermore, obesity is responsible for 6% of health care spending in countries within the WHO Europe region [Branca 2007].

Table 5: Prevalence of overweight and obesity according to IASO in % (BMI in kg/m²)

Country	males		females	
	Overweight (BMI 25–29.9)	Obese (BMI ≥30)	Overweight (BMI 25–29.9)	Obese (BMI ≥30)

EU	42.8	16.2	29.5	18.5

Source: [International Association for the Study of Obesity 2008]

Current management of obesity

It is unusual for an overweight or obese person to seek medical help in the first instance. They are likely to have tried an array of 'self-help' measures to manage their weight before approaching a health professional [National Institute for Health and Clinical Excellence 2006a]. Primary healthcare plays an important role in the identification, assessment and management of obesity.

Currently, no gold standard exists concerning the management of obesity with or without Type 2 DM [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, Hauner 2007, IDF Clinical Guidelines Task Force 2005, National Health & Medical Research Council 2003, National Horizon Scanning Centre 2011, National Institute for Health and Clinical Excellence 2006a, Scottish Intercollegiate Guidelines Network 2010a]. Several approaches are in place: dietary advice, exercise, lifestyle changes, drug therapy and bariatric surgery including endoscopic techniques.

Obesity is usually managed in stepwise approaches; firstly, general advice on weight control, diet and physical exercise is given, aimed at influencing lifestyle [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, Hauner 2007, IDF Clinical Guidelines Task Force 2005, National Health & Medical Research Council 2003, National Horizon Scanning Centre 2011, National Institute for Health and Clinical Excellence 2006a].

This may be supported by drug therapy as part of an overall plan for managing obesity including diet, physical activity and behavioral changes [Scottish Intercollegiate Guidelines Network 2010a]. Orlistat is the only drug specifically licensed for use in the treatment of obesity. It is a non-systemically acting anti-obesity agent that, in conjunction with a calorie-restricted diet, has been shown to promote weight loss and help prevent weight regain. Orlistat binds to pancreatic and gastric lipase in the GI tract. It is approved for obese patients with a BMI of ≥30 kg/m² or of ≥27 kg/m² in the presence of other risk factors, such as diabetes, hypertension or hyperlipidaemia. Through weight loss, orlistat improves the comorbidities associated with obesity. Serious AEs are liver failure and oxalate nephropathy, with renal failure [Micromedex Drugdex Database 2013]. In addition to lipase inhibitors, appetite suppressants are used. For the appetite suppressant sibutramine, market authorisation was suspended in 2010 because of cardiovascular events [National Institute for Health and Clinical Excellence 2006a] (note was added in guideline after publication).

Finally, in extreme cases (failure of conservative therapy, obesity grade II + comorbidities or obesity grade III without comorbidities), bariatric surgery may be indicated. Surgical procedures either aim to reduce the size of the stomach (like gastric banding or sleeve gastrectomy), to decrease patient capacity to absorb food (jejunoileal bypass; of historical interest only) or they combine both approaches (e.g. Roux-en-Y gastric bypass or biliopancreatic diversion) [ECRI Institute 2012].The final decision for or against bariatric surgery including the type of surgery (open or laparoscopic) is dependent on the BMI, the individual risk, comorbidities and patient preferences, and should be made after a comprehensive risk–benefit assessment [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, Arroyo 2010, DeWald 2006, Ibrahim 2010, IDF Clinical Guidelines Task Force 2005, National Horizon Scanning Centre 2011, Padwal 2011, Scottish Intercollegiate Guidelines Network 2010a, Tessier 2008]. According to the Agency for Healthcare Research and Quality (AHRQ), only gastric bypass surgery has demonstrated long-term efficacy for morbidly obese patients [ECRI Institute 2012]. The surgery carries significant risks of morbidity and mortality. Like pharmacotherapy, bariatric surgery needs to be accompanied by a structured weight management programme (dietetic monitoring, psychological support, etc.) [National Institute for Health and Clinical Excellence 2007].

2) Type 2 DM

Definition

DM is defined as a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action, or both [Fauci 2013, Gale 2012, Scottish Intercollegiate Guidelines Network 2010b, World Health Organization 2006]. Several types of DM exist that can be classified into Type 1 and Type 2 DM, gestational diabetes and other less common forms of diabetes that are caused by genetic defects, endocrine pancreas disorders, endocrinopathies or infections or that are medication-induced [Rieder 2004].

Criteria for the diagnosis of DM include one of the following:

- FPG ≥7.0 mmol/l
- Plasma glucose ≥11.1 mmol/l 2 hours after a 75 g oral glucose load (oral glucose tolerance test (OGTT))
- Random blood glucose concentration ≥11.1 mmol/l in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis
- HbA1c >6.5%.

The results should be confirmed by repeated testing unless unequivocal hyperglycaemia is present [American Diabetes Association 2013, Fauci 2013, Gale 2012, World Health Organization 2011].

Type 2 DM results from a progressive insulin secretory defect with a variable degree of insulin resistance in the background [American Diabetes Association 2013, Fauci 2013, Gale 2012]. People are normally thought to have Type 2 DM if they do not have Type 1 DM (rapid onset, often in childhood, insulin-dependent, ketoacidosis if neglected) or other medical conditions or treatment suggestive of secondary diabetes. However, there can be uncertainty in the diagnosis, particularly in overweight people of younger age, children or adolescents. The true diagnosis may become more obvious over time [American Diabetes Association 2013, The Royal College of Physicians 2008]. According to the ICD-10 classification, the code for Type 2 DM is 'E11' [International Statistical Classification of Diseases and Related Health Problems 2013b].

Risk factors and natural course of Type 2 DM

Increasing age, obesity, ethnicity and family history are the four major determinants of Type 2 DM, of which being overweight or obese is the main contributing factor, increasing the risk 80-100 fold [Gale 2012]. In addition, having a large waist circumference increases the risk of developing Type 2 DM. Men are at high risk if they have a waist circumference of 94–102 cm (37–40 inches). They are at very high risk if it is >102 cm (>40.0 inches). Women are at high risk if they have a waist circumference of 80–88 cm (31.5–35.0 inches).They are at very high risk if it is >88 cm (>35.0 inches). Some population groups, for example South Asian adults or older people, may be at risk of developing Type 2 DM even if they have a BMI lower than the overweight classification [National Institute for Health and Clinical Excellence 2011]. Also, high rates affect people of Middle-eastern and Hispanic American origin living western lifestyles [Gale 2012].

Type 2 DM is preceded by an asymptomatic stage, called prediabetes that is characterised by mild hyperglycaemia, insulin resistance, and early decrements in insulin secretory capacity [Inzucchi 2012]. Under certain circumstances, Type 2 DM can lead to acute situations of metabolic disturbance.

Diabetes is usually irreversible and its late complications result in increased morbidity and reduced life expectancy [Gale 2012, Inzucchi 2012]. In the long term, Type 2 DM increases the risk of microvascular damage (retinopathy, nephropathy and neuropathy). Furthermore, it is associated with macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease) [Fauci 2013, Gale 2012, World Health Organization 2006]. Many people with Type 2 DM have the same risk of a cardiovascular event as

someone without diabetes who has already had their first heart attack; people with diabetes and a previous cardiovascular event are at very high risk – around 10 times of the average (background) population [The Royal College of Physicians 2008]. Additionally, Type 2 DM is associated with increased risk of further diseases such as cancer, psychiatric diseases, cognitive decline or chronic liver disease [Inzucchi 2012].

Clinical presentation of diabetes can be acute, subacute or asymptomatic. Common symptoms are polyuria, polydipsia, weight loss, thirst, fatigue, weakness, blurred vision, superficial infection, poor wound healing and paraesthesias [American Diabetes Association 2013, Fauci 2013, Gale 2012]. Additionally, Type 2 DM is associated with diminished quality of life [World Health Organization 2006].

Epidemiology

Like obesity, Type 2 DM is considered a global health problem. The prevalence of Type 2 DM is increasing worldwide as well as in Europe due to the increasing prevalence of obesity, decreased physical activity, but also increased longevity after diagnosis thanks to better cardiovascular risk protection [The Royal College of Physicians 2008, World Health Organization 2006]. DM is considered the fifth leading cause of death worldwide [Fauci 2013].

According to the International Diabetes Federation [International Diabetes Federation (IDF) 2013] 366 million people worldwide had diabetes in 2011 and the number is expected to rise to 552 million by 2030. However, 80% of people with diabetes live in low- and middle-income countries. Type 2 DM accounts for 85–95% of all diabetes cases [International Diabetes Federation (IDF) 2013].

The WHO stated in 2002 that in Europe 22.5 million people suffer from diabetes, of whom 80–95% have Type 2 DM [World Health Organization 2002]. Data from the International Diabetes Federation show considerably higher figures of 52.8 million people (20–79 years) in 2011 (8.1%) for the European region [International Diabetes Federation (IDF) 2013].

The disease has changed from an 'old people's disease' to a disease afflicting people in the first half of their life [World Health Organization 2002]. The greatest number of people with diabetes is in the 40–59 years age group and, globally (not yet in individual countries), the prevalence in males and females is almost equivalent [International Diabetes Federation (IDF) 2013].

The costs of diabetes internationally range from 5% to 10% of the total health care spending [Rieder 2004, World Health Organization 2002]. A cost-of-illness study that covered eight European countries estimated annual direct medical costs/patient of € 2,834 and total costs of € 29 billion [Jönsson 2002].

Estimates indicate that at least USD 131 billion was spent on healthcare due to diabetes in Europe in 2011, accounting for almost one-third of global healthcare expenditures due to diabetes [International Diabetes Federation (IDF) 2013].

Current management

Type 2 DM is a progressive long-term medical condition that is predominantly managed by the person with the diabetes and/or their carer as part of their daily life [The Royal College of Physicians 2008]. Type 2 DM is addressed by a combination of several strategies including structured education about lifestyle interventions, psychological interventions, pharmacological management and management of diabetes-related diseases such as CVDs, kidney diseases, visual impairment and nerve damage [Fauci 2013, Gale 2012, Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]. Updated standards of medical care in diabetes have recently been published by the American Diabetes Association [American Diabetes Association 2013].

Like obesity, Type 2 DM is usually managed in a stepwise approach. With current recommendations, management usually start with structured education that meets the cultural, linguistic, cognitive and literacy needs of the patient and lifestyle management with non-pharmacological management (e.g. dietary advice, smoking cessation, man-

agement of psychosocial distress). This needs to be accompanied by clinical monitoring of blood glucose levels by means of HbA1c [Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008].

The primary HbA1c goal is <6.5%. A reasonable HbA1c goal for many non-pregnant adults is <7%. HbA1c <8% may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions and in those in whom the general goal is difficult to achieve despite all appropriate care [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012].

If the target level of HbA1c is not achieved by non-pharmacological management, pharmacological glucose control therapies are required (biguanides, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonist or insulins). Blood glucose control deteriorates inexorably in most people with Type 2 diabetes over a period of years, due to a waning of insulin production. In these circumstances, oral glucose-lowering therapies can no longer maintain blood glucose control and insulin replacement therapy becomes inevitable [The Royal College of Physicians 2008].

Metformin is the optimal first-line drug (Figure 1). If metformin therapy is contraindicated or not tolerated, other drugs could be used: combination therapy with an additional one or two oral or injectable agents is reasonable, aiming to minimise side effects where possible. Many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. A patient-centred approach should be used to guide choice of therapy, bearing in mind their efficacy, side effects, cost, comorbidities, and patient preferences [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012].

Figure 1: Pharmacological therapy for Type 2 DM

Monotherapy

Metformin as a first choice
(if not contraindicated and if tolerated)

If it is contraindicated and not tolerated, further drugs could be used*:*

- **Sulfonylurea**
- **Pioglitazone**
- **DPP-4 inhibitor.**

Dual therapy

If non-insulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA1c target level over 3–6 months, **the second oral agent, GLP-1 receptor agonist or insulin could be added:**

- **Sulfonylurea**
- **Pioglitazone**
- **DPP-4 inhibitor**
- **GLP-1 agonist**
- **Basal insulin**.

Triple therapy

- **Metformin + sulfonylurea* + thiazolidinedione or DPP-4 inhibitor or GLP-1 receptor agonist or insulin (basal: NPH, glargine or detemir)**
- **Metformin + thiazolidinedione + sulfonylurea* or DPP-4 inhibitor or GLP-1 receptor agonist or insulin (basal: NPH, glargine or detemir)**
- **Metformin + DPP-4 inhibitor + sulfonylurea* or thiazolidinedione or insulin (basal: NPH, glargine or detemir)**
- **Metformin + GLP-1 receptor agonist + sulfonylurea* or thiazolidinedione or insulin (basal: NPH, glargine or detemir)**
- **Metformin + insulin (basal: NPH, glargine or detemir) + thiazolidinedione or DPP-4 inhibitor or GLP-1 receptor agonist.**

Insulin (multiple daily doses)

NPH: Neutral protamine Hagedorn; *meglitinides therapy in case of late postprandial hypoglycaemia during sulfonylurea therapy; Source: [Inzucchi 2012]

In managing diabetes-related CVDs, blood pressure therapy and managing blood-lipid levels play a most important role, starting with lifestyle management followed by antihypertensive medication and lipid-lowering drugs [Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]. Additionally, antithrombotic therapy may be indicated [The Royal College of Physicians 2008].

Furthermore, measurement of several laboratory parameters is recommended to detect and monitor diabetes-related kidney disease. Regular structured eye surveillance is recommended to detect eye damage as is enquiry for neuropathic symptoms to detect nerve damage [Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008].

The DJBS

The DJBS has been introduced as an alternative treatment for managing obesity in patients with or without Type 2 DM. Different perspectives exist concerning the ultimate indication:

According to the manufacturer [GI Dynamics 2010, GI Dynamics 2012] and to a horizon scanning document from 2011 [National Horizon Scanning Centre 2011], the DJBS is currently indicated for patients with Type 2 DM and/or obesity.

However, an Australian horizon scanning document from 2010 [Australian Government: Department of Health and Ageing 2010] as well as a recently finished technology assessment [National Institute for Health and Clinical Excellence 2012] state that the DJBS is indicated for managing obesity. The manufacturer confirms that the initial primary indication of the device was obesity [GI Dynamics 2013].

There are no general contraindications except for pregnant women and patients with anatomic abnormities of the GI tract [Gersin 2010, GI Dynamics 2012, Rodriguez 2009].

The initial therapeutic aim of the intervention was to reduce body weight in general and in particular before surgical intervention as well as to manage an accompanying Type 2 DM and, thus, to reduce the adverse health consequences of obesity [Australian Government: Department of Health and Ageing 2010, ECRI Institute 2012, National Institute for Health and Clinical Excellence 2012].

The therapeutic aim has been changed by the manufacturer because of signs that the DJBS may be able to elicit glycaemic control independent of weight loss in obese Type 2 diabetes patients. The device is now implanted for glycaemic control in Type 2 DM patients, while weight loss is considered a positive side effect [GI Dynamics 2013].

The commercialised version (EndoBarrier®) that has been developed out of a prototype has CE-mark approval in Europe and is clinically used in the UK, the Netherlands, Germany, Spain, Switzerland, Denmark, the Czech Republic and Austria. Outside Europe, it is available in Chile, Qatar and Israel and it has a TGA approval in Australia. The commercialised version is intended for the treatment of patients with Type 2 DM and/or obesity for implantation up to 12 months. EndoBarrier® is not approved for sale in the USA and is considered investigational in the USA [GI Dynamics 2012]. GI Dynamics is conducting a pivotal clinical trial (the ENDO Trial) in the US for the treatment of patients who have uncontrolled Type 2 DM and are obese.

The procedure requires inpatient treatment. Average length of stay depends on the health care system. For example, in Austria the average duration of stay is 2 days (minimum 2, maximum 3).

Expected annual utilisation is unclear. Expert opinions in a recent overview on future utilization [National Institute for Health and Clinical Excellence 2012] range from slow diffusion speed, as the AEs and the price are high, to rapid uptake of the procedure in the next 2–5 years, mainly in the private sector. According to an estimate from a hospital provider in Austria, the annual frequency of implanting a DJBS will be around 250 procedures (3.1/100,000).

The reimbursement status differs markedly between European countries. In some countries, the DJBS is not on the market yet (e.g. Croatia); in others, it is authorised for use and reimbursed in selected hospitals (e.g. Spain). In some countries, it is paid by achieving statutory independent grants (e.g. France, the UK, Italy, the Czech Republic), in others by achieving the status of innovative procedure (the Netherlands) or by using existing diagnosis-related group (DRG) codes (e.g. Germany).

Discussion

Currently, there seems to be controversy over the primary target population and indication for the DJBS. While some sources and most of the studies define obese adults (with or without comorbidities) as the primary target population [Australian Government: Department of Health and Ageing 2010, de Moura 2011, Escalona 2012, Escalona 2010, Gersin 2010, National Institute for Health and Clinical Excellence 2012, Rodriguez-Grunert 2008, Schouten 2010, Tarnoff 2009], others – including, recently, the manufacturer – state that the device is primarily designed as a treatment for patients with Type 2 DM while obesity plays a subordinate role [de Moura 2012, GI Dynamics 2010, GI Dynamics 2012, National Horizon Scanning Centre 2011, Rodriguez 2009]. According to the manufacturer's information, there has been a shift in the primary indication because of signals that the DJBS may be able to elicit glycaemic control independent of weight loss in obese Type 2 diabetes patients. While the original indication was high-grade obesity with or without existing comorbidities (especially Type 2 DM), the current indication is Type 2 DM and/or obesity ≥grade I.

There is currently little objective information on the expected utilisation of the device and expert opinions range from slow diffusion speed to rapid uptake.

3. DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

Methods

Domain framing

No deviation was required from the general scope of the project, according to the final project plan.

Research questions

Element ID	Research question
B0001	What is the DJBS and what are evidence-based alternatives?
B0002	What is the approved indication and claimed benefit of the DJBS and the comparators?
B0003	What is the phase of development and implementation of the DJBS and the comparators?
B0004	Who performs DJBS and who performs or administers the comparators?
B0005	In what context and level of care are the DJBS and the comparators used?
B0008	What kind of special premises are needed to use the DJBS and the comparators?
B0009	What supplies and equipment are needed to use the DJBS and the comparators?

Sources

The questions from the domain 'description and technical characteristics of the technology' (B0001, B0002, B0003, B0005, B0008, B0009) were answered by using information from the following and supplemented by expert opinions:

- The manufacturer [GI Dynamics 2010, GI Dynamics 2012]
- Published evidence reports [National Institute for Health and Clinical Excellence 2012]
- Horizon scanning documents [Australian Government: Department of Health and Ageing 2010, ECRI Institute 2012, National Horizon Scanning Centre 2011, National Institute for Health and Clinical Excellence 2012]

Information on the characteristics of the comparators (B0004, B0005) was retrieved from:

- Clinical practice guidelines on the treatment of obesity and Type 2 DM and on bariatric surgery from the UK, the USA and Germany [Hauner 2007, National Institute for Health and Clinical Excellence 2006a, National Institute for Health and Clinical Excellence 2007, National Institute for Health and Clinical Excellence 2006b, Scottish Intercollegiate Guidelines Network 2010a, Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]
- HTA-reports [Shekelle 2004]
- National horizon scanning documents [Australian Government: Department of Health and Ageing 2010, ECRI Institute 2012, National Horizon Scanning Centre 2011].

Analysis

The sources were sufficient to answer the questions. We did not perform additional data analysis. No quality assessment was performed of the sources used.

Synthesis

The results are presented in plain text format.

Main results

Features of the DJBS

The commercialised version of the DJBS that has been developed out of a prototype is a 60 cm long impermeable sleeve-like device (fluoropolymer), placed endoscopically into the small intestine for up to 12 months. It is inserted under general anaesthesia using dynamic fluoroscopic imaging; in the future, however, it may be possible to implant the device with the patient under conscious sedation. When implanted, the device is anchored within the duodenal bulb (small area of the small intestine just outside the stomach) by a 5.5-cm nitinol (alloy of nickel and titanium) self-expanding stent with barbs that penetrate into the muscular wall of the intestine. The anchor system in the commercialised version has been modified: longer barbs to ensure implant duration for 12 months. The sleeve extends down through parts of the small intestine (duodenum and proximal jejunum) and is purported to mimic the effects of GI bypass surgery. The device is removed endoscopically by collapsing the nitinol stent and withdrawing the device from the stomach up through the oesophagus [Australian Government: Department of Health and Ageing 2010, de Moura 2012, de Moura 2011, ECRI Institute 2012, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009].

The device allows chyme (partially digested food leaving the stomach) to move through the GI tract without mixing with digestive enzymes or allowing nutrients to be absorbed through the intestinal walls.

After insertion, patients are placed on a diet that typically involves progression from fluids to semi-solid food avoiding solid foods for several weeks; this results in a substantial decrease in calorie intake [National Institute for Health and Clinical Excellence 2012].

The only provider of the device currently (February 2013) is GI Dynamics (GI Dynamics, Inc., Lexington, Massachusetts, USA). The brand name is EndoBarrier® [de Moura 2012, de Moura 2011, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. At least two large device companies have reportedly invested in the device's development in the USA [ECRI Institute 2012].

Claimed benefits

The claimed benefit is that the DJBS stimulates the secretion of GLP-1, which mediates glucose dependent insulin secretion, and peptide YY (PYY), which suppresses appetite and food intake, in the GI tract, leading to significant improvements in glycaemic control and the additional benefit of significant weight loss [GI Dynamics 2013].

Personnel and technical requirements

The DJBS is primarily implanted under general anaesthesia. More recently, the device has also been implanted under local anaesthesia [Montana 2012]. Implantation of the DJBS is done by a surgeon. This is identical to bariatric surgery. However, experts suggest that the intervention could shift the type of specialist providing bariatric services from surgeons to GI physicians accustomed to performing endoscopies [National Institute for Health and Clinical Excellence 2012].

In terms of level of care, it takes place in secondary or tertiary care specialist centres. In addition to the surgeon, an anaesthetist and nursing staff are required, as well as input from a radiological service.

To implant the device, an endoscope is required in addition to equipment for administering the anaesthetic and for managing hygiene. Access to an emergency unit is also needed in the event of serious complications such as bleeding or obstruction.

Alternatives to the DJBS (possible comparators)

According to the EUnetHTA guidelines on choosing an appropriate comparator [European Network for Health Technology Assessment (EUnetHTA) 2013b], the following alternatives can be defined:

1) If the primary indication is obesity ≥grade II in people where non-surgical measures of weight reduction have failed, the alternative is bariatric surgery. Weight loss in bariatric surgery is achieved via one of two mechanisms: mechanically restricting the size of the stomach or bypassing a portion of the intestines; however, several procedures exert their effects by using both mechanisms [Shekelle 2004]. Today, the most commonly used bariatric technique is the Roux-en-Y gastric bypass (RYGB); the current use of the term 'gastric bypass' typically refers to RYGB [ECRI Institute 2012]. Further types of bariatric surgery that are currently practiced are sleeve gastrectomy, vertical banded gastroplasty (VBG), adjustable silicone gastric banding (ASGB), and biliopancreatic diversion (BPD) with or without duodenal switch. All five procedures may be performed by open or laparoscopic technique. More recently, techniques that mimic one aspect of bariatric surgery (gastric restriction) have been developed that are of a temporary nature and have been recommended for restrictive use only: gastric balloon and gastric plication [National Institute for Health and Clinical Excellence 2012, Verdam 2012]

Because the DJBS is a temporary intervention, gastric balloon or gastric plication seem an appropriate alternative. If compared with technologies that have a similar mechanism of action (restricting capacity to absorb food), surgical Roux-en-Y gastric bypass or biliopancreatic diversion are of relevance.

2) If the primary indication for the device is Type 2 DM and/or obesity, the primary comparator is optimal antidiabetes pharmacotherapy and lifestyle changes for glycaemic control.

All of those technologies (bariatric surgery, drug therapy, lifestyle changes) either have the therapeutic aim of reducing body weight and obesity-related morbidity and mortality or improving glycaemic control and reducing the negative health consequences related to Type 2 DM.

Like the implantation of a DJBS, bariatric surgery is performed in secondary or tertiary care centres and requires anaesthesia. It is either performed as an open or laparoscopic procedure. Pre- and postoperative assessment and dietary monitoring are required and psychological support before and after surgery is recommended [National Institute for Health and Clinical Excellence 2007]. The length of stay is likely to be longer with bariatric surgery than implanting the DJBS, but it depends on the procedure.

Drug therapy and lifestyle advice to manage obesity are primarily provided in primary care by medical specialists or by general practitioners [National Institute for Health and Clinical Excellence 2006b]. They do not require specific premises or equipment.

People diagnosed with Type 2 DM require access to immediate and ongoing care. Who provides this care, and where and when, will depend on local circumstances, but it needs to be organised in a systematic way. A multidisciplinary approach has been recommended including nurses trained in teaching skills and adult education and formally trained dietitians and podiatrists within the specifically relevant areas of diabetes care [American Diabetes Association 2013, IDF Clinical Guidelines Task Force 2005].

Discussion

There have been ongoing discussions concerning the appropriate alternative for the device and a consensus on the question has not been reached [National Institute for Health and Clinical Excellence 2012]. Advisers' views range from pointing out that there are no acceptable comparators (e.g. gastric bands and bypass are permanent procedures and as such not comparable with the DJBS) and that the closest one would be dietary counselling and gastric balloon; others state that relevant comparators would be best medical treatment of Type 2 DM, intensive weight management in tandem with DJBS or laparoscopic proximal RYGB or laparoscopic sleeve gastrectomy.

There may be interspeciality controversy over the procedure between bariatric surgeons and gastroenterologists, as it may not be appropriate to undertake the procedures in gastroenterology departments that lack standard bariatric or diabetological multidisciplinary support. Good interventional and upper GI endoscopic skills are needed to perform the procedure, so practical training is needed. The following are also essential: radiation protection training, a good knowledge of patient selection, management of implantation and explantation, management of the device in situ and postexplantation management. Treatment-specific training is also needed for nurse, dietician, and physician follow-up teams [National Institute for Health and Clinical Excellence 2012].

According to existing documents [ECRI Institute 2012], most of the experts providing comments on the DJBS do not see potential for a shift in care setting. Some observed, however, that bariatric procedures are generally surgical procedures whereas the EndoBarrier® would likely be implanted in an endoscopy suite. This could involve capital equipment purchases for facilities that do not currently employ endoscopy in their bariatric practices.

4. SAFETY

Methods

Domain framing

No deviation was required from the general scope of the project, according to the final project plan.

Research questions

Element ID	Research question
C0001	What are the AEs and serious AEs with a DJBS in a) all patients b) patients with Type 2 DM and obesity and c) in patients with high-grade obesity (and comorbidities)?
C0002	Is there a relationship between the length of time the DJBS has been implanted and the harm to patients?
C0004	How does the frequency or severity of harm change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed?
C0007	Can AEs adverse events be caused by the behaviour of patients, professionals or manufacturers?
C0008	What is the safety of the DJBS in relation to conservative therapy, pharmacotherapy, bariatric surgery or sham-procedure in a) all patients b) patients with Type 2 DM and obesity and c) in patients with high-grade obesity (and comorbidities)?

Sources

For answering the research questions in the domain ‘safety’, the results from a systematic literature search (appendix 1) in:

- bibliographic databases
- the Cochrane Library
- the database of the Centre for Reviews and Dissemination
- complemented by a SCOPUS handsearch,

were used. Selection of relevant documents was done by two people independently (figure 2). In terms of study design, any prospective study was included provided that safety outcomes were reported.

Analysis

The sources were sufficient to answer the questions. We did not perform additional data analysis. Quality was assessed using the Cochrane risk of bias checklist (Table 9).

Synthesis

The questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix 1.

Main results

The following AEs have been reported (see Table 6, Table 7 and GRADE Table 10 to 12 for details): procedural pain, nausea and vomiting, general nausea and vomiting, abdominal

pain, abdominal distention, flatulence, erosive duodenitis, constipation, diarrhea, gastritis/gastroenterits, esophagitis, epigastric discomfort, hematemesis, dyspepsia, anemia, pyrexia, pseudopolyp formation, implant site inflammation, back pain.

The following serious AEs have been reported (see data extraction Table 6 and Table 7 and GRADE Table 10 to 12 for details): gastrointestinal bleeding (with hematemesis).

AEs were reported in nine out of 10 studies [Cohen 2013, de Moura 2012, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. AEs were observed in 64–100% of 201 patients who received a DJBS (+ diet) compared with 0–27% of 25 patients who received diet (only) [Schouten 2010, Tarnoff 2009]. Whether between-group differences are statistically significant has not been reported.

Serious AEs were reported in eight studies including 162 patients who received the EndoBarrier® (+ diet) [de Moura 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. In six (0–12%) of the patients, serious AEs in the form of GI bleeding occurred compared with 0% of 25 patients who received diet only [Schouten 2010, Tarnoff 2009].

Safety in relation to sham procedure has not been reported. No studies have been identified that compared the DJBL to optimal pharmacotherapy (in the management of Type 2 DM or obesity) or bariatric surgery. Hence, the safety of the DJBL in relation to pharmacotherapy or bariatric surgery is unknown.

Unexpected explantation of the device ahead of schedule was reported in 10 studies: it was required in 67 out of 282 (0–42%) study participants in the intervention groups [Cohen 2013, de Moura 2012, de Moura 2011, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009].

The frequencies of AEs in the studies that primarily included obese patients was not different from those that primarily included patients with Type 2 DM (see GRADE Table 11 and GRADE Table 12).

Intervention-related mortality has not been reported. Additionally, the studies we identified did not provide data on the relationship between length of time the DJBS had been implanted and harm to the patients, on whether the frequency of harm changed over time or in different settings, on susceptible patient groups that were more likely to be harmed and on whether AEs could be caused by the behaviour of patients, professionals or manufacturers.

Discussion

AEs occur in the majority of patients who receive the device; however, they are primarily mild such as pain, nausea, vomiting, constipation [de Moura 2012, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009].

The safety of the device in relation to a number of relevant comparators (optimised pharmacotherapy in Type 2 DM, bariatric surgery in obesity) has not been evaluated in the studies identified and can, therefore, not be defined on the basis of the current evidence. Furthermore, four out of the six domain questions cannot be answered because of lack of evidence. Seven of the 10 studies investigated a prototype rather than the commercialised type of the device. This is problematic because the prototype was implanted for 3 months, whereas the commercialised version stays implanted for up to 12 months and differs in some technical features.

The overall quality of evidence is low because of unclear allocation concealment, lack of blinding of study participants and outcome assessors, high drop-out rates in some studies, different drop-out rates between intervention and control groups, lack of or unclear intention-to-treat analysis, small numbers of study participants and very short follow-up periods in most of the studies.

5. CLINICAL EFFECTIVENESS

Methods

Domain framing

No deviation was required from the general scope of the project, according to the final project plan.

Endpoints for assessing clinical effectiveness were derived from the three main categories of endpoints 'mortality', 'morbidity' and 'quality of life' that have been defined in the EUnetHTA guideline on clinical endpoints [European Network for Health Technology Assessment (EUnetHTA) 2013a].

In terms of mortality, we considered overall mortality, Type 2 DM- or obesity-related mortality (because obesity and Type 2 diabetes are associated with premature mortality) and mortality due to other causes than the diseases. In terms of morbidity, we considered the effect of the DJBS on weight loss, cardiovascular events, diabetes-associated complications (e.g. diabetic nephropathy) and on further obesity-related morbidity (e.g. musculoskeletal morbidity) because these are the final morbidity endpoints that result from the claimed clinical benefit (see B0002). With regard to weight loss, clinically relevant weight loss was defined as a loss of at least 5–10% from baseline weight over 6 months, although it needs to be acknowledged that these are relatively arbitrary historical standards [Bray 2013, Hauner 2007, Jackson 2012].

Markers of metabolic function (HbA1c, fasting blood glucose) were considered because they are widely used in the management of Type 2 DM (see A0002a, A0025) but in the knowledge that they are surrogate endpoints and relation to the final therapeutic objective cannot be directly extrapolated. The same is true for the outcome 'reduction in drug use' (diabetic medication, antihypertensive medication).

Finally, generic and disease-specific health-related quality of life and patient satisfaction were considered.

Research questions

Element ID	Research question
D0001	What is the effect of the intervention on overall mortality in a) all patients b) patients with Type 2 DM and obesity and c) in patients with high-grade obesity (and comorbidities)?
D0002	What is the effect on the disease-specific mortality in a) all patients b) patients with Type 2 DM and obesity and c) in patients with high-grade obesity (and comorbidities)?
D0003	What is the effect of the intervention on the mortality due to other causes than the target disease in a) all patients b) patients with Type 2 DM and obesity and c) in patients with high-grade obesity (and comorbidities)?
D0004	What is the rate of direct mortality related to the use of the DJBS in a) all patients b) patients with Type 2 DM and obesity and c) in patients with high-grade obesity (and comorbidities)?

Element ID	Research question
D0005	How does the DJBS affect further outcomes compared to standard/usual care or practice in a) all patients b) patients with Type 2 DM and obesity and c) in patients with high-grade obesity (and comorbidities)? - weight loss (temporary, long-term) - reduction in drug use (e.g. diabetic medication, antihypertensive medication) - surrogate parameters (blood pressure, markers of metabolic function: HbA1c, fasting blood glucose, insulin, C-peptide, LDL, TG levels)
D0011	What is the effect of the DJBS in a) all patients b) patients with Type 2 DM and obesity and c) in patients with high-grade obesity (and comorbidities) on: - reduction in cardiovascular events (myocardial infarction, stroke, etc.), - reduction in diabetes-associated microangiopathic complications (diabetic nephropathy, retinopathy), compared to standard/usual care or practice?
D0012	What is the effect of the DJBS on generic health-related quality of life a) all patients b) patients with Type 2 DM and obesity and c) in patients with high-grade obesity (and comorbidities) compared to standard/usual care or practice?
D0013	What is the effect of the DJBS on disease-specific quality of life a) all patients b) patients with Type 2 DM and obesity and c) in patients with high-grade obesity (and comorbidities) compared to standard/usual care or practice?
D0016	How does the use of DJBS affect activities of daily living compared to standard/usual care or practice?
D0017	Were patients satisfied overall with the DJBS?
D0018	Would the patient be willing to use the DJBS again?
D0023	How does the DJBS modify the need for the use of other technologies resources?

Sources

For answering the research questions in the domain ‘effectiveness’, the results from a systematic literature search (Appendix 1: documentation of search strategy) in:

- bibliographic databases
- the Cochrane Library
- the database of the Centre for Reviews and Dissemination
- complemented by a SCOPUS handsearch

were used. Selection of relevant documents was done by two people independently (see figure 2 for study selection). In terms of study design, prospective controlled studies were included, provided that any of the defined outcomes were reported.

Analysis

The sources were sufficient to answer the questions. We did not perform additional data analysis. Quality was assessed using the Cochrane risk of bias checklist (Table 9).

Synthesis

The questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix 1.

Main results

Mortality

Concerning the relevant research questions, the following have not been provided in the selected studies: data on overall mortality, disease-specific mortality, mortality due to other causes or the rate of direct mortality related to the use of the DJBS.

Morbidity

In terms of effects of the DJBS on morbidity, the following study results have been reported.

EWL relative:
In two RCTs and one non-randomised controlled study that investigated 137 patients in total, excess overweight was reduced by 12–22% in the intervention group and by 3–7% in the control group within a follow-up period of 12 weeks. The control groups either received diet (only) or sham procedure. The between-group differences were statistically significant in all three studies [Gersin 2010, Schouten 2010, Tarnoff 2009] (see also data extraction Table 6, GRADE Table 10 and 11). All three studies included obese patients with or without comorbidities.

Weight loss absolute:
In two RCTs and one non-randomised controlled study that investigated 114 patients in total, an average weight loss per patient of 8–10 kg was observed after 12 weeks in the intervention group. Patients in the control group who received diet or sham procedures lost 2–7 kg on average. Statistical significance of the between-group differences was presented in two studies only [Gersin 2010, Rodriguez 2009] of which the difference reached statistical significance in one [Gersin 2010] (see also data in GRADE Table 10).

Two of those studies [Gersin 2010, Tarnoff 2009] included obese patients with or without comorbidities (GRADE Table 11). In one study [Rodriguez 2009], the primary inclusion criterion was Type 2 DM (GRADE Table 12). The between-group difference in absolute weight loss was significant in one study on obese patients and not significant in the Type 2 DM population.

Reduction in drug use:
One RCT (18 patients with Type 2 DM and obesity) documented the use of oral antidiabetic drugs [Rodriguez 2009]. All patients took antidiabetic medication at study entry. In 42% of patients in the intervention group, medication was ceased after 12 weeks, and in 40% after 24 weeks. In the control group, 17% of patients stopped using antidiabetics after 12 weeks, and 25% after 24 weeks. Statistical significance of the between-group difference was not reported (see also data in GRADE Table 12).

*Surrogate parameters (*see Table 6 and GRADE Table 10 to Table 12):
HbA1c (%): In three RCTs that investigated 99 patients overall, HbA1c (%) was measured in 63 study participants [Rodriguez 2009, Schouten 2010, Tarnoff 2009]. However, one study presents the results for four patients only and was, therefore, not selected for further analysis [Tarnoff 2009]. One of the studies included patients with Type 2 DM and obesity [Rodriguez 2009]; the other two included patients with obesity with or without comorbidities [Schouten 2010, Tarnoff 2009].

After 12 weeks, HbA1c fell by 1.1 to 1.3%-points in the intervention groups and by 0.4 to 0.8%-points in the control groups. Statistical significance was only measured in one study [Rodriguez 2009], where the between-group differences were not statistically significant.

After 24 weeks (measured in one study only [Rodriguez 2009]), it fell by 2.4%-points in the intervention group and by 0.8%-points in the control group compared with baseline. The between-group difference was not statistically significant.

FPG change: two RCTs (one included obese patients, the other one patients with Type 2 DM), with 59 participants in total, investigated FPG change (in mg/dl) [Rodriguez 2009, Schouten 2010]. After 12 weeks, the level fell by 18 to 45 mg/dl in the intervention group and by 8 to 9 mg/dl in the control group. Where measured, between-group differences were not statistically significant [Rodriguez 2009].

After 24 weeks, FPG dropped by 83 mg/dl (compared with study entry) in the intervention group and rose by 16 mg/dl in the control group. The between-group difference was again not statistically significant.

Concerning the effect on other markers of metabolic function and on blood pressure, no studies were identified that addressed this question.

Function

No studies have been identified that addressed the reduction in cardiovascular events (myocardial infarction, stroke, etc.), the reduction in diabetes-associated microangiopathic complications (diabetic nephropathy, retinopathy) or how the DJBS affects activities of daily living.

Quality of life

Neither studies that addressed generic health-related quality of life nor ones that addressed disease-specific quality of life have been identified.

Patient satisfaction

No studies that addressed patient satisfaction have been identified.

Change in management

No studies that addressed change in management have been identified.

Discussion

Studies that included obese patients (≥grade II) with or without comorbidities have consistently shown a significantly higher and clinically relevant short-term (12 weeks) reduction in excess weight in the intervention compared with the control groups (diet or sham procedure). For all other parameters, the benefit in the intervention groups compared with the control groups is unclear because the differences are either not consistently statistically significant (weight loss absolute) or the outcome of interest has not been measured (e.g. reduction in drug use).

In the single study that included patients with Type 2 DM, the effect on weight loss, drug use or metabolic function is unclear because the between-group differences are either not statistically significant or statistical significance has not been reported for between-group differences.

A major limitation in the studies is that none of the studies has evaluated the patients' point of view (e.g. health-related quality of life, dietary compliance, satisfaction).

Another limitation in those RCTs that address obesity as primary indication is that the comparator does not reflect standard or usual care. If the DJBS is intended for patients for whom conservative measures of weight reduction have failed, diet or doing nothing does not represent standard or usual care, as bariatric surgery would have to be consid-

ered. This is of even greater importance, as systematic reviews have shown that bariatric surgery is an effective weight loss intervention in selected patients [Scottish Intercollegiate Guidelines Network 2010a]. If the DJBS is intended for patients with manifest Type 2 DM, the intervention needs to be compared with optimal pharmacotherapy, whereas patients in the study received a sham procedure combined with limited pharmacotherapeutic management. While a sham procedure increases the validity of the study results, as compared with an unblinded trial, we do not know whether the DJBS results in a net benefit compared with optimal standard care.

Furthermore, the studies investigated a prototype of the device that has been implanted for 3 months only, whereas the commercialised device is intended for implantation up to 12 months and differs in some technical features.

Finally, the mean BMI in the controlled studies ranges between 39 and 49 kg/m^2. This is considerably higher than the manufacturer's concept of offering the treatment to patients with a BMI ≥30 kg/m^2. It may be possible that the effect size is greater in patients with a BMI >40 kg/m^2, resulting in an overestimation of DJBS's benefit.

The overall quality of evidence is low because of unclear allocation concealment, lack of blinding of study participants and outcome assessors, high and unexplained drop-out rates in some studies, different drop-out rates between intervention and control group, lack of or unclear intention-to-treat analysis, small numbers of study participants and very short follow-up periods in most of the studies. Furthermore, some outcome parameters lack information on how they were calculated and it is unclear whether they were defined consistently across studies (e.g. EWL).

Based on the current evidence, there is little effect of the DJBS on weight management in patients with obesity ≥grade II and currently there is no evidence on whether the relative reduction of excess weight is sustained beyond 3 months. This is of concern because the aim of obesity management is not a maximum weight loss, but rather a moderate yet sustainable reduction of weight. Furthermore, it is unclear whether the weight loss is caused by the device or by the diet patients are put on after device implantation.

The manufacturer has recently shifted the primary indication for the DJBS. In contrast to the originally proposed purpose of weight reduction, the current online information from the manufacturer propagates its use for Type 2 DM, while the treatment of obesity is regarded as secondary because of signals that the DJBS may be able to elicit glycaemic control independent of weight loss in obese Type 2 diabetes patients [GI Dynamics 2010, GI Dynamics 2012]. However, the studies that have been analysed in this report to address clinical effectiveness questions are primarily aimed at obesity [de Moura 2012, de Moura 2011, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009].

Furthermore, consequences for Type 2 DM metabolism have mostly been analysed as a secondary outcome for a very short follow-up period only [Gersin 2010, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. Hence, on the basis of the current evidence, the effectiveness of the EndoBarrier® on the management of Type 2 DM is unclear.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

METHODS

The assessment is based on a systematic literature search (without restrictions on publication date), complemented by a SCOPUS-handsearch in the following sources:

- biomedical databases (Medline via Ovid, Embase)
- The Cochrane Library
- Centre for Reviews and Dissemination
- In addition, the following clinical trials registries will be assessed, for registered ongoing clinical trials or observational studies: ClincalTrials.gov, ISRCTN, *meta*Register of Controlled Trials (*m*RCT) and International Clinical Trials Registry Platform (ICTRP).
- Request to manufacturer (GI-Dynamics)

Relevant articles for the report-domains have been selected by the first author and co-author independently. References have been included or excluded according to the Population-Intervention-Control-Outcome (PICO)-scheme described earlier. In terms of study design, prospective controlled trials have been selected for answering questions related to the domain 'clinical effectiveness', while for questions in the 'safety domain' any prospective study has been included, provided that it reported outcomes on safety. For other domains (health problem and current use of the technology, description and technical characteristics), no restrictions concerning study design were applied.

Where questions from the domains 'Health problem and current use of technology' and 'Description and technical characteristics of technology' could not be answered by the information retrieved from the systematic search described above, an additional handsearch in specific information sources (e.g. databases for clinical guidelines) was carried out.

In terms of language, documents in German, English and Croatian language were included.The quality of the studies was analysed by using the Cochrane risk of bias checklist. The results are used in the GRADE tables for grading the final quality of the evidence.

From the selected studies, study characteristics, results concerning efficacy/effectiveness and safety were extracted into a data extraction table (Table 6, Table 7). Effectiveness and safety were assessed by using the GRADE-methodology as this methodology allows for a transparent summary of the evidence in a qualitative manner (Table 10 to Table 12). Since we did not identify a sufficient number of homogeneous RCTs, we did not carry out a quantitative meta-analysis. Main issues of heterogeneity are different study populations and different or unclear definitions of outcome measures (e.g. EWL).

The HTA Core Model for Rapid Relative Effectiveness was the main source for selecting relevant assessment element. One deviation from the final version of the project plan is that some of the research questions in the result cards have been specified in more detail (e.g. C0008: What is the safety of the DJBS in relation to conservative therapy, pharmacotherapy, bariatric surgery or sham-procedure in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity [and comorbidities])? Another deviation is that question no A0004b was skipped because the answer was already provided in question no A0004a. No further deviations from the project plan in terms of method have been made.

Documentation of the search strategies

Search strategy for Medline via Ovid

Database: Ovid MEDLINE(R) <1946 to November Week 3 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 06, 2012>, Ovid MEDLINE(R) Daily Update <November 14, 2012>, Ovid OLDMEDLINE(R) <1946 to 1965>		
Search Strategy		
Date of Search: December 10, 2012		
1	obes*.mp	189478
2	exp Obesity	126256
3	exp Obesity, Morbid	9805
4	exp Diabetes Mellitus, Type 2	76354
5	Type 2 Diabetes Mellitus.mp	16826
6	exp Hypertension/	201338
7	hypertension*.mp.	345511
8	1 or 2 or 3 or 4 or 5 or 6 or 7	571214
9	duodenojejunal bypass*.mp.	26
10	((duoden* or jejun*) adj5 (bypass* or implant*)).mp.	2151
11	EndoBarrier.mp.	7
12	gastrointestinal liner*.mp	2
13	*Jejunum/su [Surgery]	3337
14	*Duodenum/su [Surgery]	2509
15	13 or 14	5547
16	exp Bariatric Surgery/	12482
17	15 and 16	134
18	9 or 10 or 11 or 12 or 17	2242
19	8 and 18	1318
20	exp Clinical Trial/ or double-blind method/ or (clinical trial* or randomized controlled trial or multicenter study).pt. or exp Clinical Trials as Topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab.	1049144
21	19 and 20	98

Search strategy for Embase

Database: Embase, Date of Search: December 10, 2012		
Search Strategy		
27	obes* OR 'obesity'/exp OR 'morbid obesity'/exp 'non insulin dependent diabetes mellitus'/exp OR 'type 2 diabetes mellitus' OR 'type ii diabetes mellitus' OR 'hypertension'/exp OR hypertension* AND ('duodenojejunal bypass' OR (duoden* OR jejun*) NEAR/1 (bypass* OR implant*) OR endobarrier:dn OR endobarrier* OR 'gastrointestinal liner' OR ('jejunum'/mj/dm_su OR 'duodenum'/mj/dm_su AND ('bariatric surgery'/exp OR 'bariatric surgery'))) AND ('case report'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'major clinical study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de) AND 'human'/de OR (obes* OR 'obesity'/exp OR 'morbid obesity'/exp OR 'non insulin dependent diabetes mellitus'/exp OR 'type 2 diabetes mellitus' OR 'type ii diabetes mellitus' OR 'hypertension'/exp OR hypertension* AND ('duodenojejunal bypass' OR (duoden* OR jejun*) NEAR/1 (bypass* OR implant*) OR endobarrier:dn OR endobarrier* OR 'gastrointestinal liner' OR ('jejunum'/mj/dm_su OR 'duodenum'/mj/dm_su AND ('bariatric surgery'/exp OR 'bariatric surgery'))) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim))	323

26	obes* OR 'obesity'/exp OR 'morbid obesity'/exp 'non insulin dependent diabetes mellitus'/exp OR 'type 2 diabetes mellitus' OR 'type ii diabetes mellitus' OR 'hypertension'/exp OR hypertension* AND ('duodenojejunal bypass' OR (duoden* OR jejun*) NEAR/1 (bypass* OR implant*) OR endobarrier:dn OR endobarrier* OR 'gastrointestinal liner' OR ('jejunum'/mj/dm_su OR 'duodenum'/mj/dm_su AND ('bariatric surgery'/exp OR 'bariatric surgery'))) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	28
25	obes* OR 'obesity'/exp OR 'morbid obesity'/exp 'non insulin dependent diabetes mellitus'/exp OR 'type 2 diabetes mellitus' OR 'type ii diabetes mellitus' OR 'hypertension'/exp OR hypertension* AND ('duodenojejunal bypass' OR (duoden* OR jejun*) NEAR/1 (bypass* OR implant*) OR endobarrier:dn OR endobarrier* OR 'gastrointestinal liner' OR ('jejunum'/mj/dm_su OR 'duodenum'/mj/dm_su AND ('bariatric surgery'/exp OR 'bariatric surgery'))) AND ('case report'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'major clinical study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de) AND 'human'/de	323
24	obes* OR 'obesity'/exp OR 'morbid obesity'/exp 'non insulin dependent diabetes mellitus'/exp OR 'type 2 diabetes mellitus' OR 'type ii diabetes mellitus' OR 'hypertension'/exp OR hypertension* AND ('duodenojejunal bypass' OR (duoden* OR jejun*) NEAR/1 (bypass* OR implant*) OR endobarrier:dn OR endobarrier* OR 'gastrointestinal liner' OR ('jejunum'/mj/dm_su OR 'duodenum'/mj/dm_su AND ('bariatric surgery'/exp OR 'bariatric surgery'))) AND ('case report'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'major clinical study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de)	639
23	obes* OR 'obesity'/exp OR 'morbid obesity'/exp OR 'non insulin dependent diabetes mellitus'/exp OR 'type 2 diabetes mellitus' OR 'type ii diabetes mellitus' OR 'hypertension'/exp OR hypertension* AND ('duodenojejunal bypass' OR (duoden* OR jejun*) NEAR/1 (bypass* OR implant*) OR endobarrier:dn OR endobarrier* OR 'gastrointestinal liner' OR ('jejunum'/mj/dm_su OR 'duodenum'/mj/dm_su AND ('bariatric surgery'/exp OR 'bariatric surgery')))	1,249
22	'duodenojejunal bypass' OR (duoden* OR jejun*) NEAR/1 (bypass* OR implant*) OR endobarrier:dn OR endobarrier* OR 'gastrointestinal liner' OR ('jejunum'/mj/dm_su OR 'duodenum'/mj/dm_su AND ('bariatric surgery'/exp OR 'bariatric surgery'))	1,707
21	'jejunum'/mj/dm_su OR 'duodenum'/mj/dm_su AND surgery'/exp OR 'bariatric surgery')	19
20	'bariatric surgery'/exp OR 'bariatric surgery'	15,012
19	'jejunum'/mj/dm_su OR 'duodenum'/mj/dm_su	3,405
18	'duodenum'/mj/dm_su	1,805
17	'jejunum'/mj/dm_su	1,765
16	'gastrointestinal liners'	
15	'gastrointestinal liner'	11
14	endobarrier*	37
13	endobarrier:dn	22
12	(duoden* OR jejun*) NEAR/1 (bypass* OR implant*)	1,684
11	'duodenojejunal bypasses'	
10	'duodenojejunal bypass'	49
9	obes* OR 'obesity'/exp OR 'morbid obesity'/exp OR 'non insulin dependent diabetes mellitus'/exp OR 'type 2 diabetes mellitus' OR 'type ii diabetes mellitus' OR 'hypertension'/exp OR hypertension*	910,464
8	obes*	607,680
7	'obesity'/exp	438,795
6	'morbid obesity'/exp	2,462
5	'non insulin dependent diabetes mellitus'/exp	24,335
4	'type 2 diabetes mellitus'	117,855
3	'type ii diabetes mellitus'	10,214
2	'hypertension'/exp	246,275
1	hypertension*	302,345

Search strategy for Cochrane

Search Name: Endobarrier Last Saved: 10/12/2012 14:55:52.971	
1	obes* (Word variations have been searched)
2	MeSH descriptor: [Obesity] explode all trees
3	MeSH descriptor: [Obesity, Morbid] explode all trees
4	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
5	Type 2 Diabetes Mellitus (Word variations have been searched)
6	Type II Diabetes Mellitus (Word variations have been searched)
7	MeSH descriptor: [Hypertension] explode all trees
8	hypertension* (Word variations have been searched)
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10	duodenojejunal bypass* (Word variations have been searched)
11	(duoden* or jejun*) near (bypass* or implant*) (Word variations have been searched)
12	EndoBarrier* (Word variations have been searched)
13	MeSH descriptor: [Jejunum] this term only and with qualifiers: [Surgery - SU]
14	MeSH descriptor: [Duodenum] this term only and with qualifiers: [Surgery - SU]
15	#13 or #14
16	MeSH descriptor: [Bariatric Surgery] explode all trees
17	#15 and #16
18	#10 or #11 or #12 or #17
19	#9 and #18
	81 Hits

Search strategy for Centre for Reviews and Dissemination

Search Name: Endobarrier Last Saved: 30/01/2013	
1	obes*
2	MeSH DESCRIPTOR Obesity EXPLODE ALL TREES
3	MeSH DESCRIPTOR Obesity, Morbid EXPLODE ALL TREES
4	MeSH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES
5	Type 2 Diabetes Mellitus
6	MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES
7	hypertension*
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	duodenojejunal bypass*
10	(duoden* OR jejun*) NEAR (bypass* OR implant*)
11	gastrointestinal liner*
12	MeSH DESCRIPTOR Jejunum EXPLODE ALL TREES WITH QUALIFIER SU
13	MeSH DESCRIPTOR Duodenum EXPLODE ALL TREES WITH QUALIFIER SU
14	#12 OR #13
15	MeSH DESCRIPTOR Bariatric Surgery EXPLODE ALL TREES
16	#14 AND #15
17	EndoBarrier
18	#10 OR #16 OR #17
19	#8 AND #18
	10 Hits

Flow chart of study selection

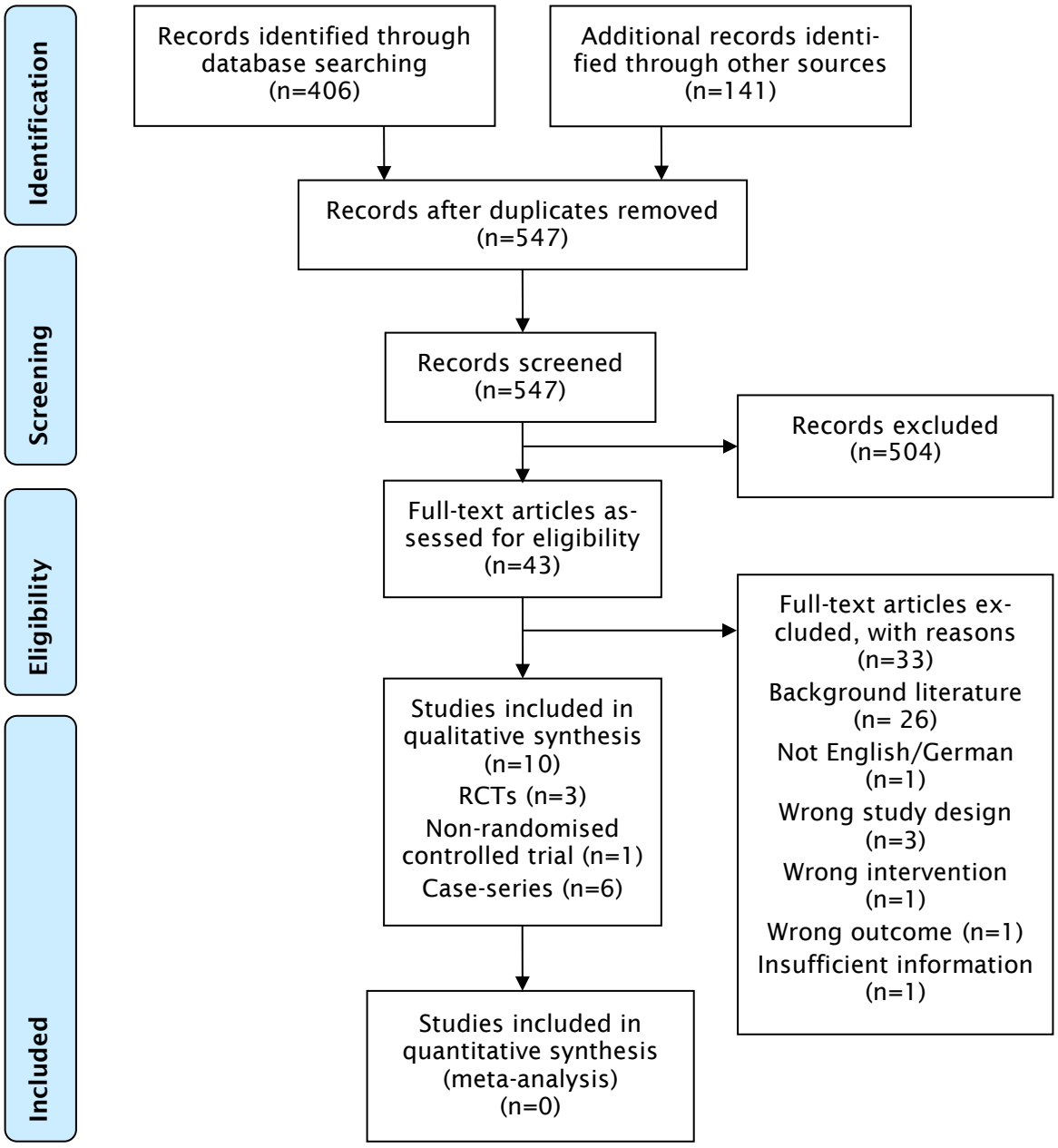

Figure 2: Flow chart of study selection

DESCRIPTION OF THE EVIDENCE USED

In the evaluation of clinical effectiveness, 3 RCTs [Gersin 2010, Rodriguez 2009, Schouten 2010] and 1 non-randomised controlled trial [Tarnoff 2009] with a total of 155 study participants fulfilled our inclusion criteria. A DJBS has been implanted in 95 patients. In the control groups 35 patients underwent a sham procedure [Gersin 2010, Rodriguez 2009] and 25 patients received diet only [Schouten 2010, Tarnoff 2009]. In 3 studies, the primary indication was obesity (+ comorbidities). In 1 RCT, the primary indication was Type 2 DM and obesity. All 4 studies evaluated a former version of the DJBS that differs from the commercialised version in implant duration (3 months versus up to 12 months) and some technical features.

Study participants were on average 38-45 years in the intervention groups and 41-51 years in the control groups. Patients in the intervention group weighed on average 103-143 kg and had a BMI of 39-49 kg/m². Those in the control group weighed 106-138 kg and had the same BMI. 60-73% and 50-89% were females in the intervention and control group respectively. Follow up was usually 12 weeks. In one study [Rodriguez 2009] the period was 24 to 52 weeks. 17-52% of patients in the intervention groups and 17-71% of those in the control groups were lost to follow-up.

Except for one study [Schouten 2010] risk of bias in the studies was rated as high (Table 9). This is due to missing information on sequence generation, allocation concealement and blinding of participants, personnel and outcome assessors. Furthermore, outcome data were incomplete which has, however, not been addressed in the studies. For example, statistical differences of between-group differences have not been reported and in some cases.

In the evaluation of safety 6 non-randomised single arm studies, in addition to the controlled studies, fulfilled our inclusion criteria [Cohen 2013, de Moura 2011, de Moura 2012, Escalona 2012, Escalona 2010, Rodriguez-Grunert 2008]. A DJBS has been implanted in 187 patients. In 4 studies [de Moura 2011, Escalona 2012, Escalona 2010, Rodriguez-Grunert 2008], the primary indication was obesity (+ comorbidity) and in the remaining 2 studies [Cohen 2013, de Moura 2012], Type 2 DM was the primary inclusion criterion.

Study participants in the single arm studies were on average 36-51 years old and their mean weight was 84-119 kg (BMI 30-45 kg/m²). Between 16% and 86% were females. Follow-up was between 12 and 52 weeks and up to 53% of the participants were lost to follow-up. 3 out of 6 single arm studies evaluated a former version of the DJBS that differs from the commercialised version in implant duration (3 months versus up to 12 months) and some technical features.

Evidence tables of individual studies included

Table 6: Results from controlled trials analysing the DJBS versus diet or sham procedure

Author, year, reference number	Tarnoff [2009]	Gersin [2010]	Schouten [2010]	Rodriguez [2009]
Country	CL	USA	NL	CL
Sponsor	N/A	GI Dynamics	GI Dynamics	GI Dynamics
Intervention/ Product	duodenojejunal bypass sleeve[1,2] + diet/lifestyle advice	duodenojejunal bypass sleeve[1,2] + weight loss counselling (baseline)	duodenojejunal bypass sleeve[1,2] + diet	duodenojejunal bypass sleeve[3,2]+ diet
Comparator	diet only	Sham (upper endoscopy with mock implantation)	diet only	Sham (gastrointestinal endoscopic examination without device implantation)
Study design	Non-randomised controlled trial	RCT	RCT	RCT
Number of pts.	total: 40 intervention: 26 control: 14	total: 56 intervention: 27 control: 29	total: 41 intervention: 30 control: 11	total: 18 intervention: 12 control:6
Inclusion criteria	pts. between 18 and 55 yrs., BMI 40-60 kg/m² with or without comorbidities or BMI ≥35 kg/m² with significant comorbidities, history of failure with nonsurgical weight loss methods, candidates for Roux-en-Y gastric bypass, subjects willing to comply with study requirements, subject who signed informed consent form	pts. between 18 and 55 yrs., BMI ≥40 kg/m² or BMI 30-60 kg/m² for pts. with comorbidities, women: postmenopausal, surgically sterile, taking oral contraceptives	pts. between 18 and 55 yrs., BMI 40-60 kg/m² or ≥35 kg/m² for pts. with comorbidities	pts. between 18 and 55 yrs. with Type 2DM for ≤10 yrs., HbA_{1c} 7-10%, FPG ≤240 mg/dL, BMI 30-50 kg/m², women: postmenopausal, surgically sterile or not pregnant and taking oral contraceptives
Age of pts. in yrs: mean (SD)	total: N/A intervention: 38 control: 43	total: 44 (±9) intervention: 45 control: 43	total: N/A intervention: 41 control: 41	total: 47 (±10) intervention: 45 control: 51
Sex of pts. (M/F) in %	total: N/A intervention: 40/60 control: 43/57	total: 19/81 intervention: 29/71 control: 11/89	total: N/A intervention: 27/73 control: 18/82	total: 39/61 intervention: 33/67 control: 50/50
Mean baseline weight in kg (SD)	intervention: 114±21 control: 108 ±12	intervention: 131±21 control: 130 ±21	intervention: 143/114-189[4] control: 138/86-160[4]	intervention: 103±21 control: 106 ±22
BMI in kg/m² (SD)	intervention: 42±5 control: 40±4	intervention: 46±5 control: 46±6	intervention: 49±6 control: 49±7	intervention: 39±6 control: 39 ±7

[1] For pre-operative weight loss in bariatric surgery
[2] Prototype
[3] For treatment of Type 2DM
[4] Range

Author, year, reference number	Tarnoff [2009]	Gersin [2010]	Schouten [2010]	Rodriguez [2009]
Average duration of Type 2DM (in yrs.)	N/A	N/A	N/A	3.7 (SD±2.4)
Follow-up in weeks (in months)	12 (3)	12 (3)	12 (3)	24-52 (6-12)[5]
Loss to follow-up in n (in %) patients	intervention: 6 (23) control: 10 (71)	intervention: 14 (52) control: 5 (17)	intervention: 12 (40) control: N/A	intervention: 2 (17)[6] control: 2 (33)[6]
Outcomes				
Efficacy				
Mean weight at baseline/follow-up in kg (range)	at 12 weeks: intervention: 114/104: -10 (-4.5 to -18) control: 108/105: -3 (0 to -7.7) p=N/A	at 12 weeks: intervention: 131/123: -8 (-10.9 to -5.5) control: 130/128: -2 (-4.4 to 0.3) p=0.002	N/A	at 12 weeks/at 20 weeks: intervention: -8/-10 (SD±1.3) control: -7/-7 (SD±4.3) p=NS/ p=N/A
EWL in %¤	at 12 weeks: intervention: 22 (SD±8) control: 5 (SD±7) p=0.02	at 12 weeks: intervention: 12 (95% CI: 9 to 15) control: 3 (95% CI: -1.4 to 6.7) p<0.001	at 12 weeks: intervention: 19 (SD±10.9) control: 7 (SD±6.1) p<0.002	N/A
Reduction in drug use in % of pts. who ceased treatment[7]	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A	at 12 weeks: intervention: 42 control: 17 p=N/A at 24 weeks: intervention: 40 control: 25 p=N/A
Quality of life	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A
Reduction in cardio-vascular events	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A
Reduction in diabetes-associated microangiopathic complications	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A

[5] Device removal after 24-48 weeks, follow-up after removal: 0,5-4 weeks
[6] At week 24 (month 6)
[7] At baseline 100% of patients in each group used oral antidiabetic drugs

Author, year, reference number	Tarnoff [2009]	Gersin [2010]	Schouten [2010]	Rodriguez [2009]
Overall mortality	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A
Surrogate parameters at baseline/follow-up [difference baseline-follow-up]	**HbA_{1c}[8] (%):** at 12 weeks: intervention: 6.63/6.3 [-0.33] control: 12.6/7.8 [-4.8] p=N/A **FPG change (mg/dL):** N/A **TG/HDL ratio:** N/A	**HbA_{1c}:** N/A **FPG change:** N/A **TG/HDL ratio:** N/A	**HbA_{1c} (%):** at 12 weeks: intervention: 8.8 (±1.7)/7.7 (±1.8) [-1.1] control: 7.3 (±0.1)/6.9 (±0.6) [-0.4] p=N/A **FPG change (mg/dL):** at 12 weeks: intervention: 111/93 [-18] control: 76/67 [-9] p=N/A **TG/HDL ratio:** N/A	**HbA_{1c} (%):** at 12 weeks: intervention: 9.2/7.9 (-1.3±0.9) control:9.0/8.2 (-0.8±0.3) p>0.05 at 24 weeks: intervention: 9.2/6.8 (-2.4±0.7) control:9.0/8.2 (-0.8±0.4) p>0.05 **FPG change (mg/dL):** at 12 weeks: intervention: 199/154 (-45 ±26) control: 185/177 (-8±35) p>0.05 at 24 weeks: intervention: 199/116 (-83±39) control: 185/201 (+16±42) p>0.05 **TG/HDL ratio:** N/A

[8] Measured in 4 patients.

Author, year, reference number	Tarnoff [2009]	Gersin [2010]	Schouten [2010]	Rodriguez [2009]
Safety				
General AEs in n (in %) patients	intervention: 16[9] (64) control: 0 (0) p=N/A	intervention: N/A[10] control: N/A p=N/A	intervention: 26[11] (100) control: 3 (27) p=N/A	intervention: 12[12] (100) control: N/A p=N/A
Serious AEs in n (in %) patients	intervention:3[13] (12) control: 0 (0) p=N/A	intervention: 3[14] (11) control: N/A p=N/A	intervention: 0 (0) control: 0 (0) p=N/A	intervention: 0 (o) control: N/A p=N/A
Description of intervention-associated AEs in n (in %) patients	intervention: procedural pain: 1 (4) abdominal pain: 16 (64) nausea: 7 (28) vomiting: 8 (32) abdominal distension: 11 (44) gastrointestinal bleeding: 4 (16) constipation: 1 (4) epigastric discomfort: 1 (4) control: 0 p=N/A	intervention[15]: abdominal pain: 14 (52) procedural nausea: 10 (37) procedural vomiting: 6 (22) nausea: 6 (22) vomiting: 4 (15) constipation: 3 (11) gastrointestinal bleeding: 3 (11) hematemesis: 3 (11) dyspepsia: 2 (13) anemia: 2 (13) pyrexia: 2 (13) control: N/A p=N/A	intervention: abdominal pain: 13 (50) nausea: 20 (77) vomiting: 6 (23) pseudopolyp formation: 13 (50) implant site inflamm.: 10 (39) other: 19 (73) control: pain: 0 (0) nausea: 1 (9) vomiting: 0 (0) other: 1 (9) p=N/A	intervention: abdominal pain: 12 (100) procedural nausea: 3 (25) procedural vomiting: 2 (17) nausea: 5 (42) vomiting: 4 (33) flatulence: 3 (25) erosive duodenitis: 2 (17) constipation: 1 (8) diarrhea: 1 (8) gastritis: 1 (8) esophagitis: 1 (8) control: N/A p=N/A
Unexpected device explantations in n (in %) patients	intervention: 5 (20)[16] control: N/A	intervention: 7 (33)[17] control: N/A	intervention: 4 (15)[18] control: N/A	intervention: 5 (42)[19] control: N/A
Procedure-related mortality in n (in %) patients	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A	intervention: N/A control: N/A

Abbreviations: AE=adverse events; BMI=body mass index; CL=Chile; EWL=excess weight loss; FPG=fasting plasma glucose; HbA1c=haemoglobin A1c; HDL=high density lipoprotein; n=number; N/A=data not available; NL=The Netherlands; NS=not significant; pts.=patients; RCT=randomised controlled trial; SD=standard deviation; TG=triglyceride; Type 2DM=Type 2 diabetes mellitus; yrs.=years; ¤information on calculation of excess weight loss not provided in the studies

[9] Measured in 25 patients; total number of AEs: 56
[10] No precise data given; total number of AEs: 108
[11] Total number of AEs: 83
[12] Total number of AEs: 64
[13] Measured in 25 patients, all 3 patients had gastrointestinal bleeding
[14] Gastrointestinal bleeding with hematemesis
[15] Measured in 27 patients
[16] Reasons: 3 (12%) bleeding, 1 (4%) sleeve obstruction, 1 (4%) device migration
[17] Reasons: 3 (14%) bleeding, 4 (19%) pain, nausea and/or vomiting
[18] Reasons: 2 (8%) pain, 1 (4%) nausea and vomiting, 1 (4%) device migration
[19] Reasons: 3 (25%) device migration, 1 (8.5%) nausea and vomiting, 1 (8.5%) pain and vomiting

Table 7: Results from non-randomised single arm studies (case series) of the DJBS

Author, year, reference number	Rodriguez-Grunert [2008]	Escalona[20] [2010]	De Moura [2011]	Escalona [2012]	De Moura [2012]	Cohen [2013]
Country	USA	CL	BR	CL	BR	BR
Sponsor	GI Dynamics	GI Dynamics	GI Dynamics	GI Dynamics	GI Dynamics	GI Dynamics
Intervention/Product	duodenojejunal bypass sleeve[21,23] + weight loss counselling	duodenojejunal bypass sleeve[22,23] + diet	duodenojejunal bypass sleeve[24,23]	duodenojejunal bypass sleeve[25,26] + nutritional advice	duodenojejunal bypass sleeve[27,26] + nutritional counselling	duodenojejunal bypass sleeve[26] + nutritional counselling
Comparator	none	none	none	none	none	none
Study design	non-randomised single arm study (case series)	non-randomised single arm study (case series)	non-randomised single arm study (case series)	non-randomised single arm study (case series)	non-randomised single arm study (case series)	non-randomised single arm study (case series)
Number of pts.	12	10	81[28]	39	22	23
Inclusion criteria	pts. deemed candidates for gastric bypass operation in accordance with 1991 National Institutes of Health guidelines	pts. between 18 and 55 yrs., with failure of nonoperative weight loss methods, BMI 40-60 kg/m² or BMI ≥35 kg/m² + comorbidities, women: postmenopausal, surgically sterile or taking oral contraceptives	pts. between 18 and 65 yrs., BMI≥35 km/m², Type 2DM with or without comorbidities, TG/HDL ratio ≥3.5 (indicating insulin resistance)	pts. between 18 and 55 yrs., BMI≥35 km/m² or BMI 40-60 kg/m² for pts. with comorbidities	pts. with Type 2DM, between 18 and 55 yrs. and BMI≥40 and ≤60 kg/m²	pts. between 18 and 55 yrs., Type 2DM of ≤10 yrs. duration treated with oral glucose-lowering drugs, HbA_{1c} 7.5-10%, BMI 26-50 km/m²; women: postmenopausal, surgically sterile or taking oral contraceptives
Age of pts. (yrs): mean (SD)	41	39 (±12)	51	36 (±10)	46 (±11)	50 (±7)
Sex of pts. (M/F) in %	42/58	20/80	84/16	20/80	14/86	65/35
Mean baseline weight in kg (BMI in kg/m²)	116 (43)	108 (41)	N/A	109 (44)	119 (45)	84 (30)
Average duration of Type 2DM (in yrs.)	N/A	N/A	N/A	N/A	N/A	6.6 (±3.1)
Follow-up in weeks (in months)	12 (3)	12 (3)	24 (6)	52 (12)	52 (12)	52 (12)

[20] It can be ruled out that the two articles by Escalona (2010 and 2012) reported on overlapping patient groups. While the first article was submitted in May 2009, the second study was conducted from march 2009 to October 2010
[21] For pre-operative weight loss in bariatric surgery
[22] For weight loss
[23] Prototype
[24] For improvement of insulin resistance and reduction of cardiovascular risk
[25] For weight loss
[26] Commercialised version
[27] For improvement of metabolic function
[28] Only 54 patients were included in analysis

Author, year, reference number	Rodriguez-Grunert [2008]	Escalona[20] [2010]	De Moura [2011]	Escalona [2012]	De Moura [2012]	Cohen [2013]
Loss to follow-up in n (in %) patients	2 (17)	0 (0)	43 (53)	15 (38)	9 (41)	7 (30)
Outcomes						
Safety						
General AEs in n (in %) patients	12[29] (100)	9[30] (90)	N/A[31]	N/A[31]	22[31] (100)	22 (96)
Serious AEs in n (in %) patients	0 (0)	0 (0)	N/A[31]	N/A[31]	0 (0)	0 (0)
Description of intervention-associated AEs in n (in %) patients	abdominal pain: N/A[31] nausea: N/A[31] vomiting: N/A[31] diarrhea: 1 (5) esophageal/ pharyngeal tear: 2 (17) implant site inflamm.: 12 (100) pseudopolyp formation: N/A[31]	pain: 7 (70) procedural nausea: 4 (40) procedural vomiting: 3 (30) nausea: 2 (20) vomiting: 5 (50)	N/A	pain: 32 (81) nausea: 16 (41) vomiting: 13 (33) gastoenteritis: 2 (5)	procedural nausea: 4 (18) procedural vomiting: 3 (14) abdominal pain: 11 (50) back pain: 5 (23) nausea: 7 (32) vomiting: 7 (32) diarrhea: 1 (5)	N/A[31]
Unexpected device explantations, n (%)	2 (17)[32]	0 (0)	16 (30)[33]	15 (38)[34]	9 (41)[35]	4 (17)[36]
Procedure-related mortality, n (%)	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: BMI= body mass index; BR=Brazil; n=number; CL=Chile; N/A=data not available; pts.=patients; Type 2DM=Type 2 diabetes mellitus

[29] Total number of AEs: 71
[30] Total number of AEs: 21
[31] No precise data given
[32] Reasons: 2 (17%) abdominal pain and discomfort
[33] Reasons: 9 (17%) device migration, 4 (7%) free device anchor, 1 (2%) bleeding, 1 (2%) request of patient, 1 (2%) decision of researcher
[34] Reasons: 8 (21%) device migration, 3 (8%) device obstruction, 2 (5%) pain, 1 (2%) cholecystitis, 1 (2%) request of patient
[35] Reasons: 3 (13%) device migration, 2 (9%) pain, 2 (9%) investigators request, 1 (5%) bleeding, 1 (5%) fever
[36] Reasons: 2 (9%) device migration, 1 (4%) pain, 1 (4%) investigators request

List of planned and ongoing studies

Table 8: List of planned and ongoing studies on the duodenal-jejunal bypass sleeve

Study Identifier	Time	Study type	N	Intervention	Comparator	Patient population	Primary endpoints
NCT00985114 (Dutch Diabetes Study/NL) Sponsor: GI Dynamics	completed 1/2012	Multi-center RCT/parallel assignment, open label	71 (34/37)	DJBS (implant duration unknown)	Lifestyle counselling + diet	Type 2 DM, Obesity (BMI >30 kg/m²)	% of subjects who achieve a ≥0.5% reduction in HbA1C at 24 weeks or last visit from baseline.
NCT01728116 (ENDO Trial/USA) Sponsor: GI Dynamics	12/2012 to 6/2015	Multi-center RCT/parallel assignment, double-blind	500 (333/167)	DJBS for 12 months	Sham procedure	Type 2 DM, Obesity (BMI ≥30 kg/m²	Improvement in HbA1c at 12 months
NCT01848795 (Italy) Sponsor: The Mediterranean Institute for Transplantation and Advanced Specialized Therapies	5/2013 to 5/2017	RCT/parallel assignment, open label	90	DJBS for 12 months	BioEnterics Intragastric Balloon for 12 months	Type 2 DM, Obesity (BMI ≥30 kg/m²)	% change in HbA1c level at 12 months
ENDOMETAB not yet registered (France) Sponsor: France Ministry of Health	01/2014 to 03/2017	Multi-center RCT	174 (116/58)	DJBS for 12 months	Conventional treatment*	Metabolic syndrome subjects	Reduction in rates of metabolic syndrome, (weight reduction, improvement in cardio-vascular risk factors, QOL, cost benefit)
EME MRC Study Not yet registered (UK) Sponsor: EME MRC grant	01/2014 to 01/2017	Multi-center RCT	160 (80/80)	DJBS	Conventional treatment*	Type 2 DM in obese subjects	Significant improvement of metabolic state (IDF), (weight reduction)
ABCD Study Not yet registered Sponsor: ABCD grant	01/2014 to 10/2016	Multi-center RCT	72 (24/24/24)	DJBS	Medical treatment: -Liraglutide, 1.8mg -DJBS w/o Liraglutide -DJBS + 1.2 mg Liraglutide	Type 2 DM in obese subjects	HbA1c (weight reduction)

Study Identifier	Time	Study type	N	Intervention	Comparator	Patient population	Primary endpoints
NCT01724060 (UK) Sponsor: Imperial College London	9/2012 to 10/2014	Case-control	400	Different measures to treat obesity and Type 2 DM (including DJBS)	Different measures to treat obesity and Type 2 DM (including DJBS)	Obese patients with Type 2 DM	Change in energy intake Change in macronutrient composition at 12 months
NCT00985491 (Chile) Sponsor: GI Dynamics	10/2008 to 7/2016	Interventional, single group assignment, open label	180	DJBS	-	Obesity (BMI >35), candidate for bariatric surgery	% EWL
NCT01718457 (Israel) Sponsor: Sheba Medical Centre	12/2012 to 12/2016	Interventional, single group assignment, open label	45	DJBS for 12 months	-	Type 2 DM, Obesity (BMI ≥30 kg/m²)	% change in HbA1c level % change in BMI at 12 amd 24 months
NCT01114438 (UK) Sponsor: GI Dynamics	10/2010 to 1/2013	Interventional, single group assignment, open label	45	DJBS for 12 months	-	Type 2 DM, Obesity (BMI >30)	% change in HbA1c at 12 months

EWL = excess weight loss; *detailed information not available

Risk of bias tables

Table 9: Cochrane risk of bias checklist [European Network for Health Technology Assessment (EUnetHTA) 2012]

Study	*Sequence generation*	*Allocation concealment*	*Blinding of participants, personnel and outcome assessors*	*Incomplete outcome data Were incomplete outcome data adequately addressed?*	*Free of selective outcome reporting*	*Free of other bias?*	Risk of bias
RCTs							
Rodriguez 2009	no information	not clear	no information	incomplete data, not adequately addressed	unclear‡	no¤	**high**
Tarnoff 2009	no information	not clear	no information	incomplete data, not adequately addressed	unclear‡	no¤	**high**
Gersin 2010	no information	not clear	participants: yes personnel + outcome assessors: no	incomplete data, not adequately addressed	yes	no¤	**high**
Schouten 2010	computer generated	not clear	no information	incomplete data, not adequately addressed	yes	no¤	**moderate/high**
Case Series							
Rodriguez-Grunert 2008	-	-	-	Incomplete (not adequately addressed)	no	no¤	**high**
Escalona 2010	-	-	-	Incomplete (not adequately addressed)	no	no¤	**high**
De Moura 2011	-	-	-	Incomplete (not adequately addressed)	no	no¤	**high**
De Moura 2012	-	-	-	Incomplete (not adequately addressed)	no	no¤	**high**
Cohen 2013	-	-	-	Incomplete (not adequately addressed)	no	no¤	**high**
Eduardo 2012	-	-	-	Incomplete (not adequately addressed)	no	no¤	**high**

‡ studies not registered in standard clinical trials registries; ¤ e.g. sponsored by manufacturer, small sample size, high drop out rates that differed between study groups;

Evidence profile

Table 10: Evidence profile: efficacy and safety of the DJBS (all patients)

No of studies/ patients	Design	Limitations	Consistency of results	Directness	Effect size	Other modifying factors[37]	Quality of evidence
Efficacy (I vs.C)							
Outcome: weight loss (in % of excess weight of all patients per group) at 12 weeks							
3/137	(R)CTs	serious limitations (-1)[38]	no important inconsistency	direct	12-22 vs. 3-7 p<0.001 to 0.02	imprecise data (-1)	low
Outcome: weight loss (in kg of all patients per group) at 12 weeks							
3/114	(R)CTs	serious limitations (-1)[39]	no important inconsistency	direct	-8 to -10 vs. -2 to -7 p=0.002 to NS[40]	no	low
Outcome: weight loss (in kg of all patients per group) at 20 weeks							
1/18	RCT	serious limitations (-1)[52]	only one trial	direct	-10 vs. -7 p=N/A	sparse data (-1)	low
Outcome: reduction in drug use (in % of pts. who ceased drug treatment) at 12 weeks							
1/18	RCT	serious limitations (-1)[41]	only one trial	direct	42 vs. 17 p=N/A	imprecise/sparse data (-1)	low
Outcome: reduction in drug use (in % of pts. who ceased drug treatment) at 24 weeks							
1/18	RCT	serious limitations (-1)[52]	only one trial	direct	40 vs. 25 p=N/A	imprecise/sparse data (-1)	low
Outcome: HbA_{1c} (in %-points compared to baseline) at 12 weeks							
2/59	RCTs	serious limitations (-1)[42]	no important inconsistency	direct	-1.1 to -1.3 vs. -0.4 to -0.8 p=NS or N/A	no	low
Outcome: $HbA1_c$ (in %-points compared to baseline) at 24 weeks							
1/18	RCT	serious limitations (-1)[52]	only one trial	direct	-2.4 vs. -0.8 p=NS	sparse data	low
Outcome: quality of life							
No evidence							
Outcome: reduction in cardiovascular events							
No evidence							
Outcome: reduction in diabetes-associated microangiopathic complications							
No evidence							
Outcome: Overall mortality							
No evidence							

[37] Low incidence, lack of precise data, sparse data, strong or very strong association, high risk of publication bias, dose-efficacy gradient, residual confounding plausible
[38] Unclear allocation concealment in 1 RCT, unclear or no blinding, high loss to follow-up in all RCTs, no intention-to-treat analysis in 1 RCT
[39] Unclear allocation concealment in 2 RCTs, unclear or no blinding, relatively high loss to follow-up in all RCTs, no intention-to-treat analysis in 1 RCT
[40] Difference in one study significant, in other study not, in one study not stated
[41] Unclear allocation concealment, unclear or no blinding, relatively high loss to follow-up in all RCTs
[42] Unclear allocation concealment in 1 RCTs, blinding unclear, relatively high loss to follow-up in all RCTs

No of studies/ patients	Design	Limitations	Consistency of results	Directness	Effect size	Other modifying factors[37]	Quality of evidence
Safety (RCTs: I vs. C)							
Outcome: general intervention-associated AEs (in % of patients)							
3/99 4/67	RCTs case series	serious limitations (-1)[43]	RCTs: important inconsistency (-1) case series: no important inconsistency	direct	RCTs: 64-100 vs. 0-27 p=N/A case series: 90-100	no	RCTs: low case series: very low
Outcome: serious intervention-associated AEs (in % of patients)							
4/155 4/67	RCTs case series	serious limitations (-1)[53]	RCTs: important inconsistency (-1) case series: no important inconsistency	direct	RCTs: 0-12 vs. 0 p=N/A case series: 0	no	RCTs: low case series: very low
Outcome: unexpected device explantations (in % of patients)							
4/155 6/187	RCTs case series	serious limitations (-1)[53]	RCTs: important inconsistency (-1) case series: important inconsistency (-1)	direct	RCTs: 15-42 vs. N/A[44] p=N/A case series: 0-41	no	RCTs: low case series: very low
Outcome: procedure-related mortality (in % of patients)							
No evidence							

Abbreviations: HbA1c=haemoglobin A1c; I vs. C.=intervention versus control group; N/A=data not available; NS=not significant; pts.=patients; RCT= randomised controlled trial

[43] RCTs: unclear allocation concealment in 2 RCTs, unclear or no blinding, relatively high loss to follow-up in all RCTs, no intention-to-treat analysis in 1 RCT; case series: uncontrolled study design, high loss to follow-up

[44] There was no device implanted in any of the control groups

Table 11: Evidence profile: efficacy and safety of the DJBS in patients with obesity (and comorbidities)

No of studies/ patients	Design	Limitations	Consistency of results	Directness	Effect size	Other modifying factors[45]	Quality of evidence
Efficacy (I vs.C)							
Outcome: weight loss (in % of excess weight of all patients per group) at 12 weeks							
3/137	(R)CTs	serious limitations (-1)[46]	no important inconsistency	direct	12-22 vs. 3-7 p<0.001 to 0.02	imprecise data (-1)	low
Outcome: weight loss (in kg of all patients per group) at 12 weeks							
2/96	(R)CTs	serious limitations (-1)[46]	no important inconsistency	direct	-8 to -10 vs. -2 to -3 p=0.002[47]	no	low
Outcome: weight loss (in kg of all patients per group) at 20 weeks							
No evidence							
Outcome: HbA_{1c} (in %-points compared to baseline) at 12 weeks							
1/41	RCTs	serious limitations (-1)[48]	no important inconsistency	direct	-1.1 vs. -0.4 p=N/A	no	low
Outcome: reduction in drug use (in % of pts. who ceased drug treatment) at 12 and 24 weeks							
No evidence							
Outcome: quality of life							
No evidence							
Outcome: reduction in cardiovascular events							
No evidence							
Outcome: reduction in diabetes-associated microangiopathic complications							
No evidence							
Outcome: Overall mortality							
No evidence							
Safety (RCTs: I vs. C)							
Outcome: general intervention-associated AEs (in % of patients)							
2/81 2/22	RCTs case series	serious limitations (-1)[49]	RCTs: important inconsistency (-1) case series: no important inconsistency	direct	RCTs: 64-100 vs. 0-27 p=N/A case series: 90-100	no	RCTs: low case series: very low
Outcome: serious intervention-associated AEs (in % of patients)							
3/137 2/22	RCTs case series	serious limitations (-1)[53]	RCTs: important inconsistency (-1) case series: no important inconsistency	direct	RCTs: 0-12 vs. 0 p=N/A case series: 0	no	RCTs: low case series: very low
Outcome: unexpected device explantations (in % of patients)							
3/137 4/142	RCTs case series	serious limitations (-1)[53]	RCTs: important inconsistency (-1) case series: important inconsistency (-1)	direct	RCTs: 15-33 vs. N/A[50] p=N/A case series: 0-38	no	RCTs: low case series: very low
Outcome: procedure-related mortality (in % of patients)							
No evidence							

Abbreviations: HbA1c=haemoglobin A1c; I vs. C.=intervention versus control group; N/A=data not available; pts.=patients; RCT=randomised controlled trial

[45] Low incidence, lack of precise data, sparse data, strong or very strong association, high risk of publication bias, dose-efficacy gradient, residual confounding plausible
[46] Unclear allocation concealment in 1 RCT, unclear or no blinding, high loss to follow-up in all RCTs, no intention-to-treat analysis in 1 RCT
[47] Difference in one study significant, in one study not stated
[48] Blinding unclear, relatively high loss to follow-up
[49] RCTs: unclear allocation concealment in 1 RCT, unclear or no blinding, no intention-to-treat analysis in 1 RCT; case series: uncontrolled study design, high loss to follow-up
[50] There was no device implanted in any of the control groups

Table 12: Evidence profile: efficacy and safety of the DJBS in patients with Type 2 diabetes mellitus and obesity

No of studies/ patients	Design	Limitations	Consistency of results	Directness	Effect size	Other modifying factors[51]	Quality of evidence
Efficacy (I vs.C)							
Outcome: weight loss (in % of excess weight of all patients per group) at 12 weeks							
No Evidence							
Outcome: weight loss (in kg of all patients per group) at 12 weeks							
1/18	RCTs	serious limitations (-1)[52]	only one trial	direct	-8 vs. -7 p=NS	no	low
Outcome: weight loss (in kg of all patients per group) at 20 weeks							
1/18	RCT	serious limitations (-1)[52]	only one trial	direct	-10 vs. -7 p=N/A	sparse data (-1)	low
Outcome: reduction in drug use (in % of pts. who ceased drug treatment) at 12 weeks							
1/18	RCT	serious limitations (-1)[52]	only one trial	direct	42 vs. 17 p=N/A	imprecise/sparse data (-1)	low
Outcome: reduction in drug use (in % of pts. who ceased drug treatment) at 24 weeks							
1/18	RCT	serious limitations (-1)[52]	only one trial	direct	40 vs. 25 p=N/A	imprecise/sparse data (-1)	low
Outcome: HbA_{1c} (in %-points compared to baseline) at 12 and 24 weeks							
1/18	RCT	serious limitations (-1)[52]	only one trial	direct	12 weeks: -1.3 vs. -0.8 p=NS 24 weeks: -2.4 vs. -0.8 p=NS	sparse data (-1)	low
Outcome: quality of life							
No evidence							
Outcome: reduction in cardiovascular events							
No evidence							
Outcome: reduction in diabetes-associated microangiopathic complications							
No evidence							
Outcome: Overall mortality							
No evidence							
Safety (RCTs: I vs. C)							
Outcome: general intervention-associated AEs (in % of patients)							
1/18 2/45	RCT case series	serious limitations (-1)[53]	RCT: only one trial case series: no important inconsistency	direct	RCT: 100 vs. N/A p=N/A case series: 96-100	RCT: sparse data (-1) case series: no	RCT: low case series: no
Outcome: serious intervention-associated AEs (in % of patients)							
1/18 2/45	RCT case series	serious limitations (-1)[53]	RCT: only one trial case series: no important inconsistency	direct	RCT: 0 vs. N/A p=N/A case series: 0	RCT: sparse data (-1) case series: no	RCT: low case series: very low
Outcome: unexpected device explantations (in % of patients)							
1/18 2/45	RCT case series	serious limitations (-1)[53]	RCT: only one trial case series: important inconsistency (-1)	direct	RCT: 42 vs. N/A[54] p=N/A case series: 17-41	RCT: sparse data (-1) case series: no	RCT: low case series: very low
Outcome: procedure-related mortality (in % of patients)							
No evidence							

Abbreviations: HbA_{1c}=haemoglobin A1c; I vs. C.=intervention versus control group; N/A=data not available; NS=not significant; pts.=patients; RCT=randomised controlle

[51] Low incidence, lack of precise data, sparse data, strong or very strong association, high risk of publication bias, dose-efficacy gradient, residual confounding plausible
[52] Unclear allocation concealment, unclear blinding, relatively high loss to follow-up
[53] RCT: unclear allocation concealment in, unclear blinding, relatively high loss to follow-up; case series: uncontrolled study design, high loss to follow-up
[54] There was no device implanted in the control group

Applicability tables

For guidance see guideline 'Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals'.

Table 13: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Majority of studies include patients between 18 and 55 years (1 study: 18 – 65 years), with grade III obesity or grade II obesity with comorbidities. Only 1 RCT and 3 case series explicitly included patients with Type 2 DM. This restricts applicability of benefits in patients with Type 2 DM. The DJBS was examined mainly in patients with a BMI >40, whereas the company aims at the population with a BMI <40. Therefore it is possible that effectiveness in terms of weight loss was overestimated. On the other hand, general side effects were possibly overestimated due to the higher risk of complications with increasing BMI. 4 Studies include women only if postmenopausal. This is likely to differ from female community relevant for the management of obesity and Type 2 DM. Females of younger age may have lower risk of procedure related harms. In 8 out of 10 studies the majority of study participants were females. This may affect applicability of study results in those countries were the prevalence of obesity is greater in males than in females (e.g. Austria, Croatia) because there may be gender-specific differences in the physiological function of the device. The majority of study participants are from Latin American countries. It is unclear whether ethnicity affects the physiological function of the device. This restricts applicability to a European population.
Intervention	The characteristics of the DJBS in the majority of studies are likely to be different in routine use because the studies primarily investigated a prototype version rather than the commercialised type. The latter has a longer implantation duration and differs in some technical features (e.g. anchor system). Surgical interventions in treating obesity need to be accompanied by lifestyle changes including diet which was the case in 8 out of 10 studies. The surgeon's technical expertise likely determines the risk for local side effects. If being introduced as a new treatment method in European hospitals, the implantation of the EndoBarrier device will certainly be accompanied by a learning curve.
Comparators	If the DJBS is used in obese patients where conservative measures of weight reduction have failed, diet or doing nothing does not represent standard or usual care but bariatric surgery would have to be considered. If the DJBS is implanted in patients with manifest Type 2 DM, the intervention needs to be compared to optimal pharmacotherapy, whereas patients in the study received a sham-procedure combined with limited pharmacotherapeutic management. While a sham procedure increases the validity of the study results as compared to an unblinded trial, we do not know whether the DJBS results in a net benefit compared to optimal standard care.
Outcomes	Short-term outcomes and surrogate outcomes have been used in the studies while important clinical endpoints (cardiovascular events, diabetes-associated microangiopatic complications, daily living, quality of life, patient satisfaction) have not been analysed. The clinical benefit is therefore unknown.
Setting	Nine out of 10 studies were undertaken outside Europe, mainly in Latin America. The description of the clinical setting in which the device was implanted in the studies does not differ from the clinical setting requirements that have been described for European countries.

APPENDIX 2: RESULT CARDS

Health Problem and Current Use of the Technology

[A0001]: For which indication/for what purposes is the duodenal-jejunal bypass sleeve used and are there any contraindications?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	According to the manufacturer [GI Dynamics 2010, GI Dynamics 2012] and to a horizon scanning document from 2011[National Horizon Scanning Centre 2011], the duodenal-jejunal bypass sleeve (DJBS) is indicated for patients with Type 2 diabetes mellitus (DM) and/or obesity ≥grade I. According to an Australian horizon scanning document from 2010 [Australian Government: Department of Health and Ageing 2010] as well as to a recently finished technology assessment [National Institute for Health and Clinical Excellence 2012] the DJBS is indicated for managing obesity. The manufacturer confirms that the initial primary indication of the device was obesity [GI Dynamics 2013]. There are no general contraindications except for pregnant women and patients with anatomic abnormities of the gastrointestinal tract [Gersin 2010, GI Dynamics 2012, Rodriguez 2009]. The initial therapeutic aim of the intervention was to reduce body weight in general and in particular before surgical interventions as well as to manage an accompanying Type 2 DM and, thus, to reduce the adverse health consequences of obesity [Australian Government: Department of Health and Ageing 2010, ECRI Institute 2012, National Institute for Health and Clinical Excellence 2012]. According to the manufacturer, the therapeutic aim has changed and the device is now implanted for glycaemic control in Type 2 DM patients, while weight loss is considered a positive side effect. This is because of signals that the DJBS may be able to elicit glycaemic control independent of weight loss in obese Type 2 DM patients [GI Dynamics 2013].
Discussion	According to the manufacturer's information there has been a shift in the primary indication. While the original indication was obesity with or without existing comorbidities (especially Type 2 DM), the current indication is Type 2 DM and or obesity ≥grade I.
References	1. Australian Government: Department of Health and Ageing. Horizon Scanning Technology Prioritising Summary. EndoBarrier Gastrointestinal Liner for obesity: Commonwealth of Australia 2010:10. 2. ECRI Institute. AHRQ Health Care Horizon Scanning System - Potential High-Impact Interventions Report. Priority Area 10: Obesity. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.). Rockville, MD: Agency for Healthcare Research and Quality; 2012. 3. Gersin KS, Rothstein RI, Rosenthal RJ, Stefanidis D, Deal SE, Kuwada TS, et al. Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. Gastrointestinal Endoscopy. 2010 May;71(6):976-82.

References *continued*	4. GI Dynamics. Der EndoBarrier: Eine innovative Lösung bei der Behandlung und Kontrolle von Typ-2Diabetes mellitus und Adipositas. 2010 [cited 2013 20/02/]; Available from: http://www.endobarrier.de/fachkreise/der-endobarrier/der-endobarrier.html. 5. GI Dynamics. Learn About Endobarrier Therapy - Overview. 2012;2013(20/02). 6. GI Dynamics. Manufacturer consultation of the draft project plan for duodenal-jejunal bypass sleeve (EndoBarrier®) for the treatment of obesity. GI Dynamics 2013. 7. National Horizon Scanning Centre. Endobarrier for type 2 diabetes mellitus with obesity. Birmingham: National Horizon Scanning Centre (NHSC); 2011. 8. National Institute for Health and Clinical Excellence. Interventional procedure overview of implantation of a duodenal-jejunal bypass sleeve for managing obesity. London: National Institute for Health and Clinical Excellence; 2012. 9. Rodriguez L, Reyes E, Fagalde P, Oltra MS, Saba J, Aylwin CG, et al. Pilot clinical study of an endoscopic, removable duodenal-jejunal bypass liner for the treatment of type 2 diabetes. Diabetes Technology & Therapeutics. 2009 Nov;11(11):725-32.
Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[A0002a]: What is the precise definition of obesity and Type 2 diabetes mellitus (DM) and which diagnosis is given to obesity and Type 2 DM according to ICD-10?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	1) **Obesity** is a state of excess adipose tissue mass [Fauci 2013, Gale 2012]. It is measured using the body mass index (BMI). The BMI is defined as the individual's body weight (in kg) divided by the square of their height [Branca 2007, Scottish Intercollegiate Guidelines Network 2010a]. $$\text{BMI}=\frac{\text{kg}}{\text{m}^2}$$ People of Caucasian origin are considered as being overweight if their BMI exceeds 25kg/m² and obese if their BMI exceeds 30 kg/m² (Table 1) [Branca 2007, National Institute for Health and Clinical Excellence 2006a, Scottish Intercollegiate Guidelines Network 2010a]. Additionally, in adults, central adiposity is frequently measured by waist circumference, with raised waist circumference defined as equal to or greater than 102 cm in men and equal to or greater than 88 cm in women [National Institute for Health and Clinical Excellence 2006a]. Waist circumference may also be used, in addition to BMI, in people with a BMI less than 35 kg/m² [National Institute for Health and Clinical Excellence 2006a]. Finally, waist-to-hip ratio may be a useful predictor of diabetes and cardiovascular disease (CVD) risk in adults, but it is more difficult to measure than waist circumference [Scottish Intercollegiate Guidelines Network 2010a]. Patients with BMI >35 kg/m² are called severely obese and those with BMI >40 kg/m² morbidly obese [ECRI Institute 2012]. *Table 1: Grading of overweight and obesity* **Categories** / **BMI (kg/m²)** Healthy weight: 18.5–24.9 Overweight (Pre-obesity): 25.0–29.9 Obesity grade I: 30.0–34.9 Obesity grade II: 35.0–39.9 Obesity grade III (Obesity permagna or morbid obesity): ≥40.0 According to the ICD-10 classification, five different codes for obesity exist, which are summarised in Table 2. *Table 2: Coding of obesity according to ICD-10* **ICD-10 Code** / **Description** E66.0: Obesity due to excess calories E66.1: Drug-induced obesity E66.2: Morbid (severe) obesity with alveolar hypoventilation E66.8: Other obesity E66.9: Obesity, unspecified Source: [International Statistical Classification of Diseases and Related Health Problems 2013a]

Result *continued*	2) **Diabetes Mellitus (DM)** is defined as a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action, or both [Fauci 2013, Gale 2012, Scottish Intercollegiate Guidelines Network 2010b, World Health Organization 2006]. Several types of DM exist that can be classified into Type 1 and Type 2 DM, gestational diabetes and other less common forms of diabetes that are caused by genetic defects, endocrine pancreas disorders, endocrinopathies or infections or that are medication-induced [Rieder 2004]. Criteria for the diagnosis of DM include one of the following: • Fasting Plasma Glucose (FPG) ≥7.0 mmol/l • Plasma glucose ≥11.1 mmol/l at 2 h after a 75 g oral glucose load (oral glucose tolerance test (OGTT)) • andom blood glucose concentration ≥11.1 mmol/l in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis • Haemoglobin A1c (HbA1c)>6.5% The results should be confirmed by repeat testing unless unequivocal hyperglycaemia is present [American Diabetes Association 2013, Fauci 2013, Gale 2012, World Health Organization 2011]. **Type 2 DM** results from a progressive insulin secretory defect with a variable degree of insulin resistance in the background [American Diabetes Association 2013, Fauci 2013, Gale 2012]. People are normally thought to have Type 2 DM if they do not have Type 1 diabetes (rapid onset, often in childhood, insulin-dependent, ketoacidosis if neglected) or other medical conditions or treatment suggestive of secondary diabetes. However, there can be uncertainty in the diagnosis particularly in overweight people of younger age, children or adolescents. The true diagnosis may become more obvious over time [American Diabetes Association 2013, The Royal College of Physicians 2008]. According to the ICD-10 classification, the code for Type 2 DM is 'E11' [International Statistical Classification of Diseases and Related Health Problems 2013b].
Discussion	No comment
References	1. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2013;36:S11-S66. 2. Branca F, Nikogosian H, Lobstein T. The challenge of obesity in the WHO European region and the strategy for response. Kopenhagen: WHO Regional Office for Europe; 2007. 3. ECRI Institute. AHRQ Health Care Horizon Scanning System - Potential High-Impact Interventions Report. Priority Area 10: Obesity. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.). Rockville, MD: Agency for Healthcare Research and Quality; 2012. 4. Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J, et al. Harrison's manual of medicine. 18th edition: Obesity and Diabetes Mellitus. New York: McGraw-Hill 2013. 5. Gale E, Anderson J. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. Clinical Medicine 2012 8th edition. Edinburgh: Elsevir 2012:1001-45. 6. International Statistical Classification of Diseases and Related Health Problems. Overweight and obesity E66. 2013a [cited 2013 19/02/]; Available from: http://www.icd10data.com/ICD10CM/Codes/E00-E89/E65-E68/E66-/E66. 7. International Statistical Classification of Diseases and Related Health Problems. Diabetes mellitus E10-E14. 2013b [cited 2013 20/02/]; Available from: http://www.icd-code.de/icd/code/E10-E14.html.

References *continued*	8. National Institute for Health and Clinical Excellence. Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. London: NICE; 2006a. 9. Rieder A, Rathmanner T, Kiefer I, Dorner T, Kunze M. Österreichischer Diabetesbericht; 2004. 10. Scottish Intercollegiate Guidelines Network. Management of Obesity: A National Clinical Guideline. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010a. 11. Scottish Intercollegiate Guidelines Network. Management of Diabetes. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010b. 12. The Royal College of Physicians. Type 2 diabetes. National clinical guideline for primary and secondary care (update). London: The Royal College of Physicians; 2008. 13. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. 2006. 14. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Geneve: World Health Organisation; 2011.
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐X • Partly ☐ • Not ☐

[A0002b]: What are the main features of obesity and Type 2 DM?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	**1) Obesity** Obesity is characterised by an excess accumulation of body weight in the form of body fat. Obesity develops when daily energy intake exceeds expenditure over a long-term period [National Institute for Health and Clinical Excellence 2006b]. **2) Type 2 DM** The underlying disorder for Type 2 DM is usually insulin insensitivity combined with a failure of pancreatic insulin secretion to compensate for increased glucose levels. The insulin insensitivity is usually evidenced by excess body weight or obesity, and exacerbated by overeating and inactivity. It is commonly associated with raised blood pressure and a disturbance of blood lipid levels. The insulin deficiency is progressive over time, leading to a need for lifestyle change often combined with blood glucose lowering therapy [National Institute for Health and Clinical Excellence 2011].
Discussion	No comment
References	1. National Institute for Health and Clinical Excellence. Preventing type 2 diabetes. Population and community level interventions. London: National Institute for Health and Clinical Excellence; 2011. 2. National Institute for Health and Clinical Excellence, National Collaborating Centre for Primary Care. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. 2006b.
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[A0003]: What are the known risk factors for obesity and Type 2 DM?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	**1) Obesity** The fundamental cause of overweight and obesity is 'energy imbalance': however, the causes of this imbalance remain unclear. In adults, reasons for energy imbalance are environment, genes, stress and psychological factors, current medication, life stage (early childhood and adolescence, pregnancy and childbirth, menopause) and life events (quitting smoking, marriage, giving up sport, holidays) [Elmadfa 2012, Hauner 2007, National Institute for Health and Clinical Excellence 2006a, Scottish Intercollegiate Guidelines Network 2010a]. It has been observed that the prevalence of obesity increases with age, that obesity is more prevalent among lower socioeconomic and lower-income groups, with a particularly strong social class gradient among women, that obesity is more prevalent among certain ethnic groups, and that it shows regional variations [National Institute for Health and Clinical Excellence 2006a, Scottish Intercollegiate Guidelines Network 2010a]. **2) Type 2 DM** Increasing age, obesity, ethnicity and family history are the four major determinants of Type 2 DM [Gale 2012]. Being overweight or obese is the main contributing factor for Type 2 diabetes, increasing the risk 80-100 fold [Gale 2012]. In addition, having a large waist circumference increases the risk of developing Type 2 diabetes. Men are at high risk if they have a waist circumference of 94–102 cm (37.0–40.0 inches). They are at very high risk if it is more than 102 cm. Women are at high risk if they have a waist circumference of 80–88 cm (31.5–35.0 inches).They are at very high risk if it is more than 88 cm. Some population groups, for example South Asian adults or older people may be at risk of developing Type 2 DM even if they have a BMI lower than the overweight classification [National Institute for Health and Clinical Excellence 2011]. Also, high rates affect people of Middle-eastern and Hispanic American origin living western lifestyles [Gale 2012].
Discussion	No comment
References	1. Elmadfa I, Hasenegger V, Wagner K, Putz P, Weidl N-M, Wottawa D, et al. Österreichischer Ernährungsbericht 2012. Wien; 2012. 2. Gale E, Anderson J. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. Clinical Medicine 2012 8th edition. Edinburgh: Elsevir 2012:1001-45. 3. Hauner H, Buchholz G, Hamann B, Koletzko B, Liebermeister H, Wabitsch M, et al. Prävention und Therapie der Adipositas. Evidenzbasierte Leitlinie. 2007. 4. National Institute for Health and Clinical Excellence. Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. London: NICE; 2006a. 5. National Institute for Health and Clinical Excellence. Preventing type 2 diabetes. Population and community level interventions. London: National Institute for Health and Clinical Excellence; 2011.

References *continued*	6. Scottish Intercollegiate Guidelines Network. Management of Obesity: A National Clinical Guideline. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010a.
Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

<table>
<tr><th colspan="2">[A0004a]: What is the natural course of obesity and Type 2 DM?</th></tr>
<tr><td>Methods</td><td>Source of information:
• Basic documentation x☐
• Domain search ☐
• Other:
Critical appraisal criteria not applicable
Method of synthesis not applicable</td></tr>
<tr><td>Result</td><td>1) Obesity
Obesity can be considered as a disease itself and as a risk factor for other diseases, most importantly Type 2 DM [Branca 2007, Elmadfa 2012, Hauner 2007, National Institute for Health and Clinical Excellence 2006b, Scottish Intercollegiate Guidelines Network 2010a] which is in 80% of people caused by obesity [Branca 2007]. Table 1 presents the relative risks of other diseases in obese adult and Table 2 presents relative risks for the most common diseases stratified by gender.

Table 1: Diseases and conditions associated with obesity
<table>
<tr><th>Relative risk (RR)</th><th>Associated with metabolic consequences</th><th>Associated with excess weight</th></tr>
<tr><td>Greatly increased RR >3</td><td>Type 2 diabetes
Gall bladder disease
Hypertension
Dyslipidaemia

Insulin resistance
Non-alcoholic fatty liver</td><td>Sleep apnoea
Breathlessness
Asthma
Social isolation and depression

Daytime sleepiness and fatique</td></tr>
<tr><td>Moderately increased RR 2-3</td><td>Coronary heart disease
Stroke
Gout and hyperuricaemia</td><td>Osteoarthritis
Respiratory disease
Hernia
Psychological problems</td></tr>
<tr><td>Slightly increased RR 1-2</td><td>Cancer*
Reproductive abnormalities and impaired fertility
Polycystic ovaries
Skin complications
Cataract</td><td>Varicose veins
Musculoskeletal problems

Bad back
Stress incontinence
Oedema and cellulitis</td></tr>
</table>
* Breast, endometrial, colon and others; Source: [National Health & Medical Research Council 2003]

Table 2: Gender-specific relative risk of other diseases in obese adults
<table>
<tr><th>Disease</th><th colspan="2">Relative Risk</th></tr>
<tr><th></th><th>Women</th><th>Men</th></tr>
<tr><td>Type 2 diabetes</td><td>12.7</td><td>5.2</td></tr>
<tr><td>Hypertension</td><td>4.2</td><td>2.6</td></tr>
<tr><td>Heart attack</td><td>3.2</td><td>1.5</td></tr>
<tr><td>Colon cancer</td><td>2.7</td><td>3.0</td></tr>
<tr><td>Angina</td><td>1.8</td><td>1.8</td></tr>
<tr><td>Gall bladder disease</td><td>1.8</td><td>1.8</td></tr>
<tr><td>Ovarian cancer</td><td>1.7</td><td>Not applicable</td></tr>
<tr><td>Osteoarthritis</td><td>1.4</td><td>1.9</td></tr>
<tr><td>Stroke</td><td>1.3</td><td>1.3</td></tr>
</table>
n.a.: not applicable; source: National Audit Office. Tackling obesity in England. London: The Stationery Office, 2001, cited in [National Institute for Health and Clinical Excellence 2006b].

Additionally, a high BMI is associated with premature mortality [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, Hauner 2007].</td></tr>
<tr><td>Result
continued</td><td>2) Type 2 DM
Type 2 DM is preceded by an asymptomatic stage, called prediabetes that is char-</td></tr>
</table>

	acterised by mild hyperglycaemia, insulin resistance, and early decrements in insulin secretory capacity [Inzucchi 2012]. Under certain circumstances, Type 2 DM can lead to acute situations of metabolic disturbance. Diabetes is usually irreversible and its late complications result in reduced life expectancy [Gale 2012, Inzucchi 2012]. In the long term, Type 2 DM increases the risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life [Fauci 2013, Gale 2012, World Health Organization 2006]. Additionally, Type 2 DM is associated with increased risk of further diseases such as cancer, psychiatric diseases, cognitive decline or chronic liver disease [Inzucchi 2012]. Many people with Type 2 DM have the same risk of a cardiovascular event as someone without diabetes who has already had their first heart attack; people with diabetes and a previous cardiovascular event are at very high risk – around 10 times the background population [The Royal College of Physicians 2008].
Discussion	No comment
References	1. Agence d'évaluation des technologies et des modes d'intervention en santé. Surgical Treatment of Morbid Obesity: An Update. Montréal: AETMIS; 2006. 2. Branca F, Nikogosian H, Lobstein T. The challenge of obesity in the WHO European region and the strategy for response. Kopenhagen: WHO Regional Office for Europe; 2007. 3. Elmadfa I, Hasenegger V, Wagner K, Putz P, Weidl N-M, Wottawa D, et al. Österreichischer Ernährungsbericht 2012. Wien; 2012. 4. Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J, et al. Harrison's manual of medicine. 18th edition: Obesity and Diabetes Mellitus. New York: McGraw-Hill 2013. 5. Gale E, Anderson J. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. Clinical Medicine 2012 8th edition. Edinburgh: Elsevir 2012:1001-45. 6. Hauner H, Buchholz G, Hamann B, Koletzko B, Liebermeister H, Wabitsch M, et al. Prävention und Therapie der Adipositas. Evidenzbasierte Leitlinie. 2007. 7. Inzucchi S, Bergenstal R, Buse J, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia 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). Diabetes Care 2012:1364-79. 8. National Health & Medical Research Council. Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults. Canberra: NHMRC; 2003. 9. National Institute for Health and Clinical Excellence, National Collaborating Centre for Primary Care. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. 2006b. 10. Scottish Intercollegiate Guidelines Network. Management of Obesity: A National Clinical Guideline. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010a. 11. The Royal College of Physicians. Type 2 diabetes. National clinical guideline for primary and secondary care (update). London: The Royal College of Physicians; 2008. 12. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. 2006.

Importance and transferability	How important is this piece of information for decision making? Critical x☐ Important ☐ Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? Completely ☐ Partly x☐ Not ☐

[A0004b]: What are the adverse health consequences of obesity and Type 2 DM?	
Methods	Source of information: • Basic documentation ☐ • Domain search ☐ • Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	This question has already been answered by previous one (A0004a)
Discussion	No comment
References	
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly ☐ • Not ☐

[A0005]: What are the main symptoms and consequences for the patients?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	**1) Obesity** Apart from adverse health consequences, obesity is considered a psychosocial and social burden, often resulting in social stigma, low self-esteem, reduced mobility and a generally poorer quality of life [National Institute for Health and Clinical Excellence 2007]. See also result card no. A0004a, tables 1 and 2 for details on symptoms. **2) Type 2 DM** Clinical presentation of diabetes can be acute, subacute or asymptomatic. Common symptoms are polyuria, polydipsia, weight loos, thirst, fatigue, weakness, blurred vision, superficial infection, poor wound healing and paraesthesias [American Diabetes Association 2013, Fauci 2013, Gale 2012]. Apart from adverse health consequences, Type 2 DM is associated with diminished quality of life [World Health Organization 2006].
Discussion	No comment
References	1. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2013;36:S11-S66. 2. Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J, et al. Harrison's manual of medicine. 18th edition: Obesity and Diabetes Mellitus. New York: McGraw-Hill 2013. 3. Gale E, Anderson J. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. Clinical Medicine 2012 8th edition. Edinburgh: Elsevir 2012:1001-45. 4. National Institute for Health and Clinical Excellence. Bariatric surgical service for the treatment of people with severe obesity. Commissioning guide: National Institute for Health and Clinical Excellence; 2007. 5. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. 2006.
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

<table>
<tr><th colspan="2">[A0006] What is the burden of obesity and Type 2 DM for society (prevalence, incidence, costs)?</th></tr>
<tr><td>Methods</td><td>Source of information:
• Basic documentation x☐
• Domain search ☐
• Other:
Critical appraisal criteria not applicable
Method of synthesis not applicable</td></tr>
<tr><td>Result</td><td>1) Obesity
According to the WHO, obesity has been developed into a world wide health problem [Branca 2007, World Health Organization 2000]. According to the International Association for the Study of Obesity (IASO) [International Association for the Study of Obesity 2008] that summarises reported data from 27 countries, 16.2% of the male and 18.5% of the female population is obese in the European Union (EU) (see Table 1). For Austria, the figures are 18.5% and 15.6% for males and females respectively.
In a WHO report from 2007, the prevalence of obesity in those European countries that reported figures ranged from 5%-23% in males and from 7%-6% in females [Branca 2007].
According to the Austrian nutrition report from 2012 that presents the results from a representative sample of 1,002 persons, around 28% of the adult population (≥18 years) are overweight and 12% are obese. The proportion of overweight and obese persons has increased over the last years. Obesity and overweight is more prevalent in males (52%) than in females (28%) [Elmadfa 2012]. The prevalence of persons who are obese and at the same time suffer from Type 2 DM is unknown for Austria. [Rathmanner 2006, Statistik Austria 2010].
Table 1: Prevalence of overweight and obesity according to IASO (%)
<table>
<tr><th rowspan="2">Country</th><th colspan="2">males</th><th colspan="2">females</th></tr>
<tr><th>overweight</th><th>obese</th><th>overweight</th><th>obese</th></tr>
<tr><td>Austria</td><td>37.9</td><td>18.5</td><td>25.6</td><td>15.6</td></tr>
<tr><td>EU</td><td>42.8</td><td>16.2</td><td>29.5</td><td>18.5</td></tr>
</table>
Source: [International Association for the Study of Obesity 2008]
In Croatia, in 2003, 58.2% of the female population and 68.3% of males had a BMI >25 kg/m², 35.5% of women and 46.7% of man had a BMI of 25-29.9 kg/m² and 22.7% of women and 21.6% man had a BMI ≥30kg/m². In people who have diabetes, 82.87% and 40.34% have a BMI ≥25 kg/m² and a BMI ≥30 kg/m² respectively [Croatian National Institute of Public Health 2012, Croatian National Institute of Public Health 2013, Ministarstvo zdravstva i socijalne skrbi Republike Hrvatske 2010].
According to the WHO, obesity is responsible for 6% of health care spending in countries within the WHO-Europe region [Branca 2007].
2) Type 2 DM
Type 2 DM is considered a global health problem. The prevalence of Type 2 DM is increasing worldwide as well as in Europe due to the increasing prevalence of obesity, decreased physical activity, but also increased longevity after diagnosis thanks to better cardiovascular risk protection [The Royal College of Physicians 2008, World Health Organization 2006]. DM is connected with serious morbidity and significant mortality, as fifth leading cause of death worldwide [Fauci 2013].</td></tr>
</table>

Result *continued*	According to the International Diabetes Federation [International Diabetes Federation (IDF) 2013] 366 million people *worldwide* had diabetes in 2011 and the number is expected to rise to 552 million by 2030. However, 80% of people with diabetes live in low- and middle-income countries. Type 2 DM accounts for 85% to 95% of all diabetes cases [International Diabetes Federation (IDF) 2013]. The WHO stated in 2002 that in *Europe* 22.5 million people suffer from diabetes, of whom 80%-95% have Type 2 DM [World Health Organization 2002]. Data from the International Diabetes Federation show considerably higher figures of 52.8 million people (20-79 years) in 2011 (8.1%) for the European region [International Diabetes Federation (IDF) 2013]. The disease has changed from an 'old people's disease' to a disease afflicting people in the first half of their life [World Health Organization 2002]. The greatest number of people with diabetes is in the 40-59-years age group and, gobally, there is little gender distribution [International Diabetes Federation (IDF) 2013]. In **Austria** detailed data on the incidence and prevalence of Type 2 DM in adults are missing. In a WHO-estimation prevalence of DM overall in adults >20 years was 2.1% or 130,000 in 2000. 55% of those were female. In a health survey in 1999 prevalence of self-reported DM was also 2.1% [Rieder 2004]. Other data show a prevalence of Type 2 DM of 6% [Rathmanner 2006, Statistik Austria 2010]. The standardised discharge rates with the diagnosis DM were 546.44 per 100,000 inhabitants of the same age, sex and federal state (544.75 for men, 548.04 for women) [Rieder 2004]. The prevalence of Type 2 diabetes increases with age and body weight. In Croatia, the prevalence of DM is 6.1%. The majority (90%) have Type 2 DM [Metelko 2008]. According to the Croatian Registry [Croatian Diabetes Registry 2013, Croatian National Institute of Public Health 2013], the overall number of patients registered is 115,149, while in 2012 registrations were collected for 32,572 patients. The costs of diabetes internationally range from 5% to 10% of the total health care spending [Rieder 2004, World Health Organization 2002]. A cost-of-illness study that covered eight European countries estimated annual direct medical costs/patient of € 2,834 and € 29 billion in total [Jönsson 2002]. Estimates indicate that at least USD 131 billion was spent on healthcare due to diabetes in the Europe Region in 2011, accounting for almost one-third of global healthcare expenditures due to diabetes [International Diabetes Federation (IDF) 2013]. Detailed cost-of-illness figures for Austria are not available. The same is true for Croatia
Discussion	No comment
References	1. Branca F, Nikogosian H, Lobstein T. The challenge of obesity in the WHO European region and the strategy for response. Kopenhagen: WHO Regional Office for Europe; 2007. 2. Croatian Diabetes Registry. Croatian Diabetes Registry. 2013 [cited 2013 05 05]; Available from: http://www.idb.hr/CDN_2011.pdf, http://www.hzjz.hr/publikacije/crodiabreg2011.pdf. 3. Croatian National Institute of Public Health. Croatian Health Service Yearbook 2011. 2012. 4. Croatian National Institute of Public Health. Croatian Health Service Yearbook 2012. 2013. 5. Elmadfa I, Hasenegger V, Wagner K, Putz P, Weidl N-M, Wottawa D, et al. Österreichischer Ernährungsbericht 2012. Wien; 2012. 6. Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J, et al. Harrison's manual of medicine. 18th edition: Obesity and Diabetes Mellitus. New York: McGraw-Hill 2013.

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Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly x☐ • Not ☐

[A0007]: What is the target population in this assessment?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	In this assessment the target population of the DJBS are adult obese patients (grade III obesity or grade II obesity with comorbidities) or patients with Type 2 DM and obesity ≥grade I.
Discussion	Currently, there seems to be a controversy over the primary target population and indication. While some sources and most of the studies define obese adults (with or without Type 2 DM) as the primary target population [Australian Government: Department of Health and Ageing 2010, de Moura 2011, Escalona 2012, Escalona 2010, Gersin 2010, National Institute for Health and Clinical Excellence 2012, Rodriguez-Grunert 2008, Schouten 2010, Tarnoff 2009], others - including, recently, the manufacturer – state that the device is primarily designed as a treatment for patients with Type 2 diabetes while obesity plays a subordinate role. This is because of signals that the DJBS may be able to elicit glycaemic control independent of weight loss in obese Type 2 diabetes patients [de Moura 2012, GI Dynamics 2010, GI Dynamics 2012, National Horizon Scanning Centre 2011, Rodriguez 2009].
References	1. Australian Government: Department of Health and Ageing. Horizon Scanning Technology Prioritising Summary. *EndoBarrier Gastrointestinal Liner for obesity*: Commonwealth of Australia 2010:10. 2. de Moura EGH, Martins BC, Lopes GS, Orso IR, de Oliveira SL, Galvao Neto MP, et al. Metabolic improvements in obese type 2 diabetes subjects implanted for 1 year with an endoscopically deployed duodenal-jejunal bypass liner. Diabetes Technology & Therapeutics. 2012 Feb;14(2):183-9. 3. de Moura EGH, Orso IRB, Martins BdC, Lopes GS, de Oliveira SL, Galvao-Neto MdP, et al. Improvement of insulin resistance and reduction of cardiovascular risk among obese patients with type 2 diabetes with the duodenojejunal bypass liner. Obesity Surgery. 2011 Jul;21(7):941-7. 4. Escalona A, Pimentel F, Sharp A, Becerra P, Slako M, Turiel D, et al. Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal-jejunal bypass liner. Annals of Surgery. 2012 Jun;255(6):1080-5. 5. Escalona A, Yanez R, Pimentel F, Galvao M, Ramos AC, Turiel D, et al. Initial human experience with restrictive duodenal-jejunal bypass liner for treatment of morbid obesity. Surgery for Obesity & Related Diseases. 2010 Mar 4;6(2):126-31. 6. Gersin KS, Rothstein RI, Rosenthal RJ, Stefanidis D, Deal SE, Kuwada TS, et al. Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. Gastrointestinal Endoscopy. 2010 May;71(6):976-82. 7. GI Dynamics. Der EndoBarrier: Eine innovative Lösung bei der Behandlung und Kontrolle von Typ-2Diabetes mellitus und Adipositas. 2010 [cited 2013 20/02/]; Available from: http://www.endobarrier.de/fachkreise/der-endobarrier/der-endobarrier.html. 8. GI Dynamics. Learn About Endobarrier Therapy - Overview. 2012;2013(20/02). 9. National Horizon Scanning Centre. Endobarrier for type 2 diabetes mellitus with obesity. Birmingham: National Horizon Scanning Centre (NHSC); 2011.

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Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[A0011]: What is the expected annual utilisation of the DJBS?	
Methods	Source of information: • Basic documentation ☐ • Domain search ☐ • Other: expert opinion Critical appraisal criteria not applicable Method of synthesis not applicable
Result	According to an estimate from a hospital provider in Austria, the annual frequency of implanting a DJBS will be around 250 procedures (3.1/100,000). In Austria, the procedure requires inpatient treatment with an average duration of stay of 2 days (minimum 2, maximum 3). There are no Croatian figures available. According to expert opinions in a recent overview [National Institute for Health and Clinical Excellence 2012] the views range from slow diffusion speed, as the AEs and the price are high, to rapid uptake of the procedure in the next 2-5 years, mainly in private sector.
Discussion	No comment
References	1. National Institute for Health and Clinical Excellence. Interventional procedure overview of implantation of a duodenal-jejunal bypass sleeve for managing obesity. London: National Institute for Health and Clinical Excellence; 2012
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly ☐ • Not x☐

[A0020]: What is the market authorization status of the DJBS (EndoBarrier®) in Europe?	
Methods	Source of information: • Basic documentation ☐ • Domain search ☐ • Other: website of manufacturer Critical appraisal criteria not applicable Method of synthesis not applicable
Result	The commercialised version EndoBarrier® has CE-mark approval in Europe and is used in the UK, the Netherlands, Germany, Spain, Switzerland, Denmark, Czech Republic and Austria. Outside Europe it is available in Chile, Qatar and Israel and it has a TGA approval in Australia. The commercialised version is intended for the treatment of patients with Type 2 DM and/or obesity for 12 months. EndoBarrier® is not approved for sale in the United States and is considered investigational [GI Dynamics 2012]. GI Dynamics is conducting a pivotal clinical trial (the ENDO Trial) in the U.S. for the treatment of patients who have uncontrolled Type 2 DM and are obese.
Discussion	No comment
References	1. GI Dynamics. Learn About Endobarrier Therapy - Overview. 2012;2013(20/02).
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[A0021]: What is the reimbursement status of the DJBS in the 'pilot-assessment countries"?	
Methods	Source of information: • Basic documentation ☐ • Domain search ☐ • Other: HTA experts, manufacturer comments Critical appraisal criteria not applicable Method of synthesis not applicable
Result	The reimbursement status differs markedly between European countries. In some countries, the DJBS is not on the market yet (e.g. Croatia); in others, it is authorised for use and reimbursed in selected hospitals (e.g. Spain). In some countries, it is paid by achieving statutory independent grants (e.g. France, the UK, Italy, the Czech Republic), in others by achieving the status of innovative procedure (the Netherlands) or by using existing diagnosis-related group (DRG) codes (e.g. Germany). The DJBS has so far not been included into the publicly financed benefit catalogue for hospital technologies in Austria. If patients are implanted the device, reimbursement will currently be via a general diagnostic related group code (no extra reimbursement). In Croatia the DJBS is not on the market.
Discussion	No comment
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important ☐ • Optional x ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly ☐ • Not x☐

[A0024]: How are obesity and Type 2 DM currently diagnosed according to published guidelines and in practice?	
Methods	Source of information: Basic documentation x☐ Domain search ☐ Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	**1) Obesity** It is unusual for an overweight or obese person to seek medical help in the first Instance – they are likely to have tried an array of 'self-help' measures to manage their weight before approaching a health professional [National Institute for Health and Clinical Excellence 2006a]. Primary healthcare plays an important role in the identification, assessment and management of obesity. In adults, body mass index (BMI, kg/m²) is frequently used as a measure of overweight and obesity, with overweight being defined as a BMI 25–29.9 kg/m² and obesity as a BMI equal to or greater than 30 kg/m² [National Institute for Health and Clinical Excellence 2006b]. Additionally, in adults, central adiposity is frequently measured by waist circumference, with raised waist circumference defined as equal to or greater than 102 cm in men and equal to or greater than 88 cm in women [National Institute for Health and Clinical Excellence 2006a]. Additionally, waist circumference may be used, in addition to BMI, in people with a BMI less than 35 kg/m² [Scottish Intercollegiate Guidelines Network 2010a]. Finally, waist-to-hip ratio may be a useful predictor of diabetes and cardiovascular disease risk in adults, but it is more difficult to measure than waist circumference [Scottish Intercollegiate Guidelines Network 2010a]. **2) Type 2 DM** Criteria for the diagnosis of DM include one of the following: • Fasting plasma glucose (FPG) ≥7.0 mmol/l • Plasma glucose ≥11.1 mmol/l at two hours after a 75 g oral glucose load (oral glucose tolerance test (OGTT) • Random blood glucose concentration ≥11.1 mmol/l in patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis • Haemoglobin A1c >6.5% The results should be confirmed by repeat testing unless unequivocal hyperglycaemia is present [Fauci 2013, Gale 2012, World Health Organization 2011]. HbA1c is a key measure for assessing glycaemic control in people with established diabetes [Scottish Intercollegiate Guidelines Network 2010b, World Health Organization 2006].
Discussion	No comment

References	1. Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J, et al. Harrison's manual of medicine. 18th edition: Obesity and Diabetes Mellitus. New York: McGraw-Hill 2013. 2. Gale E, Anderson J. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. Clinical Medicine 2012 8th edition. Edinburgh: Elsevir 2012:1001-45. 3. National Institute for Health and Clinical Excellence. Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. London: NICE; 2006a. 4. National Institute for Health and Clinical Excellence, National Collaborating Centre for Primary Care. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. 2006b. 5. Scottish Intercollegiate Guidelines Network. Management of Obesity: A National Clinical Guideline. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010a. 6. Scottish Intercollegiate Guidelines Network. Management of Diabetes. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010b. 7. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. 2006. 8. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Geneve: World Health Organisation; 2011.
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly x☐ • Not ☐

[A0025]: How are obesity and Type 2 DM currently managed according to published guidelines and in practice?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	**1) Obesity** Currently, no gold standard exists concerning the management of obesity with or without Type 2 diabetes [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, Hauner 2007, IDF Clinical Guidelines Task Force 2005, National Health & Medical Research Council 2003, National Horizon Scanning Centre 2011, National Institute for Health and Clinical Excellence 2006a, Scottish Intercollegiate Guidelines Network 2010a]. Several approaches are in place: dietary advice, exercise, lifestyle changes, drug therapy and bariatric surgery including endoscopic techniques. Obesity is usually managed in stepwise approaches; firstly, general advice on weight control, diet and physical exercise is given aimed at influencing lifestyle [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, Hauner 2007, IDF Clinical Guidelines Task Force 2005, National Health & Medical Research Council 2003, National Horizon Scanning Centre 2011, National Institute for Health and Clinical Excellence 2006a]. This may be supported by drug therapy as part of an overall plan for managing obesity including diet, physical activity and behavioural changes [Scottish Intercollegiate Guidelines Network 2010a]. Orlistat is the only drug specifically licensed for use in the treatment of obesity. It is a non-systemically acting anti-obesity agent that, in conjunction with a calorie-restricted diet, has been shown to promote weight loss and help prevent weight regain. Orlistat binds to pancreatic and gastric lipase in the gastrointestinal (GI) tract. It is approved for obese patients with a BMI of ≥30 kg/m² or of ≥27 kg/m² in the presence of other risk factors, such as diabetes, hypertension, or hyperlipidaemia. Through weight loss, orlistat improves the comorbidities associated with obesity. Serious AEs are liver failure and oxalate nephropathy, with renal failure [Micromedex Drugdex Database 2013]. In addition to lipase inhibitors, appetite suppressants are used. For the appetite suppressant sibutramine, market authorisation has been suspended because of AEs [National Institute for Health and Clinical Excellence 2006a] (note added after publication of report). Finally, in extreme cases (failure of conservative therapy, obesity grade II + comorbidities or obesity grade III without comorbidities), bariatric surgery may be indicated. Surgical procedures either aim to reduce the size of the stomach (like gastric banding or sleeve gastrectomy), to decrease patient capacity to absorb food (jejunoileal bypass: of historical interest only) or they combine both approaches (e.g. Roux-en-Y gastric bypass or biliopancreatic diversion) [ECRI Institute 2012]. The final decision for or against bariatric surgery including the type of surgery (open or laparoscopic) is dependent on the BMI, the individual risk, comorbidities and patient preferences, and should be made after a comprehensive risk-benefit assessment. [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, Arroyo 2010, DeWald 2006, Ibrahim 2010, IDF Clinical Guidelines Task Force 2005, National Horizon Scanning Centre 2011, Padwal 2011, Scottish Intercollegiate Guidelines Network 2010a, Tessier 2008]. According to the Agency for Healthcare Research and Quality (AHRQ), only gastric bypass surgery has demonstrated long-term efficacy for morbidly obese patients [ECRI Institute 2012]. The surgery carries significant risks of morbidity and mortality. Like pharmacotherapy, bariatric surgery needs to be accompanied by a structured weight management programme (dietetic monitoring, psychological support, etc.).
Result	**2) Type 2 DM**

continued	Type 2 DM is a progressive long-term medical condition that is predominantly managed by the person with the diabetes and/or their carer as part of their daily life [The Royal College of Physicians 2008]. Type 2 DM is addressed by a combination of several strategies including education and lifestyle interventions, psychological interventions, pharmacological management and management of diabetes-related diseases such as cardio-vascular diseases, kidney diseases, visual impairment and nerve damage [Fauci 2013, Gale 2012, Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]. Standards of medical care in diabetes have recently been published by the American Diabetes Association [American Diabetes Association 2013]. Like obesity, Type 2 DM is usually managed in a stepwise approach. In existing recommendations management usually start with structured education that meets the cultural, linguistic, cognitive and literacy needs of the patient and lifestyle management with non-pharmacological management (e.g. dietary advice, smoking cessation, management of depression). This needs to be accompanied by clinical monitoring of the blood glucose level by means of glycated haemoglobin (HbA1c) [Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]. The primary HbA1c goal is <6.5%. A reasonable HbA1c goal for many non-pregnant adults is <7%. HbA1c <8% may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions and in those in whom the general goal is difficult to achieve despite all appropriate care [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012]. If the target level of HbA1c is not achieved by non-pharmacological management, pharmacological glucose control therapies are required (biguanides, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonist or insulins). Blood glucose control deteriorates inexorably in most people with Type 2 diabetes over a period of years, due to a waning of insulin production. In these circumstances, oral glucose-lowering therapies can no longer maintain blood glucose control and insulin replacement therapy becomes inevitable [The Royal College of Physicians 2008]. Metformin is the optimal first-line drug (Box 1). If metformin is contraindicated or not tolerated, other drugs could be used: combination therapy with an additional one or two oral or injectable agents is reasonable, aiming to minimise side effect where possible. Many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. A patient-centered approach should be used to guide choice of therapy, bearing in mind their efficacy, side effects, cost, comorbidities, and patient preferences [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012].

Result *continued*

Box 1. Pharmacological therapy for Type 2 DM

Monotherapy

Metformin as a first choice

(if not contraindicated and if tolerated)

If it is contraindicated and not tolerated, further drugs could be used*:*

- **Sulfonylurea**
- **Pioglitazone**
- **DPP-4 inhibitor.**

Dual therapy

If non-insulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA1c target level over 3–6 months, **the second oral agent, GLP-1 receptor agonist or insulin could be added:**

- **Sulfonylurea**
- **Pioglitazone**
- **DPP-4 inhibitor**
- **GLP-1 agonist**
- **Basal insulin**.

Triple therapy

- **Metformin + sulfonylurea* + thiazolidinedione or DPP-4 inhibitor or GLP-1 receptor agonist or insulin (basal: NPH, glargine or detemir)**
- **Metformin + thiazolidinedione + sulfonylurea* or DPP-4 inhibitor or GLP-1 receptor agonist or insulin (basal: NPH, glargine or detemir)**
- **Metformin + DPP-4 inhibitor + sulfonylurea* or thiazolidinedione or insulin (basal: NPH, glargine or detemir)**
- **Metformin + GLP-1 receptor agonist + sulfonylurea* or thiazolidinedione or insulin (basal: NPH, glargine or detemir)**
- **Metformin + insulin (basal: NPH, glargine or detemir) + thiazolidinedione or DPP-4 inhibitor or GLP-1 receptor agonist.**

Insulin (multiple daily doses)

NPH: Neutral protamine Hagedorn; *meglitinides therapy in case of late postprandial hypoglycaemia during sulfonylurea therapy; Source: [Inzucchi 2012]

Result *continued*	In managing diabetes-related cardiovascular diseases, blood pressure therapy and managing blood-lipid levels play a most important role (starting with life-style management followed by anti-hypertensive medication and lipid-lowering drugs) [Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]. Additionally, antithrombotic therapy may be indicated [The Royal College of Physicians 2008]. Furthermore, measurement of several laboratory parameters is recommended to detect and monitor diabetes-related kidney disease. Regular structured eye surveillance is recommended to detect eye damage as is enquiry for neuropathic symptoms to detect nerve damage [Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008].
Discussion	No comment
References	1. Agence d'évaluation des technologies et des modes d'intervention en santé. Surgical Treatment of Morbid Obesity: An Update. Montréal: AETMIS; 2006. 2. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2013;36:S11-S66. 3. Arroyo K, Kini SU, Harvey JE, Herron DM. Surgical therapy for diabesity. Mount Sinai Journal of Medicine. 2010;77(5):418-30. 4. DeWald T, Khaodhiar L, Donahue MP, Blackburn G. Pharmacological and surgical treatments for obesity. American Heart Journal. 2006;151(3):604-24. 5. ECRI Institute. AHRQ Health Care Horizon Scanning System - Potential High-Impact Interventions Report. Priority Area 10: Obesity. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.). Rockville, MD: Agency for Healthcare Research and Quality; 2012. 6. Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J, et al. Harrison's manual of medicine. 18th edition: Obesity and Diabetes Mellitus. New York: McGraw-Hill 2013. 7. Gale E, Anderson J. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. Clinical Medicine 2012 8th edition. Edinburgh: Elsevir 2012:1001-45. 8. Hauner H, Buchholz G, Hamann B, Koletzko B, Liebermeister H, Wabitsch M, et al. Prävention und Therapie der Adipositas. Evidenzbasierte Leitlinie. 2007. 9. Ibrahim M, Blero D, Deviere J. Endoscopic Options for the Treatment of Obesity. Gastroenterology. 2010;138(7):2228-32.e1. 10. IDF Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. Brussels: International Diabetes Federation; 2005. 11. Inzucchi S, Bergenstal R, Buse J, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia 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). Diabetes Care 2012:1364-79. 12. Micromedex Drugdex Database. Thompson Reuters; 2013. 13. National Health & Medical Research Council. Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults. Canberra: NHMRC; 2003. 14. National Horizon Scanning Centre. Endobarrier for type 2 diabetes mellitus with obesity. Birmingham: National Horizon Scanning Centre (NHSC); 2011. 15. National Institute for Health and Clinical Excellence. Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. London: NICE; 2006a.

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Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly x ☐ • Not ☐

Description and technical characteristics of Technology

[B0001]: What is the DJBS and what are evidence-based alternatives?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	The DJBS is a 60 cm long impermeable sleeve-like device (fluoropolymer), placed endoscopically into the small intestine for up to 12 months. It has been developed out of a prototype that has been implanted for three months. The DJBS is inserted under general anaesthesia using dynamic fluoroscopic imaging; in the future, however, it may be possible to implant the device with the patient under conscious sedation. When implanted, the device is anchored within the duodenal bulb (small area of the small intestine just outside of the stomach) by a 5.5-cm nitinol (alloy of nickel and titanium), self-expanding stent with barbs that penetrate into the muscular wall of the intestine. The anchor system in the commercialised version has been modified: longer barbs to ensure implant duration for 12 months. The sleeve extends down through parts of the small intestine (duodenum and proximal jejunum) and is purported to mimic the effects of gastrointestinal (GI) bypass surgery. The device is removed endoscopically by collapsing the nitinol stent and withdrawing the device from the stomach up through the oesophagus [Australian Government: Department of Health and Ageing 2010, de Moura 2012, de Moura 2011, ECRI Institute 2012, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. The device allows chyme (partially digested food leaving the stomach) to move through the GI tract without mixing with digestive enzymes or allowing nutrients to be absorbed through the intestinal walls. After the insertion, patients are placed on a diet that typically involves progression from fluids to semi-solid food avoiding solid foods for several weeks. This results in a substantial decrease in calorie intake [National Institute for Health and Clinical Excellence 2012]. The only provider of the device currently (February 2013) is GI Dynamics (GI Dynamics, Inc., Lexington, Massachusetts, USA). The brand name is EndoBarrier® [de Moura 2012, de Moura 2011, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. At least two large device companies have reportedly invested in the device's development in the USA [ECRI Institute 2012]. According to the EUnetHTA guidelines [European Network for Health Technology Assessment (EUnetHTA) 2013b] on choosing the appropriate comparator the following alternatives can be defined:

Result *continued*	1) If the primary indication is obesity ≥grade II in people where non-surgical measures of weight reduction have failed, the alternative is bariatric surgery. Weight loss in bariatric surgery is achieved via of one of two mechanisms: mechanically restricting the size of the stomach or bypassing a portion of the intestines; however, several procedures exert their effects by using both mechanisms [Shekelle 2004]. Today, the most commonly used bariatric technique is the Roux-en-Y gastric bypass (RYGB); the current use of the term 'gastric bypass' typically refers to RYGB [ECRI Institute 2012]. Further main types of bariatric surgery that are currently practiced are sleeve gastrectomy, vertical banded gastroplasty (VBG), adjustable silicone gastric banding (ASGB), and biliopancreatic diversion (BPD) with or without duodenal switch. All five procedures may be performed as an open or laparoscopic technique. More recently, techniques that mimic one aspect of bariatric surgery (gastric restriction) have been developed that are of a temporary nature and have been recommended for restrictive use only: gastric balloon, gastric plication [National Institute for Health and Clinical Excellence 2012, Verdam 2012]. Because the DJBS is a temporary intervention, gastric balloon or gastric plication seem an appropriate alternative. If compared with technologies that have a similar mechanism of action (restricting capacity to absorb food), surgical Roux-en-Y gastric bypass or biliopancreatic diversion are of relevance. 2) If the primary indication for the device is Type 2 DM and/or obesity, the primary comparator is optimised antidiabetes pharmacotherapy and lifestyle changes for glycaemic control.
Discussion	There have been ongoing discussions concerning the appropriate alternative for the device and a consensus on the question has not been reached [National Institute for Health and Clinical Excellence 2012]. Advisers' views range from pointing out that there are no accepted comparators (e.g. gastric bands and bypass are permanent procedures and as such not comparable with the DJBS) and that the closest one would be dietary counselling and gastric balloon; others state that relevant comparators would be best medical treatment of Type 2 DM, intensive weight management in tandem with DJBS or laparoscopic proximal gastric bypass Roux-en-Y or laparoscopic sleeve gastrectomy.
References	1. Australian Government: Department of Health and Ageing. Horizon Scanning Technology Prioritising Summary. EndoBarrier Gastrointestinal Liner for obesity: Commonwealth of Australia 2010:10. 2. de Moura EGH, Martins BC, Lopes GS, Orso IR, de Oliveira SL, Galvao Neto MP, et al. Metabolic improvements in obese type 2 diabetes subjects implanted for 1 year with an endoscopically deployed duodenal-jejunal bypass liner. Diabetes Technology & Therapeutics. 2012 Feb;14(2):183-9. 3. de Moura EGH, Orso IRB, Martins BdC, Lopes GS, de Oliveira SL, Galvao-Neto MdP, et al. Improvement of insulin resistance and reduction of cardiovascular risk among obese patients with type 2 diabetes with the duodenojejunal bypass liner. Obesity Surgery. 2011 Jul;21(7):941-7. 4. ECRI Institute. AHRQ Health Care Horizon Scanning System - Potential High-Impact Interventions Report. Priority Area 10: Obesity. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.). Rockville, MD: Agency for Healthcare Research and Quality; 2012. 5. Escalona A, Pimentel F, Sharp A, Becerra P, Slako M, Turiel D, et al. Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal-jejunal bypass liner. Annals of Surgery. 2012 Jun;255(6):1080-5. 6. Escalona A, Yanez R, Pimentel F, Galvao M, Ramos AC, Turiel D, et al. Initial human experience with restrictive duodenal-jejunal bypass liner for treatment of morbid obesity. Surgery for Obesity & Related Diseases. 2010 Mar 4;6(2):126-31.

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Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[B0002]: What is the approved indication and claimed benefit of the DJBS and the comparators?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: expert opinion, manufacturer comments Critical appraisal criteria not applicable Method of synthesis not applicable
Result	EndoBarrier® has CE-mark approval in Europe and is used in the UK, the Netherlands, Germany, Spain, Switzerland, Denmark, Czech Republic and Austria. Outside Europe it is available in Chile, Qatar and Israel and it has a TGA approval in Australia. It is intended for the treatment of patients with Type 2 DM and/or obesity (BMI ≥ 30) for up to 12 months [GI Dynamics 2012]. The claimed benefit is that the DJBS stimulates the secretion of glucagon-like peptide-1 (GLP-1), which mediates glucose dependent insulin secretion, and peptide YY (PYY), which suppresses appetite and food intake, in the GI tract leading primarily to significant improvements in glycaemic control and the additional benefit of significant weight loss [GI Dynamics 2013]. The comparators (bariatric surgery, drug therapy, lifestyle changes) either have the therapeutic aim of reducing body weight and obesity-related morbidity and mortality or improving glycaemic control and reducing the negative health consequences related to Type 2 DM.
Discussion	No comment
References	1. GI Dynamics. Learn About Endobarrier Therapy - Overview. 2012;2013(20/02). 2. GI Dynamics. Manufacturer consultation of the draft project plan for duodenal-jejunal bypass sleeve (EndoBarrier®) for the treatment of obesity. GI Dynamics 2013.
Importance and transferability	How important is this piece of information for decision making? • Critical x ☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[B0003]: What is the phase of development and implementation of the DJBS and the comparators?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: Critical appraisal criteria not applicable Method of synthesis not applicable
Result	DJBS: The current commercialised version of the DJBS has been developed out of a prototype. Four small-scale (randomised) controlled studies have been completed on the prototype. Three further RCTs (USA/FDA, Netherlands, Italy), one observational study that compares the effects of several treatments (including the DJBS) on obesity and three single-arm studies (Chile, UK, Israel) are currently registered as ongoing or have just been completed. Three publicly financed RCTs are planned (UK/EME MRC Study, France/ENDOMETAB Study, ABCD Study) but have not been registered yet. In the USA, the DJBS is currently considered as investigational. Bariatric surgery: has existed for more than 20 years, however, some of the procedures (e.g. jejunoileal bypass) have been abandoned due to severe adverse effects [Shekelle 2004]. Today, the most commonly used bariatric technique is the Roux-en-Y gastric bypass (RYGB) [ECRI Institute 2012]. Some less invasive technologies (e.g. gastric balloon, gastric plication) that mimic one aspect of bariatric surgery (gastric restriction) have been developed more recently, however they have either not been recommended for routine use due to limited evidence on safety and efficacy [National Institute for Health and Clinical Excellence 2012] or have been recommended primarily as a bridge to surgery [Verdam 2012]. Pharmacotherapy in obesity: Orlistat is the only drug specifically licensed for use in the treatment of obesity. Preliminary phase II or III data are available on several drugs or medical devices and procedures for treatment of obesity, like controlled release phentermine/ topiramate, liraglutide, lorcaserin, methionine aminopeptidase 2 inhibitor, naltrexone and bupropion HCL or tesofensine, Full Sense Bariatric device, Maestro vagus nerve block system. Pharmacotherapy in Type 2 DM: Different pharmacological glucose control therapies are used for treatment of Type 2 DM (biguanides, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonist or insulins). Metformin is the optimal first-line drug. If metformin therapy is unsuccessful or contraindicated, other drugs could be used: combination therapy with an additional one or two oral or injectable agents is reasonable, aiming to minimise side effect where possible. Many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012] Canagliflozin (approved in USA by FDA), dapagliflozin (approved by EMA in EU) and empagliflozin (under review by EMA) are new oral agents acting by a novel, insulin-independent mechanism of action to improve glycaemic control in adults with Type 2 DM who are inadequately controlled on their current treatment regimen.
Discussion	No comment

References	1. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2013;36:S11-S66. 2. ECRI Institute. AHRQ Health Care Horizon Scanning System - Potential High-Impact Interventions Report. Priority Area 10: Obesity. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.). Rockville, MD: Agency for Healthcare Research and Quality; 2012. 3. Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J, et al. Harrison's manual of medicine. 18th edition: Obesity and Diabetes Mellitus. New York: McGraw-Hill 2013. 4. Inzucchi S, Bergenstal R, Buse J, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia 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). Diabetes Care 2012:1364-79. 5. National Institute for Health and Clinical Excellence. NICE International procedure guidance 432. Laparoscopic gastric plication for the treatment of severe obesity. London: National Institute for Health and Clinical Excellence; 2012. 6. Shekelle P, Morton S, Maglione M, Suttorp M, Tu W, Li Z, et al. Pharmacological and Surgical Treatment of Obesity. Evidence Report/Technology Assessment No. 103. (Prepared by the Southern California–RAND Evidence-Based Practice Center, Santa Monica, CA, under contract Number 290-02-0003.) Rockville, MD: Agency for Healthcare Research and Quality; 2004. 7. Verdam FJ, Schouten R, Greve JW, Koek GH, Bouvy ND. An update on less invasive and endoscopic techniques mimicking the effect of bariatric surgery. J Obes. 2012;2012:597871.
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[B0004]: Who performs the DJBS and who performs or administers the comparators?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: expert opinion Critical appraisal criteria not applicable Method of synthesis not applicable
Result	Implantation of the DJBS is done by a surgeon. This is identical in bariatric surgery. However, experts suggested that the intervention could shift the type of specialist providing bariatric services from surgeons to gastro-intestinal physicians accustomed to performing endoscopies [National Institute for Health and Clinical Excellence 2012]. Drug therapy and lifestyle advice to manage obesity are primarily provided by other medical specialists or by general practitioners [National Institute for Health and Clinical Excellence 2006b]. People diagnosed with Type 2 DM require access to immediate and ongoing care. Who provides this care, and where and when, will depend on local circumstances, but it needs to be organised in a systematic way. A multidisciplinary approach has been recommended including nurses trained in teaching skills and adult education and formally trained dietitians and podiatrists within the specifically relevant areas of diabetes care [American Diabetes Association 2013, IDF Clinical Guidelines Task Force 2005].
Discussion	There may be interspeciality controversy over the procedure between bariatric surgeons and gastroenterologist; procedure may not be for use in gastroenterology departments that lack standard bariatric or diabetological multidisciplinary support. Good interventional and upper gastro-intestinal endoscopic skills are needed to perform the procedure, so practical training is needed. Radiation protection training, a good knowledge of patient selection and management of implantation and explantation, management of the device in situ and post explantation is also essential. Treatment-specific training is also needed for nurses, dieticians and physician follow-up teams [National Institute for Health and Clinical Excellence 2012].
References	1. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2013;36:S11-S66. 2. IDF Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. Brussels: International Diabetes Federation; 2005. 3. National Institute for Health and Clinical Excellence. Interventional procedure overview of implantation of a duodenal-jejunal bypass sleeve for managing obesity. London: National Institute for Health and Clinical Excellence; 2012. 4. National Institute for Health and Clinical Excellence, National Collaborating Centre for Primary Care. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. 2006b.
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly x☐ • Not ☐

[B0005]: In what context and level of care are the DJBS and the comparators used?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: expert opinion Critical appraisal criteria not applicable Method of synthesis not applicable
Result	The DJBS is primarily implanted under general anaesthesia. More recently, the device has also been implanted under local anaesthesia [Montana 2012]. In terms of level of care, it takes place in hospital care in specialist centres. Comparators: Bariatric surgery is also performed in high-level care and requires anaesthesia. It is either performed as open or laparoscopic procedure. Pre- and post-operative assessment and dietetic monitoring are required and psychological support before and after surgery is recommended [National Institute for Health and Clinical Excellence 2007]. Drug therapy and lifestyle advice are primarily provided in primary care.
Discussion	No comment
References	1. Montana R, Slako M, Escalona A. Implantation of the duodenal-jejunal bypass sleeve under conscious sedation: A case series. Surgery for Obesity and Related Diseases. 2012;8(5):e63-e5. 2. National Institute for Health and Clinical Excellence. Bariatric surgical service for the treatment of people with severe obesity. Commissioning guide: National Institute for Health and Clinical Excellence; 2007.
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important ☐ • Optional x☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly x☐ • Not ☐

[B0008]: What kind of special premises are needed to use the DJBS and the comparators?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: expert opinion Critical appraisal criteria not applicable Method of synthesis not applicable
Result	In Austria, the intervention takes place in hospitals (specialist centres). In addition to the surgeon, an anaesthetist and nursing staff is required, as well as input from a radiological service (expert opinion). Comparators: Bariatric surgery is also performed in hospitals. The length of stay is likely to be longer with bariatric surgery than implanting the DJBS, but it depends on the procedure. Drug therapy and lifestyle advice are located in primary care and do not require specific premises.
Discussion	According to existing documents [ECRI Institute 2012], most of the experts providing comments on the DJBS did not see potential for a shift in care setting, but some observed that bariatric procedures are generally surgical procedures, whereas the EndoBarrier® would likely be implanted in an endoscopy suite, which could involve capital equipment purchases for facilities that do not currently employ endoscopy in their bariatric practices.
References	1. ECRI Institute. AHRQ Health Care Horizon Scanning System - Potential High-Impact Interventions Report. Priority Area 10: Obesity. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.). Rockville, MD: Agency for Healthcare Research and Quality; 2012
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important ☐ • Optional x☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly x ☐ • Not ☐

[B0009]: What supplies and equipment are needed to use the DJBS and the comparators?	
Methods	Source of information: • Basic documentation x☐ • Domain search ☐ • Other: expert opinion Critical appraisal criteria not applicable Method of synthesis not applicable
Result	To implant the device an endoscope is required in addition to equipment for administering the anaesthetic and for managing hygiene. Endoscopic facilities with suitable equipment and access to an emergency unit is also needed in the event of serious complications such as bleeding or obstruction. For bariatric surgery, access to suitable equipment, including scales, theatre tables, Zimmer frames, commodes, hoists, bed frames, pressure-relieving mattresses and seating suitable for patients undergoing bariatric surgery, and staff trained to use them is required [National Institute for Health and Clinical Excellence 2007]. For drug therapy and lifestyle advice apart from scales, no specific equipment is required.
Discussion	No comment
References	1. National Institute for Health and Clinical Excellence. Bariatric surgical service for the treatment of people with severe obesity. Commissioning guide: National Institute for Health and Clinical Excellence; 2007.
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important ☐ • Optional x ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly x☐ • Not ☐

Safety

[C0001]: What are the AEs and serious AEs with a DJBS in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity (and comorbidities)?	
Methods	Source of information: • Basic documentation ☐ • Domain search x☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	The following AEs and serious AEs have been reported (see data extraction Table 6 and Table 7 and GRADE Table 10 to Table 12 for details): procedural pain, nausea and vomiting, general nausea and vomiting, abdominal pain, abdominal distention, flatulence, erosive duodenitis, constipation, diarrhea, gastritis/gastroenterits, esophagitis, gastrointestinal bleeding, epigastric discomfort, hematemesis, dyspepsia, anemia, pyrexia, pseudopolyp formation, implant site inflammation, back pain. AEs were reported in three RCTs, one non-randomised controlled trial and five non-interventional studies with 261 patients in total [Cohen 2013, de Moura 2012, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]: Overall, in 64-100% of patients who received a DJBS, AEs were reported. Eight studies (222 patients in total) reported whether serious AEs occurred [Cohen 2013, de Moura 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. Serious AEs occurred in two studies affecting three patients in each. Overall, they accounted for 0-12% of patients in the intervention groups and they were all gastrointestinal bleedings. Intervention-related mortality has not been evaluated. Unexpected explantation of the device ahead of schedule was reported in 10 studies: it was required in 0-42% of the study participants in the intervention groups [Cohen 2013, de Moura 2012, de Moura 2011, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. The frequencies of AEs in the studies that primarily included obese patients was not different from those that primarily included patients with Type 2 DM (see GRADE Table 10 to 12).
Discussion	AEs occur in the majority of patients who receive the device, however, they are primarily mild such as pain, nausea, vomiting, constipation [de Moura 2012, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. A limitation of the safety evidence is that the majority of studies investigated a prototype that has been implanted for three months only, whereas the commercialised type is implanted for up to 12 months and contains different technical features (e.g. different anchor system).
References	1. Cohen RV, Galvao Neto MP, Correa J, Sakai P, Martins B, Schiavon PA, et al. A Pilot Study of the Duodenal-Jejunal Bypass Liner in Low Body Mass Index Type 2 Diabetes. Journal of Clinical Endocrinology and Metabolism. 2013;98(2):E279-E82. 2. de Moura EGH, Martins BC, Lopes GS, Orso IR, de Oliveira SL, Galvao Neto MP, et al. Metabolic improvements in obese type 2 diabetes subjects implanted for 1 year with an endoscopically deployed duodenal-jejunal bypass liner. Diabetes Technology & Therapeutics. 2012 Feb;14(2):183-9.

References *continued*	3. de Moura EGH, Orso IRB, Martins BdC, Lopes GS, de Oliveira SL, Galvao-Neto MdP, et al. Improvement of insulin resistance and reduction of cardiovascular risk among obese patients with type 2 diabetes with the duodenojejunal bypass liner. Obesity Surgery. 2011 Jul;21(7):941-7. 4. Escalona A, Pimentel F, Sharp A, Becerra P, Slako M, Turiel D, et al. Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal-jejunal bypass liner. Annals of Surgery. 2012 Jun;255(6):1080-5. 5. Escalona A, Yanez R, Pimentel F, Galvao M, Ramos AC, Turiel D, et al. Initial human experience with restrictive duodenal-jejunal bypass liner for treatment of morbid obesity. Surgery for Obesity & Related Diseases. 2010 Mar 4;6(2):126-31. 6. Gersin KS, Rothstein RI, Rosenthal RJ, Stefanidis D, Deal SE, Kuwada TS, et al. Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. Gastrointestinal Endoscopy. 2010 May;71(6):976-82. 7. Rodriguez-Grunert L, Galvao Neto MP, Alamo M, Ramos AC, Baez PB, Tarnoff M. First human experience with endoscopically delivered and retrieved duodenal-jejunal bypass sleeve. Surgery for Obesity & Related Diseases. 2008 Jan-Feb;4(1):55-9. 8. Rodriguez L, Reyes E, Fagalde P, Oltra MS, Saba J, Aylwin CG, et al. Pilot clinical study of an endoscopic, removable duodenal-jejunal bypass liner for the treatment of type 2 diabetes. Diabetes Technology & Therapeutics. 2009 Nov;11(11):725-32. 9. Schouten R, Rijs CS, Bouvy ND, Hameeteman W, Koek GH, Janssen IMC, et al. A multicenter, randomized efficacy study of the EndoBarrier Gastrointestinal Liner for presurgical weight loss prior to bariatric surgery. Annals of Surgery. 2010 Feb;251(2):236-43. 10. Tarnoff M, Rodriguez L, Escalona A, Ramos A, Neto M, Alamo M, 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. Surgical Endoscopy. 2009 Mar;23(3):650-6.
Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[C0002]: Is there a relationship between the length of time the bypass sleeve has been implanted and the harm to patients?	
Methods	Source of information: • Basic documentation ☐ • Domain search x ☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[C0004]: How does the frequency or severity of harm change over time or in different settings?	
Methods	Source of information: • Basic documentation ☐ • Domain search x ☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[C0005]: What are the susceptible patient groups that are more likely to be harmed?	
Methods	Source of information: • Basic documentation ☐ • Domain search x ☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[C0007]: Can AEs be caused by the behaviour of patients, professionals or manufacturers?	
Methods	Source of information: • Basic documentation ☐ • Domain search x ☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[C0008]: What is the safety of the DJBS in relation to conservative therapy, pharmacotherapy, bariatric surgery or sham-procedure in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity (and comorbidities)?	
Methods	Source of information: • Basic documentation ☐ • Domain search x ☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	The following AEs have been reported (see Table 6, Table 7 and GRADE Table 10 to 12 for details): procedural pain, nausea and vomiting, general nausea and vomiting, abdominal pain, abdominal distention, flatulence, erosive duodenitis, constipation, diarrhea, gastritis/gastroenterits, esophagitis, epigastric discomfort, hematemesis, dyspepsia, anemia, pyrexia, pseudopolyp formation, implant site inflammation, back pain. The following serious AEs have been reported (see data extraction Table 6 and Table 7 and GRADE Table 10 to 12 for details): gastrointestinal bleeding (with hematemesis). AEs were reported in nine out of 10 studies [Cohen 2013, de Moura 2012, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. AEs were observed in 64-100% out of 201 patients who received a DJBS (+ diet) compared with 0-27% out of 25 patients who received diet (only) [Schouten 2010, Tarnoff 2009]. Whether between-group differences are statistically significant has not been reported. Serious AEs were reported in eight studies including 162 patients who received the EndoBarrier® (+diet) [Cohen 2013, de Moura 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. In six (0-12%) of the patients serious AEs in the form of gastrointestinal bleeding occurred compared with 0% out of 25 patients who received diet (only) [Schouten 2010, Tarnoff 2009]. Safety in relation to sham procedure has not been reported. No studies have been identified that compared the DJBL to optimal pharmacotherapy (in the management of Type 2 DM or obesity) or bariatric surgery. Hence, the safety of the DJBL in relation to pharmacotherapy or bariatric surgery is unknown.
Discussion	The safety of the device in relation to a number of relevant comparators (optimal pharmacotherapy in Type 2 DM, bariatric surgery in obesity) has not been evaluated in the studies identified and can therefore not be answered on the basis of the current evidence. A limitation of the safety evidence is that the majority of studies investigated a prototype that has been implanted for three months only, whereas the commercialised type is implanted for up to 12 months and contains different technical features (e.g. anchor system). The overall quality of evidence is low because of unclear allocation concealment, lack of blinding of study participants and outcome assessors, high drop-out rates in some studies, different drop-out rates between intervention and control-group, lack of/unclear intention-to-treat analysis, small numbers of study participants and very short follow-up periods in most of the studies.

References	1. Cohen RV, Galvao Neto MP, Correa J, Sakai P, Martins B, Schiavon PA, et al. A Pilot Study of the Duodenal-Jejunal Bypass Liner in Low Body Mass Index Type 2 Diabetes. Journal of Clinical Endocrinology and Metabolism. 2013;98(2):E279-E82. 2. de Moura EGH, Martins BC, Lopes GS, Orso IR, de Oliveira SL, Galvao Neto MP, et al. Metabolic improvements in obese type 2 diabetes subjects implanted for 1 year with an endoscopically deployed duodenal-jejunal bypass liner. Diabetes Technology & Therapeutics. 2012 Feb;14(2):183-9. 3. Escalona A, Pimentel F, Sharp A, Becerra P, Slako M, Turiel D, et al. Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal-jejunal bypass liner. Annals of Surgery. 2012 Jun;255(6):1080-5. 4. Escalona A, Yanez R, Pimentel F, Galvao M, Ramos AC, Turiel D, et al. Initial human experience with restrictive duodenal-jejunal bypass liner for treatment of morbid obesity. Surgery for Obesity & Related Diseases. 2010 Mar 4;6(2):126-31. 5. Gersin KS, Rothstein RI, Rosenthal RJ, Stefanidis D, Deal SE, Kuwada TS, et al. Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. Gastrointestinal Endoscopy. 2010 May;71(6):976-82. 6. Rodriguez-Grunert L, Galvao Neto MP, Alamo M, Ramos AC, Baez PB, Tarnoff M. First human experience with endoscopically delivered and retrieved duodenal-jejunal bypass sleeve. Surgery for Obesity & Related Diseases. 2008 Jan-Feb;4(1):55-9. 7. Rodriguez L, Reyes E, Fagalde P, Oltra MS, Saba J, Aylwin CG, et al. Pilot clinical study of an endoscopic, removable duodenal-jejunal bypass liner for the treatment of type 2 diabetes. Diabetes Technology & Therapeutics. 2009 Nov;11(11):725-32. 8. Schouten R, Rijs CS, Bouvy ND, Hameeteman W, Koek GH, Janssen IMC, et al. A multicenter, randomized efficacy study of the EndoBarrier Gastrointestinal Liner for presurgical weight loss prior to bariatric surgery. Annals of Surgery. 2010 Feb;251(2):236-43. 9. Tarnoff M, Rodriguez L, Escalona A, Ramos A, Neto M, Alamo M, 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. Surgical Endoscopy. 2009 Mar;23(3):650-6.
Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

Clinical Effectiveness

[D0001]: What is the effect of the intervention on overall mortality in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity (and comorbidities)?	
Methods	Source of information: • Basic documentation ☐ • Domain search x☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? Critical x☐ Important ☐ Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[D0002]: What is the effect on the disease-specific mortality in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity (and comorbidities)?	
Methods	Source of information: • Basic documentation ☐ • Domain search x☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[D0003] What is the effect of the intervention on the mortality due to other causes than the target disease in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity (and comorbidities)?	
Methods	Source of information: • Basic documentation ☐ • Domain search x☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[D0004] What is the rate of direct mortality related to the use of the DJBS in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity (and comorbidities)?	
Methods	Source of information: • Basic documentation ☐ • Domain search x ☐ • Other: Critical appraisal criteria Cochrane risk of bias tool Method of synthesis GRADE
Result	The rate of direct mortality related to the use of the DJBS has not been reported.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[D0005]: How does the DJBS affect further outcomes compared to standard/usual care or practice in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity (and comorbidities)	
	• weight loss (temporary, long-term) • reduction in drug use (e.g. diabetic medication, antihypertensive medication) • surrogate parameters (blood pressure, markers of metabolic function: HbA1c, fasting blood glucose, insulin, C-peptide, LDL, triglyceride levels)
Methods	Source of information: • Basic documentation ☐ • Domain search x☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis GRADE
Result	EWL relative: In three (R)CTs that investigated 137 patients in total, excess weight was reduced by 12-22% in the intervention group and by 3-7% in the control group within a follow-up period of 12 weeks. The control-groups either received diet (only) or sham procedure. The between-group differences were statistically significant in all three studies [Gersin 2010, Schouten 2010, Tarnoff 2009] (see also data extraction Table 6 and GRADE Table 10 to 12). All three studies included obese patients with or without comorbidities. Weight loss absolute: In three (R)CTs that investigated 114 patients in total, an average weight loss per patient of 8-10kg was observed after 12 weeks in the intervention group. Patients in the control-group who received diet or sham procedures lost 2-7kg on average. Statistical significance of the between-group differences was presented in two studies only [Gersin 2010, Rodriguez 2009] of which the difference reached statistical significance in one [Gersin 2010] (see also data in GRADE Table 10). Two of those studies [Gersin 2010, Tarnoff 2009] included obese patients with or without co-comorbidities (GRADE Table 11). In one study [Rodriguez 2009], the primary inclusion criterion was Type 2 DM (GRADE Table 12). The between-group difference in absolute weight loss was partly significant in the former and not significant in the later. Reduction in drug use: One RCT (18 patients with Type 2 DM and obesity) documented the use of oral antidiabetic drugs [Rodriguez 2009]. All patients took antidiabetic medication at study entry. In 42% of patients in the intervention group, medication was ceased after 12 weeks, and in 40% after 24 weeks. In the control group, 17% of patients stopped using antidiabetics after 12 weeks, and 25% after 24 weeks. Statistical significance of the between-group difference was not reported (Table 12). Surrogate parameters: HbA1c (%): In three (R)CTs that investigated 99 patients overall, HbA1c (in%) was measured in 63 study participants [Rodriguez 2009, Schouten 2010, Tarnoff 2009]. However, one study presents the results for four patients only and was, therefore, not selected for further analysis [Tarnoff 2009]. One of the studies included patients with Type 2 DM and obesity [Rodriguez 2009]; the other two included patients with obesity with or without comorbidities [Schouten 2010, Tarnoff 2009].

Result *continued*	After 12 weeks, HbA1c fell by 1.1 to 1.3%-points in the intervention groups and by 0.4 to 0.8%-points in the control groups. Statistical significance was only measured in one study [Rodriguez 2009], where the between-group differences were not statistically significant. After 24 weeks (measured in one study only [Rodriguez 2009]) it fell by 2.4%-points in the intervention group and by 0.8%-points in the control group compared with baseline. The between-group difference was not statistically significant. Fasting plasma glucose (FPG)-change: two RCTs (one included obese patients, the other one patients with Type 2 DM) with 59 participants in total investigated FPG change (in mg/dl) [Rodriguez 2009, Schouten 2010]. After 12 weeks the level fell by 18 to 45 mg/dl in the intervention group and by 8 to 9 mg/dl in the control group. Where measured, between-group differences were not statistically significant [Rodriguez 2009]. After 24 weeks FPG dropped by 83 mg/dl (compared with study entry) in the intervention group and rose by 16mg/dl in the control group. The between-group difference was again not statistically significant. Concerning the effect on other markers of metabolic function and on blood pressure, no studies were identified that addressed this question.
Discussion	Studies that included obese patients with or without comorbidities have consistently shown a significantly and clinically relevant higher short-term (12 weeks) reduction in excess weight in the intervention than in the control groups (diet or sham procedure). However, it is unclear how EWL was calculated and whether calculations were consistent across studies. For all other parameters, the benefit in the intervention groups compared with the control groups is unclear because the differences are either not consistently statistically significant (weight loss absolute), or the outcome of interest has not been measured (e.g. reduction in drug use). In the single study that included patients with Type 2 DM, the effect on weight loss, drug use or metabolic function is unclear because the between-group differences are either not statistically significant or statistical significance has not been reported for between-group differences. A limitation in those RCTs that address obesity as primary indication is that the comparator does not reflect standard or usual care. If the DJBS is intended for patients for whom conservative measures of weight reduction have failed, diet or doing nothing does not represent standard or usual care, as bariatric surgery would have to be considered. This is of even greater importance, as systematic reviews have shown that bariatric surgery is an effective weight loss intervention in selected patients [Scottish Intercollegiate Guidelines Network 2010a]. If the DJBS is intended for patients with manifest Type 2 DM, the intervention needs to be compared with optimal pharmacotherapy, whereas patients in the study received a sham-procedure combined with limited pharmacotherapeutic management. While a sham procedure increases the validity of the study results, compared with an unblinded trial, we do not know whether the DJBS results in a net benefit compared with optimal standard care. Another limitation of the efficacy evidence is that the studies investigated a prototype that has been implanted for three months only, whereas the commercialised type is implanted for up to 12 months and contains different technical features (e.g. different anchor system). Furthermore, the mean BMI in the controlled studies ranges between 39 and 49 kg/m². This is considerably higher than the manufacturer's concept of offering the treatment to patients with a BMI ≥30 kg/m². It may be possible that the effect size is greater in patients with a BMI >40 kg/m² resulting in an overestimation of DJBS's benefit.

Result *continued*	The overall quality of evidence is low because of unclear allocation concealment, lack of blinding of study participants and outcome assessors, high and unexplained drop-out rates in some studies, different drop-out rates between intervention and control-group, lack of or unclear intention-to-treat analysis, small numbers of study participants and very short follow-up periods in most of the studies. Based on the current evidence, there is little effect of the DJBS on weight management in patients with obesity ≥grade II and evidence on whether the relative reduction of excess weight is sustained beyond 3 months is unknown. This is of concern because the aim of obesity management is not a maximum weight loss, but rather a moderate yet sustainable reduction of weight. Furthermore, it is unclear whether the weight loss is caused by the device or by the diet patients are put on after device implantation. Furthermore, none of the studies has evaluated the patients' point of view (e.g. health-related quality of life, dietary compliance, satisfaction) and a number of relevant end-points have not been evaluated so far. The manufacturer has recently shifted the primary indication for the DJBS. In contrast to the originally proposed purpose of weight reduction, the current online information from the manufacturer propagates its use for Type 2 DM, while the treatment of obesity is regarded as secondary [GI Dynamics 2010, GI Dynamics 2012]. However, the studies that have been analysed in this report to address clinical effectiveness questions are primarily aimed at obesity [de Moura 2012, de Moura 2011, Escalona 2012, Escalona 2010, Gersin 2010, Rodriguez-Grunert 2008, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. Furthermore, consequences for Type 2 DM metabolism have mostly been analysed as a secondary outcome for a very short follow-up period only [Gersin 2010, Rodriguez 2009, Schouten 2010, Tarnoff 2009]. Hence, on the basis of the current evidence, the effectiveness of the EndoBarrier® on the management of Type 2 DM is unclear.
References	1. de Moura EGH, Martins BC, Lopes GS, Orso IR, de Oliveira SL, Galvao Neto MP, et al. Metabolic improvements in obese type 2 diabetes subjects implanted for 1 year with an endoscopically deployed duodenal-jejunal bypass liner. Diabetes Technology & Therapeutics. 2012 Feb;14(2):183-9. 2. de Moura EGH, Orso IRB, Martins BdC, Lopes GS, de Oliveira SL, Galvao-Neto MdP, et al. Improvement of insulin resistance and reduction of cardiovascular risk among obese patients with type 2 diabetes with the duodenojejunal bypass liner. Obesity Surgery. 2011 Jul;21(7):941-7. 3. Escalona A, Pimentel F, Sharp A, Becerra P, Slako M, Turiel D, et al. Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal-jejunal bypass liner. Annals of Surgery. 2012 Jun;255(6):1080-5. 4. Escalona A, Yanez R, Pimentel F, Galvao M, Ramos AC, Turiel D, et al. Initial human experience with restrictive duodenal-jejunal bypass liner for treatment of morbid obesity. Surgery for Obesity & Related Diseases. 2010 Mar 4;6(2):126-31. 5. Gersin KS, Rothstein RI, Rosenthal RJ, Stefanidis D, Deal SE, Kuwada TS, et al. Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. Gastrointestinal Endoscopy. 2010 May;71(6):976-82. 6. GI Dynamics. Der EndoBarrier: Eine innovative Lösung bei der Behandlung und Kontrolle von Typ-2Diabetes mellitus und Adipositas. 2010 [cited 2013 20/02/]; Available from: http://www.endobarrier.de/fachkreise/der-endobarrier/der-endobarrier.html.

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Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[D0011]: What is the effect of the DJBS in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity (and comorbidities)	
	on: • reduction in cardiovascular events (myocardial infarction, stroke, etc.), • reduction in diabetes-associated microangiopathic complications (diabetic nephropathy, retinopathy), • compared to standard/usual care or practice?
Methods	Source of information: • Basic documentation ☐ • Domain search x☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely ☐ • Partly ☐ • Not ☐

[D0012]: What is the effect of the DJBS on generic health-related quality of life in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity (and comorbidities) compared to standard/usual care or practice?	
Methods	Source of information: • Basic documentation ☐ • Domain search x☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[D0013]: What is the effect of the DJBS on disease-specific quality of life in a) all patients b) patients with Type 2 DM and/or obesity and c) in patients with high-grade obesity (and comorbidities) compared to standard/usual care or practice?	
Methods	Source of information: • Basic documentation ☐ • Domain search x☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical x ☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[D0016]: How does the use of DJBS affect activities of daily living compared to standard/usual care or practice?	
Methods	Source of information: • Basic documentation ☐ • Domain search x☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical x☐ • Important ☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[D0017]: Were patients satisfied overall with the DJBS?	
Methods	Source of information: • Basic documentation ☐ • Domain search x ☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[D0018]: Would the patient be willing to use the DJBS again?	
Methods	Source of information: • Basic documentation ☐ • Domain search x ☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No studies that addressed this question were identified.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

[D0023]: How does the DJBS modify the need for the use of other technologies resources?	
Methods	Source of information: • Basic documentation ☐ • Domain search x☐ • Other: Critical appraisal criteria: Cochrane risk of bias tool Method of synthesis: GRADE
Result	No data are available on whether the DJBS modifies the need for the use of other technologies.
Discussion	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
References	-
Importance and transferability	How important is this piece of information for decision making? • Critical ☐ • Important x☐ • Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? • Completely x☐ • Partly ☐ • Not ☐

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/ nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be ethically relevant? If morbid obesity is the primary indication, the DJBS is less invasive than standard surgical approaches; if Type 2 DM is the primary indication, the DJBS is more invasive than standard pharmacological approaches	Yes
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparators require organisational changes? Capacities and training (learning the procedure) will be required for endoscope placement of the device and its removal up to one year later	Yes
2.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be organisationally relevant? Probably, the device may lead to a reduction in surgical/endoscopic procedures performed for treating obesity, and thus may lead to some excess capacities for other surgical interventions, if successful.	Yes
3. Social:	
3.1. Does the introduction of the new technology and its potential use/ nonuse instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be socially relevant?	No
4. Legal:	
4.1. Does the introduction of the new technology and its potential use/ nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be legally relevant?	No

APPENDIX 4: INPUT FROM MANUFACTURER, EXTERNAL REVIEWER, CONSUMERS' ORGANISATION AND STRAND B MEMBERS ON V 1.2 OF PILOT RAPID ASSESSMENT

Input from manufacturer

No	Page	Line	Comment	Reply
1	18	417	No rational for deviation from project plan was included: I. The device that was evaluated for efficacy assessment is not the device that is described as the intervention in the Project Plan. This needs to be clearly described and highlighted in the final report. II. The intervention that is the subject of this HTA was described in the Project Plan (page 147) as: EndoBarrier®/ duodenal-jejunal bypass sleeve (DJBS): impermeable flouropolymer sleeve that is placed endoscopic via the mouth and anchored in the first part of the small bowel in a procedure that takes about 30 minutes. The device remains in the bowel up to 12 month and is removed hereafter. The DJBS which was used in the assessed RCT's for this report was an early device development, investigational prototype (3 month device) to the device described as the intervention in the Project Plan (12 month device). It's a different product. The prototype was never commercialized and differed substantially from the currently available commercial device. The prototype utilized an early anchor design with different barb dimensions, different sleeve technology and design and remained only 3 month in situ. The experience gained from the prototype RCT's drove the development and design for the current commercialized device. Several clinical trials were conducted with the commercialized device which displayed improved efficacy and overall product performance. The commercialized device received CE-Mark approval October 2010 with approval for 12 month implantation. III. Based on our study and clinical experiences the population indicated in the report is not specific enough and it contains some misinterpretations. The population best suited for DJBS is: men and women (≥18 years), with: - Type 2 diabetes mellitus patient who are not adequately controlled with medications (oral and/or insulin) and lifestyle intervention (HbA1c ≥7.5%) and obesity (BMI≥30).	Information concerning the issue prototype vs. commercialised type has been included in the revised version in the summary section, in the result section, in the description of the evidence section and in the according result cards. Additionally, in the project scope (field 'intervention') we added the information that the report considers all generations of the device. The report addresses two subpopulations (see comment no. 7 for justification); the second subpopulation reflects the definition suggested by the manufacturer; in the revised version we have changed the BMI from ≥35 to ≥30 and added '... who are not adequately controlled with medications (oral and/ or insulin) and lifestyle intervention (HbA1c ≥7.5%)' in the project scope.

			The current population in the Project Plan (page 147) is described as: men and women (≥18 years), with: - obesity III (BMI ≥ 40) or - Type 2 diabetes mellitus + obesity ≥ grade II (Body Mass Index/BMI ≥ 35-40) This population has been changed the HTA report (page 7) to: men and women (≥18 years), with: - obesity: grade III (Body Mass Index/BMI ≥ 40) or grade II (BMI 35-39.9) with comorbidities - Type 2 diabetes mellitus + obesity ≥ grade II (BMI ≥ 35-39.9) The change has been explained due to better represent the population that would be eligible for bariatric surgery. This change reflects a significant misinterpretation because it positions the DJBS procedure focused on the bariatric surgery space. This procedure is not acceptable for a standard and independent HTA.	The change is related to the definition of obesity (former version: obesity grade III; revised version: obesity grade III or grade II + comorbidities); this was done to reflect the comments by the manufacturer; paragraph has been rephrased.
2	7/17/139		**Inclusion/Exclusion criteria:** It was assumed that the studies considered in the efficacy assessment would be for device described as the intervention in the Project Plan (the 12 month product) and not consider data associated with other devices not meeting the conditions of the intervention. The intention to include data related to a product other than that identified as the intervention was not described.	Information concerning the issue prototype vs. commercialised type has been included in the revised version in the summary section, in the result section, in the description of the evidence section and in the according result cards. Additionally, in the project scope (field 'intervention') we added the information that the report considers all generations of the device.
3	65		**Quality assessment tools:** The appraisal tools are appropriate for drug therapy; they are not appropriate for a medical device because they mistakenly consider data from a different prototype device not intended for commercial use. DJBS RCT's that would be appropriate for an HTA assessment are currently underway and/or planned. Please see the summary of scheduled RCT's (section: FURTHER GENERAL AND SPECIFIC COMMENTS FOR THE AUTHOR – page 71 – Table 11)	The quality assessment tool that has been used is the Cochrane risk of bias tool. It is a standard tool and a generally accepted state of the art to assess different designs of studies (mainly RCTs) regardless whether they evaluate drugs or devices [European Network for Health Technology Assessment (EunetHTA) 2012]. We disagree with the manufacturer that this tool is inappropriate for assessing RCTs on the DJBS. Information concerning the issue prototype

				vs. commercialised type has been included in the revised version in the summary section, in the result section, in the description of the evidence section and in the according result cards. The information on the scheduled RCT has been revised according to information from the manufacturer; the description of the upcoming evidence has been rephrased to provide more details on the ongoing studies.
4	7/17		Comparator It was appropriate for this analysis but unfortunately was applied to the prototype device and not the commercially available device, which is the intervention described in the Project Plan.	Information concerning the issue prototype vs. commercialised type has been included in the revised version in the summary section, in the result section, in the description of the evidence section and in the according result cards.
5	72 (?)		Risk of bias: The assumption of bias and the discounting trial data as the result of company sponsorship is inappropriate. It is typical in medical device development for industry to sponsor research through the pre-clinical through early stages commercialization.	Reporting the sponsorship of a study is a standard in HTA to make potential conflict of interest transparent. As the manufacturer correctly points out, it is typical that the industry sponsors research. However, research has also demonstrated that industry-sponsored studies tend to show more favourable results than otherwise financed studies [e.g. Beckelmann 2003, Lexchin 2003]. Hence, industry-sponsorship represents a potential risk of bias.

6	7/17/139		Choice of study types: The panel was provided over 23 peer reviewed publications for both the prototype and current commercial device described as the intervention in the Project Plan. The panel based its efficacy assessment on the four studies for the prototype device. The efficacy assessment is not based on data associated with the device described as the intervention in the Project Plan. We consider the choice of study types to be flawed since the efficacy assessment and the overall conclusions are based largely on data that is not for the intervention described in the Project Plan. Efficacy data are not yet available from RCTs at this stage in the DJBS commercial lifecycle so the HTA assessment is premature. A review of the data from studies related to the intervention described in the Project Plan will show that the current commerical device does exert important metabolic effects in patients with Type 2 diabetes mellitus and/or obesity. Two Type 2 diabetes studies (Cohen et al, Moura et al) demonstrating, a robust lowering of HbA1c (~1.5%) as observed out to 12 months that is competitive with or superior to established pharmacologies. In a third study (Escalona et al), where obese subjects were studied, some of whom had Type 2 diabetes, a striking weight loss was observed at 12 months (-20%). This degree of weight loss is unattainable with weight lowering pharmacology (at best 5-7% placebo-corrected) and is competitive with weight loss seen with bariatric surgery interventions. It should be noted similarly significant weight loss was also observed in the two Type 2 diabetes studies. It is inappropriate to omit efficacy data from these single arm studies at this stage in the commercial lifecycle of a medical device. It was expected that the studies used to support the assessment would be for the intervention described in the Project Plan and not for a prototype of the intervention that differs markedly both in design and indication.	Study selection was based on the method described in the project plan. This part of the project plan has been agreed on by the reviewers of the project plan including the manufacturer. In the project plan it was described that for efficacy analysis any controlled study will be used and for safety analysis prospective studies will be used. This is based on methodological EUnetHTA-standards on how to evaluate efficacy and safety of health technologies [European Network for Health Technology Assessment (EunetHTA) 2012, European Network for Health Technology Assessment (EunetHTA) 2012a]. As a consequence, a number of studies that were provided by the manufacturer had to be excluded from the analysis, for example animal studies. Other studies were considered for safety analysis only because they were uncontrolled. Unfortunately, the list of publications provided by the manufacturer did not indicate that the publications are related to different types of the device. Information concerning the issue prototype vs. commercialised type has been included in the revised version in the summary section, in the result section, in the description of the evidence section and in the according result cards.

7	7/17/36		**Indirect comparisons/choice of comparator:** There are multiple references in the HTA report suggesting that DJBS should be compared to bariatric surgery and other surgical interventions. There was no disclosure of the source of these references and/or if there is published supporting data. DJBS is not a comparator to these interventions because: 1) DJBS therapy should be used after drug therapy has failed and prior to invasive and high risk surgical procedures. 2) DJBS can claim a non surgical non pharmaceutical mechanism of action that elicits glycemic control independent of weight loss. The report described that results from DJBS studies in process now will have these same limitations. It is standard practice to design studies for diabetes and/or bari-	The report addresses two types of indication: 1) high grade obesity ≥grade II (with co-morbidities) and 2) Type 2 DM with obesity ≥ grade I; the former indication has been chosen because the majority of published studies (particularly the RCTs) as well as recent HTA-reports from renowned HTA-Institutes [National Institute for Health and Clinical Excellence 2012] address obesity as primary indication; the latter has been added because of the manufacturer's comment that the primary indication has been shifted to Type 2 DM in the meantime. We rephrased the decision for the indications in the report and included references to clarify this issue. If high grade obesity is considered as primary indication, the DJBS needs to be compared to another standard approach for high grade obese patients, which is bariatric surgery. The limitations of this comparator have been discussed in the report (e.g. p. 10, result card A0001). If Type 2 DM is considered as primary indication, the DJBS needs to be compared to current standard management for Type 2 DM, which is optimal pharmacotherapy. The results have been presented for both approaches separately so that the reader can easily distinguish between the two indications or use the results for the more recent indication only. The information on the scheduled RCT has been revised according to infor-

			atric procedures with surrogate endpoints, most notably reduction in HbA1c.	mation from the manufacturer; the description of the upcoming evidence has been rephrased to provide more details on the ongoing studies.
8	36/144		Time points for measuring outcomes: The time point for assessment associated with the intervention described in the Project Plan was the remaining time of 12 months. However, the data considered in the efficacy assessment was based on a 3 month time point associated with the prototype device.	In EUnetHTA definition, the term 'time points for measuring outcomes' relates to the follow-up measurements and not to the duration of time the device has been implanted. The time point of ≥12 months has been defined to identify any sustainable and long-term effects of the device. This is based on methodological standards in EUnetHTA, particularly on the requirement to focus on final therapeutic objectives. Unfortunately, in most of the available RCTs the follow-up was only three months. Hence, we were not able to report outcome data for >12months.
9	7/17		Transparency of assessment: We note commentary concerning the endpoints of HbA1c and weight loss. HbA1c is the gold standard surrogate measure for glycemic control in Type 2 diabetes patients. Body weight is an important metabolic measure in both Type 2 diabetes and obese patients. Cardiovascular outcomes data are not yet available. This research is typically only possible in the latter part in the life cycle of a medical device, occurring in most cases 5-10 years after large scale commercialization, extracted from large sample size studies. It is only in the last 5 years that this standard has been established in the assessment of Type 2 diabetes and obesity therapies. The DJBS has not yet reached this stage to conduct such clinical work. However, we note that metabolic improvement data appears also to be accompanied by improvement in cardiovascular markers.	The validity of endpoints is based on current standards in HTA, particularly on the EUnetHTA-guidelines on clinical endpoints and on surrogate endpoints [European Network for Health Technology Assessment (EUnetHTA) 2013a, European Network for Health Technology Assessment (EunetHTA) 2013c]. As stated in the report, markers of the metabolic function (HbA1c, fasting blood glucose) were considered because they are widely used in the management of Type 2 DM. However, HbA1c and weight loss are by definition surrogate endpoints and as such not as valid as final endpoints: "A surrogate endpoint is an objectively measured endpoint that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit or

			Understanding what has been observed in gastric bypass surgery variants and the analogous biological effects elicited by DJBS, one would predict glycemic control and weight lowering mechanisms. We then note that the review speculates on the rationale for utility in either obesity or T2DM populations. We have deemed that leveraging the combined anti-diabetic and weight lowering effects exerted by DJBS,the intervention,in obese Type 2 diabetes patients is a more favorable approach: a high unmet and growing disease segment with pharmacology shortcomings and compliance issues (a problem circumvented by DJBS).	harm based on epidemiologic, pathophysiologic, therapeutic and other scientific evidence. … Final endpoints relate to the final therapeutic objective for the use of the technology, not just to clinical outputs, which is why they have greater relevance for the patient and for overall prioritisation. … **It should be acknowledged that the relationship between a surrogate and a final endpoint can never be considered as definite."** [European Network for Health Technology Assessment (EUnetHTA) 2013c]. We have acknowledged the comment by the manufacturer that the indication 'Type 2 DM + obesity ≥grade I' is a more favourable approach and have presented the results for this indication separately in the report. Since the majority of publications and even some ongoing studies address a different indication (obesity ≥grade II [+ comorbidities]) we found it relevant to present the results for this subpopulation, too.
10	14		Discussion: The summary as with the rest of the document, as it pertains to efficacy, does not reflect data related to the intervention identified in the project scope. The summary is not based on data for the intervention described in the project scope. Personal opinion stated as fact in the summary is not considered useful or allowed for HTA assessments.	Information concerning the issue prototype vs. commercialised type has been included in the revised version in the summary section, in the result section, in the description of the evidence section and in the according result cards.
11	Cover page	Title	The current commercialized device received CE-mark in October 2010 and can be implanted for 12 months. The device in the selected RCT's was the prototype version of the device which could be only implanted for 3 months. The report needs to clearly state that the HTA assessed the prototype device which is not commercialized.	Information concerning the issue prototype vs. commercialised type has been included in the revised version in the summary section, in the result section, in the description of the evidence section and in the according result cards.
12	7	130	Incorrect definition of the population and needs to be adjusted. Correct definition:	See previous comments; The report addresses two subpopula-

			- Type 2 diabetes mellitus who are not adequately controlled with medications (oral and/or insulin) and lifestyle intervention (HbA1c ≥7.5%) and obesity (BMI≥30)	tions; the second one reflects the definition suggested by the manufacturer; in the revised version we have changed the BMI from ≥35 to ≥30 and added '…who are not adequately controlled with medications (oral and/or insulin) and lifestyle intervention (HbA1c ≥7.5%)' in the project scope.
13	Page 14	343-352 369-370	The first RCT's done with prototype with obese populations and associated primary endpoints showed important signals results Type 2 diabetes mellitus surrogates (HbA1c; FPG). The results are documented in the summary tables on page 13 + 14 of the report. It is interesting that there was no difference in weight loss between patients with or without Type 2 diabetes mellitus. These results were the first signal that DJBS was able to elicit glycemic control independent of weight loss in obese Type 2 diabetes patients. Upon further refinement of the prototype device to the current commercial device design, a clinical team Brazil carried out a 12 month investigation in obese Type 2 diabetes patients. They reported statistically significant reductions in fasting plasma glucose (FPG) and HbA1c by the end of the 12months in 13 patients (Moura EG et al). The unique mechanism of action needed to be explored further, so the company conducted a randomized controlled trial in the Netherlands. This RCT has been completed and the results will be published at the beginning of 2014. Patient population and bariatric surgery as a comparator are inappropriate and should be adapted because of the report reflects only the early views presented in evidence / literature related to the prototype of DJBS. There is an inappropriate statement included that the manufacturer has shifted the primary indication for DJBS away from obesity because the effect on weight management in obese patients was unsatisfactory. <u>This is unfounded conjecture and need to be removed.</u>	Information concerning the issue prototype vs. commercialised type has been included in the revised version in the summary section, in the result section, in the description of the evidence section and in the according result cards. Information on the scheduled RCT has been revised according to information from the manufacturer; the description of the upcoming evidence has been rephrased to provide more details on the ongoing studies. Unfortunately we cannot present results from RCTs that have not been completed and published. It has been defined in the project plan that results from uncontrolled studies can be considered for safety issues only (see previous comments). Paragraph has been rephrased.
14	Page 15	354-368	The discussion underlines the fact that you are comparing therapies which are based on pharmacology with medical device interventions. This is inadequate and a methodical failure because RCT's with medical devices typically including substantially smaller numbers of patients with an initial primary goal to develop and refine a procedures to place, remove and use the device. It is logical that the available evidence is limited in the early DJBS commercialization lifecycle. Ongoing RCT's are in place	The fact that RCTs have already been completed and further RCTs are ongoing and planned demonstrates that devices can be as rigorously evaluated in clinical studies as drugs. Concerning the methodological stand-

			and associated evidence will be published from 2015 to 2018.	ards on evaluating other health technologies than drugs, this pilot project will be used to define similarities and differences between the evaluation of drugs and other health technologies. Comments by the stakeholders involved and experiences from this project will be integrated in methodological discussions.
15	Page 15	374-375	HbA1c is a standard efficacy endpoint for clinical trials designed to study interventions for Type 2 diabetes mellitus. Based on UKPDS data patient related outcomes and benefits could be extrapolated from HbA1c changes. It's unrealistic to measure patient related end points within the current state of the device development. Furthermore pharmacology products report on patient related outcome (e.g. survival rates) with post market studies which are in process for DJBS. We have chosen all specific study endpoints in our scheduled RCT's with the main reimbursement authorities (e.g. France = HAS, USA = FDA) and other local HTA agencies as well as with external experts from the regional government.	See comment 9: The validity of endpoints is based on current standards in HTA, particularly on the EUnetHTA-guidelines on clinical endpoints and on surrogate endpoints [European Network for Health Technology Assessment (EUnetHTA) 2013a, European Network for Health Technology Assessment (EunetHTA) 2013c]. As stated in the report,markers of the metabolic function (HbA1c, fasting blood glucose) were considered because they are widely used in the management of Type 2 DM. However, HbA1c and weight loss are by definition surrogate endpoints and as such not as valid as final endpoints: "A surrogate endpoint is an objectively measured endpoint that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit or harm based on epidemiologic, pathophysiologic, therapeutic and other scientific evidence. … Final endpoints relate to the final therapeutic objective for the use of the technology, not just to clinical outputs, which is why they have greater relevance for the patient and for overall prioritisation. … **It should be acknowledged that the rela-**

				tionship between a surrogate and a final endpoint can never be considered as definite" [European Network for Health Technology Assessment (EUnetHTA) 2013c].
			There is an inappropriate comment on line 374 that future trials would not add relevant data. This is inaccurate and is personal conjecture. The comment reflects reviewer bias and reflects an unfounded opinion that disregards the efficacy evidence from 12 mo results of published studies. The comment also reflects an opinion that the RCTs will not reveal positive data such effectively "discarding" the DJBS therapy based on results from early stage data of a prototype design.	The conclusion on upcoming evidence read as follows: "Ongoing RCTs will add only little relevant information because they use the same limited comparators and surrogate outcome parameters". This conclusion is related to the limitations in the study design in the ongoing studies and not to study results. Paragraph has been revised to clarify the issue.
16	Page 32	946 - 991	This and following sections continue to separate Type 2 diabetes and obesity as though the disease states are not being addressed conjointly by DJBS. The present positioning of the device is for individuals with both Type 2 diabetes and obesity (BMI ≥30) who are not adequately controlled with medications (oral and/or insulin) and lifestyle intervention (HbA1c≥7.5%). Metabolic syndrome is a well documented disease state with increasing global prevalence. Type 2 diabetes and obesity are inextricably linked metabolic conditions and should not be separated.	In the previous comments we have explained why two subpopulations were analysed in the report. As defined in the project scope and repeated several times throughout the report, both subpopulations include obesity + comorbidities in conjunction.
17	Page 35	1046 -	The data referenced is based on development stage trials with the prototype device and not on the currently commercialized device. Therefore, the conclusions are misleading as they do not consider data from the commercial device. The prototype device was implanted for 3 month duration and provided proof of concept data but is not the CE-mark commercial product with an indication for a 1 year treatment.	Information concerning the issue prototype vs. commercialised type has been included in the revised version in the summary section, in the result section, in the description of the evidence section and in the according result cards.
18	ALL	ALL	The following personal conjecture and bias that must be omitted - "predictions" about whether future trials will be successful - constant references to individual country nuances that are not relevant to	The information on the scheduled RCT has been revised according to information from the manufacturer; the description of the upcoming evidence has been rephrased to provide more details on the ongoing studies. Admission and reimbursement state-

			the overall discussion, particularly given that these were "development" trials that are being used out of context - wrong statements concerning regional admissions, status of reimbursement and clinical use Please note that GI Dynamics, Inc. is disappointed that this personal bias and personal "agenda" is present in the HTA report and it brings into question if this report can be fairly presented; this assessment focuses on arbitrary rather than relevant data.	ments have been corrected according to the manufacturer's information Data selection and presentation in the report has been done according to predefined criteria and HTA-standards. Data synthesis is transparently documented in the report tables and figures. We disagree with the manufacturer that data have been chosen arbitrarily and we strongly disagree that the report presents our personal agenda. We can assure the manufacturer that the report has been produced according to standards of transparency and objectivity.
19	Page 71	Table 12	Please use the full table of scheduled studies (RCT's): - "Dutch Diabetes Study" (NL) – RCT with cross over – multi center – 34/37 – primary endpoint: reduction in HbA1c – finalized – publication expected early 2014 – sponsored by GI Dynamics - "ENDO Trial" (USA) – RCT double blinded – multi center – 330/170 – primary endpoint: reduction in HbA1c – study designed by FDA – sponsored by GI Dynamics - "ENDOMETAB"(France) – RCT – multi center – 116/58 – primary endpoint: improvements in metabolic syndrome – study sponsored by French Government - "EME MRS study" (UK) – RCT – multi center – 80/80 – primary endpoint: proportion of substantial improvement in their metabolic syndrome with an HbA1c reduced by 20% and a lowering of blood pressure below 135/85 – study design aligned with EME – sponsored by an academic grant - "EndoBarrier versus Intragastric Balloon" – RCT – single center – 45/45 – primary endpoint: reduction in HbA1c and measurement of diabetes metabolic control – study designed and sponsored by ISMETT	The information on the scheduled RCT has been revised according to information from the manufacturer; the description of the upcoming evidence has been rephrased to provide more details on the ongoing studies.

References (input from manufacturer)

1. Beckelmann J, Li Y, Gross C. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA. 2003;289:454-65.
2. European Network for Health Technology Assessment (EunetHTA). Levels of evidence: Internal validity. 2012.
3. European Network for Health Technology Assessment (EunetHTA). Endpoints used in REA of pharmaceuticals: Safety: EUnetHTA; 2012a.
4. European Network for Health Technology Assessment (EUnetHTA). Endpoints used for relative effectiveness assessment of pharmaceuticals: clinical endpoints: EUnetHTA; 2013a.
5. European Network for Health Technology Assessment (EunetHTA). Endpoints used in relative effectiveness assessment of pharmaceuticals: surrogate endpoints: EUnetHTA; 2013c.
6. Lexchin J, Bero L, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. British Medical Journal. 2003;326:1167-70.
7. National Institute for Health and Clinical Excellence. Interventional procedure overview of implantation of a duodenal-jejunal bypass sleeve for managing obesity. London: National Institute for Health and Clinical Excellence; 2012.

Input from external reviewer

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Are appropriate contact details for further information provided in the report?	X			
Are authoring, co-authoring and reviewing agencies listed?	X			
Is a statement regarding the conflict of interest included?	X			
Was there a need to deviate from the Project Plan (protocol) in terms of clinical problem, population, intervention(s), comparison(s) and outcome(s)? If the answer is NO, please move directly to the Part 2 of the reviewer form.			X	
Was a rationale included for the deviation from the scope that was proposed in the project plan?				
Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	X			
Are the quality appraisal tools appropriate?	X			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis?	X			
Is the risk of bias sufficiently assessed, both on study level and on an outcome level?	X			
Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?	X			
Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?	X			
If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?				n/a no indirect comparisons were found in this assessment, but are not of relevance here
Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?	X			
Details on sources of information and literature search strategies provided?	X In the methods section including Appendix 1 all above mentioned sources of information including the mentioned parameters are described in sufficient detail. Primary data were not included; other information resources include guidelines from various countries and medical societies			
Information on basis for the assessment and interpretation of selected data and information?	X All parameters are described in extensive detail making the process of assessment and interpretation of selected data plus information clearly reproducible			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	X			
Are the supporting references current and do they provide an international picture of the problem?	X			
Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	X			
Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	X			
Are the supporting references current and do they provide an international picture of the problem?	X			
Is the risk of bias clearly reported?	X			
Is quality of data sufficiently evaluated?	X			
Are both relative and absolute effect measures presented for each dichotomous outcome?	X			
Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?	X			
In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?				n/a No time-to-event analysis was performed in the studies
Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported?	X			
Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?	X			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?				n/a No adverse events were incorporated in utility values of quality of
Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?				n/a The transformation of the surrogate outcomes into patient-relevant final outcomes was not considered
Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	X			
Can the results be applied to the intended population?	X			
Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	X			
Does the summary present a balanced representation of the content of the report?	X			
Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	X			
Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	X			

Input from consumers' organisation

No	Page	Line	Comment	Reply
1	19		Health Problem and Current Use concerning description of incidence/prevalence/description of current use: references to the different groups of the population in pag.26	Unclear, which paragraph reviewer is referring to; references were already included for prevalence and incidence figures
2	4	53	it would be good to indicate which definition of conflict of interest you used. We recommend using the EMA guidelines on COI	The form has been defined by EUnetHTA; information has been included in report
3	14/72		More info could be provided on how the risk of bias has been managed and weighted	A sentence has been included in the method section to inform the reader on how the results from the risk of bias table were further used in grading the evidence

Input from Strand B members

Comment #	Page	Line	Agency/ Organisation	Comment	Reply
1	2	11	HIQA	Consider adding Conor Teljeur as a reviewer for HIQA as he has assisted the review as Shelley is on maternity leave.	Reviewer has been included after COI-statement was received
2	7	130	IQWiG	In the table, the population of interest is generally well-defined, but the two subpopulations (morbidly obese patients vs. patients with diabetes and obesity) do overlap each other. This leads to an ambiguity of methods, because some studies will fit both definitions. If a study included patients with a BMI of 35 to 40 and diabetes, this study would fit the definition of morbid obesity, since diabetes represents an obesity-related comorbidity. On the other hand, the same study could also be included for the subgroup of diabetes. It remains unclear how it was decided which group such studies belonged to. I suggest to accept studies for the subgroup of morbid obesity, if some but not necessarily all patients also suffered from diabetes. If diabetes was required as an inclusion criterion (and thus was present in 100% of patients), the study should be put into the second group of studies.	Precise definitions of subpopulations have been included in footnotes
3	2	?	HVB	Bettina Maringer, Main Association of the Austrian Social Securi-	Has been corrected

Comment #	Page	Line	Agency/ Organisation	Comment	Reply
				ty Institutions (instead of Institutsion)	
4	7 17 36 38 50 124 148 157	In the table - - 1172 - - - -	"A Gemelli" University Hospital	As above mentioned section outcome the transition to bariatric surgery seems not appropriate. It could be considered as adverse event because the bariatric surgery is more invasive than the intervention	Transition to bariatric surgery has been excluded as an outcome parameter in the second reversion. Firstly, because of the reviewer's comment that it may also be an adverse event and secondly, because the therapeutic aim of the DJBS has changed from weight loss to improvement of glycemic control.
5	9	193	IQWiG	The term "patients with type 2 DM and/or obesity" creates ambiguity. Does the manufacturer truly propose to use the DJBS in diabetic patients with a BMI < 30? If not, I would propose to speak of "patients with obesity with or without diabetes" or "patients with grade II obesity and those with grade I obesity and diabetes".	The term has been used from the manufacturer's webpage. In our understanding the term 'patients with Type 2 DM **and/or** obesity' in any case includes obesity (by including the operators **'and/or obesity**'); this means that the DJBS is either for patients with Type 2 DM + obesity OR for obesity only; thus, obesity is a requirement for all patients; the definition does not include patients with a BMI <30. Term was left unchanged
6	9	212	IQWiG	The word "domains" appear twice where only one word would be needed.	Has been corrected
7	9 29 99 104	186 828 - -	"A Gemelli" University Hospital	The CE Mark gives the authorization to commercialize Device in all European countries not only for UK, Netherlands, Germany, and Austria. Regarding Chile is the CE mark valid in that country?	Information on CE-marking has corrected according to manufacturer comments
8	10	235	IQWiG	The study by Tarnoff et al. was only partly randomized and thus should be labelled as a non-randomized controlled trial. In the article, Tarnoff et al. state that "the last 15 consecutive patients to enrol were assigned to the device arm of the study for the purpose of increasing the number of subjects with the DJBS in this pilot trial." This very unusual step in a study also explains	Term has been changed into non-randomised trial and relevant paragraphs have been changed accordingly

Com-ment #	Page	Line	Agency/ Organisation	Comment	Reply
				why the two patient groups differed in size (26 vs. 14), which is very unlikely to occur by chance in a randomized trial. In truth, only 11 vs. 14 patients were randomized, and the remaining 15 patients were added in a non-randomized fashion. This invalidates all of the results, because no results were presented only for the 25 randomized patients. If there was time, it would be worthwhile to contact the study authors to clarify the conduct of the study and to obtain data for only the randomized patients.	
9	10	244	IQWiG	A case-control study is mentioned here. Although the study design is labelled "case-control study" in the study registry (NCT01724060), the study should be called "prospective controlled trial" here. The epidemiologic term "case-control study" should be reserved for those studies, where groups are defined by outcome (present vs. absent) with retrospective assessment of cause.	Term has been changed into prospective controlled trial
10	10	259	IQWiG	Please correct as follows: "the DJBS is was associated…"	Has been corrected
11	11	290	IQWiG	It appears appropriate also to mention the 20 week weight loss data here.	Has been added
12	13	332	IQWiG	The table would be easier to understand, if data from Schouten and Tarnoff would be presented in separate lines.	The studies have been presented in separate lines
13	14	350	HIQA	I am a little concerned about the accuracy of the following statement ,*If the DJBS is intended for patients with manifest Type 2 DM, standard care would include pharmacotherapy, whereas patients in the study received a sham-procedure. This likely results in an overestimation of the benefits of the DJBS.*' This could be interpreted that these patients with T2DM are on no antidiabetic treatment. In the trial, it is documented that the patients could be taking metformin and sulphonylureas (but no other agents). On pages 27/28, we document that first line treatment is metformin with dual therapy of metformin + sulphonylurea being indicated as second line treatment for those who fail to achieve HbA1C control. If uncontrolled, there is an option to step up to triple therapy or to use insulin. Should the conclusion be that standard care would include **optimal** pharmacotherapeutic management (i.e including the use of triple therapy or insulin in patients failing to achieve HbA1C control on mono or dual therapy) whereas in this trial, the comparator was a sham procedure	Paragraph has been rephrased

Com-ment #	Page	Line	Agency/ Organisation	Comment	Reply
				combined with limited pharmacotherapeutic management? The conclusion is still correct ie: '*this likely results in an overestimation of the benefits of the DJBS'*	
14	14	351, 352	IQWiG	The authors assume that the use of a sham procedure likely resulted "in an overestimation of the benefits of the DJBS". However, using a sham procedure for blinding patients and/or outcome assessors generally increases the validity of study results as compared to an unblinded trial design. Only if patients in the control group received just the sham procedure but no other treatment, this would lead to overestimation. In the trial by Gervin et al., however, "both groups received identical nutritional counseling." It can also be assumed that regular drug medication was not discontinued in any of the study patients. Therefore, it is probably not tenable to discuss the sham procedure as a source of overestimation. The true reason for overestimated effects is the lack of any additional intervention in the control group (e.g. gastric balloon), as correctly mentioned elsewhere in this EUnetHTA report.	Paragraph has been rephrased
15	15	378	HIQA	Suggest slight rewording as phrasing is a little awkward: *Based on the current evidence, DJBS has little effect on weight management in obese patients ≥ grade II. Evidence on whether the relative reduction of excess weight sustains beyond 3 months and on whether the DJBS is more successful than established surgical methods is insufficient or lacking.*	Paragraph has been rephrased
16	15	382	HIQA	Suggest slight rewording as phrasing is a little awkward: *Additionally, on the basis of the current evidence, the effectiveness of the EndoBarrier® **in** the management of Type 2 DM is insufficient.*	Has been rephrased
17	15	359	IQWiG	I agree that data on %EWL are sometimes reported using different definitions of normal or ideal weight, which may result in different point estimates (Montero et al.; Surg Obes Relat Dis 2011; 7: 531-4). Nevertheless, the vast majority of the bariatric surgery community is in good agreement on how to calculate %EWL (Deitel; Surg Obes Relat Dis 2011; 7: 534-5). In fact, only some US surgeons still use the Metropolitan Life Height-Weight Tables when calculating %EWL. Therefore, I believe that this problem is having probably not enough relevance and thus does not need to be mentioned here.	Sentence has been removed

Com-ment #	Page	Line	Agency/ Organisation	Comment	Reply
18	15	359	IQWiG	What could be added as a potential problem is the fact that mean BMI in the 4 included RCTs ranged between 39 and 49 kg/m2. This BMI is quite far away from the manufacturer's concept of offering a treatment option for obese but not morbidly obese patients. In addition, it is well possible that effect sizes are larger in patients with BMI > 40, so that these results represent an overestimation when counselling for patients with lower BMI.	Limitation has been added
19	17		HIQA	Suggest slight word change: EndoBarrier®/duodenal-jejunal bypass sleeve (DJBS): impermeable flouropolymer sleeve that is placed **endoscopically** via the mouth	Word has been changed
20	17	395	IQWiG	In the table line on "intervention", the word "bowl" needs to be replaced by "bowel". I would also suggest to write: "The presumed effects of DJBS are based on …"	'bowl' has been corrected and sentence has been rephrased
21	18	417	GYMESZI	Deviation from Project Plan: Population description supplemented with "or grade II (BMI 35-39.9) with comorbidities")	Was left unchanged
22	18	417	"A Gemelli" University Hospital	Scope/deviation from project Plan: In the section outcome the transition to bariatric surgery seems not appropriate. It could be considered as adverse event	Transition to bariatric surgery has been excluded as an outcome parameter in the second reversion. Firstly, because of the reviewer's comment that it may also be an adverse event and secondly, because the therapeutic aim of the DJBS has changed from weight loss to improvement of glycemic control
23	26	684	HIQA	Can you also give 22.5 million as a percentage of the European population (as you do in the next section for 52.8 million". Also, these figures are clearly at odds with each other, would it be possible to briefly explain the very big difference in the estimates – do they reflect a trend?	Unfortunately the WHO document does not provide further details on percentages
24	26	721	HVB	„management of depression": I suggest management of psychosocial problems or psychological distress (it´s broader, and not every DM-patient is depressive, but has to cope with stress or problems in the family that upset.	Has been rephrased
25	28	825	IQWiG	Typo: „paitents"	Has been corrected
26	28	825	HVB	patients (instead of paitents)	Has been corrected

Com-ment #	Page	Line	Agency/ Organisation	Comment	Reply
27	31	931 to 934	IQWiG	This paragraph describes that surgeons or gastroenterologists are required to insert the device. Therefore, this paragraph should be moved under the heading “personnel and technical requirements”.	Paragraph has been moved
28	32	974	IQWiG	It is unclear what is meant by “secondary care”. Since many bariatric surgery centres are located in tertiary care hospitals, it would be more appropriate to speak of secondary or tertiary care. (The same wording should probably be used on the same page in line 939)	Term has been rephrased
29	32	952	HVB	“...via one oder two...” instead of “via of one”?	Has been corrected
30	33	1000	HVB	Dietary councelling (better than diet supervision)	Has been rephrased
31	36	1111	IQWiG	Typo: „arbirtrary“	Has been corrected
32	38	1167	IQWiG	As stated above (comment regarding page 7, line 130), it remains questionable why the study by Gersin was considered to address a different research question as compared to the other 3 studies.	Comment is unclear; Tarnoff, Schouten and Gersin were categorised into those group of studies that address obesity as primary condition whereas Rodriguez was defined as study addressing Type 2 DM (as outlined in the inclusion criteria of study description)
33	38	1173	IQWiG	It appears doubtful that no trial results are available to compare the rates of patients, in whom bariatric surgery was performed. i. In the study by Tarnoff et al., I read the following: “The five explanted patients were not included in this analysis because they went on to have gastric bypass surgery within weeks of the explantation.” Therefore, it is clear that at least 5/26 patients went onto bariatric surgery. ii. It also should be mentioned here, that some of the studies used the JBJS as a measure for preoperative weight loss, and in fact all study patients were scheduled for bariatric surgery. Gersin states that his trial had the objective to study JBJS as method for “Weight loss before bariatric surgery to decrease perioperative complications.” Furthermore, Gersin et al. reported on bariatric surgery: “Of the 21 DJBL subjects, 12 underwent a bariatric surgical procedure (9 RYGB, 3 adjustable gastric bands)	Transition to bariatric surgery has been excluded as an outcome parameter in the second reversion. Firstly, because of the reviewer’s comment that it may also be an adverse event and secondly, because the therapeutic aim of the DJBS has changed from weight loss to improvement of glycemic control

Com-ment #	Page	Line	Agency/ Organisation	Comment	Reply
				while the clinical trial was active." This information is missing in the present report.	
34	49	1264	HVB	Type	Has been corrected
35	57	1555	IQWiG	It would be helpful to state the number of non-randomized controlled trials in the trial flow sheet, even if there were zero.	Number of non-randomised controlled trials has been stated
36	58	1571	IQWiG	I would have thought that the "description of the evidence that was used" would include not only a description of patients but also a description of risk of bias. Why not add a few sentences here to summarize the information contained in table 13?	Description on risk of bias has been included; furthermore, description of evidence has been extended to include evidence on safety
37	59	Table 7	HIQA	Data on mean baseline weight and BMI have a +/-, which I presume is SD but is unlabelled	Label has been included
38	59	Table 7	IQWiG	In the line labelled "comparator", the sham procedure should be explained, e.g. by writing "sham upper endoscopy with mock implantation"	Sham procedure has been explained
39	59	3	HIQA	Table 7 & 8 Minor wording change: ‚Mean weigh in' not ‚'mean weight in'	Comment not relevant (was misunderstanding and clarified with HIQA)
40	60	Table 7	IQWiG	What does the small "+" symbol (after EWL in % in the first column) stand for?	Symbol is explained in table legend; symbol has been changed to avoid confusion with mathematical formulas
41	60	Table 7	IQWiG	Why does the table have no extra line for results on "transition to bariatric surgery"? This outcome is mentioned on page 38.	Transition to bariatric surgery has been excluded as an outcome parameter in the second reversion. Firstly, because of the reviewer's comment that it may also be an adverse event and secondly, because the therapeutic aim of the DJBS has changed from weight loss to improvement of glycemic control
42	60		HVB	intervention:143/114-189 control: 138/86-160: how to interpret the kg (schouten 2010)? Baseline/follow up? Where is the second range?	Explanation in first column has been added (figures after the slash present ranges)

Comment #	Page	Line	Agency/ Organisation	Comment	Reply
43	61	Table 7	IQWiG	Tarnoff et al. provided HbA1c results on only 4 patients (1 vs. 3). Such data can be extracted into this table here, but are much too thin for reporting them in the results section or the summary.	Results from Tarnoff on HbA1c have been excluded from summaries and result reporting
44	61		HVB	Turnoff 2009: HbA1c baseline/ follow up: control: 12.6/7.8 [-4.8]: only by diet after 3 months, no change in medication??? Not a good matching with an intervention group with HbA1c 6, 63% at baseline. Are the data correct? High differences in HbA1c-baseline data between intervention und control	See previous comment; results are probably due to very low number of patients in whom HbA1c has been measured
45	64	Table 8	IQWiG	Many readers will wonder whether the two publications by Escalona (2010 and 2012) truly contained separate non-overlapping groups of patients. Perhaps this problem should be addressed in a footnote: "It can be ruled out that the two articles by Escalona et al. reported on overlapping patient groups. While the first article was submitted in May 2009, the second study was conducted from March 2009 to October 2010."	Footnote has been included
46	64	Table 8	IQWiG	Footnote 24 is difficult to understand, because there is a large unexplained difference between the number in the table (n= 81) and the number in the footnote (n= 54).	Footnote was rephrased
47	66	Table 9	IQWiG	The table contains weight loss results only in the format of absolute kg lost. As %EWL is a more appropriate outcome measure, this data should be added here as a separate line.	Comment unclear; all GRADE tables contain % EWL as outcome parameter
48	66	Table 9	IQWiG	Footnote 37 ends with the word "relatively", and it appears as if some words were lost here. In addition, the lack of power calculations should not be considered under "limitations", because the limitations address qualitative risk of bias. Quantitative imprecision is already included in the column "other modifying factors", where "imprecise/sparse data" are correctly mentioned as one of the bigger problems of this data.	Sentence has been completed Lack of power calculation has been removed
49	66	Table 9	IQWiG	In footnote 38, there is again a mixture between qualitative bias and quantitative imprecision. Furthermore, it is mentioned here that "no blinding of operators" was present in any of the trials. The surgeon or gastroenterologist, who implants the device, (i.e. the operator) can impossibly be blinded and any discussion of this issue is absurd. Please use the same terminology here as in Table 13 (Cochrane Risk-of-Bias tool).	Footnotes have been corrected

Com-ment #	Page	Line	Agency/ Organisation	Comment	Reply
50	71	Table 12	IQWiG	There are few typos in this table: Change “Dez” to “Dec” and “Mulit-” to “Multi-“.	Have been corrected
51	72	Table 13	IQWiG	Allocation concealment is described as “clear” for two RCTs, but when reading the methods sections of these papers I find only information about the generation of the random sequence: i. Gersin et al. write: “Subjects were assigned to a treatment arm based on a computer-generated randomization schedule prepared by the sponsor. The randomization was balanced by using randomly permuted blocks and stratified by clinical site.” ii. Schouten et al. write: “Patients were assigned to 1 of 2 treatment groups (diet control or device) based on a computer generated randomization schedule after informed consent was obtained and signed by both patient and surgeon. Because of the design of the study (efficacy), randomization was employed in a 3:1 fashion favoring the device by using randomly permuted blocks stratified by center.” Both articles fail to contain any description of a sealed envelope, telephone or internet randomization process. Therefore, I would rather write “not clear”, unless there was additional information from the trialists available.	Entries in risk of bias checklist (allocation concealment) in Gersin and Schouten study have been changed
52	72	Table 13	IQWiG	It would nice if the reader could learn from a footnote, why all studies were considered to possibly suffer from selective outcome reporting. If none of these trials was registered, this should be shortly mentioned.	Column of selective outcome reporting has been revised; footnote on studies that are not registered has been included
53	74	Table 14	IQWiG	See comment above (regarding page 14, line 351)	Entry has been rephrased
54	74	Table 14	IQWiG	A few other aspects might be relevant when judging on the applicability of the studies: i. The DJBS was examined mainly in patients with a BMI >40, whereas the company aims at the population with a BMI < 40. Therefore it is possible that effectiveness in terms of weight loss was overestimated. On the other hand, general side effects were possibly overestimated due to the higher risk of complications with increasing BMI. ii. The surgeon’s technical expertise likely determines the risk for local side effects. If being introduced as a new treatment method in European hospitals, the implantation of the EndoBarrier device will certainly be accompanied by a learning curve. Schouten et al.	Both issues have been included into table 14 (now table 15)

Comment #	Page	Line	Agency/ Organisation	Comment	Reply
				even present data on the presence of a learning curve.	
55	74	Table 14	IQWiG	In the line on “comparators”, the lack of pharmacotherapy is criticized. As explained above, it can be assumed that all diabetic patients who were on drugs simply continued their drug regimen during the course of the study. Therefore, you could only criticize here that drug therapy was not intensified in the control group.	Has been rephrased
56	74	Table 14	IQWiG	Please correct the typo in “microangiopahtic”	Has been corrected
57	124		HIQA	The following does not quite make sense *‘In 3 RCTs that investigated 137 patients in total, overweight was reduced by 12-22 % in the intervention group and by 3-7 % in the control group within a follow’* – should this read ‘excess weight was reduced by 12-22%’?	Has been corrected
58	126		HIQA	As above (page 14)– re the accuracy of the wording supporting the conclusion in relation to the comparator for the procedure in patients with T2DM	Was rephrased
59	Appendix 3		"A Gemelli" University Hospital	Ethical considerations: Maybe for ethical aspect there is a concern if we consider the differences in bariatric surgery as comparator in term of difference in the invasiveness	Invasiveness has been addressed in section “ethical considerations”
60	General		GYMESZI	extracted data/applicability/transparency: only REA of DJBS vs. diet and sham procedure were assessed	Comment unclear; limitations of diet and sham as comparators have been described in report already

APPENDIX 5: PROJECT PLAN

Duodenal-jejunal bypass sleeve (EndoBarrier®) for the treatment of obesity with or without Type 2 diabetes mellitus

Project ID: WP5-SB-11

Project description and planning

Ludwig Boltzmann Institute for Health Technology Assessment/Austria

Contents:

A. VERSION LOG

Version number	Date	Name (Initials)	Modification	Reason for the modification
V1	05/04/13 (EUnetHTA reviewer, SAG, public consultation comments)	Ingrid Zechmeister-Koss (IZ)	• Project title: 'with/without Type 2 diabetes mellitus' added • B 3.0 (project scope/population): BMI has been changed • B 3.0 (project scope/outcome): Justification for endpoint selection has been included • B 4.0: Justification of GRADE-methodology included • B 4.0 (assessment elements) and B 3.0 (project scope/outcome): research question on element D0011 and 'outcomes' in project scope have been extended	• title should reflect more precisely the population the device is intended for • according to stakeholder comment no.2 + after consultation of further guidelines • because of stakeholder comment no. 8 • because of stakeholder comment no. 13 • according to stakeholder comment no.21
V2	26/04/13 (manufacturer comments)	Ingrid Zechmeister-Koss (IZ)	• PICO question 'population': changed into 'obesity grade III or Type 2 diabetes mellitus + obesity ≥ grade II" • PICO question 'intervention': 'gut hormonal signalling changes" have been added to description of intervention • PICO question 'comparator': comparator was added for both indications separately PICO question 'outcome': surrogate outcomes have been categorised into 'primary surrogate outcomes' (diabetes-related) and 'secondary surrogate outcomes' Assessment elements in domain 'health problem and current use of technology': research	• manufacturer stresses that diabetes needs to be added as main indication • according to manufacturer comments • as a result from changing 'population' and according to manufacturer comment • according to manufacturer comments • as a result from changing PICO question

			questions have been adapted to represent Type 2 DM as indication more precisely Milestones/Deliverables: time schedule has been extended Participants: list of participants has been restricted to those that sent COI statement	• due to delayed manufacturer comments and pilot process changes • COI statement was not sent by all dedicated reviewers

B. PROJECT PLAN

1.0 PARTICIPANTS

#	Name	Role in the project	Agency	Country
1.	Ingrid Zechmeister-Koss	Author(s)	Ludwig Boltzmann Institute for Health Technology Assessment	Austria
2.	Mirjana Huic Stefan Fischer	Co-Author(s)	Agency for Quality and Accreditation in Health Care and Social Welfare Ludwig Boltzmann Institute for Health Technology Assessment	Croatia Austria
3.	Shelley O'Neill Patricia Harrington	Reviewer	Health Information and Quality Authority (HIQA)	Ireland
4.	Bettina Maringer	Reviewer	Hauptverband der Österreichischen Sozialversicherungsträger	Austria
5.	Zoltan Huszti	Reviewer	National Institute for Quality and Organisational Development in Health Care and Medicine (GYEMSZI)	Hungary
6.	Iñaki Imaz	Reviewer	Instituto de Salud Carlos III (ISC III)	Spain
7.	Katrine Frønsdal Tove Ringerike	Reviewer	Norwegian Knowledge Centre for the Health Services (NOKC)	Norway
8.	Jana Skoupá	Reviewer	Ministry of Health (Czech Republic)	Czech Republic
9.	To be confirmed	External Reviewer(s)		

1.1 PROJECT STAKEHOLDERS

Please describe/list project stakeholders*.

Organisation	Contact (name, e-mail, tel)	Comments
GI Dynamics	17th December 2012: dan@purecommunicationsinc.com (Dan Budwick for media inquires) 18th January 2013: info@gidynamics.com (head office for general inquires)	The draft Project Plan was submitted on 21st of March 2013, the manufacturer submitted their

* Here the term 'stakeholder' has a generic meaning that goes beyond (yet may include) the identified EUnetHTA Stakeholder groups (as described in the EUnetHTA Stakeholder Policy).

	21st March 2013: info@gidynamics.com – response received from Gerd Gottschalk (ggottschalk@gidynamics.com)	comments and relevant publications on the 12th of April 2013

2.0 PROJECT INTRODUCTION/RATIONALE

Project introduction/rationale
The rational for this pilot assessment report is to test the capacity of national HTA bodies to collaboratively produce structured rapid Core HTA information on pharmaceuticals (strand A) and other medical technologies, such as medical devices, surgical interventions or diagnostics (strand B). In addition, the application (transportation) of those collaboratively produced HTAs in the national contexts will be tested.

3.0 PROJECT SCOPE AND OBJECTIVES

	List of project objectives	**Indicator (and target)**
1.	To test the capacity of national HTA bodies to collaboratively produce structured rapid Core HTA	Production of 1 pilot rapid assessment
2.	To test the application of these collaboratively produced rapid assessments into a national/local context	Production of ≥1 national/local report per pilot rapid assessment

This pilot rapid assessment addresses the research question whether the placement of a duodenal jejunal bypass sleeve in adult obese patients (with or without Type 2 diabetes mellitus) is more effective and/or safer than conservative therapy (e.g., diet), pharmacotherapy, bariatric surgery or sham procedure. According to the Core Health Technology Assessment Model (Core HTA Model) for pharmaceutical, PICO and scope will be re- check after assessment of the first two domains (health problem and current use of the technology, description and technical characteristics).

Description	**Project scope**
Population	men and women (≥18 years), with: • obesity III (BMI ≥40) or • Type 2 diabetes mellitus + obesity ≥ grade II (Body Mass Index/BMI ≥35-40) Mesh-terms: Obesity; Obesity, Morbid; Diabetes Mellitus, Type 2;

	ICD-10 code: E 66, E 11 Intended use: treatment
Intervention	EndoBarrier®/duodenal-jejunal bypass sleeve (DJBS): impermeable fluoropolymer sleeve that is placed endoscopically via the mouth and anchored in the first part of the small bowel in a procedure that takes about 30 minutes. The device remains in the bowel up to 12 months and is removed hereafter. The uptake of nutrients and calories from the first part of the small bowel (duodenum and first section of jejunum) are reduced. The effects of DJBS are based on gut hormonal signalling changes which lead to normalization of glycaemic control. Mesh-terms: Jejunum/su [Surgery]; Duodenum/su [Surgery]; Bariatric Surgery
Comparison	• primary comparator for indication obesity grade III: bariatric surgery and endoscopic techniques (gastric band, gastric balloon, gastric bypass, etc.) • primary comparator for indication 'Type 2 diabetes mellitus + obesity ≥ grade II' : anti-diabetes pharmacotherapy and lifestyle changes • further comparators: sham procedures Mesh-terms: N/A* Rationale for choosing the comparators: a) evidence-based clinical guidelines and HTA-reports [Agence d'évaluation des technologies et des modes d'intervention en santé 2006, Hauner 2007, National Institute for Health and Clinical Excellence 2006a, National Institute for Health and Clinical Excellence 2007, National Institute for Health and Clinical Excellence 2011, National Institute for Health and Clinical Excellence 2012, National Institutes of Health 2009, Rieder 2004, Shekelle 2004, The Royal College of Physicians 2008, World Health Organization 2006] b) manufacturer comment
Outcomes	<u>Efficacy</u>: • weight loss (temporary, long-term >12 months to 36 months) • transition to bariatric surgery (gastric bypass surgery) • reduction in drug use (e.g. diabetic medication, antihypertensive medication) • health related quality of life • reduction in cardiovascular events (myocardial infarction, stroke, etc.)

	• reduction in diabetes-associated microangiopathic complications (diabetic nephropathy, retinopathy) • reduction in further obesity-related morbidity (e.g. musculoskeletal morbidity) • overall mortality • surrogate parameters: primary surrogate parameters: HbA1c, fasting blood glucose, insulin levels (short term and long-term after 12 to 36 months) Secondary surrogate parameters: blood pressure, further markers of metabolic function: C-peptide, LDL, triglyceride levels (short term and long-term after 12 to 36 months)

	Safety: • AEs and serious AEs (short term, long term) during/after implantation, after explantation (e.g. device removal, abdominal pain, procedure related mortality, etc.) Rationale: Of primary interest are patient-relevant endpoints including objective (mortality) and subjective endpoints. Surrogate markers (e.g. for metabolic function) will be extracted but they will have little weight for assessing benefit-harm relations. The selection of endpoints is based on recommendations from the EUnetHTA methods guideline on clinical endpoints [European Network for Health Technology Assessment (EUnetHTA) 2013a]
Study design	Efficacy: prospective controlled trials Safety: all prospective studies

* for the search ‚population' will be linked with ‚intervention' but not with 'comparator', hence MesH-terms are not applicable.

4.0 PROJECT APPROACH AND METHOD

Project approach and method

The report will be based on a systematic literature search, complemented by a SCOPUS-handsearch in the following sources:

- biomedical databases (Medline via Ovid, Embase)
- The Cochrane Library and Centre for Reviews and Dissemination
- In addition, the following clinical trials registries will be assessed, for registered ongoing clinical trials or observational studies: ClincalTrials.gov, ISRCTN, metaRegister of Controlled Trials (mRCT) and International Clinical Trials Registry Platform (ICTRP).
- Request to manufacturer (GI-Dynamics)

Relevant articles for the report-domains will be selected by the first author and co-author independently. References will be included or excluded according to the Population-Intervention-Control-Outcome (PICO)-scheme described earlier. In terms of study design, prospective controlled trials are selected for answering questions related to the domain 'clinical effectiveness', while for questions in the 'safety domain' any prospective study will be included. For other domains (health problem and current use of the technology, description and technical characteristics), no restrictions concerning study design are applied.

If questions from the domains 'Health problem and current use of technology' and 'Description and technical characteristics of technology' cannot be answered by the information retrieved from the systematic search described above, an additional handsearch in specific information sources (e.g. databases for clinical guidelines) will be carried out.

The quality of the studies will be analysed by using the Cochrane risk of bias checklist (for randomised controlled trials/RCTs) and checklist for non-randomised studies.

From the selected studies, study characteristics, results concerning efficacy/effectiveness and safety will be extracted into a data extraction table covering the following elements (see subsequent table). Efficacy and safety will be assessed by using the GRADE-methodology as this methodology allows for a transparent summary of the evidence in a qualitative manner. Since we do not expect a sufficient number of homogeneous RCTs we will not carry out a quantitative meta-analysis.

Preliminary evidence table
Author, year, reference number
Country
Sponsor
Intervention/product
Comparator
Study design
Number of patients
Inclusion criteria
Patient characteristics: age, sex
Mean baseline weight in kg (BMI in kg/m²)
Author Disclosure (Conflict of interest)
Follow-up (months)
Loss-to-follow-up, n (%)
Outcomes
Efficacy
Mean weight at baseline/follow-up in kg [mean weight loss in kg (EWL in %)]
Reduction in drug use in % of patients who ceased drug treatment
Quality of life
Reduction in cardiovascular events
Reduction in diabetes-associated microangiopathic complications
Overall mortality
Surrogate parameters at baseline/follow-up (HbA1c, fasting blood glucose, insulin, C-peptide, LDL, triglyceride levels)
Safety
Adverse events (AE) in n (%) of patients
Description of AE in n (%) of patients
Serious adverse events (serious AEs) in n (%) of patients
Description of serious AEs in n (%) of patients

Selected assessment elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessments elements contained in the document 'Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals'. Additionally, assessment elements from other EUnetHTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/merged with the existing questions if deemed relevant.

ID	Domain	Topic	Issue *[copy all the generic questions from the Model for Rapid REA in this column]*	Relevance in this assessment Yes/No	Reason for non-relevance/ Preliminary research question(s) *[If you selected yes, translate the generic issue into actual research question(s). If you selected no, provide an explanation why you deemed this element as not relevant.]*	Source of assessment element *[Indicate from which HTA Core Model Application the assessment element was selected from: REA Model, Model for Medical Surgical Intervention, Diagnostics, Screening]*
Health problem and current use of technology						
A0002a	Health Problem and Current Use of the Technology	Target Condition	What is the disease or health condition which is in the scope of this assessment?	Yes	What is the precise definition of obesity and of Type 2 diabetes mellitus (DM) and which diagnosis is given to obesity and Type 2 DM according to ICD-10?	HTA Core Model for Rapid Relative Effectiveness Analysis (REA)
A0002b	Health Problem and Current Use of the Technology	Target Condition	What is the disease or health condition which is in the scope of this assessment?	Yes	What are the main features of obesity and of Type 2 DM?	HTA Core Model for Rapid REA
A0003	Health Problem and Current Use of the Technology	Target Condition	Which are the known risk factors for the condition?	Yes	What are the known risk factors for obesity and for Type 2 DM?	HTA Core Model for Rapid REA
A0004a	Health Problem and Current Use of the Technology	Target Condition	What is the natural course of the condition?	Yes	What is the natural course of obesity and of Type 2 DM?	HTA Core Model for Rapid REA
A0004b	Health Problem and Current Use of the Technology	Target Condition	What is the natural course of the condition?	Yes	What are the adverse health consequences of obesity and of Type 2 DM?	HTA Core Model for Rapid REA

A0005	Health Problem and Current Use of the Technology	Target Condition	What is the burden of disease for the patient?	Yes	What are the main symptoms and consequences for the patients?	HTA Core Model for Rapid REA
A0006	Health Problem and Current Use of the Technology	Target Condition	What is the burden of the disease for society?	Yes	What is the burden of the obesity and of Type 2DM for society (prevalence, incidence, costs)?	HTA Core Model for Rapid REA
A0007	Health Problem and Current Use of the Technology	Target Population	What is the target population in this assessment?	Yes	What is the target population in this assessment?	HTA Core Model for Rapid REA
A0023	Health Problem and Current Use of the Technology	Target Population	How many people belong to the target population?	No	As this is mainly required for budget impact analysis, this is outside the scope of the assessment (overall burden of disease answered by A006 anyway)	HTA Core Model for Rapid REA
A0001	Health Problem and Current Use of the Technology	Utilisation	For which (all) health conditions and populations and for which purposes is the technology used?	Yes	For which indication/ for what purposes is the duodenal-jejunal bypass sleeve used and are there any contraindications?	HTA Core Model for rapid REA
A0011	Health Problem and Current Use of the Technology	Utilisation	How much are the technologies utilised?	Yes	What is the expected annual utilisation of the duodenal-jejunal bypass?	HTA Core Model for Rapid REA
A0024	Health Problem and Current Use of the Technology	Current Management of the Condition	How is the health condition currently diagnosed according to published guidelines and in practice?	Yes	How are obesity and Type 2 DM currently diagnosed according to published guidelines and in practice?	HTA Core Model for Rapid REA
A0025	Health Problem and Current Use of the Technology	Current Management of the Condition	How is the health condition currently managed according to published guidelines and in practice?	Yes	How are obesity and Type 2 DM currently managed according to published guidelines and in practice?	HTA Core Model for Rapid REA
A0020	Health Problem and Current Use of the Technology	Regulatory Status	What is the market authorization status of the technology?	Yes	What is the market authorization status of the duodenal-jejunal bypass sleeve (Endobarrier®) in Europe?	HTA Core Model for Rapid REA

A0021	Health Problem and Current Use of the Technology	Regulatory Status	What is the reimbursement status of the technology?	Yes	What is the reimbursement status of the duodenal-jejunal bypass sleeve in Europe?	HTA Core Model for Rapid REA
Description and technical characteristics of technology						
B0001	Description and technical characteristics of technology	Features of the technology	What is the technology and the comparator?	Yes	What is the duodenal-jejunal bypass sleeve and what are evidence-based alternatives?	HTA Core Model for Rapid REA
B0002	Description and technical characteristics of technology	Features of the technology	What is the approved indication and claimed benefit of the technology and the comparator?	Yes	What is the approved indication and claimed benefit of the duodenal-jejunal bypass sleeve and the comparators?	HTA Core Model for Rapid REA
B0003	Description and technical characteristics of technology	Features of the technology	What is the phase of development and implementation of the technology and the comparator?	Yes	What is the phase of development and implementation of the duodenal-jejunal bypass sleeve and the comparators?	HTA Core Model for Rapid REA
B0004	Description and technical characteristics of technology	Features of the technology	Who performs or administers the technology and the comparator?	Yes	Who performs the duodenal-jejunal bypass sleeve and who performs or administers the comparators?	HTA Core Model for Rapid REA
B0005	Description and technical characteristics of technology	Features of the technology	In what context and level of care is the technology and the comparator used?	Yes	In what context and level of care are the duodenal-jejunal bypass sleeve and the comparators used?	HTA Core Model for Rapid REA
B0008	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator?	Yes	What kind of special premises are needed to use the duodenal-jejunal bypass sleeve and the comparators?	HTA Core Model for Rapid REA
B0009	Description and technical characteristics of technology	Investments and tools required to use the technology	What supplies are needed to use the technology and the comparator?	Yes	What supplies and equipment are needed to use the bypass sleeve and the comparators?	HTA Core Model for Rapid REA

B0010	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of data and records are needed to monitor the use of the technology and the comparator?	No	Not relevant for the purpose of this pilot assessment	HTA Core Model for Rapid REA
B0011	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of registry is needed to monitor the use of the technology and comparator?	No	Not relevant for the purpose of this pilot assessment	HTA Core Model for Rapid REA
Safety						
C0001	Safety	Patient safety	What kind of harm can use of the technology cause to the patient?	Yes	What are the AEs and serious AEs in patients with a duodenal-jejunal bypass sleeve?	HTA Core Model for Rapid REA
C0002	Safety	Patient safety	What is the dose relatedness of the harm to patients?	Yes	Is there a relationship between the length of time the bypass sleeve has been implanted and the harm to patients?	HTA Core Model for Rapid REA
C0004	Safety	Patient safety	How does the frequency or severity of harm change over time or in different settings?	Yes	How does the frequency or severity of harm change over time or in different settings?	HTA Core Model for Rapid REA
C0005	Safety	Patient safety	What are the susceptible patient groups that are more likely to be harmed?	Yes	What are the susceptible patient groups that are more likely to be harmed?	HTA Core Model for Rapid REA
C0007	Safety	Patient safety	What is the user dependent harm?	Yes	Can AEs be caused by the behaviour of patients, professionals or manufacturers?	HTA Core Model for Rapid REA
C0008	Safety	Patient safety	What is the safety of the technology in relation to the comparator?	Yes	What is the safety of the bypass sleeve in relation to conservative therapy, pharmacotherapy, bariatric surgery or sham-procedure	HTA Core Model for Rapid REA
C0040	Safety	Environmental safety	What kind of harm is there for public and environment?	No	Not relevant for the technology	HTA Core Model for Rapid REA
Clinical effectiveness						

D0001	Clinical Effectiveness	Mortality	What is the intended beneficial effect of the intervention on overall mortality?	Yes	What is the effect of the intervention on overall mortality?	HTA Core Model for Rapid REA
D0002	Clinical Effectiveness	Mortality	What is the intended beneficial effect on the disease-specific mortality?	Yes	What is the effect on the disease-specific mortality (mortality related to obesity and Type 2 diabetes?	HTA Core Model for Rapid REA
D0003	Clinical Effectiveness	Mortality	What is the effect of the intervention on the mortality due to other causes than the target disease?	Yes	What is the effect of the intervention on the mortality due to other causes than the target diseases obesity and Type 2 diabetes?	HTA Core Model for Rapid REA
D0004	Clinical Effectiveness	Mortality	What is the rate of direct mortality related to the use of the technology?	Yes	What is the rate of direct mortality related to the use of the duodenal-jejunal bypass sleeve?	HTA Core Model for Rapid REA
D0005	Clinical Effectiveness	Morbidity	How does the technology affect symptoms and findings?	Yes	How does the duodenal-jejunal bypass sleeve affect further outcomes compared to standard/usual care or practice[55] • weight loss (temporary, long-term) • transition to bariatric surgery (gastric bypass surgery) • reduction in drug use (e.g. diabetic medication, antihypertensive medication) • surrogate parameters (blood pressure, markers of metabolic function: HbA1c, fasting blood glucose, insulin, C-peptide, LDL, triglyceride levels)	HTA Core Model for Rapid REA
D0006	Clinical Effectiveness	Morbidity	How does the technology affect progression of disease?	No	Addressed in D0005?	HTA Core Model for Rapid REA
D0008	Clinical Effectiveness	Morbidity	What is the rate of direct morbidity related to the use of the technology?	No	Addressed in C001	HTA Core Model for Rapid REA

[55] Standard care includes all measures that have been defined in the PICO-scheme under ‚comparator'

D0011	Clinical Effectiveness	Function	What is the effect of the technology on patient's body functions?	Yes	What is the effect of the duodenal-jejunal bypass sleeve on • reduction in cardiovascular events (myocardial infarction, stroke, etc.) • reduction in diabetes-associated microangiopathic complications (diabetic nephropathy, retinopathy) • reduction in further obesity-related morbidity (e.g. musculoskeletal morbidity) compared to standard/usual care or practice	HTA Core Model for Rapid REA
D0016	Clinical Effectiveness	Function	How does the use of technology affect activities of daily living?	Yes	How does the use of duodenal-jejunal bypass sleeve affect activities of daily living compared to standard/usual care or practice?	HTA Core Model for Rapid REA
D0012	Clinical Effectiveness	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes	What is the effect of the duodenal-jejunal bypass sleeve on generic health-related quality of life compared to standard/usual care or practice?	HTA Core Model for Rapid REA
D0013	Clinical Effectiveness	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes	What is the effect of the duodenal-jejunal bypass sleeve on disease-specific (obesity and Type 2-diabetes) quality of life compared to standard/usual care or practice?	HTA Core Model for Rapid REA
D0017	Clinical Effectiveness	Patient satisfaction	Was the use of the technology worthwhile?	Yes	Were patients satisfied overall with the duodenal-jejunal bypass sleeve?	HTA Core Model for Rapid REA
D0018	Clinical Effectiveness	Patient satisfaction	Is the patient willing to use the technology?	Yes	Would the patient be willing to use the duodenal-jejunal bypass sleeve again?	HTA Core Model for Rapid REA
D0023	Clinical Effectiveness	Change in management	How does the technology modify the need for other technologies and use of resources?	Yes	How does the duodenal-jejunal bypass sleeve modify the need for the use of other technologies resources?	HTA Core Model for Rapid REA

Checklist for potential ethical, organisational, social and legal aspects

The following checklist should be considered in order to determine whether there are specific ethical, organisational, social and legal aspects which also need to be addressed. Since the assessment is comparative in nature, only new issues should be dealt with, which arise from a difference between the technology to be assessed and its major comparator(s). Already known problems/issues with regard to ethical, organisational, social and legal aspects which are common to the technology to be assessed and its comparator(s) will, as a rule, not be addressed, as it is not to be expected that the addition of a new technology will lead to changes.

If a question is answered with 'yes', further analysis of these issues may be warranted. If they are answered with no, the domains need not be dealt with further.

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparators require organisational changes? Capacities and training (learning the procedure) will be required for endoscope placement of the device and its removal up to one year later	Yes
2.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be organisationally relevant? Probably, the device may lead to a reduction in surgical/endoscopic procedures performed for treating obesity, and thus may lead to some excess capacities for other surgical interventions, if successful.	Yes
3. **Social**:	
3.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be socially relevant?	No
4. **Legal**:	
4.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s)	No

give rise to any legal issues?	
4.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be legally relevant?	No

5.0 ORGANISATION OF THE WORK

5.1 MILESTONES AND DELIVERABLE(S)

Milestones/Deliverables	**Start date**	**End date**
Project duration	**12/2012**	**05/2013**
Pilot's team building	12/2012	01/2013
Scoping phase	01/2013	06/04/2013
Contact with manufacturer (Project Plan draft, request for further information)	01/2013	03/2013
Consultation of draft Project Plan (Public consultation and Stakeholder Forum)	21/03/2013	04/04/2013
Final Project Plan	04/04/2013	29/04/2013
Assessment phase	03/2013	24/06/2013
First draft available		24/05/2013
Review by dedicated reviewers	24/05/2013	03/06/2013
Second draft available		14/06/2013
Review by ≥ 1 external clinical expert, manufacturer, patient representatives, WP5 members	14/06/2013	24/06/2013
Final pilot rapid assessment		05/07/2013
Local Reports (if applicable)		
Local (national or regional) REA N°1 [*Institution, country*]		
Local (national or regional) REA N°2 [*Institution, country*]		

5.2 MEETINGS

Besides face-to-face meetings mentioned in the Work Plan of WP5, no further face-to-face meetings are planned for this specific project.

Up to 4 e-meetings may be scheduled for this pilot rapid assessment (see section 6.0), if considered necessary.

6.0 COMMUNICATION

Communication Type	Description	Date	Format	Participants/ Distribution
Project Plan draft with timelines	Review of methods and assessment elements chosen, discussion of time-lines	01-03/2013	Permanent e-mail exchange	Author(s), Co-author(s), dedicated reviewers, Coordinating Team
Final Project Plan	Review of methods and assessment elements chosen, discussion of time-lines considering comments from Stakeholder Forum, public, manufacturer	03/2013	E-mail exchange (e-meeting if required)	Author(s), Co-author(s), dedicated reviewers, Coordinating Team
First draft of the pilot assessment	To be reviewed by dedicated reviewers	04/2013	E-mail	Dedicated reviewers
	To discuss comments of dedicated reviewers (optional)	04/2013	E-Mail (e-meetings if required)	Author(s), co-author(s), dedicated reviewers
Second draft of the pilot assessment	To be consulted with ≥1 clinical expert, WP5 members, other potential stakeholders	05/2013	E-mail	≥1 clinical expert, WP5 members, other potential stakeholders

6.1 DISSEMINATION PLAN

The final pilot rapid assessment will be distributed as laid-out in the Work Plan of WP5.

7.0 COLLABORATION WITH STAKEHOLDERS

The Stakeholder Forum as well as the public will be invited to comment on the Project Plan for this pilot rapid assessment. The project plan will be made publicly available on the EUnetHTA website for a period of 10 days.

Further the manufacturer will also receive the draft Project Plan and will be asked for further information (e.g. C/E mark, on-going studies, available evidence).

8.0 COLLABORATION WITH EUnetHTA WPs

For the individual pilot rapid assessment, no collaboration with other WPs is planned.

9.0 RESOURCE PLANNING

9.1 HUMAN RESOURCES

Role	**Total number of person days**	**Source**	
		Staff of participating organisations	**Subcontracting**
Author	60 person days	60 person days	-
Co-Author	30 person days	30 person days	-
Reviewer	3 person days each	3 person days each	-
External reviewer	5 person days	-	5 person days

9.2 OTHER EXPENDITURES

see Appendix

9.3. FINANCING SOURCES

see Appendix

10.0 RISK ANALYSIS

see Appendix

11.0 CONFLICT OF INTEREST MANAGEMENT

Conflicts of interest will be handled according to EUnetHTA JA2 Conflict of Interest Policy. As conflict of interest may be topic dependent, Conflict of interest declarations will be collected from authors and reviewers involved in a specific pilot assessments. Authors and reviewers who declare conflict of interest will be excluded from parts of, or the whole work under this specific topic. However, they may still be included in other pilots.

If external experts are involved in WP5 a Conflict of interest declarations will be collected from them regarding the topic. External experts who declare conflict of interest will be excluded from parts of, or the whole work under this specific topic. However, they may still be included in other pilots.

12.0 EXPECTED OUTCOME(S)

Project outcome(s)
The capacity of national HTA bodies to collaboratively produce structured rapid Core HTA and the translation into local reports will have been proven. Redundancies will have been reduced and therefore efficiency gains achieved. Applicability of the HTA Core Model for Rapid REAs to other technologies will have been elicited and the Model accordingly adapted.

C. REFERENCES (Project Plan)

1. Agence d'évaluation des technologies et des modes d'intervention en santé. Surgical Treatment of Morbid Obesity: An Update. Montréal: AETMIS; 2006.

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8. National Institutes of Health. Bariatric Surgery for Severe Obesity: NIH publication no. 48-4006. 2009.

9. Rieder A, Rathmanner T, Kiefer I, Dorner T, Kunze M. Österreichischer Diabetesbericht; 2004.

10. Shekelle P, Morton S, Maglione M, Suttorp M, Tu W, Li Z, et al. Pharmacological and Surgical Treatment of Obesity. Evidence Report/Technology Assessment No. 103. (Prepared by the Southern California–RAND Evidence-Based Practice Center, Santa Monica, CA, under contract Number 290-02-0003.) Rockville, MD: Agency for Healthcare Research and Quality; 2004.

11. The Royal College of Physicians. Type 2 diabetes. National clinical guideline for primary and secondary care (update). London: The Royal College of Physicians; 2008.

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