EUnetHTA WP5 Joint Action 2 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

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The assessment represents a consolidated view of the non-binding recommendations of the EUnetHTA network members and is in no case the official opinion of the participating institutions or individuals.

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Stakeholder involvement

1) Project Plan

SAG:

1. Genzyme
2. Standing Committee of European Doctors (CPME)
3. Siemens AG Healthcare Sector
4. Eurordis
5. Philips Healthcare
6. Mutualités Libres Onafhankelijke Ziekenfondsen

Answer received, but no comments:

1. Association of the European Self-Medication Industry (AESGP)
2. European Social Insurance Platform (ESIP)

Public consultation:

1. European Diagnostic Manufacturers Association

Manufacturer:

1. GI Dynamics

2) Pilot rapid assessment (V1.2)

Consumers' Organisation:

1. The European Consumer' Organisation

Manufacturer:

1. GI Dynamics

Conflict of interest:

All authors and reviewers involved in the production of this pilot assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA conflicts of interest (COI) statement form.

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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 Européenne (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 Gesundheitswesens; 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	<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, LDL cholesterol, TG levels (short-term and long-term after 12 to 36 months) <u>Safety:</u> - 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/m² are called severely obese and those with BMI >40 kg/m² 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/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].

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	Cancer*	Varicose veins

Relative risk (RR)	Associated with metabolic consequences	Associated with excess weight
RR 1-2	Reproductive abnormalities and impaired fertility	Musculoskeletal problems
	Polycystic ovaries	Bad back
	Skin complications	Stress incontinence
	Cataract	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, management 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)?

Element ID	Research question
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)?
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 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, 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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