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Study Protocol: A randomized controlled trial of a duodenal-jejunal bypass sleeve device (EndoBarrier®) compared with standard medical therapy for the management of obese subjects with type 2 diabetes mellitus.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018598
Article Type:	Protocol
Date Submitted by the Author:	12-Jul-2017
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism, Surgery
Keywords:	Obesity, Type 2 diabetes mellitus, Endobarrier, Duodenal-jejunal bypass sleeve, Duodenal-jejunal bypass liner

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Study Protocol: A randomized controlled trial of a duodenal-jejunal bypass sleeve device (EndoBarrier®) compared with standard medical therapy for the management of obese subjects with type 2 diabetes mellitus.

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Abstract

Introduction: The prevalence of obesity and obesity-related diseases, including type 2 diabetes mellitus (T2DM) is increasing. Exclusion of the foregut, as occurs in Roux-en-Y gastric bypass, has a key role in the metabolic improvements that occur following bariatric surgery, which are independent of weight-loss. Endoscopically-placed duodenal-jejunal bypass sleeve (DJBS) devices, such as the EndoBarrier[®] (GI Dynamics Inc, Lexington MA), have been designed to create an impermeable barrier between chyme exiting the stomach and the mucosa of the duodenum and proximal jejunum. The non-surgical and reversible nature of these devices represents an attractive therapeutic option for patients with obesity and T2DM by potentially improving glycaemic control and reducing their weight.

Methods and Analysis: In this multicentre, randomised, controlled, non-blinded trial, male and female patients aged 18–65 years with a BMI 30–50 kg/m² and inadequately controlled T2DM on oral anti-hyperglycaemic medications (HbA1C 58-97mmol/mol) will be randomised in a 1:1 ratio to receive either the EndoBarrier[®] device (n=80) for 12 months or conventional medical therapy, diet and exercise (n=80). The primary outcome measure will be a reduction in HbA1C by 20% at 12 months. Secondary outcome measures will include percentage weight loss, change in cardiovascular risk factors and medications, quality of life, cost, QALYs accrued and adverse events. Three additional sub-groups will investigate the mechanisms behind the effect of the EndoBarrier[®] device, looking at changes in: gut hormones, metabolites, bile acids, microbiome, food hedonics and preferences, taste, brain reward system responses to food, eating and addictive behaviours, body fat content, insulin sensitivity, and intestinal tissue gene expression.

Ethics and Dissemination: Research ethics approval was granted by Fulham Research Ethics Committee, London, (Reference 14/LO/0871) on 10th July 2014. All subjects will give informed written consent. Study findings will be disseminated through peer-reviewed journals, national and international conferences.

Strengths and Limitations of this study:

- This study will represent the largest randomised controlled trial of the EndoBarrier[®] device compared with conventional medical therapy, diet and exercise over a treatment period of 1 year and will also provide the longest follow-up data (1 year) of any trial to date.
- This study will provide: (1) unique data on the mechanism of action of the DJBS and the effect of foregut exclusion on an individual's metabolic profile, (2) a cost-effectiveness analysis, (3) quality of life assessment outcomes, and (4) extensive safety data.
- The unblinded design of this trial introduces the risk of bias.

Key words: Obesity, Type 2 diabetes mellitus, Endobarrier, Duodenal-jejunal bypass sleeve, Duodenal-jejunal bypass liner

Trial Registration: ISRCTN30845205, ClinicalTrials.gov Identifier NCT02459561

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Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Funding and Acknowledgements:

This project is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and National Institute for Health Research (NIHR) partnership.

This paper presents independent research funded by the EME Programme and supported by the NIHR CRF and BRC at Imperial College Healthcare NHS Trust and University Hospital Southampton NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the EME Programme, the NHS, the NIHR or the Department of Health

This study is being executed with the support of GI Dynamics, Inc. and with kind support of Nutricia Advanced Medical Nutrition for providing oral nutritional supplements. Special thanks are given to Brunel University London and the Wolfson Centre for Translational Research, University of Surrey, for their support in sample analysis and to Professors Desmond Johnston, Jeremy Nicholson, and Elaine Holmes as co-applicants for the trial and for their valuable support in the set-up and design of this trial.

Competing interests statement:

Dr. Miras reports grants from Fractyl, personal fees from Novo Nordisk, and personal fees from Astra Zeneca outside the submitted work.

Dr. Goldstone reports funding supported by UK Medical Research Council and Wellcome Trust, outside of the submitted work.

Prof. Poulter's institution reports grants from HTA, during the conduct of the study.

Dr. le Roux reports grants from Science Foundation Ireland, grants from Health Research Board, during the conduct of the study; other from NovoNordisk, other from GI Dynamics, personal fees from Eli Lilly, grants and personal fees from Johnson and Johnson, personal fees from Sanofi Aventis, personal fees

1 from Astra Zeneca, personal fees from Janssen, personal fees from Bristol-Myers Squibb, personal fees
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Protocol Version

Current version 4.0

Revision chronology:

- Minor amendment 3 29/09/16
 - Protocol V4.1 – number of randomised patients increased from 160 to 170
- Minor amendment 2 11/05/16
 - Extension of funding for 6 months
- Substantial amendment 10/08/15
 - Protocol V4.0 - Changes of inclusion (Section 4.2) and exclusion criteria (section 4.3)
 - Additional correction of minor transcription error in section 5.3
- Minor amendment 1 03/08/15
 - Protocol V3.1 - minor correction of inclusion criteria (section 4.2)
- Substantial amendment 16/03/15
 - Protocol V3.0 - Substantial amendment to protocol
 - Additional amendments to PIS, recruitment advert, business cards, news story.
- Substantial amendment 23/09/14
 - Protocol V2.0 - amendments to duration of liquid diet, questionnaires, blood sampling schedule, testing procedures and addition of biopsies.
 - Additional amendments to PIS, GP/consultant information sheets and letters, participant invitation letters, diet sheets, consent forms and questionnaires.
- Original submission 10/07/14
 - Protocol V1.0

Trial Steering Committee (TSC)

A Trial Steering committee (TSC) with an independent Chair will be appointed and will be responsible for overseeing the progress of the trial. A TSC Charter will be devised to list the roles and responsibilities of the TSC members. TSC will be convened biannually either in person or by teleconference. Two PPI representatives will sit on the Trial Steering Committee and will provide input from a patient perspective at trial meetings.

Trial Management Group (TMG)

The Trial Management Group will be set up by the Chief Investigator (CI). TMG will convene on a monthly basis and will discuss on the recruitment, and other practical aspects of the trial. The TMG will include the CI, Project Manager, ICTU representative and PI at the Southampton site as well as other site staff when appropriate. The day-to-day management of the trial will be co-ordinated through the Imperial Clinical Trials Unit via the Project Manager and the Chief Investigator.

Data Monitoring & Ethical Committee (DMEC)

An independent Data Monitoring and Ethical Committee (DMEC) will be set up to monitor progress, patient safety and any ethical issues involved in this trial. They will review trial progress, recruitment rates, event rates and safety data. A separate charter will be drawn up defining their exact remit and criteria for reporting to the trial steering committee. There will be 6-monthly meetings of the independent DMEC.

Background

Recent years have witnessed a global increase in obesity and obesity-related diseases. In 2014, it was estimated that 39% of the world population were overweight (clinically defined as a body mass index (BMI) of 25 – 30 kg/m²) and 13% were obese (BMI ≥ 30 kg/m²) and it has been projected that there will be an additional 11 million obese adults in the UK by 2030.[1] Being overweight or obese increases the risk of developing 'metabolic syndrome' and is the main modifiable risk factor for developing insulin resistance and type 2 diabetes mellitus (T2DM). Having a BMI of >25kg/m² increases the risk of developing T2DM by 5 times and 90% of adult patients with T2DM are obese or overweight.[2] The prevalence of T2DM has therefore also increased in recent years with an estimated 7.4% of the UK population currently affected and is projected to increase by a further 2.1% in the next 15 years.[3] Compared to the general population patients with T2DM are 87.6% more likely to be admitted to hospital for a myocardial infarction, 121.1% more likely to be admitted for heart failure, 59.1% for a stroke, and are 32% more likely to die prematurely.[4] This represents a significant socioeconomic burden for a largely preventable condition with combined healthcare costs for these conditions estimated to increase by up to 2 billion pounds each year in the UK.[5]

Adipose tissue is a highly active endocrine organ and acts to modulate metabolism by releasing pro-inflammatory cytokines (TNF- α , IL-6, MCP-1).[6] hormones (leptin and adiponectin), glycerol and, importantly, non-esterified fatty acids (NEFA).[7-11] In obesity, especially those with centrally placed adipose tissue, there is increased production of many of these mediators that leads to the development of insulin resistance and pancreatic beta cell dysfunction. T2DM occurs when an already insulin-resistant individual develops beta cell dysfunction and is therefore unable to produce the necessary amount of insulin that is required to maintain normoglycaemia and, as a result, hyperglycaemia predominates.

Dietary modification, exercise, and hypoglycaemic medication remain the mainstay of management for patients with T2DM. Unfortunately, these measures have generally sub-optimal and poorly sustained outcomes. Bariatric, or metabolic, surgery remains the most effective long-term means of treating these patients by producing usually profound and sustained weight loss and weight-loss independent improvements in insulin secretion and sensitivity, consequently ameliorating, or even eliminating, associated co-morbidities and reducing mortality. Roux-en-Y gastric bypass (RYGB) surgery can achieve approximately 23-35% weight loss and 72-90% of patients with T2DM undergoing RYGB are able to achieve sustained euglycaemia without oral hypoglycaemic agents.[12-19] There are several mechanisms by which these outcomes are achieved, namely: (1) gastric exclusion from food by producing a small gastric pouch, (2) exclusion of food from the duodenum and proximal jejunum, (3) early delivery of food to the terminal ileum, and (4) disrupted bile flow. Within the first few days and weeks following surgery, before weight loss has occurred, early improvements in glycaemic control occur through rapid modulation of hepatic insulin resistance (causing reduced hepatic glucose output). This is then followed by sustained long-term weight loss, via entero-neuro-hormonal mechanisms, with an associated reduction in peripheral insulin resistance.[17, 20]

Rubino et al. demonstrated in 2006 that the foregut plays a key role in the metabolic changes that occur following bariatric surgery.[21] They demonstrated that exclusion of the proximal small bowel, as occurs in RYGB and similar procedures such as biliopancreatic diversion (BPD) +/- duodenal switch (DS), results in improved glucose tolerance that occurs independently of effects from reductions in food intake and body weight, malabsorption, or nutrient delivery to the hindgut. These findings have further been substantiated in other studies.[21-24] The proposed mechanisms by which these changes occur include: decreased secretion of orexigenic hormones (ghrelin); increased secretion of glucose-dependent insulinotropic polypeptide (GIP) and cholecystikinin (CCK), increased anorexigenic and incretin hormone secretion (e.g. glucagon-like peptide 1 (GLP-1), peptide YY (PYY), oxyntomodulin), and increased circulating concentrations of plasma bile acids. Additionally, stimulation of vagal afferent nerves in the small bowel cause entero-neuro-endocrine modulation within the gut-liver-brain axis. The resulting net effects include: increased insulin secretion, decreased glucagon secretion, decreased hepatic glucose output, increased pancreatic beta cell mass (via increased proliferation and decreased apoptosis), increased insulin sensitivity, decreased hunger, early satiety and altered food preferences and hedonics and brain reward system responses away from high-energy foods.[20, 25-35]

Such observations have led to the development of novel, endoscopically-placed duodenal-jejunal bypass sleeves (DJBS) or liners. These create an impermeable barrier between chyme exiting the stomach and the intestinal mucosa of the duodenum and proximal jejunum, thus preventing absorption within the foregut. The non-surgical and reversible nature of these devices has sparked much interest in recent years due to the prospect of avoiding the associated surgical mortality and morbidity of bariatric procedures (RYGB: 1 year morbidity 14.9%, 30 day mortality 0.5%).^[17] First described by Milone et al in animal models in 2006,^[36] the effects of DJBS insertion on reducing weight and potentially improving glycaemic regulation, above that of control interventions, has been validated in five randomised controlled trials (RCTs) and numerous observational studies.^[30, 37-49] In a recent systematic review and meta-analysis by Rohde et al.,^[50] they concluded that subjects implanted with DJBS achieved an additional 12.6% weight loss compared to sham controls or dietary intervention alone, and a mean greater weight loss of 5.1kg. In the largest of the RCT (DJBS + diet n=38 vs. diet alone n=39) amongst the DJBS arm a significant reduction in HbA1C of -0.9% was found.^[37] This finding however was not seen in the meta-analysis by Rohde et al. where the mean difference in HbA1C reduction of 0.8% was non-significant.^[50] Finally, evidence exists for DJBS having positive effects on other metabolic parameters, including blood pressure and serum lipid profile.^[37, 44, 45]

The EndoBarrier[®] DJBS (GI Dynamics Inc., Lexington, MA) is delivered endoscopically and comprises of a nitinol metal anchor, which is used to reversibly affix the device to the wall of the duodenal bulb, and an impermeable fluoropolymer sleeve that extends 60cm through the duodenum and into the jejunum (Figure 1). The implant is open at both ends to allow for passage of chyme from the stomach into the lower jejunum and prohibits nutrient absorption along its length by creating a barrier between the partially digested food and the absorptive surface of the small intestine. Whilst the chyme passes through the inside of the EndoBarrier[®] device, all bile and pancreatic secretions pass on the outside the liner and only mix with the food when they come into contact at the end of the sleeve.

Robust evidence for the clinical use of the DJBS is hence still lacking. The small number of published trials include small participant numbers with high degrees of inter-trial heterogeneity and the results are therefore not generalizable to routine clinical practice. Mechanistic data is also limited. There is therefore a call for more long-term, high quality trial data to validate the efficacy and mechanism of action of this device as a potential tool in the treatment of obesity and metabolic syndrome. In this paper, we describe the methodology for a government funded randomised controlled trial comparing DJBS against best practice medical therapy for the treatment of patients with obesity and T2DM with inadequate glycaemic control.

Methodology

Aims and Objectives

Primary Objective and Endpoint

The primary objective of this study is to evaluate the efficacy of DJBS compared with conventional medical therapy, diet and exercise on glycaemic control. As defined by the International Diabetes Federation (IDF) a substantial improvement in an individual's metabolic state occurs with an improvement in glycosylated haemoglobin (HbA1c) by 20%.^[51] Our primary endpoint therefore is a:

- i. Reduction in HbA1c by 20% after 12 months of treatment.

Secondary Objectives and Endpoints

The secondary objectives of this study are to evaluate the efficacy, acceptability and cost-effectiveness of DJBS compared against conventional medical therapy, diet and exercise. Secondary endpoints are:

- i. HbA1C of < 6%, equivalent to 42 mmol/mol (this infers optimisation of the metabolic state as defined by the IDF)^[51]
- ii. Blood pressure < 135/85

- iii. Weight loss > 15%
- iv. Reduction in dose/number of medications
- v. Cost of interventions and related health/social care
- vi. Quality-adjusted life years (QALY) accrued (calculated from area under the EQ-5D-5L questionnaire curve)
- vii. Incremental cost per QALY within the trial period and extrapolated through modelling.

Data will also be obtained to investigate the mechanism of action of the EndoBarrier® device via changes in:

- i. Gut hormones
- ii. Bile acids
- iii. Microbiome
- iv. Appetite
- v. Food hedonics and preference
- vi. Taste
- vii. Eating behaviour
- viii. Brain reward system responses to food evaluation and addictive behaviours using functional magnetic resonance imaging (MRI)
- ix. Body fat content
- x. Total body and tissue-specific insulin sensitivity
- xi. Intestinal gene expression

Safety Objective

The safety of the EndoBarrier® DJBS will be evaluated during this trial and the type and frequency of adverse events shall be reported.

Research Approval

This study shall be conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions. Local research ethics approval was granted by Fulham Research Ethics Committee, London, (Reference 14/LO/0871) on 10th July 2014. All subjects will give informed written consent.

Study Design

This study is a randomised controlled trial of the EndoBarrier® DJBS compared with conventional medical therapy, diet and exercise for the management of subjects with both obesity and T2DM. Over a two year period (1 year of treatment and 1 year follow-up) the study will be performed over two investigational sites in the United Kingdom: Imperial College Healthcare NHS Trust in London and University Hospital Southampton NHS Foundation Trust. The overall schema for the trial is summarised in Figures 2a and 2b. To ensure that the study is adequately powered and allowing for drop-outs, n=80 patients will be randomised into each of the two treatment arms equally across the two sites (Table 1).

Table 1. Summary of treatment group

Treatment Group	Number of subjects	Treatment period 1	Follow-up period 2
EndoBarrier Device	80	12 months	12 months
Standard Medical Therapy	80	12 months	12 months
Total number of subjects	160		

In order to investigate the mechanism of the effect of the EndoBarrier[®] device, both treatment arms will be divided into three optional sub-groups, which will have the following additional assessments during the course of the trial:

- Sub-group 1: functional MRI of food reward and addictive behaviours, eating behaviour assessment and post-meal gut hormones.
- Sub-group 2: Euglycaemic, hyperinsulinaemic clamps (total body and tissue-specific insulin resistance).
- Sub-group 3: assessment of taste and food preference, eating behaviour assessment and post-meal gut hormones.

Table 2 summarises the visit schedule, the data to be collected across both study arms and supplementary data that will be collected from the three optional mechanistic sub-groups. In addition to routine follow-up visits, all patients will receive regular telephone counseling from a specialist dietitian to assess their wellbeing and motivation in the trial.

Table 2. Summary of study visit schedule

Activities	Screening			Baseline			Treatment										Follow-up							
	V1	V2	V3	V4	T1	V5	V6	T2	V7	T3	V8	T4	V9	T5	V10	V11	T6	V12	T7	V13	T8	V14	V15	
Week/ Month/Day		- 4w ±7d	- 2w ±7d	- 0w ±3d	+ 5d± 3d	+ 10d ±3	+ 1m ±7d	+ 2m ±7d	+ 3m ±7d	+ 4.5m ±7d	+ 6m ±7d	+ 7.5m ±7d	+ 9m ±7d	+ 10.5m ±7d	+ 11.5m ±7d	+ 12m ±7d	+ 13.5m ±7d	+ 15m ±7d	+ 16.5m ±7d	+ 18m ±7d	+ 19.5m ±7d	+ 23m ±7d	+ 24m ±7d	
Informed consent (5.1)	X																							
Inclusion & exclusion criteria (4.2, 4.3)	X																							
Demographics (5.1)	X																							
Medical history (including meds) (5.1)	X																							
Physical examination (5.5.4)	X																							
ECG (5.5.5)	X																							
Vital signs (5.5.7)	X	X	X	X		X	X		X		X		X		X	X		X		X		X	X	
Body weight (5.5.8)	X	X	X	X		X	X		X		X		X		X	X		X		X		X	X	
Height (5.5.8)	X																							
Waist circumference (5.5.9)	X	X	X	X		X	X		X		X		X		X	X		X		X		X	X	
Routine blood tests (5.5.10)	X		X			X	X		X		X		X		X	X		X		X		X	X	
Urine dipstick and female pregnancy test (5.5.6)	X																							
Changes in medical history/medication (5.5.4)		X	X	X		X	X		X		X		X		X	X		X		X		X	X	
Randomisation (5.2)		X																						
Health Economic Questionnaires (5.5.12)			X			X	X		X		X				X								X	
Dietary counselling (5.5.3)		X		C																				
Dietitian follow up (5.5.3)							X		X				X			X		X		X				X
Urine albumin:creatinine ratio (5.5.11)			X			X					X				X								X	
Reporting of AEs (6)		X	X	X		X	X		X		X		X		X	X		X		X		X	X	
DNA & RNA sampling (5.5.13)			X			X					X					X								X
Telephone counselling (5.5.3)					X			X		X		X		X			X		X		X			
Diabetologist Review (5.5.1 and 5.5.2)		X		C			X		X				X			C		X		X				X

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Activities	Screening	Baseline		Treatment												Follow-up								
	V1	V2	V3	V4	T1	V5	V6	T2	V7	T3	V8	T4	V9	T5	V10	V11	T6	V12	T7	V13	T8	V14	V15	
Week/ Month/Day		- 4w ±7d	- 2w ±7d	- 0w ±3d	+ 5d± 3d	+ 10d ±3	+ 1m ±7d	+ 2m ±7d	+ 3m ±7d	+ 4.5m ±7d	+ 6m ±7d	+ 7.5m ±7d	+ 9m ±7d	+ 10.5m ±7d	+ 11.5m ±7d	+ 12m ±7d	+ 13.5m ±7d	+ 15m ±7d	+ 16.5m ±7d	+ 18m ±7d	+ 19.5m ±7d	+ 23m ±7d	+ 24m ±7d	
Metabolomics (5.5.14)			X			X					X				X								X	
Bioelectrical Impedance (5.5.15)			X			X					X				X								X	

EndoBarrier Group Only

PPI and H. Pylori test (5.5.16)		X																						
Distribution of Proton Pump Inhibitors (5.5.2)		T																						
EndoBarrier Implant (5.5.2)				T																				
Preparation for EndoBarrier removal (5.5.2)													T											
EndoBarrier removal (5.5.2)																T								
Biopsies during Implant and Explant (5.5.2)				T												T								
Gastroenterologist appointment (5.5.2)		T						T					T			T				T*				T

Sub-groups

Fixed/test meal and post-meal gut hormones and metabolites (Group 1 and 3) (5.6.4)			X			X					X				X									
Gut hormones and metabolites (Fasting only) (Group 1-3) (5.6.4)			X			X					X				X								X	
Food diaries (Groups 1-3) (5.6.2)			X			X					X				X								X	
Eating & Behaviour Questionnaires (Groups 1-3) (5.6.1)			X								X				X								X	
Appetite Visual Analogues Scales (Group 1-3) (5.6.3)			X			X					X				X								X	
Eating behaviour computerised tasks (Group 1 and 3) (5.6.5)			X								X				X								X	
Metal Check Form (Group 1) (5.1)	X																							
Handedness Questionnaire (Group 1) (5.1)	X																							

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Additional pregnancy tests			F																				
	Screening	Baseline		Treatment										Follow-up									
Activities	V1	V2	V3	V4	T1	V5	V6	T2	V7	T3	V8	T4	V9	T5	V10	V11	T6	V12	T7	V13	T8	V14	V15
Week/ Month/Day		- 4w ±7d	- 2w ±7d	- 0w ±3d	+ 5d± 3d	+ 10d ±3	+ 1m ±7d	+ 2m ±7d	+ 3m ±7d	+ 4.5m ±7d	+ 6m ±7d	+ 7.5m ±7d	+ 9m ±7d	+ 10.5m ±7d	+ 11.5m ±7d	+ 12m ±7d	+ 13.5m ±7d	+ 15m ±7d	+ 16.5m ±7d	+ 18m ±7d	+ 19.5m ±7d	+ 23m ±7d	+ 24m ±7d
DS-R disgust questionnaire (Group 1) (5.6.6)			X																				
Functional MRI (Group 1) (5.6.9)			X								X												
Insulin Clamps (Groups 2) (5.6.10)			X			X					X												
Cognitive assessment tasks (Group 1) (5.6.9)			X								X				X								X
Food Preference / Taste Assessment (Group 3) (5.6.11)			X			X					X												
24hr Dietary Recall (Group 3) (5.6.11)			X			X					X				X								X

X performed in all patients unless otherwise stated
 F performed in Females only
 C performed in Control arm (Standard medical therapy) only
 T performed in Treatment arm (EndoBarrier) only
 * optional (at request of the patient)

Study Population

Male and female patients, aged 18–65 years, with a BMI 30–50 kg/m² and confirmed diagnosis of T2DM for at least 1 year, who have inadequate glycaemic control and are on oral anti-hyperglycaemic medications. See Table 3 for complete inclusion and exclusion criteria.

Table 3. Study inclusion and exclusion criteria

Inclusion Criteria	
1.	Age 18–65 years (male or female)
2.	Type 2 diabetes mellitus for at least one year
3.	HbA1C 7.7–11.0% equivalent to 58 – 97 mmol/mol
4.	On oral hypoglycaemic medications
5.	BMI 30 – 50 kg/m ²
Exclusion Criteria	
1.	Language barrier, mental incapacity, unwillingness or inability to understand and be able to complete questionnaires. ☒
2.	Non-compliance with eligibility criteria. ☒
3.	Females of childbearing potential who are pregnant, breast-feeding or intend to become ☒pregnant or are not using adequate or reliable contraceptive methods.
4.	Evidence of absolute insulin deficiency as indicated by clinical assessment, a long duration of ☒T2DM and a fasting plasma C-peptide of <333pmol/L. ☒
5.	Current use of insulin. ☒
6.	Previous diagnosis with type 1 DM or a history of ketoacidosis. ☒
7.	Requirement of NSAIDs (non-steroidal anti-inflammatory drugs) or prescription of ☒anticoagulation therapy during the implant period. ☒
8.	Current iron deficiency and/or iron deficiency anaemia.
9.	Symptomatic gallstones or kidney stones at the time of screening.
10.	History of coagulopathy, upper gastro-intestinal bleeding conditions such as oesophageal or gastric varices, congenital or acquired intestinal telangiectasia.
11.	Previous gastrointestinal surgery that could affect the ability to place the device or the function of the implant. ☒
12.	History or presence of active H. pylori (if subjects are randomised into the EndoBarrier [®] arm☒and have a history or presence of active H. pylori tested at study visit 2 they can☒receive appropriate treatment and then subsequently enrol into the study). ☒
13.	Family history of a known diagnosis or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder.
14.	Severe liver impairment (i.e. AST, ALT or gGT >4 times upper limit of the reference range) or kidney impairment (i.e. estimated Glomerular Filtration Rate (GFR) < 45 ml/min/1.73m ²).
15.	Severe depression, unstable emotional or psychological characteristics (including Beck Depression Inventory II score >28).
16.	Poor dentition and inability to adequately chew food.
17.	Planned holidays up to three months following the EndoBarrier Implant.

Study Recruitment

Participants will be identified from several areas across primary, secondary and tertiary healthcare and community settings:

- i. Diabetes research registers (e.g. Diabetes Alliance for Research in England (DARE), REC 2002/7/118)
- ii. Hospital or General Practice (GP) patient databases (Participant Identification Centres)
- iii. Patients referred to diabetes and bariatric specialist clinics
- iv. Other research studies within the Imperial College Healthcare NHS Trust and the Local Clinical Research Network (LCRN)
- v. Study websites
- vi. Local and national media – websites, radio, newspaper articles and adverts

- vii. Posters
- viii. Diabetes, Obesity and other support groups
- ix. Social media websites

Potential patients who, after reading a summary Patient Information Sheet (PIS), would like to enter the trial will give their verbal consent for preliminary telephone screening to check basic inclusion and exclusion criteria. Written consent will then be taken from the patient to allow the study team to contact their GP for the purpose of obtaining additional information on the patient's medical history, current medical therapies and to identify any other clinical reasons as to why the patient should not participate. Patients who appear to meet eligibility criteria will be provided with a full trial PIS and then invited to a formal screening visit at one of the study centres. At this stage the patient will be fully informed of the nature of the study and given relevant information about the objectives of the research, benefits and possible adverse events, verbally and in writing. The patient will have the opportunity to ask questions about the trial and formal written consent will be taken for the patient to participate in the main study \pm additional consent for one of the three optional mechanistic sub-groups. Once consent has been obtained then the subject's full eligibility will be checked against all inclusion and exclusion criteria (Table 3). Each patient will be informed of their eligibility for the trial once all results are available (usually within one week from obtaining consent).

Randomisation

Eligible patients will be randomised into one of the two trial arms using the InForm Integrated Trial Management system, a secure web-based data entry platform. This will be programmed with a randomisation schedule by an independent statistician and protect against bias in the randomisation process as group allocation will be concealed and automatic. The randomisation will be at a ratio of 1:1 and stratified by site and two BMI groups, 30–40 and 40–50 kg/m². Each patient will be informed of their randomisation allocation and will be assigned a unique study identification number. Only the subject number and initials will be recorded in the case report form (CRF). All other patient-identifiable data will be completely anonymised.

Trial Interventions

EndoBarrier[®] Gastrointestinal Liner

The EndoBarrier[®] Gastrointestinal liner device received CE Mark for 12 months implant duration on 11th December 2009 and is a single use, minimally invasive device, used to achieve weight loss and improve T2DM status in subjects who are obese (Figure 1).

At visit 2 (- 4 weeks), participants who have been randomised to receive the EndoBarrier[®] device will be tested for the presence of *Helicobacter pylori*, either by faecal antigen or urea breath testing. Those patients testing positive will be offered 1 week of triple-eradication therapy, as per guidance published within the British National Formulary, and will then be retested after a further 4 weeks to confirm complete eradication before continuing with implantation of the EndoBarrier[®] device. Subsequently, all patients will be prescribed a proton pump inhibitor (PPI) (Omeprazole 40mg twice daily) and instructed to commence this three days prior to the implant procedure. They will continue this for the duration of the implant period (12 months) and for a further two weeks following device removal.

At visit 4 (0 weeks), after an eight-hour fast, subjects will have the EndoBarrier[®] device implanted under a general anaesthetic. The implant is delivered endoscopically on a custom catheter and the anchor is sited in the duodenal bulb using a custom delivery system under fluoroscopic x-ray guidance (mean fluoroscopic x-ray time for insertion is 7 minutes, range 1-20 minutes). The 60cm sleeve is unfurled and then the final positioning plus patency is confirmed by assessing for the free flow of radio-opaque contrast through the device. Videos and photos of the fluoroscopy images are recorded to help the investigators make treatment decisions. During implantation eight gastric and small bowel biopsies will be taken using standard biopsy forceps. Four biopsies will be used for routine histology and four biopsies will be used for RNA extraction to perform genome-wide expression analysis. Participants will be discharged from hospital the same day with an implant information card, which describes the implant, identifies who to call in

1 the case of an emergency, and what symptoms to look for following the implant. Subjects will have their dose of
2 sulphonylurea medication reduced by 50% at the time of EndoBarrier[®] implant to avoid potential hypoglycaemic
3 episodes.
4

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6 The device will be removed at visit 11 (after 12 months) under sedation or general anaesthetic. The gastroscop
7 which is fitted with a foreign body retrieval hood, is used to locate the implant and a custom grasper is passed
8 through the working channel of the gastroscop to grab a polypropylene tether located on the proximal portion of
9 the anchor. Pulling on this tether will collapse the proximal end of the anchor, which can then be pulled into the
10 foreign body hood and removed by withdrawing the gastroscop through the subject's mouth. During this removal,
11 eight further biopsies will be taken for histology and RNA extraction. Following removal of the EndoBarrier[®] device,
12 patients will be followed up for a further 12 months.
13

14 **Diabetes Review**

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16 Participants in both arms of the trial will have their T2DM managed in accordance with the guidelines of the
17 American Diabetes Association (ADA).[52, 53] These guidelines have been chosen as they would adhere to the
18 current best worldwide practice that would still be relevant when the results are published following study
19 completion. Both treatment groups will have a review of their T2DM by a suitably trained physician at visits 2, 6, 7,
20 9, 12, 13 and 15. Additionally, the standard care arm of the trial will have an additional review at visits 4 and 11
21 in place of the EndoBarrier[®] implant and removal. Adjustments to a patient's oral anti-hyperglycaemic medication and
22 escalation of therapy is at the investigators discretion and will comply with general recommendations laid out by the
23 ADA.[53]
24
25

26 **Dietary Counselling and Physical Activity**

27
28 At visit 2, all patients historical and current eating behaviours will be assessed by a qualified dietitian using the
29 following information: anthropometry; biochemistry; co-morbidities; activity levels; eating habits including previous
30 diets; lifestyle including smoking, drug and alcohol misuse; weight history; psychiatric history; family history of
31 obesity, diabetes, mental illness or eating disorders; available support network; work status; readiness and
32 motivation for change. Patients will then receive dietary and physical activity counselling in accordance with local
33 standards with the intention of providing each subject with lifestyle/behavioural modification information and good
34 eating practices. Patients will then receive dietary and physical activity counselling in accordance with local
35 standards with the intention of providing each subject with lifestyle/behavioural modification information and good
36 eating practices. In addition, subjects in the EndoBarrier[®] arm will receive written information on how their diet will
37 change after implantation of the device and they will receive specialist guidance for eating with their EndoBarrier[®].
38

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40 All patients will be reviewed by a specialist dietitian at visits 2, 6, 7, 9, 12, 13 and 15. In addition, participants in the
41 standard care arm of the trial will have an additional review at visits 4 and 11 in place of the EndoBarrier[®] implant
42 and removal. During the course of the trial, participants will be recommended to consume 600 kcal less every day,
43 depending on their age, gender, activity levels and body weight. Guidelines for daily amounts are between 1200 and
44 1500 kcal for women and between 1500 and 1800 kcal for men. In accordance with standard dietary practice,
45 subjects will be advised: to eat regularly every day (5 times per day); to control their portion sizes and intake of
46 carbohydrates/starchy foods; to increase their intake of low glycaemic index (GI) and high protein foods, as well as
47 vegetables; and to reduce their intake of foods high in fat and sugar, and alcohol. Participants will be advised to
48 include more physical activity in their daily routine and encouraged to do more activity in their leisure time. Their
49 goal will be to include 150 minutes a week of moderate intensity, and 75 minutes a week of vigorous intensity
50 aerobic activity and muscle strengthening activities, on more than 2 days a week. Changes in physical activity level
51 will be monitored using the International Physical Activity Questionnaire (IPAQ).[54]
52

53 **Liquid Diet**

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55 To avoid disruption of the device in the immediate period following implantation, patients will follow a liquid diet for
56 the 7 days before and 13 days (\pm 3 days) after the intervention visit (visit 4). The liquid diet will be guided by the
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specialist dietitian and will comprise of 125ml Fortisip Compact drinks (Nutricia, UK): 5 per day for males, 4 per day for females, containing per 100 mL: 240 kcal, 9.6g protein (16% total energy), 29.7 g carbohydrate (49%), 15g sugars, 9.3g fat (35%). Patients will also be allowed to consume sugar-free squashes, smooth/clear soup (1 medium bowl per day), tea or coffee without sugar, or unsweetened puree. To standardise both therapy groups, all patients across both arms will follow the liquid diet for this duration and period of the study.

Assessment of Objectives

Assessment of Primary Objective

Each study participant will have their IFCC (International Federation of Clinical Chemistry) HbA1C measured at screening and then subsequently at visits 5, 7, 8, 9, 10, 12, 13 and 15. Samples will be processed at the laboratory local to each study centre using standard methods. Results will be recorded on the InForm system.

Assessment of Secondary Objectives

Individuals in both study arms will be invited for regular medical check-ups (Figure 2), which will include routine anthropometric measurements (height, weight, waist circumference, pulse and blood pressure) and blood tests (Table 4). Any changes to the participants’ health or medications will be carefully documented on the CRF and all adverse events will be reported in detail in line with standard principles of GCP.

Table 4. Summary of blood tests at each study visit

Blood test	V1	V3	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Haematology (Full blood count)	x	x	x	x	x	x	x	x	x	x	x	x	x
Routine Biochemistry (including Urea and Electrolytes)	x	x	x	x	x	x	x	x	x	x	x	x	x
Liver function tests	x	x	x	x	x	x	x	x	x	x	x	x	x
Fasting glucose	x	x	x	x	x	x	x	x	x	x	x	x	x
Creatinine	x	x	x	x	x	x	x	x	x	x	x	x	x
HbA1C	x		x		x	x	x	x		x	x		x
Fasting lipids (cholesterol, HDL, LDL, triglycerides)	x	x	x	x	x	x	x	x		x	x	x	x
C-peptide	x												
Insulin (Fasting)	x	x	x			x		x				x	
Vitamin D	x					x		x					
Iron studies	x					x		x					
Vitamin B12	x					x		x					
Serum Folate	x					x		x					
Free Thyroxine	x							x					x

TSH	x							x						x
Cortisol (Sub-group 1 only)		x				x								
Oestradiol (Sub-group 1 only)		x				x								
Progesterone (Sub-group 1 only)		x				x								
LH (Sub-group 1 only)		x				x								
FSH (Sub-group 1 only)		x				x								

Patients in both treatment arms will be asked to complete health economics questionnaires at visits 3, 5, 6, 7, 8, 10 and 14. These comprise of the EQ-5D-5L questionnaire to assess health-related quality of life and a bespoke questionnaire designed to collect information about patients' use of health and social care resources (for costing purposes).^[55] The Resource Use questionnaire will be adapted from existing instruments and will include:^[56, 57]

- i. Medications for diabetes, weight loss, blood pressure, lipid control and cardiovascular disease
- ii. Primary care consultations (with GP, nurse or other healthcare professional) [□]
- iii. Hospital outpatient clinic visits (by specialty) [□]
- iv. A&E attendances (admitted/not-admitted) [□]
- v. Inpatient stays and procedures [□]
- vi. Investigations
- vii. Use of any other NHS-related community health and social services (e.g. chiropody). [□]

Costs for private health and social care, out-of-pocket expenditure by patients, and 'indirect costs' per patient time will not be included.

In addition, data will be collected in the CRF from hospital information systems and case notes to cost the EndoBarrier[®] intervention and the diet/exercise intervention. Information to be collected will include:

- i. Routine assessments required before implantation and removal of the EndoBarrier[®]
- ii. Disposables and staff time for the insertion and removal procedures, including day case and overnight stay if required
- iii. Treatment of any adverse events related to the procedures (additional inpatient stays, [□]clinic visits and re-admissions)
- iv. Dietitian time to deliver the diet and physical activity counselling and for telephone follow-up
- v. Routine hospital follow-up and diabetes care
- vi. Hospital treatment for cardiovascular events or other complications of diabetes [□]

Mechanistic Study Groups

In addition to the routine data collected above, at visits 3, 5, 8, 10, and 14, mechanistic data will be gathered from all patients across both study arms:

- i. Body fat mass (kg and % of body weight) measured by bio-electrical impedance analysis
- ii. Collection of stool, urine and plasma for assessment of metabolomics using nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS), and microbiome analysis
- iii. Measurement of insulin, gut hormones (ghrelin, GLP-1, PYY), bile acids, leptin and other adipocytokines, and markers of insulin resistance and inflammation from venous blood samples (fasting for all visits and then

- 1 following a meal in sub-groups 1 and 3 at visits 3, 5, 8 and 10)
- 2
- 3 iv. DNA and RNA from venous blood samples for examination of genetic variants that may predict weight loss,
- 4 cause or contribute to obesity
- 5 v. Urinary albumin:creatinine ratio
- 6 vi. Comprehensive 3-day food diary
- 7

8 **Sub-group 1: Functional MRI**

9 Subjects in each study arm, at the London site only, will have fMRI scans to examine brain function related to food
10 reward and addictive behaviours contributing to overeating at baseline (visit 3) and at 6 months (visit 8) after
11 intervention. These will be supplemented by and correlated with psychological questionnaires, computerised tasks
12 and test meals at these and other visits. The study visits will last up to 6-8 hours (scanning visits 3 and 8). Subjects
13 will have structural and functional MRI brain scans lasting up to 90 minutes using a 3.0 Tesla Siemens Verio MR
14 scanner after an overnight fast. Whilst in the scanner, subjects view a mirror reflecting a computer screen and can
15 respond to instructions using a keypad held in their hand.

16 The following anatomical brain scans will be collected at both visits:

- 17
- 18
- 19 i. Anatomical T1 and T2-weighted MR scans to provide structural neuroimaging data and allow image
20 registration to standard space.
- 21 ii. Diffusion tensor imaging to examine white matter tract integrity.
- 22

23 The following resting state functional MRI scans will be collected at both visits:

- 24 i. Arterial spin labelling to measure resting regional cerebral blood flow.[58, 59]
- 25 ii. Resting state blood oxygen level-dependent (BOLD) functional MRI to measure resting state functional
26 connectivity.[60]
- 27

28 The following task-related functional MRI scans will be collected at both visits:

- 29 i. Food picture evaluation task: to assess reward system activation when subjects view a variety of different
30 pictures (high-energy and low-energy foods, household objects, blurred pictures as a baseline) and
31 simultaneously rate how 'appealing' the pictures are using the keypad as a measure of anticipatory food
32 reward or food due reactivity.[32, 34, 61-63]
- 33 ii. Monetary incentive delay (MID) task: a game in which subjects need to press a button during a specific time
34 window when given a cue on the computer screen in order to win or prevent the loss of hypothetical
35 monetary prizes to assess anticipatory non-food reward responsiveness.[64-66]
- 36 iii. Go-NoGo task: to assess motor response inhibitory control as a measure of compulsivity.[67-69] The task
37 contrasts brain activation during responses to infrequent no-go signals (e.g. 'do not press' button when
38 viewing one symbol) compared to an implicit go baseline (e.g. 'do press' button when viewing a different
39 symbol).[66]
- 40 iv. Negative emotional reactivity task: to assess brain response during viewing of unpleasant, negatively valent
41 pictures compared to neutral control pictures.[66]
- 42
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44 Study visits without scanning at visits 5, 10 and 14 will last 3-6 hours. At visits 3, 8, 10 and/or 14, subjects in sub-
45 group 1 will also complete several questionnaires and perform several computer-based tasks to assess eating and
46 addictive behaviours and cognition, including:

47

- 48
- 49 i. WTAR word reading list: to document baseline intellectual status (visit 3 only)
- 50 ii. Kirby delay discounting task: to assess temporal impulsivity to a hypothetical non-food monetary rewards
51 (visits 3, 8, 10 and 14).[70]
- 52 iii. Leeds Food Preference Questionnaire: to assess bias of food preference to foods high in fat and sugar and
53 explicit and implicit liking of foods high/low in fat/sugar (visits 3, 8, 10 and 14).[71]
- 54 iv. Progressive ratio task: to measure breakpoint of effort that subjects are willing to spend by having to press a
55 computer mouse an increasing number of times to receive a chocolate M&M™ sweet, to assess appetitive
56 food reward and motivation (visits 3 and 8).[33, 34]
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59 An *ad libitum* test meal will be performed at visits 3 and 8, in which subjects first taste and rate the palatability,
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intensity and acceptability of different foods high or low in fat and sugar, and then eat as much of whichever foods they want, to assess food taste, preference and choice, total energy intake and macronutrient composition. Subjects will also complete visual analogue ratings of appetite, anxiety, stress and sleepiness, and measurement of fasting and post-meal hormones and metabolites over the study visit.[32, 63]

At visit 5, 10 and 14 subjects will consume a fixed mixed meal tolerance test with measurement of fasting and post-prandial hormones and metabolites.

Sub-group 2: Euglycaemic, hyperinsulinaemic clamp

On visit 3, 5, and 8, patients in each study arm, at the Southampton site only, will undergo a euglycaemic hyperinsulinaemic clamp with stable isotope infusion to determine overall insulin and compartment-specific insulin sensitivity (liver, muscle and adipose depot). Patients will be instructed to consume a standardised meal or meal replacement the evening prior to their study visit. A venous catheter will be inserted into a vein of each arm on the study morning. The first cannula will be used for infusions and the other for blood sampling. If blood glucose levels are higher than 6 mmol/L on arrival then a variable rate insulin infusion will be started to attain a stable glucose level (4.0 -6.0 mmol/L) prior to commencement of the hyperinsulinaemic euglycaemic clamp.

A primed continuous infusion of 6, 6-²H₂-glucose, a stable isotope tracer, will be started and maintained for 7 hours. Two hours later a two-stage hyperinsulinaemic-euglycaemic clamp procedure will be started and continued for 5 hours. During stage 1 of the clamp procedure, in which hepatic insulin resistance is assessed, insulin will be infused at a low dose (0.3-0.5 mU/kg/min) for 2 hours. During stage 2 of the clamp procedure, in which peripheral insulin resistance is assessed, insulin will be increased to a higher dose (1.5 mU/kg/min) for 2 hours. Euglycaemia will be maintained by infusing 20% dextrose at a variable rate. Blood samples will be taken every 5 minutes to measure blood glucose concentration and the dextrose infusion will be adjusted accordingly. The exogenous glucose infusion will be enriched with 6, 6-²H₂-glucose to prevent a fall in plasma tracer enrichment and underestimation of endogenous glucose production rate. Blood samples will be obtained before the start of the tracer infusions, every 10 min during the final 30 min of the basal period and stages 1 and 2 of the clamp procedure and every 30 minutes between these periods to determine glucose enrichment and concentration, free fatty acid, insulin, C-peptide, glucagon, gut hormones, and metabolite concentrations. At the same time points participants will be asked to complete appetite visual analogue scales.

The isotopic enrichment of plasma glucose will be determined by gas chromatography mass spectrometry (GCMS) at the Wolfson Centre for Translational Research, Postgraduate Medical School, University of Surrey, United Kingdom.

Sub-group 3: Taste and Food Preference Assessment

On visit 3, 5, 8, 10 and 14, patients in each study arm, at both the London and Southampton sites, will attend the research facility after an overnight fast. The total duration of these visits will be up to 7 hours (visits 3, 5, 8, 10) and 5 hours (visit 14). On the morning of those visits patients will perform two behavioural computerized tasks: the Kirby Delay Discounting Task to assess temporal impulsivity to non-food monetary reward (visits 3, 8, 10 and 14).[70] and the Leeds Food Preference Questionnaire to assess bias of food preference to foods high in fat and sugar and explicit and implicit liking of foods high/low in fat/sugar (visits 3, 8, 10 and 14).[71]

Sweet taste detection testing will be performed at visits 3, 5, 8 by following the method of constant stimuli in which seven ascending sucrose concentrations in solution will be used to determine sweet detection thresholds.[72] At the same visits consummatory taste reward will be assessed in which five ascending sucrose solutions will be used to test responses in intensity ratings and hedonic reward. To assess the appetitive behaviour towards a sweet and fatty food reward, a Progressive Ratio Task (PRT) will be performed 2 hours after the consumption of a fixed meal.[33]

Total caloric intake and macronutrient composition will be assessed using three-day food diaries and a 24-hour recall that is carried out by a trained dietitian/nutritionist on all visits. Patients will also complete the EPIC Food Frequency questionnaire at visit 3, 8, and 10. Finally, a fixed mixed meal tolerance test with measurement of post-meal hormones and metabolites will be performed.

Additional sub-group specific procedures and measurements

Across all three sub-groups only, the following additional data will also be collected during the mechanistic study visits:

- i. Trait, state and symptom questionnaires: to evaluate aspects of eating behaviour (e.g. dietary restraint, emotional eating, disinhibition, hunger, external eating), reward sensitivity, mood, impulsivity, aversive symptoms, symptoms of dumping syndrome, including Dutch Eating Behaviour Questionnaire, Three Factor Eating Questionnaire, Yale Food Addiction Scale, Binge Eating Scale, Beck Depression Inventory II, Hospital Anxiety and Depression Scale (HADS), Barratt Impulsiveness Scale (BIS), UPPS-P Impulsive Behavior Scale.
- ii. Visual analogue scale (VAS) ratings: to assess subjective feelings of hunger, nausea, fullness, sleepiness, stress and anxiety when fasted and during meal tests.

Power Calculation

Conservatively, it was estimated that 15% of patients in the control arm will achieve the target but we believe this to be an overestimate. The Steno study is the best quality randomised study (n=80 patients in each arm) into the effect of best medical therapy published to date and demonstrated over an average 7.8 years significant improvements in HbA1c amongst those having intensive medical therapy from 8.4 ± 1.6 to 7.7 ± 1.2 , but no change in HbA1c amongst those continuing with standard medical therapy.^[73] This study defines the very best that could realistically be achieved in the control arm, but expect there to be very little if any change in this group. The reporting of HbA1c as an outcome measure was not in accordance with the newly defined IDF criteria, but considering the small average reduction achieved in the Steno study, it will be assumed that a target of 15% of patients reaching the endpoint is a conservative estimate. Company data on the small number of patients who have reached a year with the device in place suggest that 40% will achieve this target.

According to our own experience with the device in a commercially sponsored study, up to 30% of patients in the treatment group may have the device removed early. Nevertheless other commercially sponsored (unpublished) studies of this device have achieved lower explant rates (J Tetreault – GI Dynamics). To allow for up to 30% early removal we have therefore diluted the treatment effect from 40% vs. 15% to 35% vs. 15% achieving the target of 20% reduction in HbA1c for treatment arm vs. standard arm. With these assumptions, n=73 patients per group will give 80% power with a two-sided alpha 0.05 to detect a significant effect. Adding 10% loss of follow-up increases the sample size to n=80 per group.

The dilution was calculated starting from the assumption that 40% of patients with the device will reach the target (this estimate is based on company data based on diabetic patients in the same range of BMI as in the present proposal). If 30% of patients in the treatment group need to remove the device early but remain available for follow-up, in the worst case scenario, the proportion reaching the target is the same as in the control group, bringing the estimate for the treatment group to 32.5%. However most of them will keep the device for some time, having some benefit, so it is plausible to assume that the estimate is higher than 32.5%. Dividing the main effect 15% vs. 40% in three parts we assume that in the 30% of patients with removal, for 1/3 the same effect will be achieved as in the control group (15% reaching the target), for 1/3 it will be increased (23% reach the target) and for 1/3 more increased (31% reach the target). Overall, this would give an estimate of 35% for the treatment group.

Statistical Analysis

Patient characteristics will be summarized. Summaries of continuous variables will be presented as means and standard deviations if normally distributed, and as medians and inter-quartile ranges for skewed data, whilst categorical variables will be presented as frequencies and percentages. The difference between the two study groups in the proportion of patients achieving substantial improvement in the metabolic syndrome both at 12 and 18 months will be analysed using logistic regression adjusting for the stratification variables (BMI groups and sites). Analysis of secondary outcomes will be conducted using standard statistical procedures applicable to categorical or continuous data as appropriate. For missing values we will explore the pattern and the extent of missingness and we

1 will carry out an appropriate form of multiple imputation if required. The analysis will be performed according to the
2 intention to treat principle. All statistical tests will be two-tailed with a 5% significance level.
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5 **Metabonomics and Microbiome Analyses**

6 Metabonomic datasets will be analysed using principal component analysis (PCA) and orthogonal partial least-
7 squares analysis (O-PLS). The metabolic and microbial data will also be analysed in relation to response
8 measurements such as BMI, gut hormone levels etc. using O-PLS regression analysis and Bayesian approaches. A
9 range of statistical methods will be optimised and applied to the data to identify weight loss and T2DM-associated
10 microbiota and metabolites.
11

12 **Health Economics**

13 The economic health analysis will be conducted following the NICE Reference Case, which includes the use of QALYs
14 as the measure of health outcome, and adoption of an NHS and Personal Social Services perspective for costs (Guide
15 to the methods of technology appraisal 2013, <http://publications.nice.org.uk/pmg9>).
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18 **Within trial analysis**

19 EQ-5D-5L health states will be scored using the English value set to give a utility values at each time point (-2 weeks,
20 10 days, 1, 3, 6, 11.5, and 23 months).^[74] QALYs will be estimated for each patient using an area-under-the curve
21 approach.
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23

24 The cost of the EndoBarrier[®] intervention, the lifestyle intervention, and other related health and social care will be
25 estimated from resource use data. Unit costs for the included services will be obtained from standard national
26 sources (BNF or Drug Tariff for drug prices, Department of Health Reference Costs for investigations, procedures and
27 outpatient visits, PSSRU estimates for other primary and community health and social services). Total costs will be
28 estimated for each patient over the 24-month trial period.
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31 Patient-level cost and QALY estimates will be combined to estimate an Incremental Cost Effectiveness Ratio (ICER)
32 for the EndoBarrier[®] device compared with standard medical therapy over the 24 month trial period. The analysis
33 will combine multiple imputation to account for missing EQ-5D and resource use data with bootstrap regression to
34 estimate mean cost and QALYs for the two patient groups. Missing data is often a particular problem for economic
35 analysis, even in studies with good follow-up of primary endpoints, as area under the curve approach requires data
36 from multiple time points. A bootstrap regression approach will be used to account for non-normal distributions of
37 cost data, to adjust for baseline differences in utility or other patient characteristics, and to allow for correlations
38 between costs and QALYs.
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41 **Cost-effectiveness modelling**

42 A decision analytic model will be developed to estimate clinical outcomes, QALYs, and costs beyond 24 months. The
43 time horizon for the modelling will be for the remainder of the patient's predicted lifetimes, as recommended in
44 modelling guidelines.^[75, 76] Before commencing this modelling exercise, a review of published economic decision
45 models for weight loss interventions for people with T2DM will be conducted in order to identify possible model
46 structures and sources of input parameters. The conceptual design of the model will be discussed and agreed
47 amongst the research team before programming commences. It is anticipated that the model will take the form of
48 an individual patient simulation, using either a discrete time or discrete event approach to simulate the onset of
49 diabetes/obesity related complications, and hence QALYs and costs under alternative treatment strategies.
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52 Data from the trial will be used to provide estimates of the effect of the EndoBarrier[®] compared with conventional
53 management. In addition, published systematic reviews and meta-analyses of bariatric surgery for similar a patient
54 population will be reviewed. If recent evidence of sufficient relevance and quality is available, we will extend our
55 model to include indirect comparisons with these other interventions. Other model parameters will be sourced from
56 targeted literature reviews and routine data sources. The choice of software for the model will be made after
57 specification of the conceptual design. Before use, the model will be validated by an experienced health economist
58 not involved in the development of the model. This will be done using a checklist developed by the Brunel Health
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Economics Research Group, which includes a range of suggestions for checking that a model is free from errors (verification) and that it is consistent with internal and external data (validation).

Probabilistic sensitivity analysis (PSA) will be used to estimate the impact of uncertainty over model parameters, and value of information (VOI) analysis to estimate the value of conducting further research. In addition, deterministic sensitivity analysis will be used to examine the impact of uncertainties over the model structure.

Gut hormones, metabolites and bile acids

These will be measured in the fasted and/or postprandial state for each patient and compared within and between the groups using parametric/non-parametric repeated measures statistical testing.

Food hedonics and brain reward responses

Brain activation during fMRI paradigms and outcomes from behavioural measures of eating and addictive behaviours and questionnaires, will be compared between groups using a 2x2 ANOVA design including group (control vs. EndoBarrier®) as a between subject factor, time (baseline vs. follow-up visit) as a within subject factor, and group x time interaction to identify differential effects between groups. For fMRI studies, analysis will use region of interest (e.g. for food picture evaluation task: orbitofrontal cortex (OFC), amygdala, caudate, nucleus accumbens, anterior insula) and whole brain analyses to compare groups using statistical thresholds of voxel-wise correction false discovery rate (FDR) $P < 0.05$ or cluster-wise family wise error (FWE) correction $P < 0.05$. Correlations of BOLD signal will be made with other behavioural variables by linear regression analysis to examine the relevance of changes in brain activation.

Food Preference and Sweet Taste

Dietary energy intake, macronutrient composition, sweet taste detection thresholds, and visual analogue taste ratings will be quantified for each patient and compared within and between the groups at different time points using parametric/non-parametric repeated measures statistical testing. Regressions will be performed with clinical outcomes (e.g. weight loss, HbA1c) to identify predictive markers and generate mechanistic hypotheses.

Hyperinsulinaemic Euglycaemic Clamps

Overall and tissue specific insulin sensitivity will be quantified for each patient and compared within and between the groups at 3 time points using parametric/non-parametric repeated measures statistical testing.

In addition, linear regression will be performed to correlate mechanistic variables collected from each of the sub-groups 1-3 at baseline or during the intervention with clinical outcomes at 1 year e.g. weight loss and decreases in HbA1c, to generate predictive markers and generate mechanistic hypotheses.

Discussion

Experience of 3717 EndoBarrier® devices distributed worldwide has demonstrated a favourable risk-to-benefit ratio (GI Dynamics, February 2017) and their minimally invasive and reversible nature represents a very attractive treatment modality for patients with obesity and T2DM. Evidence already exists in the literature in support of the efficacy of DJBS by reducing weight and potentially improving glycaemic control.[37, 38, 40, 42, 44-46, 50] Nonetheless, it is reported that up to 100% of patients will experience a non-serious adverse event (predominantly abdominal discomfort and nausea immediately following implantation)[50] and 7.4% will suffer a serious adverse event (SAE) (GI Dynamics safety reporting 2008 to March 2017). The exact nature of these events are summarised in Table 5.

Table 5. Serious Adverse Events from the EndoBarrier® device

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017 (Jan-Mar)	TOTAL
Distributed (Denominator)	25	143	157	275	391	812	987	482	383	43	
Hepatic Abscess	0	0	0	0	1	8	12	9	4	2	36
Hepatic Abscess Rate											1.0%
Hepatic abscess with explant ≤ 12 months	0	0	0	0	1	5	9	7	1	2	25
Hepatic Abscess Rate											0.7%
Intolerance	0	5	4	12	5	10	11	4	18	0	69
Intolerance Rate											1.9%
Liner Obstruction	0	4	0	5	3	1	10	2	0	0	25
Liner Obstruction Rate											0.7%
GI Bleed	0	1	3	6	5	9	20	8	4	1	57
GI Bleed Rate											1.5%
Migration/ Movement	0	10	6	4	1	6	11	13	0	1	52
Migration/Movement Rate											1.4%
Pancreatitis	0	0	0	0	4	1	7	0	0	0	12
Pancreatitis Rate											0.3%
Perforation	0	0	1	0	0	5	2	2	1	0	11
Perforation Rate											0.3%
Surgical Removal	0	0	0	1	1	0	8	1	1	0	12
Surgical Removal Rate											0.3%
Total Incidences	0	20	14	28	20	40	81	39	28	4	274
Total Cumulative Rate											7.4%

GI dynamics safety reporting 2008 to March 20

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Notably, the pivotal U.S ENDO trial (EndoBarrier[®] vs. Sham procedure) was terminated in July 2015 after only 325 subjects were randomised (n=216 EndoBarrier subjects) due to a higher than expected hepatic abscess (HA) rate of 3.5% (compared to a global incidence of 0.73%). This high incidence of HA is not the experience within Europe with 1.2% being reported in 1901 distributed devices (UK hepatic abscess rate in 523 cases is 1.34%). There have also been no deaths attributed to the EndoBarrier[®] and all patients experiencing an SAE have recovered without long-term sequelae.

Research to date therefore validates the EndoBarrier[®] DJBS as a potential treatment option for patients who are obese with or without T2DM. These studies however have been limited by their low participant numbers, short follow-up duration and wide inter-trial heterogeneity. Thus, there is a call for more robust clinical trial data to investigate its efficacy, safety and acceptability, and to establish where its use may fall within the treatment algorithm of such patients. This study will represent the largest randomised controlled trial of the EndoBarrier[®] device compared with conventional medical therapy, diet and exercise over a treatment period of 1 year and will also provide the longest follow-up data (1 year) of any trial to date. Additionally, this study will provide: (1) unique data on the mechanism of action of the DJBS and the effect of foregut exclusion on an individual's metabolic profile, (2) a cost-effectiveness analysis, (3) quality of life assessment outcomes, and (4) extensive safety data.

As this study is an open trial, in which the participants, clinicians and hospital staff will not be blinded to their treatment allocation, it is at risk of bias, particularly performance or observer bias. A control group undergoing a sham endoscopy would significantly reduce this bias but would expose a large number of patients to the risks of an unnecessary endoscopic procedure and general anaesthetic. Therefore, to reduce the effect of bias: (1) participants will undergo a concealed computer-generated randomisation process by an independent statistician, (2) multiple assessors across both study sites will follow structured assessment protocols and utilise validated measurement tools in order to minimise subjectivity from the data collection, (3) data collection will be monitored regularly to ensure adherence to the protocol and to perform source data verification, and (4), where possible, outcomes and results will be reported by an independent person who is unaware of the treatment allocation of the participant (e.g. the primary outcome measure of HbA1c and all other haematological or biochemical samples will be measured and reported by an independent laboratory technician at each hospital). Attrition bias will be minimised by performing regular scheduled follow-up visits across both treatment groups and regular telephone follow-ups will be performed in order to assess the patient's wellbeing and motivation on the trial. Patients selected for this trial will be a very motivated subset of the population of interest. The effects of this sampling bias will be minimized through effective randomization but will reduce the generalisability of any significant treatment effect identified.

To conclude, we hypothesize that exclusion of the foregut by means of an EndoBarrier[®] device will improve glycaemic control, above that of conventional medical therapy, diet and exercise via: (i) decreased hepatic insulin resistance and increased insulin production, that occurs independent of weight loss and caloric restriction, and (ii) through reduction in total body and tissue-specific insulin resistance as a result of consequent weight loss. We also hypothesize that this device will produce weight loss, above that of control patients, by reducing hunger, increasing satiety (therefore reducing food intake) and changing food preferences and hedonics away from high-energy sweet and fatty foods. If the EndoBarrier[®] is effective at achieving long-lasting weight loss and glycaemic control, there is an obvious potential for health benefit and savings on future health and social care; through the avoidance of T2DM and related complications.

51 Trial Status

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The trial opened for recruitment at Imperial College Healthcare NHS Trust in London on 18th November 2014 and then in University Hospital Southampton NHS Foundation Trust on 5th June 2015. Recruitment was completed across both sites on 18th October 2016 and all EndoBarrier[®] devices were inserted by 23rd January 2017. Participant follow-up continues across both sites with the anticipated trial completion date being 23rd January 2019.

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Figure 1. EndoBarrier Gastrointestinal Bypass Liner



view only

Figure 2a. Study interventions and follow-up schedule

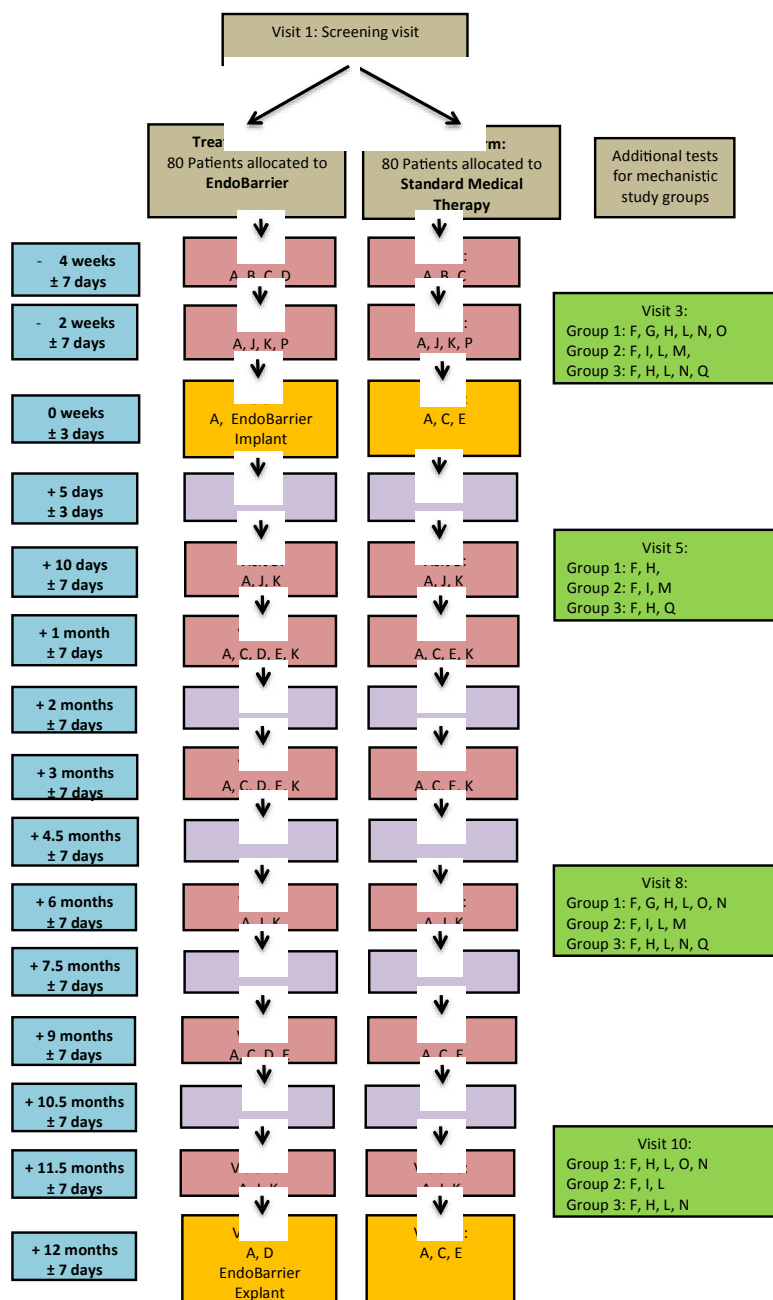
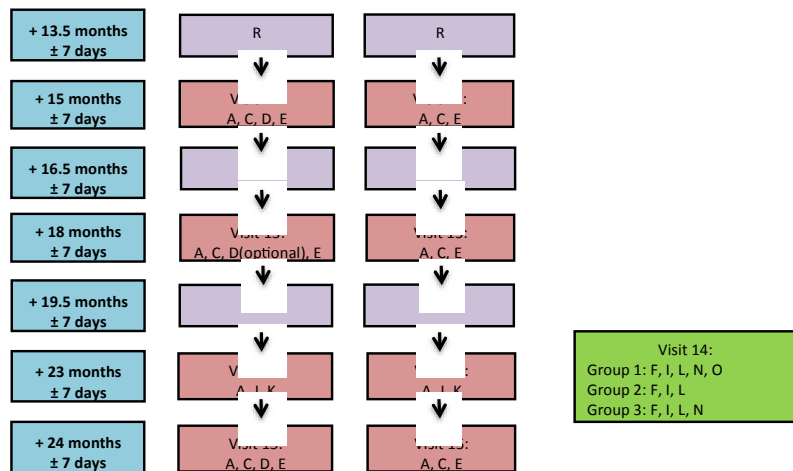


Figure 2b. Study interventions and follow-up schedule



Legend:

- A = Weight, waist, blood pressure, routine bloods, adverse events, changes in medication/medical history
- B = Dietary Counselling
- C = Medical Therapy (Diabetologist/Endocrinologist)
- D = Gastroenterologist
- E = Dietitian follow up
- F= Bioelectrical impedance
- G= fMRI
- H = Gut hormones(fasting and post-meal profile)
- I= Gut hormones(fasting only)
- J = Metabolomics
- K = Health Economics questionnaires
- L = Eating and behaviour questionnaires
- M = Insulin clamps
- N= Eating behaviour computerised tasks
- O= Cognitive assessment tasks
- P= DNA Sample
- Q= Food preference and taste assessment
- R= Telephone counselling

only

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Figure 1. EndoBarrier Gastrointestinal Bypass Liner

344x258mm (300 x 300 DPI)

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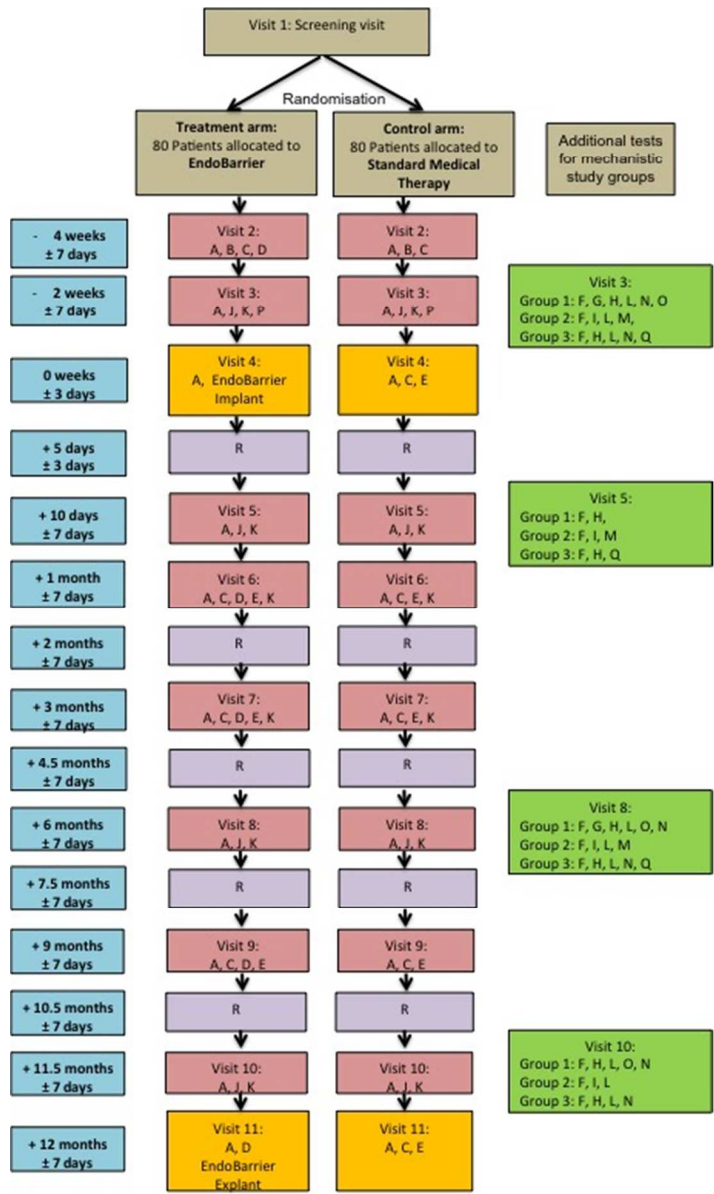
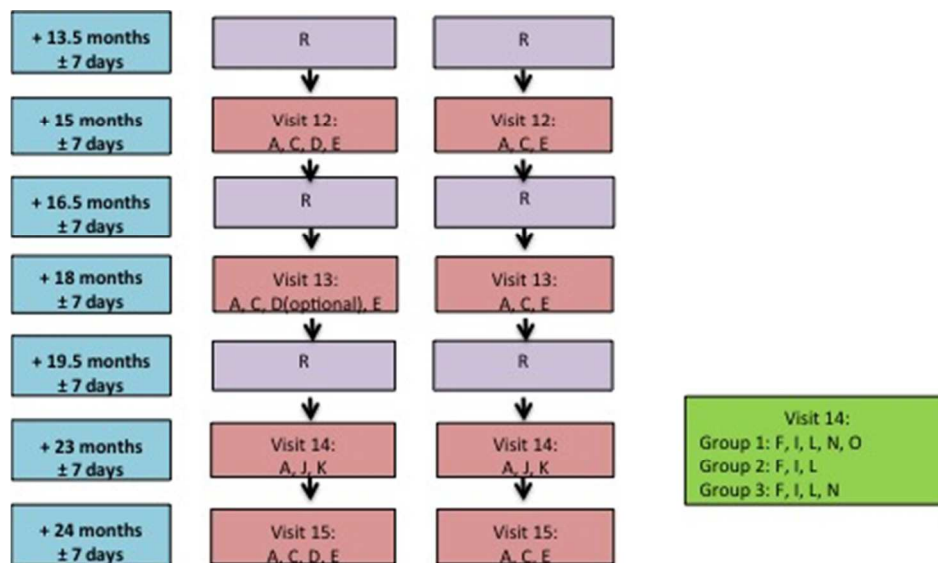


Figure 2a. Study interventions and follow-up schedule

161x275mm (72 x 72 DPI)



Legend:
 A = Weight, waist, blood pressure, routine bloods, adverse events, changes in medication/medical history
 B = Dietary Counselling
 C = Medical Therapy (Diabetologist/Endocrinologist)
 D = Gastroenterologist
 E = Dietitian follow up
 F = Bioelectrical impedance
 G = fMRI
 H = Gut hormones(fasting and post-meal profile)
 I = Gut hormones(fasting only)
 J = Metabolomics
 K = Health Economics questionnaires
 L = Eating and behaviour questionnaires
 M = Insulin clamps
 N = Eating behaviour computerised tasks
 O = Cognitive assessment tasks
 P = DNA Sample
 Q = Food preference and taste assessment
 R = Telephone counselling

Figure 2b. Study interventions and follow-up schedule

165x197mm (72 x 72 DPI)



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____4_____
	2b	All items from the World Health Organization Trial Registration Data Set	https://clinicaltrials.gov/ct2/show/record/NCT02459561
Protocol version	3	Date and version identifier	_____8_____
Funding	4	Sources and types of financial, material, and other support	_____5_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1-3_____
	5b	Name and contact information for the trial sponsor	_____5_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____5_____

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3	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____8_____
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Introduction

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13	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____9-10_____
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16		6b	Explanation for choice of comparators	_____9-12_____
17				
18	Objectives	7	Specific objectives or hypotheses	_____10-11_____
19				
20	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____11_____
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Methods: Participants, interventions, and outcomes

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26	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____11, 16-17_____
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29	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____16_____
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32	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____17-19_____
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35		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____17-19_____
36				Main protocol
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39		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____27_____
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3		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial _____ 16 _____
4	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended _____ 10-11, 19-23 _____
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10	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) _____ 13-15, 29-30 _____
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13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations _____ 23 _____
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16	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size _____ 16-17 _____
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19	Methods: Assignment of interventions (for controlled trials)		
20	Allocation:		
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22	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions _____ 17 _____
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28	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned _____ 17 _____
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32	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions _____ 17 _____
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35	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how _____ N/A _____
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39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial _____ N/A _____
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Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___19-23___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___23-24, 27___
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___19, 27___ Main protocol Section 9, 11.9 & 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___23-25___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___23-25___
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___23-25___
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___8___ Main protocol Section 12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___N/A___
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___19___ Main protocol section 6

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Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____ 8, 27 _____ Main protocol section 12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____ N/A _____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____ N/A _____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 17 _____ Main protocol section 11.5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ 17 _____ Main protocol section 11.5
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____ 5 _____ Main protocol section 11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 5-6 _____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 5 _____ Main protocol section 12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ N/A _____

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____ N/A ____ Main protocol section 12.8
		31b	Authorship eligibility guidelines and any intended use of professional writers	____ N/A ____
		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____ N/A ____
Appendices				
	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____ N/A ____
	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____ N/A ____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Study Protocol: A randomized controlled trial of a duodenal-jejunal bypass sleeve device (EndoBarrier®) compared with standard medical therapy for the management of obese subjects with type 2 diabetes mellitus.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018598.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Sep-2017
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism, Surgery
Keywords:	Obesity, Type 2 diabetes mellitus, Endobarrier, Duodenal-jejunal bypass sleeve, Duodenal-jejunal bypass liner

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Study Protocol: A randomized controlled trial of a duodenal-jejunal bypass sleeve device (EndoBarrier®) compared with standard medical therapy for the management of obese subjects with type 2 diabetes mellitus.

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Abstract

Introduction: The prevalence of obesity and obesity-related diseases, including type 2 diabetes mellitus (T2DM) is increasing. Exclusion of the foregut, as occurs in Roux-en-Y gastric bypass, has a key role in the metabolic improvements that occur following bariatric surgery, which are independent of weight-loss. Endoscopically-placed duodenal-jejunal bypass sleeve (DJBS) devices, such as the EndoBarrier[®] (GI Dynamics Inc, Lexington MA), have been designed to create an impermeable barrier between chyme exiting the stomach and the mucosa of the duodenum and proximal jejunum. The non-surgical and reversible nature of these devices represents an attractive therapeutic option for patients with obesity and T2DM by potentially improving glycaemic control and reducing their weight.

Methods and Analysis: In this multicentre, randomised, controlled, non-blinded trial, male and female patients aged 18–65 years with a BMI 30–50 kg/m² and inadequately controlled T2DM on oral anti-hyperglycaemic medications (HbA1C 58-97mmol/mol) will be randomised in a 1:1 ratio to receive either the EndoBarrier[®] device (n=80) for 12 months or conventional medical therapy, diet and exercise (n=80). The primary outcome measure will be a reduction in HbA1C by 20% at 12 months. Secondary outcome measures will include percentage weight loss, change in cardiovascular risk factors and medications, quality of life, cost, QALYs accrued and adverse events. Three additional sub-groups will investigate the mechanisms behind the effect of the EndoBarrier[®] device, looking at changes in: gut hormones, metabolites, bile acids, microbiome, food hedonics and preferences, taste, brain reward system responses to food, eating and addictive behaviours, body fat content, insulin sensitivity, and intestinal tissue gene expression.

Ethics and Dissemination: Research ethics approval was granted by Fulham Research Ethics Committee, London, (Reference 14/LO/0871) on 10th July 2014. All subjects will give informed written consent. Study findings will be disseminated through peer-reviewed journals, national and international conferences.

Strengths and Limitations of this study:

- This study will represent the largest randomised controlled trial of the EndoBarrier[®] device compared with conventional medical therapy, diet and exercise over a treatment period of 1 year and will also provide the longest follow-up data (1 year) of any trial to date.
- This study will provide: (1) unique data on the mechanism of action of the DJBS and the effect of foregut exclusion on an individual's metabolic profile, (2) a cost-effectiveness analysis, (3) quality of life assessment outcomes, and (4) extensive safety data.
- The unblinded design of this trial introduces the risk of bias.

Key words: Obesity, Type 2 diabetes mellitus, Endobarrier, Duodenal-jejunal bypass sleeve, Duodenal-jejunal bypass liner

Trial Registration: ISRCTN30845205, ClinicalTrials.gov Identifier NCT02459561

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Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Funding and Acknowledgements:

This project is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and National Institute for Health Research (NIHR) partnership.

This paper presents independent research funded by the EME Programme and supported by the NIHR CRF and BRC at Imperial College Healthcare NHS Trust and University Hospital Southampton NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the EME Programme, the NHS, the NIHR or the Department of Health

This study is being executed with the support of GI Dynamics, Inc. and with kind support of Nutricia Advanced Medical Nutrition for providing oral nutritional supplements. Special thanks are given to Brunel University London and the Wolfson Centre for Translational Research, University of Surrey, for their support in sample analysis and to Professors Desmond Johnston, Jeremy Nicholson, and Elaine Holmes as co-applicants for the trial and for their valuable support in the set-up and design of this trial.

Competing interests statement:

Dr. Miras reports grants from Fractyl, personal fees from Novo Nordisk, and personal fees from Astra Zeneca outside the submitted work.

Dr. Goldstone reports funding supported by UK Medical Research Council and Wellcome Trust, outside of the submitted work.

Prof. Poulter's institution reports grants from HTA, during the conduct of the study.

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1 from Astra Zeneca, personal fees from Janssen, personal fees from Bristol-Myers Squibb, personal fees
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Protocol Version

Current version 4.0

Revision chronology:

- Minor amendment 3 29/09/16
 - Protocol V4.1 – number of randomised patients increased from 160 to 170
- Minor amendment 2 11/05/16
 - Extension of funding for 6 months
- Substantial amendment 10/08/15
 - Protocol V4.0 - Changes of inclusion (Section 4.2) and exclusion criteria (section 4.3)
 - Additional correction of minor transcription error in section 5.3
- Minor amendment 1 03/08/15
 - Protocol V3.1 - minor correction of inclusion criteria (section 4.2)
- Substantial amendment 16/03/15
 - Protocol V3.0 - Substantial amendment to protocol
 - Additional amendments to PIS, recruitment advert, business cards, news story.
- Substantial amendment 23/09/14
 - Protocol V2.0 - amendments to duration of liquid diet, questionnaires, blood sampling schedule, testing procedures and addition of biopsies.
 - Additional amendments to PIS, GP/consultant information sheets and letters, participant invitation letters, diet sheets, consent forms and questionnaires.
- Original submission 10/07/14
 - Protocol V1.0

Trial Steering Committee (TSC)

A Trial Steering committee (TSC) with an independent Chair will be appointed and will be responsible for overseeing the progress of the trial. A TSC Charter will be devised to list the roles and responsibilities of the TSC members. TSC will be convened biannually either in person or by teleconference. Two PPI representatives will sit on the Trial Steering Committee and will provide input from a patient perspective at trial meetings.

Trial Management Group (TMG)

The Trial Management Group will be set up by the Chief Investigator (CI). TMG will convene on a monthly basis and will discuss on the recruitment, and other practical aspects of the trial. The TMG will include the CI, Project Manager, ICTU representative and PI at the Southampton site as well as other site staff when appropriate. The day-to-day management of the trial will be co-ordinated through the Imperial Clinical Trials Unit via the Project Manager and the Chief Investigator.

Data Monitoring & Ethical Committee (DMEC)

An independent Data Monitoring and Ethical Committee (DMEC) will be set up to monitor progress, patient safety and any ethical issues involved in this trial. They will review trial progress, recruitment rates, event rates and safety data. A separate charter will be drawn up defining their exact remit and criteria for reporting to the trial steering committee. There will be 6-monthly meetings of the independent DMEC.

Background

Recent years have witnessed a global increase in obesity and obesity-related diseases. In 2014, it was estimated that 39% of the world population were overweight (clinically defined as a body mass index (BMI) of 25 – 30 kg/m²) and 13% were obese (BMI ≥ 30 kg/m²) and it has been projected that there will be an additional 11 million obese adults in the UK by 2030.[1] Being overweight or obese increases the risk of developing 'metabolic syndrome' and is the main modifiable risk factor for developing insulin resistance and type 2 diabetes mellitus (T2DM). Having a BMI of >25kg/m² increases the risk of developing T2DM by 5 times and 90% of adult patients with T2DM are obese or overweight.[2] The prevalence of T2DM has therefore also increased in recent years with an estimated 7.4% of the UK population currently affected and is projected to increase by a further 2.1% in the next 15 years.[3] Compared to the general population patients with T2DM are 87.6% more likely to be admitted to hospital for a myocardial infarction, 121.1% more likely to be admitted for heart failure, 59.1% for a stroke, and are 32% more likely to die prematurely.[4] This represents a significant socioeconomic burden for a largely preventable condition with combined healthcare costs for these conditions estimated to increase by up to 2 billion pounds each year in the UK.[5]

Adipose tissue is a highly active endocrine organ and acts to modulate metabolism by releasing pro-inflammatory cytokines (TNF- α , IL-6, MCP-1),[6] hormones (leptin and adiponectin), glycerol and, importantly, non-esterified fatty acids (NEFA).[7-11] In obesity, especially those with centrally placed adipose tissue, there is increased production of many of these mediators that leads to the development of insulin resistance and pancreatic beta cell dysfunction. T2DM occurs when an already insulin-resistant individual develops beta cell dysfunction and is therefore unable to produce the necessary amount of insulin that is required to maintain normoglycaemia and, as a result, hyperglycaemia predominates.

Dietary modification, exercise, and hypoglycaemic medication remain the mainstay of management for patients with T2DM. Unfortunately, these measures have generally sub-optimal and poorly sustained outcomes. Bariatric, or metabolic, surgery remains the most effective long-term means of treating these patients by producing usually profound and sustained weight loss and weight-loss independent improvements in insulin secretion and sensitivity, consequently ameliorating, or even eliminating, associated co-morbidities and reducing mortality. Roux-en-Y gastric bypass (RYGB) surgery can achieve approximately 23-35% weight loss and 72-90% of patients with T2DM undergoing RYGB are able to achieve sustained euglycaemia without oral hypoglycaemic agents.[12-19] There are several mechanisms by which these outcomes are achieved, namely: (1) gastric exclusion from food by producing a small gastric pouch, (2) exclusion of food from the duodenum and proximal jejunum, (3) early delivery of food to the terminal ileum, and (4) disrupted bile flow. Within the first few days and weeks following surgery, before weight loss has occurred, early improvements in glycaemic control occur through rapid modulation of hepatic insulin resistance (causing reduced hepatic glucose output). This is then followed by sustained long-term weight loss, via entero-neuro-hormonal mechanisms, with an associated reduction in peripheral insulin resistance.[17, 20]

Rubino et al. demonstrated in 2006 that the foregut plays a key role in the metabolic changes that occur following bariatric surgery.[21] They demonstrated that exclusion of the proximal small bowel, as occurs in RYGB and similar procedures such as biliopancreatic diversion (BPD) +/- duodenal switch (DS), results in improved glucose tolerance that occurs independently of effects from reductions in food intake and body weight, malabsorption, or nutrient delivery to the hindgut. These findings have further been substantiated in other studies.[21-24] The proposed mechanisms by which these changes occur include: decreased secretion of orexigenic hormones (ghrelin); increased secretion of glucose-dependent insulinotropic polypeptide (GIP) and cholecystikinin (CCK), increased anorexigenic and incretin hormone secretion (e.g. glucagon-like peptide 1 (GLP-1), peptide YY (PYY), oxyntomodulin), and increased circulating concentrations of plasma bile acids. Additionally, stimulation of vagal afferent nerves in the small bowel cause entero-neuro-endocrine modulation within the gut-liver-brain axis. The resulting net effects include: increased insulin secretion, decreased glucagon secretion, decreased hepatic glucose output, increased pancreatic beta cell mass (via increased proliferation and decreased apoptosis), increased insulin sensitivity, decreased hunger, early satiety and altered food preferences and hedonics and brain reward system responses away from high-energy foods.[20, 25-35]

Such observations have led to the development of novel, endoscopically-placed duodenal-jejunal bypass sleeves (DJBS) or liners. These create an impermeable barrier between chyme exiting the stomach and the intestinal mucosa of the duodenum and proximal jejunum, thus preventing absorption within the foregut. The non-surgical and reversible nature of these devices has sparked much interest in recent years due to the prospect of avoiding the associated surgical mortality and morbidity of bariatric procedures (RYGB: 1 year morbidity 14.9%, 30 day mortality 0.5%).^[17] First described by Milone et al in animal models in 2006,^[36] the effects of DJBS insertion on reducing weight and potentially improving glycaemic regulation, above that of control interventions, has been validated in five randomised controlled trials (RCTs) and numerous observational studies.^[30, 37-49] In a recent systematic review and meta-analysis by Rohde et al.,^[50] they concluded that subjects implanted with DJBS achieved an additional 12.6% weight loss compared to sham controls or dietary intervention alone, and a mean greater weight loss of 5.1kg. In the largest of the RCT (DJBS + diet n=38 vs. diet alone n=39) amongst the DJBS arm a significant reduction in HbA1C of -0.9% was found.^[37] This finding however was not seen in the meta-analysis by Rohde et al. where the mean difference in HbA1C reduction of 0.8% was non-significant.^[50] Finally, evidence exists for DJBS having positive effects on other metabolic parameters, including blood pressure and serum lipid profile.^[37, 44, 45]

The EndoBarrier[®] DJBS (GI Dynamics Inc., Lexington, MA) is delivered endoscopically and comprises of a nitinol metal anchor, which is used to reversibly affix the device to the wall of the duodenal bulb, and an impermeable fluoropolymer sleeve that extends 60cm through the duodenum and into the jejunum (Figure 1). The implant is open at both ends to allow for passage of chyme from the stomach into the lower jejunum and prohibits nutrient absorption along its length by creating a barrier between the partially digested food and the absorptive surface of the small intestine. Whilst the chyme passes through the inside of the EndoBarrier[®] device, all bile and pancreatic secretions pass on the outside the liner and only mix with the food when they come into contact at the end of the sleeve.

Robust evidence for the clinical use of the DJBS is hence still lacking. The small number of published trials include small participant numbers with high degrees of inter-trial heterogeneity and the results are therefore not generalizable to routine clinical practice. Mechanistic data is also limited. There is therefore a call for more long-term, high quality trial data to validate the efficacy and mechanism of action of this device as a potential tool in the treatment of obesity and metabolic syndrome. In this paper, we describe the methodology for a government funded randomised controlled trial comparing DJBS against best practice medical therapy for the treatment of patients with obesity and T2DM with inadequate glycaemic control.

Methodology

Aims and Objectives

Primary Objective and Endpoint

The primary objective of this study is to evaluate the efficacy of DJBS compared with conventional medical therapy, diet and exercise on glycaemic control. As defined by the International Diabetes Federation (IDF) a substantial improvement in an individual's metabolic state occurs with an improvement in glycosylated haemoglobin (HbA1c) by 20%.^[51] Our primary endpoint therefore is a:

- i. Reduction in HbA1c by 20% after 12 months of treatment.

Secondary Objectives and Endpoints

The secondary objectives of this study are to evaluate the efficacy, acceptability and cost-effectiveness of DJBS compared against conventional medical therapy, diet and exercise. Secondary endpoints are:

- i. HbA1C of < 6%, equivalent to 42 mmol/mol (this infers optimisation of the metabolic state as defined by the IDF)^[51]
- ii. Blood pressure < 135/85

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- iii. Weight loss > 15%
 - iv. Reduction in dose/number of medications
 - v. Cost of interventions and related health/social care
 - vi. Quality-adjusted life years (QALY) accrued (calculated from area under the EQ-5D-5L questionnaire curve)
 - vii. Incremental cost per QALY within the trial period and extrapolated through modelling.

Data will also be obtained to investigate the mechanism of action of the EndoBarrier® device via changes in:

- i. Gut hormones
- ii. Bile acids
- iii. Microbiome
- iv. Appetite
- v. Food hedonics and preference
- vi. Taste
- vii. Eating behaviour
- viii. Brain reward system responses to food evaluation and addictive behaviours using functional magnetic resonance imaging (MRI)
- ix. Body fat content
- x. Total body and tissue-specific insulin sensitivity
- xi. Intestinal gene expression

Safety Objective

The safety of the EndoBarrier® DJBS will be evaluated during this trial and the type and frequency of adverse events shall be reported.

Research Approval

This study shall be conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions. Local research ethics approval was granted by Fulham Research Ethics Committee, London, (Reference 14/LO/0871) on 10th July 2014. All subjects will give informed written consent.

Study Design

This study is a randomised controlled trial of the EndoBarrier® DJBS compared with conventional medical therapy, diet and exercise for the management of subjects with both obesity and T2DM. Over a two year period (1 year of treatment and 1 year follow-up) the study will be performed over two investigational sites in the United Kingdom: Imperial College Healthcare NHS Trust in London and University Hospital Southampton NHS Foundation Trust. The overall schema for the trial is summarised in Figure 2. To ensure that the study is adequately powered and allowing for drop-outs, n=80 patients will be randomised into each of the two treatment arms equally across the two sites (Table 1).

Table 1. Summary of treatment group

Treatment Group	Number of subjects	Treatment period 1	Follow-up period 2
EndoBarrier Device	80	12 months	12 months
Standard Medical Therapy	80	12 months	12 months
Total number of subjects	160		

In order to investigate the mechanism of the effect of the EndoBarrier[®] device, both treatment arms will be divided into three optional sub-groups, which will have the following additional assessments during the course of the trial:

- Sub-group 1: functional MRI of food reward and addictive behaviours, eating behaviour assessment and post-meal gut hormones.
- Sub-group 2: Euglycaemic, hyperinsulinaemic clamps (total body and tissue-specific insulin resistance).
- Sub-group 3: assessment of taste and food preference, eating behaviour assessment and post-meal gut hormones.

Table 2 summarises the visit schedule, the data to be collected across both study arms and supplementary data that will be collected from the three optional mechanistic sub-groups. In addition to routine follow-up visits, all patients will receive regular telephone counseling from a specialist dietitian to assess their wellbeing and motivation in the trial.

Table 2. Summary of study visit schedule

Activities	Screening			Baseline			Treatment										Follow-up							
	V1	V2	V3	V4	T1	V5	V6	T2	V7	T3	V8	T4	V9	T5	V10	V11	T6	V12	T7	V13	T8	V14	V15	
Week/ Month/Day		- 4w ±7d	- 2w ±7d	- 0w ±3d	+ 5d± 3d	+ 10d ±3	+ 1m ±7d	+ 2m ±7d	+ 3m ±7d	+ 4.5m ±7d	+ 6m ±7d	+ 7.5m ±7d	+ 9m ±7d	+ 10.5m ±7d	+ 11.5m ±7d	+ 12m ±7d	+ 13.5m ±7d	+ 15m ±7d	+ 16.5m ±7d	+ 18m ±7d	+ 19.5m ±7d	+ 23m ±7d	+ 24m ±7d	
Informed consent (5.1)	X																							
Inclusion & exclusion criteria (4.2, 4.3)	X																							
Demographics (5.1)	X																							
Medical history (including meds) (5.1)	X																							
Physical examination (5.5.4)	X																							
ECG (5.5.5)	X																							
Vital signs (5.5.7)	X	X	X	X		X	X		X		X		X		X	X		X		X		X	X	
Body weight (5.5.8)	X	X	X	X		X	X		X		X		X		X	X		X		X		X	X	
Height (5.5.8)	X																							
Waist circumference (5.5.9)	X	X	X	X		X	X		X		X		X		X	X		X		X		X	X	
Routine blood tests (5.5.10)	X		X			X	X		X		X		X		X	X		X		X		X	X	
Urine dipstick and female pregnancy test (5.5.6)	X																							
Changes in medical history/medication (5.5.4)		X	X	X		X	X		X		X		X		X	X		X		X		X	X	
Randomisation (5.2)		X																						
Health Economic Questionnaires (5.5.12)			X			X	X		X		X				X								X	
Dietary counselling (5.5.3)		X		C																				
Dietitian follow up (5.5.3)							X		X				X			X		X		X				X
Urine albumin:creatinine ratio (5.5.11)			X			X					X				X								X	
Reporting of AEs (6)		X	X	X		X	X		X		X		X		X	X		X		X		X	X	
DNA & RNA sampling (5.5.13)			X			X					X					X								X
Telephone counselling (5.5.3)					X			X		X		X		X			X		X		X			
Diabetologist Review (5.5.1 and 5.5.2)		X		C			X		X				X			C		X		X				X

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Activities	Screening	Baseline		Treatment												Follow-up								
	V1	V2	V3	V4	T1	V5	V6	T2	V7	T3	V8	T4	V9	T5	V10	V11	T6	V12	T7	V13	T8	V14	V15	
Week/ Month/Day		- 4w ±7d	- 2w ±7d	- 0w ±3d	+ 5d± 3d	+ 10d ±3	+ 1m ±7d	+ 2m ±7d	+ 3m ±7d	+ 4.5m ±7d	+ 6m ±7d	+ 7.5m ±7d	+ 9m ±7d	+ 10.5m ±7d	+ 11.5m ±7d	+ 12m ±7d	+ 13.5m ±7d	+ 15m ±7d	+ 16.5m ±7d	+ 18m ±7d	+ 19.5m ±7d	+ 23m ±7d	+ 24m ±7d	
Metabolomics (5.5.14)			X			X					X				X								X	
Bioelectrical Impedance (5.5.15)			X			X					X				X								X	

EndoBarrier Group Only

PPI and H. Pylori test (5.5.16)		X																						
Distribution of Proton Pump Inhibitors (5.5.2)		T																						
EndoBarrier Implant (5.5.2)				T																				
Preparation for EndoBarrier removal (5.5.2)													T											
EndoBarrier removal (5.5.2)																T								
Biopsies during Implant and Explant (5.5.2)				T												T								
Gastroenterologist appointment (5.5.2)		T						T					T			T				T*				T

Sub-groups

Fixed/test meal and post-meal gut hormones and metabolites (Group 1 and 3) (5.6.4)			X			X					X				X									
Gut hormones and metabolites (Fasting only) (Group 1-3) (5.6.4)			X			X					X				X								X	
Food diaries (Groups 1-3) (5.6.2)			X			X					X				X								X	
Eating & Behaviour Questionnaires (Groups 1-3) (5.6.1)			X								X				X								X	
Appetite Visual Analogues Scales (Group 1-3) (5.6.3)			X			X					X				X								X	
Eating behaviour computerised tasks (Group 1 and 3) (5.6.5)			X								X				X								X	
Metal Check Form (Group 1) (5.1)	X																							
Handedness Questionnaire (Group 1) (5.1)	X																							

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Additional pregnancy tests			F																				
	Screening	Baseline		Treatment										Follow-up									
Activities	V1	V2	V3	V4	T1	V5	V6	V7	T2	T3	V8	T4	V9	T5	V10	V11	T6	V12	T7	V13	T8	V14	V15
Week/ Month/Day		- 4w ±7d	- 2w ±7d	- 0w ±3d	+ 5d± 3d	+ 10d ±3	+ 1m ±7d	+ 3m ±7d	+ 2m ±7d	+ 4.5m ±7d	+ 6m ±7d	+ 7.5m ±7d	+ 9m ±7d	+ 10.5m ±7d	+ 11.5m ±7d	+ 12m ±7d	+ 13.5m ±7d	+ 15m ±7d	+ 16.5m ±7d	+ 18m ±7d	+ 19.5m ±7d	+ 23m ±7d	+ 24m ±7d
DS-R disgust questionnaire (Group 1) (5.6.6)			X																				
Functional MRI (Group 1) (5.6.9)			X								X												
Insulin Clamps (Groups 2) (5.6.10)			X			X					X												
Cognitive assessment tasks (Group 1) (5.6.9)			X								X				X								X
Food Preference / Taste Assessment (Group 3) (5.6.11)			X			X					X												
24hr Dietary Recall (Group 3) (5.6.11)			X			X					X				X								X

X performed in all patients unless otherwise stated
 F performed in Females only
 C performed in Control arm (Standard medical therapy) only
 T performed in Treatment arm (EndoBarrier) only
 * optional (at request of the patient)

For peer review only

Study Population

Male and female patients, aged 18–65 years, with a BMI 30–50 kg/m² and confirmed diagnosis of T2DM for at least 1 year, who have inadequate glycaemic control and are on oral anti-hyperglycaemic medications. See Table 3 for complete inclusion and exclusion criteria.

Table 3. Study inclusion and exclusion criteria

Inclusion Criteria	
1.	Age 18–65 years (male or female)
2.	Type 2 diabetes mellitus for at least one year
3.	HbA1C 7.7–11.0% equivalent to 58 – 97 mmol/mol
4.	On oral hypoglycaemic medications
5.	BMI 30 – 50 kg/m ²
Exclusion Criteria	
1.	Language barrier, mental incapacity, unwillingness or inability to understand and be able to complete questionnaires. ☒
2.	Non-compliance with eligibility criteria. ☒
3.	Females of childbearing potential who are pregnant, breast-feeding or intend to become ☒pregnant or are not using adequate or reliable contraceptive methods.
4.	Evidence of absolute insulin deficiency as indicated by clinical assessment, a long duration of ☒T2DM and a fasting plasma C-peptide of <333pmol/L. ☒
5.	Current use of insulin. ☒
6.	Previous diagnosis with type 1 DM or a history of ketoacidosis. ☒
7.	Requirement of NSAIDs (non-steroidal anti-inflammatory drugs) or prescription of ☒anticoagulation therapy during the implant period. ☒
8.	Current iron deficiency and/or iron deficiency anaemia.
9.	Symptomatic gallstones or kidney stones at the time of screening.
10.	History of coagulopathy, upper gastro-intestinal bleeding conditions such as oesophageal or gastric varices, congenital or acquired intestinal telangiectasia.
11.	Previous gastrointestinal surgery that could affect the ability to place the device or the function of the implant. ☒
12.	History or presence of active H. pylori (if subjects are randomised into the EndoBarrier [®] arm☒and have a history or presence of active H. pylori tested at study visit 2 they can☒receive appropriate treatment and then subsequently enrol into the study). ☒
13.	Family history of a known diagnosis or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder.
14.	Severe liver impairment (i.e. AST, ALT or gGT >4 times upper limit of the reference range) or kidney impairment (i.e. estimated Glomerular Filtration Rate (GFR) < 45 ml/min/1.73m ²).
15.	Severe depression, unstable emotional or psychological characteristics (including Beck Depression Inventory II score >28).
16.	Poor dentition and inability to adequately chew food.
17.	Planned holidays up to three months following the EndoBarrier Implant.

Study Recruitment

Participants will be identified from several areas across primary, secondary and tertiary healthcare and community settings:

- i. Diabetes research registers (e.g. Diabetes Alliance for Research in England (DARE), REC 2002/7/118)
- ii. Hospital or General Practice (GP) patient databases (Participant Identification Centres)
- iii. Patients referred to diabetes and bariatric specialist clinics
- iv. Other research studies within the Imperial College Healthcare NHS Trust and the Local Clinical Research Network (LCRN)
- v. Study websites
- vi. Local and national media – websites, radio, newspaper articles and adverts

- vii. Posters
- viii. Diabetes, Obesity and other support groups
- ix. Social media websites

Potential patients who, after reading a summary Patient Information Sheet (PIS), would like to enter the trial will give their verbal consent for preliminary telephone screening to check basic inclusion and exclusion criteria. Written consent will then be taken from the patient to allow the study team to contact their GP for the purpose of obtaining additional information on the patient's medical history, current medical therapies and to identify any other clinical reasons as to why the patient should not participate. Patients who appear to meet eligibility criteria will be provided with a full trial PIS and then invited to a formal screening visit at one of the study centres. At this stage the patient will be fully informed of the nature of the study and given relevant information about the objectives of the research, benefits and possible adverse events, verbally and in writing. The patient will have the opportunity to ask questions about the trial and formal written consent will be taken for the patient to participate in the main study \pm additional consent for one of the three optional mechanistic sub-groups. Once consent has been obtained then the subject's full eligibility will be checked against all inclusion and exclusion criteria (Table 3). Each patient will be informed of their eligibility for the trial once all results are available (usually within one week from obtaining consent).

Randomisation

Eligible patients will be randomised into one of the two trial arms using the InForm Integrated Trial Management system, a secure web-based data entry platform. This will be programmed with a randomisation schedule by an independent statistician and protect against bias in the randomisation process as group allocation will be concealed and automatic. The randomisation will be at a ratio of 1:1 and stratified by site and two BMI groups, 30–40 and 40–50 kg/m². Each patient will be informed of their randomisation allocation and will be assigned a unique study identification number. Only the subject number and initials will be recorded in the case report form (CRF). All other patient-identifiable data will be completely anonymised.

Trial Interventions

EndoBarrier[®] Gastrointestinal Liner

The EndoBarrier[®] Gastrointestinal liner device received CE Mark for 12 months implant duration on 11th December 2009 and is a single use, minimally invasive device, used to achieve weight loss and improve T2DM status in subjects who are obese (Figure 1).

At visit 2 (- 4 weeks), participants who have been randomised to receive the EndoBarrier[®] device will be tested for the presence of *Helicobacter pylori*, either by faecal antigen or urea breath testing. Those patients testing positive will be offered 1 week of triple-eradication therapy, as per guidance published within the British National Formulary, and will then be retested after a further 4 weeks to confirm complete eradication before continuing with implantation of the EndoBarrier[®] device. Subsequently, all patients will be prescribed a proton pump inhibitor (PPI) (Omeprazole 40mg twice daily) and instructed to commence this three days prior to the implant procedure. They will continue this for the duration of the implant period (12 months) and for a further two weeks following device removal.

At visit 4 (0 weeks), after an eight-hour fast, subjects will have the EndoBarrier[®] device implanted under a general anaesthetic. The implant is delivered endoscopically on a custom catheter and the anchor is sited in the duodenal bulb using a custom delivery system under fluoroscopic x-ray guidance (mean fluoroscopic x-ray time for insertion is 7 minutes, range 1–20 minutes). The 60cm sleeve is unfurled and then the final positioning plus patency is confirmed by assessing for the free flow of radio-opaque contrast through the device. Videos and photos of the fluoroscopy images are recorded to help the investigators make treatment decisions. During implantation eight gastric and small bowel biopsies will be taken using standard biopsy forceps. Four biopsies will be used for routine histology and four biopsies will be used for RNA extraction to perform genome-wide expression analysis. Participants will be discharged from hospital the same day with an implant information card, which describes the implant, identifies who to call in

1 the case of an emergency, and what symptoms to look for following the implant. Subjects will have their dose of
2 sulphonylurea medication reduced by 50% at the time of EndoBarrier[®] implant to avoid potential hypoglycaemic
3 episodes.
4

5
6 The device will be removed at visit 11 (after 12 months) under sedation or general anaesthetic. The gastroscop
7 which is fitted with a foreign body retrieval hood, is used to locate the implant and a custom grasper is passed
8 through the working channel of the gastroscop to grab a polypropylene tether located on the proximal portion of
9 the anchor. Pulling on this tether will collapse the proximal end of the anchor, which can then be pulled into the
10 foreign body hood and removed by withdrawing the gastroscop through the subject's mouth. During this removal,
11 eight further biopsies will be taken for histology and RNA extraction. Following removal of the EndoBarrier[®] device,
12 patients will be followed up for a further 12 months.
13

14 **Diabetes Review**

15
16 Participants in both arms of the trial will have their T2DM managed in accordance with the guidelines of the
17 American Diabetes Association (ADA).[52, 53] These guidelines have been chosen as they would adhere to the
18 current best worldwide practice that would still be relevant when the results are published following study
19 completion. Both treatment groups will have a review of their T2DM by a suitably trained physician at visits 2, 6, 7,
20 9, 12, 13 and 15. Additionally, the standard care arm of the trial will have an additional review at visits 4 and 11
21 in place of the EndoBarrier[®] implant and removal. Adjustments to a patient's oral anti-hyperglycaemic medication and
22 escalation of therapy is at the investigators discretion and will comply with general recommendations laid out by the
23 ADA.[53]
24
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28 **Dietary Counselling and Physical Activity**

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30 At visit 2, all patients historical and current eating behaviours will be assessed by a qualified dietitian using the
31 following information: anthropometry; biochemistry; co-morbidities; activity levels; eating habits including previous
32 diets; lifestyle including smoking, drug and alcohol misuse; weight history; psychiatric history; family history of
33 obesity, diabetes, mental illness or eating disorders; available support network; work status; readiness and
34 motivation for change. Patients will then receive dietary and physical activity counselling in accordance with local
35 standards with the intention of providing each subject with lifestyle/behavioural modification information and good
36 eating practices. In addition, subjects in the EndoBarrier[®] arm will receive written information on how their diet will
37 change after implantation of the device and they will receive specialist guidance for eating with their EndoBarrier[®].
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41 All patients will be reviewed by a specialist dietitian at visits 2, 6, 7, 9, 12, 13 and 15. In addition, participants in the
42 standard care arm of the trial will have an additional review at visits 4 and 11 in place of the EndoBarrier[®] implant
43 and removal. During the course of the trial, participants will be recommended to consume 600 kcal less every day,
44 depending on their age, gender, activity levels and body weight. Guidelines for daily amounts are between 1200 and
45 1500 kcal for women and between 1500 and 1800 kcal for men. In accordance with standard dietary practice,
46 subjects will be advised: to eat regularly every day (5 times per day); to control their portion sizes and intake of
47 carbohydrates/starchy foods; to increase their intake of low glycaemic index (GI) and high protein foods, as well as
48 vegetables; and to reduce their intake of foods high in fat and sugar, and alcohol. Participants will be advised to
49 include more physical activity in their daily routine and encouraged to do more activity in their leisure time. Their
50 goal will be to include 150 minutes a week of moderate intensity, and 75 minutes a week of vigorous intensity
51 aerobic activity and muscle strengthening activities, on more than 2 days a week. Changes in physical activity level
52 will be monitored using the International Physical Activity Questionnaire (IPAQ).[54]
53
54

55 **Liquid Diet**

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57 To avoid disruption of the device in the immediate period following implantation, patients will follow a liquid diet for
58 the 7 days before and 13 days (\pm 3 days) after the intervention visit (visit 4). The liquid diet will be guided by the
59
60

specialist dietitian and will comprise of 125ml Fortisip Compact drinks (Nutricia, UK): 5 per day for males, 4 per day for females, containing per 100 mL: 240 kcal, 9.6g protein (16% total energy), 29.7 g carbohydrate (49%), 15g sugars, 9.3g fat (35%). Patients will also be allowed to consume sugar-free squashes, smooth/clear soup (1 medium bowl per day), tea or coffee without sugar, or unsweetened puree. To standardise both therapy groups, all patients across both arms will follow the liquid diet for this duration and period of the study.

Assessment of Objectives

Assessment of Primary Objective

Each study participant will have their IFCC (International Federation of Clinical Chemistry) HbA1C measured at screening and then subsequently at visits 5, 7, 8, 9, 10, 12, 13 and 15. Samples will be processed at the laboratory local to each study centre using standard methods. Results will be recorded on the InForm system.

Assessment of Secondary Objectives

Individuals in both study arms will be invited for regular medical check-ups (Figure 2), which will include routine anthropometric measurements (height, weight, waist circumference, pulse and blood pressure) and blood tests (Table 4). Any changes to the participants' health or medications will be carefully documented on the CRF and all adverse events will be reported in detail in line with standard principles of GCP.

Table 4. Summary of blood tests at each study visit

Blood test	V1	V3	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Haematology (Full blood count)	x	x	x	x	x	x	x	x	x	x	x	x	x
Routine Biochemistry (including Urea and Electrolytes)	x	x	x	x	x	x	x	x	x	x	x	x	x
Liver function tests	x	x	x	x	x	x	x	x	x	x	x	x	x
Fasting glucose	x	x	x	x	x	x	x	x	x	x	x	x	x
Creatinine	x	x	x	x	x	x	x	x	x	x	x	x	x
HbA1C	x		x		x	x	x	x		x	x		x
Fasting lipids (cholesterol, HDL, LDL, triglycerides)	x	x	x	x	x	x	x	x		x	x	x	x
C-peptide	x												
Insulin (Fasting)	x	x	x			x		x				x	
Vitamin D	x					x		x					
Iron studies	x					x		x					
Vitamin B12	x					x		x					
Serum Folate	x					x		x					
Free Thyroxine	x							x					x

TSH	x							x						x
Cortisol (Sub-group 1 only)		x				x								
Oestradiol (Sub-group 1 only)		x				x								
Progesterone (Sub-group 1 only)		x				x								
LH (Sub-group 1 only)		x				x								
FSH (Sub-group 1 only)		x				x								

Patients in both treatment arms will be asked to complete health economics questionnaires at visits 3, 5, 6, 7, 8, 10 and 14. These comprise of the EQ-5D-5L questionnaire to assess health-related quality of life and a bespoke questionnaire designed to collect information about patients' use of health and social care resources (for costing purposes).[55] The Resource Use questionnaire will be adapted from existing instruments and will include:[56, 57]

- i. Medications for diabetes, weight loss, blood pressure, lipid control and cardiovascular disease
- ii. Primary care consultations (with GP, nurse or other healthcare professional) ☐
- iii. Hospital outpatient clinic visits (by specialty) ☐
- iv. A&E attendances (admitted/not-admitted) ☐
- v. Inpatient stays and procedures ☐
- vi. Investigations
- vii. Use of any other NHS-related community health and social services (e.g. chiropody). ☐

Costs for private health and social care, out-of-pocket expenditure by patients, and 'indirect costs' per patient time will not be included.

In addition, data will be collected in the CRF from hospital information systems and case notes to cost the EndoBarrier[®] intervention and the diet/exercise intervention. Information to be collected will include:

- i. Routine assessments required before implantation and removal of the EndoBarrier[®]
- ii. Disposables and staff time for the insertion and removal procedures, including day case and overnight stay if required
- iii. Treatment of any adverse events related to the procedures (additional inpatient stays, ☐ clinic visits and re-admissions)
- iv. Dietitian time to deliver the diet and physical activity counselling and for telephone follow-up
- v. Routine hospital follow-up and diabetes care
- vi. Hospital treatment for cardiovascular events or other complications of diabetes ☐

Mechanistic Study Groups

In addition to the routine data collected above, at visits 3, 5, 8, 10, and 14, mechanistic data will be gathered from all patients across both study arms:

- i. Body fat mass (kg and % of body weight) measured by bio-electrical impedance analysis
- ii. Collection of stool, urine and plasma for assessment of metabonomics using nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS), and microbiome analysis
- iii. Measurement of insulin, gut hormones (ghrelin, GLP-1, PYY), bile acids, leptin and other adipocytokines, and markers of insulin resistance and inflammation from venous blood samples (fasting for all visits and then

- 1 following a meal in sub-groups 1 and 3 at visits 3, 5, 8 and 10)
- 2
- 3 iv. DNA and RNA from venous blood samples for examination of genetic variants that may predict weight loss,
- 4 cause or contribute to obesity
- 5 v. Urinary albumin:creatinine ratio
- 6 vi. Comprehensive 3-day food diary
- 7

8 **Sub-group 1: Functional MRI**

9 Subjects in each study arm, at the London site only, will have fMRI scans to examine brain function related to food
10 reward and addictive behaviours contributing to overeating at baseline (visit 3) and at 6 months (visit 8) after
11 intervention. These will be supplemented by and correlated with psychological questionnaires, computerised tasks
12 and test meals at these and other visits. The study visits will last up to 6-8 hours (scanning visits 3 and 8). Subjects
13 will have structural and functional MRI brain scans lasting up to 90 minutes using a 3.0 Tesla Siemens Verio MR
14 scanner after an overnight fast. Whilst in the scanner, subjects view a mirror reflecting a computer screen and can
15 respond to instructions using a keypad held in their hand.

16

17

18 The following anatomical brain scans will be collected at both visits:

- 19 i. Anatomical T1 and T2-weighted MR scans to provide structural neuroimaging data and allow image
20 registration to standard space.
- 21 ii. Diffusion tensor imaging to examine white matter tract integrity.
- 22

23 The following resting state functional MRI scans will be collected at both visits:

- 24 i. Arterial spin labelling to measure resting regional cerebral blood flow.[58, 59]
- 25 ii. Resting state blood oxygen level-dependent (BOLD) functional MRI to measure resting state functional
26 connectivity.[60]
- 27

28 The following task-related functional MRI scans will be collected at both visits:

- 29 i. Food picture evaluation task: to assess reward system activation when subjects view a variety of different
30 pictures (high-energy and low-energy foods, household objects, blurred pictures as a baseline) and
31 simultaneously rate how 'appealing' the pictures are using the keypad as a measure of anticipatory food
32 reward or food due reactivity.[32, 34, 61-63]
- 33 ii. Monetary incentive delay (MID) task: a game in which subjects need to press a button during a specific time
34 window when given a cue on the computer screen in order to win or prevent the loss of hypothetical
35 monetary prizes to assess anticipatory non-food reward responsiveness.[64-66]
- 36 iii. Go-NoGo task: to assess motor response inhibitory control as a measure of compulsivity.[67-69] The task
37 contrasts brain activation during responses to infrequent no-go signals (e.g. 'do not press' button when
38 viewing one symbol) compared to an implicit go baseline (e.g. 'do press' button when viewing a different
39 symbol).[66]
- 40 iv. Negative emotional reactivity task: to assess brain response during viewing of unpleasant, negatively valent
41 pictures compared to neutral control pictures.[66]
- 42
- 43

44 Study visits without scanning at visits 5, 10 and 14 will last 3-6 hours. At visits 3, 8, 10 and/or 14, subjects in sub-
45 group 1 will also complete several questionnaires and perform several computer-based tasks to assess eating and
46 addictive behaviours and cognition, including:

47

- 48
- 49 i. WTAR word reading list: to document baseline intellectual status (visit 3 only)
- 50 ii. Kirby delay discounting task: to assess temporal impulsivity to a hypothetical non-food monetary rewards
51 (visits 3, 8, 10 and 14).[70]
- 52 iii. Leeds Food Preference Questionnaire: to assess bias of food preference to foods high in fat and sugar and
53 explicit and implicit liking of foods high/low in fat/sugar (visits 3, 8, 10 and 14).[71]
- 54 iv. Progressive ratio task: to measure breakpoint of effort that subjects are willing to spend by having to press a
55 computer mouse an increasing number of times to receive a chocolate M&MTM sweet, to assess appetitive
56 food reward and motivation (visits 3 and 8).[33, 34]
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59 An *ad libitum* test meal will be performed at visits 3 and 8, in which subjects first taste and rate the palatability,
60

1 intensity and acceptability of different foods high or low in fat and sugar, and then eat as much of whichever foods
2 they want, to assess food taste, preference and choice, total energy intake and macronutrient composition. Subjects
3 will also complete visual analogue ratings of appetite, anxiety, stress and sleepiness, and measurement of fasting
4 and post-meal hormones and metabolites over the study visit.[32, 63]

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7 At visit 5, 10 and 14 subjects will consume a fixed mixed meal tolerance test with measurement of fasting and post-
8 prandial hormones and metabolites.
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10 **Sub-group 2: Euglycaemic, hyperinsulinaemic clamp**

11 On visit 3, 5, and 8, patients in each study arm, at the Southampton site only, will undergo a euglycaemic
12 hyperinsulinaemic clamp with stable isotope infusion to determine overall insulin and compartment-specific insulin
13 sensitivity (liver, muscle and adipose depot). Patients will be instructed to consume a standardised meal or meal
14 replacement the evening prior to their study visit. A venous catheter will be inserted into a vein of each arm on the
15 study morning. The first cannula will be used for infusions and the other for blood sampling. If blood glucose levels
16 are higher than 6 mmol/L on arrival then a variable rate insulin infusion will be started to attain a stable glucose
17 level (4.0 -6.0 mmol/L) prior to commencement of the hyperinsulinaemic euglycaemic clamp.
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20 A primed continuous infusion of 6, 6-²H₂-glucose, a stable isotope tracer, will be started and maintained for 7 hours.
21 Two hours later a two-stage hyperinsulinaemic-euglycaemic clamp procedure will be started and continued for 5
22 hours. During stage 1 of the clamp procedure, in which hepatic insulin resistance is assessed, insulin will be infused
23 at a low dose (0.3-0.5 mU/kg/min) for 2 hours. During stage 2 of the clamp procedure, in which peripheral insulin
24 resistance is assessed, insulin will be increased to a higher dose (1.5 mU/kg/min) for 2 hours. Euglycaemia will
25 be maintained by infusing 20% dextrose at a variable rate. Blood samples will be taken every 5 minutes to measure
26 blood glucose concentration and the dextrose infusion will be adjusted accordingly. The exogenous glucose infusion
27 will be enriched with 6, 6-²H₂-glucose to prevent a fall in plasma tracer enrichment and underestimation of
28 endogenous glucose production rate. Blood samples will be obtained before the start of the tracer infusions, every
29 10 min during the final 30 min of the basal period and stages 1 and 2 of the clamp procedure and every 30 minutes
30 between these periods to determine glucose enrichment and concentration, free fatty acid, insulin, C-peptide,
31 glucagon, gut hormones, and metabolite concentrations. At the same time points participants will be asked to
32 complete appetite visual analogue scales.
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36 The isotopic enrichment of plasma glucose will be determined by gas chromatography mass spectrometry (GCMS) at
37 the Wolfson Centre for Translational Research, Postgraduate Medical School, University of Surrey, United Kingdom.
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40 **Sub-group 3: Taste and Food Preference Assessment**

41 On visit 3, 5, 8, 10 and 14, patients in each study arm, at both the London and Southampton sites, will attend the
42 research facility after an overnight fast. The total duration of these visits will be up to 7 hours (visits 3, 5, 8, 10) and 5
43 hours (visit 14). On the morning of those visits patients will perform two behavioural computerized tasks: the Kirby
44 Delay Discounting Task to assess temporal impulsivity to non-food monetary reward (visits 3, 8, 10 and 14);[70] and
45 the Leeds Food Preference Questionnaire to assess bias of food preference to foods high in fat and sugar and explicit
46 and implicit liking of foods high/low in fat/sugar (visits 3, 8, 10 and 14).[71]
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49 Sweet taste detection testing will be performed at visits 3, 5, 8 by following the method of constant stimuli in which
50 seven ascending sucrose concentrations in solution will be used to determine sweet detection thresholds.[72] At the
51 same visits consummatory taste reward will be assessed in which five ascending sucrose solutions will be used to
52 test responses in intensity ratings and hedonic reward. To assess the appetitive behaviour towards a sweet and fatty
53 food reward, a Progressive Ratio Task (PRT) will be performed 2 hours after the consumption of a fixed meal.[33]
54
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56 Total caloric intake and macronutrient composition will be assessed using three-day food diaries and a 24-hour recall
57 that is carried out by a trained dietitian/nutritionist on all visits. Patients will also complete the EPIC Food Frequency
58 questionnaire at visit 3, 8, and 10. Finally, a fixed mixed meal tolerance test with measurement of post-meal
59 hormones and metabolites will be performed.
60

Additional sub-group specific procedures and measurements

Across all three sub-groups only, the following additional data will also be collected during the mechanistic study visits:

- i. Trait, state and symptom questionnaires: to evaluate aspects of eating behaviour (e.g. dietary restraint, emotional eating, disinhibition, hunger, external eating), reward sensitivity, mood, impulsivity, aversive symptoms, symptoms of dumping syndrome, including Dutch Eating Behaviour Questionnaire, Three Factor Eating Questionnaire, Yale Food Addiction Scale, Binge Eating Scale, Beck Depression Inventory II, Hospital Anxiety and Depression Scale (HADS), Barratt Impulsiveness Scale (BIS), UPPS-P Impulsive Behavior Scale.
- ii. Visual analogue scale (VAS) ratings: to assess subjective feelings of hunger, nausea, fullness, sleepiness, stress and anxiety when fasted and during meal tests.

Power Calculation

Conservatively, it was estimated that 15% of patients in the control arm will achieve the target but we believe this to be an overestimate. The Steno study is the best quality randomised study (n=80 patients in each arm) into the effect of best medical therapy published to date and demonstrated over an average 7.8 years significant improvements in HbA1c amongst those having intensive medical therapy from 8.4 ± 1.6 to 7.7 ± 1.2 , but no change in HbA1c amongst those continuing with standard medical therapy.[73] This study defines the very best that could realistically be achieved in the control arm, but expect there to be very little if any change in this group. The reporting of HbA1c as an outcome measure was not in accordance with the newly defined IDF criteria, but considering the small average reduction achieved in the Steno study, it will be assumed that a target of 15% of patients reaching the endpoint is a conservative estimate. Company data on the small number of patients who have reached a year with the device in place suggest that 40% will achieve this target.

According to our own experience with the device in a commercially sponsored study, up to 30% of patients in the treatment group may have the device removed early. Nevertheless other commercially sponsored (unpublished) studies of this device have achieved lower explant rates (J Tetreault – GI Dynamics). To allow for up to 30% early removal we have therefore diluted the treatment effect from 40% vs. 15% to 35% vs. 15% achieving the target of 20% reduction in HbA1c for treatment arm vs. standard arm. With these assumptions, n=73 patients per group will give 80% power with a two-sided alpha 0.05 to detect a significant effect. Adding 10% loss of follow-up increases the sample size to n=80 per group.

The dilution was calculated starting from the assumption that 40% of patients with the device will reach the target (this estimate is based on company data based on diabetic patients in the same range of BMI as in the present proposal). If 30% of patients in the treatment group need to remove the device early but remain available for follow-up, in the worst case scenario, the proportion reaching the target is the same as in the control group, bringing the estimate for the treatment group to 32.5%. However most of them will keep the device for some time, having some benefit, so it is plausible to assume that the estimate is higher than 32.5%. Dividing the main effect 15% vs. 40% in three parts we assume that in the 30% of patients with removal, for 1/3 the same effect will be achieved as in the control group (15% reaching the target), for 1/3 it will be increased (23% reach the target) and for 1/3 more increased (31% reach the target). Overall, this would give an estimate of 35% for the treatment group.

Statistical Analysis

Patient characteristics will be summarized. Summaries of continuous variables will be presented as means and standard deviations if normally distributed, and as medians and inter-quartile ranges for skewed data, whilst categorical variables will be presented as frequencies and percentages. The difference between the two study groups in the proportion of patients achieving substantial improvement in the metabolic syndrome both at 12 and 18 months will be analysed using logistic regression adjusting for the stratification variables (BMI groups and sites). Analysis of secondary outcomes will be conducted using standard statistical procedures applicable to categorical or continuous data as appropriate. For missing values we will explore the pattern and the extent of missingness and we

1 will carry out an appropriate form of multiple imputation if required. The analysis will be performed according to the
2 intention to treat principle. All statistical tests will be two-tailed with a 5% significance level.
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5 **Metabonomics and Microbiome Analyses**

6 Metabonomic datasets will be analysed using principal component analysis (PCA) and orthogonal partial least-
7 squares analysis (O-PLS). The metabolic and microbial data will also be analysed in relation to response
8 measurements such as BMI, gut hormone levels etc. using O-PLS regression analysis and Bayesian approaches. A
9 range of statistical methods will be optimised and applied to the data to identify weight loss and T2DM-associated
10 microbiota and metabolites.
11

12 **Health Economics**

13 The economic health analysis will be conducted following the NICE Reference Case, which includes the use of QALYs
14 as the measure of health outcome, and adoption of an NHS and Personal Social Services perspective for costs (Guide
15 to the methods of technology appraisal 2013, <http://publications.nice.org.uk/pmg9>).
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18 **Within trial analysis**

19 EQ-5D-5L health states will be scored using the English value set to give a utility values at each time point (-2 weeks,
20 10 days, 1, 3, 6, 11.5, and 23 months).[74] QALYs will be estimated for each patient using an area-under-the curve
21 approach.
22
23

24 The cost of the EndoBarrier[®] intervention, the lifestyle intervention, and other related health and social care will be
25 estimated from resource use data. Unit costs for the included services will be obtained from standard national
26 sources (BNF or Drug Tariff for drug prices, Department of Health Reference Costs for investigations, procedures and
27 outpatient visits, PSSRU estimates for other primary and community health and social services). Total costs will be
28 estimated for each patient over the 24-month trial period.
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31 Patient-level cost and QALY estimates will be combined to estimate an Incremental Cost Effectiveness Ratio (ICER)
32 for the EndoBarrier[®] device compared with standard medical therapy over the 24 month trial period. The analysis
33 will combine multiple imputation to account for missing EQ-5D and resource use data with bootstrap regression to
34 estimate mean cost and QALYs for the two patient groups. Missing data is often a particular problem for economic
35 analysis, even in studies with good follow-up of primary endpoints, as area under the curve approach requires data
36 from multiple time points. A bootstrap regression approach will be used to account for non-normal distributions of
37 cost data, to adjust for baseline differences in utility or other patient characteristics, and to allow for correlations
38 between costs and QALYs.
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41 **Cost-effectiveness modelling**

42 A decision analytic model will be developed to estimate clinical outcomes, QALYs, and costs beyond 24 months. The
43 time horizon for the modelling will be for the remainder of the patient's predicted lifetimes, as recommended in
44 modelling guidelines.[75, 76] Before commencing this modelling exercise, a review of published economic decision
45 models for weight loss interventions for people with T2DM will be conducted in order to identify possible model
46 structures and sources of input parameters. The conceptual design of the model will be discussed and agreed
47 amongst the research team before programming commences. It is anticipated that the model will take the form of
48 an individual patient simulation, using either a discrete time or discrete event approach to simulate the onset of
49 diabetes/obesity related complications, and hence QALYs and costs under alternative treatment strategies.
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52 Data from the trial will be used to provide estimates of the effect of the EndoBarrier[®] compared with conventional
53 management. In addition, published systematic reviews and meta-analyses of bariatric surgery for similar a patient
54 population will be reviewed. If recent evidence of sufficient relevance and quality is available, we will extend our
55 model to include indirect comparisons with these other interventions. Other model parameters will be sourced from
56 targeted literature reviews and routine data sources. The choice of software for the model will be made after
57 specification of the conceptual design. Before use, the model will be validated by an experienced health economist
58 not involved in the development of the model. This will be done using a checklist developed by the Brunel Health
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Economics Research Group, which includes a range of suggestions for checking that a model is free from errors (verification) and that it is consistent with internal and external data (validation).

Probabilistic sensitivity analysis (PSA) will be used to estimate the impact of uncertainty over model parameters, and value of information (VOI) analysis to estimate the value of conducting further research. In addition, deterministic sensitivity analysis will be used to examine the impact of uncertainties over the model structure.

Gut hormones, metabolites and bile acids

These will be measured in the fasted and/or postprandial state for each patient and compared within and between the groups using parametric/non-parametric repeated measures statistical testing.

Food hedonics and brain reward responses

Brain activation during fMRI paradigms and outcomes from behavioural measures of eating and addictive behaviours and questionnaires, will be compared between groups using a 2x2 ANOVA design including group (control vs. EndoBarrier®) as a between subject factor, time (baseline vs. follow-up visit) as a within subject factor, and group x time interaction to identify differential effects between groups. For fMRI studies, analysis will use region of interest (e.g. for food picture evaluation task: orbitofrontal cortex (OFC), amygdala, caudate, nucleus accumbens, anterior insula) and whole brain analyses to compare groups using statistical thresholds of voxel-wise correction false discovery rate (FDR) $P < 0.05$ or cluster-wise family wise error (FWE) correction $P < 0.05$. Correlations of BOLD signal will be made with other behavioural variables by linear regression analysis to examine the relevance of changes in brain activation.

Food Preference and Sweet Taste

Dietary energy intake, macronutrient composition, sweet taste detection thresholds, and visual analogue taste ratings will be quantified for each patient and compared within and between the groups at different time points using parametric/non-parametric repeated measures statistical testing. Regressions will be performed with clinical outcomes (e.g. weight loss, HbA1c) to identify predictive markers and generate mechanistic hypotheses.

Hyperinsulinaemic Euglycaemic Clamps

Overall and tissue specific insulin sensitivity will be quantified for each patient and compared within and between the groups at 3 time points using parametric/non-parametric repeated measures statistical testing.

In addition, linear regression will be performed to correlate mechanistic variables collected from each of the sub-groups 1-3 at baseline or during the intervention with clinical outcomes at 1 year e.g. weight loss and decreases in HbA1c, to generate predictive markers and generate mechanistic hypotheses.

Discussion

Experience of 3717 EndoBarrier® devices distributed worldwide has demonstrated a favourable risk-to-benefit ratio (GI Dynamics, February 2017) and their minimally invasive and reversible nature represents a very attractive treatment modality for patients with obesity and T2DM. Evidence already exists in the literature in support of the efficacy of DJBS by reducing weight and potentially improving glycaemic control.[37, 38, 40, 42, 44-46, 50] Nonetheless, it is reported that up to 100% of patients will experience a non-serious adverse event (predominantly abdominal discomfort and nausea immediately following implantation)[50] and 7.4% will suffer a serious adverse event (SAE) (GI Dynamics safety reporting 2008 to March 2017). The exact nature of these events are summarised in Table 5.

Table 5. Serious Adverse Events from the EndoBarrier® device

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017 (Jan – March)	Total
Distributed devices	25	143	157	275	391	812	987	482	383	43	
Hepatic Abscess	0	0	0	0	1	8	12	9	4	2	36
Hepatic Abscess Rate											1.0%
Hepatic Abscess with explant ≤ 12 months	0	0	0	0	1	5	9	7	1	2	25
Hepatic Abscess Rate											0.7%
Intolerance	0	5	4	12	5	10	11	4	18	0	69
Intolerance Rate											1.9%
Liner Obstruction	0	4	0	5	3	1	10	2	0	0	25
Liner Obstruction Rate											0.7%
GI Bleed	0	1	3	6	5	9	20	8	4	1	57
GI Bleed Rate											1.5%
Migration/Movement	0	10	6	4	1	6	11	13	0	1	52
Migration/Movement Rate											1.4%
Pancreatitis	0	0	0	0	4	1	7	0	0	0	12
Pancreatitis Rate											0.3%
Perforation	0	0	1	0	0	5	2	2	1	0	11
Perforation Rate											0.3%
Surgical Removal	0	0	0	1	1	0	8	1	1	0	12
Surgical Removal Rate											0.3%
Total Incidences	0	20	14	28	20	40	81	39	28	4	274
Total Cumulative Rate											7.4%

GI dynamics safety reporting 2008 to March 2017

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Notably, the pivotal U.S ENDO trial (EndoBarrier[®] vs. Sham procedure) was terminated in July 2015 after only 325 subjects were randomised (n=216 EndoBarrier subjects) due to a higher than expected hepatic abscess (HA) rate of 3.5% (compared to a global incidence of 0.73%). This high incidence of HA is not the experience within Europe with 1.2% being reported in 1901 distributed devices (UK hepatic abscess rate in 523 cases is 1.34%). There have also been no deaths attributed to the EndoBarrier[®] and all patients experiencing an SAE have recovered without long-term sequelae.

Research to date therefore validates the EndoBarrier[®] DJBS as a potential treatment option for patients who are obese with or without T2DM. These studies however have been limited by their low participant numbers, short follow-up duration and wide inter-trial heterogeneity. Thus, there is a call for more robust clinical trial data to investigate its efficacy, safety and acceptability, and to establish where its use may fall within the treatment algorithm of such patients. This study will represent the largest randomised controlled trial of the EndoBarrier[®] device compared with conventional medical therapy, diet and exercise over a treatment period of 1 year and will also provide the longest follow-up data (1 year) of any trial to date. Additionally, this study will provide: (1) unique data on the mechanism of action of the DJBS and the effect of foregut exclusion on an individual's metabolic profile, (2) a cost-effectiveness analysis, (3) quality of life assessment outcomes, and (4) extensive safety data.

As this study is an open trial, in which the participants, clinicians and hospital staff will not be blinded to their treatment allocation, it is at risk of bias, particularly performance or observer bias. A control group undergoing a sham endoscopy would significantly reduce this bias but would expose a large number of patients to the risks of an unnecessary endoscopic procedure and general anaesthetic. Therefore, to reduce the effect of bias: (1) participants will undergo a concealed computer-generated randomisation process by an independent statistician, (2) multiple assessors across both study sites will follow structured assessment protocols and utilise validated measurement tools in order to minimise subjectivity from the data collection, (3) data collection will be monitored regularly to ensure adherence to the protocol and to perform source data verification, and (4), where possible, outcomes and results will be reported by an independent person who is unaware of the treatment allocation of the participant (e.g. the primary outcome measure of HbA1c and all other haematological or biochemical samples will be measured and reported by an independent laboratory technician at each hospital). Attrition bias will be minimised by performing regular scheduled follow-up visits across both treatment groups and regular telephone follow-ups will be performed in order to assess the patient's wellbeing and motivation on the trial. Patients selected for this trial will be a very motivated subset of the population of interest. The effects of this sampling bias will be minimized through effective randomization but will reduce the generalisability of any significant treatment effect identified.

To conclude, we hypothesize that exclusion of the foregut by means of an EndoBarrier[®] device will improve glycaemic control, above that of conventional medical therapy, diet and exercise via: (i) decreased hepatic insulin resistance and increased insulin production, that occurs independent of weight loss and caloric restriction, and (ii) through reduction in total body and tissue-specific insulin resistance as a result of consequent weight loss. We also hypothesize that this device will produce weight loss, above that of control patients, by reducing hunger, increasing satiety (therefore reducing food intake) and changing food preferences and hedonics away from high-energy sweet and fatty foods. If the EndoBarrier[®] is effective at achieving long-lasting weight loss and glycaemic control, there is an obvious potential for health benefit and savings on future health and social care; through the avoidance of T2DM and related complications.

51 Trial Status

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The trial opened for recruitment at Imperial College Healthcare NHS Trust in London on 18th November 2014 and then in University Hospital Southampton NHS Foundation Trust on 5th June 2015. Recruitment was completed across both sites on 18th October 2016 and all EndoBarrier[®] devices were inserted by 23rd January 2017. Participant follow-up continues across both sites with the anticipated trial completion date being 23rd January 2019.

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Figure Legends

Figure 1. EndoBarrier[®] Gastrointestinal Bypass Liner

Figure 2. Study interventions and follow-up schedule

For peer review only



Figure 1. EndoBarrier Gastrointestinal Bypass Liner

344x258mm (300 x 300 DPI)

ew only

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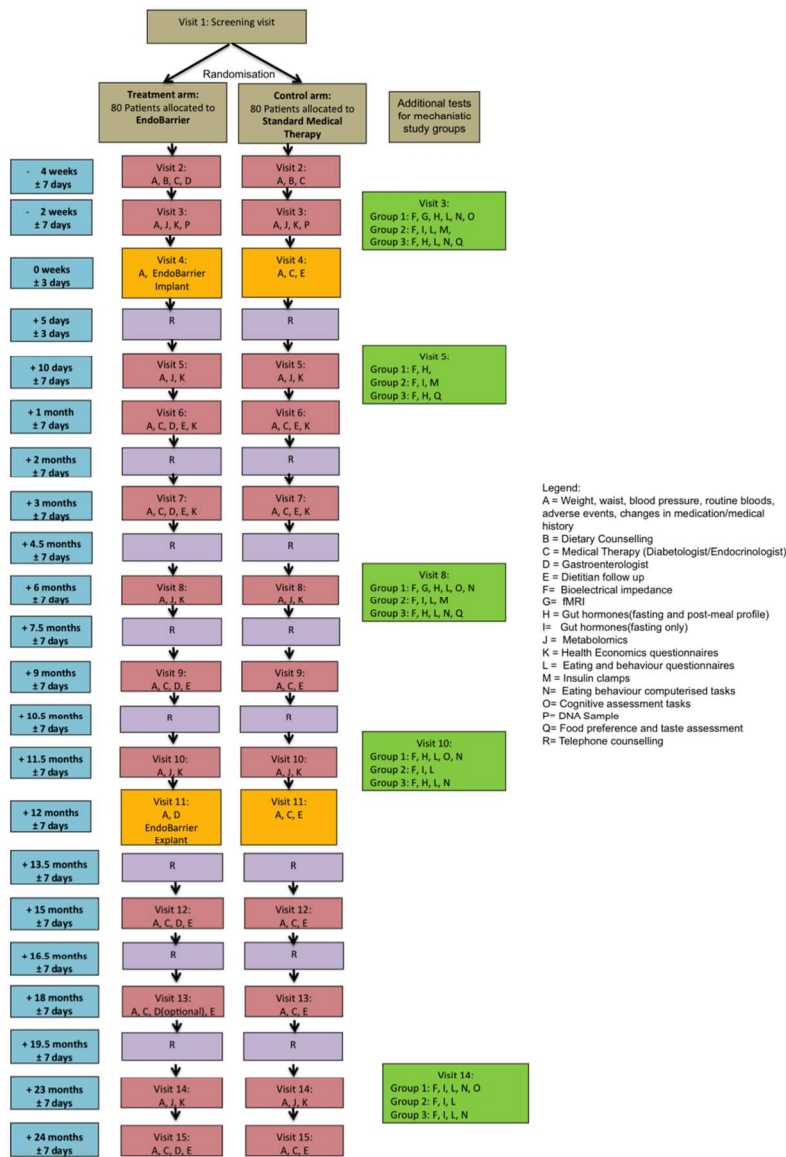


Figure 2. Study interventions and follow-up schedule

95x138mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____ 1 _____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____ 4 _____
	2b	All items from the World Health Organization Trial Registration Data Set	https://clinicaltrials.gov/ct2/show/record/NCT02459561
Protocol version	3	Date and version identifier	_____ 8 _____
Funding	4	Sources and types of financial, material, and other support	_____ 5 _____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____ 1-3 _____
	5b	Name and contact information for the trial sponsor	_____ 5 _____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____ 5 _____

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	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____8_____
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Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____9-10_____
	6b	Explanation for choice of comparators	___ 9-12_____
Objectives	7	Specific objectives or hypotheses	_____10-11_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____11_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__11, 16-17__
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____16_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___17-19_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___17-19_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____27_____

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3		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial _____ 16 _____
4	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended _____ 10-11, 19-23 _____
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10	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) _____ 13-15, 29-30 _____
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13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations _____ 23 _____
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16	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size _____ 16-17 _____
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19	Methods: Assignment of interventions (for controlled trials)		
20	Allocation:		
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22	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions _____ 17 _____
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28	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned _____ 17 _____
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32	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions _____ 17 _____
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35	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how _____ N/A _____
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39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial _____ N/A _____
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Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___19-23___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___23-24, 27___
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___19, 27___ Main protocol Section 9, 11.9 & 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___23-25___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___23-25___
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___23-25___

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___8___ Main protocol Section 12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___N/A___
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___19___ Main protocol section 6

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3	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___ 8, 27 ___ Main protocol section 12
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7	Ethics and dissemination			
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9	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ N/A ___
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12	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ N/A ___
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15	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___ 17 ___ Main protocol section 11.5
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21		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___ 17 ___ Main protocol section 11.5
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25	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___ 5 ___ Main protocol section 11
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29	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___ 5-6 ___
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33	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___ 5 ___ Main protocol section 12
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37	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___ N/A ___
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Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____ N/A ____ Main protocol section 12.8
	31b	Authorship eligibility guidelines and any intended use of professional writers	____ N/A ____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____ N/A ____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____ N/A ____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____ N/A ____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.