The role of an endoscopic duodenal jejunal exclusion device on the metabolic profile, glycaemic control and weight loss in Type II Diabetes: a multi centred randomised control trial

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Declaration of Originality

I hereby certify that this piece of work presented in this thesis is entirely my own research and was conducted in the Department of Surgery and Cancer at Imperial College London between October 2014 and October 2018. All published and unpublished material has been given full acknowledgement. Copyright and permissions have been sought and granted and this is clearly stated in this thesis where applicable.

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Abstract

The incidence and prevalence of obesity and type 2 diabetes (T2DM) is increasing at an alarming rate and now poses a global threat to mankind. Bariatric surgery is now an established strategy for combating both these conditions but recent years have also seen the emergence of endoscopic treatments designed to mimic the effects of surgery. These devices have the added advantage of being minimally invasive and easily reversible. The Endobarrier (EB) is an endoluminal duodenal-jejunal bypass liner (DJBL) licensed for up to 12 months of treatment in patients with type 2 diabetes who are obese.

In this thesis I explored the feasibility and safety of this device as an effective method of weight loss and glycaemic control in the setting of nationally funded multicenter randomised control trial. This clinical trial compared the device implanted for 1 year versus standard medical therapy (control) in a cohort of 170 obese patients with type 2 diabetes. Body weight decreased by 10.8±5.3kg in the EB group and 12.1±7.8 at 6 and 12 months respectively. In comparison the control group lost 6.3±5.5kg at 6 months and 6.2± 6.4 at 12 months (*P*=<0.001). Significant improvements in fasting insulin levels, total cholesterol and liver biochemistry were also seen between both patient cohorts. Plasma, urine and stool from participants were also analysed using nuclear magnetic resonance to identify key metabolic perturbations between both patient cohorts. The metabolite trimethylamine N-oxide (TMAO) which is associated with the development of diabetes was found to reduce in the plasma of Endobarrier patients. Microbial derived metabolites phenylacetylglycine and 3-indoxylsulfate were found in increasing amounts in the urine whilst a reduction in tricarboxylic acid cycle intermediates fumarate and malate were seen in the stool.

The results of this study help in defining the current role of the DJBL in the treatment algorithm of patients with diabetes and obesity but also identifies some of the devices similarities to gastric bypass surgery. Crucially this research provides a possible insight into the mechanisms of how this device

may elicit its effect which may include altering the gut microbiome, reducing levels of TMAO and increasing anaerobic energy metabolism.

Table of Contents

List of Tables

List of Figures

Abbreviations

ADA – American Diabetes Association

AE - Adverse Event

ALT – Alanine Aminotransferase

ALP – Alkaline Phosphatase

AST – Aspartate Aminotransferase

BA – Bile Acid

BCAA - Branch Chained Amino Acids

BMD – Bone Mineral Density

BMI - Body Mass Index

CCK - Cholecystokinin

CKD – Chronic Kidney Disease

CPMG - Carr-Purcell-Meiboom-Gill|

CTR – Click Through Rate

CVD – Cardiovascular Disease

DNA – Deoxyribonucelic Acid

EB – Endobarrier

EWL – Excess Weight Loss

FDA - Food and Drug Administration

FPG – Fasting Plasma Glucose

GADA – Glutamic Acid Decarboxylase

GM – Gut Microbiota

GIB – Gastrointestinal Bleeding

GGT - Gamma-Glutamyl Transpeptidase

GLP – Glucagon Like Peptide

HDL - High Density Lipoprotein

IGB – Intragastric Balloon

LDL – Low Density Lipoprotein

LFTs – Liver Function Tests

ICHT - Imperial College Health Trust

MS - Mass Spectrometry

NAFLD – Non-alcoholic fatty liver disease

NMR - Nuclear Magnetic Resonance

OPLS-DA – Orthogonal Projections to Latent Structures Discriminant Analysis

PC – Principle Component

PCA – Principle Component Analysis

PLS – Partial Least Squares

PPI – Proton Pump Inhibitor

REC – Research Ethics Committee

RCT - Randomised Control Trial

RNA – Ribonucleic Acid

RYGB - Roux-en-Y Gastric Bypass

SAE - Serious Adverse Event

SD – Standard Deviation

T2DM – Type 2 Diabetes Mellitus

TBWL – Total Body Weight Loss

TCA – Tricarboxylic Acid

TMAO – Trimethylamine N-oxide

UHS – University Hospital Southampton

UPLC – Ultra Performance Liquid Chromatography

Publications & Abstracts

Included in this thesis with direct extracts which have been referenced at the beginning of each chapter and necessary permissions and copyright obtained:

1. **Ruban A**, Stoenchev K, Ashrafian H, Teare JP. Current Treatments for Obesity. Clinical Medicine 2019 19:205-212; doi:10.7861/clinmedicine.19-3-205

2. **Ruban A**, Ashrafian H, Teare JP. The Endobarrier: Duodenal Jejunal Bypass Liner for Diabetes & Weight Loss. Gastroenterology Research and Practice 2018. https://doi.org/10.1155/2018/7823182/.

3. **Ruban A**, A Uthayakumar, Ashrafian H, Teare JP. Mentored Reviews: Endoscopic Interventions in the Treatment of Obesity & Diabetes. *Digestive Diseases and Sciences* 2018 https://doi.org/10.1007/s10620-018-5117-1

4. **Mohanaruban A**. Could the Endobarrier be the next weapon of mass reduction? Imperial Medicine Blog 2018. http://wwwf.imperial.ac.uk/blog/imperial medicine/2018/03/28/endobarrier-next-weapon-mass reduction/

5. Patel N, **Mohanaruban A**, Ashrafian H et al. Endobarrier: A safe and effective novel treatment for obesity and type 2 diabetes. *Obesity Surgery* 2018. https://doi.org/10.1007/s11695-018-3123-1

6. Glaysher M, **Mohanaruban A**, Prechtl CG et al. A randomised 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 mellulitis. *BMJ Open* 2017; doi: 10.1136/bmjopen-2017-018598

7. **Mohanaruban A**, Patel N, Ashrafian H *et al* Endobarrier: A safe and effective novel treatment for obesity and type 2 diabetes. *BSG abstract June 2017*

8. Featured in Daily Mail Article May 2016: The no-surgery "gastric band" that helps patient's shed a quarter of their weight AND beat diabetes. http://www.dailymail.co.uk/health/article-3594540/The-no-surgery-gastric-band-helps-patients-shed-quarter-weight-beat-diabetes.html

Chapter 1: Introduction

This chapter contains direct extracts from the following publications, with permission:

1. **Ruban A,** Stoenchev K, Ashrafian H, Teare JP. Current Treatments for Obesity. Clinical Medicine 2019 19:205-212; doi:10.7861/clinmedicine.19-3-205

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1.1 Obesity

1.1.1 Epidemiology

Obesity is defined by the World Health Organisation (WHO) as "abnormal or excessive fat accumulation that presents a risk to health." [1] Obesity has reached epidemic proportions with the WHO estimating that approximately 2.3 billion adults worldwide are overweight, and more than 700 million obese. In 2015, 58% of the female population in the UK and 68% of the male population were overweight or obese with obesity prevalence increasing from 15% in 1993 to 27% in 2015.[2] The Department of Health estimates that obesity could cost society and the economy £50 billion by 2050 if obesity rates continue to double.[3]

1.1.2 Genetic Susceptibility of Obesity

Although increasing obesity prevalence is believed to be largely driven by multiple environmental factors including increased consumption of high calorie foods and a reduction in physical activity there is wealth of evidence which also points to the genetic susceptibility of developing obesity.[4, 5] The emergence of genome wide association studies (GWAS) has aided in identifying a number of genetic variants predisposing to obesity. One of the first of these genes to be identified was the FTO (fat mass and obesity associated) gene in 2007.[6, 7] This minor allele increases the risk of obesity by 1.20 fold and is thought to do so by a variety of mechanisms including increasing dietary intake, reducing satiety and by repressing thermogenesis in the mitochondria of adipocyte precursor cells.[8-10] The FTO loci remains to date to have the largest effect on obesity although numerous others have been subsequently identified which appear to have a lesser impact.[11] Some of these gene loci were found to map close to hypothalamus regulators of energy balance whereas other genes for fat distribution were in abundance in adipose tissue itself. Despite novel insights from GWAS into the biology of obesity, many of the loci identified have a low proportion of heritability which may not make them useful predictive tools for the development of obesity.[12] Nevertheless in identifying those gene loci associated with obesity may help in elucidating new physiological pathways and mechanistic information that allow the development of new treatments in the future.

1.1.3 Classification and Assessment

The Body Mass Index (BMI) is the most widely adopted classification to assess weight (Table 1.1) and is calculated by weight in kilograms divided by height in meters squared (kg^2/m^2). BMI is simple to calculate, but does have its limitations, where factors such as age, muscle mass and ethnicity can influence the relationship between BMI and body fat. An example of this is that Asians have a higher percentage of body fat in comparison to their Caucasian counterparts of the same sex, age and

BMI.[13] A WHO expert group concluded that the proportion of Asians with risk factors for type 2 diabetes and cardiovascular disease even at BMI cutoff point of 25kg/m^2 was not insignificant.

Table 1. 1 WHO adult BMI classification

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal Weight	18.5-24.9
Overweight	25.0-29.9
Obese Class I	30.0-34.9
Obese Class II	35.0-39.9
Obese Class III	≥40

Anthropometric measures such as skinfold thickness, waist circumference and waist-to-hip ratio are increasingly used as alternatives to BMI in assessing an individual's risk of obesity related conditions such as type 2 diabetes and cardiovascular disease.[14-16] Skin fold anthropometry measurement allows body fat and muscle stores to be predicted by calculation but with numerous skin fold calipers available measurements may differ depending on expertise and type of caliper used.[17] Waist circumference provides a useful marker of excess abdominal adiposity and has been positively associated with obese-related premature mortality.[18] In men 94–102 cm is deemed high and more than 102 cm is very high whilst in women, waist circumference of 80–88 cm is high and more than 88 cm is very high.[19] Its advantageous as it only relies on a single measurement taken with a simple non stretch tape measure but its major limitations in practice are the inconsistencies in how and where it is measured. Various landmarks can be chosen including positioning the tape midway between costal margin and iliac crest or the minimum abdominal circumference and at the level of the

umbilicus yielding significantly different values.[20] In order not to impair serial measurements it is therefore crucial to record the site measured. Due to the relative ease of obtaining waist circumference, this method is preferred over waist-hip ratio (waist circumference divided by hip circumference) measurements.

From the anthropometric variables listed above, it is clear that no one method or technique is superior, but BMI remains the most popular chiefly as it is easily measured and calculated in the clinical setting and without the need for specialist equipment.

1.1.4 Dietary Therapy

Weight loss hinges on the concept of kilocalories as units of energy quantification, which can be achieved by a net energy deficit as a result of reducing dietary calorie intake. The daily energy expenditure per kilogram of body weight for an adult is estimated to be approximately 22 kcal.[21] There are three main dietary methods of achieving a negative balance; low calorie diets, macronutrient control and dietary styles (Table 1.2).

Table 1. 2 Summary of Dietary interventions for Weight loss

Diet	Principles	Mechanisms of Action	Variants
Low calorie diet (LCD)	800-1600 kcal/day	Negative energy balance (net deficit of calories)	Weight Watchers Nutrisystems diet Intermittent Fasting Biggest Loser SlimFast Jenny Craig
Very low-calorie diet (VLCD)	200-800 kcal/day		
Low calorie diet: meal replacement	Pre-cooked low kcal meals		
Low fat diet (LFD)	Fat accounts for <30% of energy intake	Negative energy balance achieved by reduction of dietary fat, which is the most energy-dense macronutrient (9 calories/gram)	LEARN Ornish Rosemary Conley
Low carbohydrate diet (LCHD)	LCHD: <130 g/day	1. Negative energy balance achieved by reduction of dietary carbohydrates (3.75 cal/gram) 2. Mobilization of glycogen stores, and associated water loss 3. Ketogenesis	Atkins South Beach Zone
Very-low carbohydrate diet (VLCHD)	VLCHD: <60 g/day		
High protein diet (HPD)	Protein accounts for >30% of energy intake	Increased satiety leading to reduced passive overconsumption of other macronutrients, thus achieving a lower energy balance	
Mediterranean-style diet (MSD)	High intake of fruits, vegetables, grains; moderate intake of fat (mostly mono-unsaturated) and diary (mostly cheese), reduced intake of meats (fish and poultry in preference to red meat)	1. Lipid reduction 2. Lowering of oxidative stress and improved endothelial function 3. Anti-inflammatory effects 4. Gut microbiota changes	Regional variation

1.1.4.1 Low and Very Low Calorie Diets

Very low (<800kcal/day) and Low calorie diets (typically 800-1600 kcal/day achieve significant weight loss by limiting the ingestion of all nutrients to achieve a negative energy balance).[22] Calorie reduction can be largely achieved either by control on portion size or by selective omission of high-calorie foods. However, the requirement for calorie counting by the latter limits diet adherence and thus weight loss, partially circumvented by the advent of pre-prepared low-calorie meals.

A commercial weight loss program in Sweden evaluated weight loss and drop rate after 1 year in individuals on a 500kcal liquid formula VLCD group, 1200-1500kcal formula and food combination and 1500-1800kcal restricted normal food diet.[23] Weight loss was largest in the VLCD group at −11.4 ± 9.1 kg compared to −6.8 ± 6.4 kg in the LCD, and −5.1 ± 5.9 kg with the restricted normal-food diet. Furthermore dropout rates were lowest in the VLCD group (18%) compared with 23% and 26% in the LCD group, and 26% in the restricted normal-food group. The favourable weight loss and dropout rate in the VLCD group in this study suggests an approximately linear dose response relation between energy intake and reduced body weight. A recent systematic review demonstrated good evidence on the use of VLCD in diabetic patients with a mean weight loss of 13.2kg and mean reduction of glycosylated haemoglobin of 1.4% in the 17 studies reviewed.[24] Many of the studies included were heterogenous and trials with long term VLCD outcomes are still awaited.

1.1.4.2 Macronutrient control

The three primary dietary macronutrients are fat, carbohydrate and protein, which provide 9, 3.75 and 4 calories per gram, respectively.[25] Fat is the least satiating, most readily absorbed and calorie-dense macronutrient, making it the most appealing target for weight loss intervention. Although lipids may have a weak effect on generating satiety signals this is outweighed by passive overconsumption from the high energy density and high palatability of high fat foods.[26, 27] Recent meta-analysis of

low-fat diets show significant weight loss when compared to a usual diet (-5.41 kg) but not when compared to other dietary interventions, including high-fat diet.[28]

Low carbohydrate diets (LCHDs) are particularly popular as they provide a rapid initial weight loss, yielding greater results compared to low-fat diets at 6-12 months (by up to 3.3 kg).[29] However, much of this has been attributed to loss of glycogen stores and water amounting to 1-2 kg within the first 14 days, after which the rate of weight loss slows.[30]

Protein is the most satiating macronutrient, which limits overall energy intake and prevents passive overconsumption of less-satiating and more energy-dense macronutrients.[27] Mellinkoff in the early 1950s suggested that high circulating plasma amino acids may serve as satiety signals thus reducing food intake.[31] The effects of high-protein diets (HPDs) were illustrated in numerous RCTs, noting increased satiety, weight loss (primarily from fat mass) and weight loss maintenance for up to 24 months. However, more recent meta-analyses have concluded that a HPD has either no effect on body weight, or a small effect of questionable benefit (WMD -0.36 kg).[32, 33]

1.1.4.3 Meal Replacement

Meal replacement, either full or partial, involves nutritionally replete but low-calorie substitutes for daily meals, offering an easy and convenient method for calorie intake restriction. Significant weight loss benefits of meal replacement compared to conventional calorie restriction were illustrated by a meta-analysis of 6 studies by Heymsfield *et al*. Partial meal replacement (PMR) yielded greater weight loss at 3 months (-2.54 kg) and 1 year (-2.63 kg), with a lower attrition rate.[34] Similar effects were demonstrated by a subsequent systematic review, where PMR yielded a 3.8 kg weight loss benefit over control diets at 1 year.[35] Furthermore, although PMR subjects experience more weight re-gain

in the long term compared to conventional diets, the overall weight loss remains greater (-7.8% vs -5.9% at 40 weeks).[36]

Of note, dietary weight loss is accompanied by improvement and even remission of obesity-associated complications, namely type 2 diabetes mellitus. The DiRECT study of 298 participants demonstrated remission of type 2 diabetes mellitus in 73% of participants who lost >10 kg of weight after 12 months of low calorie diet replacement.[37] The postulated mechanisms for this include reduced hepatic gluconeogenesis, net hepatic glycogenolysis and improved hepatic insulin sensitivity.[38] Further beneficial effects noted by the DiRECT trial include improvements in blood pressure and triglyceride levels.

1.1.4.4 Dietary styles

The Mediterranean-style diet (MSD) originates from olive-growing regions of the Mediterranean and has a variety of regional differences. The core principles include a high intake of fruits, vegetables and grains, a moderate intake of fat (most of which from mono-unsaturated fats) and dairy (primarily from cheese), and a reduced intake of meat (fish and poultry in preference to red meat). This can result in significant weight loss (mean range -4.1 kg to -10.1 kg weight loss at 12 months) as well as beneficial effects on multiple cardiovascular risk factors, yet it is less restrictive than other diets.[39]

1.1.4.5 Diet Choice

Seemingly, VLCDs may lead to impressive weight loss outcomes in the short term but due to their strict nature of the number of calories that are allowed to be consumed by an individual, this might be unsustainable in the long term. The Atkins diet (a form of LCD) may be more realistic option to adhere to and has shown promising results in both short and long term weight loss but more studies are required to measure changes in nutritional status and body consumption following this intervention.[40, 41]

A Mediterranean style diet includes a great variety of foods which are eaten in moderation and in a social environment and so would appear to be not only the most attractive choice but also the one most likely to succeed due to the likelihood of dietary compliance.

However, with no clear leading diet emerging to date, calorie restriction remains the common factor for weight loss, irrespective of macronutrient composition. This is dependent on diet adherence, especially as dietary effects on weight loss plateau with time due to compensatory adaptation.

For the treatment of obesity, the current NICE guidelines recommend: [19]
A dietary approach with lower energy intake than expenditure.
A deficit of 600 kcal/day (via LCD or LFD) is recommended for sustainable weight loss, together with expert support and intensive follow-up.
Consider LCD at 800-1600 kcal/day but ensure it is nutritionally complete.
200-800 kcal/day diets are not recommended unless clinical need for rapid weight loss.

1.1.5 Pharmacological Treatments

NICE currently recommends pharmacological treatment for weight loss maintenance in addition to a reduced-calorie diet and optimal physical exercise. Pharmacological options currently available on the NHS are fairly limited with most licensed for weight loss maintenance in patients with BMI of >27 kg/m^2 with associated risk factors, or those with BMI of ≥30 kg/m^2. Treatment should be discontinued at 3 months if less than 5% weight loss has been achieved whilst on the drug.

1.1.5.1 Orlistat

Orlistat irreversibly inhibits pancreatic lipases which break down dietary fat to absorbable free fatty acids, preventing the absorption of up to 32% of ingested fats which are excreted in the faeces.[42]

Gastro-intestinal side-effects are thus common leading to oily stool, faecal urgency and incontinence. To combat this, patients are advised to follow a low-fat diet with medication taken during a meal or up to 1 hour after food consumption. A meta-analysis of 33 RCTs showed a mean reduction in body weight of -2.12kg although mean duration of therapy varied from 2 months to 3 years.[43] Orlistat treatment also led to modest reductions in cholesterol and triglyceride levels but not lipoprotein(a) levels. Orlistat treatment also led to modest reductions in cholesterol and triglyceride levels.[42] In a 4-year double-blind RCT (XENDOS trial), orlistat resulted in significantly more weight loss than placebo (-10.6 kg vs -6.2 kg at one year respectively, and -5.8 kg vs -3.0 kg after 4 years, respectively), in addition to a reduction in cardiovascular disease risk factors including a 37.3% relative risk reduction of type 2 diabetes.[44]

1.1.5.2 Liraglutide (Saxenda)

Liraglutide is a glucagon -like peptide-1 receptor agonist (GLP-1) which is administered once daily subcutaneously. GLP-1 is an incretin hormone released from the gastrointestinal tract in response to glucose and fat ingestion acting both peripherally (slows GI transit, alters glucose homeostasis) and centrally (appetite suppression).[45, 46] Gastrointestinal upset is the most commonly experienced side effect, but cases of acute pancreatitis have also been reported.[47] GLP-1 therapy leads to average weight reduction of 3.2kg but has also been shown to have beneficial effects on glycaemic control (HBA1c reduction of 1%), cholesterol and blood pressure.[48]

The efficacy of liraglutide on weight loss has been demonstrated by the Safety and Clinical Adiposity – Liraglutide Evidence (SCALE) trials. The SCALE obesity and pre-diabetes double-blind RCT demonstrated significantly higher weight loss in the liraglutide group vs placebo (-8.4 kg vs -2.8 kg, respectively) at one year, with a larger proportion of participants losing >5% of their initial body weight (63.2% vs 27.1%, respectively).[49] These findings were supported by the SCALE diabetes RCT, which demonstrated dose-dependent weight loss in overweight patients with T2DM on

liraglutide vs placebo (-6% 3 mg, -4.7% 1.8 mg, -2% placebo respectively).[50] Furthermore the LEADER double blinded RCT showed a lower occurrence rate of mortality from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke, when compared with the control arm.[51]

1.1.5.3 Newer Agents

Previously available drugs primarily acting on the central nervous system such as rimonabant and sibutramine have now been withdrawn due to unacceptable side effects and safety concerns such as an increased suicide risk, myocardial infarction and cerebrovascular events.[52, 53] However, there are several newer anti-obesity drugs on the market which are summarised in Table 1.3.

Table 1. 3 Novel Anti-Obesity Drugs

DRUG	PROPOSED MECHANISM OF ACTION	SIDE EFFECTS
Naltrexone/Bupropion (Mysimba)	Buproprion is a norepinephrine dopamine reuptake inhibitor. Naltrexone reduces the hedonistic response to food.	Nausea and vomiting Hypertension Caution in depression
Lorcaserin (Belviq)	5-HT (serotonin) agonist acting centrally to suppress appetite.	Nausea and vomiting Potential valvulopathy Caution in depression
Phentermine/Topiramate (Qsymia)	Combination of phentermine (sympathomimetric agent) a centrally acting appetite suppressant and topiramate, an antiepileptic that also appears to induce weight loss possibly by increased energy utilization.	Dizziness, insomnia, dry mouth, constipation

There are also numerous pharmacological treatments currently in the clinical trial phase and these include:

- CNS agents: monoamine reuptake inhibitors such as Tesofensine (initially developed for neurodegenerative diseases) and Zonisamide–Bupropion (where Zonisamide was initially developed for epilepsy).[54] Additionally, there are novel D_3 dopamine antagonists, μ-Opioid inverse agonists, AgRP inhhibitors and Neuropeptide YY5 receptor antagonists such as Velneperit.
- Gut specific agents: Cetilistat (pancreatic lipase inhibitor), Oxyntomodulin (dual agonist of GLP-1 receptor and Glucagon receptor precursor) and inhibitors of the sodium-dependent glucose co-transporters and diglyceride acyltransferase (DGAT-1).
- Systemic agents: resveratrol (activates the caloric restriction driven molecule Sirtuin 1) and Beloranib (methionine aminopeptidase 2 (MetAP2) inhibitor).

1.1.6 Intragastric Balloon

The intragastric balloon (IGB) has been a useful anti-obesity intervention since 1985, and commonly consists of an endoscopically-deployed silicone balloon which is filled with saline and inflated in the stomach for a duration of 6 months. IGBs provide an alternative option for weight loss in those patients who decline or are not fit for bariatric surgery. A Cochrane review concluded that currently there is little data to support its efficacy for weight loss when compared with conventional medical management.[55] The main limitations of the IGB is the inability to promote sustained weight loss compared with conventional bariatric procedures with some studies reporting only 10% maintained mean excess weight loss (EWL) in 47% of patients 2 years after balloon removal.[56] The IGB is also less effective in the resolution of co-morbidities such as diabetes and cardiovascular disease when

compared with the gastric bypass and sleeve (discussed later in this chapter) therefore at present it has limited utility in the management of obesity.

1.1.7 Bariatric Surgery

Bariatric surgery is the treatment of choice when all other interventions have failed. Regardless of the type of bariatric surgery performed, its effects on weight loss and associated co-morbidities are superior when compared with non-surgical interventions.[57]

The Swedish Obesity Study (SOS) is one of the largest prospective studies to date providing observational data on the impact of bariatric surgery on obesity and long-term outcomes.[58] The study reported a greater degree of weight loss in the surgical group (n=2010) than the control group (n=2037), as well as major improvements in obesity related co-morbidities. In particular, there was a 72% remission rate of T2DM after 2 years, dropping to 36% at 10 years. More recent RCTs have shown bariatric surgery to have better long-term outcomes in terms of weight loss and diabetes resolution than medical treatment alone for obese diabetic patients.[59, 60] Based on estimates, the reduction in diabetes medications and in patient stay from diabetes complications could lead to potential savings of approximately £18.1million over a 4-year period after surgery.[61] Indeed, surgery is emerging as the more cost effective management option for patients with diabetes and other obesity related co-morbidities.[62]

Current NICE guidance advises referral of patients for bariatric surgery if all of the following criteria are fulfilled:

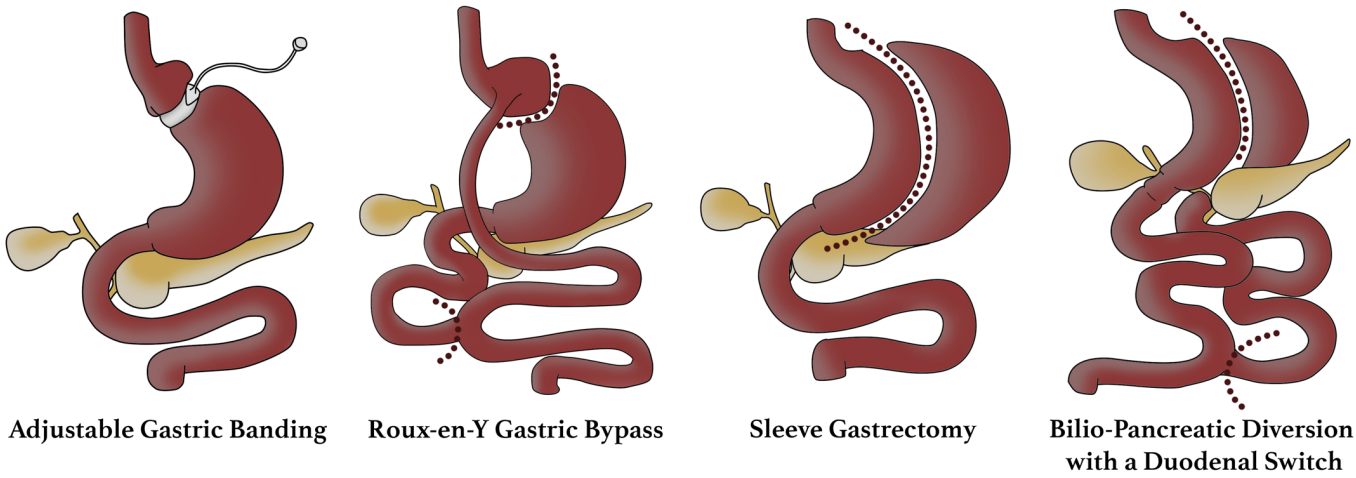
- BMI ≥40 kg/m^2
- BMI ≥35 kg/m^2 with associated co-morbidities that could be improved with weight loss
- BMI of 30–34.9 kg/m^2 who have recent-onset type 2 diabetes

- Other conservative and medical weight loss options have been explored but have failed
- Patient is receiving or will receive intensive management in a tier 3 service (a service based weight loss programme)
- Patient is fit for anaesthesia and the surgery proposed
- Patient shows commitment to long term follow up

Furthermore, NICE advises bariatric surgery as the treatment of choice in patients with BMI >50 kg/m2.

The common types of bariatric surgery performed are described below and depicted in Figure 1.1

Figure 1. 1 Common types of Bariatric Surgery



1.1.7.1 Adjustable Gastric Banding (AGB)

An inflatable silicone band is placed around the upper part of the stomach to narrow its lumen. This narrowing restricts food passage and forms a small proximal pouch of stomach, which limits the quantity of food that can be ingested and has beneficial effects on hunger and satiety.[63] The band's patency and thus degree of narrowing can be further adjusted by injecting fluid through a subcutaneous port.

AGB is performed laparoscopically and can result in a EWL of 33% and 54% at one and two years post-insertion, respectively.[64] It can also promote remission of diabetes (74%), hypertension (54%), dyslipidaemia (40%) and sleep apnoea (94%), and has a low overall mortality rate (0.14%), but it is sometimes poorly tolerated with a 13% complication rate (including nausea, dysphagia, oesophageal dilatation and band migration and erosion).

1.1.7.2 Roux-en-Y Gastric Bypass (RYGB)

During RYGB, the stomach is divided at its upper part, which forms a small proximal stomach pouch. The small intestine is also separated at the jejunal level, where the distal part of the intestine is attached to the new stomach pouch. As a result, ingested food passes through the small pouch (limiting its amount) and flows directly into the distal part of the small intestine, thus bypassing the proximal part (limiting its absorption). The excised middle fragment of intestine (distal stomach and proximal small intestine) is reattached to the small intestine further down, allowing digestive enzymes to mix with ingested food more distally.[65] This configuration facilitates the BRAVE actions (bile flow changes, restriction of stomach size, anatomical gastrointestinal rearrangement, vagal manipulation, enteric hormonal modulation) which contributes to the metabolic mechanisms of this procedure.

RYGB is mostly done laparoscopically and often yields dramatic results; with an EWL of up to 73% within one year, good long-term weight loss maintenance, and remission of comorbidities such as diabetes (95%), dysplidaemia (80%), hypertension (81%) and sleep apnoea (95%).[66] The overall mortality rate is 0.39% and complication rate of up to 21% (namely early anastomotic leak, anastomotic strictures, bowel obstruction). Post-operatively, dumping syndrome can develop where the stomach is unable to regulate emptying leading to symptoms such as sweating, dizziness, palpitations, abdominal pain, nausea and vomiting.[67]

1.1.7.3 Sleeve Gastrectomy (SG)

During SG, 80% of the stomach is excised, leaving a narrow medial aspect ('sleeve'). The reduced-size stomach has lower motility and restricts the volume of ingested content passing through it, thereby limiting calorie intake.

SG is usually performed laparoscopically and can yield EWL of up to 70% within one year, which is maintained to at least three years. Like RYGB, SG increases remission rates of diabetes (86%), hypertension (82%), dyslipidaemia (83%) and sleep apnoea (91%). SG is irreversible and has a mortality rate of 0.34%, and overall complication rate of 13% (including acid reflux, nausea, vomiting and rarely leakage, bleeding, strictures). Dumping syndrome also occurs in SG, albeit less commonly than in RYGB.[68]

1.1.7.4 Biliopancreatic Diversion with a Duodenal Switch (BPD-DS)

BPD-DS is a two stage, open or laparoscopic procedure which is also usually irreversible. Firstly, a SG-like gastrectomy is performed, leaving a tubular pouch. Secondly, the small intestine is cut in two places; proximally just after the pylorus, and distally approximately 250 cm before the ileocaecal valve. The distal small intestine is brought up and anastomosed to the duodenum. The distal end of the middle fragment is then anastomosed to the small intestine approximately 100 cm before the ileocaecal valve (Figure 1.1). BPD-DS can achieve EWL of up to 73% via both restrictive and malabsorptive mechanisms akin to RYGB, with significant effects on comorbidities such as T2DM.[69] BPD-DS is a more complex procedure which is now less commonly performed due to higher complication rates.

1.1.7.5 Revision and Reversal of Bariatric Surgery

AGB revision or removal are relatively simple and commonly performed procedures due to high rates of band intolerance (e.g. nausea, dysphagia), complications (e.g. slippage) or failure.[70, 71] Despite increasing evidence showing that laparoscopic RYGB reversal is feasible and can result in resolution of complications and their symptoms, RYGB reversal remains uncommon.[72] Similarly, SG is irreversible and revision/reversal of BPD-DS is possible but carries considerable risk.[73] It is thus vital that patients are well informed of potential side effects and complications prior to undertaking any form of bariatric surgery.

1.1.7.6 Nutritional Deficiencies

All bariatric procedures affect nutritional intake and can also have an impact on the absorption of micro- and macronutrients, in particular procedures which affect absorption (RYGB, SG, BPD-DS). Most patients will require lifelong nutrient supplements in addition to a balanced diet. Multivitamins and minerals (including folate, zinc, copper and selenium) iron, B12, calcium and vitamin D are advised.[74] Additional fat-soluble vitamins are recommended in patients who have undergone a duodenal switch procedure.

1.2 Type 2 Diabetes

1.2.1 Definition

Diabetes mellitus is a chronic condition whereby the body is unable to produce or respond to insulin which is a hormone crucial in the regulation of blood glucose levels. This results in hyperglycaemia (high blood sugar levels) which can ultimately lead to deleterious effects on the body.

Diabetes can be categorised as type I or type 2 diabetes mellitus. Type 1 diabetes mellitus (T1DM) is an autoimmune condition where the body's immune system is overactive and destroys the cells located within the pancreas which produce insulin resulting in an absolute deficiency of insulin. Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes, where the pancreas is able to produce insulin, but either it does not produce enough or the insulin it produces is inefficient, so the body is resistant to the effects of the hormone. More recently a group of Swedish researchers have further sub-stratified T2DM into five subgroups[75]:

1. Severe Autoimmune Diabetes (SAID): early onset disease, relatively low BMI, insulin deficiency and presence of glutamic acid decarboxylase antibodies (GADA)
2. Severe Insulin Deficient Diabetes (SIDD) is GADA negative but otherwise similar to group 1 above with low insulin secretion.
3. Severe Insulin Resistant Diabetes (SIRD): insulin resistance and high BMI.
4. Mild Obesity Related Diabetes: high BMI without insulin resistance
5. Mild Age Related Diabetes (MARD): older patients with modest metabolic derangement.

Clustering these patients into five specific phenotypes based on parameters such as age, BMI and estimates of insulin function helped identify patients at high risk of diabetes complications at diagnosis. An example of this, is that patients in group 3 had a significantly higher risk of diabetic renal disease than group 4 and 5, and the insulin deficient group 2 had the highest risk of retinopathy. at diagnosis and to provide information on underlying disease mechanisms thus tailoring therapy for these patients.

Diabetes UK estimate that currently there are 4.5million people living with diabetes in the UK with 90% of these having T2DM.[76] T2DM typically occurred in the older or middle aged population but is now increasingly being observed in the younger overweight population.

1.2.2 Diagnosis & Monitoring

The WHO have been producing guidelines for the diagnosis and classification of diabetes since 1965 and the current recommendations are summarised in table 1.4.[77, 78]

Table 1. 4 T2DM Diagnostic Criteria

T2DM Diagnostic Criteria

Random plasma glucose	≥ 11.1mmol/L
OR Fasting plasma glucose	≥ 7.0mmol/L
OR 2hr plasma glucose[1]	≥ 11.1mmol/L
HbA1c[2]	≥ 48mmol/mol (6.5%)

[1]Following ingestion of 75g oral glucose load

[2]An HbA1c of < 48mmol/mol (6.5%) does not exclude diabetes using glucose tests.

In the absence of diabetes symptoms such as polyuria or polydipsia it is recommended that at least one additional glucose result is obtained on another day with a value in the diabetic range.[79] Glycosylated haemoglobin (HbA1c) is formed when glucose reacts non-enzymatically with the beta chain of haemoglobin resulting in the formation of A1c.[80] This reaction is potentiated in patients with diabetes who have higher circulating levels of glucose. [81] As the life cycle of these red blood cells is 120 days HbA1c is now utilised as a marker of long term glycaemic control giving an indication of average blood glucose levels over a 3 month period.[82] The International Diabetes Federation (IDF) guidelines state that patients with diabetes should aim to maintain a HbA1c of below 53mmol/mol (7.0%) to mimimise the risk of developing complications. These recommendations are based on the findings from the UK Prospective Diabetes Study (UKPDS) where intensive blood glucose control (maintaining an HBA1c < 7.0%) over a 10 year period was associated with a 10% reduction for any diabetes death and a 6% lower for all-cause mortality when compared to the control group.

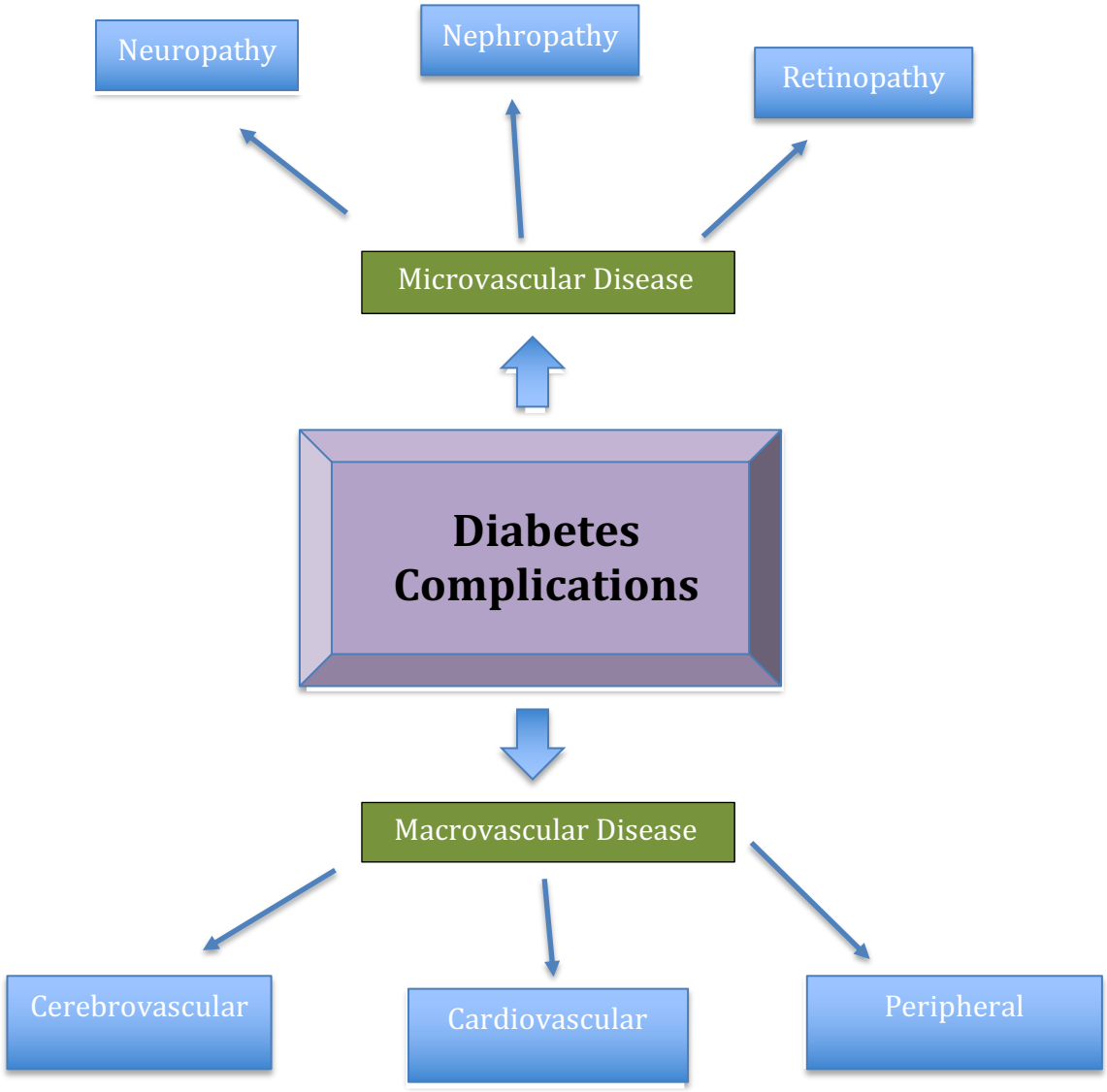
The control group were managed with diet alone, with medication being added only if hyperglycaemic symptoms occurred or fasting plasma glucose (FPG) reached 15 mmol/L.[83]

1.2.3 Complications of T2DM

The complications of T2DM can be categorized into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) as summarised in figure 1.2**.** Cardiovascular disease (CVD) is the commonest cause of death amongst adults with T2DM and the risk of CV complications is 2-2.5 times that of the general population. [84, 85] CV complications include angina, ischaemic heart disease and heart failure.

Risk of end stage kidney disease is 4.5 times greater for people with T2DM than the general population and it is the leading cause of dialysis in the UK.[85] Diabetic neuropathy encompasses a wide range of disorders affecting the large and small nerve fibers primarily caused by axonal degeneration from metabolic factors which include high circulating blood sugars.[86] It is the commonest complication of diabetes and responsible for a large proportion of non-traumatic amputations.[87] Peripheral arterial disease is also a major risk factor for lower limb amputation particularly in this cohort of patients as abnormalities of endothelial function and vascular regulation occur with diabetes which in turn accelerates atherosclerotic processes in the arterial vessels .[88, 89] Strict glycaemic control is paramount in avoiding the long-term complications of this chronic condition.

Figure 1. 2 Diabetes Complications



1.2.4 Treatment

T2DM remission, defined as the alleviation of diabetic symptoms and requirement for medication to control diabetes is possible through intensive lifestyle changes and with the advent of bariatric surgery.[90]

1.2.4.1 Lifestyle Modification

The majority of patients with T2DM (80-90%) are obese or overweight so weight loss interventions are favourable in the management of this condition.[91, 92] Intensive weight loss interventions have been shown to lead to 10-15% remission rates at one year follow up.[93] However sole reliance on lifestyle modification therapy may only be successful in a minority of patients in establishing good glycaemic control and ultimately this benefit may be short lived. The Look Ahead trial showed remission rates of 7% at four year follow up in the intensive lifestyle intervention arm and the Predimed study reported remission rates of 5% at six year follow up in their lifestyle intervention arm where participants followed a Mediterranean diet.[94, 95] A recent meta-analysis of lifestyle weight-loss interventions in overweight or obese adults with T2DM found that the majority of patients achieved weight loss of <5% and this did not result in beneficial metabolic outcomes.[35] These interventions included energy intake restriction, regular physical activity, education and support from healthcare professionals. The various types of diet have already been summarised in the section 1.13. Lifestyle interventions remain an important role in diabetes management which compliment pharmacotherapy and surgery.

1.2.4.2 Pharmacology

1.2.4.2.1 Metformin

Metformin is a biguanide medication and although it has been used in diabetes treatment for over 30 years it is still considered first line therapy in T2DM.[96] It reduces hepatic glucose production which consequently leads to improved insulin sensitivity and improved glucose uptake. There is good evidence that metformin has a beneficial effect on mortality and CV disease with significant risk reductions for any diabetes-related end point (21%, P=0.01), myocardial infarction (33%, P=0.005), and death from any cause (27%, P=0.002) over a 10 year follow up period.[97] Metformin does not

cause weight gain, leads to lower insulin dosage and is safe to use in heart failure, with the main contraindication to its use being severe progressive renal impairment.[98] Diarrhoea, indigestion and nausea are commonly reported side effects.

1.2.4.2.2 Sulfonylureas

Sulfonlyureas (e.g. gliclazide) are insulin secretagogues which bind to ATP sensitive potassium channels on beta islet cells of the pancreas leading to insulin release.[99] Sulfonylureas require residual pancreatic beta cell function to be preserved so are usually implemented as second line therapy when metformin alone has not achieved adequate control, or in those patients intolerant of metformin.[100] The main disadvantages of sulphonylurea therapy are the increased risk of hypoglycaemic events and the promotion of weight gain.

1.2.4.2.3 Dipeptidylpeptidase-4 inhibitors (DPP-4i)

The enzyme DPP-4 is responsible for the breakdown of glucagon like peptide (GLP-1), an incretin hormone which is produced in the small intestine. GLP-1 has numerous positive effects in diabetes including inhibiting glucagon, stimulating insulin release and increasing satiety thus reducing appetite.[101] Gliptins (e.g. sitagliptin) are a class of drug which inhibit DPP-4 enzyme leading to increased levels of GLP-1 thus potentiating its effects and enhancing insulin secretion. It is prescribed as a second or third line agent in addition to metformin, or first line in those intolerant to metformin.

1.2.4.2.4 Thiazolidinediones

This class of drug act on perioxisome proliferator activated receptor gamma (PPAR-γ) pathway with leads to enhancement in insulin sensitivity through activation of intracellular pathways.[102] Currently only pioglitazone is licensed for use for diabetes in the UK, either as monotherapy or in conjunction with other anti-diabetes medication or insulin.

1.2.4.2.5 Sodium glucose transporter-2 inhibitors

Sodium glucose transporter-2 (SGLT-2) is located in the proximal convoluted tubules of the kidney and is responsible for glucose reabsorption.[103] Blockade of this receptor leads to excretion of more glucose in the urine leading to lower circulating plasma glucose and weight loss. The potential mechanisms of weight loss may arise from reduced body fat secondary to calorie loss or fluid loss as a consequence of the osmotic diuresis.[104] Examples include dapagliflozin and empagliflozin which can be used as second or third line treatment.

1.2.4.2.6 GLP-1 Analogues

GLP-1 is an incretin hormone produced from the small intestine which stimulates insulin release and inhibits glucagon.[105] Synthetic analogues which act on GLP receptors include liraglutide and exenatide and are administered by subcutaneous injection. They are licensed where maximal oral hypoglycaemic therapy has failed. GLP-1 analogues can also be prescribed in addition to insulin as insulin sparing agents particularly where high insulin requirements are leading to weight gain. Liraglutide has been shown in multiple large multicentered trials to be well tolerated and effective adjuncts to oral anti-diabetes therapy. The liraglutide effect and action in diabetes (LEAD) studies compared liraglutide to the current standard treatments for T2DM including metformin sulphonylureas, thiazolidinediones, insulin and exenatide.[106-109] The addition of liraglutide to existing regimes of metformin or sulfonylureas lead to significant improvements in HBA1c of around 1% at 26 weeks from baseline. A meta-analysis of liraglutide add on therapy to existing treatments with anti-diabetic medications from the 6 LEAD randomised phase III trials containing over 4000 patients showed a 1.4% mean reduction in HBA1c levels.[110]

1.2.4.2.7 Insulin Therapy

Insulin was first introduced for the treatment of diabetes in 1922 for type 1 diabetes but since then there are now an increasing number of patients with T2DM on insulin therapy. UK estimates from a population study between 1991-2010 estimates the number of patients using insulin has trebled owing largely to a considerable increase in the prevalence of type 2 diabetes.[111]

Insulin therapy is usually indicated as third line therapy when a combination of oral anti-diabetic medication has not lead to adequate glycaemic control.[112] Other indications for commencing insulin include short term therapy where hyperglycaemia occurs during sepsis or concurrent steroid use, during pregnancy or in diabetic foot disease. However some patients may delay commencing insulin therapy if there are concerns regarding weight gain or impact on occupation such as a taxi driver. Insulin therapy must be individualised; there are numerous routes and methods of prescribing and administering insulin which is beyond the scope of this thesis.

1.2.4.3 Bariatric Surgery

Diet, medication and exercise to control diabetes have limited long term efficacy when compared with bariatric surgery with less than half of patients achieving glycaemic control using these approaches.[113, 114] The types of bariatric surgery have already been summarised in the previous section (Bariatric Surgery 1.1.7)**.**

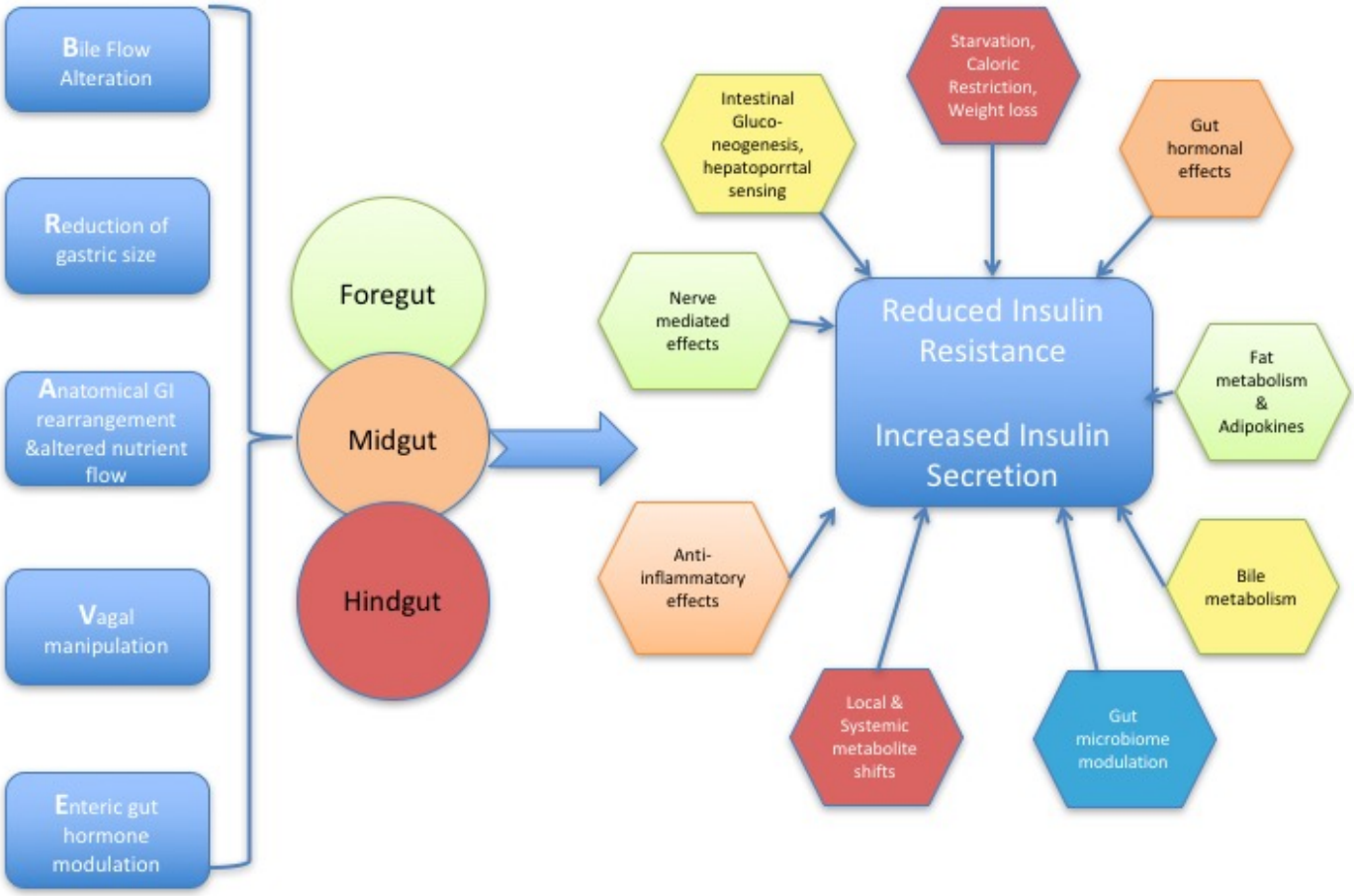
Bariatric surgery has been proven to achieve impressive effects on weight loss as well as a significant improvements or remission of diabetes as well as other co-morbidities including obstructive sleeve apnoea and decreased cardiovascular risk although the results for hyperlipidaemia are not so pronounced.[69, 115, 116] Following the 2nd Diabetes Surgery Summit in 2015 several national diabetes societies such as the American Diabetes Association (ADA) and Diabetes UK have recommended the use of bariatric surgery in obese type 2 diabetics reporting diabetes remission

rates of between 30-60% following surgery.[117] The recently published STAMPEDE (Surgical Therapy And Medications Potentially Eradicate Diabetes Efficiently) randomised trial demonstrated that bariatric surgery (gastric bypass or sleeve gastrectomy) plus intensive medical therapy was superior to intensive medical therapy alone for the treatment of obese patients with type 2 diabetes.[60] In the 134 patients who completed the 5 year study only 5% of patients in the medical therapy group achieved the primary end point; a HBA1c of 6% or less compared with 29% in the gastric bypass group and 23% in the sleeve gastrectomy group. Reductions in body weight and BMI were also greater in the surgical intervention arm than the medical therapy group.

1.2.4.3.1 Proposed Mechanisms of Action

The exact mechanisms underpinning the clinical effects observed in weight loss and glycaemic improvement post bariatric surgery (in particular RYGB) still remain a mystery. Interestingly reduction in plasma glucose appears to occur within days of the surgery independent of any weight loss.[118] Various theories have been postulated including the so called BRAVE effects (bile flow changes, restriction of stomach size, anatomical gastrointestinal rearrangement, vagal manipulation, enteric hormonal modulation).[119] These BRAVE effects take place within minutes of RYGB surgery to induce multiple short and long-term beneficial metabolic sequelae such as foregut exclusion and modified hindgut signals (figure 1.3).

Figure 1. 3 BRAVE Effects



1.2.4.3.1.1 Enteric Gut Hormone Modulation

Observations that diabetes remission can result from bariatric surgery independent of weight loss have led increasing focus on the mechanistic effects of enteric gut hormones including glucagon-like peptide 1 and pancreatic polypeptide YY, which are responsible for maintenance of homeostatic mechanisms such as appetite, gut motility, nutrient absorption and plasma nutrient regulation. There is increasing evidence that alterations in these hormones significantly contribute to many of the beneficial effects seen post bariatric surgery.[120] It is now widely accepted that altering the gastrointestinal anatomy following RYGB, alters the flow of nutrients leading to important changes in gut derived hormones by foregut exclusion and modified hindgut signals. This in turn positively

influences the metabolic changes seen following surgery including improvement in glycaemic control and weight loss. Evidence for this hypothesis was demonstrated in non-obese diabetic rats who after undergoing duodenal jejunal bypass showed rapid diabetes resolution compared to sham controls, despite having no differences in weight loss or food intake.[121] Fundamental to this is the paradigm of the "incretin effect" which is the concept that insulin secretion is also directly influenced by hormonal cues resultant from food intake and energy expenditure.[122] In fact it is estimated that the incretin effect accounts for as much as 50-70% of insulin secretion in response to an oral glucose load.[123] However this incretin response is thought to be significantly impaired in patients who are obese or have T2DM.[124] Two key incretin hormones are glucagon like peptide-1 (GLP-1) and glucagon-dependent insulinotropic polypeptide (GIP) which are both released following a meal from intestinal enteroendocrine cells known as L-and K-cells respectively.

Following RYGB undigested nutrients bypass the proximal intestine rapidly reaching the distal small bowel leading to an increase in GLP-1 levels by nutrient stimulation of L-cells.[125] GLP-1 stimulates insulin secretion from the pancreas, increases insulin sensitivity and inhibits glucagon thus reducing gluconeogenesis and hepatic glucose output. GLP-1 is also an anorexigenic hormone that acts centrally in the hypothalmus and nucleus tractus solitarius to increase satiety and reduce appetite and calorie intake.[126] It is a combination of these responses from increased levels of GLP-1 which is thought to play a pivotal role in the metabolic changes seen after RYGB.

GIP is primarily secreted in the proximal intestine as this is where the majority K-cells are located and has various physiological effects including both post prandial secretion of insulin and glucagon release during hypoglycaemia or a euglycaemic state.[127] Following RYGB, the role of GIP is more unclear as there are conflicting reports of GIP levels with some studies showing an increase whilst others show decreased levels or no change at all.[125, 128, 129] Nevertheless it is hypothesised that the blunting

in levels of GIP observed in some studies following RYGB contribute to the antidiabetogenic effects of this type of surgery.

Similarly to GLP-1, Polypeptide YY is also produced in enteroendocrine L cells in the distal small bowel and colon and is cleaved by the enzyme dipeptidyl-peptidase-IV (DPP-IV) where it then binds to the Y2 receptor to promote satiety.[130] Its main role is in the central regulation appetite as well as having other effects including delaying gastric emptying, and reducing post prandial insulin secretion.[131, 132] Infusion of PYY has been shown to reduce calorie intake, and in obese subjects levels of PYY appear blunted post prandially compared to healthy volunteers.[131, 133] Bariatric surgery leads to increased levels of PYY post prandially which may also account for the reduction in calorie intake and appetite seen post-surgery.[134] The rise in PYY levels are as a consequence of enhanced stimulation of L cells in the distal small bowel by the diversion of nutrients to this region.

Ghrelin is orexigenic (hunger) hormone produced primarily in the stomach and duodenum, rising shortly before, and falling shortly after a meal.[135, 136] Ghrelin is believed to have a key role in the long term regulation of body weight mainly through regulation of appetite but studies have shown a high variability on the impact of bariatric surgery on levels of ghrelin with some studies showing a decrease, increase or no change at all.[137-139] This may be in part due to the heterogenicity of the studies, with differences in follow up time post-surgery making it difficult to make direct comparisons on ghrelin levels. Another explanation may be owing to differences in surgical techniques with regards to gastric pouch size and shape in bypass surgery, as this will impact on the number of ghrelin producing cells available predominantly located in the gastric fundus.[140] To date, ghrelin influence on weight loss post bariatric surgery remains controversial.

1.2.4.3.1.2 Vagal manipulation

Sensory information from the stomach is conveyed to the brainstem via vagal afferents.[141]One of the key functions of this abdominal vagal afferent stimuli is the control of ingestive behaviour by responding to gastrointestinal stimuli.[142] During bariatric surgery, gastric branches of the vagus nerve are cut which can alter the sensory input from the gastrointestinal tract leading to vagal dysfunction. This may lead to changes in food preference as well as a reduction in food intake by a variety of mechanisms including a reduction in ghrelin levels.[143] It is also been hypothesised that following RYGB surgery the influx of undigested nutrients to the distal small bowel may overstimulate chemo- and mechano-sensors leading to exaggerated satiety signaling via vagal afferents thus contributing to body weight loss.[144]

1.2.4.3.1.3 Bile Flow Alteration

Bile acids (BA) are synthesised in the liver and then stored in the gallbladder before being secreted via the bile duct into the duodenum to facilitate the absorption of cholesterol, lipid soluble vitamins and lipids.[145]The majority of BAs are reabsorbed in the small intestine by BA transporters or by passive diffusion in the ileum and colon.[146] BA metabolism appears to vary between obese and lean individuals with several studies demonstrating decreased circulating levels of BAs in obese relative to lean individuals.[147, 148] BAs are believed to play an integral role in regulating satiety as well as influencing lipid, cholesterol and glucose metabolism through complex interactions which include stimulating the secretion of incretin hormones GLP-1 and PYY, growth factors and disruption of the gut microbiota.[149]

The primary bile acid receptor farnesoid X receptor (FXR) has been linked with elucidating some of these positive metabolic effects.[150] BA FXR activation can lead to improvements in both glucose tolerance and insulin sensitivity by decreasing gluconeogenesis and stimulating glycogen production

in the liver.[151, 152] Another bile acid G-protein coupled receptor (TGR-5) found in multiple sites (sinusoidal endothelia cells, skeletal muscle, adipose tissue) in the body prompts the release of GLP-1 from intestinal L-cells, and also suppresses hepatic glycogenolysis when activated.[153, 154] Finally, fibroblast growth factor (FGF) 19 is also stimulated by BAs and has been shown to influence glycogen metabolism, independent of insulin and may improve insulin resistance.[155]

In diet induced obesity rodent models, bile diversion from gallbladder to ileum resulted in a reduction in free fatty acids and triglycerides and an increase in BA levels following which sustained improvements were observed in weight and glucose tolerance.[156] RYGB surgery appears to impact BA homeostasis by altering this enterohepatic circulation leading to increased levels of plasma BAs post-surgery compared with baseline.[157] The altered anatomy following gastric bypass increases delivery of undiluted BAs to the distal small bowel which may potentiate its effects on FGF-19 and TGR-5.[158] RYGB may also mimic the effects of BA sequestrants such as cholestyramine and colesevelam which have also been shown to reduce fasting glucose levels in patients with T2DM through potentially similar mechanisms.[159]

1.2.4.3.1.4 Microbiome Changes

The gut microbiota (GM) have been implicated in numerous disease processes and obesity is no different. Manipulation of the host gut microbiome using faecal transplantation has been shown to alter host phenotype as evidenced by improvements in insulin resistance observed in obese individuals following transplantation with lean microbiota.[160] Conversely transplantation of GM from obese mice to normal weight germ free mice lead to increased weight gain in these recipients.[161] In another study transplantation of the bacterium *akkermansia muciniphila* into high fat diet fed rats led to an increase in GLP-1 secretion and improvements in insulin sensitivity.[162]

Obese individuals have significant differences in their GM compared with lean individuals with the key difference being the low microbial gene richness found in obese subjects which may make this group susceptible to metabolic disorders such as insulin resistance, weight gain and low grade inflammation.[163] Two particular species of bacteria which have been found to be both beneficial and dominant in the gut are Bacteroidetes and the firmicutes. A reduction in the proportion of Bacteroidetes has been observed in obese individuals when compared with lean individuals and these species of bacteria appear to increase post bariatric surgery.[164, 165] Increased levels of Actinobacteria have also been found in observational studies of the GM of obese individuals compared with their lean twin.[166] Obese microbiota may have the tendency to produce more short chain fatty acids leading to alterations in glucose metabolism by impaired incorporation of glucose into adipocytes, and a relative reduction in energy expenditure.[167]

Changes in dietary intake have also been shown to change microbiota composition significantly. In an RCT investigating the impact of dietary fat on GM, faecal metabolites and cardiometabolic risk factors, lower fat diets led to an increase in abundance of organisms.[168] Moderate and higher fat diets decreased the ratio of firmicutes to Bacteriodetes. Bacteriodetes not only increased in abundance following a high fat diet but were also associated with an increase in plasma lipid markers. This conflicts with previous data suggesting that higher levels of bacteriodetes may be beneficial as observed in lean individuals and in post bariatric surgical patients. A possible explanation for this, is the difference in the patient populations being studied as in the dietary study this included 217 healthy individuals from China. The GM composition of patients in the Far East including China would be expected to vary greatly with that of western populations due to differences in both environmental and genetic factors making it hard to generalise these results to Western populations. Bacteriodetes has also been found to be more abundant in the stool of Chinese patients with T2DM than in subjects

with normal glucose metabolism suggesting that in this particular patient demographic, bacteriodetes may have a detrimental effect on weight loss and glucose metabolism. [169]

Following RYGB the GM alters with an increase in bacterial richness as a consequence of changes in pH levels in the proximal small bowel, alteration in gastric motility and nutrient flow.[170] As RYGB surgery delays glucose and amino acids absorption, the increase in simple sugars reaching the distal small bowel and colon may stimulate bacteria here to derive energy from these malabsorbed nutrients.[171]

Numerous studies have shown an increase in certain bacterial species which include Gammaproteobacteria following RYGB and a lower relative abundance of Bacteriodetes.[172, 173] An increased population of Proteobacteria was also observed in diet induced mice with obesity following RYGB.[174] The increase in abundance of Proteobacteria has been linked with improvements in insulin sensitivity following antibiotic therapy in obese mice.[175] Levels of Enterobacter have also been shown to increase post RYGB surgery whereas levels have Clostridria have been shown to decrease.[173, 176]

Researchers in Canada were able to demonstrate in mice that a simple dietary intervention led to beneficial effects in obesity prevention by inducing changes in GM and energy expenditure.[177]Consumption of an extract from *Myrciara dubia,* an Amazonian fruit prevented weight gain, improved glucose tolerance and insulin sensitivity. These effects were linked to changes in plasma BAs and alterations in GM with increased abundance of *Akkermansia muciniphilia* and strong reduction of *Lactobacillus*. Furthermore, germ free mice transplanted with GM from mice treated with *Myrciara dubia* gained less through higher energy expenditure and activation of brown adipose tissue. Other effects observed in these mice included reductions in visceral and liver steatosis.

These results provide further evidence to support manipulation of the GM and BA pool as potential therapeutic targets in obesity and diabetes. Alterations in GM may influence calorie intake, intestinal absorption and energy balance as evidenced by the human and mice studies detailed above.

Currently there are three different types of microbiota-driven therapies for weight loss; probiotics, symbiotics and prebiotics.[178] Probiotics refer to live organisms in liquid or tablet form which when ingested target the intestine in their active state and are aimed at achieving positive health benefits. Prebiotics are carefully selected ingredients mainly consisting of dietary fibres aimed at promoting the growth of healthy bacteria in the intestine. Symbiotics are essentially a combination of the two products. Further explorations into the changes in GM following surgery are required and this might in turn uncover new therapeutic targets for the treatment of obesity and diabetes.

1.3 Endoscopic Interventions

Although bariatric surgery appears to be the most effective treatment for long-term weight and glycaemic control particularly in the severe and morbidly obese it is a victim of its own success and currently there is a considerable shortfall between the number of bariatric procedures being performed annually and the number of potential patients who qualify for bariatric surgery but whom are unable to access these services. These barriers include long waiting lists, which is a particular issue in the United Kingdom and financial constraints such as in the US where the type of surgery performed may be limited by the insurance policy of a patient. It is estimated that only 1% of patients eligible for bariatric surgery worldwide receive this treatment option.[179] The rising obesity and diabetes epidemic will only continue to stretch resources further in the future.

Although the risk of mortality associated with bariatric surgery is extremely low (0.1-0.3%) these procedures are associated with known risks.[180] These include anastomotic leaks, strictures,

gastrointestinal bleeding and hernias as well as the general risks of surgery such as wound healing and pulmonary embolism.[181]

Endoscopic treatments may become increasingly popular amongst a cohort of patients who are unwilling to accept the potential complication associated with surgery, or where surgery is contraindicated due to pre-existing co-morbidities making them a high anaesthetic risk. In recent years, we have seen the development of relatively non-invasive endoscopic therapies that manipulate anatomical and physiological mechanisms in the upper GI tract to achieve weight loss.[92] Often these devices attempt to mimic the effects of bariatric surgery on weight reduction. Endoscopic treatments may also be utilised as bridging therapy, inducing weight loss in the super morbidly obese patients who can then proceed to more definitive treatment such as bariatric surgery.

The novel bariatric endoscopic devices (either clinically available or at an investigational stage) are described below and categorised according to the anatomical location whereby they elicit their effects in the upper GI tract either as targeted gastric, duodenal or combined gastro-duodenal interventions.

1.3.1 Gastric interventions

1.3.1.2 Intragastric balloons (IGB)

The intragastric balloon has been used in obesity treatment since 1985, though it has changed considerably since then in terms of structure, safety and efficacy profile.[182] Its weight loss mechanism is based primarily on its restrictive, space occupying effects causing early satiety and subsequent reduced food intake.

Indications for IGB are weight loss in patients with BMI >35 kg/m^2 where bariatric surgery is contraindicated due to numerous comorbidities, failed dietary or pharmacotherapy assisted weight loss, or for weight loss therapy prior to bariatric surgery to reduce intraoperative risk.[183]

Contraindications include conditions increasing balloon insertion risk such as active gastric

inflammation or ulceration, large hiatus hernia >5cm, severe cardiovascular or respiratory comorbidities, and coagulopathy. The most frequently used intragastric balloons are manufactured from silicone and contain saline to varying volumes.

The Obera, ReShape Duo and Obalon IGB have been approved by the FDA and the Ellipse and Spatz balloon have also been approved for European use.[184] The deflated balloon is deployed endoscopically under conscious sedation into the stomach, and filled via an attached catheter with methylene-blue mixed saline, or in some cases, air.[185] The methylene blue is a safety feature, which turns green once excreted in the urine thus alerting the patient to a balloon leak or rupture.[186]

Though the insertion of intragastric balloons is relatively simple, there are adverse effects associated with each type, which were assessed in a meta-analysis by the Bariatric Endoscopy Task force.[187] These are primarily short lived and include abdominal pain (33.7%), nausea and vomiting (29%) which can often be resolved with medical management. More harmful adverse events such as upper gastrointestinal bleeding or balloon migration are reported at rates of 2% and 1.4% respectively.[188] Serious events including perforation, gastric necrosis, small bowel obstruction, and death are extremely rare, with quoted rates of 0.1%, 0.3% and 0.08% respectively.[189] More recently, the FDA issued a warning regarding increasing complications of spontaneous hyperinflation and acute pancreatitis.[190]

The greatest proportion of weight loss appears to occur within the first 3 months, with 80% of the total excess weight loss (EWL) being achieved during this initial period.[191] There are no established guidelines for standard pre and post procedural management, balloon content and volume, and balloon dwell time but the majority of balloons have a volume of 500mls and are left in place for 6 months. A study of 500 patients showed successful long term maintenance of 20% EWL weight loss in

83% of individuals 5 years following balloon removal.[192] In contrast, some studies have shown only 10% maintained EWL in 47% of patients 2 years after balloon removal.[56] In a meta-analysis of 30 clinical studies involving intragastric balloons and totalling 4,877 patients only one of three sham controlled studies showed benefit. Weight loss in non-randomised studies averaged 17.8kg with corresponding reduction in BMI of 4.0-9.0kg/m^2.[188] This is also supported by a meta-analysis of the Orbera balloon in 3698 patients, which showed an average reduction in BMI of 5.7kg/m^2.[193]

In addition to weight loss benefits, IGBs have an added effect on diabetes control and related metabolic consequences of obesity. A recent systematic review and meta-analysis reported a mean 12.7% reduction in baseline fasting baseline glucose (FBG) after 6months IGB therapy.[194] A similar pattern was seen in HbA1C levels at 6 months with 0.6% reduction overall, and a greater (1.1%) reduction where baseline HbA1c was greater than 6.5%, compared with a 0.2% reduction where baseline HbA1c <6.5%. In a study of 18 patients with obesity and poorly controlled diabetes (baseline HbA1c > 8), in the 6 patients with IGB inserted for 6 months, HbA1C improved to 7.3% compared to 9% in the control group (P = 0.002).[195] Another study of 143 obese patients also showed a similar improvement with reduced incidence of T2DM from 32.6% pre-IGB placement, to 20.9% after 6 months IGB treatment (P= 0.039).[196] This was maintained at 6 and 12 month follow up, and there were also corresponding improvements in other aspects of the metabolic syndrome.

One of the proposed mechanisms of how IGB elicit weight loss is by delaying gastric emptying resulting in increased satiety and this has been shown in gastric scintigraphy studies. In 10 obese patients gastric emptying time lengthened from 114minutes prior to IGB placement, to 375minutes 3months post IGB placement.[197] A prospective RCT with 29 obese patients randomised to either Orbera IGB placement or control, showed comparable baseline gastric retention percentages, which increased at 8 and 16 weeks following IGB placement.[198] At 16 weeks, gastric retention percentage

2 hours post ingestion was 62.1% in the IGB group compared to 18.7% in the control group (P<0.001). These rates had returned to near-baseline levels of 30% just 3 weeks following IGB removal.

Stomach distension may also stimulate gastric mechanoreceptors and thereby send signals via the vagal nerve to achieve early satiety (this mechanism is also likely to contribute to the side-effects of vomiting in IGB patients who may activate their central vomiting centres through this route), and there may be an additional effect on neurohormonal mechanisms, involving changes in release of cholecystokinin, pancreatic polypeptide and leptin.[199] In a study of 42 patients who received either IGB treatment or sham treatment, cholecystokinin and pancreatic polypeptide levels decreased in the balloon group, and results were replicated when the sham group received IGB therapy. [200] These changes were independent of factors such as balloon position. These changes are unexpected, as one would expect levels of these satiety hormones CCK and PP to increase with gastric distension caused by IGB. In early acute gastric distension, CCK levels do increase but the chronicity of IGB treatment for several months may partly explain the changes seen here.[201] Additionally, CCK levels are partly stimulated in response to intestinal nutrient delivery, and so the reduction in gastric emptying as a consequence of IGB may also account for the reduced CCK level seen in this study. Furthermore, leptin levels were shown to decrease in 21 patients with IGB, with a transient early rise in ghrelin levels 1 month after balloon insertion, whereas these levels remained stable in a control group of 15 patients.[202] Similarly, a study in 66 obese patients with metabolic syndrome also showed an initial transient rise in ghrelin and an initial reduction in leptin, which returned to baseline post IGB removal.[203] Adiptonectin and PYY levels remained stable throughout the study. The initial transient rise in ghrelin may be due to a negative calorific balance in the first weeks of IGB treatment, and reduction in adipose tissue with weight loss may account for reduced leptin secretion. These small studies suggest a possible synergistic role of neurohormonal mechanisms in facilitating weight loss

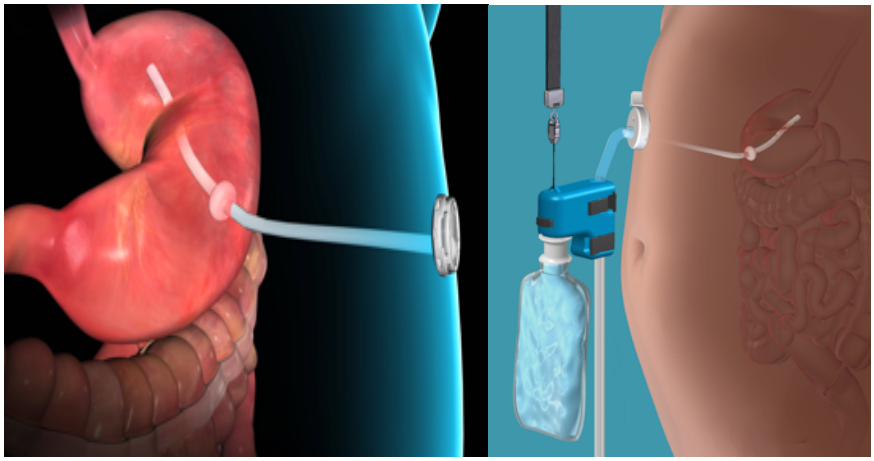
with IGB therapy, though the mechanism is unclear and further studies are required to accurately establish this.

IGB may represent an effective therapeutic strategy for weight loss in the short term, and are typically used in the super obese to achieve a safe weight prior to definitive bariatric surgery. Further research is required to determine properties such as optimum material and dwell time in order to achieve long-term success in weight maintenance.

1.3.1.3 Aspiration

Aspire Assist is an endoscopically placed silicone percutaneous gastrostomy tube which lies in the gastric antrum allowing for aspiration of approximately 30% gastric contents post consumption of meals.[204] It has recently been approved for use by the FDA. The device is inserted using a similar method to PEG feeding tubes, under mild sedation, with 7 days post procedure antibiotic prophylaxis. Patients are instructed to aspirate approximately one third of meals greater than 200kcal, 30 minutes after it is consumed, via a connector and device (figure 1.4). A reservoir with water is infused into the stomach via the connector, with flow then being reversed to allow food particles to be flushed out. This process takes 10-15 minutes. Patients are required to chew food well and drink large amounts of water with meals to aid the aspiration process. A valve within the skin port prevents accidental leakage or aspiration without the connector. A safety feature of the connector in preventing long term unsupervised use, is by locking after 115 aspiration cycles, which occurs after approximately 6 weeks, requiring the patient to return to clinic for a new connector to continue therapy. By reducing the volume of food being transferred to the small intestine, it subsequently leads to weight loss. Electrolyte abnormalities are minimised with concurrent medical therapy using omeprazole and potassium chloride supplementation if required.

Figure 1. 4 Aspire Assist



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A randomised pilot study in 18 patients showed significantly greater excess weight loss in the aspiration group compared to lifestyle therapy group who used dietary weight loss modifications alone (49.0 % vs 14.9%) at the 1 year follow up period.[204] In the aspiration group, 7 subjects who completed a further year of follow up maintained 54.6 % excess weight loss. In this pilot study there were no noted adverse effects on eating behaviour. Reported side effects were nausea, peristomal pain and peristomal infections in 3 patients. A prospective study of 25 patients in Sweden who had the AspireAssist placed after completing a 1 month very low calorie diet, with the addition of cognitive behavioural therapy (CBT), showed a mean weight loss at 6 months of 16.5kg (%EWL 40.8%).[205] CBT involved teaching and raising awareness of portion size, reducing high calorie foods, exploring eating behaviour and the importance of physical activity. There were 4 adverse events reported; abdominal pain in 2 patients occurring within 1 week of tube insertion, with one patient requiring inpatient observation. Another patient developed an aseptic intra-abdominal fluid collection whilst another had peristomal skin breakdown. There were no electrolyte abnormalities reported. A recent multicentre RCT in the US of 111 subjects showed 37% EWL at 1 year in those receiving aspire-assist combined with lifestyle counselling, significantly greater than 13% in the group receiving lifestyle dietary therapy alone.[206]

AspireAssist may also have a beneficial effect on glycaemic control. In the recent RCT, 3 patients in the treatment arm had T2DM with a 0.36% reduction in HbA1c at 1 year (P< 0.0001), compared to the 8 patients with T2DM in the lifestyle therapy group with 0.22% reduction (P<0.0001).

These studies suggest that AspireAssist is an effective endoscopic weight loss method for longer durations, up to 1 year, compared to IGBs which are mostly licensed for 6 month use. Limitations of the aspiration therapy process which requires carefully chewed food, large amounts of water, minimising snacking between meals, and frequency of aspiration, may restrict its popularity. In addition, due to the nature of aspiration therapy there remain concerns over the risk of developing eating disorders as well as micronutrient and electrolyte deficiencies, though these have not been found to be clinically significant within these preliminary studies described. Altered eating habits themselves may contribute to the degree of observed weight loss to a greater extent than the physical calorie reduction through aspiration. Analysis of aspiration frequency in the recent RCT showed that patients consumed an average 1 or more meals without aspirating afterwards, and overall less than 30% of daily calorific intake was estimated to be aspirated. Given the degree of weight loss observed, it is possible that there are alternate mechanisms which act synergistically to aspiration to result in weight loss. This also highlights the importance of chronic lifestyle behaviours in driving food consumption and weight loss.

1.3.1.4 Intragastric Injection of Botulinum Toxin A

Botulinum toxin A elicits its effects by selectively blocking acetylcholine at the neuromuscular junction culminating in the inhibition of muscular contractions of smooth and striated muscles in the stomach.[207] The suggested mechanism of action is a delay in gastric emptying and early satiety induction with a sensation of gastric fullness.[208] The toxin is injected endoscopically to multiple sites, usually in the antrum at a dose of 100-500iU.[209] In a recent meta-analysis of 115 patients in 7 studies, including 5 RCTs showed a modest benefit of 1-7kg weight loss compared with a control

group (injections of normal saline).[210] A major limitation of this therapy is its short duration of effect as it typically lasts approximately 3-6 months so further repeat procedures may be required which has cost benefit implications.

1.3.1.5 Endoscopic Sleeve Gastroplasty (ESG)

EndoCinch is a device originally used for the treatment of gastro oesophageal reflux disease, which allows superficial mucosal sutures to be placed endoscopically leading to transoral outlet reduction. It has since been developed to perform an endoluminal vertical gastroplasty without the need for incisions, in the treatment of obesity. Tissue is suctioned into a capsule attached to the endoscope, and sutures are deployed from the proximal fundus to distal stomach body, thus reducing its luminal capacity. An initial study in 64 patients who underwent the procedure showed 21.1% (+/- 6.2%) EWL at 1 month follow up, 39.6% +/- 11.3% at 3 month follow up, and 58.8% +/- 19.9% at 12 months.[211] Furthermore, the procedure was quick, approximately 45 minutes per case, and was well tolerated with no serious adverse events, and only 2 patients reporting self-limiting reflux symptoms. 3 patients had disrupted suture configuration requiring repeat procedure in 2 cases. Furthermore, it has been used to treat weight regain in RYGB patients where dilation of the gastro-jejunal anastomosis occurs.[212] The RESTORE suture system is a similar device but showed poorer durability and subsequently more modest weight loss, EWL 27.7% in a trial of 14 patients. This is possibly due to reduced suture tension and in 13 patients there was either partial or complete suture release.[213] The TOGA system is a similar sleeve stapling device with results from a multicentre single-arm trial in 53 patients showing 29.3% EWL at 3 months, 36.8% at 6 months and 38.7% at 12months.[214]However staple line gaps and dehiscence remains a limitation of this procedure.

Newer devices such as the Overstitch by Apollo surgery utilises a double channel therapeutic endoscope allowing full thickness continuous suturing creating a more durable gastric pouch or sleeve, compared to staple –line dehiscence which can occur with earlier devices.

By introducing a series of sutures through the gastric wall extending from the pre-pyloric antrum to the gastro-oesphageal junction results in a reduction in gastric capacity in a similar fashion to that seen in a sleeve gastrectomy. In a prospective study of 10 patients, mean %EWL was 18% after 1 month, 26% at 3 months and 30% after 6 months.[215] The mean procedure time was 157 minutes and there were only mild side effects of abdominal pain and nausea.

In a small study of 25 patients who underwent ESG between 2012 and 2015 with a median follow up period of 9 months, there was a 56% ± 23% reduction in excess body weight.[216] These results show a similar efficacy to vertical banded gastroplasty which has an EWL of 50-55% but less than sleeve gastrectomy which produces a 60-80% EWL at one year.[217, 218] From this cohort of 25 patients, 4 patients agreed to physiological analysis 3 months following ESG. This analysis included gastric emptying studies, gut hormone analysis of GLP, PYY, leptin and ghrelin as well as insulin sensitivity studies. Gastric emptying of solids was significantly delayed but gastric emptying of liquids was not. Fasting and post prandial levels of ghrelin were found to be reduced by 29.4% and post prandial levels of insulin were also reduced but these were not found to be statistically significant. There were no statistically significant changes in leptin, GLP-1, and PYY levels. The study concluded that the effects on gastric reservoir volume and gastric emptying following ESG leads to increased satiation resulting in a more significant and durable weight loss. The study was limited by the small sample size, short follow up period and only a small subset of subjects participated in the mechanistic studies. Further randomised controlled trials are required to evaluate the efficacy of this device as a future weight loss therapy.

A multicentre study of 242 patients who underwent this procedure and were followed up for up to 18 months reported a total body weight loss (TBWL) of 16.8 ± 6.4 at six months, 18.2 ± 10 at one year,

and 19.8 ± 11.6 at 18 month respectively.[219] At two years, the percentage of patients achieving >10% TBWL was 84.2 and 53% with per protocol and intention to treat analysis respectively. Weight loss performance in the early stages of treatment was shown to be a significant predictor of long term outcome, as of those patients who achieved ≤10%TBWL at 6 month, only 18% achieved ≥10%TBWL at 2 years. This study reported a 2% adverse events profile; two patients requiring percutaneous drainage and antibiotics for inflammatory fluid collections adjacent to the fundus, one splenic laceration leading to haemorrhage, a pulmonary embolism 72 hours post procedure and one pneumoperitoneum and pneumothorax requiring a chest drain.

1.3.1.6. Primary Obesity Surgery Endolumenal (POSE) Procedure

POSE utilises a per-oral incisionless operating platform designed by USGI medical and involves the placement of gastric transmural plications in the fundus and pre-antral region in order to restrict the size of the stomach, inducing early satiety. A long flexible tube similar to an overtube is placed into the stomach through which a specialised set of endoscopic surgical tools specifically for incisionless procedures are inserted. The tools allow the deployment of specialised suture anchors to create folds in the stomach thus reducing the capacity of the stomach. A large randomised control trial of 332 patients compared 221 patients who received the POSE in addition to low-intensity lifestyle interventions for 12 months compared with 111 patients who received a sham procedure and lifestyle interventions alone.[220] These patients achieved a 4.94%±7% TBWL compared to 1.38%±5.6% TBWL in the control group and the study concluded that POSE was associated with clinically significant weight loss compared with lifestyle therapy alone, and was safe and well tolerated.

The potential mechanism of weight loss may be as a result of plications in the fundus and antrum to limit gastric capacity, and to delay gastric emptying which in turn may induce early satiety. This hypothesis was explored in a small single centre prospective series of 18 patients all undergoing POSE procedure, and followed up at 2 and 6 months with gastric emptying studies, calorific intake capacity

studies and measurement of gut hormones PYY, ghrelin and leptin.[221] Weight loss was recorded through 15 months of the study period with an EWL of 63.7%± 25.1%. Gastric emptying increased at month 2 but was back to baseline at month 6, and calorific intake capacity was reduced. Circulating levels of leptin and postprandial levels of both PYY and ghrelin also rose following POSE. Although larger numbers coupled with a longer follow up period is required, this study suggests that alterations in the neuro-hormonal network may precipitate these changes in weight loss by regulating food intake and inducing satiety.

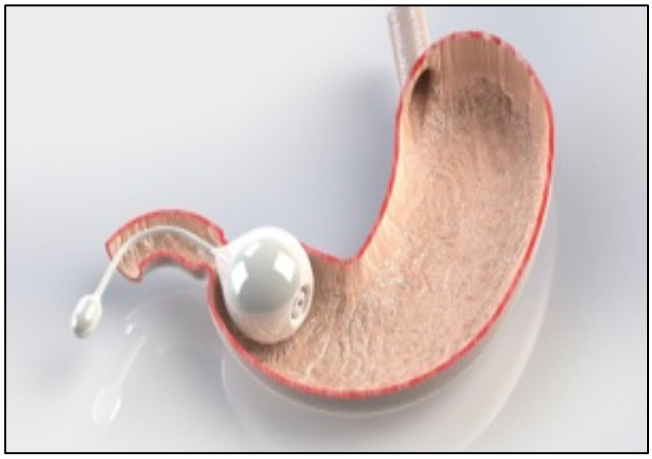
1.3.2 Gastro-duodenal

1.3.2.1 Transpyloric Shuttle

The transpyloric shuttle is a device placed and retrieved endoscopically, consisting of 2 bulbs joined by a flexible catheter (Figure 1.5), designed to cause intermittent obstruction. The smaller cylindrical bulb passes into the duodenum with the larger spherical bulb becoming trapped in the gastric antrum, occluding the pylorus intermittently with peristalsis. Though there is currently no mechanistic data available, the proposed mechanism is similar to the gastric balloon, where it elicits an effect on weight loss by slowing gastric emptying and inducing satiety. In an Australian study (ENDObesity I) of 20 patients with a mean BMI 36, all patients had the transpyloric shuttle inserted and were serially assigned to 2 equal groups; 3 or 6 month follow up.[222] The study demonstrated good tolerability with substantial and progressive linear weight loss; 31.3+/- 15.7% EWL at 3 months, and 50% +/- 26.4 % EWL at 6 months. Evidence of any effects on glycaemic control are awaited. The most frequent adverse effect was endoscopically identified mucosal erosion in 15 patients, and 2 patients requested early removal due to persistent ulceration. A multicentre RCT ENDObesity II is currently underway.

One putative mechanism of weight loss with this device is the underlying gastric physiology that suggests distal stomach mechanoreceptor activation induces greater bloating and pain than proximal stomach mechanoreceptor activation.[199] As a result, the transpyloric shuttle may take advantage of this differential effect to induce greater satiety and associated weight loss.

Figure 1. 5 Transpyloric Shuttle



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1.3.2.2 Valen Tx bypass Sleeve

The Valen Tx bypass sleeve is a 120cm long gastroduodenojejunal bypass sleeve which requires a combination of endoscopy and laparoscopy for implantation in order to insert and secure at the gastrooesophageal junction (GOJ), and is removed after 1 year endoscopically. It extends from the GOJ to the mid-jejunum thus stops nutrient absorption at this point, mimicking effects following RYGB procedure.

An initial 3 month trial showed 39.7% EWL in 17 of 22 patients who had the device inserted.[223] A further 12 month prospective study in the US in 12 patients showed an mean EWL of 54% in the 6 patients with fully functioning devices at the end of the trial and mean 39.4% EWL in all patients, with improvements also seen in diabetic control, hypertension and hyperlipidaemia.[224] Four patients

with T2DM saw a 38% improvement in fasting plasma glucose at 12 months and of those, 3 patients had >1% reduction in HBA1c values. The device was removed early in 2 patients due to side effects of odynophagia, and the remaining 4 patients were found to have partially detached devices with associated inferior %EWL. In addition, 5 patients maintained 30% EWL at 14month follow up post sleeve removal. Currently a major limitation is the duration of the device implantation procedure which takes an average 1.5hrs and the need for laparoscopic assistance. Developments of a variation negating the need for laparoscopic oesophageal fixation may increase its use.

This device is intended to replicate RYGB so presumably has a similar proposed mechanism of action which may include enteric gut hormone modulation as a result of the altered flow of nutrients bypassing the proximal small intestine and reaching the distal small bowel. Early satiety may be induced as a consequence of the sleeve starting at the GOJ, thus bypassing the stomach. Currently there is no data in the literature to support how this device may elicit its effects in terms of weight loss or diabetes. Putatively it may mimic several comparable metabolic and weight loss effects seen in RYGB including the BRAVE actions.

1.3.3 Duodenal interventions

1.3.3.1 Duodenal mucosal resurfacing (DMR)

The Revita™ System consists of a console and a novel single use balloon catheter which allows submucosal saline recirculation followed by radiofrequency thermal ablation of superficial duodenal mucosa, and has been shown in early trials, to improve glycaemic control in type 2 diabetes.[225] The mucosal surface between the ampulla of Vater and ligament of Treitz is targeted. Proposed mechanisms include absence of nutrient exposure to the duodenal surface, with subsequent increased nutrient delivery rate to the distal ileum, which may increase GLP-1 levels and so improve glycaemic control. Additionally, the process may restore enteroendocrine cell signalling in diseased duodenal cells.[226]

In terms of comparability to the BRAVE effects seen in other bariatric procedures, there is no stomach size restriction or alteration of gastrointestinal anatomy or vagal manipulation, however, this device is therefore suggested to work on the paradigm of foregut exclusion and modified hindgut signals.[227]

In the first-in-human trial in Chile, over the initial 6 month follow up period there were improvements in glycaemic control as measured by mean reduction in HbA1c (%).[228] This was more pronounced in the 28 patients who underwent a longer (9.3cm) segment of DMR compared to the 11 who had a short (3.4cm) segment ablated; 2.5% vs 1.2% HbA1C reduction respectively at 3 months ($p<0.05$), and 1.4% vs 0.7% respectively at 6 months ($p<0.3$). Reductions were also seen in liver function tests with a fall in AST and ALT levels from a mean 32 and 40pmol/L at screening to 27 and 32pmol/L at 3 months suggesting further benefits. The most common adverse effect seen in 8 patients was abdominal pain soon after the procedure, which resolved within 48hrs. Three patients required endoscopic dilatation of symptomatic duodenal stenosis.

However, the degree of improvement in glycaemic control measured by HbA1c at 3 months was greater than at 6months (2.5% reduction vs 1.4%), suggesting that repeat DMR procedure may be required to maintain adequate long-term effects. The mean weight loss after 6 months was 3% compared to 4.6% at 3 months. Weight loss and subsequent improved glycaemic control, may also have been attributable to the hypocalorific diet post-procedure, where patients progress from liquids to soft foods over a few weeks.

The exact mode of action is unclear, but proposed mechanisms stem from the observed weight loss and improved glycaemic control in bariatric bypass procedures such as RYGB which implicate the duodenum as a key metabolic signaling centre in insulin secretion and sensitivity. Studies in both animals and humans show abnormal mucosal hyperplasia and hypertrophy of enteroendocrine cells in

the duodenum of diabetic patients compared to non-diabetic patients .[229] Bypassing this abnormal duodenal mucosa led to a 50% increase in insulin sensitivity when nutrients were delivered to the jejunum directly.[230] This suggests that insulin-resistance signaling in diabetics may originate from the duodenal region. Ablating these diseased duodenal cells with DMR is thought to restore this aberrant enteroendocrine signaling. In rodent models, there was improved glucose tolerance following DMR in diabetic rats with no significant change to glucose tolerance in non-diabetic rats which received the same treatment.[228] Furthermore, the hindgut hypothesis suggests that the absence of nutrient exposure to the duodenal surface, with subsequent increased nutrient delivery rate to the distal ileum, may increase GLP-1 levels and so improve glycaemic control. Both these mechanisms are likely to act synergistically.

A large multi-centre trial (REVITA-1) is currently underway in Europe to help further characterise the perceived benefits of DMR, its mechanisms, and optimise the procedure.

1.3.3.2 SatiSphere

Endosphere's Inc. patented the Satisphere System and received CE (European Conformity) approval in 2012 as a temporary duodenal insert, reversible and potentially re-implantable. Designed as a c shape to match the natural contour of the first part of the duodenum allowing for self-anchorage, the device comprises of a 1mm nitinol wire with pigtails at either end and several mesh spheres which run the length of the device to slow nutrient transit time through the duodenum and delay gastric emptying. The first generation of this device was tested in a RCT with 21 patients receiving the device for 3 months but was terminated early following 10 device migrations in the treatment arm with 2 patients requiring emergency surgery.[231] In the 12 completers %EWL was 18.4% ($p=0.02$) compared with 4.4% in the control group who received dietary counselling only. A small sub group of 7 patients who

received the device underwent mixed meal tests to explore whether levels of GLP-1 were altered by the device but this was not found to be the case.

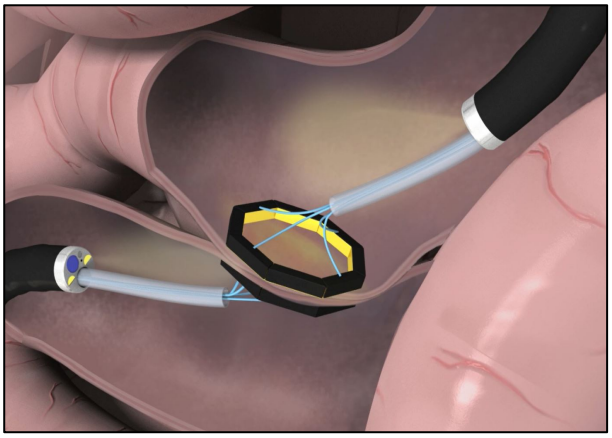
A second generation of device was designed with the addition of a self-expanding anchoring portion at the proximal end. However the device was found to be poorly tolerated in a small study of 10 patients, with all devices being explanted at 5 weeks due to patient discomfort and dyspepsia symptoms.[232]

1.3.3.3 Incision-less Anastomosis System (IAS)

A novel Incisionless magnetic anastomosis system (GI Windows) uses 2 self-forming magnets deployed from the working channel of 2 endoscopes. The self-forming magnets will eventually join together to form a compression anastomosis between 2 regions of small bowel (figure 1.6). Tissue remodeling leads to a new treatment path and subsequent diversion through the small intestine for a portion of nutrients. This therefore creates an anastomosis without the need for sutures and the complications associated with it. Once the anastomosis is fully formed, the magnets are passed in the stool. A recently published prospective single arm study of 10 patients receiving the IMAS reported %EWL of 40.2% at the end of the 1 year follow up period.[233] Average HBA1c reduction was 1.9% from baseline in the 4 patients with T2DM in the trial. Mixed meal tolerance tests were performed at baseline, month 2 and 6 in all 10 patients to investigate the impact of this procedure on gut hormone modulation. PYY levels were found to be higher than at baseline at month 2 and 6, and although GLP levels were initially higher at month 2 than at baseline this fell at month 6. Insulin and glucose levels were both reduced at month 2 and month 6 and this was found to be statistically significant. The "hindgut" mechanism is thought to be the key driver in how this anastomosis induces weight loss and glycaemic improvement through enteral diversion of nutrients to the distal small intestine stimulating anorexegenic gut hormones such as GLP and PYY.

Clearly larger randomised control trials are required before this technology becomes commercially available.

Figure 1. 6 Coupled Self-Forming Magnets



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1.4 Endobarrier: Duodenal Jejunal Bypass Liner (DJBL)

1.4.1 Background

The Endobarrier (EB) is an endoluminal duodenal-jejunal bypass liner (DJBL) developed by GI Dynamics (GID) Inc, Lexington MA for the treatment of obese patients with T2DM.[146] It consists of a single use endoscopic implant with a removable nitinol stent anchor to affix to the wall of the duodenum to which is attached an impermeable fluoropolymer sleeve extending 60cm into the small bowel (figure 1.7). As a result gastric contents bypass the proximal intestinal tract by traveling inside the sleeve, only coming into contact with pancreatic juices and bile once it exits the sleeve in the jejunum. This device is currently licensed for up to 12 months of treatment. It is envisaged that this device might mimic the effects of restrictive surgery like gastric bypass but without the risks of undergoing surgery and the possible long-term complications associated with bariatric surgery.

Figure 1. 7 Duodenal Sleeve Bypass Liner

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1.4.2 Clinical Trial Data

The first clinical trials of the EB were published in 2009, and since then there have been numerous publications investigating the efficacy, safety and mechanisms of actions of the device in both animal and human trials. To date there have been five RCTs examining the efficacy of the EB (table 1.5). The largest of which was a multi-centered trial performed in the Netherlands in which 73 patients were randomised to receive either DJBL treatment in combination with dietary intervention or dietary intervention alone (control group).[234] A total of 35 patients successfully had the EB implanted for a 6 month period. BMI at baseline was 35 and 37 in the device arm and control arm respectively and reduced to 31 and 35 respectively over the 6 month period. HBA1c at baseline was 8.3% in both groups and reduced to 7.0% and 7.9% in the device and control arm respectively. There was only one early device removal due to blockage of the DJBL with food. Patients were also followed up post removal of device for 6 months where BMI and HBA1c was measured. BMI was 32 in the device group and 36 in the control group respectively showing a slight increase following device removal in the

treatment arm. HBA1c was 7.3% and 8.0% at the end of the follow up period in both groups showing a mean reduction of 1% and 0.3% in both groups respectively.

In another study of 41 patients, 26 had the device implanted compared to a control group on a low calorie diet and had a mean loss of excess weight was 19% for the device versus 6.9% in the control group. [235]Furthermore out of 8 patients in the device arm with T2DM at baseline, improvements were seen in glucose levels and HBA1c in all but one of them.

Table 1. 5 EB RCTs

Study	No. of patients	BMI	Duration of device Implantation (weeks)	Weight Loss	Change in HBA1c	Stent Removal Rate
Gersin et al[236]	47; 21 in treatment arm	46	12	- 8.2kg ± 1.3kg in treatment arm vs. 2kg ± 1.1kg in sham arm	Not an endpoint	38%
Koehestanie et al[234]	73; 34 in treatment arm	35 device; 37 control	26	-10.6kg device; 5.3kg control	-1.3% vs. 0.4% in control	3%
Rodriguez et al[237]	18; 12 in treatment arm	39	24	-10.2kg ± 1.3kg in device arm vs 7.1±4.3kg in sham arm	-2.4 ± 0.7% vs -0.8±0.4% control	25%
Schouten [235]	41; 30 in treatment arm	49	12	19% device; 6.9% control	-1.1% vs 0.4% in control	15%
Tarnoff [238]	35; 29 in treatment arm	42 device, 40 control	12	-10.3kg ± 3.2kg vs 2.6kg ± 3.5kg in control group	Not an endpoint	20%

Betzel et al published the largest cohort of patients receiving the EB with 185 patients from 2011 to 2014 who received the device for one year.[239] EWL was 40.9% at 6 months and 46.3% at time of

explantation (p<0.001). HBA1c reduced by 6mmol from 67mmol to 61 mmol at the time of explantation (p<0.001). However 31% of devices were removed prematurely due to intolerable side effects and adverse events. The main side effects reported were abdominal discomfort and nausea, with more serious side effects including gastro intestinal bleeding, device migration or obstruction and an association with the development of hepatic abscess.

Rohde et al published a systematic review and meta-analysis in 2015 of the EB and its effects on obesity and T2DM.[240] Included were 5 RCTs and 10 observational studies with the risk of bias evaluated as high in all studies as none of these RCTs were blinded studies. Meta-analysis showed the EB did not have a statistically significant impact on T2DM but was associated with statistically significant results in terms of weight loss. Mean reduction in glycated haemoglobin and plasma glucose was 0.9% and 3.7mM respectively. Mean differences in body weight and EWL was -5.1kg and 12.6% respectively compared with dietary intervention.

1.4.3 Pilot Study

Our research group at Imperial College conducted the first post marketing clinical trial of the EB in the UK consisting of 45 patients, recruited from three centres (St Mary's Hospital London, Southampton and University Hospital Manchester).[241] In this study Participants were aged 18-65 years with T2DM, with a BMI greater than 30 kg/m^{2}and received the implant for a duration of one year. Mean HBA1c and BMI at baseline was 69mmol (8.5%) and 39.9kg/m^2 respectively.

A summary of baseline characteristics and subject demographics is shown in table 1.6**.** Of the 45 patients 31 (69%) completed the 12 month study period. Average implantation time was 27 minutes and fluoroscopic time was 7 minutes (SD 5.7). There were no procedure-related complications during implant or explant. There were 14 early withdrawals before the 12month implant period and two of

these participants had device-related adverse events requiring premature explant for melaena and device migration resulting in abdominal pain respectively. The other reasons for withdrawal included development of other medical complications precluding EB implantation and patient choice for early removal.

Table 1. 6 Baseline Characteristics

Baseline Characteristics for the Implanted Population	Subjects (n = 45)
Age, mean ± SD, y	49.9 ± 7.9
Gender, n (%)	
Male	22 (48.9)
Female	23 (51.1)
Race: Caucasian, n (%)	40 (88.9)
Weight, mean ± SD, kg	115.0 ± 21.0
BMI, mean ± SD, kg/m^2	40.0 ± 5.8
HbA1c mean ± SD (%)	8.5 ± 0.8
Duration of Diabetes, mean ± SD, y	4.6 ± 2.8
Glucose, mean ± SD, mmol/L	9.5 ± 2.95
Insulin, mean ± SD, mIU/L	18.8 ± 10.41
Total Cholesterol	4.3 ± 0.97
Systolic BP mmHg	141 ± 20
Diastolic BP mmHg	82 ± 10
Comorbidities, n (%)	
Hypertension	29 (64.4)
Hyperlipidaemia	32 (71.1)
Coronary Artery Disease	1 (2.2)
Sleep Apnoea	3 (6.7)

At 1 year, at the time of explant the average reduction in HBA1c was 0.8%. A mean reduction in BMI of 4.9kg/m^2 was observed with a mean TBWL of 15kg. These positive changes appeared to be maintained at the 6 month follow up period with small but non-significant changes in these parameters after explantation.

1.4.4 Potential Mechanisms of Action

The EB mimics the bypass portion of the RYGB surgery so it is thought to elicit its effects on weight loss and glycaemia by similar mechanisms including:

- altered flow of nutrients in the small intestine culminating in changes in enteric gut hormones.
- alterations in the gut microbiota.
- Modulation of bile flow.

Therefore the concepts previously described in Chapter 1.2.4.3.1 as potential mechanisms for the efficacy of bariatric surgery will be also be applicable to EB therapy. Currently there is a sparsity of data on how the EB influences the above mechanisms with the few studies reporting on these outcomes being described below.

1.4.4.1 Gut Hormones

De Jonge et al investigated the effects of the EB on the incretin gut hormones GLP-1 and GIP in addition to glucose, insulin and glucagon levels in 17 obese patients with T2DM receiving the EB implant for 6 months.[242] Both fasting and post prandial glucose levels were decreased in parallel with a reduction in glucagon levels but fasting insulin levels did not change. GLP-1 levels increased but GIP levels were found to be decreased at 6 months. The authors postulate that these findings are similar to those seen post RYGB suggesting the device works in a similar fashion. However, in contrast to these findings Koehestanie et al studied the effects of fasting GIP, GLP-1 and ghrelin levels at baseline, 1 and 4 weeks in 12 obese diabetic patients post implant and found no significant changes in

GIP were identified, and in fact levels of GLP-1 appeared to decrease 1 week post implant followed by an elevation back to baseline levels in the following 3 weeks.[243] Ghrelin levels were found to rise in this study particularly in the first week following EB implantation. There was no correlation identified between gut hormone changes and reductions in body weight and BMI.

Similarly Vilarassa et al investigated gut hormone changes in 21 patients with obesity and diabetes and found no differences in GLP-1 values at baseline and at 12 months although PYY and ghrelin levels increased over this period.[244] This suggests that GLP-1 may not account for the metabolic improvements seen in patients receiving the EB. Furthermore the increase in ghrelin seen in both these studies is confusing as it contradicts findings post RYGB which suggest that ghrelin levels fall.

Rohde et al compared the effect of the EB on post prandial physiology in 10 obese patients with normal glucose tolerance (NGT) and 9 age-, body weight -, BMI- matched patients with T2DM. Parameters investigated included insulin, glucose, glucagon, gut hormone secretion, gall bladder emptying, appetite and food intake using liquid mixed meal test and a subsequent ad libitum meal test at baseline, 1 week and 26 weeks following EB implantation.[245] Basal plasma concentrations of GLP-1, GIP and PYY were similar in the two groups before EB implantation and the device did not appear to affect basal concentrations significantly in any of the groups. Small but significant increases were observed in post prandial levels of GLP-1 and PYY levels at week 1 and 26 in the patient group with T2DM but not in those with NGT and overall the EB did not appear to have any impact on levels of insulin, glucose or glucagon following implantation although the numbers reported are very small. Clearly larger numbers in randomised controlled trials are required in order to draw any firm conclusion on the effects of EB on the gut hormones.

1.4.4.2 Bile Flow Modulation

Fibroblast growth factor-19 (FGF-19) is a potent stimulator of BA acid synthesis and in a small study of 30 obese patients with T2DM, levels were found to be markedly increased following EB

implantation for 10 months in these individuals.[246] Another study found that 17 obese individuals with T2DM who received the EB lead to profound increases in in unconjugated bile acid levels after 6 months, similar to the effects of bariatric surgery.[247] The increase in BA signaling in the liver might provide a partial mechanism for how the device elicits its effects on improvements in glycaemic control. Free BAs also interact closely with the microbiota found in the small intestine, so increased concentrations of these BAs may not only influence the overall number of bacteria in this region but also their composition.

1.4.4.3 Gut Microbiota

As described in chapter 1.2.4.3.1.4, increases in the abundance of bacterial species post RYGB surgery, in particular gammaproteobacterial and the firmicutes phyla have been observed, and may have a potential role in the positive metabolic changes seen following surgery. [165, 176] Similar patterns in microbiota adaptation have been seen with duodenal exclusion devices although research in this field remains in its infancy.

In a rodent model, implantation of a duodenal endoluminal sleeve stimulated an increase in abundance of species in the Gammaproteobacteria class (e.g. *E coli*) and Firmicutes phyla (e.g. *clostridium*).[248] *Clostridium perfringens* was found to increase following duodenal exclusion, and reduced levels have previously been implicated in obesity.[249]

To date, only one study investigated the impact of the EB on the gut microbiota and this was in a cohort of 17 patients who received EB therapy for 6 months and then were followed up for 6 months.[250] Faecal microbiota appeared to be profoundly altered by EB therapy, most notably associated with an increase in abundance of the Firmicutes phylum and Proteobacteria phylum. This included a 25-fold increased relative abundance of *lactobacillus gasseri et rel.,* a 11-fold increase in

lactobacillus plantarum et rel and a 5-fold increase in *Escherichia coli et rel*. over the 6 month period. It is possible that alterations in the nutrient stream by bypassing the proximal intestine might lead to shifts in colonisation of typical small intestinal microbiota such as Proteobacteria into the distal small bowel and colon. The EWL at 6 months of EB therapy was 18.3% and significant differences in EWL were still observed in these patients at 6 months following device removal but the faecal microbiota composition at the same time point appeared similar to baseline samples (prior to EB therapy). This may either suggest that the metabolic impact of EB therapy is independent of changes in the microbiome profile, or that gut microbiota alterations may initially influence the improvements seen in glycaemic control and weight loss but other mechanisms such as enteric gut hormonal changes may be chiefly responsible for the sustained impact of the device following its removal. Larger studies involving a greater patient population in a randomised setting are required to truly investigate the impact of EB on the gut microbiota and to determine which bacterial species may be influential on the metabolic improvements observed with EB therapy.

1.4.4.4 Gastric Emptying

The device's effects on gastric emptying have also been investigated in a small study of 25 patients where scintigraphy gastric emptying was performed at baseline and 16 weeks after implantation. Whilst gastric emptying was greater post EB insertion, no relationship was proven between this and T2DM control or weight loss.[251]

1.4.5 Safety Profile

By far the most commonly reported side effect of the device is GI upset such as abdominal pain and nausea. These symptoms usually resolve as the patient acclimatises to having the device in situ but a minority of patients (2%) are unable to tolerate this leading to early device removal. The other

complications include GI bleeding (1.5%) and device migration (1.4%). Rarer complications including cholestasis and pancreatitis can also occur.

Liver abscesses pose the most serious complication associated with the EB with most cases reported late (9-12months) during the course of treatment towards the time of explanation. The German DJBL registry reported 1 case in 66 patients who had received the EB for one year having previously reported 4 cases in 235 patient registry. [252] Three were documented at explantation with the other one occurring following early removal for device dislocation. All were managed with antibiotics and/or drained with no permanent sequelae.

The ENDO Trial was a multicenter, double-blind, randomized trial in the US to evaluate the safety and efficacy of the EB on glycaemic control. Unfortunately in March 2015, the Food and Drug Administration (FDA) halted the trial due to development of 7 liver abscesses (3.5%) which was much higher than anticipated. The cause for these liver abscesses is unclear but the theory is the EB creates a nidus for infection which may spread to the liver bed.

Post market surveillance data from GI Dynamics, the device manufacturer reports an incidence of 1% which is also supported by data from a world-wide registry established in 2017 by the Association of British Clinical Diabetologists.[253] From 492 EB patients there were 6 reported cases of liver abscesses. Early removal of device because of GI bleed was 4%. Device migration was 3% and liner obstruction was rare accounting for 0.3% of cases.

1.5 Metabonomics

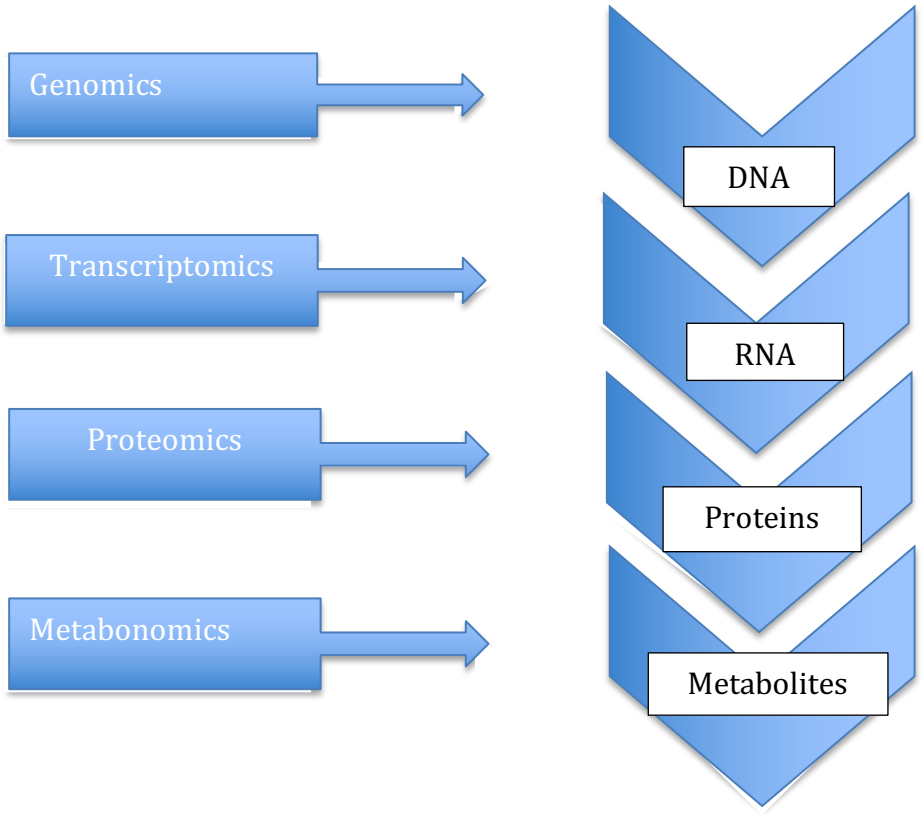
Metabonomics was defined in 1999 as “the quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification.”[254] Since then, it is a field which has advanced rapidly providing an unbiased method for quantitative and qualitative analyses of metabolites present in a biological sample such as urine, stool or plasma.

Its predecessors include the other "omic" technologies (Figure 1.8):

- the study of an organism's genome – the structure, function and expression of their DNA (genomics)
- The study of RNA transcripts (transcriptomics)
- The study of proteins - their structure and function (proteomics)

The major advantage of metabonomics is that metabolites represent the final downstream products therefore offering a strong correlation to the phenotype being studied.[255] The significance of this is that information gleaned from the study of these small molecules may be used to develop novel biomarkers, potential screening tools in disease or as indicators of prognosis and treatment response.[256] A biomarker is ''a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacologic responses to a therapeutic intervention''.[257]

Figure 1. 8 "Omic" Technologies



1.5.1 NMR Theory

Metabolic profiling often utilises high field ^{1}H nuclear magnetic resonance (NMR) spectroscopy technique to interrogate large sets of biological fluids.[258] This largely follows an untargeted approach focusing on the global metabolic profile or "fingerprint" of a sample. This differs from a targeted approach, whereby the metabolites under investigation are usually known and the focus shifts to the quantification of these selected metabolites.[256] A targeted analysis is usually carried out using LC-MS-based methods. Despite its lower sensitivity NMR spectroscopy offers many other advantages[259]:

1. High reproducibility
2. No prior knowledge of metabolic contents of a sample are required
3. Only small sample amounts required with minimal or no preparation
4. Rapid
5. Non-destructive so samples can be re-analysed.

Although NMR was originally discovered by Isaac Rabi who received the Nobel prize in 1944, it was in fact Bloch and Purcell who were credited with the development for the theoretical basis of NMR in 1946.[260] The NMR phenomenon results from the overall spin property of some nuclei, which are positively charged, generate a small magnetic field and possess the magnetic moment. When a strong external magnetic field is applied, the magnetic moment of these nuclei (e.g. proton) will either align (lower energy level) or oppose (higher energy level) the external magnetic field. When an appropriate radio frequency pulse is applied, energy transfer occurs between a lower and a higher energy levels. When the spin returns to its base level, energy is emitted at the same frequency. This generates a signal which can be measured and processed in order to generate an NMR spectrum for the nucleus concerned.

From the NMR spectrum the following molecular information can be ascertained:

- Chemical shift: resonant frequencies of nuclei in the environment with different electron densities. It is expressed as parts per million (ppm) where the positions of chemical shifts and multiplicity of the peaks can help determine the molecular structures.
- Spin-spin coupling: this is the interaction of different spin states through the chemical bonds of a molecule resulting in the splitting of NMR signals. It describes the magnetic interaction between neighbouring, non-equivalent NMR active nuclei.
- Signal intensity: the intensities of NMR signals are displayed on the vertical axis and this is proportional to the molar concentration of a metabolite and number of nuclei present in the proton spectra.

1.5.2 NMR Pulse Programs

A pulse sequence is a programme which controls and synchronises the events involved, such as the length, phase and position in time of the radio frequency. Pulse sequences are used to excite nuclei producing a specific form of NMR signal that are observed in an NMR spectrometer. One dimensional (1D) experiments consist of a sequence of radiofrequency pulses with delay periods in between with the spectrum obtained by plotting the frequency (chemical shift) on the axis against the intensity on the y axis. There are two sections to this experiment: preparation where the spin system is set to a defined state and detection where the resulting signal is recorded. 1D-^{1}H-NOESY with presaturation is the most utilised NMR pulse sequence for the collection of metabonomics ^{1}H NMR data from biofluids.[261] As water forms a large proportion of any biological fluid sample, it has the highest intensity and therefore may cover the signals from other compounds within a sample. To combat this issue, 1D-1H-NOESY with presaturation is used to suppress water signals. Carr-Purcell-Meiboom-Gill (CPMG) sequence is a spin-echo pulse sequence, which is widely used in acquiring plasma data in addition to the application of 1D-^{1}H-NOESY with presaturation.[262] The CPMG pulse sequence can

help filter out signals from large molecules such as proteins, allowing us to visualize the signals arising from the small metabolites.

1.5.3 NMR Data

A typical NMR spectrum consists of thousands of sharp lines or "peaks", which represent the various low molecular weight metabolites (<1K Da). Protein and lipoproteins generate broad bands on the proton NMR spectrum, which may then be superimposed by the sharper peaks of smaller molecules.[261] To calibrate the spectral data obtained from different samples, typically 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium (TSP) is added to the sample for spectral calibration (δ^1H=0 ppm).

1.5.4 Multivariate Statistical Data Analysis

NMR spectra of biofluids generate vast amounts of data which would be impossible to interpret manually. Using multivariate statistical data analysis methods can help in information extraction, noise reduction and fine tuning spectral information.[263] These methods typically divided into two categories: "unsupervised and "supervised" methods. Unsupervised methods are often applied where there is no prior knowledge of sample classification with the aim of identifying these sample clusters by mapping samples according to their metabolic composition. Principal component analysis (PCA) is a commonly implemented unsupervised method in metabonomic profiling. Whereas supervised methods such as partial least square (PLS) are a form of discriminant analysis, which rely on class information on a given sample set to optimise separation between two or more sample classes. The primary goal of both techniques is to identify class differences from a multivariate data set; in this case differences between patients who received the EB and those in the control group. The NMR spectra for each biofluid contain a collection of variables (e.g. NMR signals) for each participant. PCA

or PLS can then identify a combination of these variables or their defining features, which contribute to any class separation that exists in the data.[264]

1.5.4.1 Principal Component Analysis (PCA)

PCA is a statistical technique which is geared at reducing the dimensionality of a dataset whilst preserving as much variability as possible thus minimising any information loss.[265] It is usually the first step in the analysis of metabolomics data. The PCA technique involves establishing a list of weighted linear composites of original variables such that each composite (the principal component) is uncorrelated with the others. It represents this data graphically, where a line is created through the data with the minimal possible distance to all the data points using a sum of squares technique. The first principal component calculated in a model essentially represents the maximal amount of variation seen within the dataset and is a weighted linear composite of the original variables where weights are chosen so that the composite accounts for the maximum variation in the original data. The second principal component is calculated orthogonally to the first and accounts for the second maximum variation that is not accounted for the first component. This process continues up until all variance within a dataset is accounted for and therefore is a useful method for checking the variation in the data sets. The output of this method results in two different matrices; scores and loading plots.

1.5.4.2 Scores and Loadings Plots

Score plots are scatter plots displaying the co-ordinates for the samples and involve the projection onto a two-dimensional plane defined by principal components (PC). Each point represents a single NMR spectrum or a sample. Scores plots allow the visualisation of similarities or differences between the samples being analysed depending on the variation explained by each PC. The PC loading plots provide an indication of which variables carry the highest magnitude to the PC i.e. which signal or metabolite has the greatest weight on transforming the original samples from the data matrix into

their new position in the scores matrix. Each small NMR spectral region, typically 0.0005 ppm, is represented by a point on the loadings plot.

Supervised methods are however preferred when trying to reveal hidden response-related variance that may not necessary be uncovered by PCA alone particularly when the largest variation is not class-related. For example, some factors such as physiological variation like age or gender and not just the disease or intervention being studied.

1.5.4.3 Partial Least Squares (PLS) analysis

PLS is a form of supervised multivariate analysis used to model the association between two data matrices; the data matrix X, and the response matrix Y. PLS is particularly useful when analysing NMR data to explore samples which have been collected over different time points in the course of a disease or intervention. When coupled with discriminant analysis (DA), PLS can help to establish the optimal position to place a discriminant surface in order to best separate classes.[266]

1.5.4.4 Validation of Models

R^2 and Q^2 are statistical measures that depict the quality of PCA and PLS models, representing the explained variance and the predictive capability of the model respectively.[267] R^2X and R^2Y represent the fraction of explained variance of the X and Y matrix. Similarly, Q^2Y represents the predictive capability of the model. A negative Q^2 model would imply the model is not at all predictive and so good predictions would have a high Q^2. Similarly R^2 represents how closely the data fits a linear regression model and in general the higher the R^2 value, the better this model fits the data. Together the cumulative values of R^2X, R^2Y and Q^2Y will indicate the quality of the model. In addition, cross validation – analysis of variance (CV-ANOVA) is used to determine the statistical significance of multivariate PLS and Orthogonal PLS (OPLS) models. Q^2Y indicates the predictivity of the models, but CV-ANOVA allows the assessment of the statistical significance of this predictivity.[268]

1.5.5 Application of Metabonomics in Obesity and Diabetes research

Obesity remains one particular disease process which is still poorly understood and where there is a strive to identify potential biomarkers which might predict the pathophysiological processes or specific metabolic state. Branched-chain amino acids (BCAA), non-esterified fatty acids, organic acids and phospholipids have already been implicated in the development of the obese state.[269, 270]

Amino acids, both essential and non-essential groups constitute the building blocks of cell membrane and combine to form protein. Essential amino acids such as BCAA are important nutrient signals and tend to be elevated in obese individuals and are associated with insulin resistance and T2DM.[271]

BCAA include leucine and isoleucine, phenylalanine, valine and tryptophan. Newgards *et al.* (2009) identified the metabolites leucine, isoleucine and valine as being significantly elevated in obese and overweight individuals using mass spectrometry (MS).[272] A significant increase in plasma levels of both valine and leucine were also found in another study which performed metabolic profiling of plasma in overweight/obese men compared with lean men using ultra-performance liquid chromatography (UPLC)-MS.[273]

Wang *et al.* (2001) profiled baseline specimens of 189 individuals using LC-MS who were followed up over a 12-year period and had developed diabetes.[274] These were matched with case controls with respect to age, sex and BMI. In paired analysis, five metabolites including isoleucine, leucine, valine, tyrosine, and phenylalanine were found to be significantly different at baseline between the case and control subjects and therefore were correlated with a higher risk of developing T2DM. These findings suggested that amino acid metabolism might play an important role in pathogenesis of this disease.

Higher concentrations of fatty acids have also been implicated in various chronic diseases including T2DM, hypertension and cardiovascular disease.[275] Disorders in lipid metabolism are thought to be key in the development of insulin resistance and T2DM. Metabolic profiling of plasma samples from 44 obese women with T2DM indicated that certain fatty acids were potentiated including palmitoleate, oleate, palmitate and stearate.[276]

1.5.6 Metabonomics Post Bariatric Surgery

Unsurprisingly bariatric surgery results in alterations in the metabolic profiling of individuals but only a limited number of studies to date have explored these changes. A major group of metabolites which appear to alter following bariatric procedures are amino acids such as alanine, glutamate and glycine.[277, 278] BCAA such as isoleucine and valine were also affected, as well as peptides such as glutathione.[279] Following sleeve gastrectomy serum concentrations of serine and glycine were elevated whereas RYGB surgery resulted in a decrease in methionine, alanine and lysine compared with pre-surgery samples.[280]

Lipids appear to be another subset of metabolites which are influenced by bariatric surgery particularly free fatty acids and their esters.[281] Previous studies have shown an upregulation in phosphatidylcholines, and a reduction in linoleic acid post RYGB surgery.[282, 283]

Gralka et al (2015) explored the metabolic alterations occurring post bariatric surgery by analyzing the serum of over 100 obese patients using ^{1}H nuclear magnetic resonance spectroscopy.[284] In this longitudinal observational study serum samples were collected prior to and in the 1 year follow up period following bariatric surgery (sleeve gastrectomy and RYGB). In addition, serum samples were analysed from normal weight individuals and from 30 subjects with BMI that was matched with those achieved by the severely obese patients 12 months after their bariatric surgery. The study found that once again amino acids were altered significantly from samples taken pre and post-surgery with an increase in arginine and glutamine regardless of the type of surgery performed. Markedly increased

levels of isopropanol and methanol were also found in severely obese subjects and the authors speculated that elevated concentrations of these metabolites in the blood may be as a consequence of altered gut microbiota composition as these metabolites are associated with bacterial metabolism.[284]Finally, increases were seen in dimethyl sulfone concentrations after all bariatric procedures, a compound barely seen in the baseline samples prior to surgery or in normal weight individuals. Dimethyl sulfone is an intermediate metabolite of methionine metabolism and again the authors postulate that this rise might be a consequence of the altered microbiome post-surgery.[284]

1.6 Rationale for Studying the EB

A joint task force convened by the American Society of Gastroenterology and the American Society for Metabolic and Bariatric Surgery defined thresholds for determining the efficacy of endoscopic bariatric devices. [285] This was outlined in the Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) document. The first criteria specifies that endoscopic devices should fulfil a minimum threshold of 25% mean EWL at 12 months and currently only the Obera IGB and the EB meet this threshold.[286] IGBs which have been widely used for many years in obesity treatment appear to be going out of favour owing to its short term effects on weight loss and 6 month licence limiting its use. EB therapy may be able to fulfil this void in the coming years as it has a longer licence for use (12 months), and its mechanism of duodenal exclusion may yield greater effects on weight loss and glucose metabolism than merely the space occupying effects of IGBs. This has led to significant interest from research bodies such as the National Institute of Health Research (NIHR) as well as additional investment from GID into funding more rigorous RCTs to further support the already promising results obtained to date from numerous clinical trials of the EB published over the past decade.

The EB is minimally invasive and very easy to perform as it only takes 45 mins to implant and 30 mins to remove thus making it easily reversible. The training required to perform the procedure of implant

and explant is minimal and no specialised equipment is required apart from a standard endoscope, the EB implant itself, the explant device and x-ray facilities to perform fluoroscopic guidance. Although the device may be associated with significant adverse events such as bleeding, migration and hepatic abscess, in nearly all these cases patients have recovered without any permanent sequelae and no fatalities have been reported as a direct consequence of EB treatment.

Of all the endoscopic interventions described in this chapter, the EB is the only device that is designed to closely mimic and recreate the effects of an already established surgery (RYGB) that has proven to be successful in the management of obesity and diabetes. Its uniqueness probably lies in the fact that it is the only device to offer complete duodenal exclusion, which means that chyme does not interact with the proximal duodenum and nor does it come into contact with bile until much later on in its journey in the small intestine. This paves the way for a variety of potential mechanisms to be explored that might explain how the EB elicits glycaemic changes and induces weight loss (as described previously), each of which can be studied in more detail in the context of this clinical trial. A particular focus in this thesis will be effect of the EB on the metabolic profile of participants, by analysing their biofluids, and what perturbations occur over time.

1.7 Hypothesis

1. Patients in the EB treatment arm will achieve a greater degree of weight loss and improvements in their glycaemic control following 1 year of EB therapy when compared to the control group who receive dietary, medical and lifestyle therapy alone.
2. Patients in the EB treatment arm will achieve greater improvements in fasting lipids than compared with controls.
3. There will be significant differences in the metabolic profile of stool, urine and plasma of patients in the EB treatment arm over time compared with the control group.
4. There will be significant differences in the metabolic profile of the stool, urine and plasma of EB patients from baseline to 1 year.

1.8 Aims

1) To assess the efficacy of the EB compared to standard medical care for the treatment of T2DM and obesity.
2) To determine the impact of the EB on the metabolic profile of urine, plasma and stool in patients receiving the device

1.9 Objectives

1) To establish the effect of the EB device on key clinical parameters including blood glucose, weight loss, blood pressure, lipid profile and liver biochemistry.
2) To assess the safety profile of the device by recording the number of adverse events, significant adverse events and early explants.
3) To use metabolomic techniques to identify potential biomarkers and key metabolic changes that arise as a result of EB therapy.
4) To determine whether the EB truly represents a "medical bypass" by comparing the metabolic profile changes in biofluids when compared to bariatric surgery.
5) To determine the utility of the Endobarrier in the treatment algorithm of obesity and T2DM

This thesis will focus on data collected from the first half of the clinical trial which encompasses both the recruitment process and analysis of one year data for all trial participants in both the control and the EB treatment arm. The 1 year follow up data for both groups will not be considered in this thesis as data collection for this was still ongoing whilst this thesis was being written.

Chapter 2: Methodology

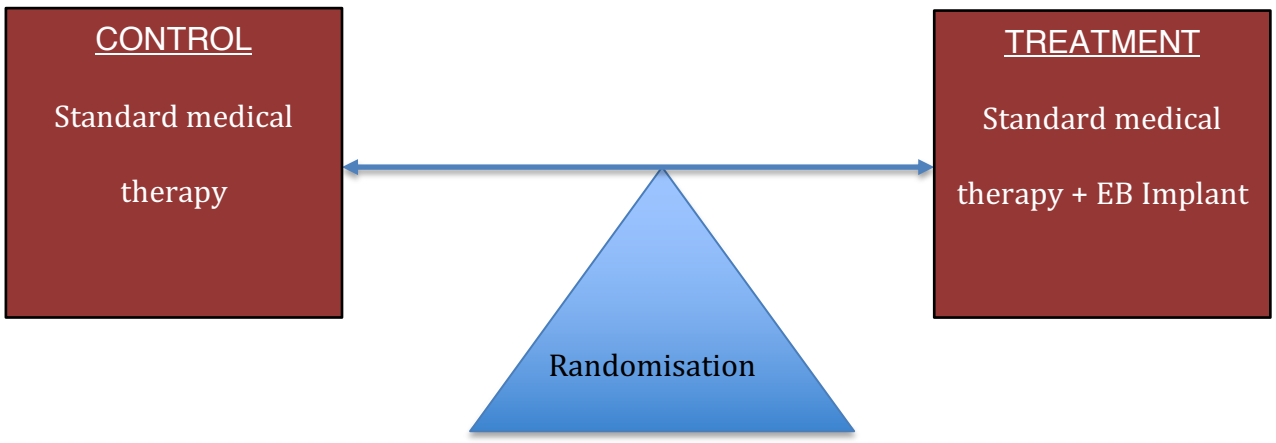
This chapter contains direct extracts from the following publications, with permission:

1. Glaysher M, **Mohanaruban A**, Prechtl CG et al. A randomised 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 mellulitis. *BMJ Open* 2017; doi: 10.1136/bmjopen-2017-018598

2.1 Clinical Trial Overview

The EB RCT is funded by the National Institute for Health Research (NIHR) and is part of the Efficacy and Mechanism Evaluation programme (EME). EME is a partnership between the Medical Research Council (MRC) and NIHR and was primarily set up to support clinical trials that test the efficacy of interventions. The study has been conducted at two investigational sites in the UK, Imperial College Healthcare NHS Trust (ICHT) which include St Mary's Hospital and Hammersmith Hospital and University Hospital Southampton (UHS). This is a two-year study in which 170 eligible patients with obesity and T2DM were recruited and randomised to either the control or treatment arm group (figure 1.9).

Figure 1. 9 Randomisation



The EB trial RCT is designed to further investigate the potential of this endoscopic implant as an effective alternative treatment to bariatric surgery and existing medical therapies in T2DM. The treatment arm received the EB device for 1 year in addition to standard medical therapy and will be followed up for a further 1 year. The control group received standard medical therapy and life style intervention therapy alone over the period of 2 years. During the time of writing this thesis, data collection for the 1 year follow up period of all patients was ongoing and will therefore not be covered in this thesis. The protocol for the clinical trial which has been previously peer reviewed and published as described in this chapter.

2.2 Recruitment Methodology

The target population for this study were males and female aged 18-65 who are obese (BMI>30kg/m^2) with T2DM but adequate insulin reserve. The study eligibility criteria are shown in Figure 1.10.

Figure 1. 10 Study Eligibility Criteria

Inclusion Criteria

- Age 18-65 years (male or female)
- T2DM for at least 1 year (HbA1c 7.5-11.0% = 58-97 mmol/mol)*
- On oral T2DM medications (any except GLP analogues e.g. liraglutide)
- BMI 30-50 kg/m^2

Exclusion Criteria

- Language barrier, mental incapacity, unwillingness or inability to understand and be able to complete questionnaires
- Non-compliance with eligibility criteria
- Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate or reliable contraceptive methods
- Current use of insulin
- Previous diagnosis with Type 1 DM or a history of ketoacidosis
- Requirement of NSAIDs (non-steroidal anti-inflammatory drugs) or prescription of anticoagulation therapy during the implant period
- Current iron deficiency and/or iron deficiency anaemia
- Symptomatic gallstones or kidney stones at the time of screening

- History of coagulopathy, upper gastro-intestinal bleeding conditions such as oesophageal or gastric varices, congenital or acquired intestinal telangiectasia
- Previous GI surgery that could affect the ability to place the device or the function of the implant
- History or presence of active H. pylori (if subjects are randomised into the EB arm and have a history or presence of active H. pylori – tested during study visit 2 - they can receive appropriate treatment and then subsequently enrol into the study)
- Family history of a known diagnosis or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder.
- Severe liver (AST, ALT or gGT >4 times upper limit) or kidney impairment estimated Glomerular Filtration Rate (GFR) <45ml/min/1.73m^2*
- Severe depression, unstable emotional or psychological characteristics (indicated by Beck Depression Inventory II score >28)
- Poor dentition and inability to adequately chew food
- Planned holidays up to three months following the EB Implant

* Modified from original eligibility criteria

Two of the eligibility criteria listed above (identified by an asterisk) were modified from the original protocol to broaden the eligibility criteria to recruit more participants:

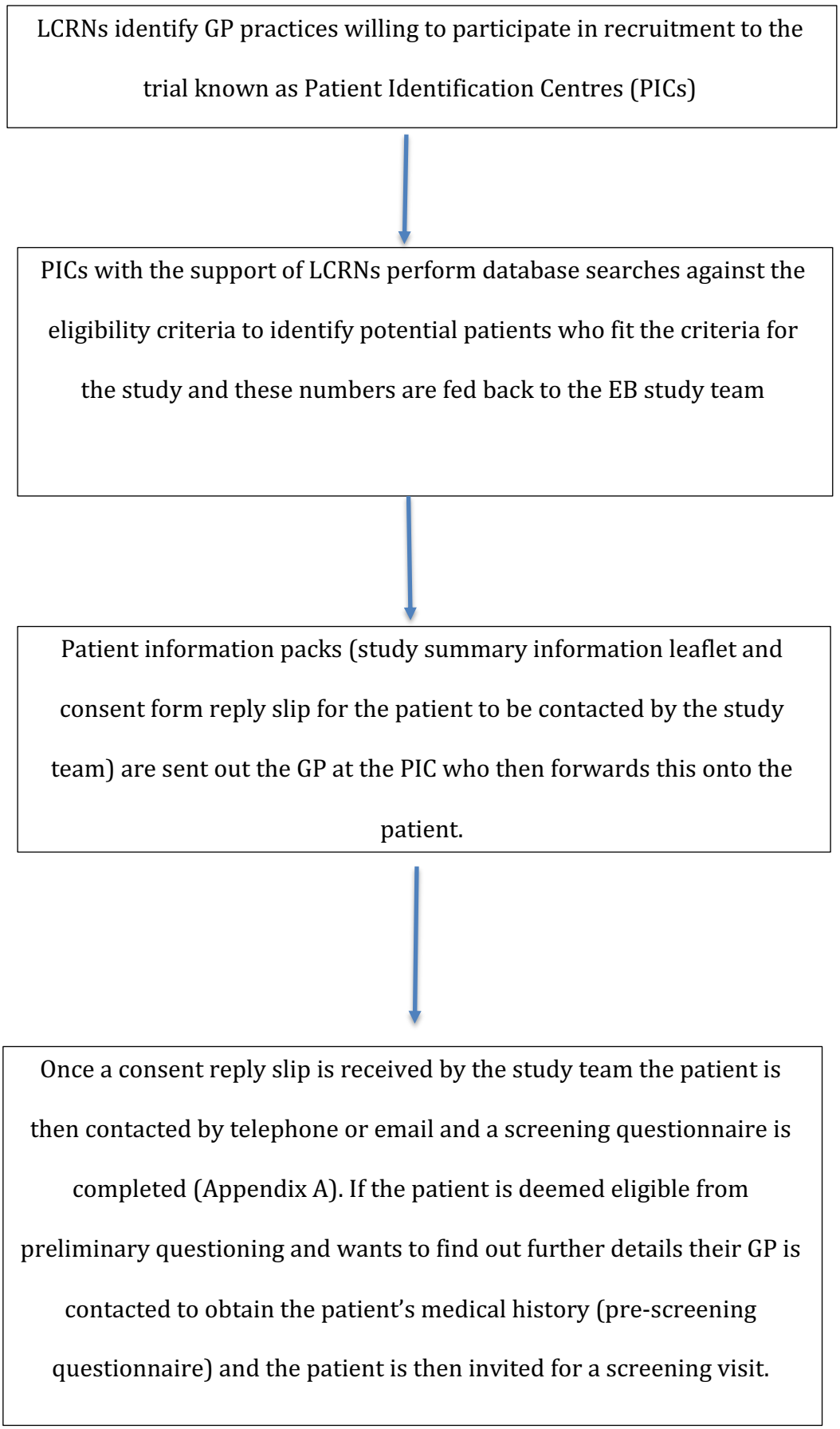
1) HBA1c upper limit was extended to 97mmol/mol from 86mmol/mol.
2) Criterion for liver and kidney disease was modified from "Severe liver (AST, ALT or GGT >4 times upper limit) or kidney failure (serum creatinine >180mmol/l), estimated Glomerular Filtration Rate (GFR) cut-off is 60" to "Severe liver (AST, ALT or GGT >4 times upper limit) or kidney impairment estimated Glomerular Filtration Rate (GFR) <45ml/min/1.73m^2".

As the vast majority of T2DM is managed in the primary care setting it was initially anticipated that GP practices would provide the most valuable resource in which to identify eligible.

ICHT is located in north west London which encompasses a population of around 2.4million people and it is estimated that around 40% of GP practices in the region are engaged and recruiting into clinical trials. Initial approaches to these local GP practices in the region on behalf of the study team was made by the Local Clinical Research Network North West London (LCRN). The LCRNs are an initiative set up by the NIHR to coordinate and support the delivery of research across the NHS in England. They fund teams of research staff to enter hospitals and GP practices in order to facilitate and increase awareness of the research opportunities available to patients.

The process of recruitment from GP practices is summarised in the flow diagram (figure 1.11)

Figure 1. 11 Patient Recruitment from GP PICs

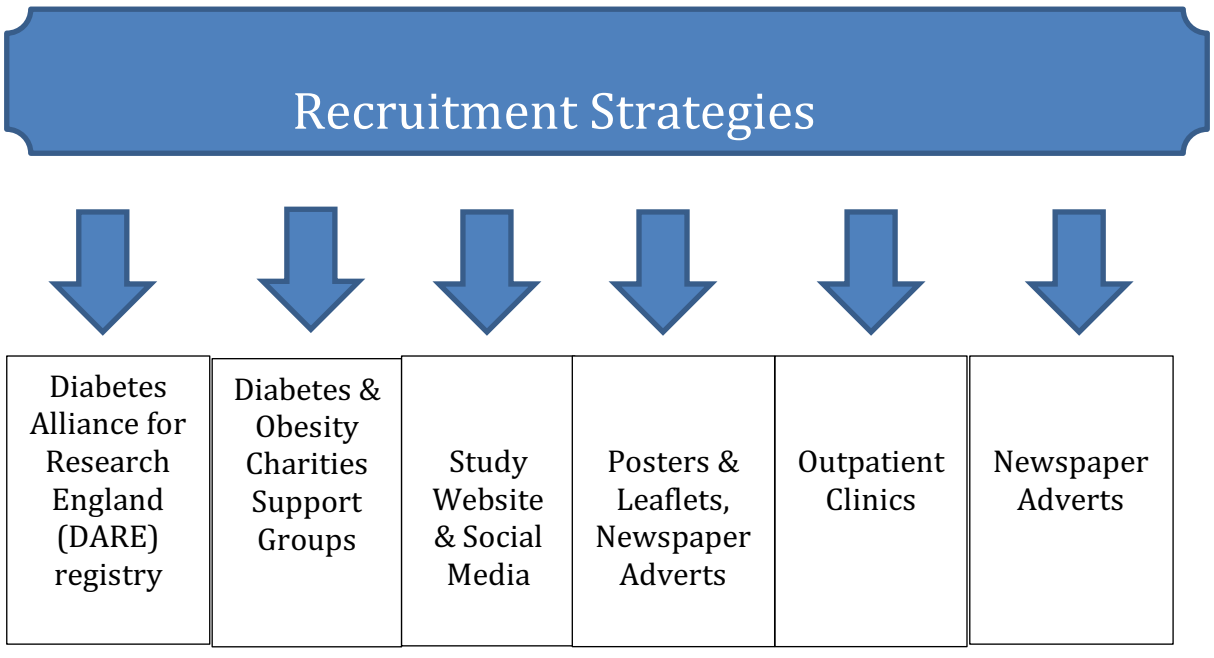


This process was incentivised with £150 paid for the database search and set up, then £0.60 per pack sent to patients, and £40 for each pre-screening questionnaire completed.

Various other strategies were also employed to compliment recruitment from GP practices (Figure 1.12). These included:

1. **Diabetes Alliance for Research England (DARE) registry** – a database of 60,000 patients nationwide with diabetes who have expressed an interest to be informed and participate in diabetes research. This database was interrogated by the clinical research fellow and patients who met the criteria were sent out patient packs with information about the study.
2. **Study website** – an official website for the trial was set up www.tinyurl.com/EB and by the Imperial College research facility: http://imperial.crf.nihr.ac.uk/studies/EB/
3. **Diabetes UK** – contacted charities including diabetes UK who promoted the study on their website and magazine
4. **Social media** – facebook posts and twitter feeds
5. **Posters and leaflets –** were placed in prominent areas in GP practices, diabetes and renal outpatient clinics.
6. **Newspaper Advertising –** a weekly advert was placed in local newspapers in London (*The Evening Standard* and *Metro*) and in Southampton (*Bournemouth Echo, Daily Echo, The News*) .

Figure 1. 12 Recruitment Strategies



2.3 Primary & Secondary endpoints

The primary objective of this clinical trial is to evaluate the efficacy of the EB compared with standard medical therapy, diet and exercise on glycaemic control. Using the International Diabetes Federation (IDF) guidelines, a substantial improvement in an individual's metabolic state will be defined as an improvement in HbA1c by 20%.[287]

Primary endpoint of the RCT - a reduction in HbA1c by 20% after one year of treatment.

The secondary objective will be to evaluate the efficacy, acceptability and cost-effectiveness of the EB when compared against standard medical therapy, diet and exercise. Secondary endpoints are as follows:

- HbA1c < 42mmol/mol
- blood pressure <135/85
- weight loss >15%
- reduction in dose and number of medications
- cost of interventions and related health and social care
- quality-adjusted life years (QALY) accrued (calculated from area under the 5-Level European Quality of Life- 5 Dimensions (EQ-5D-5L questionnaire curve)
- incremental cost per QALY within the trial period and extrapolated through modelling.

2.4 Power Calculations

No previous studies have explicitly looked at reaching an arbitrary percentage reduction in HbA1c so to derive an estimate for treatment effect in the control arm we looked at the Steno trial.[288] This was a randomised study (n=80 patients in each arm) into the effect of best medical therapy which demonstrated over an average 7.8 years significant improvements in HbA1c among those having

intensive medical therapy from 8.4±1.6% to 7.7±1.2%, but no change in HbA1c among those continuing with standard medical therapy. This study defines the very best that could realistically be achieved in the control arm and we anticipated very little if any change in the control 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 was assumed that a target of 15% of patients achieving the 20% reduction target was established as a conservative estimate.

Company data from GID 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 our pilot study up to 30% of patients in the treatment group may have the device removed early within the first year.[241] 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 versus 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 power of 80% was chosen in order to allow a 'sensible' and achievable recruitment target.

2.5 Mechanistic Studies

In order to investigate the potential mechanisms of how the EB elicits its effect, both treatment arms were divided into three optional subgroups, which will have the following additional assessments during the course of the trial:

- subgroup 1: fMRI of food reward and addictive behaviours, eating behaviour assessment and post-meal gut hormones.
- subgroup 2: euglycaemic-hyperinsulinaemic clamps (total body and tissue-specific insulin resistance).

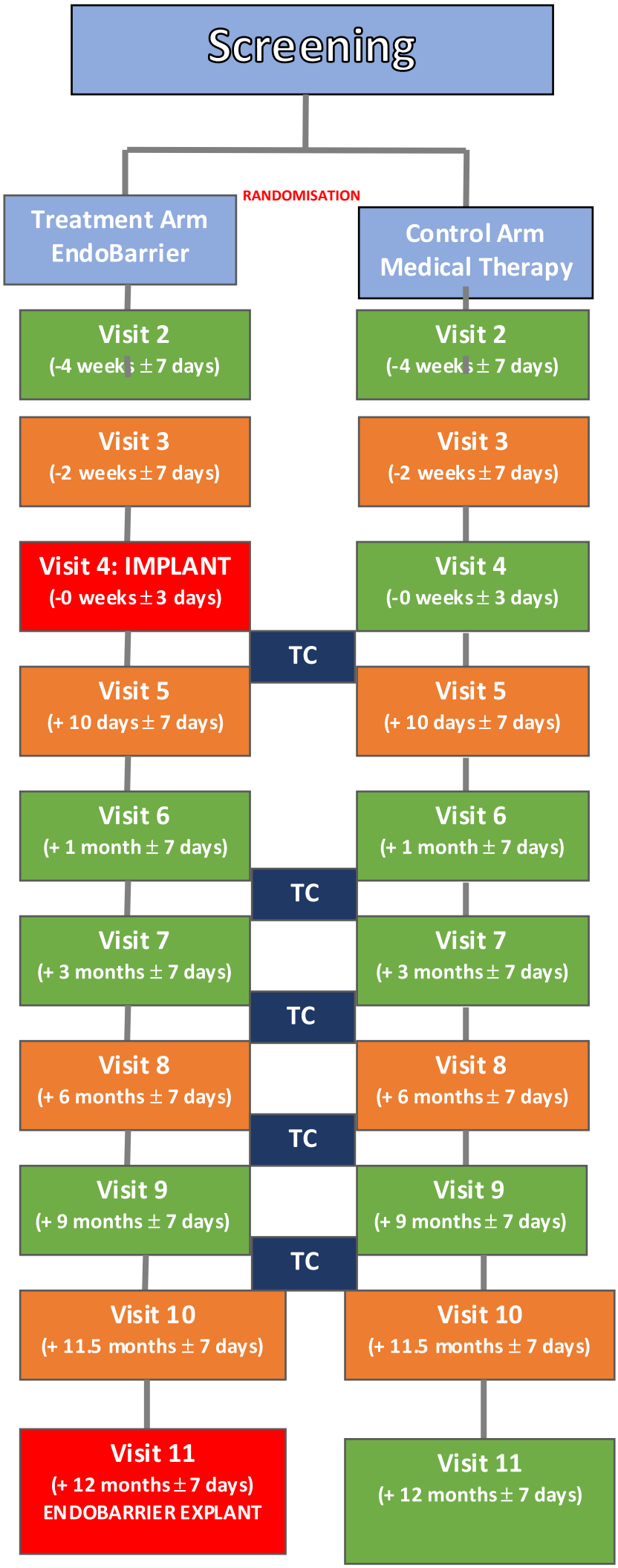
- subgroup 3: assessment of taste and food preference, eating behaviour assessment and post-meal gut hormones.

Data obtained from these three subgroups form the basis of three other PhD thesis so results of this will not be discussed any further in this thesis.

2.6 Study Schedule

The first year of the trial consisted of 11 study visits including implant of the device and explant of the device at 1 year (figure 1.13). In addition to these visits, 5 telephone consults were also performed (figure 1.14).

Figure 1. 13 Study visit schedule comprising of a total of 11 study visits within the first year of the trial. The initial screening visit, 6 clinic visits and 4 mechanistic visits.



Legend:

Green Boxes = clinical visits

Orange boxes = mechanistic visits.

Red Box = EB implant or explant

TC: Telephone consult

Figure 1. 14 Telephone Consults

Telephone Consults:

- Conducted between visit 4 and 5, 6 and 7, 7 and 8, 8 and 9, 9 and 10
- To confirm date and time of next study visit
- To ensure directions
- To remind what to bring and what to do before the next visit
- To ensure well-being, any changes in concomitant medication or illness
- To assess motivation and compliance

2.6.1 Screening Visit

After obtaining informed consent the subject's eligibility was further assessed and documented by using a questionnaire with a list of inclusion and exclusion criteria (figure 1.12). Medical history (including all medications past and current) were acquired and the following measurements were performed: body weight, height, waist circumference, blood pressure, ECG, urine dipstick and pregnancy test, blood parameters (figure 1.15) and female patients were asked to report the last day of their menstrual period, the length of their cycle and the length of their menstruation (bleeding). This information was used to ensure they are not pregnant and to help monitor any changes in their menstrual cycle during the course of the study. Patient demographics were also collected. At the screening visit, patients were given the opportunity to consent for participation in one of the mechanistic sub-groups (1-3) as described previously.

Figure 1. 15 Summary of Blood Tests at Each Study Visit

(Obtained with permission by BMJ Open Publishers)[289]

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 B_{12}	x					x		x					
Serum folate	x					x		x					
Free thyroxine	x							x					x
TSH	x							x					x
Cortisol (subgroup 1 only)		x				x							
Oestradiol (subgroup 1 only)		x				x							
Progesterone (subgroup 1 only)		x				x							
LH (subgroup 1 only)		x				x							
FSH (subgroup 1 only)		x				x							

FSH, follicle-stimulating hormone; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinising hormone; TSH, thyroid-stimulating hormone.

2.6.2 Randomisation

Eligible patients were randomised into one of the two treatment arms using the InForm Integrated Trial Management system which is a secure web-based data entry platform. This was programmed with a randomisation schedule by an independent statistician and protected against bias in the randomisation process as group allocation was concealed and automatic. The randomisation was at a ratio of 1:1 and stratified by site and two BMI groups, 30–40 and 40–50 kg/m^2. Each patient is then assigned a unique study identification number and informed of his/her randomisation allocation by phone or email before being invited for their next visit.

2.6.3 Visit 2

At visit 2 (−4 weeks), participants who had been randomised to receive the EB device were tested for the presence of *Helicobacter pylori*, either by faecal antigen or urea breath testing. Those patients testing positive were prescribed 1week of triple-eradication therapy, as per guidance published within the British National Formulary (BNF), and then retested after a further 4 weeks to confirm complete eradication before continuing to their next visit. Patients in the treatment arm also received PPI (omeprazole 40mg twice daily) which they were instructed to commence 3 days prior to the implant procedure (visit 4). They continued this for the duration of the implant period (12 months) and for a further 2 weeks following device removal.

2.6.4 Dietary Counselling

At visit 2, all patients were assessed by a qualified dietitian where a detailed analysis took place of their anthropometry; blood results; medical, psychiatric and family history; activity levels; eating habits including previous diets; lifestyle including smoking, drug and alcohol misuse. Patients also received dietary and physical activity counselling. Patients receiving the EB were provided with written information on what modifications to their diet should occur following implantation of the device. Alongside dietary measures participants in both groups were advised to increase their physical activity.

All patients were reviewed by a specialist dietitian on their clinical visits (2, 6, 7, 9). In addition, participants in the standard care arm of the trial received an additional review at visits 4 and 11 instead of the EB implant and removal. To avoid disruption of the device in the immediate period following implantation, patients were requested to adhere to a liquid diet for the 7 days prior and 13 days after implantation of the device (visit 4). Under the guidance of a specialist dietitian patients were prescribed Fortisip Compact drinks 125mL containing per 100 mL 240 kcal, 9.6 g protein (16%

total energy), 29.7 g carbohydrate (49%), 15 g sugars and 9.3 g fat (35%): five per day for men, four per day for women. Patients were free to consume sugar-free squashes, smooth/ clear soup, tea or coffee without sugar, or unsweetened puree. To standardise both therapy groups, all patients across both arms followed the same liquid diet for the same duration in the study.

2.6.5 Implant (Visit 4) and Explant (Visit 11)

All patients undergoing EB implantation adhere to strict dietary advice which involves following a liquid diet of nutritional drink supplements for at least 1 week prior to their implant date, and for 1-2 weeks post procedure. The purpose of following this regime is to facilitate clear views during endoscopy for implantation of the device, and to mimimise the risk of a food bolus obstruction of the liner in the first few weeks post procedure.

Both general and conscious sedation can be used for this procedure which also requires fluoroscopic imaging for guidance in the insertion or removal of the liner. A thorough endoscopic examination of the upper GI tract is conducted prior to the device placement to ensure suitability and to detect any potential anatomical variants such as a short duodenal bulb or peptic ulcer disease which may preclude the device from being inserted. GID advocate prescribing a proton pump inhibitor (PPI) such as omeprazole 40mg twice daily three days prior to insertion and whilst the device is in situ up until two weeks after the device is removed to minimise the risk of potential bleeding from the implant. Furthermore to reduce the potential for infection, GID also suggest administering a single dose of broad spectrum antibiotic (e.g. ceftriaxone 2g) 1-2 hours prior to implantation.

2.6.5.1 Implantation

At visit 4 (0 weeks), after an 8-hour fast, subjects received the EB under general anaesthesia. Implantation takes on average 45 minutes to perform. The patient is placed in left lateral decubitus position and a surveillance gastroscopy is performed followed by placement of the endoscope in the

first part of the duodenum. A guidewire is advanced into the duodenum through the working channel of the gastroscope and the gastroscope is removed. The EB delivery system (co axial catheter system with capsule containing the EB sleeve) is advanced over the guidewire into the duodenum and the guidewire is then removed. The delivery system has 5 steps which are followed in order, to release the device from its protective capsule into the ideal position which should be 5-10mm from the pylorus with the proximal barbs anchored in the duodenal bulb and the sleeve running distal to this. Peristalsis will ensure the sleeve unravels across its 60cm length into the duodenum. A water-soluble contrast such as gastrografin is then used to confirm the positioning of the device and to prove it is patent. During implantation eight gastric and small bowel biopsies were taken using standard biopsy forceps. Four biopsies were sent for routine histology and four biopsies have been frozen and stored for RNA extraction to perform genome-wide expression analysis at a later date. Participants were discharged from hospital the same day with an implant information card, which describes the implant, identifies who to call in case of an emergency and what if any potential side effects to look out for following the implant. Any patient on sulfonylurea medication had their dose reduced by 50% at the time of EB implant to avoid potential hypoglycaemic episodes.

2.6.5.2 Explantation

The device was removed at visit 11 (after 12 months) under general anaesthesia. Explantation takes on average 30 minutes to perform. The patient is placed in left lateral decubitus position and a surveillance gastroscopy is performed. The endoscope is then removed, and a protective hood is placed on the end of the endoscope. This circular hood is made out of a durable plastic polymer and is designed to hold within it the sharp anchors located at the proximal end of the liner. The endoscope is reintroduced into the duodenum and the anchors of the device are identified. Each of the anchors has drawstrings attached to them. A specially designed grasper with a hook on the end contained in a

protective plastic sheath is then passed down the therapeutic channel of the scope until it arrives distal to the protective hood on the end of the endoscope. The retrieval hook is then advanced forward beyond its sheath and positioned around one of the drawstrings before being retracted, pulling the drawstring with it, thus collapsing down the device. Once the anchor is fully collapsed, the retrieval device is locked in position and the endoscope with hood is advanced forward ensuring that all the collapsed anchors are captured within the hood – this can be confirmed by fluoroscopy. Under fluoroscopic guidance the endoscope, retrieval system and liner are removed together, making sure they can travel safely through the anatomy. Finally, the explant site is examined for signs of bleeding. During the removal, eight further biopsies will be taken for histology and RNA extraction. The patient is usually discharged home the same day following recovery from the anaesthetic.

The process for implant and explant have been previously described in chapter 1, section 1.4.

2.6.6 Clinical Visits (6,7,9,11)

Each clinical visit lasted an hour with a review by the clinical research fellow followed by a dietetics assessment. Any changes in the patient's health status, medical history and medication changes were documented and any adverse events logged.

The following were also performed:

- Body measurements including weight and waist circumference and vital signs
- Routine chemistry and haematology (figure 1.21)
- Health Economics questionnaire completed: Visit 6 and 7 only

At all clinical visits adjustments to a patient's oral anti-hyperglycaemic medication and escalation of therapy were made in accordance with international guidelines on the management of T2DM from the American Diabetes Association (ADA).[290]

2.6.7 Mechanistic Visits (3,5,8,10)

Patients were seen by the research fellow and in addition to the above assessments being performed the following were also obtained:

- body fat mass (kg and % of body weight) measured by bioelectrical impedance analysis
- collection of stool, urine and plasma for assessment of metabonomics using nuclear magnetic resonance spectroscopy and mass spectrometry and microbiome analysis.
- fasting venous samples taken for measurement of insulin, gut hormones (ghrelin, GLP-1, PYY), bile acids, leptin and other adipocytokines, and markers of insulin. These were fasting for all visits and then following a meal in subgroups 1 and 3 at visits 3, 5, 8 and 10.
- DNA and RNA from venous blood samples for examination of genetic variants that may predict weight loss, cause or contribute to obesity
- urinary albumin:creatinine ratio
- comprehensive 3-day food diary

2.7 Statistical Analysis

Analyses of data were performed using SAS Version 9.4. Normally distributed efficacy data are presented by variable, as means with standard deviations (SD). In the event where data is not normally distributed, data will be presented by median and inter-quartile range (IQR).

Analysis was undertaken on an intention to treat basis. A mixed-model approach incorporating fixed effects for treatment, visit (from baseline up to 1 year), age, gender, BMI group was used. To investigate for any potential treatment effect over time between the two groups, an interaction term for visit and treatment was included within the model. A random effect for patient to account for inter-subject variability was also included. Where the interaction term suggested a change in treatment effect over time ($P < 0.05$), post-hoc testing was carried out to investigate the difference at the specified timepoints of 6-months and 12-months post treatment. For post-hoc testing between

treatment groups, change from baseline was assessed at follow-up visits using the 2-sample T-Test . As before a $P< 0.05$ was denoted as statistically significant.

For the post-hoc testing, no adjustments for multiple testing have been included. This is on the basis that; a) the testing follows the initial mixed-model approach and b) the testing is post-hoc and exploratory in nature. Therefore any results from the T-Test needs to be considered on the basis that such adjustments have not been made.

2.8 Metabolic Profiling Methodology

Plasma, urine and faecal samples for metabolic profiling analysis were collected from all participants who were able to provide samples at:

- Visit 3 – pre-implant therefore considered the baseline sample
- Visit 5 – up to 10 days following EB implant
- Visit 8 - 6 months post EB implant
- Visit 10 – 1 year post EB implant and the last visit prior to explantation

For the purpose of this PhD thesis samples obtained from visit 5 i.e. immediately after EB implantation were excluded in order to keep costs down for NMR analysis. These samples from visit 5 will be analysed upon closure of the clinical trial. Samples from visit 3, 8 and 10 were all analysed. In total 810 samples were processed and then analysed. These consisted of the following:

- 309 x Plasma samples
- 255 x Urinary samples
- 246 x Faecal samples

2.8.1 Plasma sample preparation for ^{1}H NMR spectroscopic analysis

Approximately 1.2 mL of whole blood sample was collected via venipuncture into 6 ml sodium heparinized vacutainers from each participant at each visit listed above. Within 30 minutes of collection these samples were centrifuged at 1,600 *g* relative centrifuge force (RCF) at 4°C for 15 minutes. The plasma supernatant above the white blood cell layer was then transferred into Eppendorf tubes and stored at -80 °C until analysis.

The standard operating procedure (SOP) used for plasma sample preparation for NMR is as follows:

1. Defrost the plasma samples at room temperature
2. Spin samples in a centrifuge for 10 min at 20,000 *g* at 4°C
3. Place empty 1.5 mL Eppendorf tube on a rack and transfer 300 µL of Phosphate buffer into each Eppendorf tube.
4. Transfer 300 µL of plasma supernatant into each tube and label it
5. Vortex for 5 secs
6. Spin briefly (15 seconds) to let liquid down
7. Transfer 580 µL of supernatant into an NMR tube with a diameter of 5 mm
8. NMR detection

2.8.2 Urinary sample preparation for ^{1}H NMR spectroscopic analysis

Following an overnight fast, patients provided a fresh urine sample on the morning of their visit which was collected in a universal container. This was aliquoted immediately using a sterile pipette into cryotubes and stored at -80°C until NMR analysis.

The (SOP) for urine sample preparation for NMR is as follows:

1. Defrost the samples at room temperature
2. Spin samples for 10 min at 20,000 *g* relative centrifuge force (RCF) in a centrifuge at 4°C.

3. Place empty 1.5 mL Eppendorf tube on a rack and transfer 60 µL of pre-prepared phosphate buffer into each Eppendorf tube.
4. Transfer 540 µL of urine supernatant into each tube containing the phosphate buffer and label it
5. Vortex for 5 secs
6. Spin briefly (15 seconds) to let liquid down

1. Transfer 580 µL of supernatant into a 5 mm NMR tube taking care to avoid any bubbles from forming in the tube.

2.8.3 Faecal sample preparation for ^{1}H NMR spectroscopic analysis

Stool samples were collected in sterile faecal containers. Patients were advised to provide a sample on the morning of their visit. These were allocated into cryotubes and stored in a freezer at -80 until time of analysis.

Faecal water was extracted from the crude faecal samples for analysis by NMR. Metabolic profiles of faecal water samples have been shown to be more stable compared with crude samples.[291]
The SOP for faecal sample preparation for NMR is as follows:

1. Thaw the faecal sample thoroughly at the room temperature.
2. Stir it thoroughly under biosafety cabinet
3. Take 300 mg into a 2 ml Eppendorf and record the weight.
4. Add two portions of H_2O (HPLC grade) into the 2ml Eppendorf (1mg:2µl=faecal weight: water volume)
5. Vortex it for 5 mins
6. Spin at 18,000 *g* (max speed) for 10 mins at 4°C.

7. Take 400 µl of supernatant and pipette into a new 1.5 ml Eppendorf containing 60 µl 1.5 M sodium phosphate buffer (pH=7.4, 100% D_2O) and 140 µl of D_2O.
8. Vortex and spin briefly.
9. 580 µl of supernatant is then transferred into a 5mm NMR tube taking care to avoid any bubbles from forming in the tube.

2.8.4 NMR Protocol

All biological samples were run through 600 MHz ^1H NMR spectroscopy with a 5-mm tube NMR probe using the previously published protocol by Keun and Athersuch.[292]

This is as follows:

Instrument Set Up

A. Set probe temperature (e.g. 300 K), insert sample and wait for temperature equilibration (~5 min).
B. 'Lock' the instrument to the D_2O resonance.
C. Tune and match the probe.
D. Adjust shimming to optimise spectral line shape. Half-height line width of <1 Hz should be readily obtainable on samples with low protein content.
E. Using a single pulse experiment with presaturation, determine the 90◦ pulse length and optimise the spectrometer frequency offset to minimise the residual solvent resonance.
F. The receiver gain was fixed to 90.5.
G. Select suitable recycle delay (RD) for total recycle time to be of the order of 5∗T1 and for suitable water suppression. Typical parameters at 600 MHz 1H frequency might be an RD of 2 s and a total acquisition time (AQ) of 2.73 s recorded into 64 K complex data points to give a spectral width of ~12 kHz.

H. Presaturation pulse power should be the minimum required to achieve the necessary reduction in the water resonance, e.g. equivalent of 25 Hz bandwidth.

I. Specific pulse sequence optimisation. a. Change to 'NOESYpresat' pulse sequence (RD-90◦-t_1-90◦-t_m-90◦-AQ) for more effective solvent.

The NMR experiments setup was carried out by Dr. Zhigang Liu. The NMR spectra of urine and faecal water samples were acquired using 1D standard pulse sequence with water suppression at 300 K. Ninety-degree pulse was adjusted to approximately 10 μs. A total of 32 scans were acquired into 64 k data points. For plasma samples, CPMG pulse sequence was used in addition to 1D standard pulse sequence. The temperature for data acquisition is 310 K.

^{1}H NMR spectra were phased calibrated and baseline corrected automatically. The water (4.75-4.9 ppm) and TSP (-0.2-0.2 ppm) signal regions were removed from the spectra of all biofluids. Urea region from the urinary spectra was also removed. The remaining spectral data were aligned using recursive segment-wise peak alignment method and normalized using probabilistic quotient normalization.[293, 294] The resulting processed data were further modelled using the unsupervised method of PCA using SIMCA 13.0.3 software (Umetrics) to generate an unbiased overview of the major metabolic differences between the EB and control group. To explore the class-related metabolic changes, an OPLS-DA model was used to discriminate between the two groups, which was carried out in MATLAB (2014a).

Chapter 3: Recruitment & Clinical Trial Results

3.1 Introduction

The majority of clinical trials of the EB have included low numbers of participants, with short study duration and in non-randomised settings. This has led to the EB largely being limited to the clinical trial setting and not being recommended for routine use. It is therefore of great clinical interest to evaluate the applicability of the EB in clinical practice and the primary goal of this study is to investigate the effects of the EB on glycaemic control and weight loss in obese patients with T2DM in the setting of a national multicentre RCT.

In this chapter, there is an in-depth report describing the various successes and failures of the different recruitment strategies deployed in the trial. Following this is a presentation of clinical data obtained from baseline to one year from both treatment arms including indicators of glycaemic control, weight loss, lipid profile and liver biochemistry. In addition, all adverse events and the general safety profile of the device will be discussed. The chapter concludes with an overall impression of these results contextualised with the previously published literature.

3.2 Recruitment Results

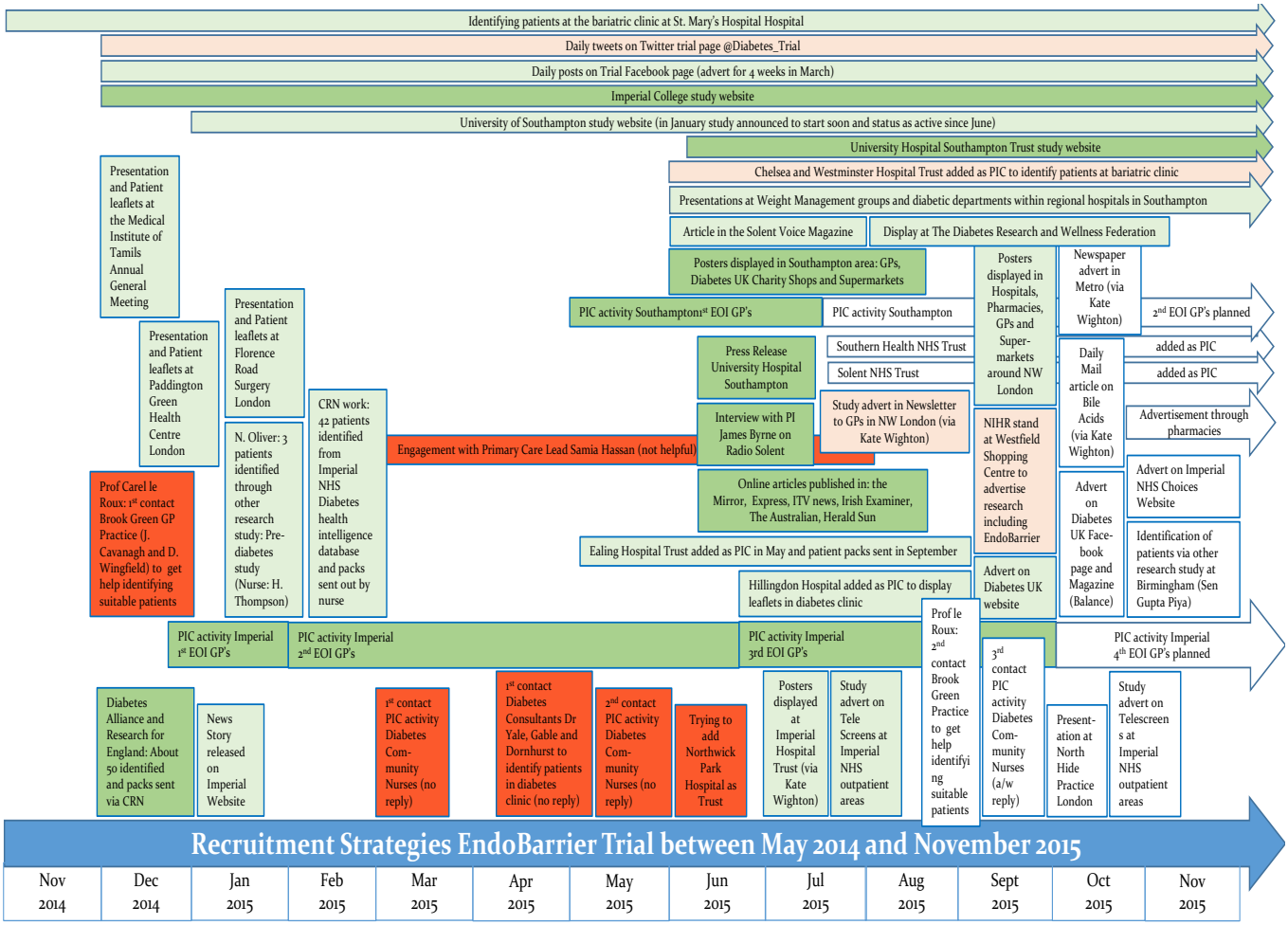
Advertising for the study commenced in May 2014 with recruitment opening in October of the same year. Recruitment to the trial took 2 years with the first patient randomised at ICHT in November 2014, and the final participant recruited in October 2016. The key dates in the recruitment process are outlined in Table 1.7.

Table 1. 7 Key dates in Recruitment Process

Key Events	Imperial College Healthcare	Southampton Hospital
Advertising for study	May 2014	May 2014
Recruitment Initiated	20th October 2014	30th April 2015
First patient Screened	28th November 2014	3rd July 2015
First patient Randomised	6th March 2015	9th July 2015
Last patient Randomised	18th October 2016	18th October 2016

The first 18 months focused on identifying PICs from the primary and secondary care setting. Presentations were made at local GP practices, meetings were held with nurse specialists and endocrinologists working in the community diabetes practices. Press releases were made online, on social media sites and in major tabloid newspapers. Figure 1.16 summarises activities conducted by the study team from the opening of recruitment until November 2015.

Figure 1. 16 Early Recruitment Progress



From November 2015 through to September 2016 a quarter page advert was placed in in two local newspapers in London (figure 1.17) – *Metro and Evening Standard*.

Figure 1. 17 Newspaper Advert

Living with Type 2 Diabetes?

Struggling with your weight?

DIABETES AND WEIGHT LOSS TRIAL

A new research study at Imperial College **London** investigates the effect of a device called the EB on diabetes and weight loss. To be able to participate you must be aged 18-65 years, have a diagnosis of type 2 diabetes (not yet on insulin), and a BMI of 30-50 kg/m^2.

For more information please contact:

Dr Aruchuna Mohanaruban
EB@imperial.nhs.uk
0207 594 5946/ 078 7285 0052

This project is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership

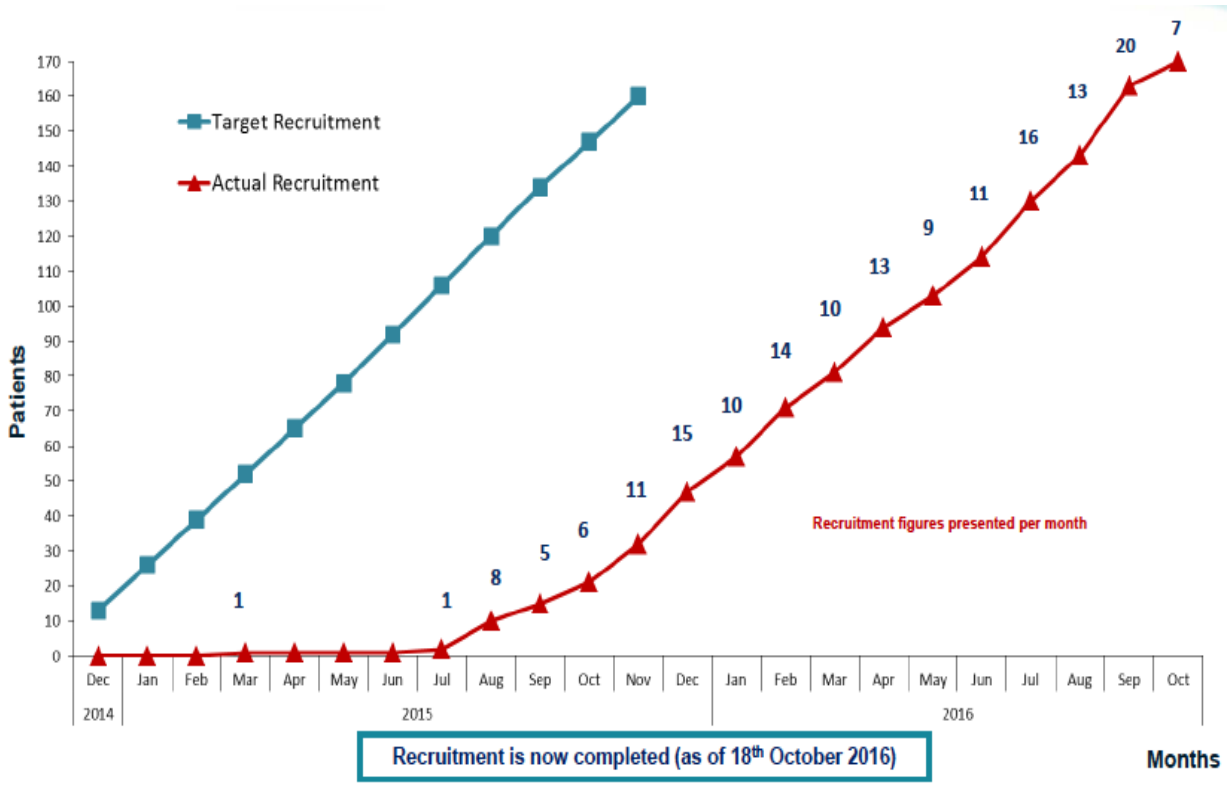
This also included a digital advertising campaign with adverts placed on desktop and tablet versions of the newspaper providing direct links to the trial study website when the advert is clicked on. Table 1.8 shows examples of how some of these adverts performed by the number of adverts accessed online and the click through rate (CTR) which refers to a percentage of people viewing the advert that clicked on it to directly access the study website. The industry standard is currently at about 0.3% as provided by the advertising team from the metro and evening standard.

Table 1. 8 Examples of Digital Adverts Performance during April and May 2017

Newspaper		**Total page views**	**Clicks**	Click Through Rate **CTR (%)**
Metro	**Digital Newspaper Advert (1)**	150,535	742	0.49%
	Tablet Advert (1)	39,873	465	1.17%
	Tablet Advert (2)	13,655	134	0.98%
Evening Standard	**Digital Newspaper Advert**	150,396	180	0.52%

The progress of recruitment at both sites from commencement through to the completion in mid-October 2016 is shown in Figure 1.18. This graph clearly shows recruitment picking up in November 2016 coinciding with the instigation of the newspaper campaign.

Figure 1. 18 Recruitment Timeline

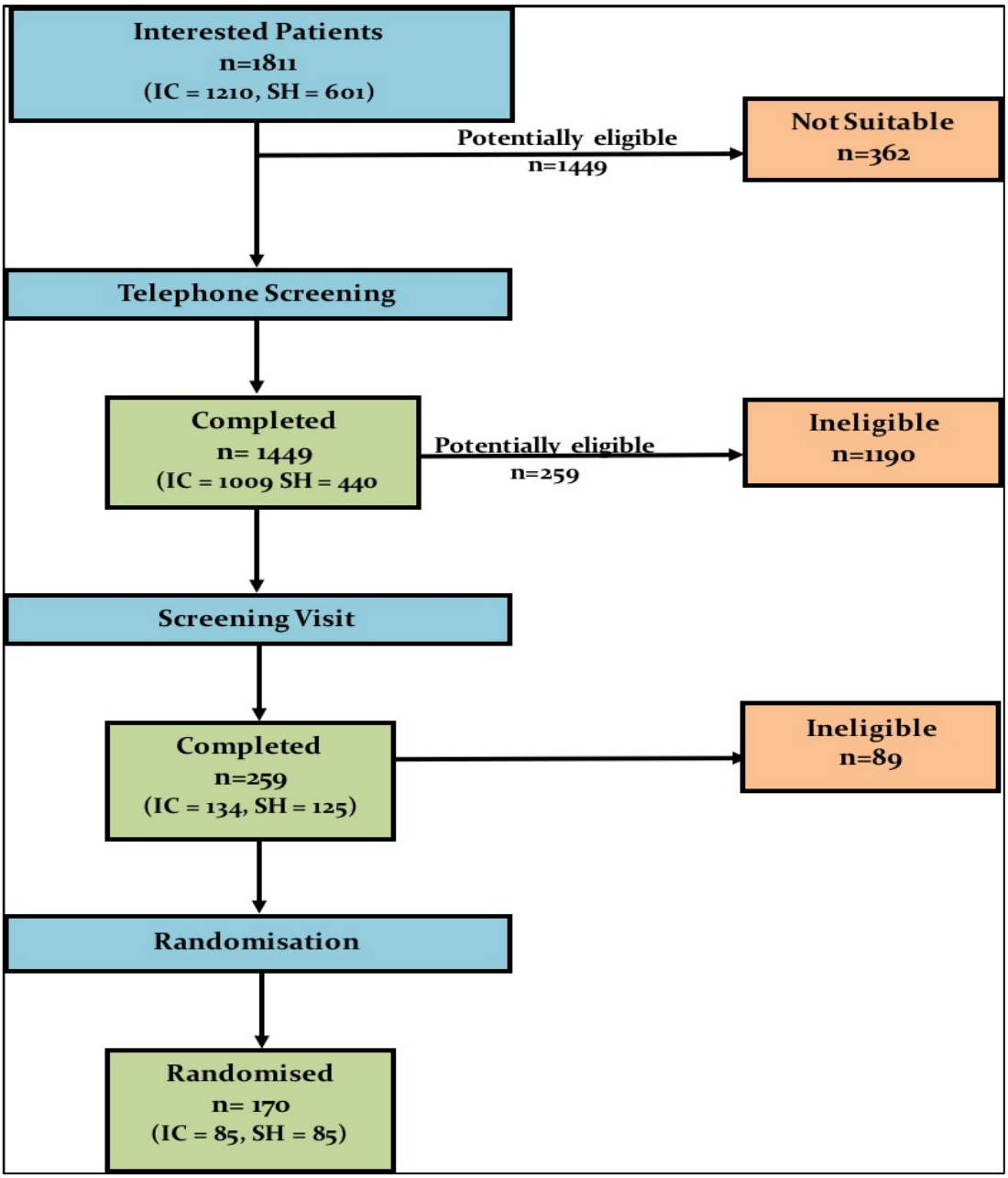


Most patients at the ICHT site were self-referred after hearing about the study from newspapers adverts. Over 1000 phone calls were received from patients following the newspaper adverts. This compared to only 65 patients' reply slips from GP practices. In comparison UHS received 397 patient reply slips from GP practices. A smaller newspaper advert campaign was run in the local newspaper in Southampton with 13 adverts published during June and July 2016 which generated 102 new telephone consults from patients. The different sources of recruitment are shown in Table 1.9 and figure 1.19 summarises the overall recruitment figures from screening right through to randomisation.

Table 1. 9 Sources of Recruitment

	Imperial College London	University Hospital Southampton	Total
PATIENTS INTERESTED	1210	567	1777
Source of Patient:			
GP	65	397	462
Newspaper Adverts	1004	102	1106
Study Website	75	9	84
DARE	16	0	16
Other / Unknown	14	28	42
Other Bariatric and Diabetes Clinics	9	9	18
Diabetes UK	7	16	23
Other Research / Science Museum	7	0	7
Poster	4	3	7
Tele Screen Outpatients Imperial NHS	4	0	4
Radio Solent Interview (after PR UHS)	0	2	2
Social Media (Facebook or Twitter)	4	0	4
Friend	1	1	2

Figure 1. 19 Recruitment Flow Chart



3.3 Clinical Trial Results

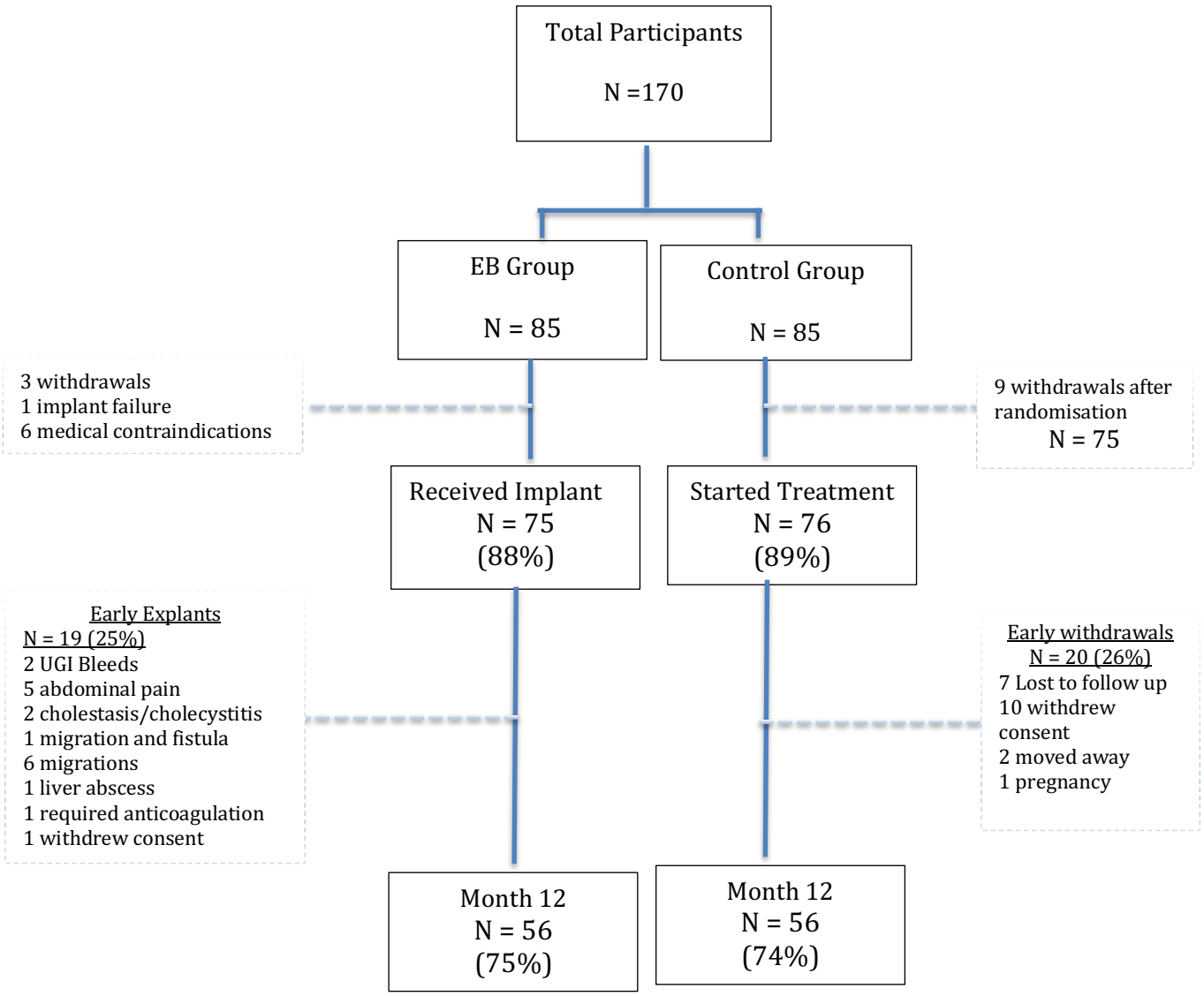
The baseline characteristics of all participants is shown in table 1.10 and figure 1.20 describes the study flow chart of participants progress during the trial. A total of 170 patients were randomised across both sites with 85 randomised into the EB arm and 85 into the control arm. Of the EB group, 75

participants went on to receive the implant. Three withdrew consent after randomisation and one was a technical failure at endoscopy due to short duodenal bulb. One patient had persistent *H.Pylori* infection, and five patients developed medical conditions which precluded them from receiving the implant (ketosis, anaemia, ureteric stones and abnormalities on CT Head). The average duration for the implant procedure was 41 minutes and the average duration for explant was 31 minutes. There were 19 (25%) early explants in the EB group and 20 (26%) early withdrawals in the control group before 12 months. Of the early explants 8 (42%) patients had the implant in for > 6 months.

Table 1. 10 Baseline Characteristics of Participants

Baseline Characteristics	Subjects (n = 170)
Age, mean ± SD, y	51.8 ± 8.2
Gender, n (%)	
Male	92 (54.1)
Female	78 (45.9)
Weight, mean ± SD, kg	107.0 ± 16.3
BMI, mean ± SD, kg/m^2	36.6 ± 4.7
HbA1c mean ± SD (mmol)	72.4 ± 10.1
Glucose, mean ± SD, mmol/L	9.8 ± 2.63
Insulin, mean ± SD, mIU/L	13.8 ± 9.89
Total Cholesterol	4.3 ± 0.97
Systolic BP mmHg	137 ± 15
Diastolic BP mmHg	87 ± 10

Figure 1. 20 Study Flow Chart



3.3.1 Effect on Glycaemic Control

At baseline the mean fasting plasma glucose of the EB group was 9.9 ± 2.7mmol versus 9.6 ± 2.6 in the control group. Fasting insulin levels were 13.3±8.5 mIU/L and 15.0 ± 12.5 in the EB and control groups respectively. The mixed-model for glucose suggested a significant effect when investigating treatment group over time (p=0.0188) with no further significant effects within the individual fixed parameters. For post-hoc testing of change from baseline values between treatment groups, there were no statistically significant changes in glucose across the 1-year follow up period. The mean

reduction in baseline was -2.4±2.5mmol at 6 months, and -2.8±3.2 at 12 months in the EB group compared with -1.8±3.0mmol and -2.3±3.3 in the control group respectively (Table 1.11 and Figure 1.21). For insulin, the mixed-model output also suggested a significant effect when investigating treatment group over time (p=0.0165) with additional significant effects for gender (p=0.0321) and BMI group (p=0.0003). At 12 months insulin levels decreased by -4.3±5.9 mIU/L from baseline in the EB group compared with -2.1± 4.9 in the control group (Table 1.12, Figure 1.22: EB vs. Control; *P*= 0.04, post-hoc T-Test).

Table 1. 11 Glucose: Change from Baseline

Laboratory Test (units)	Treatment	Visit	n	Mean	SD	Median	Min.	Max.	t test p value
Glucose (mmol)	Control	Baseline	73	0	0	0	0	0	N/A
		Day 10	69	-3.23	2.17	-3.3	-9.4	1.2	0.15
		1 month	69	-2.76	2.63	-2.5	-9.8	2.3	0.95
		3 months	62	-2.59	3.16	-2.7	-11.2	6.9	0.60
		6 months	60	-1.81	2.92	-1.45	-9.6	3.3	0.24
		9 months	56	-2.04	3.02	-2.15	-9.5	4.5	0.26
		12 months	58	-2.23	3.30	-2.2	-10.6	8.5	0.37
	Treatment	Baseline	80	0	0	0	0	0	-
		Day 10	73	-2.60	2.92	-2.4	-8.9	6.9	-
		1 month	69	-2.80	3.32	-2.8	-10.5	7.1	-
		3 months	69	-2.87	2.86	-2.8	-11.7	5	-
		6 months	61	-2.40	2.54	-2.4	-9	3.6	-
		9 months	61	-2.65	2.72	-2.7	-9.3	4.6	-
		12 months	52	-2.78	3.18	-2.95	-9.6	8.1	-

Figure 1. 21 Glucose (mmol/L) - Change from Baseline

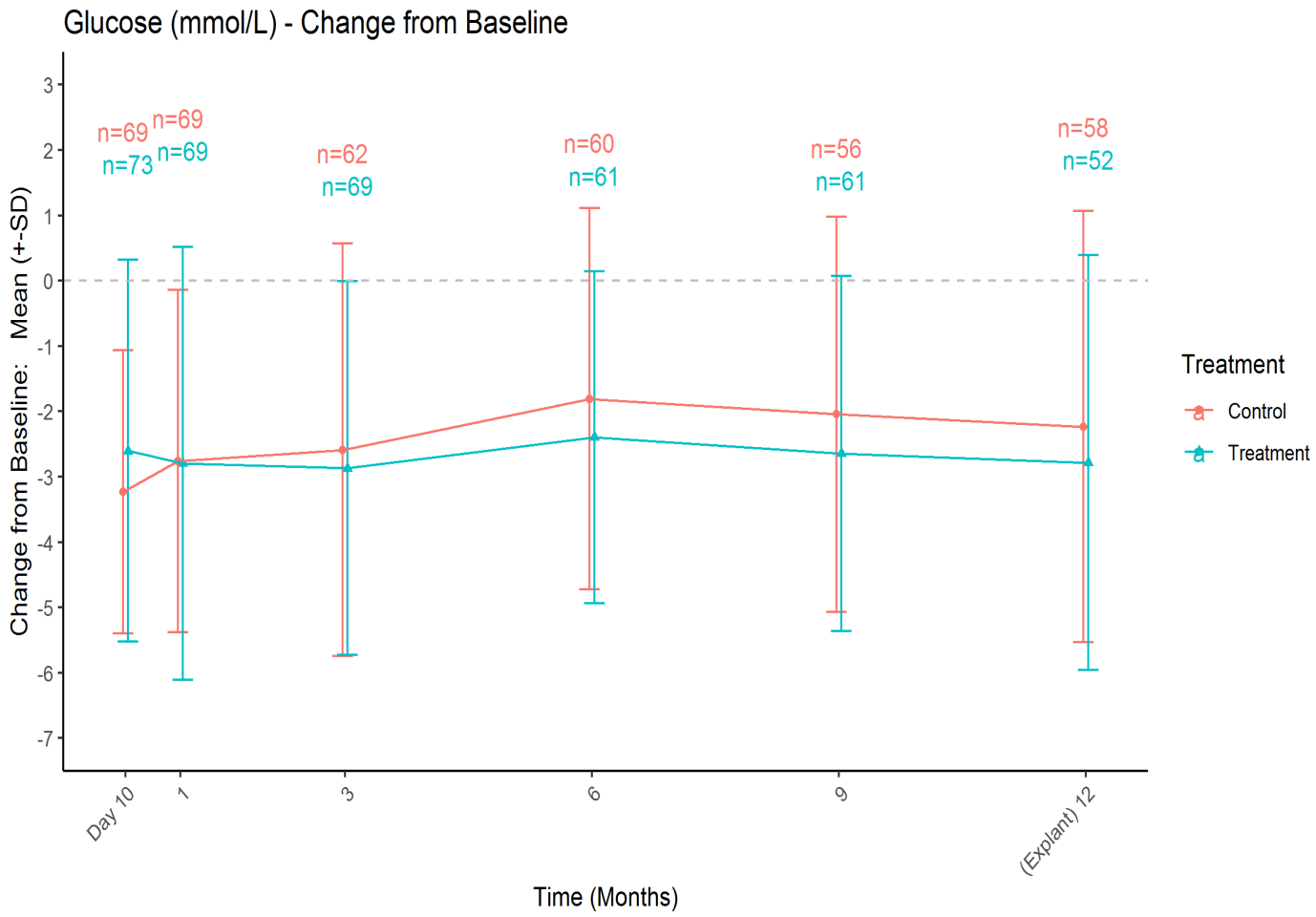
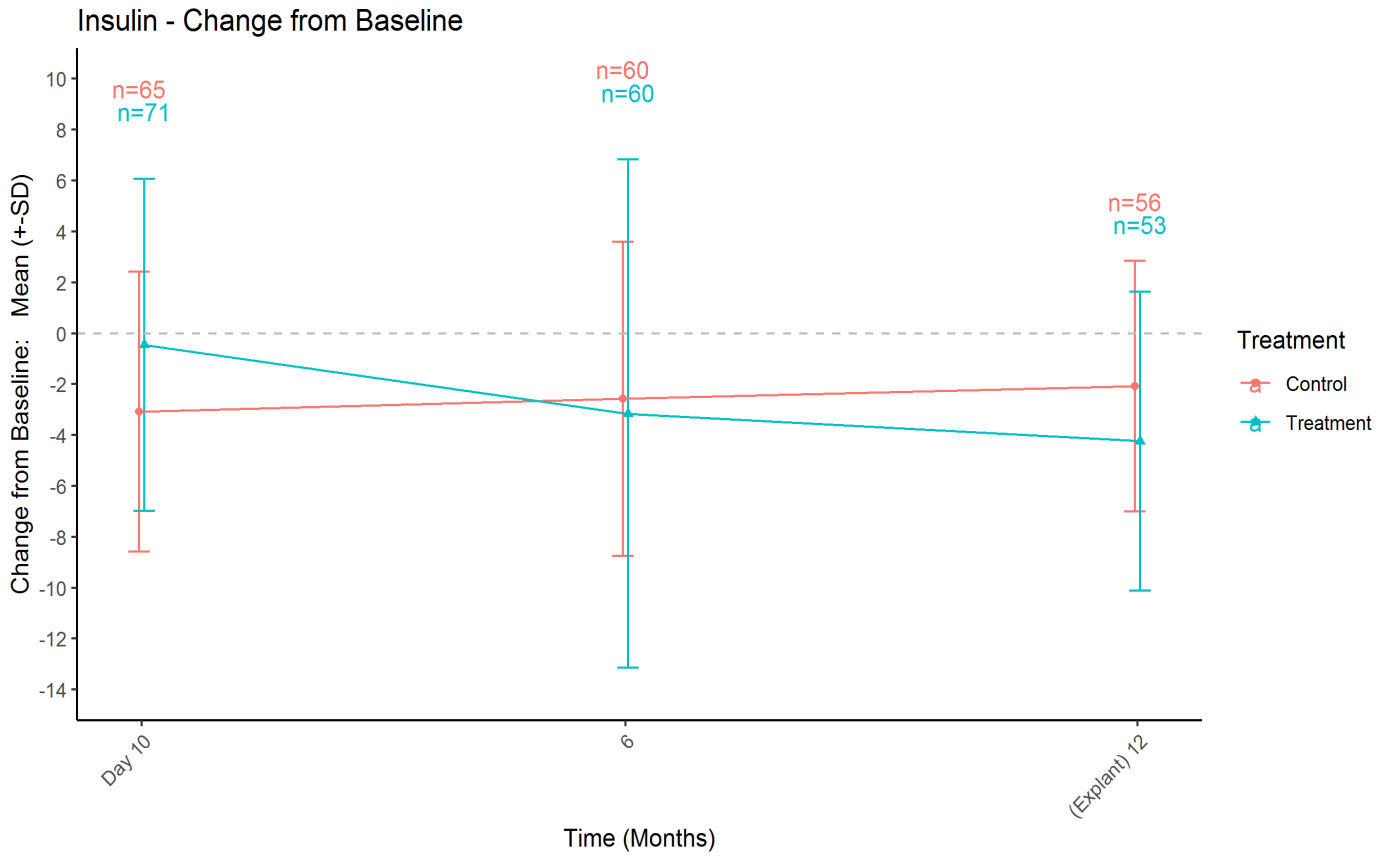


Table 1. 12 Insulin: Change from Baseline

Laboratory Test (units)	Treatment	Visit	n	Mean	SD	Median	Min.	Max.	t test p value
Insulin (mIU/L)	Control	Baseline	71	0	0	0	0	0	N/A
		Day 10	65	-3.07	5.50	-2.2	-25.1	8	0.01
		6 months	60	-2.58	6.17	-1.8	-28.5	13	0.70
		12 months	56	-2.07	4.93	-1.6	-20.9	8.6	0.04
	Treatment	Baseline	77	0	0	0	0	0	-
		Day 10	71	-0.46	6.53	-0.8	-17.7	28.4	-
		6 months	60	-3.16	9.99	-3.75	-27.2	51.3	-
		12 months	53	-4.24	5.88	-3.5	-24.4	11.3	-

Figure 1. 22 Insulin (mIU/L) Change from Baseline



3.3.2 Effect on Weight

At baseline the mean body weight of the EB group was 108.8± 17.5kg versus 105.2±16.2 in the control group. Mean BMI was 37.1± 5.0kg/m^2 in the EB group versus 36.1± 4.2 in the control group.

After 6 months body weight had decreased by 10.8±5.3kg in the EB group and 12.1±7.8at 12 months (Table 1.13, Figure 1.23). In comparison the control group lost 6.3±5.5kg (*P*=<0.001) at 6 months and 6.2± 6.4 at 12 months. The mixed-model output indicated a significant effect when investigating treatment group over time (p<0.0001) with corresponding significant effects for gender and BMI group. Post-hoc testing of change from baseline values between treatment groups provided significant results (P<0.0001, t-test) at both 6-months and 12-months. Correspondingly, when investigating BMI, the mixed-model output produced similar results (p<0.0001) but did not suggest a significant effect for gender. The mean (SD) decrease in the EB group was 4.2±2.5kg/m^2 at 12 months versus 2.1±2.2 in the control group (Table 1.14, Figure 1.24; *P*=<0.0001, t-test).

Table 1. 13 Weight: Change from Baseline

Laboratory Test (units)	Treatment	Visit	n	Mean	SD	Median	Min.	Max.	t test p value
Weight (kg)	Control	Baseline	74	0	0	0	0	0	N/A
		Day 10	70	-4.19	2.02	-4.35	-9.6	2.4	<.0001
		1 month	69	-4.75	3.03	-4.7	-10.6	6.2	<.0001
		3 months	64	-5.61	4.42	-4.85	-16.3	2.1	<.0001
		6 months	61	-6.30	5.53	-5.5	-27.6	3.9	<.0001
		9 months	57	-5.82	6.26	-4.9	-34.3	2.4	<.0001
		12 months	58	-6.17	6.39	-4.8	-38.6	4.4	<.0001
	Treatment	Baseline	80	0	0	0	0	0	
		Day 10	73	-6.06	2.77	-5.7	-15.2	0	
		1 month	70	-7.39	2.91	-7	-15.3	-1.6	
		3 months	69	-9.33	4.98	-8.8	-25.1	0.2	
		6 months	63	-10.82	5.39	-10.4	-25.3	1.5	
		9 months	62	-11.11	6.13	-10.15	-25.5	2.2	
		12 months	52	-12.10	7.83	-10.7	-38.8	2.1	

Figure 1. 23 Weight Change from Baseline

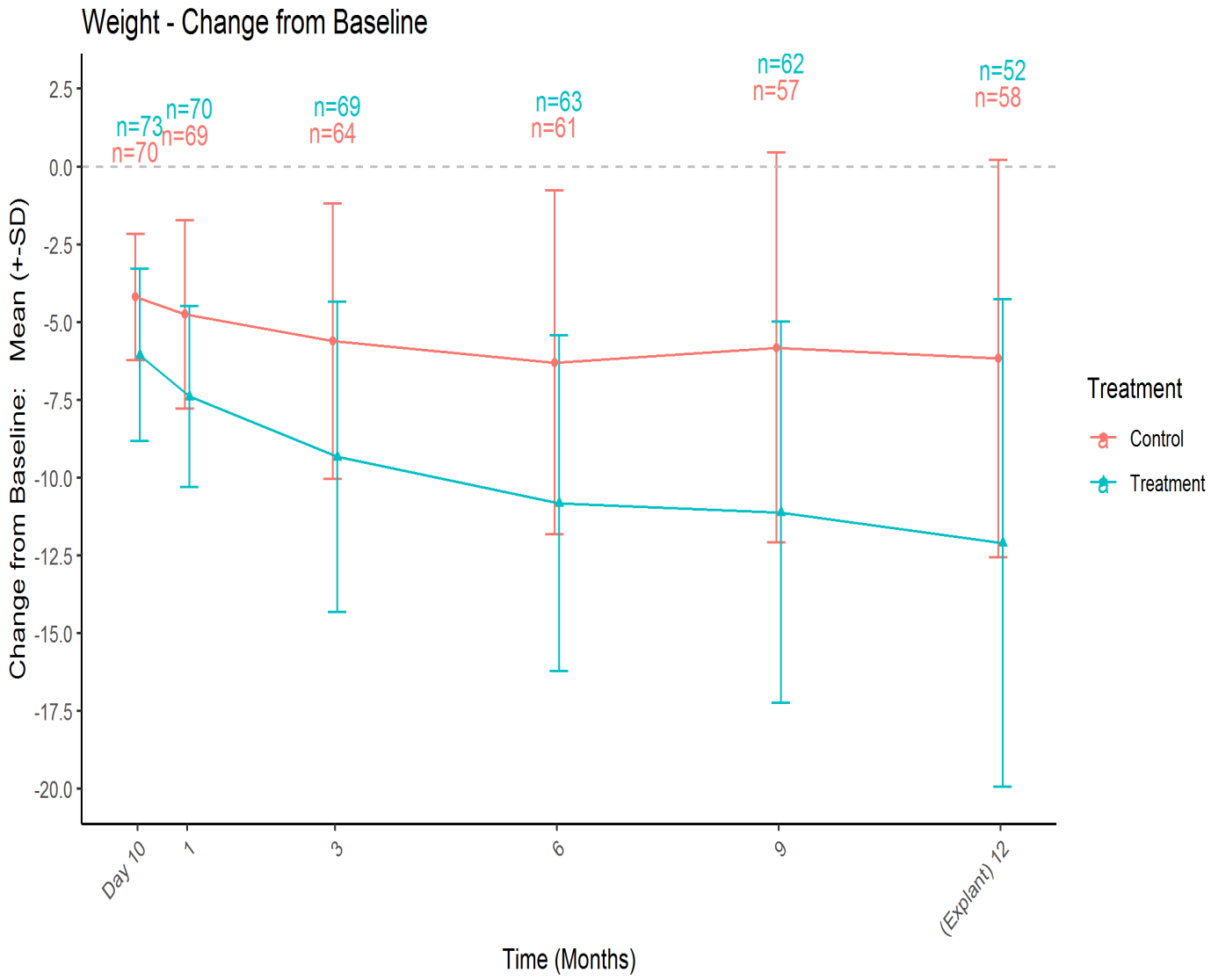
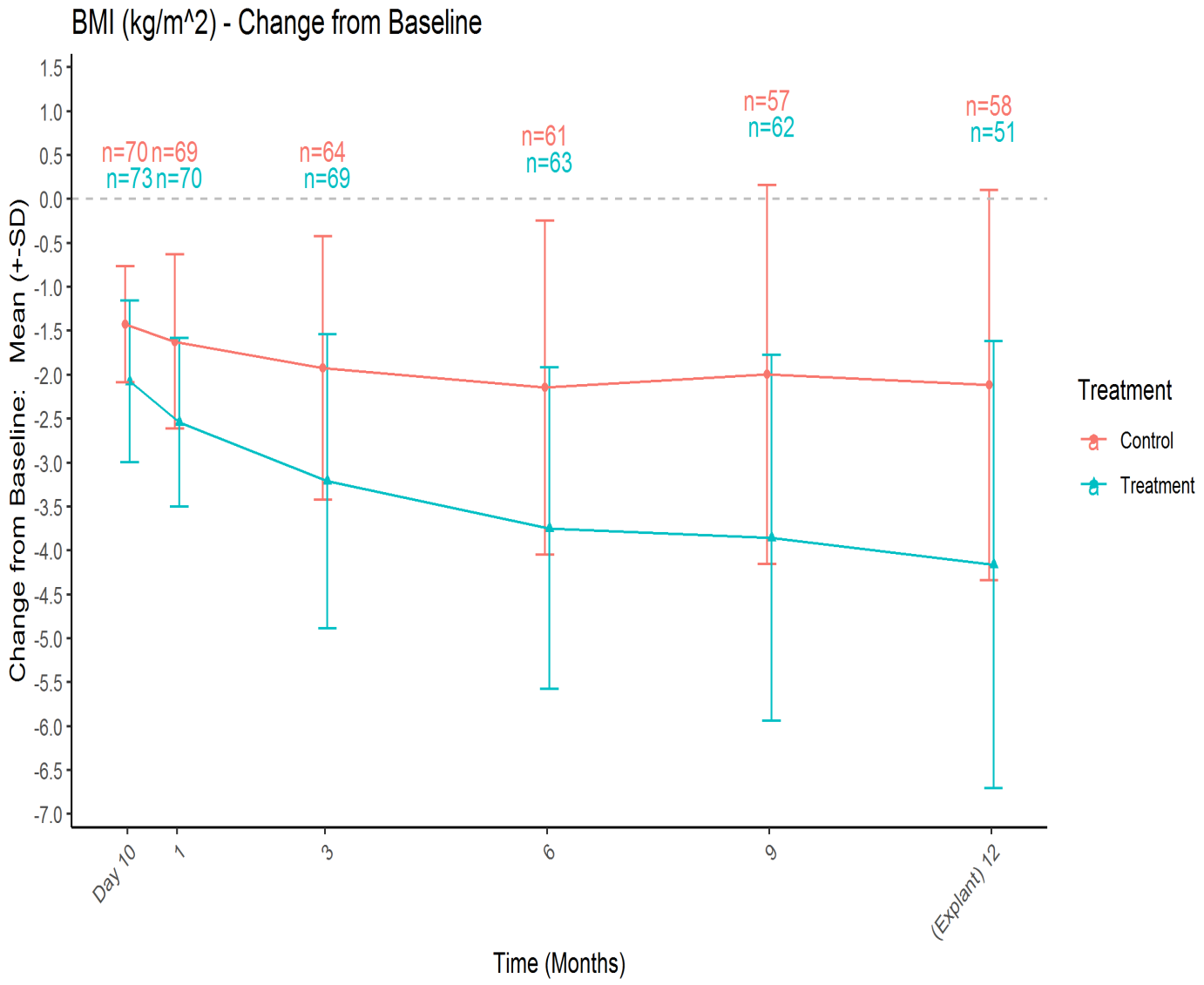


Table 1. 14 BMI Change from Baseline

Laboratory Test (units)	Treatment	Visit	n	Mean	SD	Median	Min.	Max.	t test p value
BMI (kg/m^2)	Control	Baseline	74	0	0	0	0	0	N/A
		Day 10	70	-1.43	0.66	-1.45	-3.12	0.93	<.0001
		1 month	69	-1.62	0.99	-1.71	-3.38	1.99	<.0001
		3 months	64	-1.92	1.50	-1.79	-5.92	0.81	<.0001
		6 months	61	-2.15	1.90	-1.93	-10.02	1.51	<.0001
		9 months	57	-1.99	2.16	-1.58	-12.45	0.74	<.0001
		12 months	58	-2.12	2.22	-1.54	-14.01	1.7	<.0001
	Treatment	Baseline	80	0	0	0	0	0	
		Day 10	73	-2.07	0.92	-1.93	-4.89	0	
		1 month	70	-2.54	0.96	-2.44	-5.04	-0.5	
		3 months	69	-3.21	1.67	-3.05	-8.13	0.06	
		6 months	63	-3.75	1.83	-3.51	-9.17	0.47	
		9 months	62	-3.86	2.08	-3.61	-8.59	0.69	
		12 months	51	-4.16	2.54	-3.86	-10.59	0.66	

Figure 1. 24 BMI Change from Baseline



3.3.3 Effect on Fasting Lipids

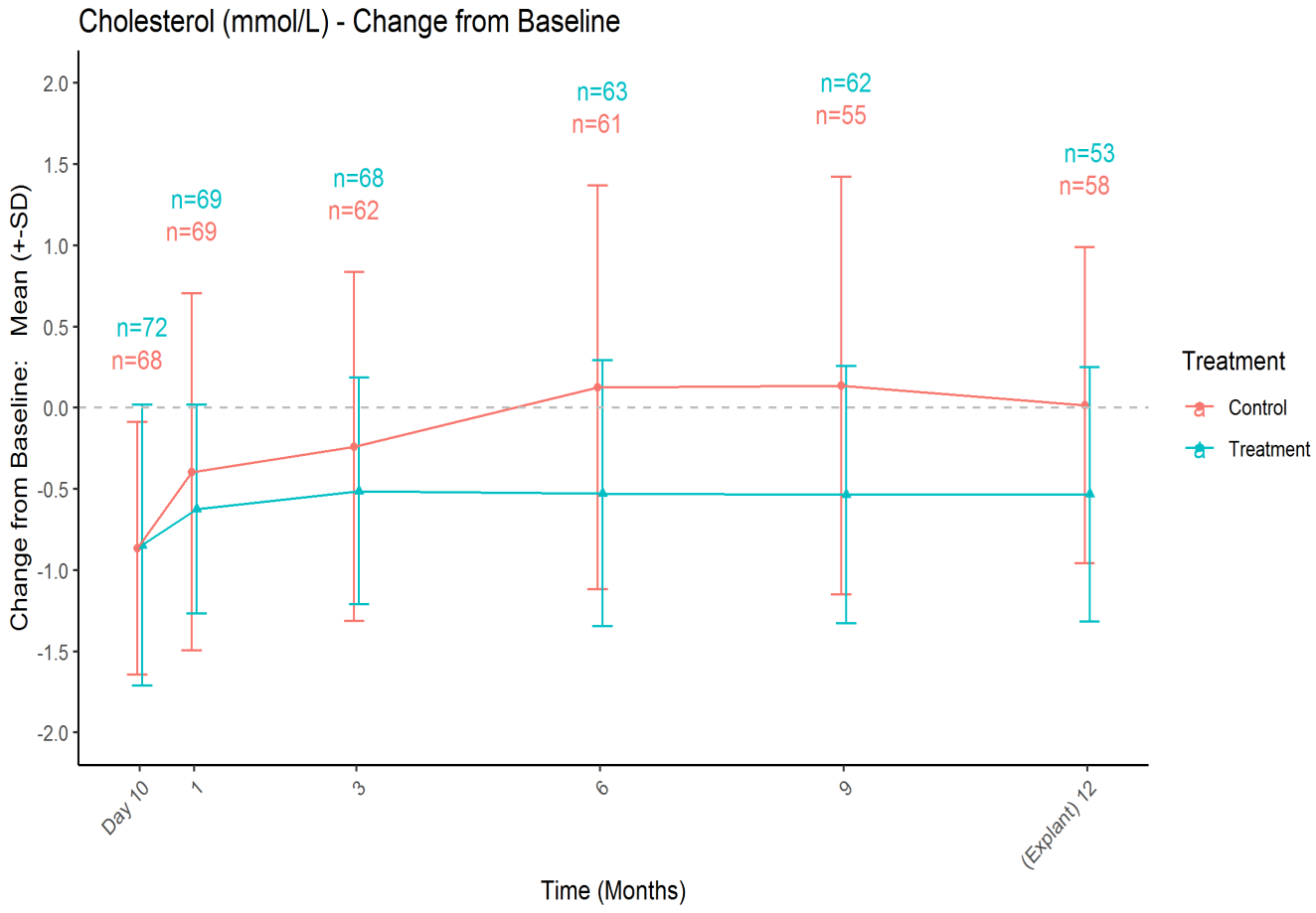
Fasting total cholesterol at baseline was 4.5±0.9mmol/L for the EB group compared with 4.6±1.2 in the control group. At both 6 and 12 months there was a reduction from baseline of -0.53±0.8mmol/L in total cholesterol within the EB group compared with 0.12±1.2 increase from baseline at 6 months in the control group, 0.02±1.0 at 12 months. Mixed-model output indicated a significant effect when investigating treatment group over time ($p<0.0001$) with corresponding significant effects for gender ($p<0.0001$) and age ($p=0.0294$). Post-hoc testing of change from baseline values between treatment groups provided significant results (Table 1.15, Figure 1.25; EB vs. Control;*P*= 0.002). Low density

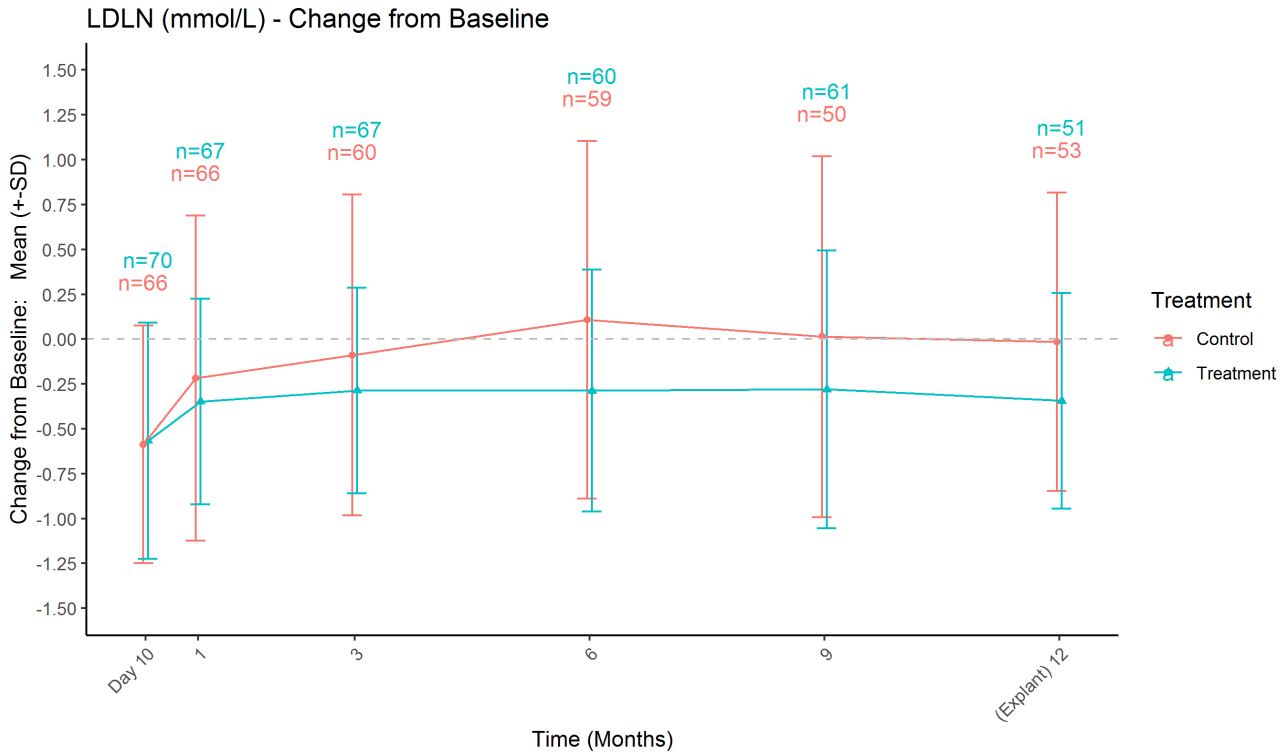
lipoprotein (LDL) levels produced similar results with the mixed model output indicated a significant effect when investigating treatment group over time ($p<0.0001$) with corresponding significant effects for gender ($p<0.0001$) and age ($p=0.0388$). The subsequent post-hoc testing indicated that LDL reduced in the EB group at 6 months from baseline by -0.29±0.6mmol/L and by-0.34±0.6mmol/L at 12 months compared to 0.11±1.0 mmol/L and -0.02±0.8 mmol/L respectively in the control group. Analysis testing the difference in mean reduction levels between the two groups at 12 months provided a significant result ($p=0.0234$, t-test) . Whislt the mixed-model analysis returned a significant result for the interaction between treatment group and visit ($p=0.0198$ for triglycerides, $p=0.0173$ for HDL) ,there were no statistically significant changes in post-hoc testing of HDL or triglyceride change from baseline levels between both treatment arms at 6 or 12 months.

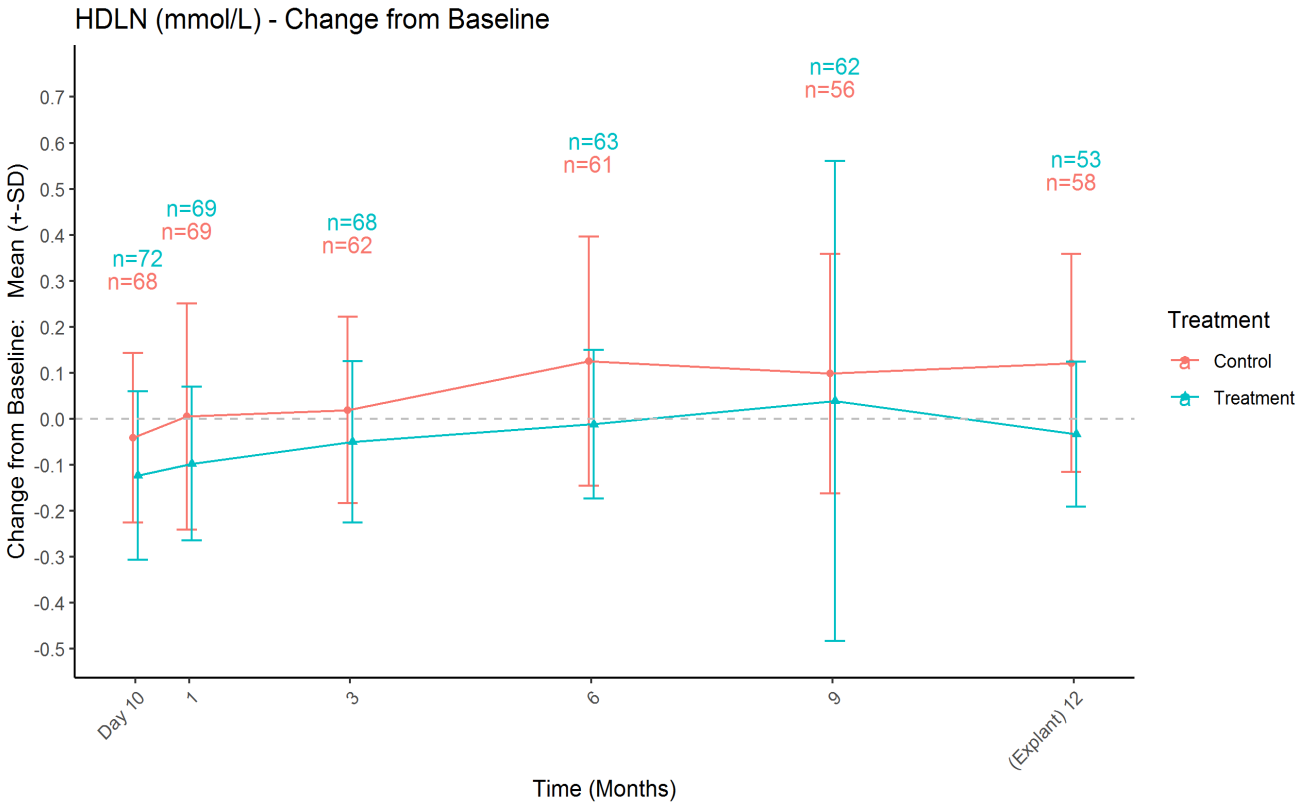
Table 1. 15 Cholesterol Change from Baseline

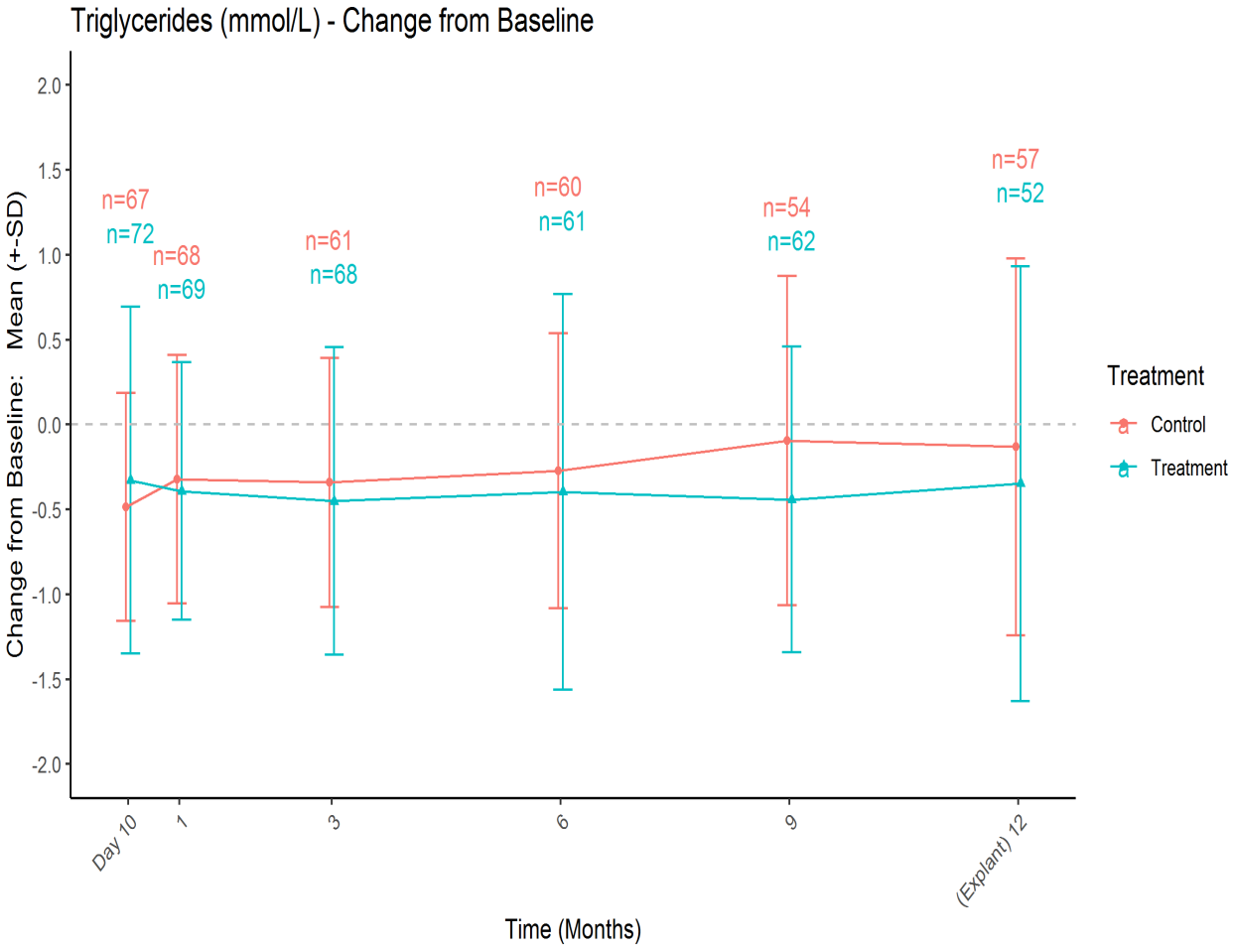
Laboratory Test (units)	Treatment	Visit	n	Mean	SD	Median	Min.	Max.	t test p value
Cholesterol mmol/L	Control	Baseline	73	0	0	0	0	0	N/A
		Day 10	68	-0.86	0.78	-0.9	-2.9	1.1	0.89
		1 month	69	-0.39	1.10	-0.3	-4.9	2.7	0.14
		3 months	62	-0.24	1.07	-0.2	-4.8	2	0.08
		6 months	61	0.12	1.24	0.1	-4.4	4.1	0.0007
		9 months	55	0.14	1.29	0.1	-4.1	4.2	0.0008
		12 months	58	0.02	0.97	0.1	-3.6	2.7	0.002
	Treatment	Baseline	80	0	0	0	0	0	
		Day 10	72	-0.85	0.87	-0.85	-4.2	1.8	
		1 month	69	-0.62	0.64	-0.6	-2.2	0.8	
		3 months	68	-0.51	0.70	-0.45	-2.3	1.3	
		6 months	63	-0.53	0.82	-0.6	-2.3	2.2	
		9 months	62	-0.54	0.79	-0.5	-2.8	2.2	
		12 months	53	-0.53	0.78	-0.6	-2.8	1.2	

Figure 1. 25 Lipid Profile: Change from Baseline





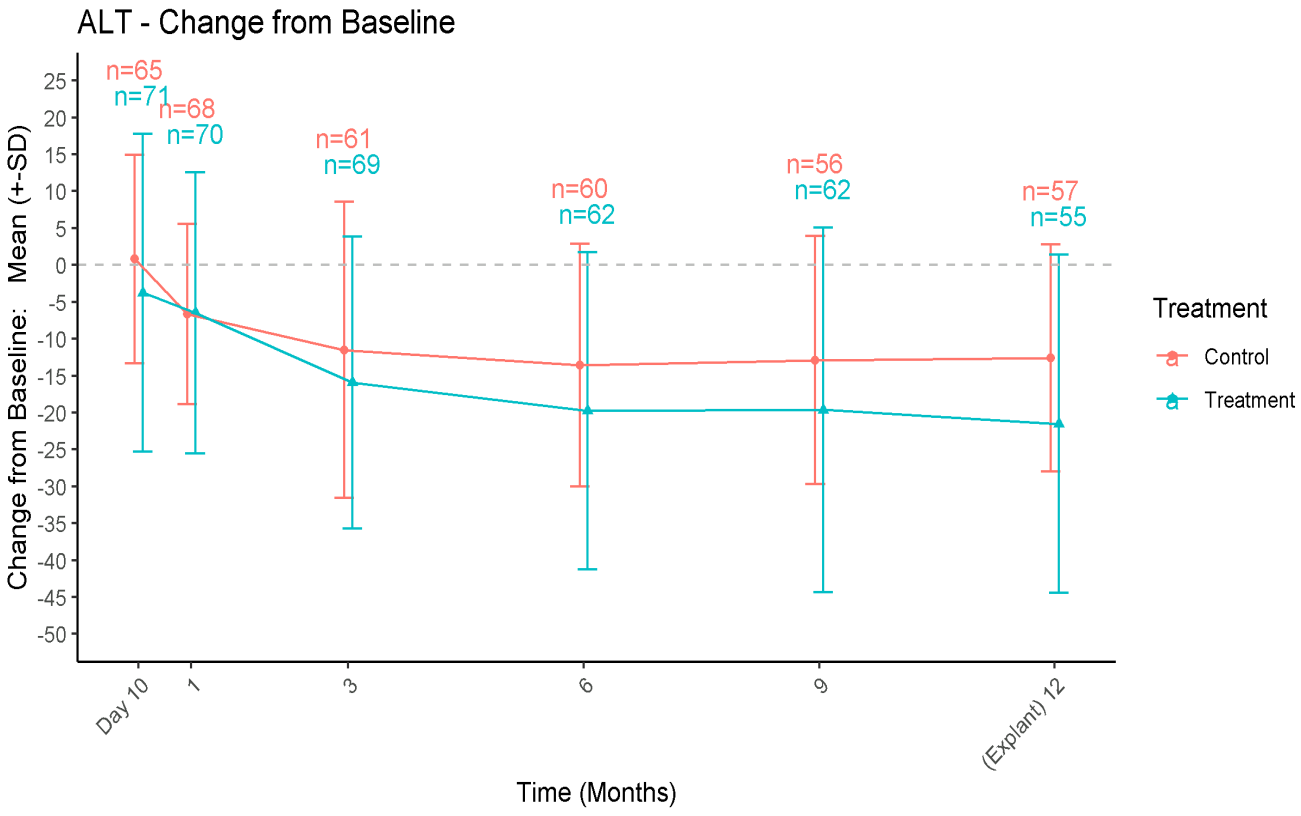

HDLN (mmol/L) - Change from Baseline
Change from Baseline: Mean (+-SD)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
n=72
n=68
n=69
n=69
n=68
n=62
n=63
n=61
n=62
n=56
n=53
n=58
Day 10
1
3
6
9
(Explant) 12
Time (Months)
Treatment
Control
Treatment

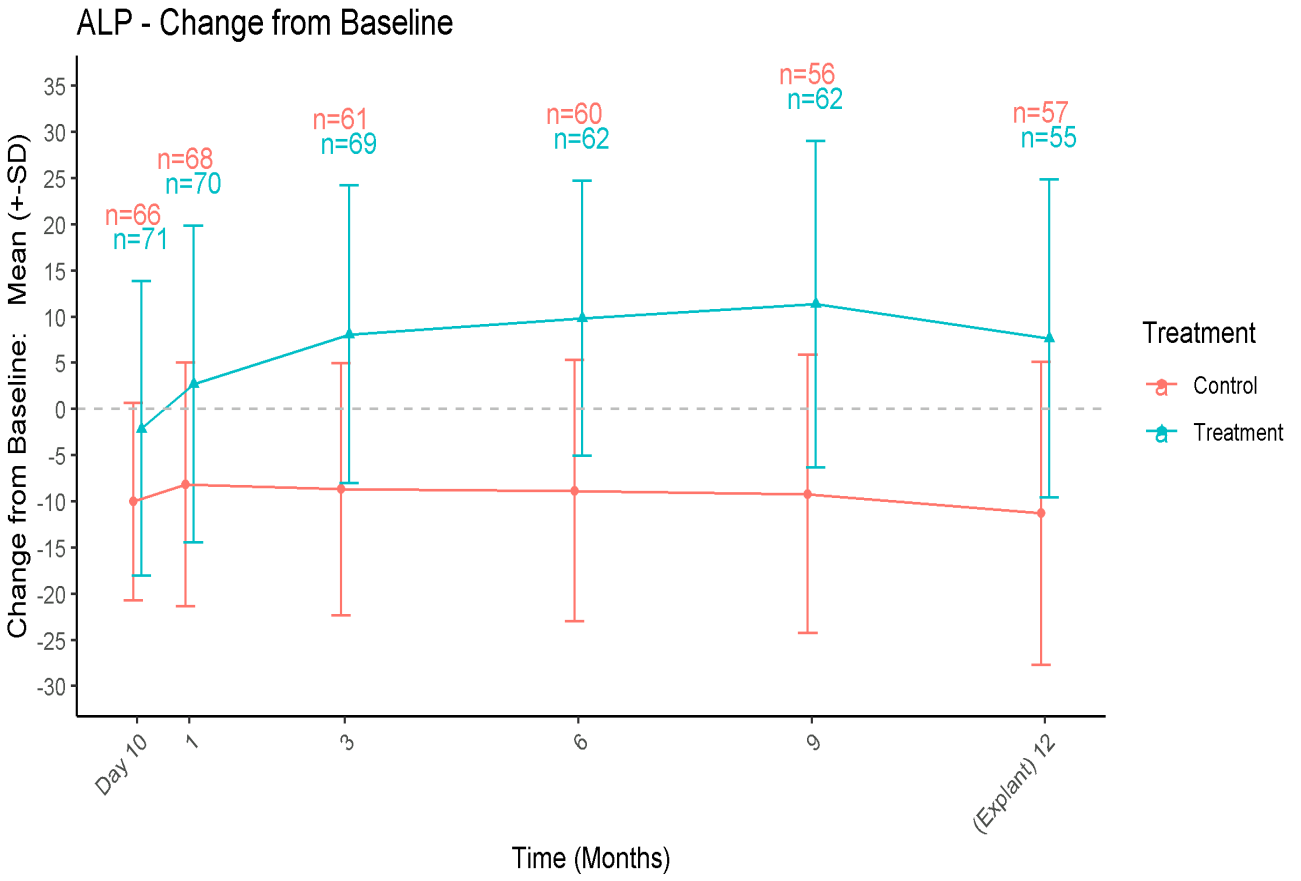

Triglycerides (mmol/L) - Change from Baseline
Change from Baseline: Mean (+-SD)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
n=67
n=72
n=68
n=69
n=61
n=68
n=60
n=61
n=54
n=62
n=57
n=52
Day 10
1
3
6
9
(Explant) 12
Time (Months)
Treatment
Control
Treatment

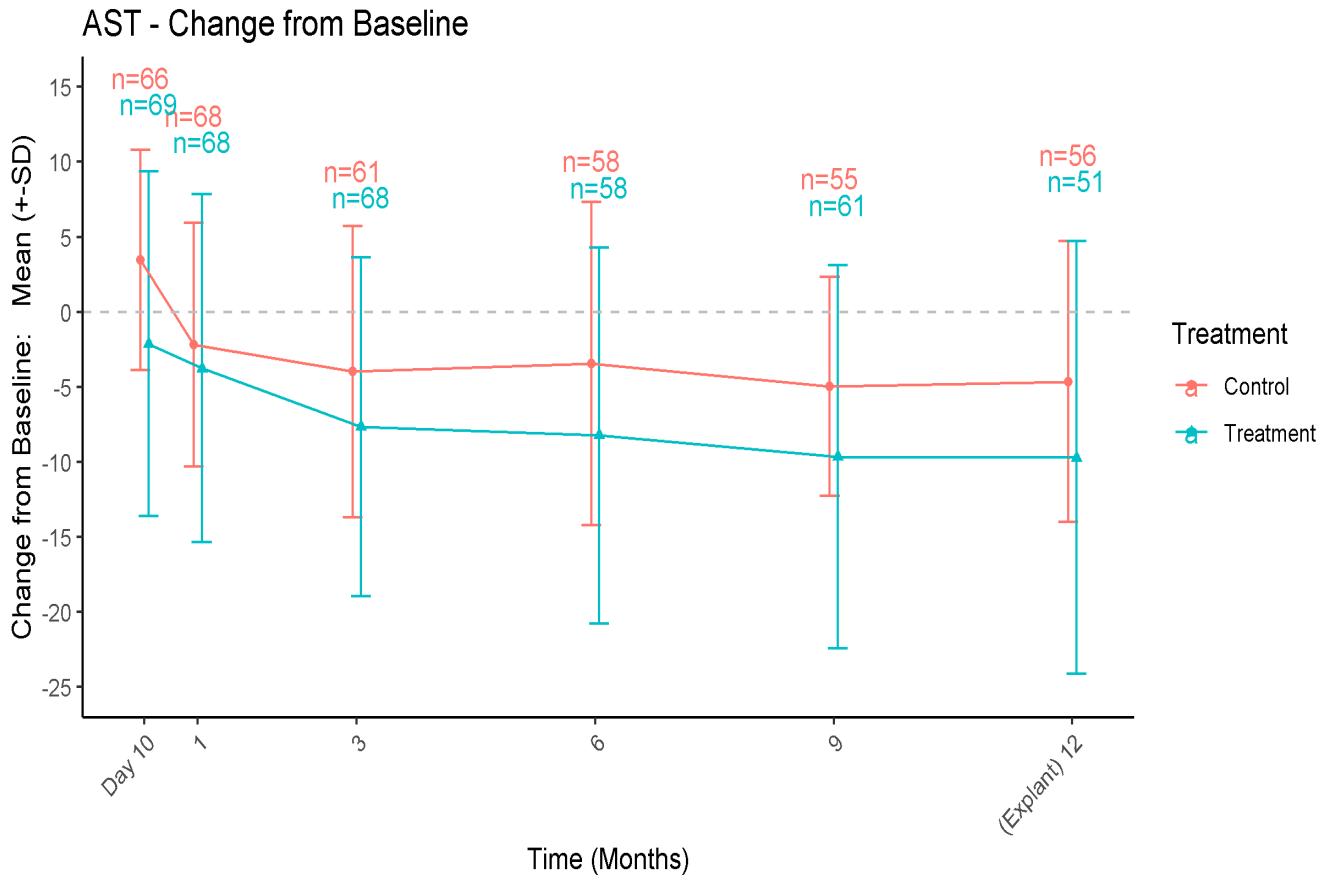
3.3.4 Effect on Liver Function Tests (LFTs)

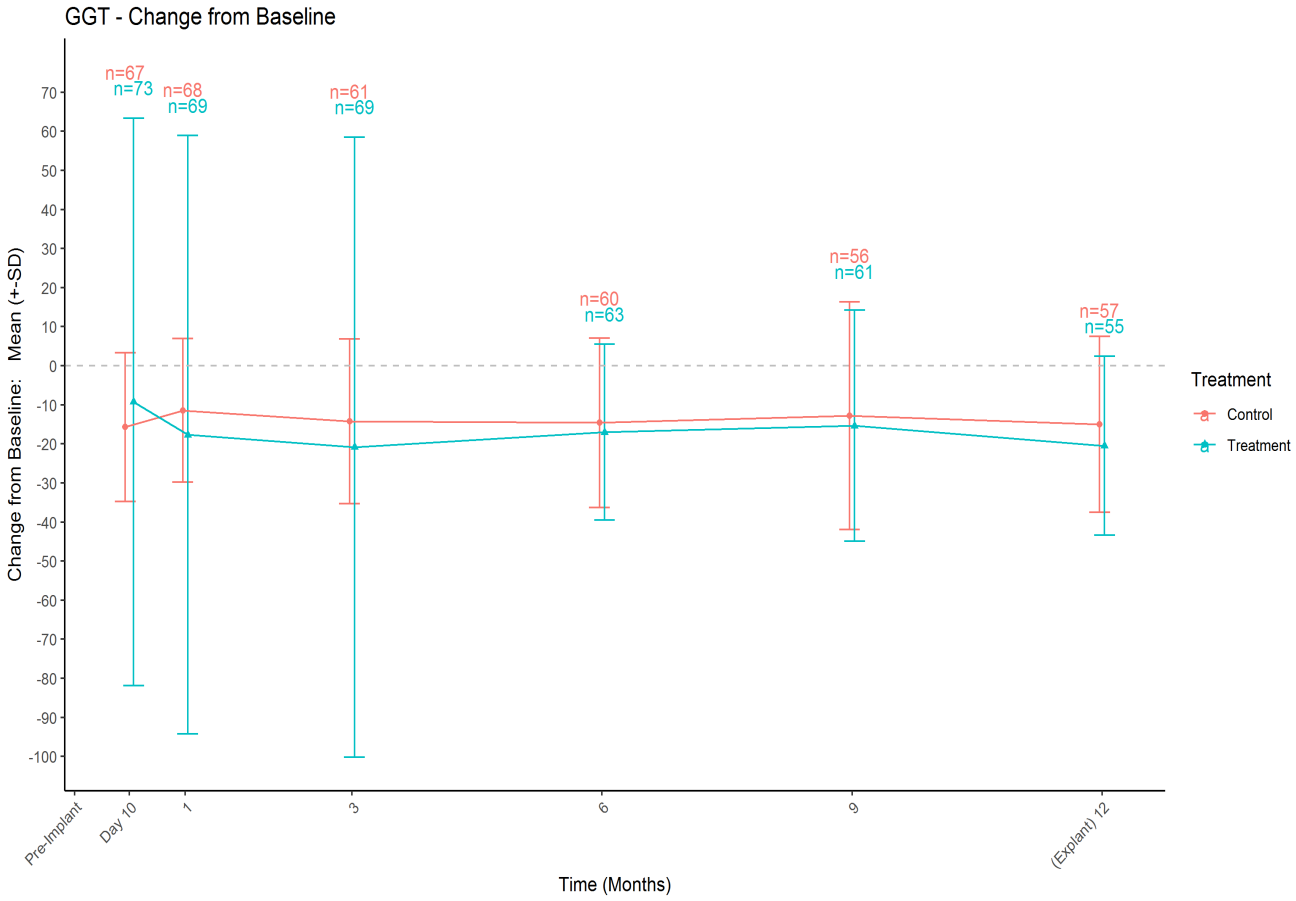
At baseline the mean alanine aminotransferase (ALT) was 39±20U/L in the EB group compared with 38±23 in the control group. ALT reduced by 22±23U/L at 12 months compared with 12±23 in the control group. Mixed-model analysis gave a significant result for the treatment group*visit interaction term (p=0.0177) and subsequent post-hoc testing of treatment group difference in change from baseline at 12 months provided a similar result (Figure 1.26; *P*=0.01). Aspartate Transaminase (AST) levels at baseline were 88±25U/L in the EB group compared with 90±25 in the control group. AST levels also decreased from baseline to 12 months by 10±14U/L in the EB group compared with a reduction of 5±9 in the control group. Mixed-model analysis gave a significant result for the treatment group*visit interaction term (p=0.0139) and subsequent post-hoc testing of treatment group difference in change from baseline at 12 months also provided a significant result (*P*=0.03). In contrast to ALT and AST, alkaline phosphatase (ALP) levels rose by 8±17U/L at 12 months compared with a reduction by 11±16 at 12 months in the control group. Analysis results were also stronger with mixed-model analysis giving a significant result for the treatment group*visit interaction term (p<0.0001) and subsequent post-hoc testing of treatment group difference in change from baseline at 12 months providing the same significant result (Figure 1.26; *P*<0.0001). Although gamma-glutamyl transpeptidase (GGT) levels reduced by 20±23U/L from baseline at 12months and provided a significant result from the mixed-model interaction tern (p=0.0083), this was not statistically significant when compared with the control group where there was a reduction of 15±23 from baseline at 12months (*P*=0.20). There were no significant changes in bilirubin or albumin levels between both treatment groups.

Figure 1. 26 LFTs: Change from Baseline






AST - Change from Baseline
Change from Baseline: Mean (+-SD)
15
10
5
0
-5
-10
-15
-20
-25
n=66
n=69
n=68
n=68
n=61
n=68
n=58
n=58
n=55
n=61
n=56
n=51
Day 10
1
3
6
9
(Explant) 12
Time (Months)
Treatment
Control
Treatment


GGT - Change from Baseline
Change from Baseline: Mean (+-SD)
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
n=67
n=73
n=68
n=69
n=61
n=69
n=60
n=63
n=56
n=61
n=57
n=55
Pre-Implant
Day 10
1
3
6
9
(Explant) 12
Time (Months)
Treatment
Control
Treatment

3.3.5 Effect on Other Variables

There was no statistically significantly difference in waist circumference and blood pressure between the two groups at baseline, 6 months or 12 months.

3.3.6 Safety Data

There have been 825 reported adverse events (AE) and 58 recorded serious adverse events (SAE) up until 26th March 2018 (Tables 1.16, 1.17 and 1.18). The most commonly reported were abdominal discomfort and pain which were classified under gastrointestinal disorders. All device related AEs and SAEs resolved without any permanent sequelae.

Table 1. 16 Number of Adverse events and SAEs and relationship to study device

	Relationship to Study Device	**Frequency**
Serious Adverse Event (SAE)	***Unrelated***	16
	Unlikely	1
	Possible	1
	Probable	6
	Definite	24
	Total	**48**
Adverse Event (AE)	***Unrelated***	426
	Unlikely	45
	Possible	98
	Probable	110
	Definite	145
	Total	**824**

Table 1. 17 Classification of Adverse Events by Organ System

System Organ Class	Definite	Probable	Possible	Unlikely	Unrelated
Gastrointestinal Disorders	110	84	59	9	73
Musculoskeletal And Connective Tissue Disorders	1	4	3	3	78
Infections And Infestations	0	0	3	2	57
Respiratory, Thoracic And Mediastinal Disorders	0	0	4	5	58
Endocrine Disorders	5	9	4	1	9
Nervous System Disorders	0	4	6	3	18
Metabolism And Nutrition Disorders	2	2	7	5	7
Surgical And Medical Procedures	0	0	1	1	24
General Disorders And Administration Site Conditions	6	1	3	0	10
Product Issues	17	0	0	0	0
Investigations	2	1	0	4	11
Injury, Poisoning And Procedural Complications	0	0	0	4	14
Skin And Subcutaneous Tissue Disorders	0	0	0	2	16
Blood And Lymphatic System Disorders	0	4	5	1	3
Eye Disorders	0	0	0	1	9
Renal And Urinary Disorders	0	0	0	3	8
Psychiatric Disorders	0	0	0	0	7
Vascular Disorders	1	1	0	0	5
Cardiac Disorders	0	0	2	0	3
Immune System Disorders	0	0	0	1	2
Pregnancy, Puerperium And Perinatal Conditions	0	0	0	0	2
Ear And Labyrinth Disorders	0	0	0	0	6
Hepatobiliary Disorders	1	0	1	0	1
Reproductive System And Breast Disorders	0	0	0	0	3
Category - TBC	0	0	0	0	2
TOTAL ADVERSE EVENTS	145	110	98	45	426

Table 1. 18 Classification of SAEs

Treatment Arm	SAE	Frequency
EB	Abdominal Pain	7
	Acute Coronary Syndrome	1
	Biliary Colic	2
	Device Migration	6
	Device Migration with fistula	1
	Device Tear	8
	Fractured Clavicle	1
	Incidental MRI Finding	1
	Unable to remove device	2
	Lithotripsy & urteric stent	1
	Liver Abscess	1
	Pneumonia Sepsis	1
	Pyelonephritis	1
	Spinal Vertebrae Decompression	1
	Upper GI Bleed	2
	Ureteric Stones	3
	Vomiting/Dehydration	4
	TOTAL	***43***
Control	Dental Procedure	1
	Elective surgery: excess skin	1
	Shingles	1
	Stroke	1
	Thyroidectomy	1
	TOTAL	***5***
Total Number of SAEs		**48**

There were 43 reported SAEs in the EB group and 5 SAEs in the control. Of these 30 (63%), were classified as “definite” or “probable” device related. There were two procedure related adverse events, both related to failed explantation of the device. On one occasion the device could not be removed as food debris obscured views and as a result the patient had to rebooked for a repeat procedure under general anaesthetic which was successful on this second attempt. Another device could not be removed endoscopically as the device appeared tethered to the duodenum and would not collapse down safely to be retrieved. This patient required laparoscopic removal under a general anaesthetic and stayed in hospital for one week for the procedure and post op recovery before being discharged with no permanent sequelae.

There was one reported liver abscess in a patient who presented to the UHS site with a one-week history of malaise, fevers, and arthralgia, 11 months after the initial implant. Blood tests revealed raised inflammatory markers (WCC 21.4, CRP 304) and deranged liver function tests (Bilirubin 35, ALT 366, ALP 462). An abdominal CT revealed a large liver abscess which was treated with intravenous antibiotics, fluids and analgesia. A CT-guided drainage of this abscess was performed and the device was removed under general anaesthetic. The patient required in patient care for 11 days and received antibiotics for a further month but subsequently made a full recovery.

3.3.6.1 Device Tears

A total of 8 torn devices were noted on explant in this study and this was notified by the primary investigator (PI) to the manufacturer GI Dynamics (GID), the sponsor (Imperial College) and the Research Ethics Committee (REC). In November 2017 the EB CE Mark was withdrawn. To date, all devices have been removed and the study continues as per study protocol unless instructed otherwise by the REC or Medicines and Healthcare products Regulatory Agency (MHRA).

3.4 Discussion

The data presented in this chapter is from the largest RCT of the EB to date reporting on the efficacy and safety of the device from baseline right through to explant of the device at one year. Both the EB arm and control group received significant amount of support during the trial period from both the clinical researcher and dietician. This included regular face to face interactions in the clinic setting, as well as telephone consults to monitor their progress. The primary aim was to compare the EB intervention, with standard medical therapy and lifestyle interventions for T2DM.

3.4.1 Recruitment

In our trial despite a clear strategy from the offset, recruitment took much longer than predicted (figure 1.17) taking 2 years to complete rather than the initially predicted 1 year. The implications of which were an application had to me made to the NIHR (funding body), for a one year extension to the trial and, in addition, to request appropriate funding to support these extended activities. There are various explanations for the slow recruitment and poor response seen, and these are discussed below.

3.4.1.1 Poor Uptake from GP practices

Unfortunately, patient recruitment from primary care at the ICHT site was extremely disappointing which was not as predicted. Although >400 GP practices were approached, fewer than 10% of these practices agreed to become PICs and completed database searches on behalf of the study team. The workloads of primary care physicians is very high, and some may feel that it is not feasible to dedicate any further time to research as this might be at the detriment of their clinical practice. A handful of practices agreed to be PICs but then did not end up performing database searches of their patients and did not respond to follow up telephone calls or emails. Similar disengagement from research by primary care practitioners has also been reported in a palliative care study[295]. In addition, GP practices in Northwest London may be saturated with calls for participation in clinical trials in the local area, as there are hundreds of clinical trials being conducted in the local region.

Database searches from agreed PICs revealed approximately 1200 patients as being suitable for the trial when matched against the eligibility criteria and patient packs were sent out to these patients. However only 65 (5%) patient reply slips were received. The small number of responses received lead to only 12 patients being invited for screening following their initial telephone consultation, of which 6 participants were randomised into the trial. This is also in stark contrast to UHS site where 397 reply slips were received in response to a similar number of patient packs being sent out.

There are multiple reasons why patients choose to participate in clinical trials with the most cited reason that patients believe they are being offered the best treatment available or knowing that participation in the trial and its results will benefit others.[296]

There are a few potential explanations for why many patients declined to contact the study team:

1) *Patient information sheet (PIS) sub- optimal*: The PIS may have contained too much information or may have made the study sound over complicated or invasive thus discouraging the participant from taking part. The PIS and patient reply slip was only available in English language and some patients may not have been literate in English to understand and act on the information. PPI involvement during the design stages may have negated this problem and improved response rates. However, a falls prevention RCT by Cockayne et al failed to demonstrate any significant increase in patient recruitment or retention through the use of an optimised PIS.[297]
2) *The letters may not have reached their intended recipient*. According to figures from 2016/2017 published by the Ministry of Housing Communities and Local Government English Housing Survey Report, 30% of households in London are private renting with a further 22% renting in the social sector.[298] It is estimated that around 37% of private renters have moved three or more times in the last 5 years. Consequently, there is more chance of these letters being sent to the wrong address and not reaching the patient at all.
3) Saturation from clinical trial invites. Patients living in the London area may well receive multiple invites to participate in clinical trials so may chose to ignore these invites if they receive too many.

3.4.1.2 ENDO Trial Suspension

The ENDO trial was a pivotal multi-centered double blinded RCT in the US where subjects were randomised to either receive the device or sham treatment in order to assess the efficacy and safety of the device. The study opened in November 2012 but was terminated early by the FDA in March 2015 after the development of 7 liver abscesses in 217 patients enrolled in the trial (3.2%). All patients with this complication were treated with antibiotics and if necessary draining with no permanent sequelae. This had a direct impact on our study leading to a 3 month hiatus in our recruitment (from April – June 2015) as a substantial amendment to the study protocol was required to include this real risk of hepatic abscess which was quoted as 1%. This also meant that patients already recruited to the trial had to be re-consented on their next visit to ensure they were aware of the risk of hepatic abscesses.

3.4.1.3 Lack of Support Staff

The newspaper advertising campaign was hugely successful generating numerous telephone calls and emails requiring urgent attention. On the days when the adverts featured in the newspapers, on average 30-50 telephone calls and emails were received by the study team at ICHT. Unfortunately the infrastructure was not in place to deal with this unprecedented demand which meant that not all telephone calls and emails were responded to promptly. As the clinical researcher, I was primarily responsible for fielding all these calls, screening all the patients for their eligibility. An administrative assistant was employed to assist me with these task from April 2016-October 2016 but as they were not medically trained, they could not screen through the telephone calls or emails independently. Calls would come directly through to the study mobile phone at any anytime which meant that some calls were missed if I had other fixed commitments at the time such as other patient study visits. Adverts in the evening standard were published in the late afternoon/evening which meant a flurry of telephone calls soon afterwards into the late evening. It was almost impossible to answer all which meant that opportunities may have been missed.

3.4.1.4 Strict Eligibility Criteria

The eligibility criteria for the study were very strict, in order to ensure patient safety and establish the appropriate diabetes status of those patients entering the study. The study required participants to have poorly controlled diabetes but whom were not on injectable diabetes medication such as GLP analogues and insulin which excluded many from the study. Modifications to the eligibility criteria, which included raising the HBA1C range and lowering the kidney function (eGFR) cut off helped to widen the recruitment net.

3.4.1.5 High drop-out rate following randomisation

During the screening and consent process patients were advised that there was a 50% chance of being in either the two arms of the study and this was reiterated in the patient information leaflet which they all received. Despite this, a small number of patients who consented to the control arm dropped out of the trial soon after randomisation. This could be linked to participants disappointment of not receiving the actual treatment. It is not uncommon for patients to hold strong preferences for particular interventions, but one would hope that those patients who expressed strong wishes to receive a particular intervention and that were at high risk of dropping out depending on this result, would have been detected and excluded at the time of screening.

To combat the early withdrawals, approval was sought and granted to recruit an additional 5 participants from each site which increased the total number of patients recruited from 160 to 170.

3.4.1.6 Reflecting on the Success of Newspaper Advertising Campaign

The fantastic response from the newspaper advertising campaign came as a surprise as reports in the literature are conflicting when judging the success of newspaper adverts for clinical trial recruitment particularly when considering the high cost implications associated with such media campaigns.

The Scotland Standard Care vs. Celecoxib Outcome Trial (SCOT) clinical trial investigating cardiovascular safety of non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis and osteoarthritis found little impact when they deployed a newspaper advertising campaign.[299] The study found that the adverts attracted relatively small numbers of respondents, and of those respondents most were not eligible to take part. This was in stark contrast to our adverts which generated a large number of respondents, from which we were able to recruit the vast majority of participant to the ICHT site.

Another study from Scotland used a widespread media campaign in 2008 called "Get Randomised" to raise the profile of clinical research using television, radio and newspaper advertising.[300] Although the media campaign improved public awareness of clinical research, again it was found to make little difference in patient responses to whether they would be more inclined to personally take part in a clinical trial.

An RCT conducted in Australia of vitamin E in the prevention of cataract and age-related maculopathy used five recruitment methods: newspaper advertising, radio advertising, GP practices, community groups, and electoral roll mail-out.[301] Recruitment was successfully completed in the anticipated time frame with newspaper adverts and electoral roll mail out found to be the most effective methods of patient recruitment in terms of both the absolute number of patient recruited and cost per participant. Similar to our experience, the newspaper adverts generated a great deal of interest and a

number of telephone calls which placed a huge strain on the study team to respond to each inquiry in a timely fashion. In addition, researchers found direct approaches to community groups or GP practices were not fruitful with the authors concluding that strong collaborative links with GP practices may be necessary for this approach to be successful.

A similar study design to the EB trial was observed in a prospective multi-centred RCT investigating RYGB versus intensive medical management for treatment of T2DM conducted at three institutions in the USA and one in Taiwan.[302] This trial successfully recruited 120 participants but this took four years and also involved lowering their BMI criteria and the addition of another centre to recruit more patients into the study. Two recruitment sites also used a mass media campaign and of the 120 randomised participants, 10% were recruited directly from newspaper adverts, and 19% were from radio advertisements. The authors concluded that their recruitment could have been accelerated by enrolling more sites and by increasing the advertising budget.

From our own experience we strongly feel that more emphasis should be placed on the role of a media and advertising campaign when planning the recruitment phase of any clinical trial to ensure it is a successful one. Funding for future grant applications should be costed accordingly so that more resources can be devoted to newspaper adverts and social media campaigns. Equally having a dedicated study team to deal with the influx of calls and emails that might be generated is imperative so that responses occur swiftly and potential opportunities to recruit participants are not missed. This team would ideally be headed by a clinician complimented by a research nurse and administrator. The major benefit of using newspaper advertising is it relies on a degree of self-motivation from the potential participant to contact the study team but also gets the message across in a non-intrusive way, as the advert is subtly placed in their daily newspaper hopefully sparking interest in the reader.

Patients who contacted us, appeared very keen to find out more information on the trial and were genuinely disappointed if they did not meet the study eligibility criteria.

One of the pitfalls encountered with the newspaper advertising is that only a small amount of information on the trial can be published in an advert which meant more time spent on telephone calls to patients explaining more details of the study. One way to combat this, is to provide links to where further information can be accessed such a link to a study website or with automated emails. Newspaper advertising is also hugely expensive so can be a disaster if ineffective; the total cost across both our sites to fund our adverts was £48,179.

It must also be noted that although recruitment from GP practices was poor at the London site, the same was not observed at our Southampton site where recruitment from primary care was considerably better. This suggests that this difference is site specific owing to the difference in patient populations between these two cities as previously identified which may have been a major contributory factor in these discrepancies in recruitment.

3.4.2 Efficacy of the Device

The device did not appear to have a significant impact on reduction of FPG compared with control. Although FPG appears to be a more accurate predictor than HBA1c of delineating diabetic from non-diabetic subjects it may not be as effective at assessing progress of glucose control therapy.[303, 304] HBA1c would have provided a more accurate picture of the impact of the device on diabetes control and likelihood of achieving remission but as reduction in HBA1c is the primary endpoint of the clinical trial study, analysis of HBA1c was not permitted for the purpose of this thesis. This decision was made by both the NIHR and the trial steering committee who felt that researchers should not analyse any of

the primary endpoint data until the conclusion of the trial to avoid any bias occurring. As a result HBA1c results for patients were not made available to me for this interim analysis.

The EB effects on FPG in this trial mirror the findings of the largest EB RCT published to date of 77 patients, which also found a decrease in FPG following EB implant at 6 months, but this again was not statistically significant when compared with the control group.[234] However, in the same study HBA1c levels were found to decrease significantly at 6 months when compared with the control group so one would expect a similar scenario to also occur in our cohort of patients when this analysis is finally conducted.

Insulin levels were found to decrease significantly from baseline at 12 months in the EB arm when compared with the control group. This is probably due to improvements in both insulin resistance and β-cell dysfunction as is seen following bariatric surgery.[305] A reduction in insulin resistance, will mean that the existing circulating insulin is more potent - driving glucose from the plasma into cells, increasing hepatic uptake and resulting in reduced insulin output from β cells and thus lower levels of insulin recorded in the blood. The potential mechanisms for these changes are:

1. Reduction in food intake thereby leading to a reduction in the number of calories ingested and absorbed.
2. Improved prandial gut hormone responses of GLP-1 and GIP resulting in an anti-diabetic effect (as explained before).
3. Diversion of bile flow to the jejunum leading to increased levels of bile acids reaching the plasma which in turn stimulate key growth factors and gut hormones that have a positive influence on insulin resistance and glucose homeostasis. Duodenal jejunal bypass in rats was shown to improve glucose tolerance and expedite transit of biliopancreatic juices.[306]

As with previous RCTs investigating the effect of the EB on obesity, the device was found to have a significant effect on weight loss and BMI when compared to the control group. On average, in this cohort of patients there was a 10-15kg reduction in weight in the EB group and a 4-6kg/m^2 in BMI at 12 months which is similar to the findings from our pilot study.[241] These reductions in weight are probably as a result of a reduction in calorie intake coupled with increased energy expenditure. Isolated duodenal exclusion in diet induced obese rats was shown to increase energy expenditure and decrease food intake.[307] As with improvements in glycaemic control the exaggerated responses of anorexigenic gut hormones such as GLP-1 may be influential in decreasing oral intake, and increasing satiety to explain the changes seen in weight loss in these individuals. Gut hormone analysis of GLP, PYY and ghrelin changes are currently in progress.

At one-year significant improvements were seen in lipid metabolism, with a decrease in total cholesterol and LDL although changes in triglyceride and HDL were not found to be statistically significant. The same pattern in lipid metabolism was seen in the analysis of 66 patients from the German EB registry.[252] Changes in lipid parameters are notoriously difficult to interpret as often they are secondary endpoints in studies coupled with a distinct lack of information on co-prescribed lipid lowering agents.

The EB lead to improvements in liver function tests which are typically associated with fatty liver disease including ALT, AST and GGT. Both ALT and AST decreased significantly at 6 months and one year. GGT levels also improved but these were found to be not significant compared with the control group. These improvements in liver biochemistry might be as a consequence of improved lipid metabolism and insulin tolerance, thus reducing fatty accumulation and inflammation in hepatocytes. A similar phenomenon is observed post bariatric surgery which has been shown to improve liver biochemistry and histology dramatically.[308] There is limited data on the effect of EB on liver

biochemistry. De Jonge et al found improvements in ALT, AST and GGT in 17 obese subjects who received the EB for 6 months but Schouten et al reported no difference in LFTs in their 6 month RCT of the EB.[235, 309] It is important to note that participants' alcohol intake was not recorded which would have been extremely useful when interpreting these improvements in LFTs seen. Fluctuation in alcohol intake could be a potential confounder but one would expect that both treatment groups would have been affected equally if this was the case.

Converse to improvements in LFTs, ALP levels increased significantly at 12 months in the EB group compared with the control; findings which have not been reported in previous studies of the EB. The most likely explanation for the rise in ALP seen in these patients, is that its origin is from bone rather than liver. VIlarrasa et al suggested that EB therapy has a negative impact on bone mineral density (BMD) by showing that DEXA scanning of 19 patients at 12 months showed a significant decrease in fat mass and BMD.[244] Patients with T2DM have an imbalance of bone mineral metabolism and the EB may potentially exacerbate this particularly in the context of nephropathy.[310] The raised ALP seen in our EB patients is probably a consequence of increased bone turnover and osteoclast activity which in turn will lead to demineralisation and a reduction in BMD. Parathyroid Hormone levels may increase as a result of lower vitamin D and calcium absorption in the small bowel as seen after gastric bypass leading to increase bone remodelling and reduced cortical density.[311] Changes in bone metabolism including a reduction in BMD are well recognised complications of bariatric surgery.[312, 313] Neurohormonal mechanisms may also play a role in bone metabolism, with the secretion of several gut hormones affected by surgery. Reduced ghrelin levels may explain bone loss, as ghrelin has been shown to enhance osteoblastogenesis.[314] Circulating adipokines including leptin have also been implicated in the regulation of bone mass, although their exact role remains conflicting.[315]

3.4.3 Safety Profile

The majority of AEs associated with the EB were classified as mild to moderate and most frequently occurred within the first couple weeks of receiving the implant. By far the most common were abdominal pain and nausea as the patient acclimatized to having the device in situ. All patients made a full recovery, including those who experienced SAEs.

The early explant rate of 25% in the trial is in keeping with previously conducted clinical trials on the EB such as Forner et al (25%) and Betzel et al. (31%).[239, 316] There was one case of liver abscess in the 75 successful implants performed - a complication rate of 1.3% which is similar to post market surveillance data from GI Dynamics which reports this known complication as 1%. This occurred in a patient who had the device in for 11months. Liver abscesses associated with the EB have historically occurred at 9-12months following implant which raises the question of what is the optimum implant dwell time that will not only provide the patient with maximum benefit from the device but that will also insure exposure to the least element of risk. Currently the EB is licenced for use for up to one year, and this is usual practice, but it might be advisable to keep the device in situ for a period of 6 months where we know the maximum benefit appears to occur.

Migration of the device still appears to be a major issue and accounted for 37% of early explants in this study. When migration occurs, patients will usually present with abdominal symptoms such as pain, cramping, vomiting and nausea. An upper GI bleed can also occur as a consequence of localised trauma from the barbs of the device on the duodenal wall as it migrates. All but one of the early explants where migration had occurred were removed with relative ease using the Endobarrier retrieval system. However, in one case of device migration a fistula was created between the stomach and duodenum. The patient presented with severe dyspepsia, and vomiting having had the device in for 11 months. The device had migrated proximally from the duodenal bulb and was embedded in the

pylorus, whilst one of the barbs had pierced the antrum of the stomach creating a small fistula between the stomach and duodenum. A grasper was used to release the barb from the antrum of the stomach, and the retrieval device was deployed to collapse and remove the implant. The patient did not require admission and was discharged the same day. A repeat endoscopy was performed 6 weeks later which showed complete resolution of the fistula.

Another complication seen in our trial which is of major concern is the increase in device tears seen on explantation. GID report that between 2012 and 2016, there were 7 instances of torn devices amounting to 2 cases a year. However, in 2017 there was a sudden increase in the number of torn devices reported including 1 in Germany and 8 in our trial. It may be due to a faulty batch which has compromised the integrity of the sleeve, but investigations are ongoing. Although a torn device is unlikely to put the patient at increased risk of complications, it may have a detrimental effect on the device's efficacy by compromising its ability to act as an impermeable sleeve or bypass.

3.4.4 Challenges & Limitations

As with any clinical trial patient retention was a major issue particularly in the control group. A total of 9 patients withdrew from the control arm immediately following their randomisation result, clearly disappointed at not being chosen to receive the EB. This is despite being made implicitly aware during the consenting process that there was a 50% chance of being randomised to either treatment arm. Over the one year period there remained a high drop-out rate observed in the control group which exceeded the EB early explant rate. Many participants cited reasons such as competing workloads or moving out of region as the reason why withdrawal from the trial was necessary and others were simply lost to follow up. The time commitment with regular appointments in the first year and lack of financial incentive were all contributory to the high dropout rate seen.

Further analysis is awaited following closure of the clinical trial earlier this year in February 2019 which will include analysis of HBA1c, the primary end point of the study. These findings will be crucial in determining the overall efficacy of this device. Changes in medication, particularly diabetes medication are yet to be assessed and once again this information will be key when interpreting the final results obtained with regards to the device's impact on glycaemic control.

Another factor to consider concerning concomitant medication is that it was solely participants in the EB group and not the control group that received high dosage PPIs (omeprazole 40mg BD) for a duration of one year. PPIs have been shown to have an impact on glucose metabolism albeit modest due to their interaction with the hormone gastrin which has been demonstrated to be an islet cell growth factor.[317] Increased levels of gastrin as a consequence of PPI therapy may have an incretin effect therefore stimulating insulin secretion. The effect of PPIs on glycaemic control remains controversial with conflicting reports in the literature showing some improvement in HBA1c or no effect at all depending on which PPI is prescribed.[318, 319] Nevertheless the potential positive impact of PPI therapy on glycaemic control in the EB vs. control group should be considered.

3.5 Conclusion

The EB provides another treatment modality for the management of obese patients with type 2 diabetes and was designed to mimic the clinical and physiological effects of bariatric surgery. These results from the first year of the clinical trial would suggest that the EB induces moderate weight loss effects but improvements in glycaemic control may be more subtle. In these patients the device has an acceptable safety profile. However, one year follow up data of these patients following device removal is still awaited and will prove crucial in determining how successful EB therapy is in the long run.

Until then its current position in the treatment algorithm for obesity and diabetes remains unclear. At present the device's utility may lie in the following situations:

- An adjunct to surgery, to induce weight loss in the superobese prior to bariatric surgery.
- To improve liver biochemistry, which may aid in conditions such as NAFLD.

It is most likely that the EB in its current form will not replace bariatric surgery but may act as a complementary intervention within the arsenal of anti-diabetes/anti-obesity therapies. Future work in this field should focus on developing the device so that it offers a longer treatment duration whilst also improving its safety profile and tolerability. Such a minimally-invasive device may then carry the potential to address some of the broader needs of the global diabesity population.

A summary of observed metabolites in biofluid samples obtained from EB and control participants is shown in Table 1.19.

Table 1. 19 List of assigned metabolites in ^{1}H NMR spectra of urine, plasma and faecal water

Metabolites	Chemical Formula	Selected δ ^{1}H (multiplicity)	Biofluids
2-aminoisobutyrate	$C_4H_9NO_2$	1.48(s)	f
3-indoxyl sulfate (IS)	$C_8H_7NO_4S$	7.7(d), 7.5(d), 7.3(s), 7.27 (t), 7.19(t)	u
4-cresyl sulfate	$C_7H_8O_4S$	2.35(s)	u
5-aminopentanoate	$C_5H_{11}NO_2$	3.00(t), 2.24(t), 1.65(m)	f
ascorbic acid	$C_6H_7O_6^-$	4.50(d)	p
creatinine	$C_4H_7N_3O$	3.05(s), 4.05(s)	u
fumuric acid	$C_4H_4O_4$	6.53(s)	f
lactate	$C_3H_6O_3$	4.11(q); 1.32(d)	p, f
malic acid	$C_4H_6O_5$	4.31(dd)	f
Phenylacetylglutamine (PAG)	$C_{13}H_{16}N_2O_4$	1.95(m), 2.1(m), 2.25(m), 3.67(d), 4.19(m), 7.36 (t), 7.43 (t)	u
propylene glycol	$C_3H_8O_2$	1.12(d)	p

trigonelline	$C_7H_7NO_2$	4.42(s)	f
trimethylamine *N*-oxide (TMAO)	3 x CH_3	3.28(s)	p
tyramine	$C_8H_{11}NO$	7.21(d); 6.90 (d); 3.23(t); 2.92(t)	f
tyrosine	$C_9H_{11}NO_3$	7.18(d); 6.88(d); 3.94(dd); 3.20(dd); 3.10(dd)	f, u
α-glucose	$C_6H_{12}O_6$	5.22(d); 3.54(dd); 3.71(t); 3.42(t); 3.83 (ddd); 3.84 (m); 3.76 (m)	f, p
β-glucose	$C_6H_{12}O_6$	4.65(d); 3.24(dd); 3.48(t); 3.40(t); 3.47(ddd); 3.72(dd); 3.90(dd)	f, p

d = doublets; f= faeces; m= multiplets; p = plasma; s = singlet; t = triplets; u = urine

4.1 Plasma

Representative 1D ^1H standard and CPMG NMR spectra of plasma are shown in Figures 1.27 and 1.28, respectively. Metabolites including glucose, lactate, ascorbate, TMAO, citrate, alanine, acetate, leucine, isoleucine and valine were observed.

Figure 1. 27 Typical 1D standard ^{1}H NMR spectra of plasma from control and EB groups at 6 months

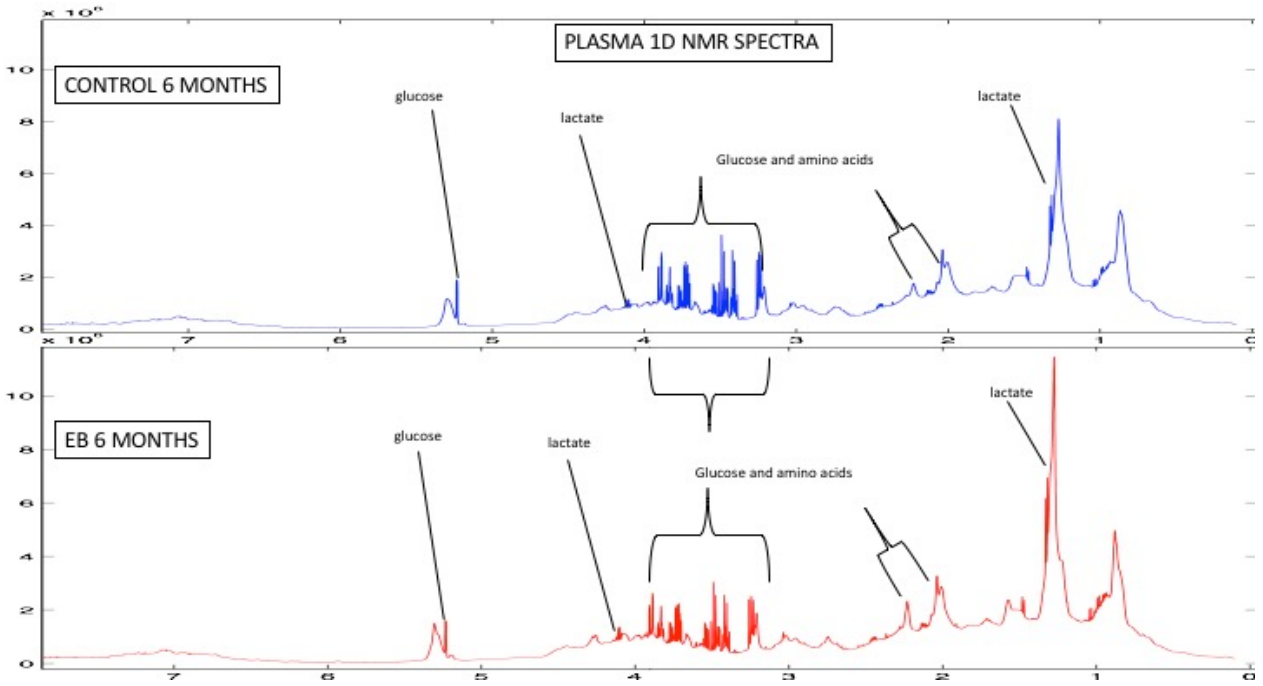
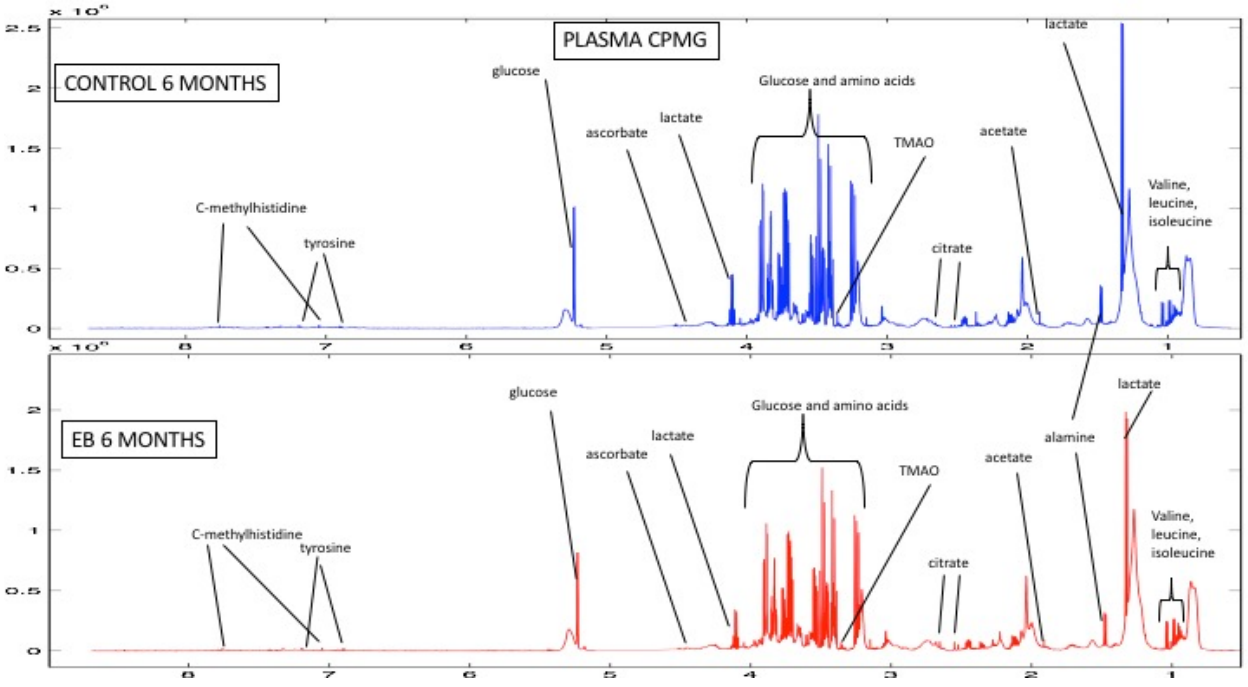


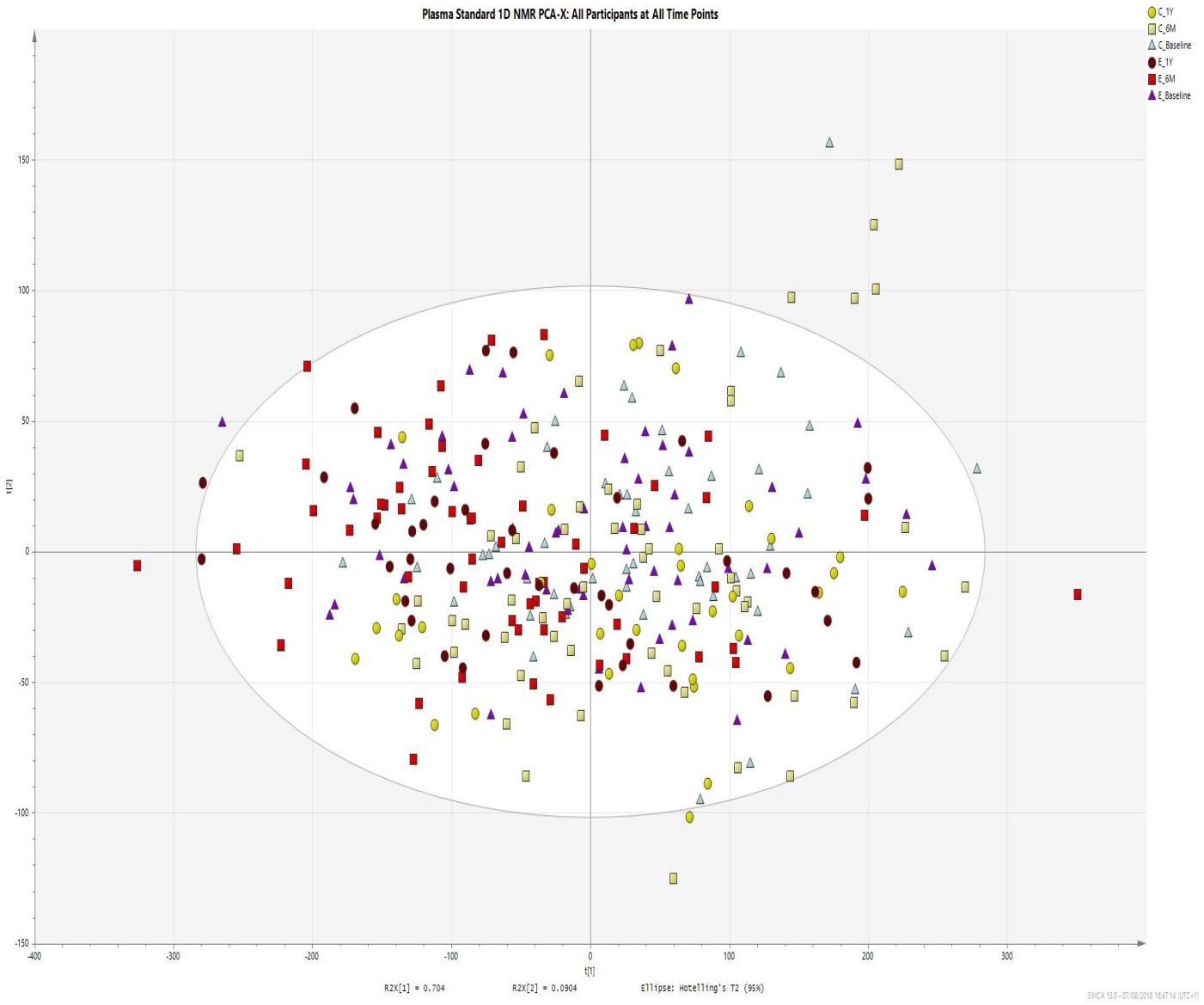
Figure 1. 28 Typical 600 MHz ^{1}H NMR CPMG spectra of plasma from a control and EB participant at 6 months



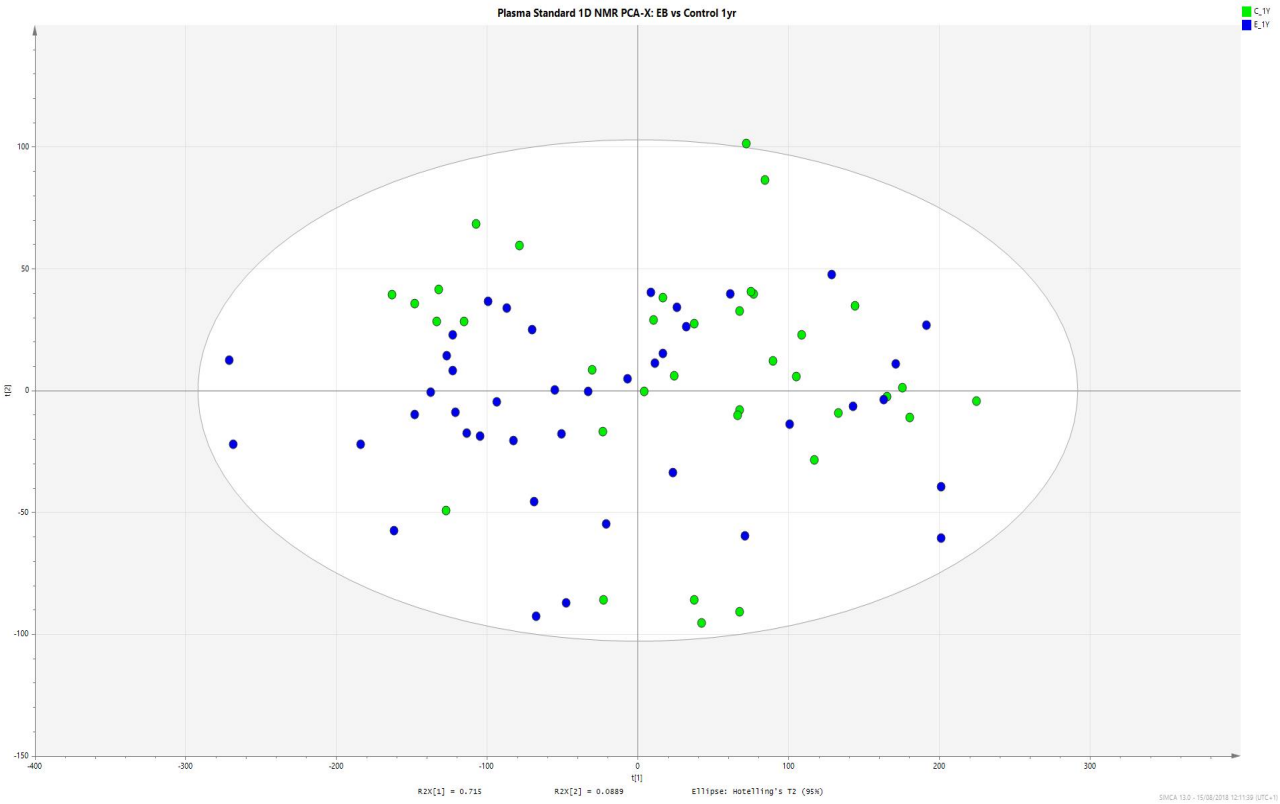
Multivariate statistical analysis including PCA and OPLS-DA was used to analyse the standard and CPMG spectral data separately. The PCA scores plots derived from the standard NMR spectra showed a cluster of EB patients at the 6 months along the first principal component (Figure 1.29A, red squares). However, no clear separation was observed between control and EB at 6 and 12 months in PCA analysis (Figures 1.29 B&C, F&G). Supervised analysis of OPLS-DA was applied to carry out the pair-wise comparisons between control and EB at each time point, and the longitudinal comparisons between different time points within each group of patients. The parameters of OPLS-DA models based on the standard plasma spectral data are summarised in Table 1.20. Those models which were found to have significant differences with $p<0.05$ were highlighted. There was no significant metabolic difference between control and EB at baseline. However, significant differences were observed between control and EB groups at 6 and 12 months (Table 1.20; Figures 1.29 D&E). In the EB arm, there were significant changes in plasma metabolic profiles of patients at 6 or 12-month EB implantation (Table 1.20; Figures 1.29 H&I) in comparison to the baseline profiles. No significant difference was observed between 6 and 12 months in the EB group. In the control arm, I only observed a significant model of comparing baseline and 12-month time points, but the p value of this model ($p=0.02$) is not as low as the models from the EB arm (baseline vs. 6 months, $p=0.001$; baseline vs. 12 months, $p=4.84 \times 10^{-5}$).

Figure 1. 29: A), B) and C) represent scores plots from the PCA of the results obtained from plasma of all participants at all time points and at 6 and 12 months comparisons respectively. D) and E) represent cross validated scores plots from supervised OPLS-DA analysis of plasma from both treatment groups at 6 months and 12 months. F) and G) are PCA plots comparing EB group at 6 months and 12 months from baseline and H) and I) are the accompanying OPLS-DA analysis of the same sample set.

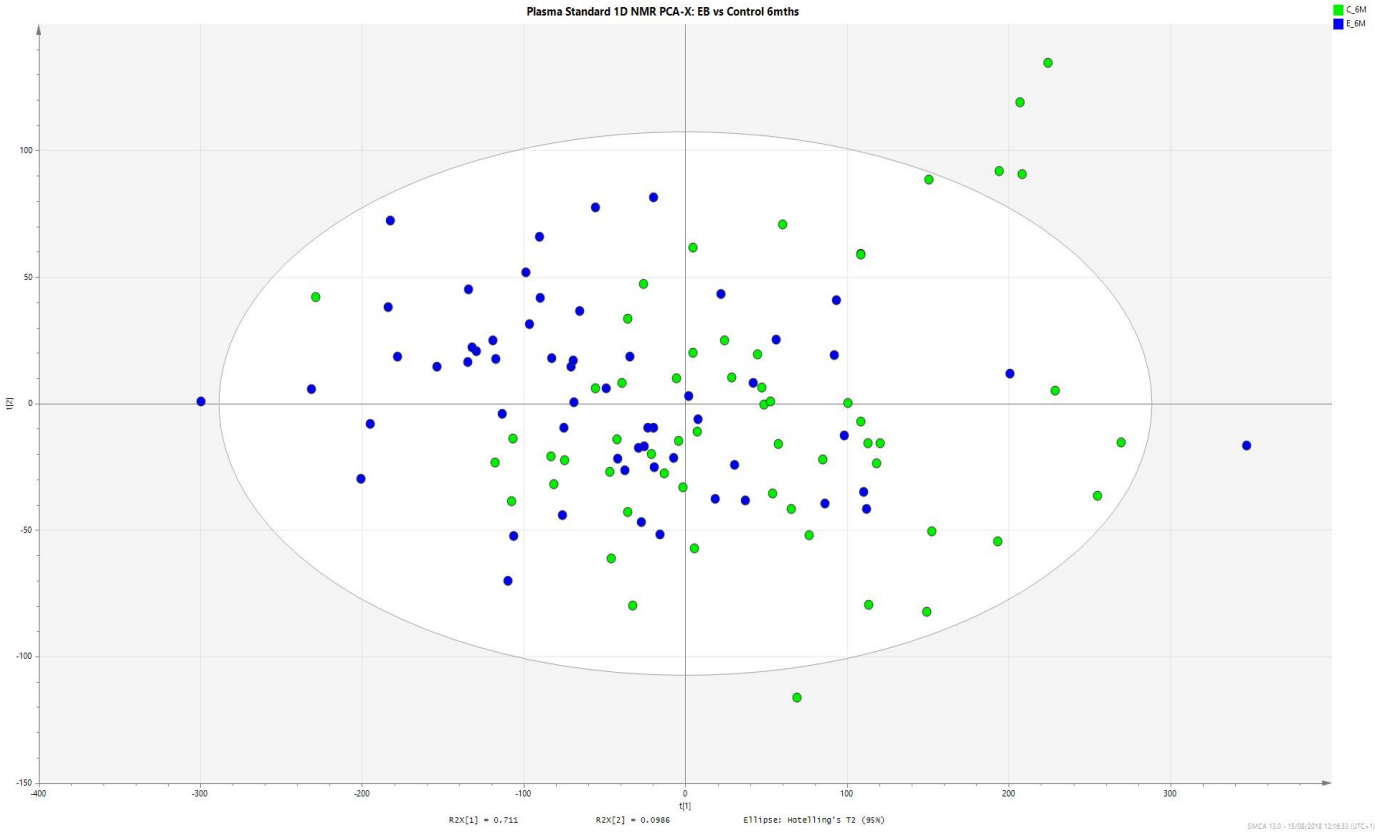
A) Plasma Standard 1D NMR PCA-X: All Participants at All Time Points



B) Plasma Standard 1D NMR PCA-X: EB vs Control 1yr

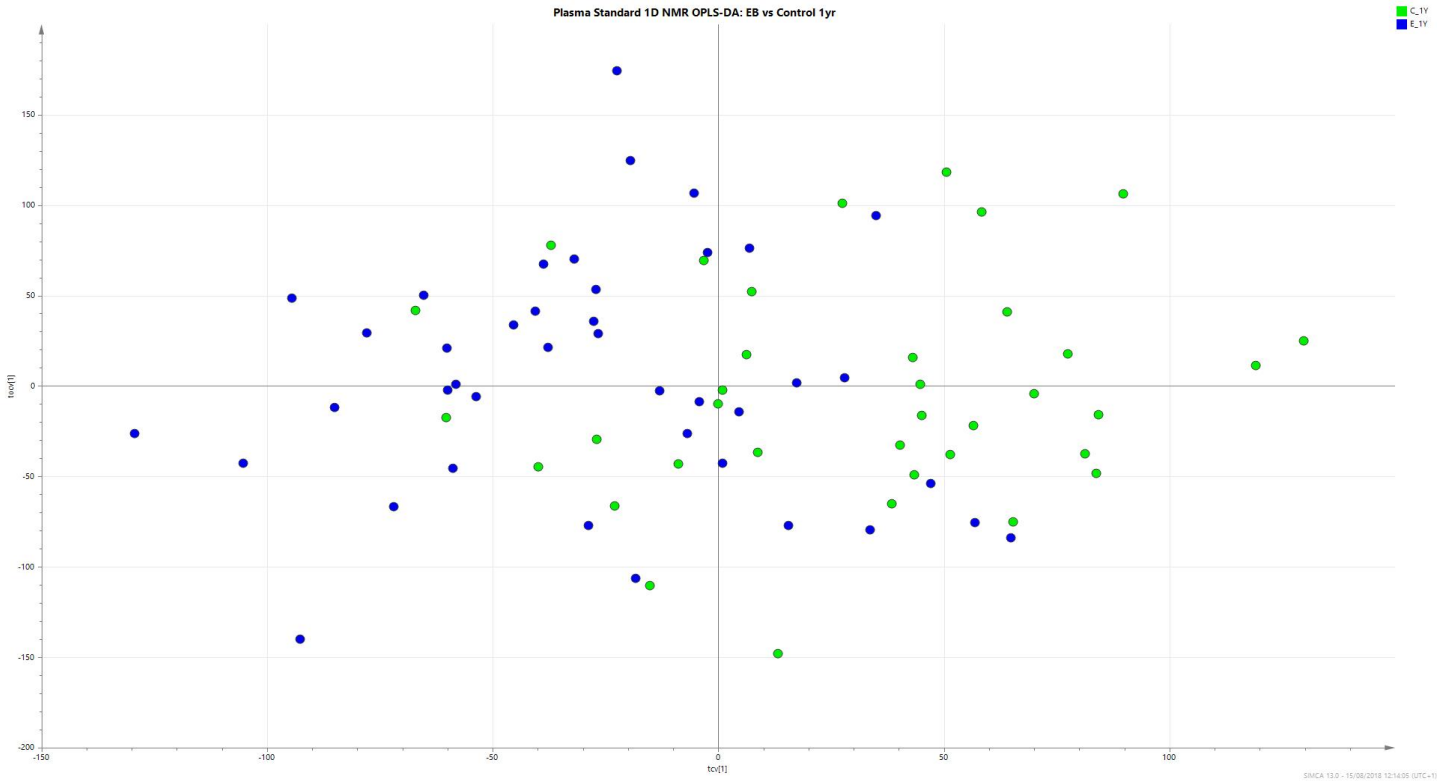


C) Plasma Standard 1D NMR PCA-X: EB vs Control 6 Months

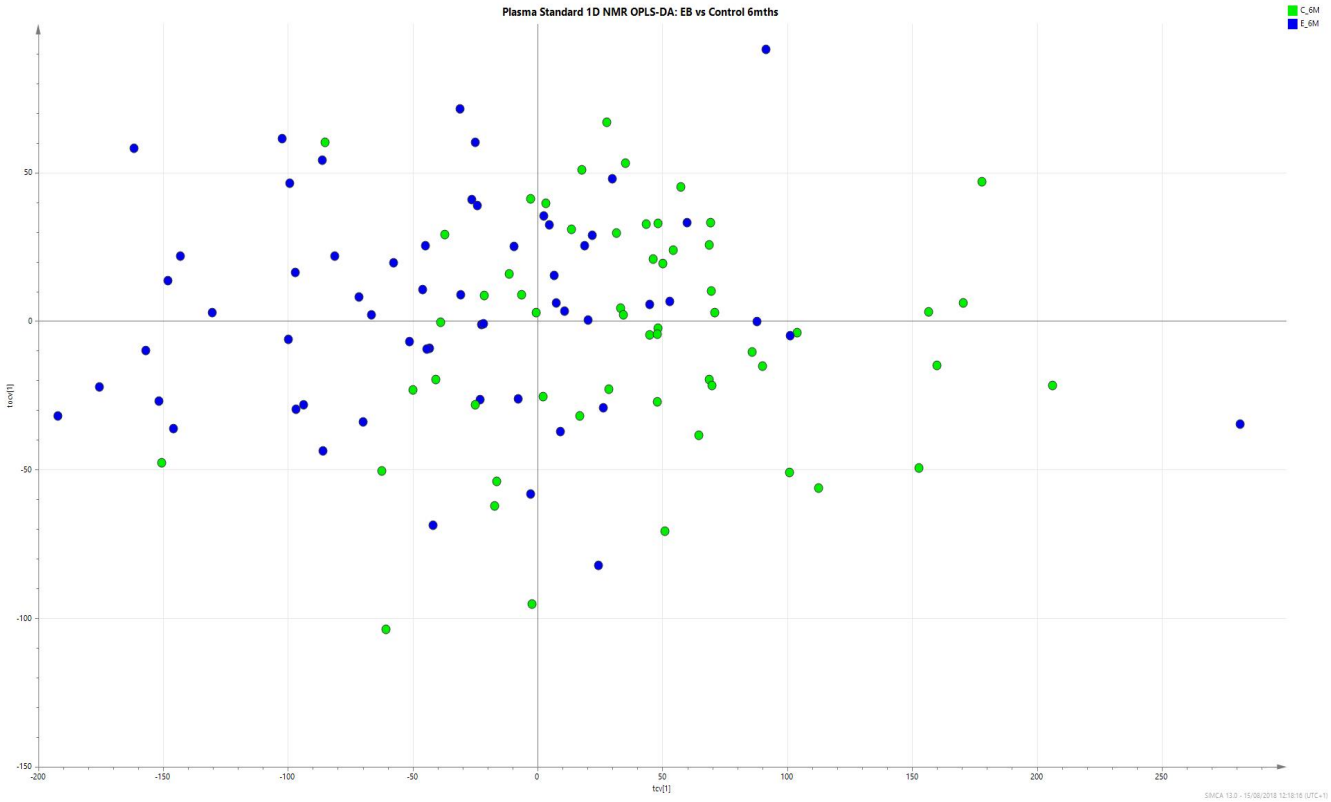


Legend Control Endobarrier

D) Plasma Standard 1D NMR OPLS-DA: EB vs Control 1yr

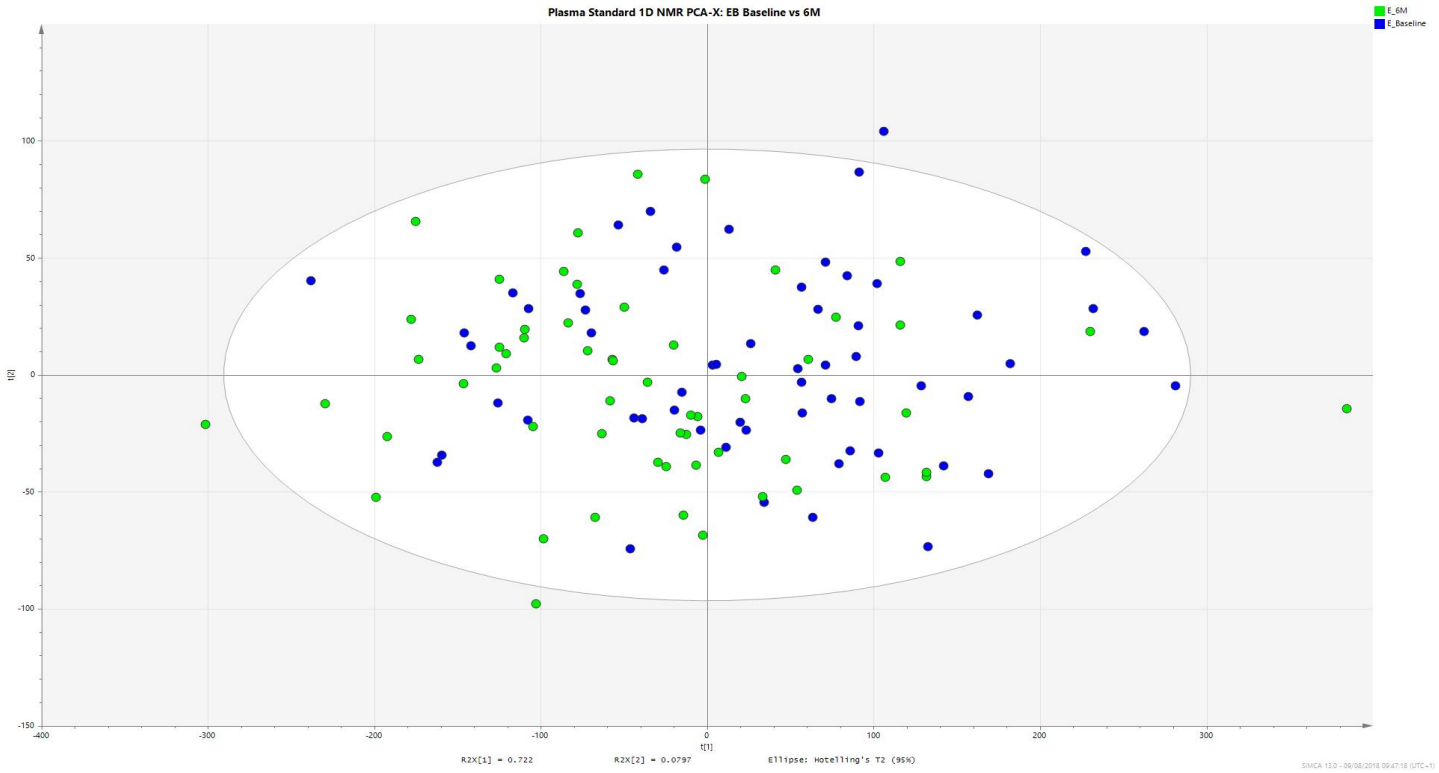


E) Plasma Standard 1D NMR OPLS-DA: EB vs Control 6 Months



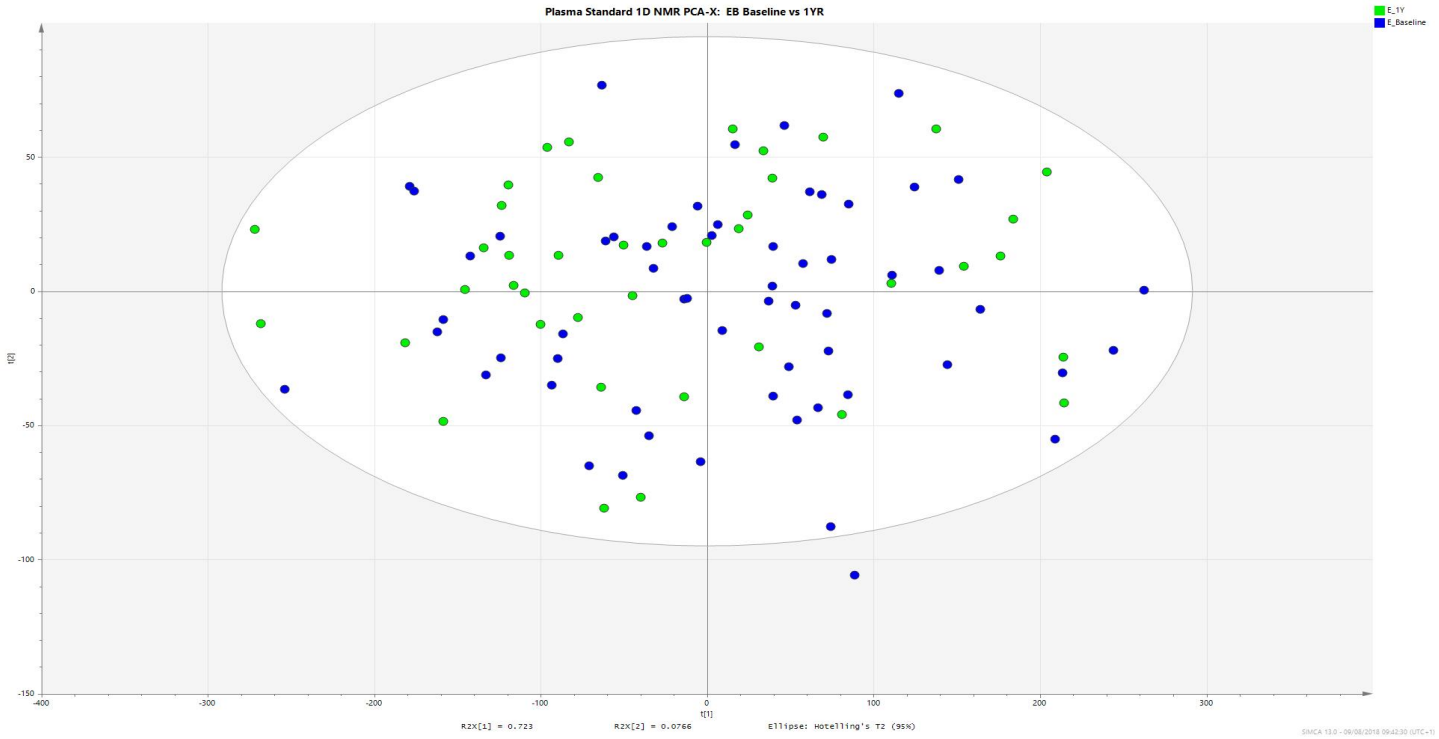
Legend Control Endobarrier

F) Plasma Standard 1D NMR PCA-X: EB Baseline vs 6 Months



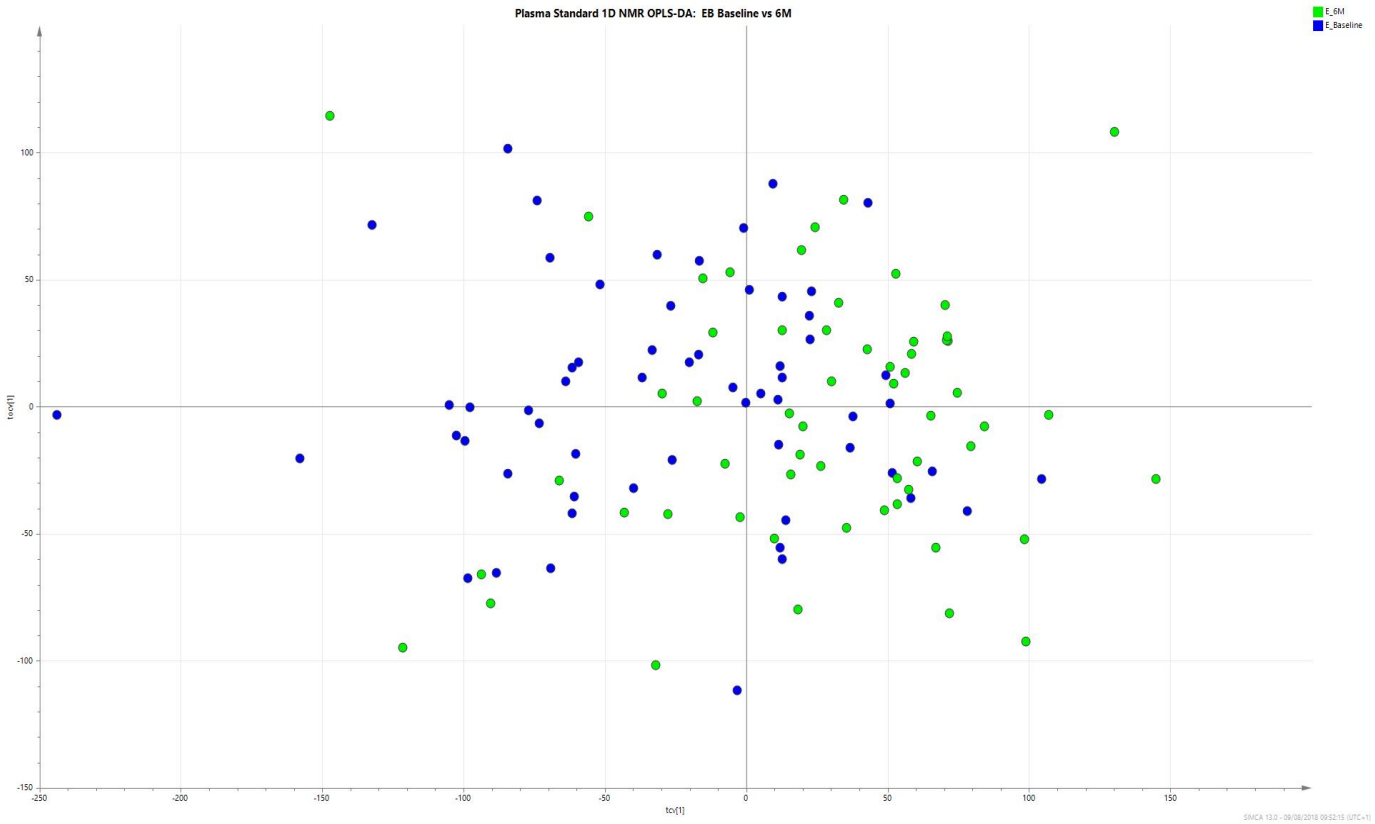
Legend EB 6 Months EB Baseline

G) Plasma Standard 1D NMR PCA-X: EB Baseline vs 1 Year



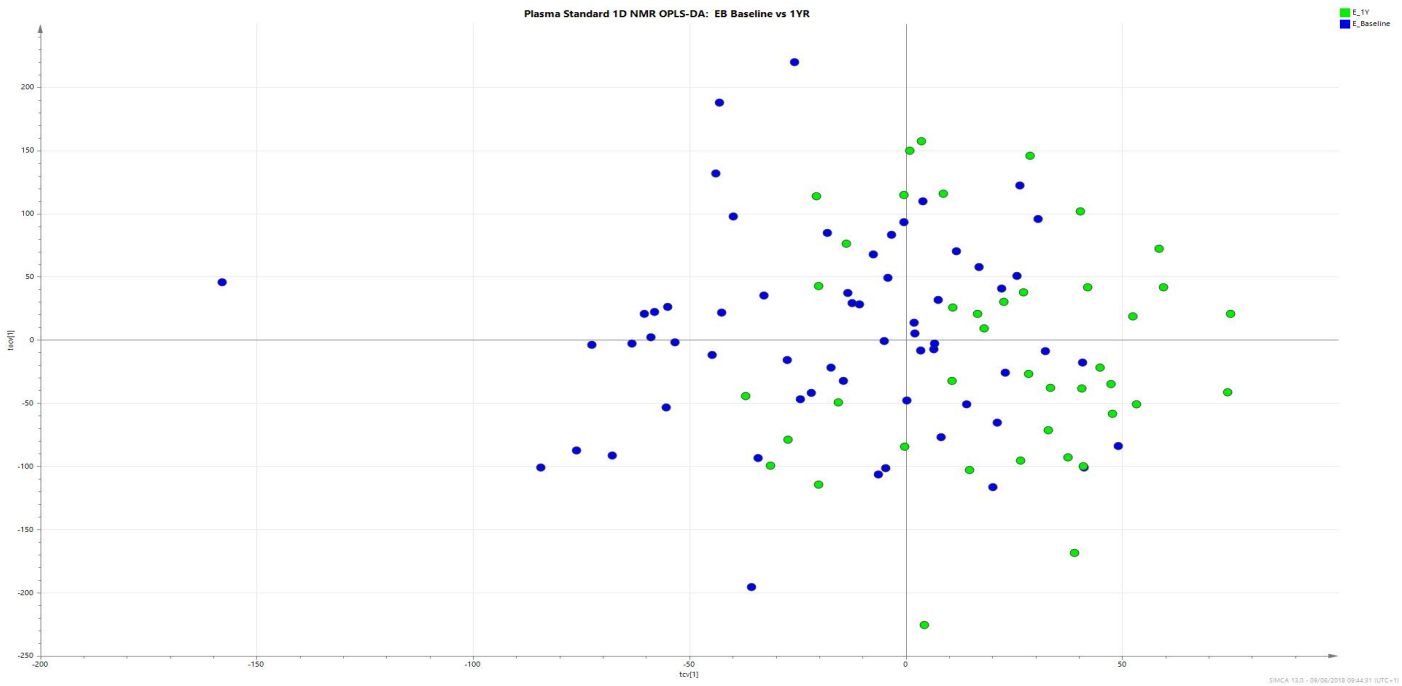
Legend EB 1 Year EB Baseline

H) Plasma Standard 1D NMR OPLS-DA: EB Baseline vs 6 Months



Legend EB 6 Months EB Baseline

I) Plasma Standard 1D NMR OPLS-DA: EB Baseline vs 1 Year



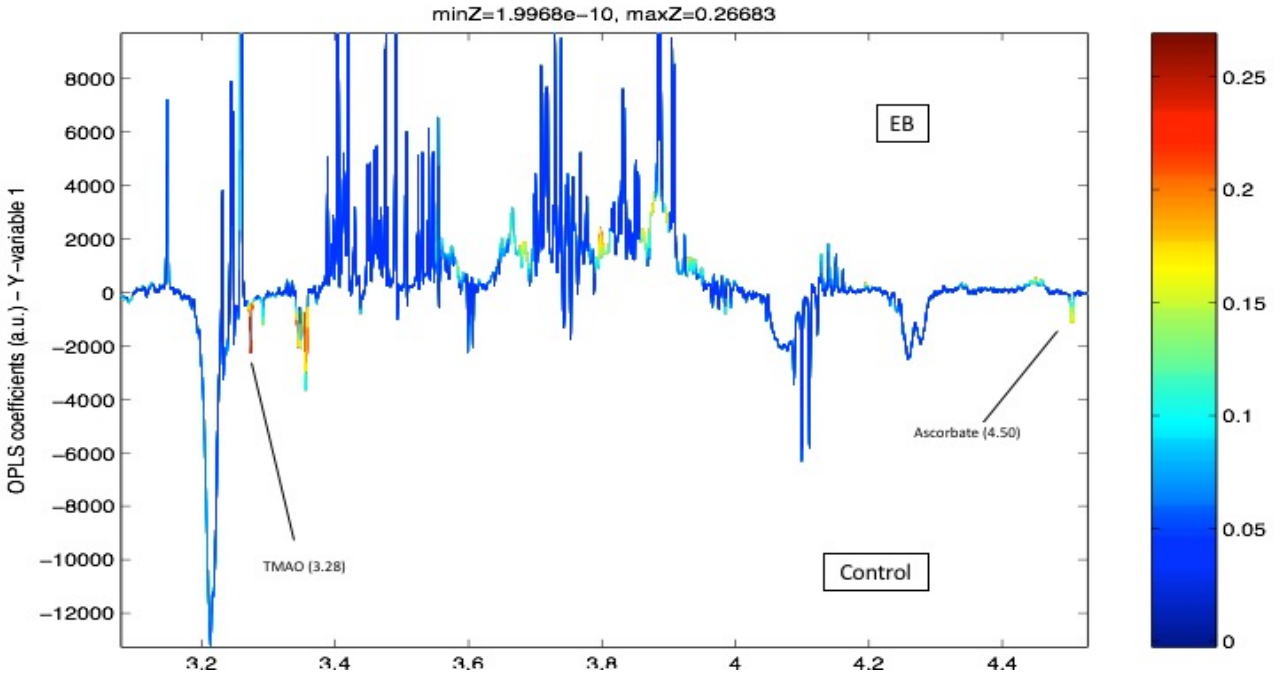
Legend EB 1 Year EB Baseline

Table 1. 20 Summary of the parameters derived from the OPLS-DA models of the standard 1D ^{1}H NMR plasma spectral data.

	Baseline vs. 6 months	**Baseline vs. 12 months**	**6 months vs. 12months**
Control	R^2X=0.738 Q^2Y=0.553 p=0.197	R^2X= 0.738 Q^2Y=0.124 p=0.02	R^2X= 0.76 Q^2Y=-0.083 p=1
EB	R^2X=0.779 Q^2Y=0.149 p=0.001	R^2X=0.773 Q^2Y=0.228 p=4.84 x 10^{-5}	R^2X=0.765 Q^2Y=-0.137 p=1
Control vs EB	**Baseline**	**6 months**	**12 months**
	R^2X= 0.738 Q^2Y= -0.164 p=1	R^2X= 0.771 Q^2Y=0.194 p=8.04 x 10^{-5}	R^2X=0.773 Q^2Y=0.27 p=0.0001

Levels of the metabolites including trimethylamine-*N*-oxide (TMAO) and ascorbate were found to be lower in the EB group at 6 months when compared with the control group (Figure 1.30). Two other unknown compounds at chemical shift 3.355 and 3.346 ppm were also found to decrease as well as another metabolite at chemical shift 1.12ppm which was putatively assigned as propylene glycol.

Figure 1. 30 OPLS-DA coefficients loadings plot of EB vs Control at 6 months showing lower concentrations of TMAO and ascorbate in the plasma of EB patients compared with controls at 6 months. Peaks pointing upwards represent higher concentrations of metabolites in EB compared with control and vice versa. The colour of the peaks represents the square of the correlation coefficient values (r^2).

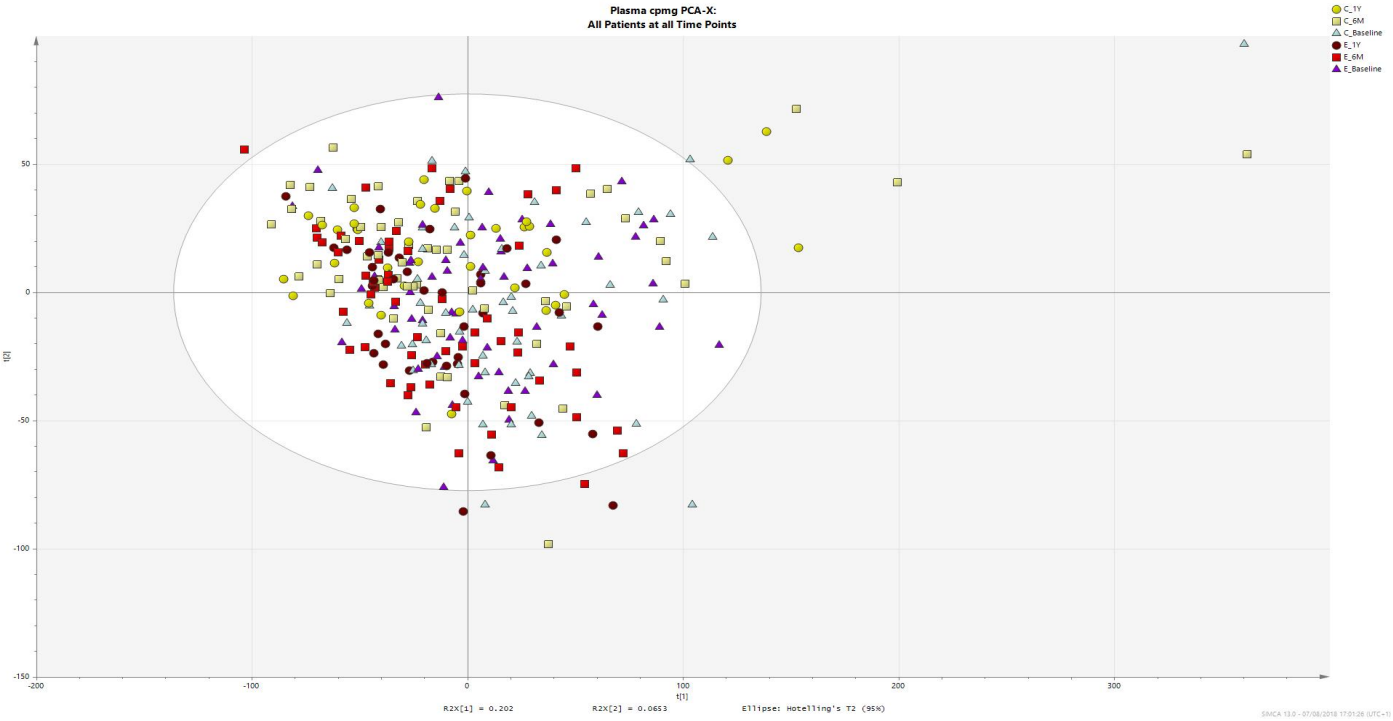


^{1}H CPMG NMR spectral data were also analysed using PCA and OPLS-DA methods. The PCA scores plots derived from the CPMG NMR spectra showed a clear separation between the EB patients and the controls at the 6 and 12 months along the second principal component (Figures 1.31 B&C). In the EB arm, the separation between baseline and 6 or 12 month time points was also observed along the first principal component (Figures 1.31 F&H). Supervised analysis of OPLS-DA was applied to carry out the pair-wise comparisons between control and EB at each time point, and the longitudinal comparisons between different time points within each group of patients. The parameters of OPLS-DA models based on the plasma CPMG spectral data are summarised in Table 1.21. Those models which were found to have significant differences with $p<0.05$ were highlighted. Similar to the findings from the standard NMR plasma spectral data, there was no significant metabolic difference between control

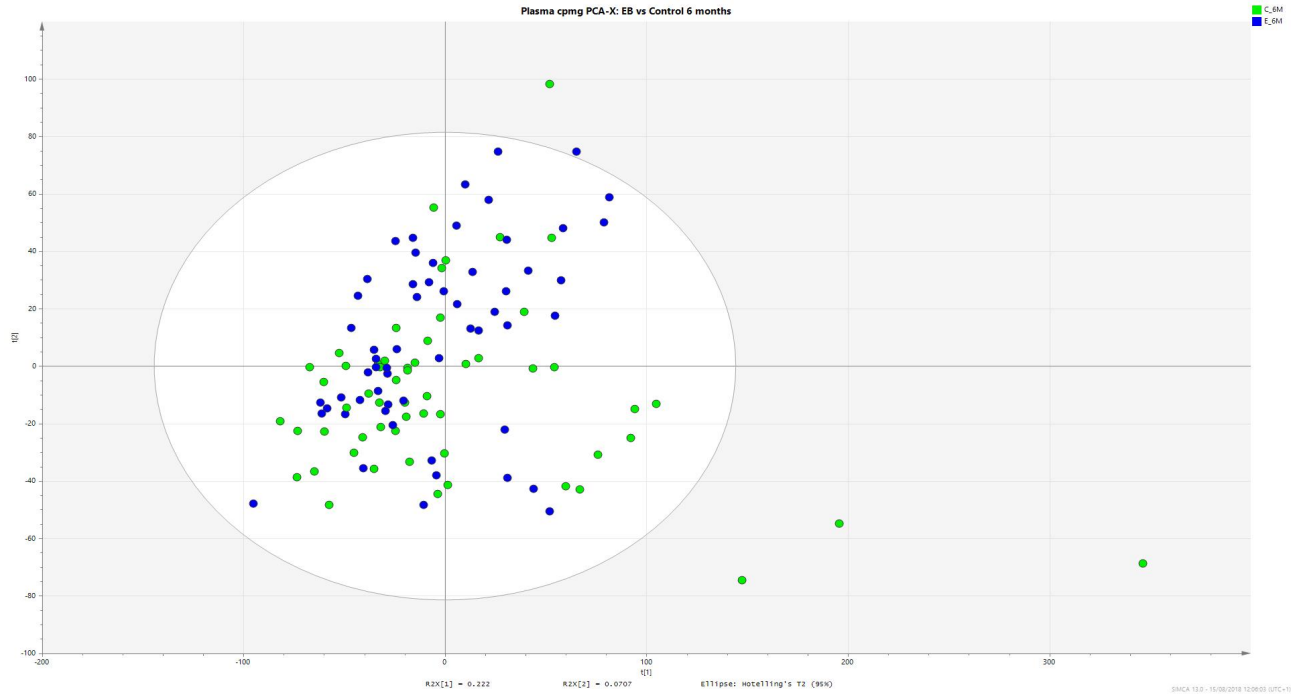
and EB at baseline. However, significant differences were observed between control and EB groups at 6 and 12 months (Figures 1.31 D&E). In the EB arm, there were significant changes in plasma metabolic profiles of patients at 6- or 12-month EB implantation (Figures 1.31 G&I) in comparison to the baseline profiles. No significant difference was observed between 6 and 12 months in the EB group. In the control arm, a significant OPLS-DA model based on samples from baseline and 12 months was also observed.

Figure 1. 31 A), B) and C) represent scores plots from the PCA of the results obtained from plasma CPMG spectra of all participants at all time points and at 6 and 12 months comparisons respectively. D) and E) represent cross-validated scores plots from supervised OPLS-DA analysis of plasma from both treatment groups at 6 months and 12 months. F) and G) are PCA plots comparing EB group at 6 months and 12 months from baseline and H) and I) are the accompanying OPLS-DA analysis of the same sample set.

A) Plasma cpmg PCA-X: All Participants at All Time Points

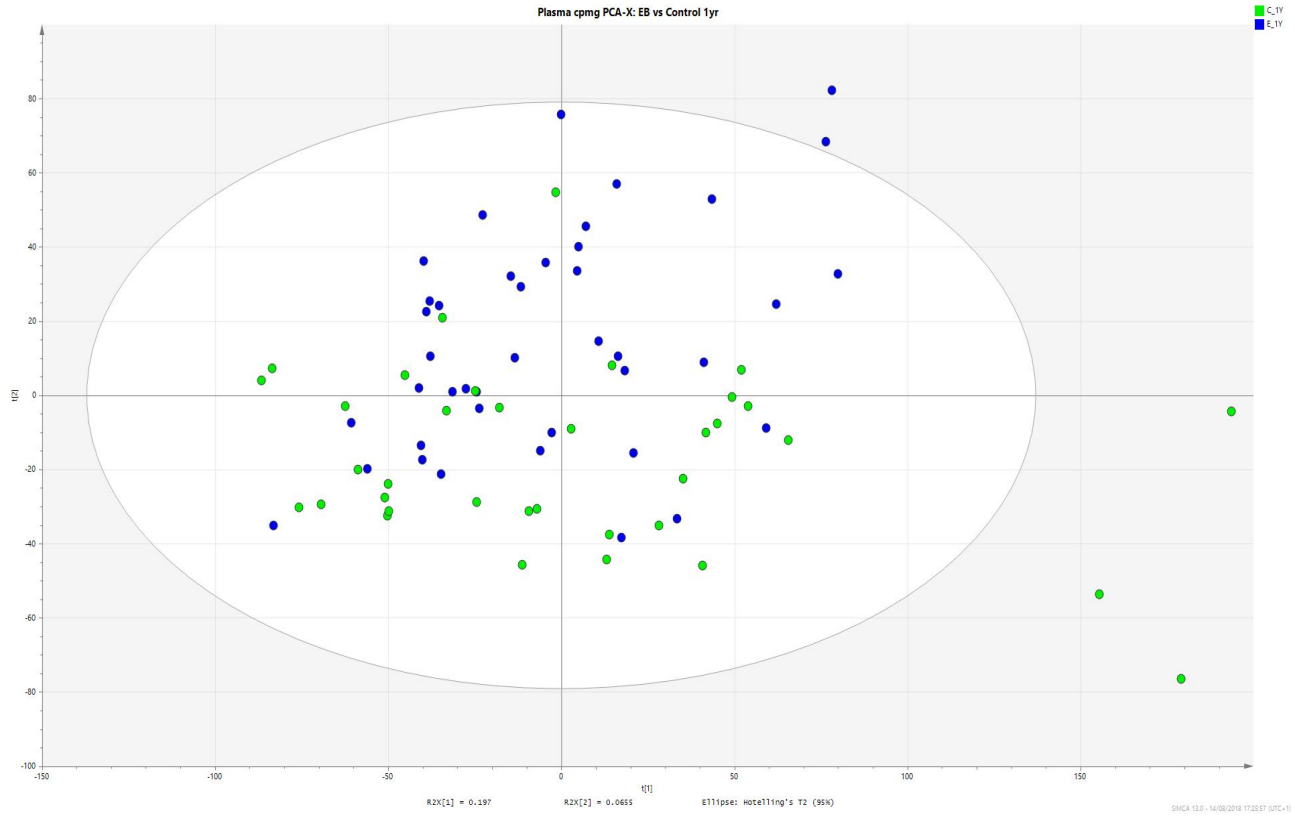


B) **Plasma cpmg PCA-X: EB vs Control 6 Months**



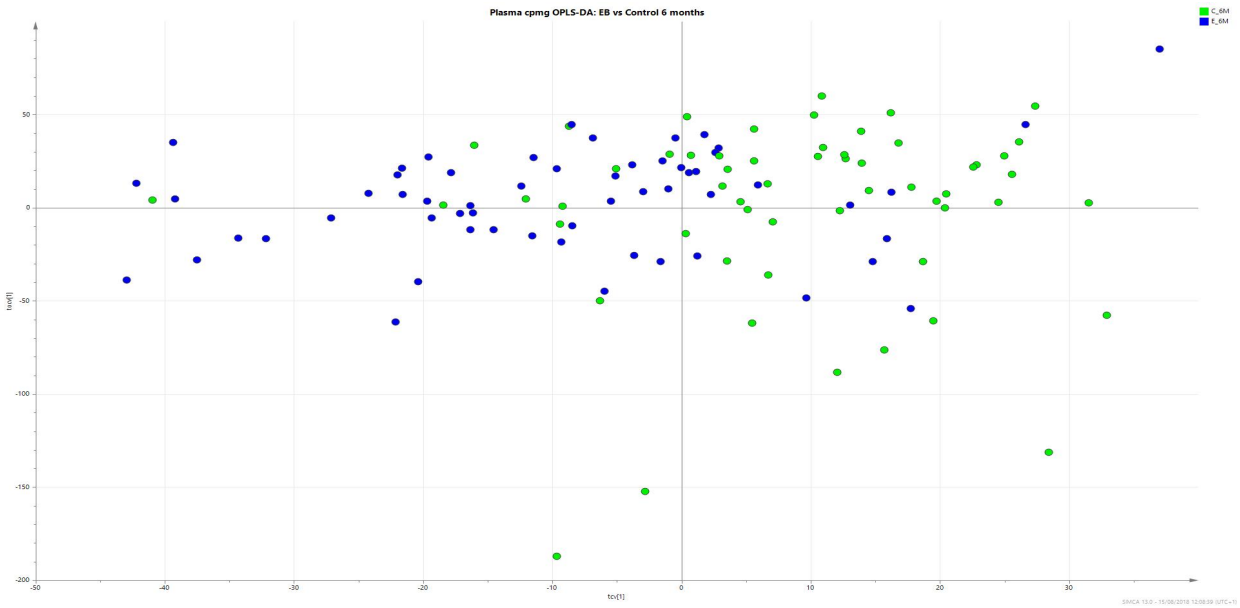
Legend Control Endobarrier

C) **Plasma cpmg PCA-X: EB vs Control 1 Year**



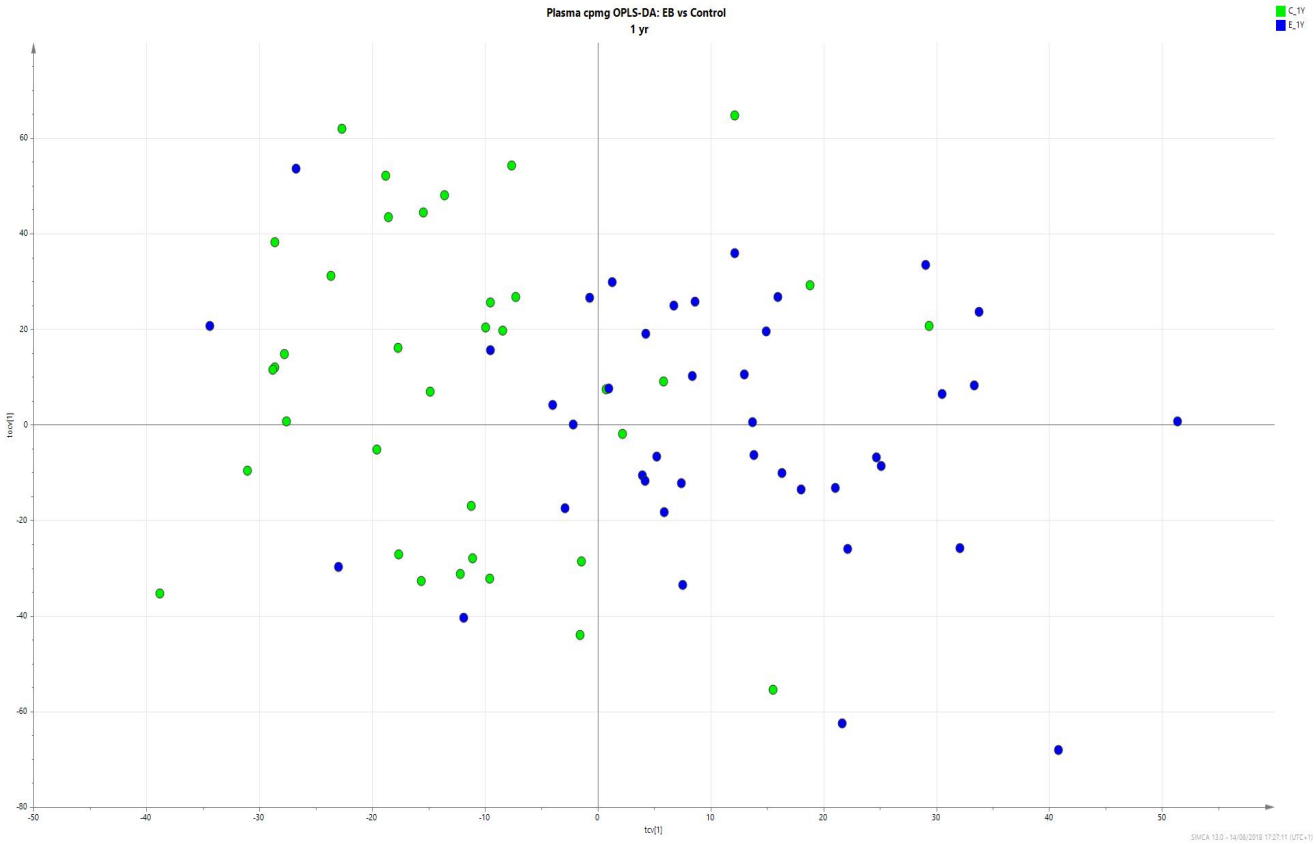
Legend Control Endobarrier

D) Plasma cpmg OPLS-DA: EB vs Control 6 Months



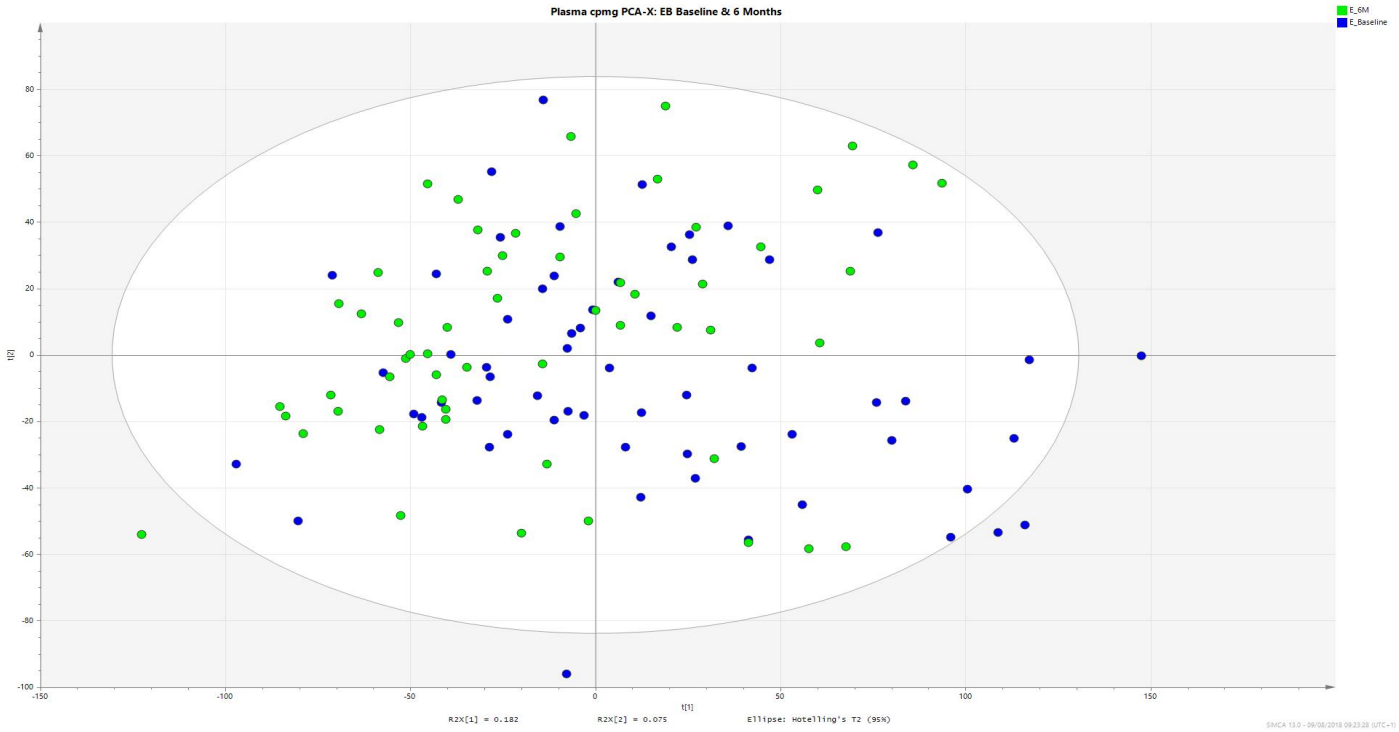
Legend Control Endobarrier

E) Plasma cpmg OPLS-DA: EB vs Control 1 Year



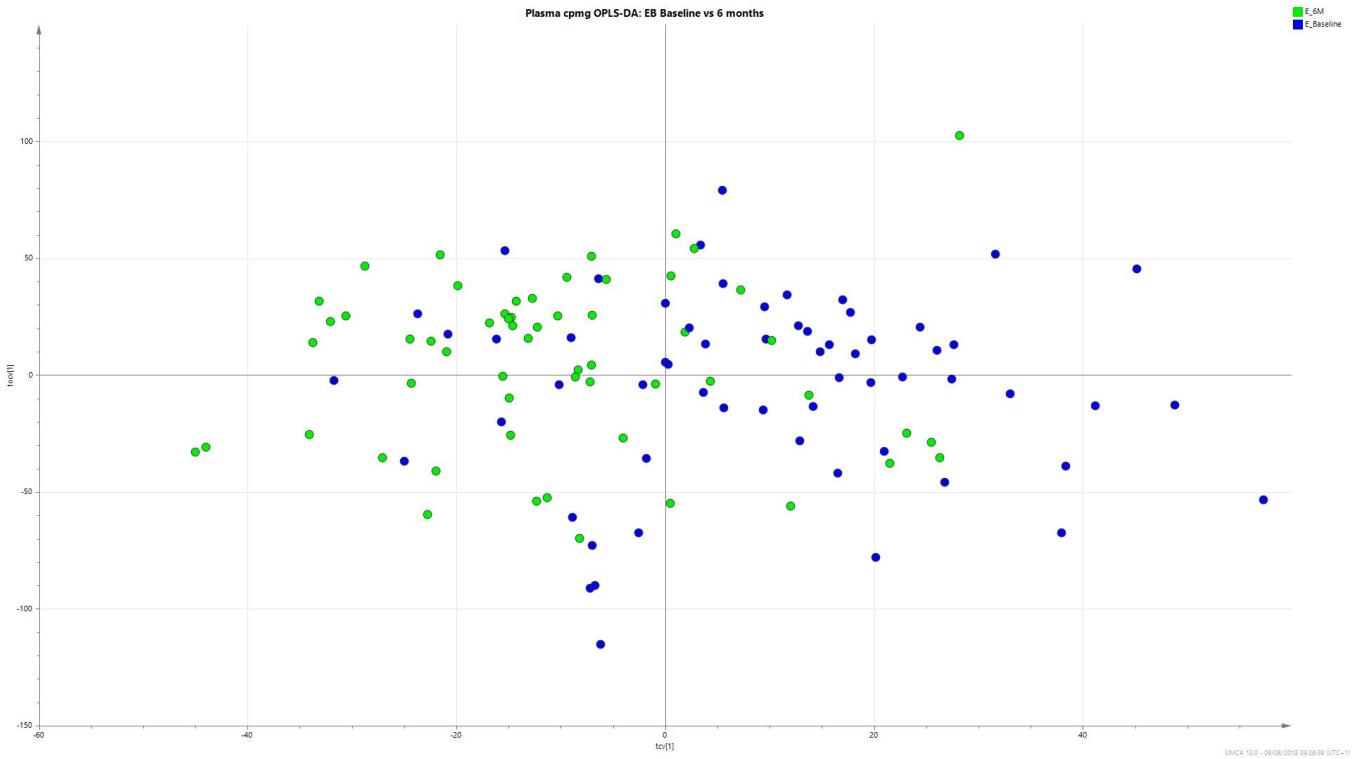
Legend Control Endobarrier

F) Plasma cpmg PCA-X: EB Baseline vs 6 Month



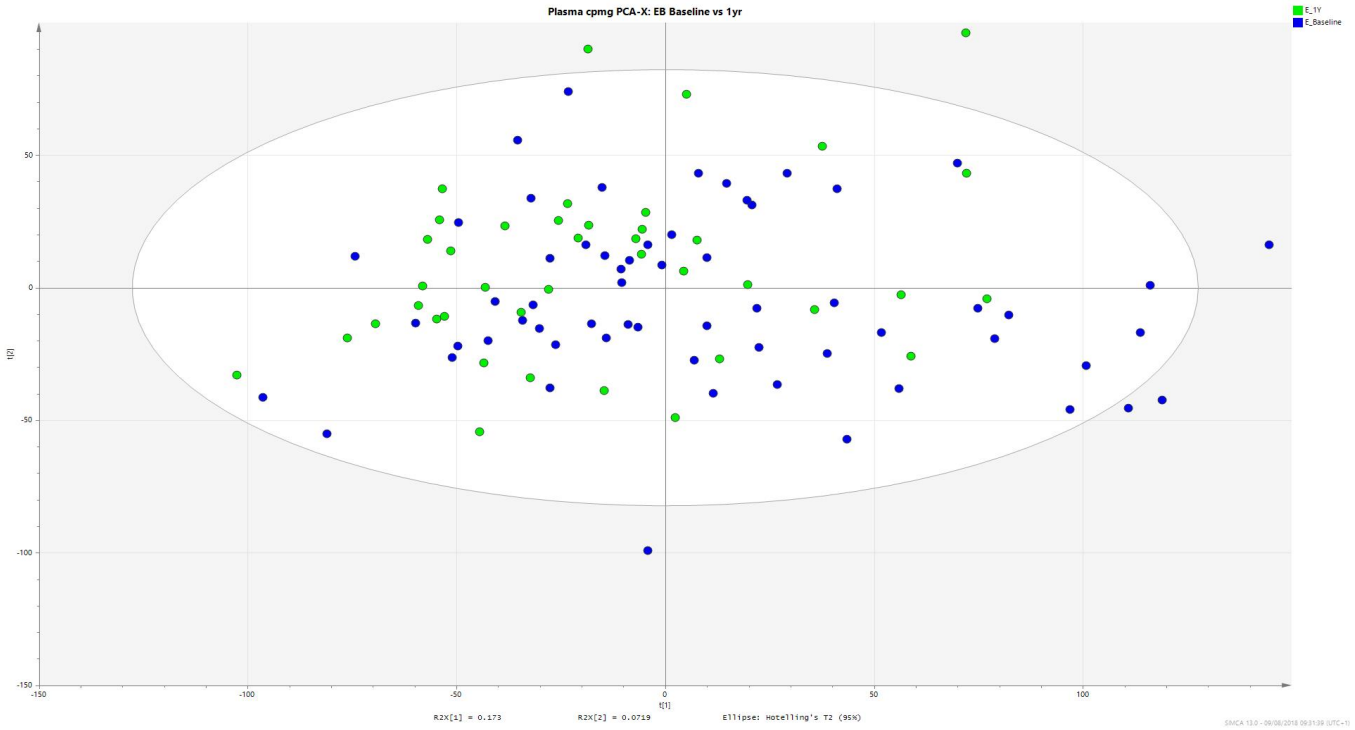
Legend EB 6 Months EB Baseline

G) Plasma cpmg OPLS-DA: EB Baseline vs 6 Month



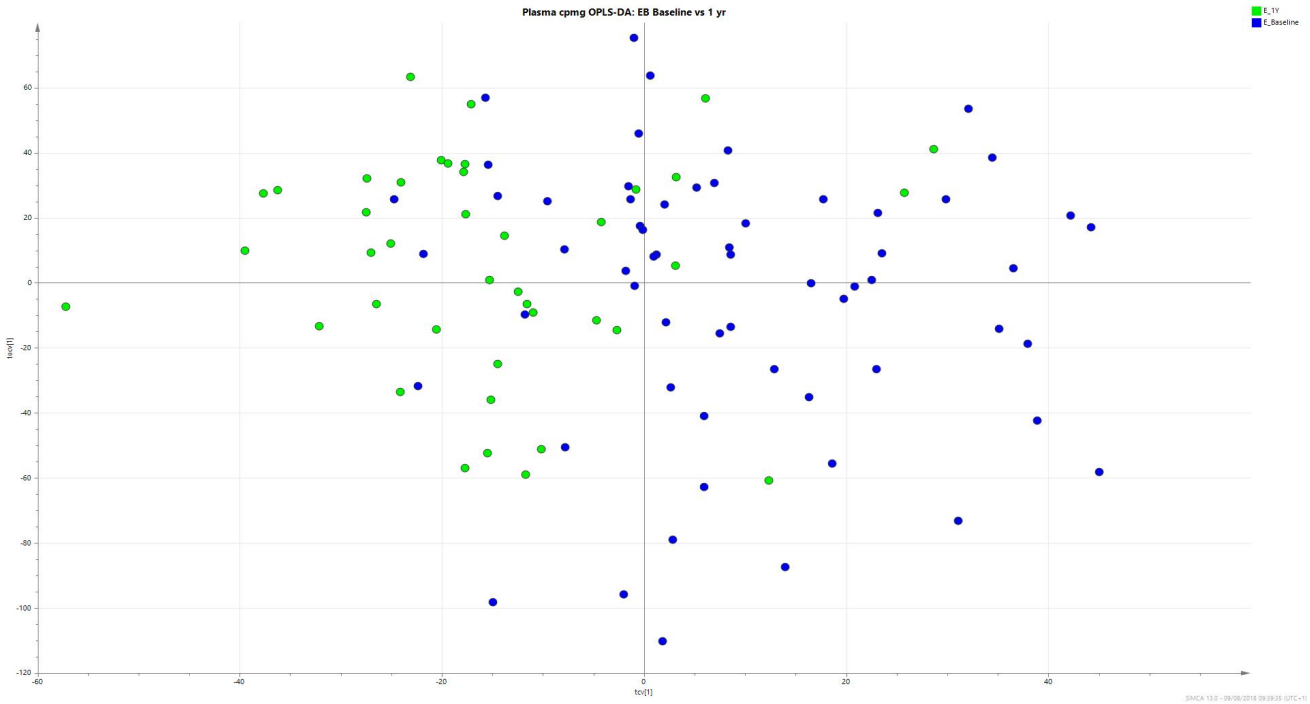
Legend EB 6 Months EB Baseline

H) Plasma cpmg PCA-X: EB Baseline vs 1 Year



Legend EB 1 Year EB Baseline

I) Plasma cpmg OPLS-DA: EB Baseline vs 1 Year



Legend EB 1 Year EB Baseline

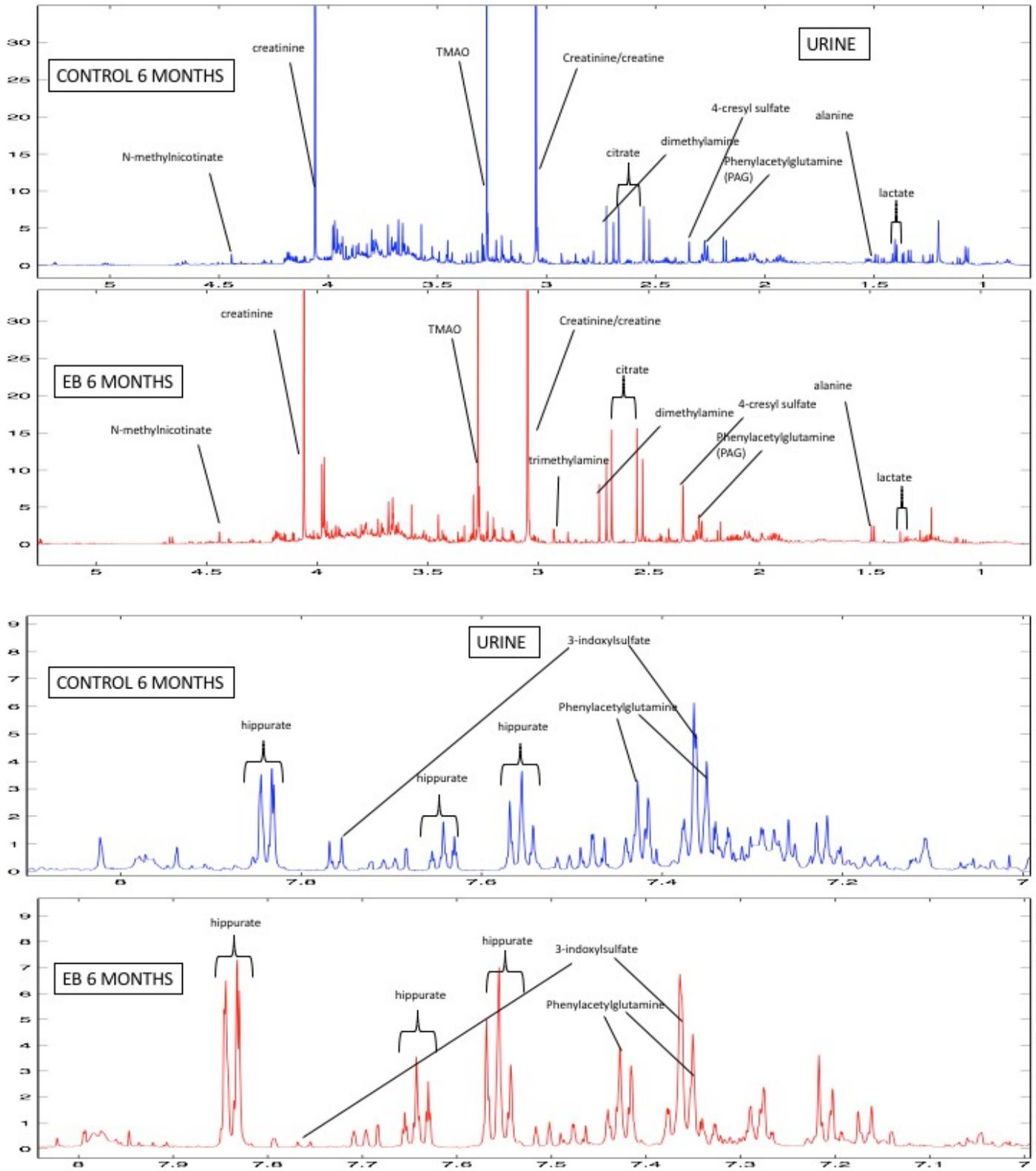
Table 1. 21 Summary of the parameters derived from the OPLS-DA models of the 1D CPMG ^{1}H NMR plasma spectral data.

	Baseline vs. 6 months	**Baseline vs. 12 months**	**6 months vs. 12months**
Control	R^2X= 0.286 Q^2Y=0.0292 p=0.53	R^2X= 0.279 Q^2Y=0.262 p=3.48 x 10^{-5}	R^2X= 0.264 Q^2Y=-0.136 p=1
EB	R^2X=0.223 Q^2Y=0.221 p=8.96 x 10^{-6}	R^2X= 0.219 Q^2Y= 0.325 p=8.72 x 10^{-8}	R^2X=0.195 Q^2Y=-0.392 p=1
Control vs EB	**Baseline**	**6 months**	**12 months**
	R^2X= 0.233 Q^2Y=-0.204 p=1	R^2X=0.267 Q^2Y=0.238 p=4.63 x 10^{-6}	R^2X= 0.241 Q^2Y=0.326 p=8.69 x 10^{-6}

4.2 Urine

Representative ^{1}H NMR spectra obtained from urinary samples of the control and treatment groups at 6 months are shown in Figure 1.32**.** Metabolites including alanine, creatinine, citrate, lactate, phenylacetylglutamine, TMAO and 3-indoxysulfate were observed.

Figure 1. 32 Typical 600 MHz ^{1}H NMR spectra of urine of control and EB groups at 6 months. The top two spectra are from chemical shift regions of 0.5-5.5 ppm and the bottom two spectra are from the chemical shift regions of 7-8.5 ppm.

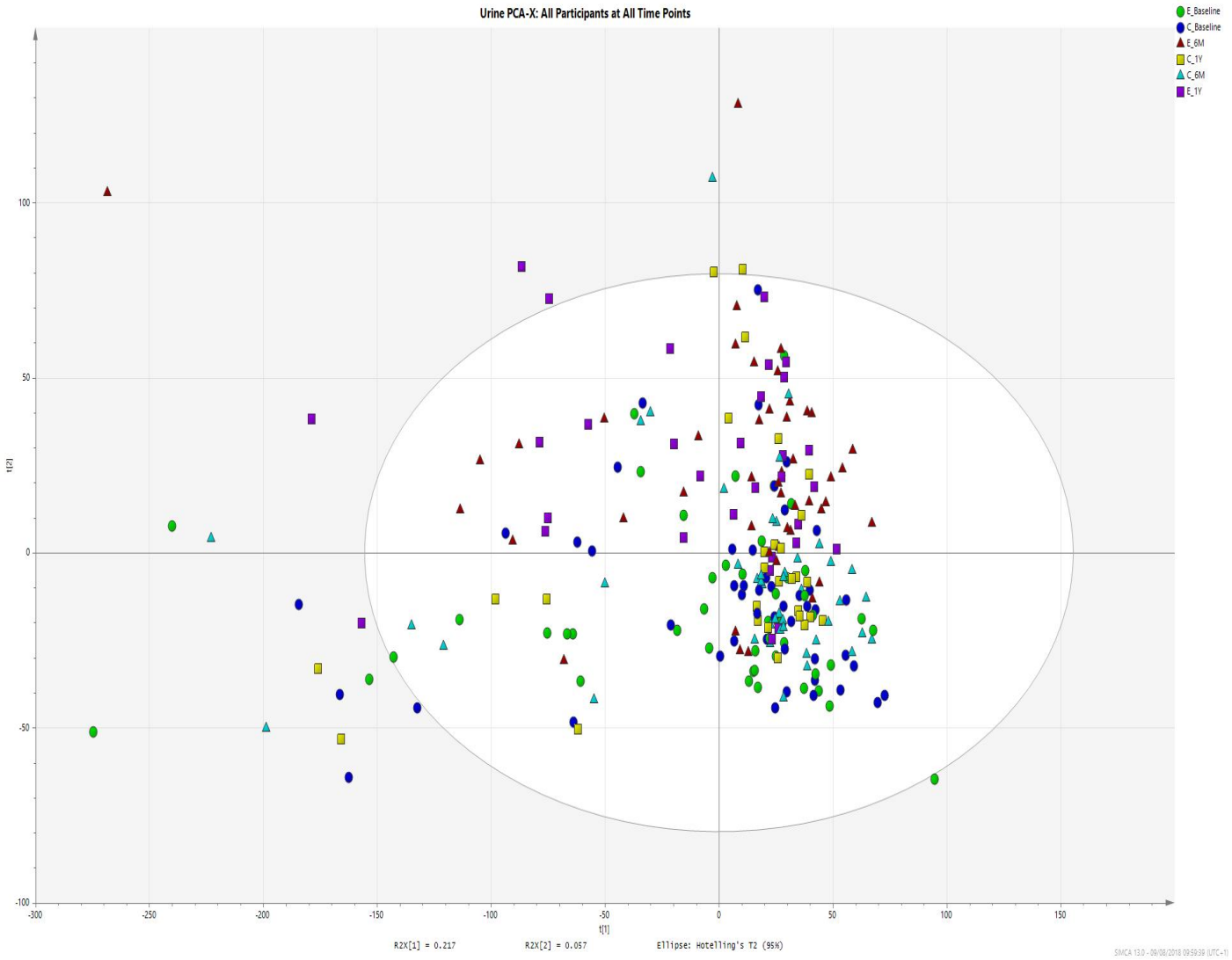


Analysis of urine samples using PCA and OPLS-DA methods was performed. The PCA scores plots derived from the urine spectra showed a clear separation between the EB patients and the controls at the 6 and 12 months along the second principal component (Figures 1.33 B&C). In the EB arm, the separation between the baseline and 6 or 12 month time points was also observed along the first principal component (Figures 1.33 F&H). Supervised analysis of OPLS-DA was applied to carry out the pair-wise comparisons between control and EB at each time point, and the longitudinal comparisons between different time points within each group of patients. Statistically significant models are highlighted in Table 1.22.

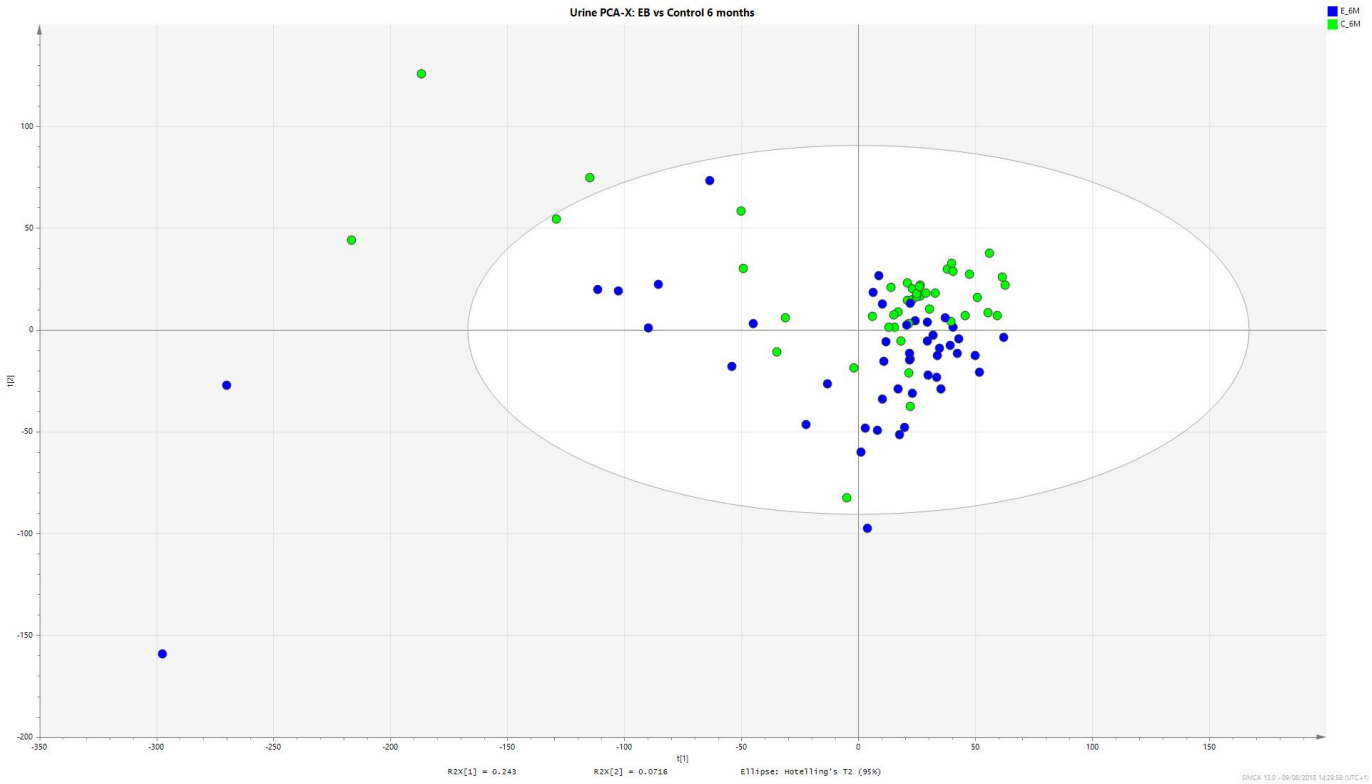
No significant metabolic differences between control and EB at baseline were observed but as observed in plasma analysis, significant differences were seen between control and EB groups at 6 and 12 months (Figures 1.33 D&E) in the urinary spectra. In the EB arm, there were significant changes in urine metabolic profiles of patients at 6- or 12-month EB implantation (Figures 1.33 G&I) in comparison to the baseline profiles. Again, no significant difference was observed between 6 and 12 months in the EB group. In the control arm, there were no significant OPLS-DA model based on samples from baseline and 12 months.

Figure 1. 33 A), B) and C) represent scores plots from the PCA of the results obtained from urine analysis of all participants at all time points and at 6 and 12 months comparisons respectively. D) and E) represent cross validated scores plots from supervised OPLS-DA analysis of urine from both treatment groups at 6 months and 12 months. F) and G) are PCA plots comparing EB group at 6 months and 12 months from baseline and H) and I) are the accompanying OPLS-DA analysis of the same sample set.

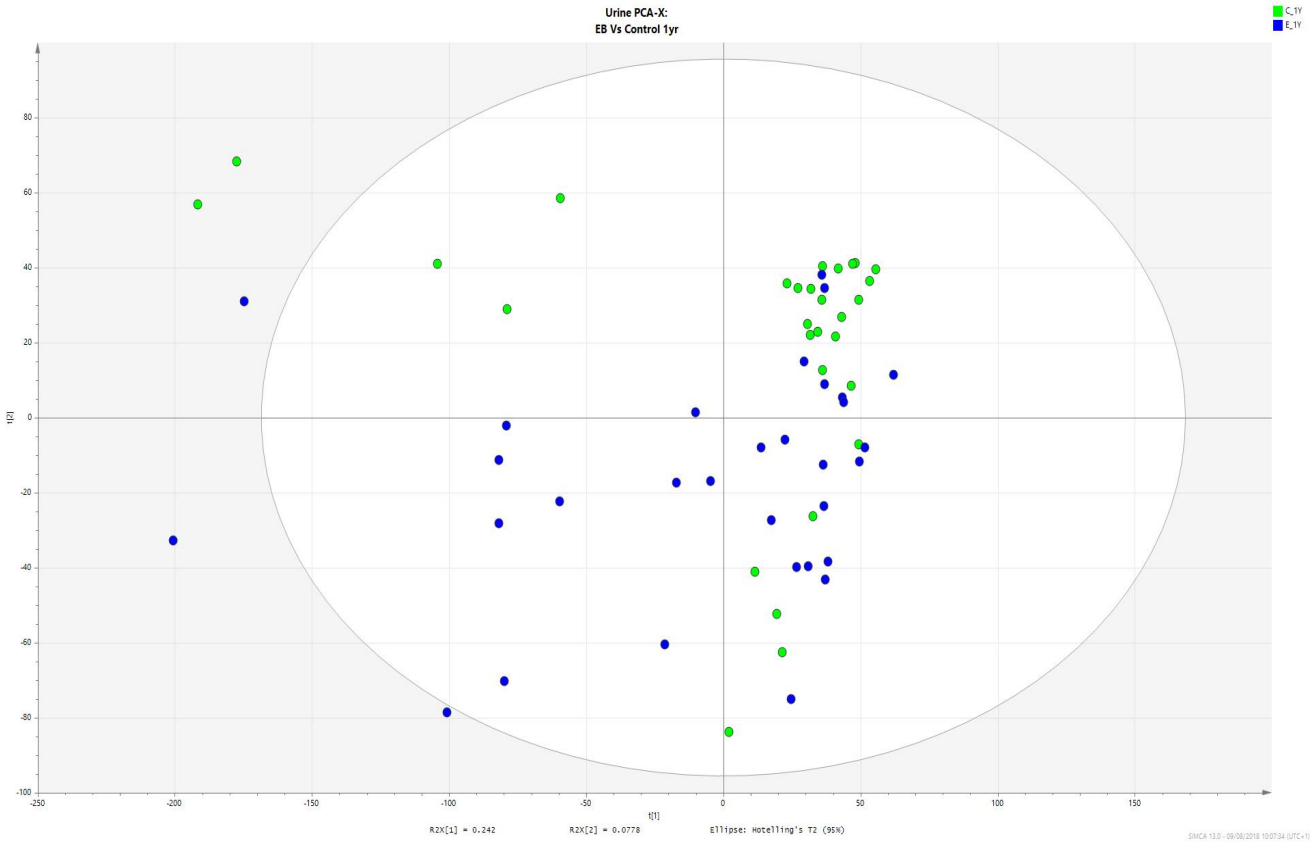
A) Urine PCA-X: All Participants at All Time Points



B) Urine PCA-X: EB vs Control 6 months

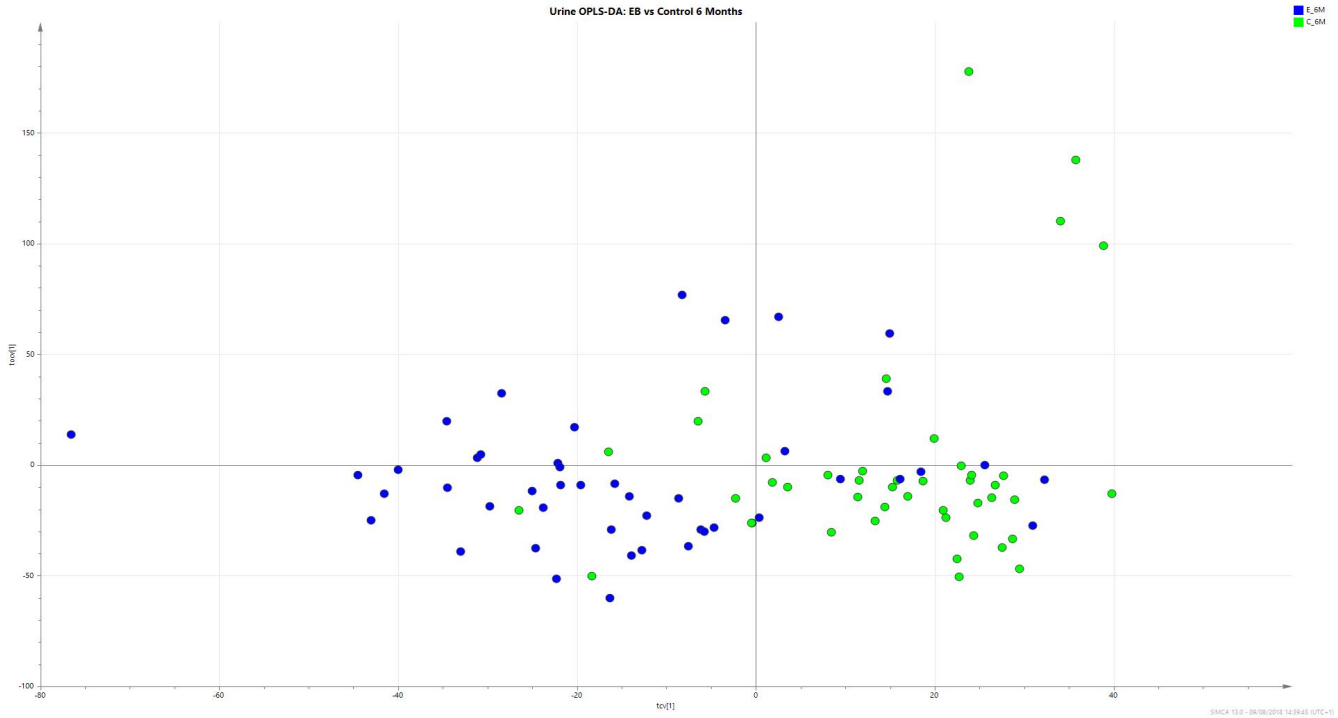


C) Urine PCA-X: EB vs Control 1 Year



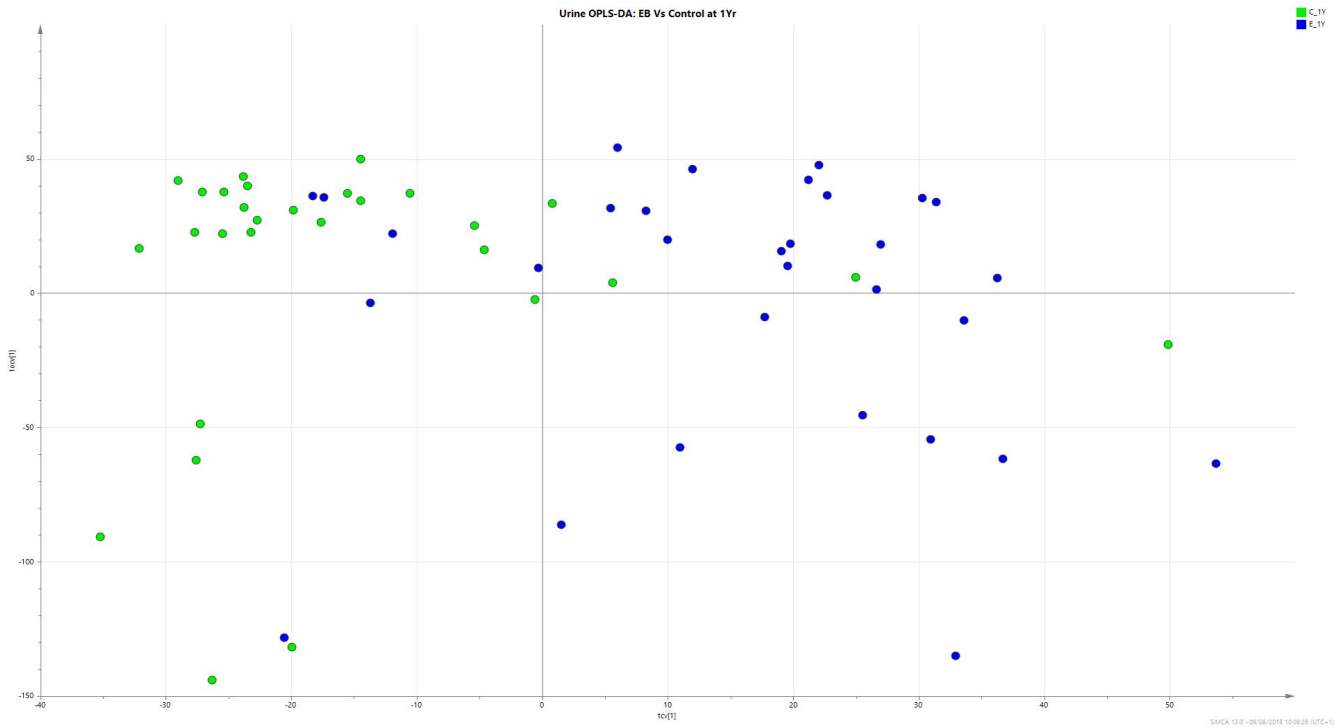
Legend Control Endobarrier

D) Urine OPLS-DA: EB vs Control 6 months



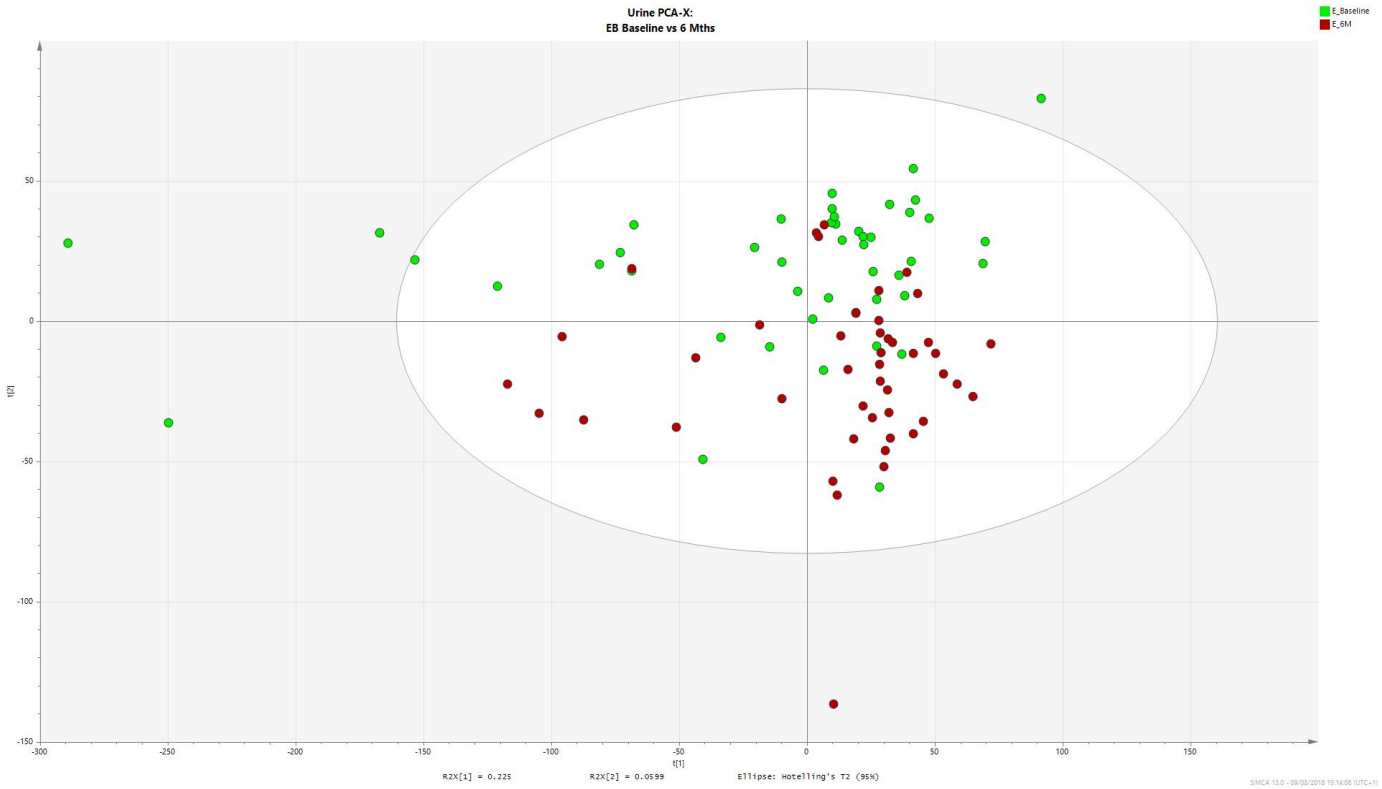
Legend Control Endobarrier

E) Urine OPLS-DA: EB vs Control 1 Year



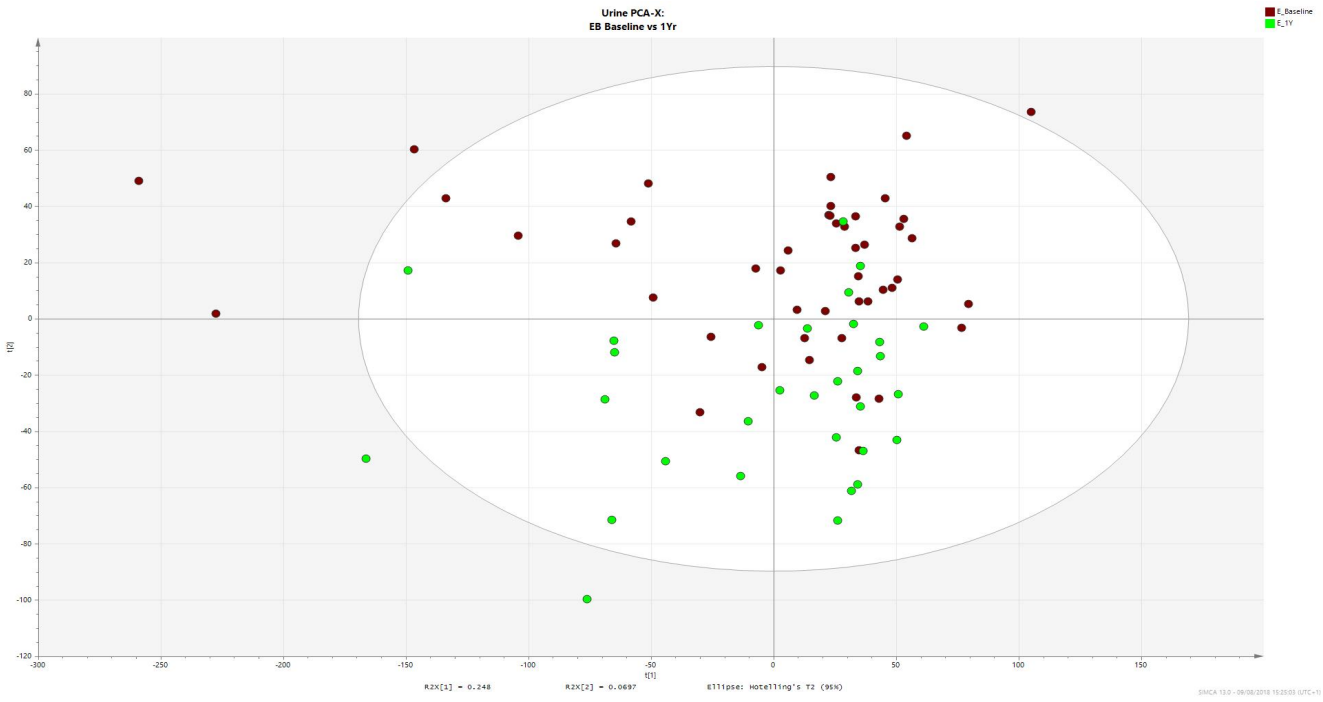
Legend Control Endobarrier

F) Urine PCA-X: EB Baseline vs 6 months



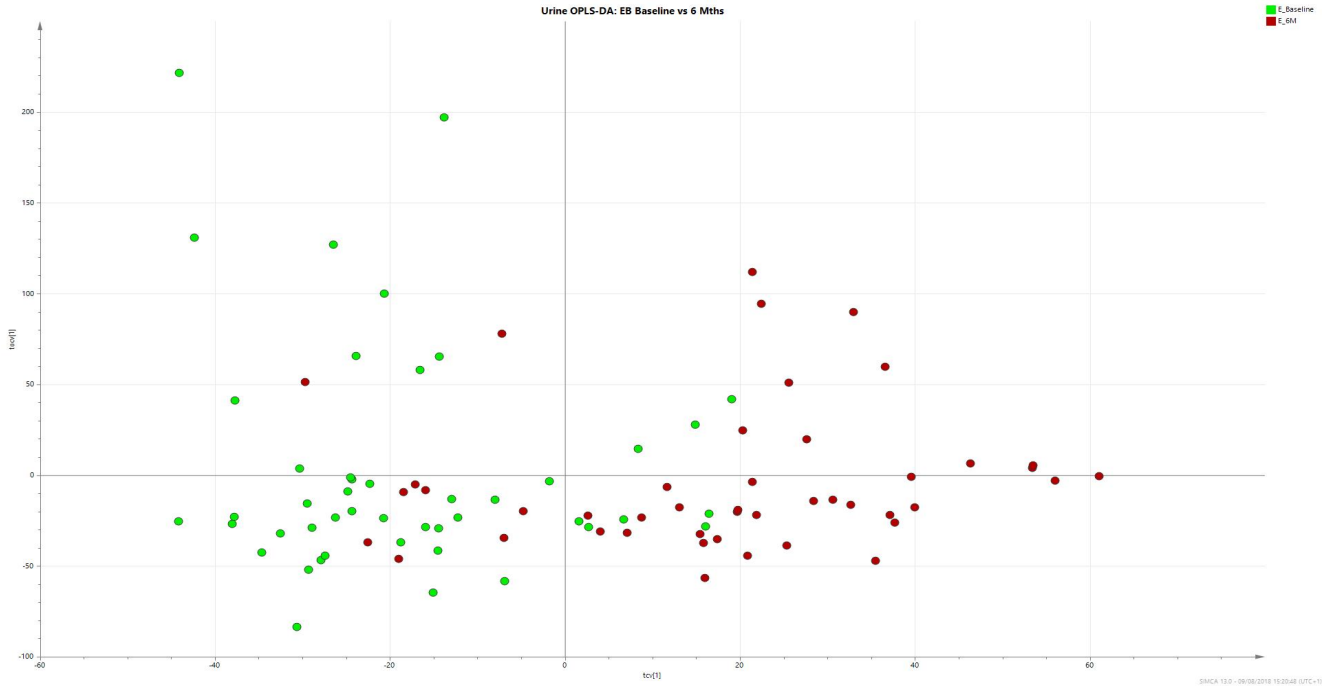
Legend EB Baseline EB 6 Months

G) Urine PCA-X: EB Baseline vs 1 Year



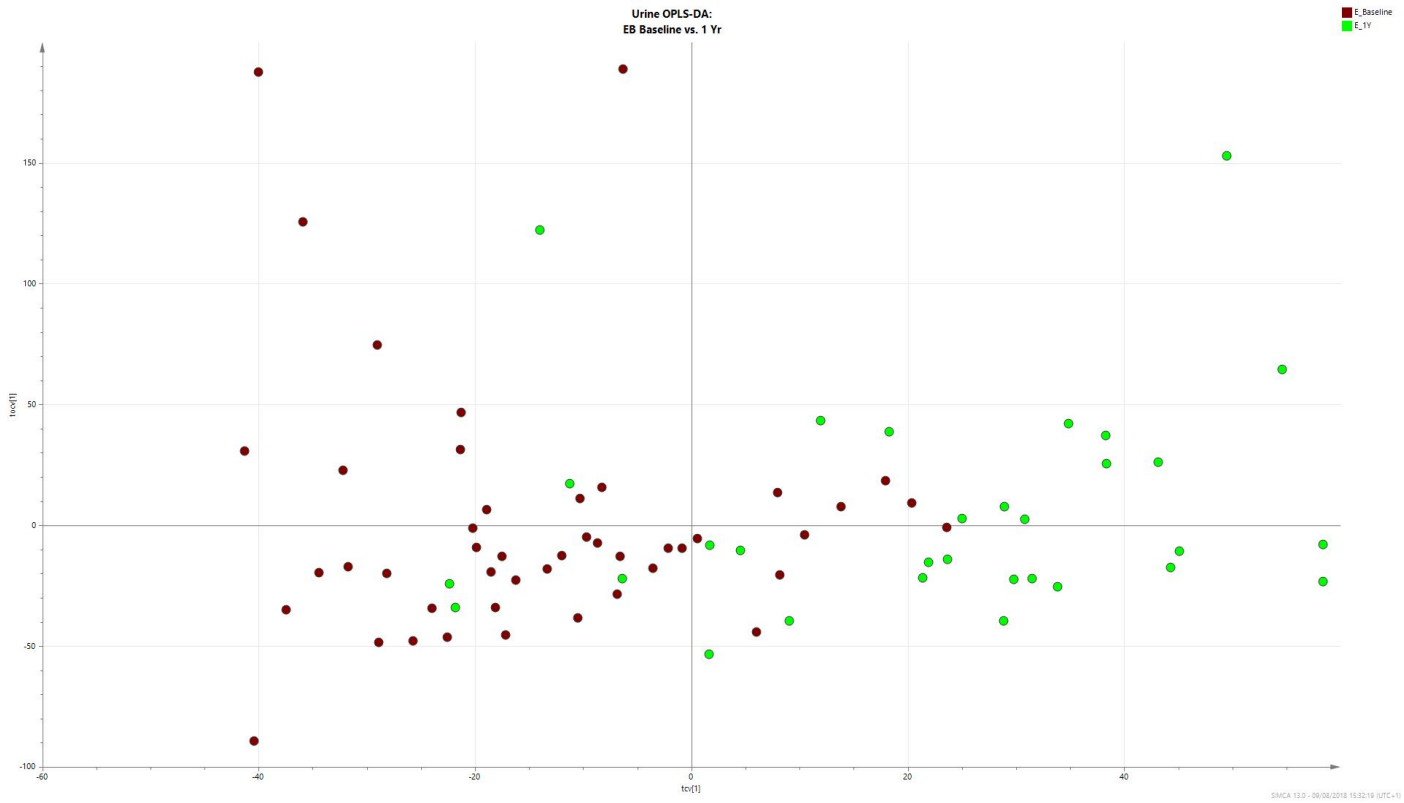
Legend EB 1 Year EB Baseline

H) Urine OPLS-DA: EB Baseline vs 6 Months



Legend EB Baseline EB 6 Months

I) Urine OPLS-DA: EB Baseline vs 1 year



Legend EB 1 Year EB Baseline

Table 1. 22 Summary of the parameters derived from the OPLS-DA models of 1D ^{1}H NMR urinary spectral data.

	Baseline vs. 6 months	**Baseline vs. 12 months**	**6 months vs. 12months**
Control	R^2X= 0.51 Q^2Y=-0.20 p=0.80	R^2X= 0.58 Q^2Y=0.02 p=1	R^2X= 0.56 Q^2Y=-0.50 p=1
EB	R^2X= 0.36 Q^2Y= 0.40 p= 9.65×10^{-10}	R^2X= 0.39 Q^2Y= 0.45 p= 2.8×10^{-9}	R^2X= 0.49 Q^2Y=-0.30 p=1
Control vs EB	**Baseline**	**6 months**	**12 months**
	R^2X= 0.33 Q^2Y=-1.12 p=1	R^2X= 0.45 Q^2Y=0.38 p= 1.54×10^{-8}	R^2X= 0.57 Q^2Y=0.29 p= 3.95×10^{-4}

Key metabolic differences between the EB group and the control at 6 and 12 months include an increase in both phenylacetylglutamine (PAG) and 3-indoxylsulfate (IS) as well as an unknown compound at a chemical shift of 1.99 ppm (Figure 1.34). Another unknown compound (6.87(d) and 7.17(d) ppm) was also found to be increased in the EB group and this was putatively assigned as tyrosine. The urinary metabolite creatinine was found to be less in the EB group than control at 6 months and 1 year (Figure 1.35). A similar picture was seen when comparing the EB patient cohort at baseline and at 6 months which showed a reduction in creatinine. At 12 months, PAG, IS, tyrosine and 4-cresyl sulfate were significantly different from baseline in EB patients but no significant differences in creatinine levels were observed.

Figure 1. 34 OPLSDA coefficients plot of EB (upwards) vs Control (downwards) showing increased PAG and IS in the urine of EB patients at 6 months

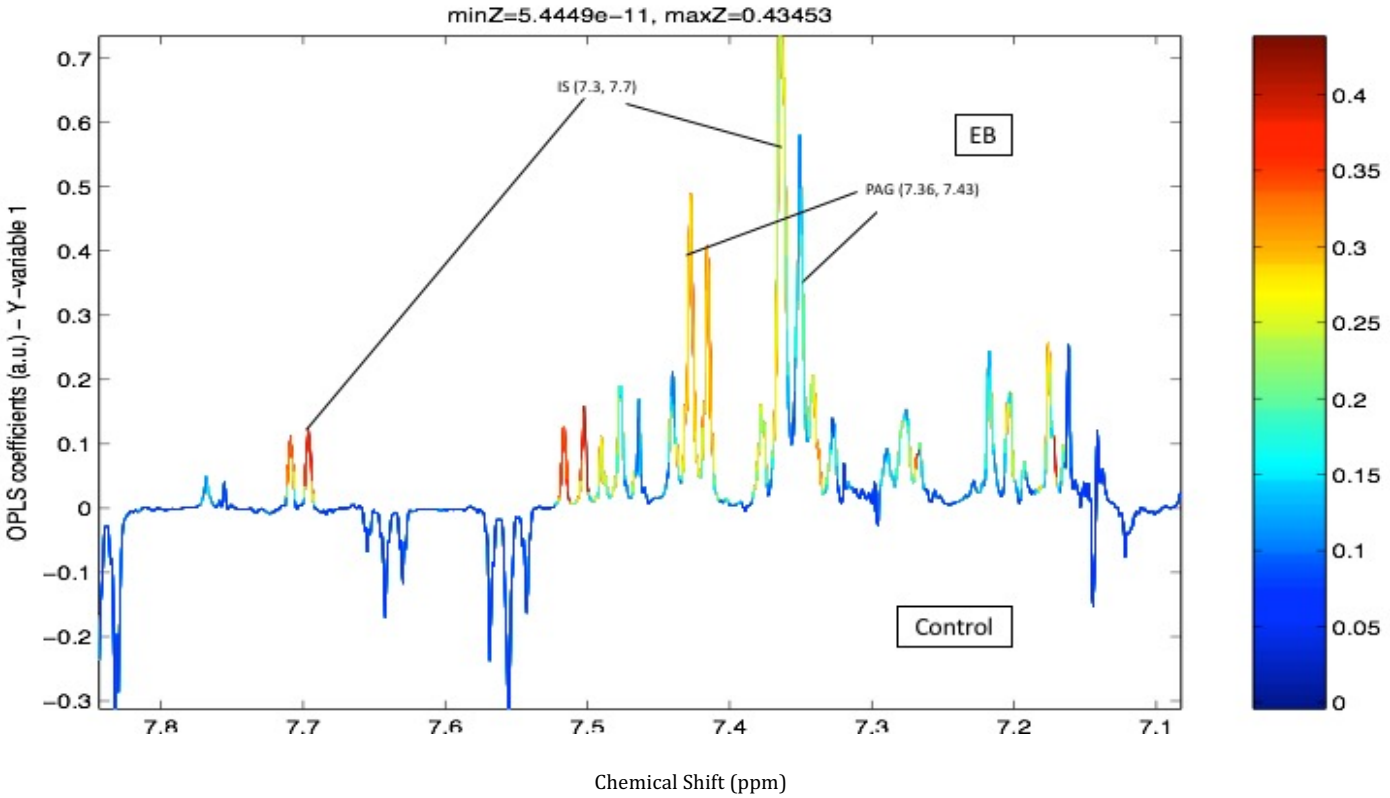
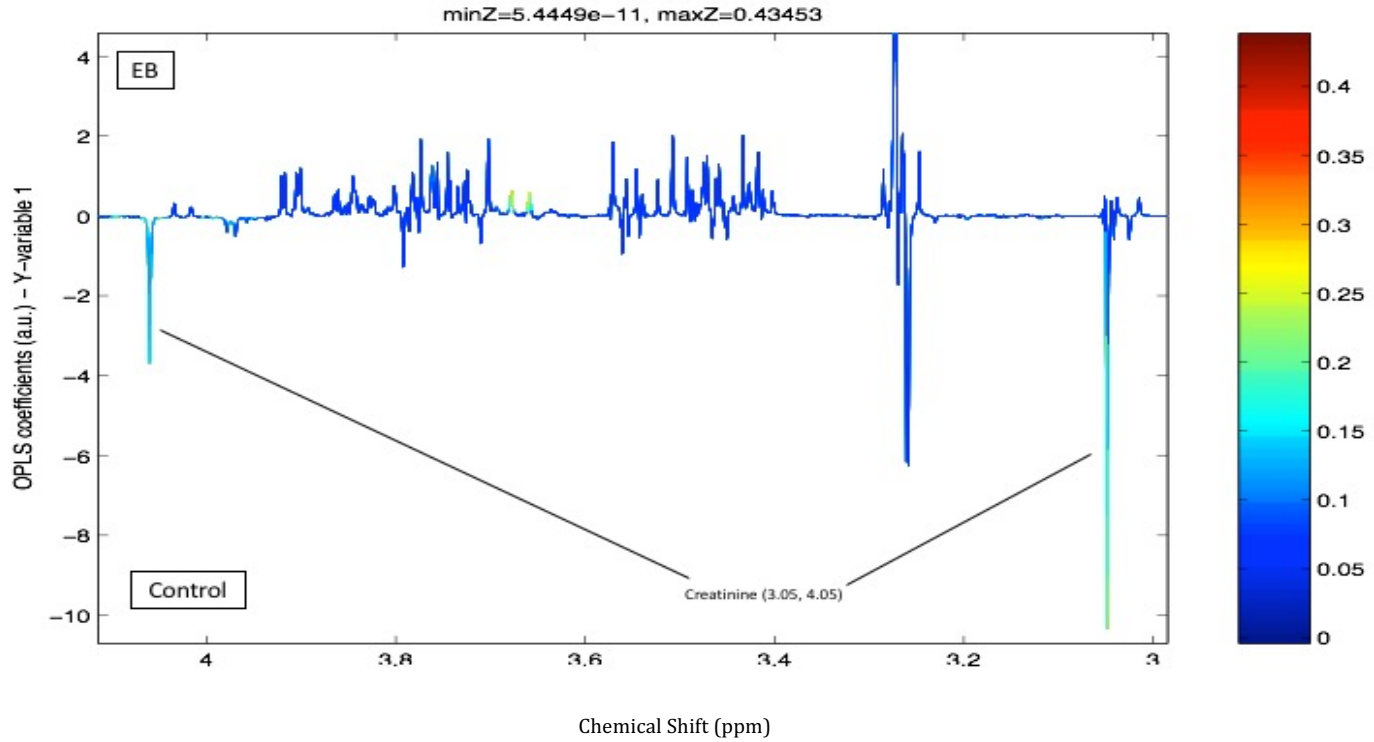


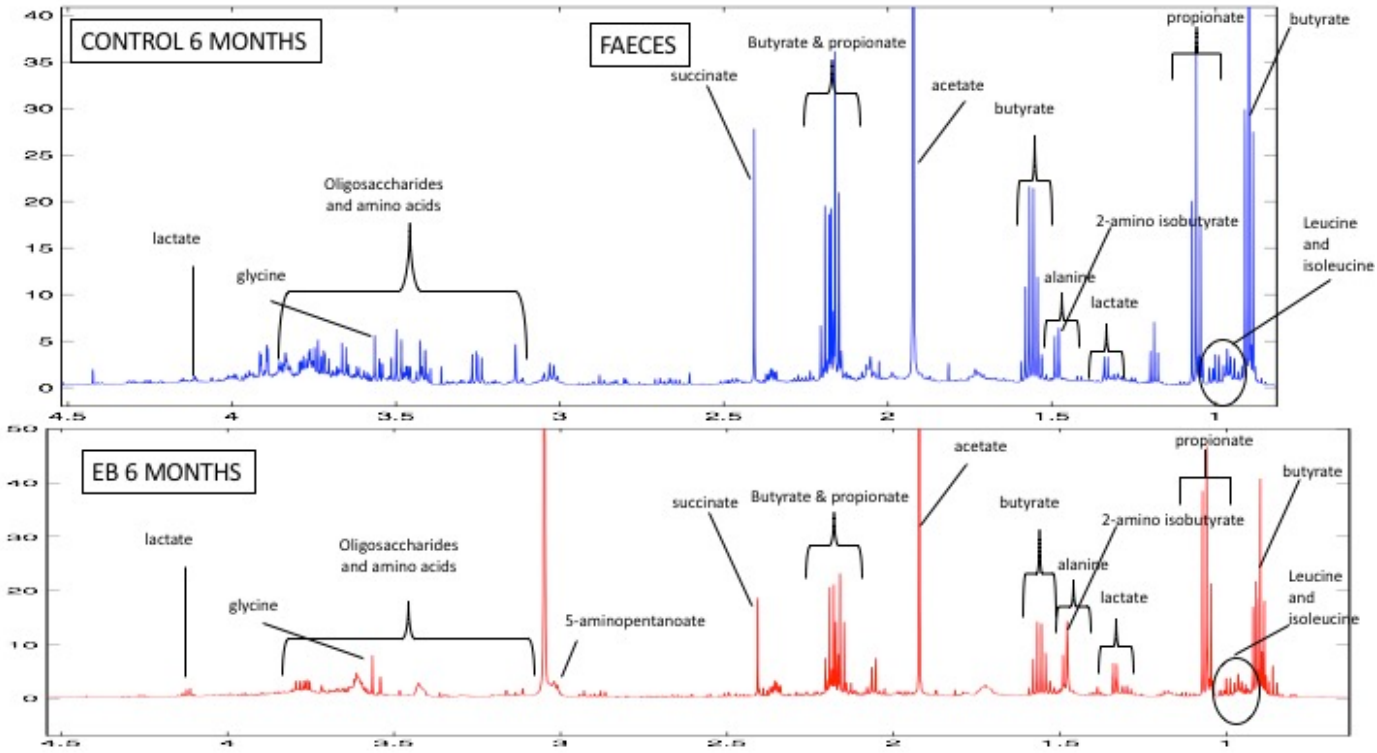
Figure 1. 35 OPLSDA coefficients plot of EB (upwards) vs Control (downwards) showing decreased levels of creatinine in the urine of EB patients at 6 months

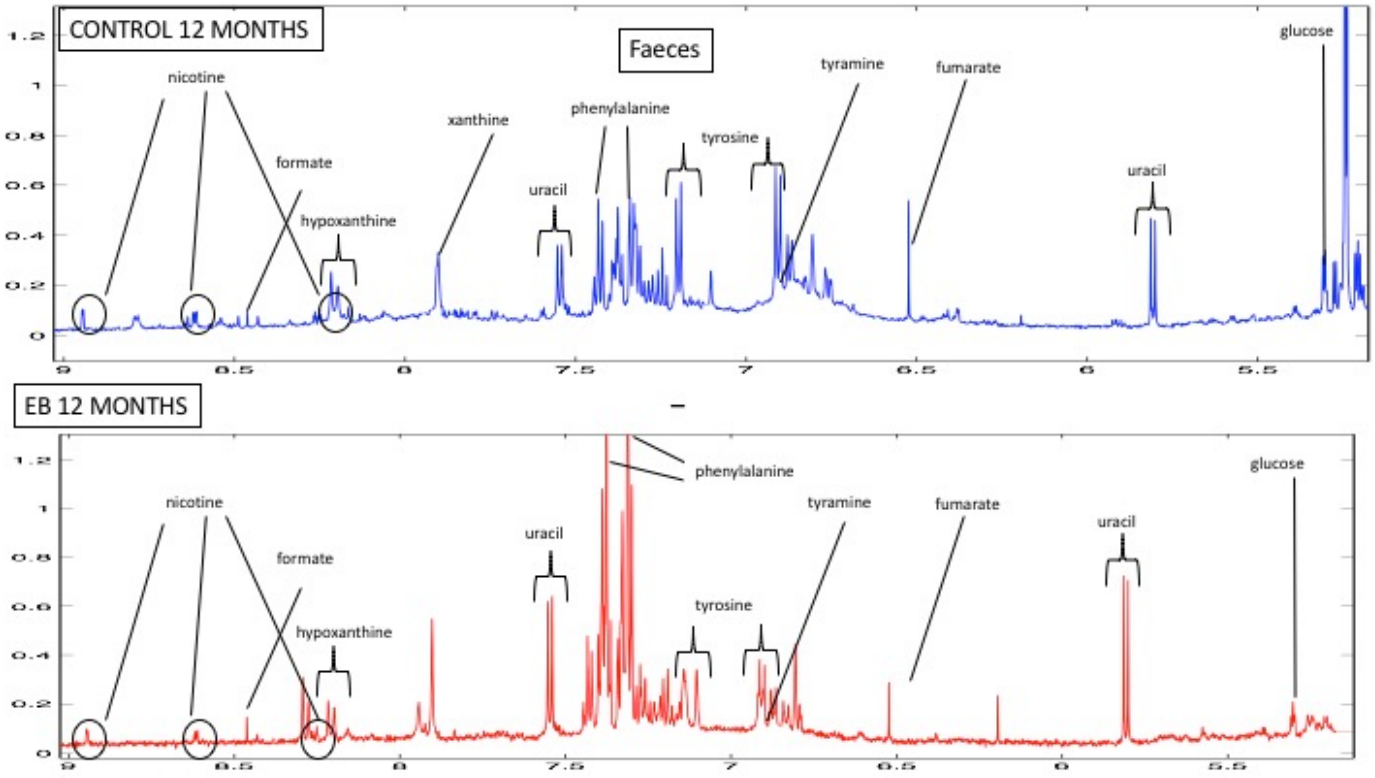


4.3 Faeces

Representative ^{1}H NMR spectra obtained from faeces metabolite profiling of both treatment groups at 6 months are shown in figure 1.36. Metabolites including lactate, alanine, glycine, leucine, isoleucine, butyrate and propionate were observed.

Figure 1. 36 Typical 600 MHz ^{1}H NMR Spectra of Faeces for Control and EB groups at 6 months



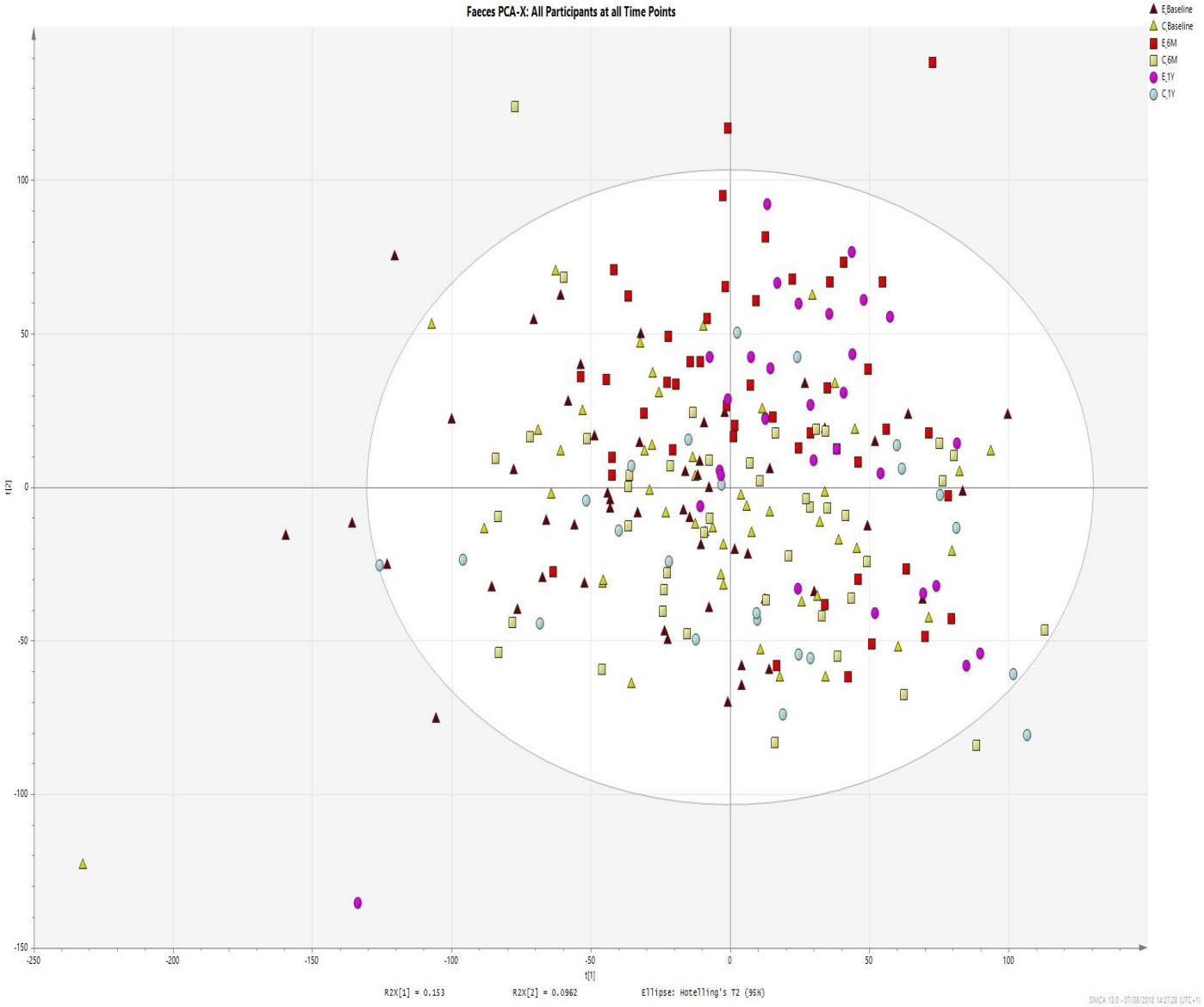


Analysis of faecal samples using PCA and OPLS-DA methods was performed. Similarly to plasma and urine analysis, PCA scores plots derived from the faecal spectra identified clear separation between the EB patients and the controls at the 6 and 12 months along the second principal component (Figures 1.37 B&C). There was also separation between the baseline and 6 or 12 month time points in the EB cohort along the first principal component (Figures 1.37 F&H). Statistically significant models are highlighted in Table 1.23.

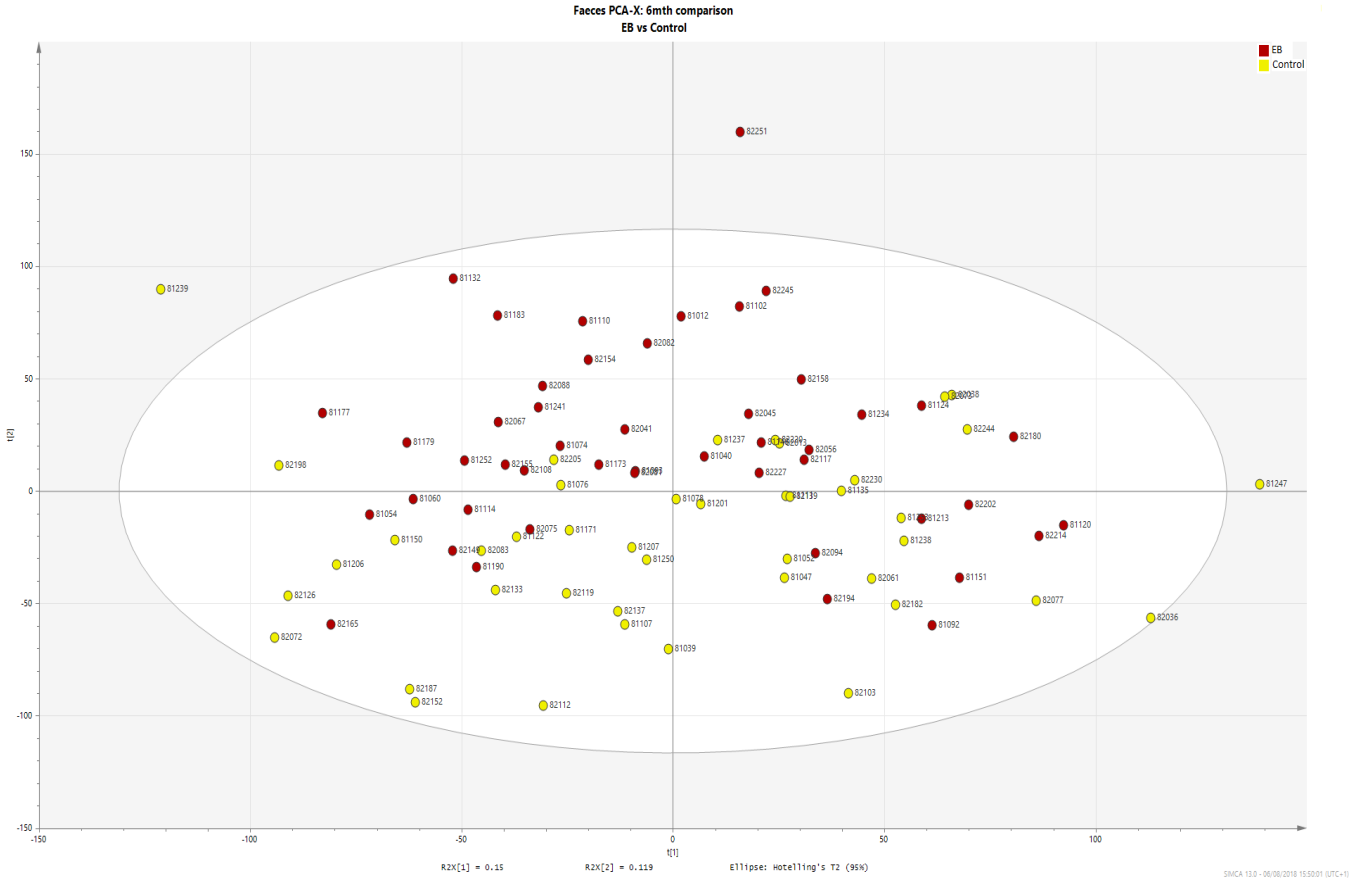
No significant metabolic differences between control and EB at baseline were observed but significant differences were seen between control and EB groups at 6 and 12 months on OPLS-DA (Figures 1.37 D&E). In the EB arm, there were significant changes in faeces metabolic profiles of patients at 6- or 12-month post EB implantation (Figures 1.37 G&I) in comparison to the baseline profiles. No significant differences were observed between 6 and 12 months in the EB group. In the control arm, there were no significant OPLS-DA model based on samples from baseline and 12 months.

Figure 1. 37 A), B) and C) represent scores plots from the PCA of the results obtained from faeces analysis of all participants at all time points and at 6 and 12 months comparisons respectively. D) and E) represent cross validated scores plots from supervised OPLS-DA analysis of faeces from both treatment groups at 6 months and 12 months. F) and G) are PCA plots comparing EB group at 6 months and 12 months from baseline and H) and I) are the accompanying OPLS-DA analysis of the same sample set.

A) Faeces PCA-X: All Participants at All Time Points

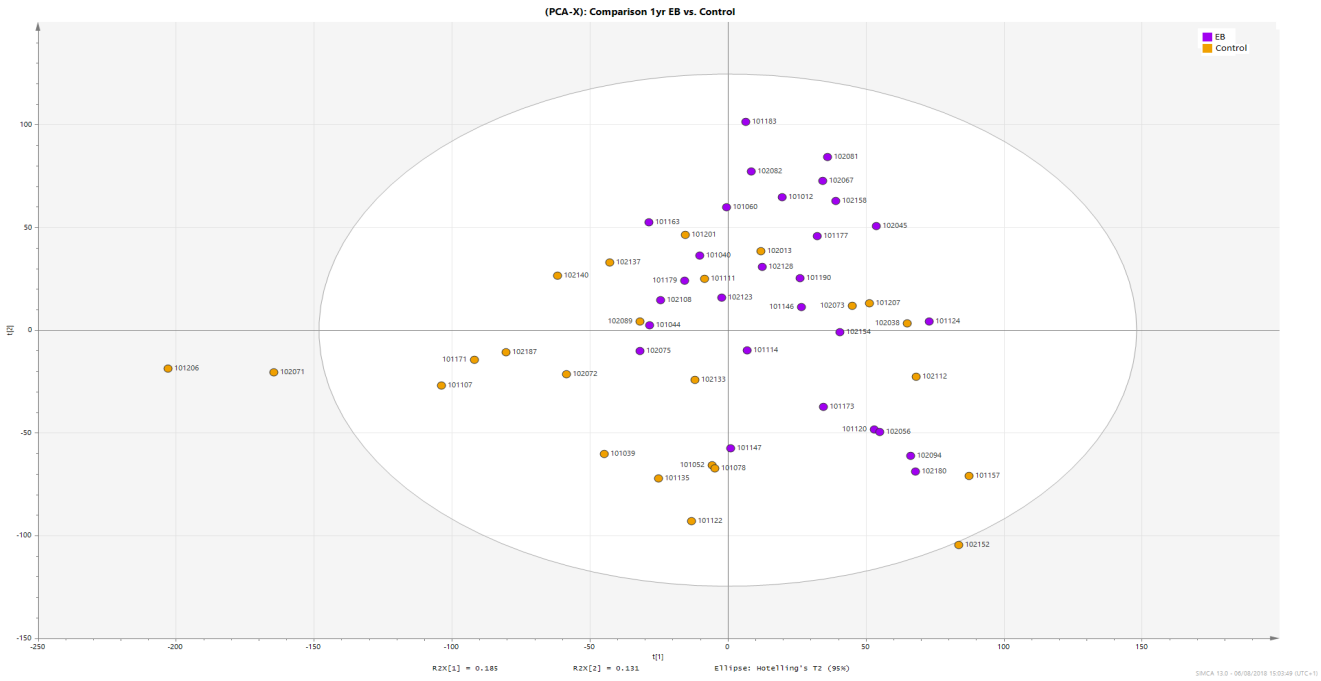


B) Faeces PCA-X: EB vs Control 6 months



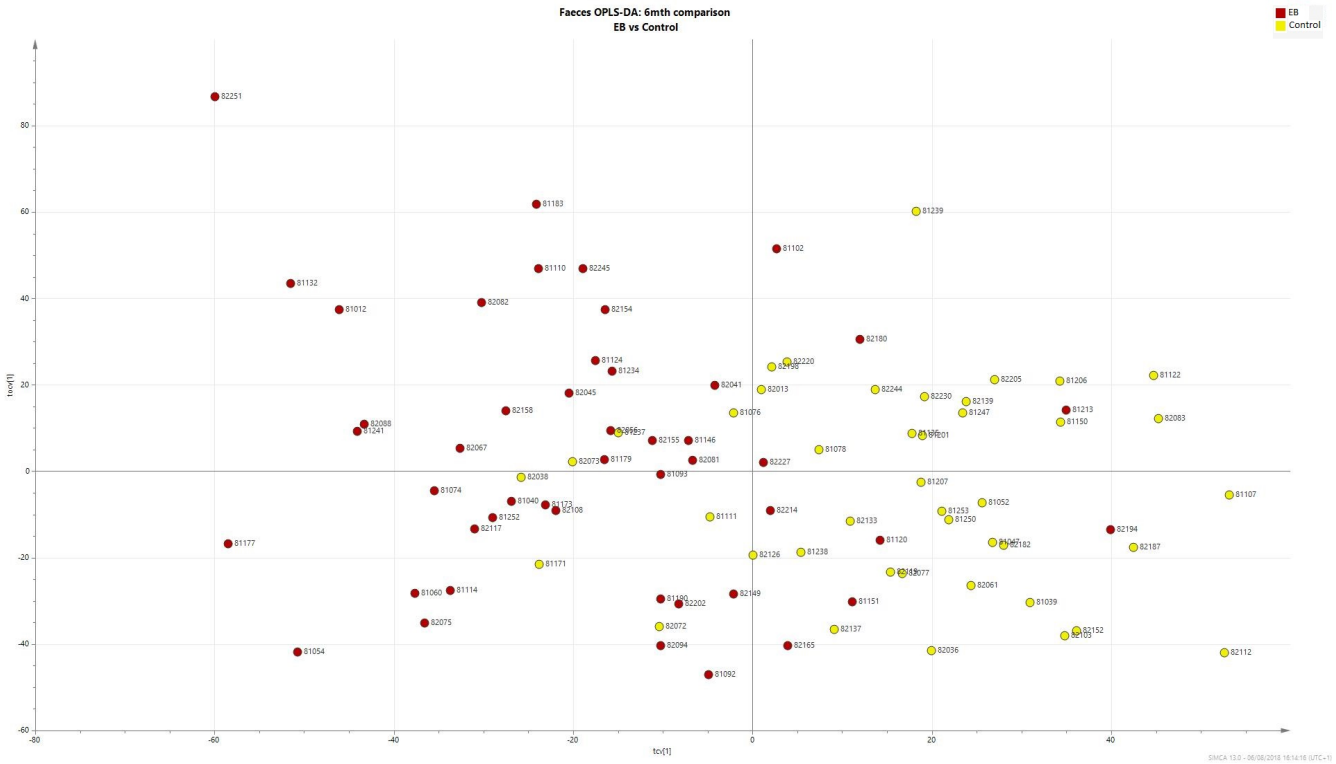
Legend Control Endobarrier

C) Faeces PCA-X: EB vs Control 1 Year



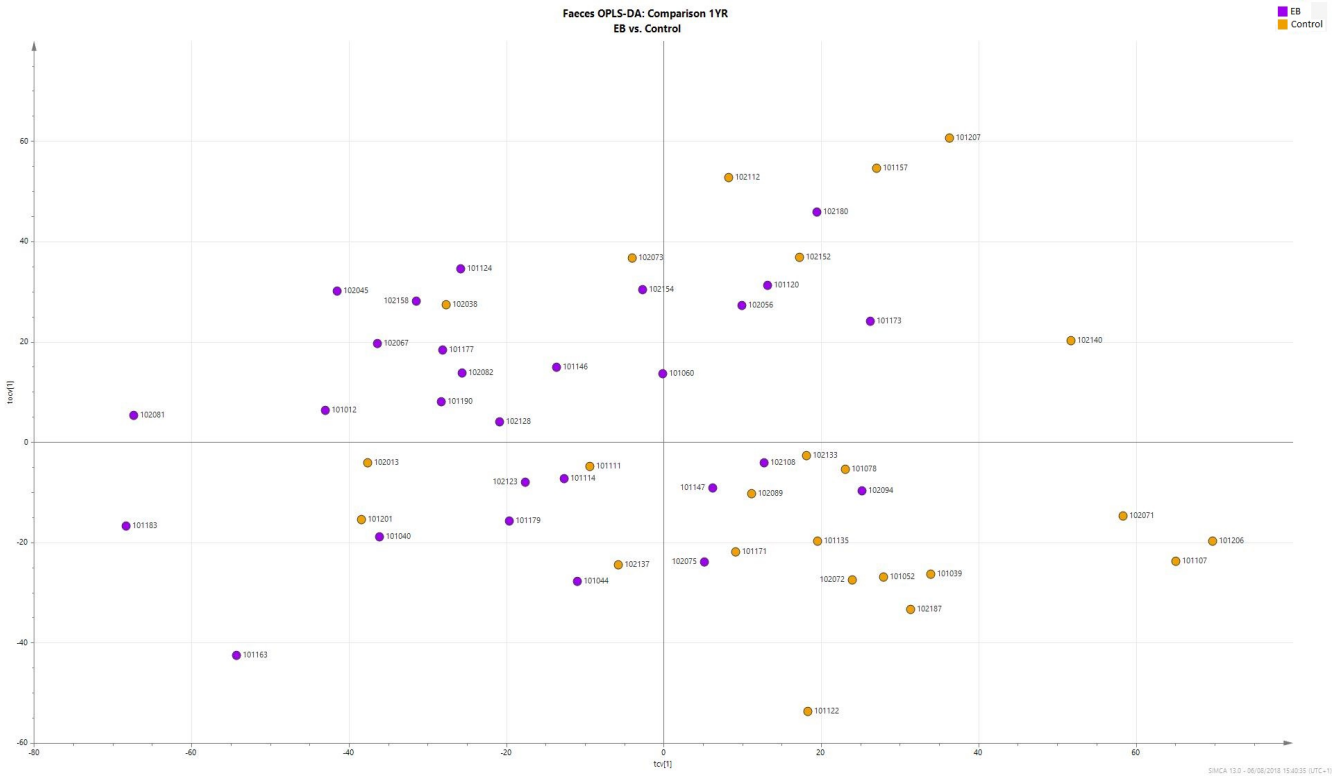
Legend Control Endobarrier

D) Faeces OPLS-DA: EB vs Control 6 months



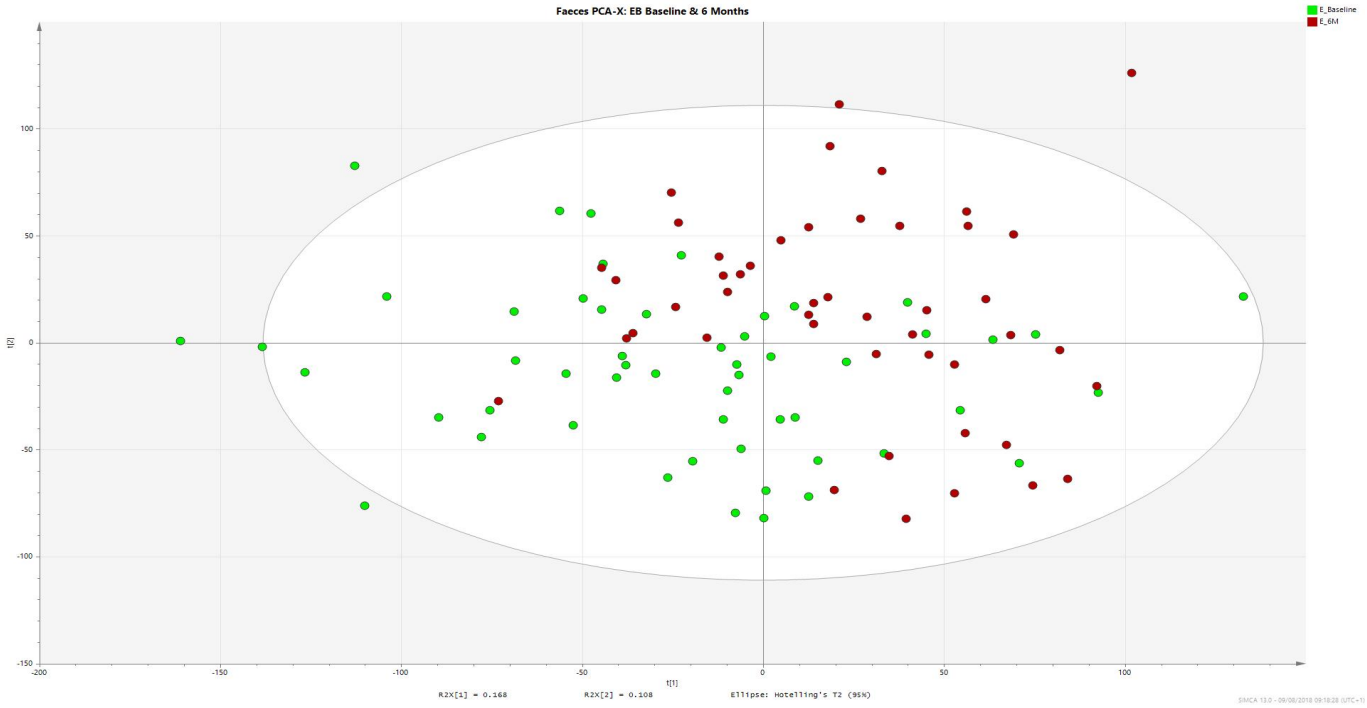
Legend Control Endobarrier

E) Faeces OPLS-DA: EB vs Control 1 Year



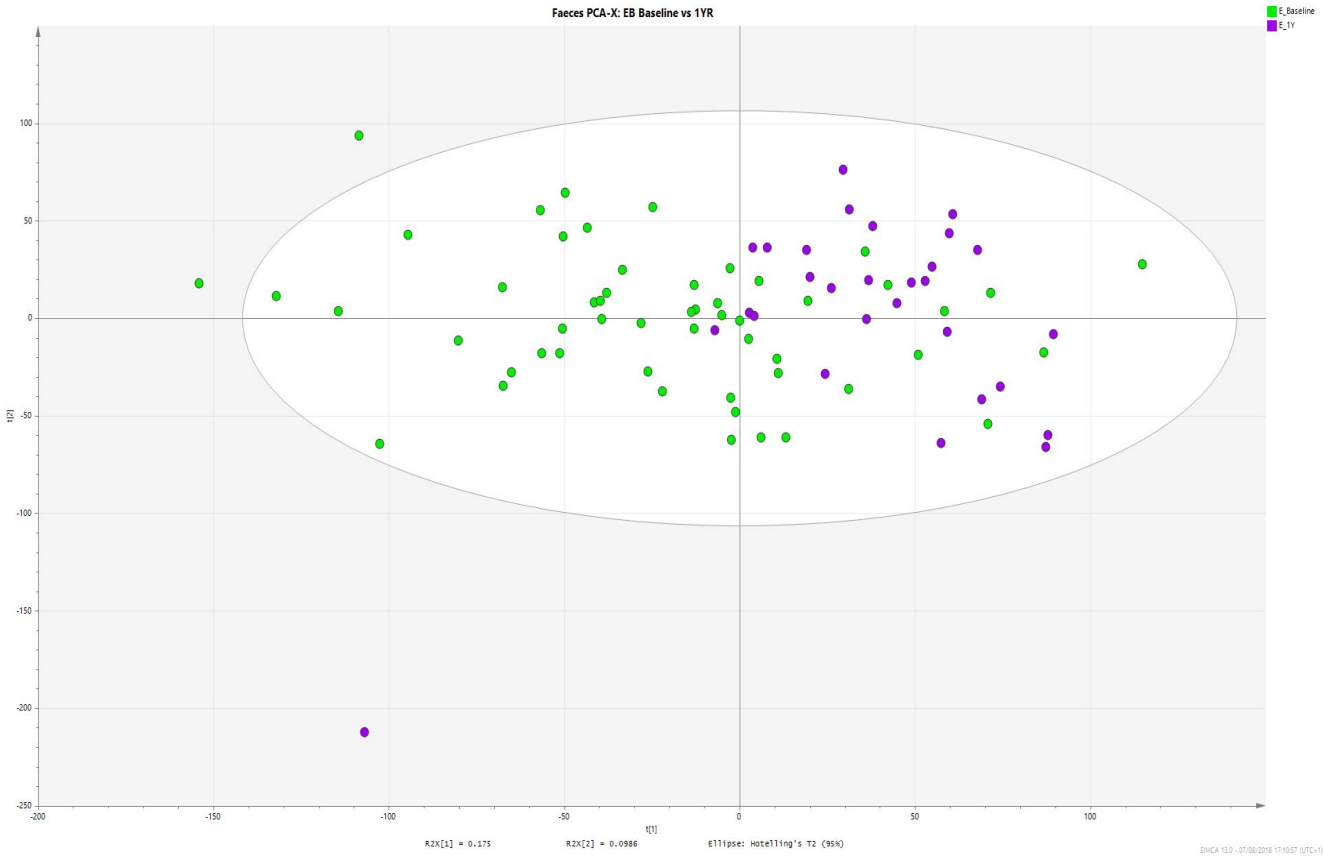
Legend Control Endobarrier

F) Faeces PCA-X: EB Baseline vs 6 months



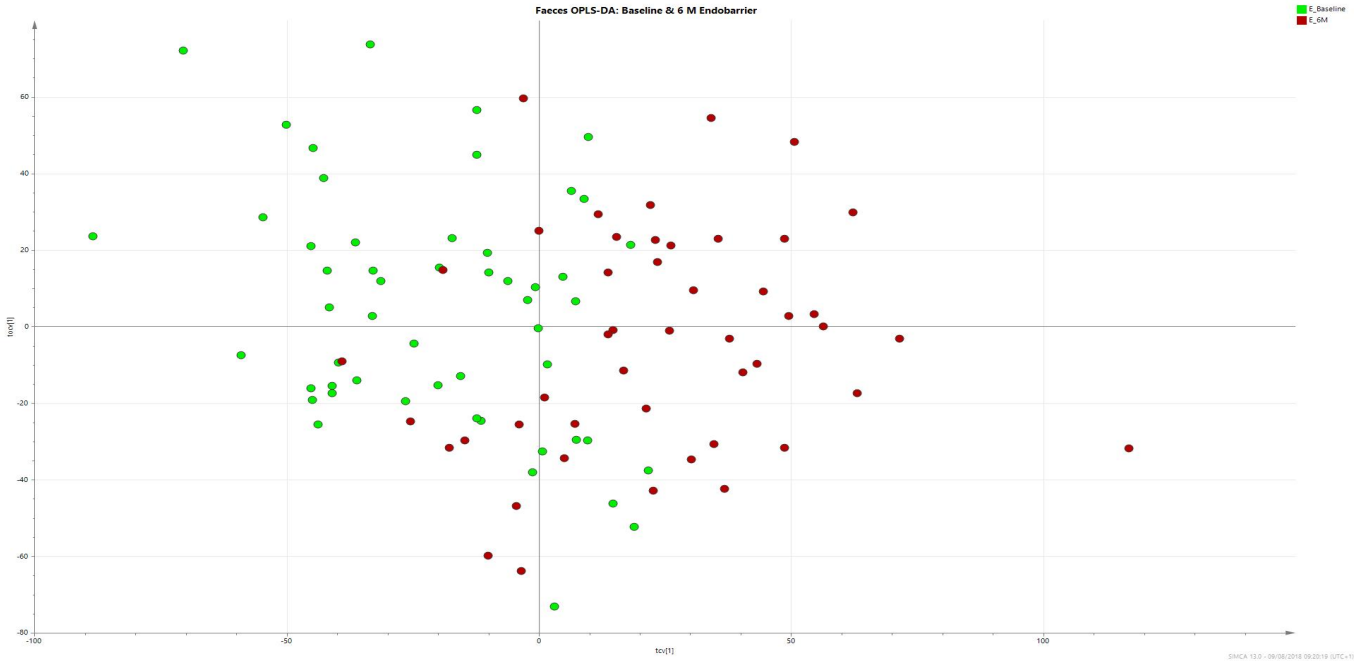
Legend EB Baseline EB 6 months

G) Faeces PCA-X: EB Baseline vs 1 Year



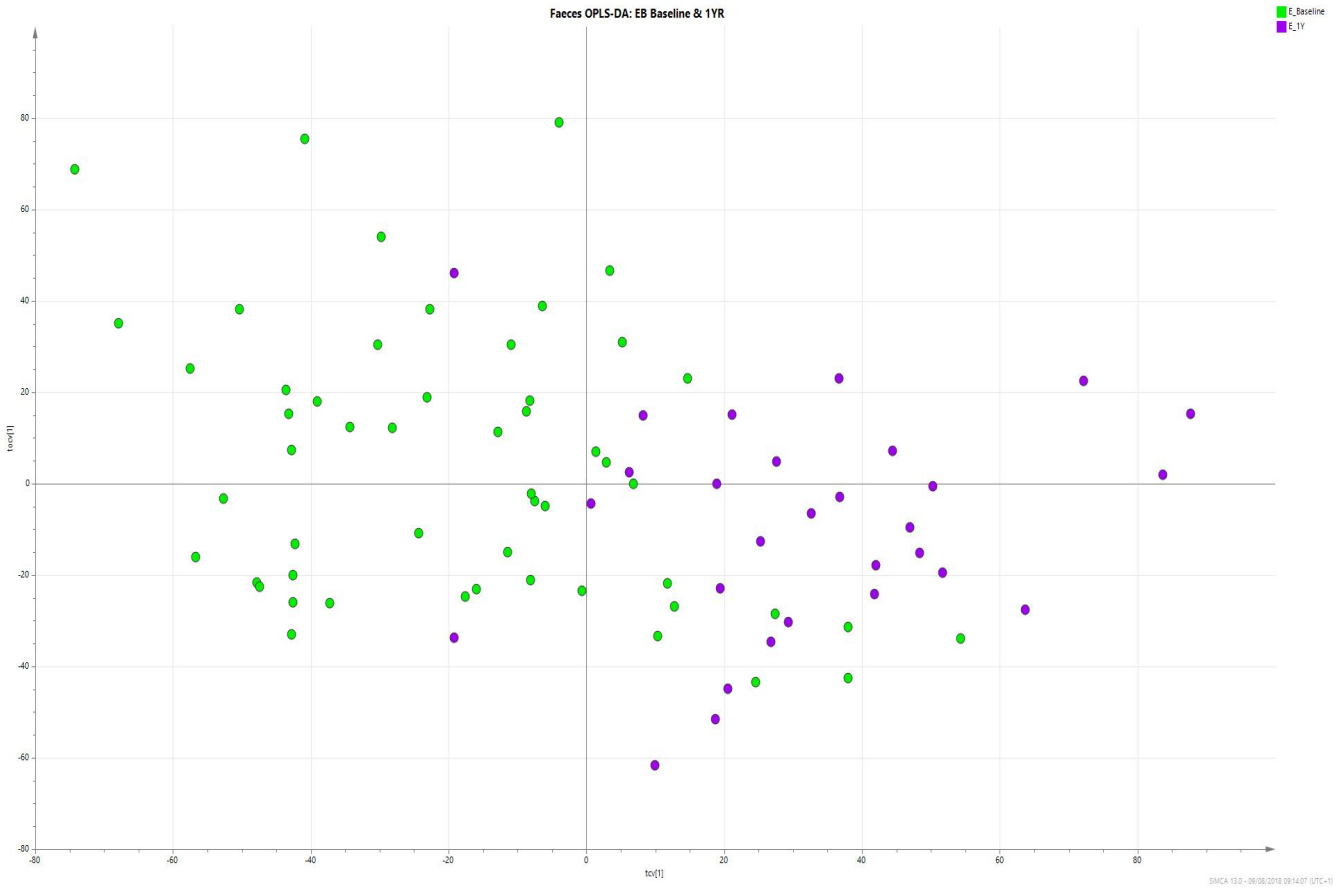
Legend EB Baseline EB 1 Year

H) Faeces OPLS-DA: EB Baseline vs 6 months



Legend EB Baseline EB 6 months

I) Faeces OPLS-DA: EB Baseline vs 1 Year



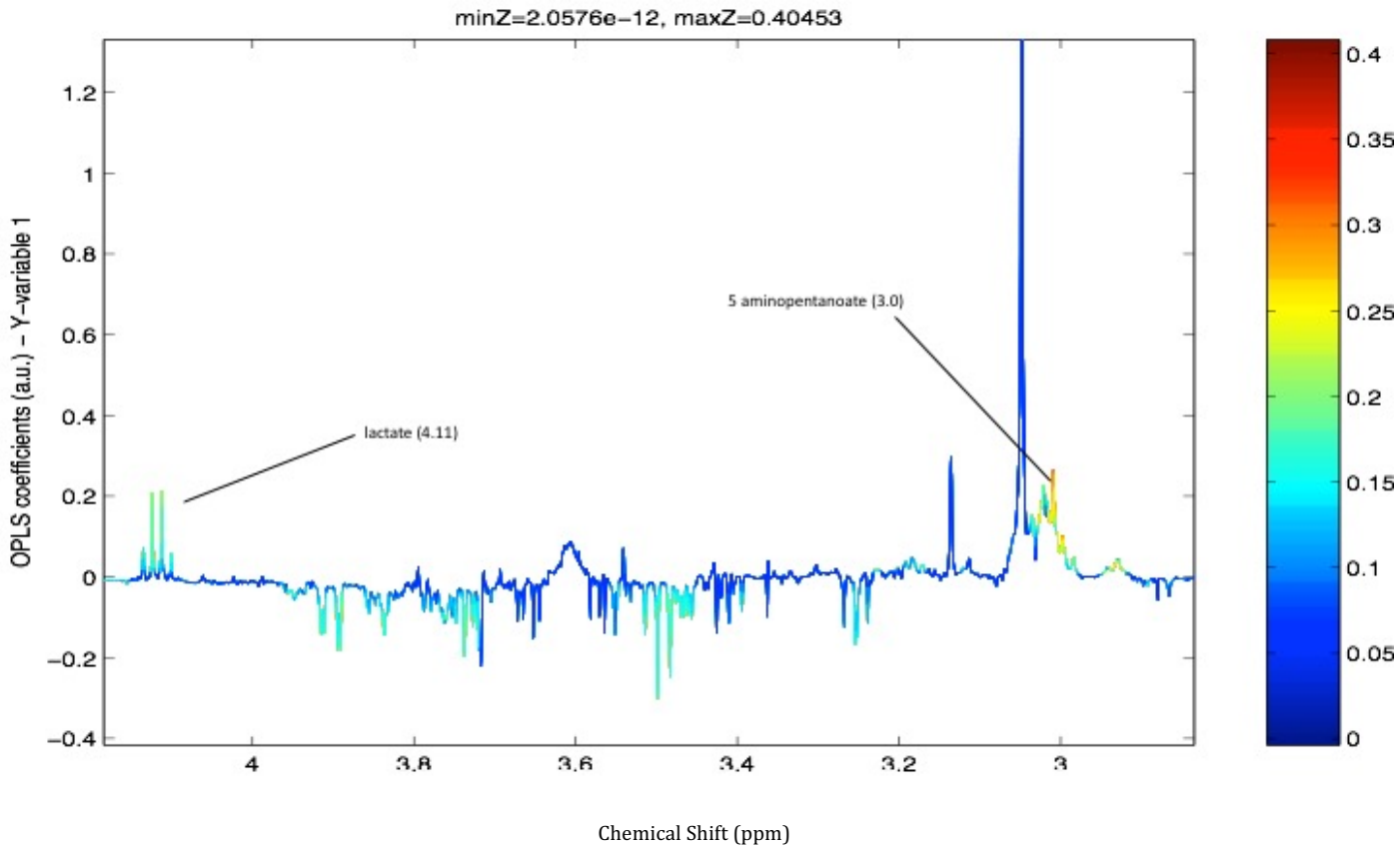
Legend EB Baseline EB 1 Year

Table 1. 23 Summary of the parameters derived from the OPLS-DA models of the standard 1D ^{1}H NMR faeces spectral data.

	Baseline vs. 6 months	**Baseline vs. 12 months**	**6 months vs. 12months**
Control	R^2X= 0.172 Q^2Y=-0.46 p=1	R^2X= 0.223 Q^2Y=-0.292 p=1	R^2X= 0.21 Q^2Y=-0.398 p=1
EB	R^2X= 0.234 Q^2Y=0.386 p=1.63 x 10^{-9}	R^2X= 0.236 Q^2Y=0.421 p=1.24 x 10^{-8}	R^2X= 0.197 Q^2Y=-0.332 p=1
Control vs EB	**Baseline**	**6 months**	**12 months**
	R^2X= 0.195 Q^2Y=-0.526 p=1	R^2X= 0.165 Q^2Y=0.422 p=1.42 x 10^{-9}	R^2X= 0.262 Q^2Y=0.272 p=0.0042

Stool analysis at 6 months showed increased levels of the metabolites; lactate, 5-aminopentanoate and tyramine in the EB group compared with control at 6 months (figure 1.38)**.** Two other unidentified metabolites were also found to be increased; at 0.84ppm and 1.12 chemical shifts. Glucose levels were decreased in the EB group compared with control at 6 months. At 12 months in addition to an increase in the metabolites lactate and tyramine seen at 6 months in the EB group, there was an also an increase in 2-aminoisobutyrate. At 12 months there was also a decrease in tyrosine, malate, fumarate, glucose and oligosaccharides in the EB group vs. control. Analysis of the EB cohort of patients at 6 months and 12 months showed increased levels of lactate and tyramine in the stool compared with baseline, but a decrease in glucose. Another metabolite trigonelline was found to lower in EB patients at 6 and 12 months respectively.

Figure 1. 38 OPLSDA coefficients plot of EB (upwards) vs Control (downwards) showing increased levels of lactate and 5-aminopentanoate in the stool of EB patients at 6 months



4.4 Discussion

This is the first study of its kind to explore the metabolic profiles of patients receiving the EB. In addition to this, the data has been collected longitudinally in a randomised setting allowing comparisons to be made over time with a control group of patients. ^{1}H NMR spectroscopic analysis of plasma, urine and faeces has revealed a number of distinct metabolic perturbations between the control and EB arms occurring at 6 months and 1 year compared with baseline. OPLS-DA has also been used to robustly discriminate between both treatment arms. Similarly, variation in the metabolic profiles of patients in the EB group over time is seen when compared with baseline samples and this change was not observed in the control group where the metabolic profiles observed did not alter

significantly over time, apart from the comparison between the baseline and 12 months in plasma samples.

Furthermore, significant metabolic differences were observed between baseline and 6 or 12 months in the EB arm but not between 6 months and 1 year, which suggest that the key metabolic changes primarily occur in the first 6 months of having the device *in situ*. This appears to correlate well with device efficacy as it is usually in the first 3-6 months that the greatest weight loss occurs.

4.4.1 Plasma Metabolite Changes

Plasma levels of trimethylamine *N*-oxide (TMAO) were found to be reduced in the EB group at 6 months when compared with the control group. TMAO is formed in the liver from trimethylamine, and is exclusively generated by gut microbiota from the metabolism of dietary carnitine and choline .[320] TMAO is believed to be responsible for promoting the formation of atherosclerosis by enhancing the accumulation of cholesterol in foam cells. Elevated plasma levels of TMAO have been implicated in the pathogenesis of cardiovascular disease and heart failure.[321, 322] In a small study of 34 obese individuals (17 who had T2DM) undergoing bariatric surgery, TMAO levels were found to increase two fold one year post bariatric surgery when measured in the plasma using high-performance liquid chromatography.[323] TMAO was not found to be elevated in the 17 obese individuals in the control group, and in fact levels reduced following lifestyle interventions. Plasma TMAO levels were also found to be elevated in rats post RYGB surgery compared with those undergoing a sham procedure.[324] The major increases seen in TMAO levels in these studies post bariatric surgery is unexpected as bariatric surgery is known to reduce cardiovascular disease risk.[325] One hypothesis for the increased levels of TMAO observed is that the shortening of small bowel that occurs post RYGB may lead to less anaerobic metabolism by the gut microbiota. Outcomes of both these studies from the bariatric literature conflict with the results from this trial which found

that plasma TMAO levels reduce in response to the EB. If the EB is meant to mimic the effects of bariatric surgery, one would have expected it to have similar effects on TMAO; causing levels to increase. However RYGB and the EB are not identical procedures and plasma TMAO levels have been shown to vary depending on the type of bariatric surgery being performed with one human metabolomics study detecting no differences in plasma TMAO levels between sleeve gastrectomy patients and controls.[284] Unlike RYGB surgery, the EB does not have a gastric component so this may account for the differences in TMAO levels seen between both therapeutic modalities. Another potential reason for this discrepancy could be the differences in dietary habits post bariatric surgery which might be more pronounced in comparison to the EB cohort of patients thus impacting on the substrates available for bacterial metabolism.

Ascorbate levels were also found to be lower in the plasma of EB patients at 6 months compared with the control group. Ascorbate, ascorbic acid or vitamin C is an essential water-soluble nutrient, usually obtained from fruits and vegetables and is actively absorbed throughout the intestinal tract. The prevalence of vitamin C deficiency is 10-50% in the bariatric population.[326] The lower levels of ascorbate in EB patients is probably due to slight decrease in absorption across the intestine from the sleeve. Deficiency of vitamin C is rare, even following surgery and is usually due to inadequate intake from food sources.[327]

4.4.2 Urinary Metabolite Changes

Key metabolic differences between the EB group and control at both 6 months and 12 months were an increase in the concentrations of both phenylacetylglutamine (PAG) and 3-indoxylsulfate (IS). Both these metabolites have been identified as by-products of colonic microbial metabolism. A rise in sulfate-containing metabolites such as IS may be expected post EB treatment, because the largest group of sulfate reducing bacteria is found amongst *Proteobacteria* which are found in abundance in

the duodenum, a site modified by the EB. The microbial fermentation of the amino acid tryptophan to indole followed by endogenous oxidation and sulfate conjugation results in the production of IS.[328] PAG results from glutamine conjugation of phenylacetic acid which is a by-product of microbial conversion of phenylalanine. Elevated levels of PAG and IS in serum have been associated with increased mortality and cardiovascular disease in patients with chronic kidney disease but the same has not been identified for urinary PAG.[329] In the urine of RYGB rats, the presence of these metabolites demonstrated an inverse correlation with cell survival.[330] In humans, elevated levels of urinary PAG are most commonly encountered in urea cycle disorders and indicative of the excretion of nitrogenous waste.[331] ^{14}C Radiolabeled urinary PAG has been shown to yield information on the relative rates of cellular reactions in the liver involved in gluconeogenesis[332] If this is the case, then we would have expected urinary PAG levels to fall as EB therapy should reduce gluconeogenesis due to its actions on enteric gut hormones and insulin sensitivity. The high urinary PAG levels observed in the EB group may merely indicate an increase in gut microbial activity within the device arm compared with the control group leading to the increased production of PAG from phenylalanine. Further analysis from this clinical trial on the impact of the EB on the gut microbiome will hopefully provide us with more information to account for the variations in these metabolites seen.

The urinary creatinine was found to be lower in the EB group than control at 6 months and 1 year. Twenty four-hour urinary creatinine excretion has been widely accepted as a surrogate marker of muscle mass owing to the fact that creatinine is formed from the non-enzymatic conversion of creatine which is found almost exclusively in skeletal muscle.[333] Creatinine is eliminated by renal excretion and is expected to be constant and equal to its production at steady state and therefore proportional to total body creatine content. A reduction in muscle mass is believed to contribute to the reduction in overall weight seen post bariatric surgery and in one study was shown to contribute 16% of the mean weight lost in 3 months and 11% of the mean weight lost at 1 year following RYGB

or sleeve gastrectomy.[334] Therefore, any reduction in urinary creatinine seen in EB patients at 6 months and 12 months may potentially be indicative of a reduction in muscle mass as a consequence of total body weight loss. However, many other factors can affect urinary creatinine levels such as strenuous exercise, gender of patient, diet and medication, none of which were considered in the analysis.

An unknown metabolite was found to differentiate EB and control groups at 6 and 12 months and this was putatively assigned as tyrosine. This molecular compound was also found to be increased in the urine of EB patients at 6 and 12 months compared with baseline. Tyrosine is non-essential amino acid synthesised from phenylalanine.[335] Increased urinary excretion of isomers of tyrosine are associated with patients with diabetes and chronic kidney disease where these amino acids are believed to be actively secreted or produced in the kidney.[336]

4.4.3 Faecal Metabolites Changes

The faecal lactate, 5-aminopentanoate and tyramine were significantly increased in the EB group compared with control at 6 months**.** 5-aminopentanoate or 5-aminovalerate is a lysine degradation product and its high levels in biofluids may indicate bacterial overgrowth or endogenous tissue necrosis.[337] Endogenous 5-aminovalerate is thought to be predominantly a microbial metabolite produced by the gut or oral microflora. Total enteric bacterial numbers have been shown to increase post duodenal jejunal bypass in rats and in humans. [172, 338] Similar changes might also occur with the EB leading to an increase in bacterial overgrowth thus seeing a rise in microbial associated metabolites such as 5-aminovalerate.

Although lactate is normally detected at low levels in adult faecal samples, it was found to be significantly elevated in the stool of EB patients compared with control at 6 and 12 months respectively. Lactate is common end product of bacterial fermentation of carbohydrates particularly

by the lactic acid bacteria *Lactobacillus* and *Bifidobactrium* which are considered integral gut microbiota due to their perceived health promoting effects. Faecal lactate concentrations are influenced by the balance between production by bacteria and by host tissue and microbial utilisation and host absorption. [339] The rise in lactate seen in the EB cohort may be as consequence of an upset in this balance from a potential rise in lactic acid forming bacteria in the intestine which increase the utilisation of carbohydrates to produce lactate.

Tyramine is a derivative from the amino acid tyrosine and is metabolised by the enzyme monoamine oxidase. Certain food types are a rich source of tyramine including cheese, fish and processed meat.[340]

At 12 months faecal concentrations of malate and fumarate were reduced in EB vs. control. Both these metabolites are dicarboxylic acids and are tricarboxylic acid cycle intermediates - a series of chemical reactions used by aerobic organisms to release energy from oxidation of acetyl-coA into carbon dioxide and adenosine triphosphate (ATP). Acetyl Co-A is derived from the metabolism of carbohydrates, fats and proteins.[341] The decreased presence of these tricarboxylic acid cycle intermediates and glucose in the stool at 12 months coupled with the increase in lactate seen may suggest increased activity of anaerobic glycolysis in the EB group. After all, the majority of gut microbiota are anaerobes and if the number of these species increases, as is the evidence with bariatric surgery this will lead to an overall net increase in anaerobic activity.

4.4.4 Limitations

Although providing a wide spectrum of information, there were five metabolites which are still yet to be identified. NMR in comparison to MS is less sensitive, but due to time and financial constraints, MS techniques were not conducted at this stage. MS techniques will be utilised in the final analysis of the trial when both the 1 year data and 1 year follow up data will be available. Not only is identification of

metabolites based on libraries meaning that the number of detected metabolites can be limited but it is also largely dependent on the computer software being used to identify the metabolites and their pathways. Databases may be inadequate, and some metabolites and pathways particularly affected by bariatric interventions such as the EB may not be included.

Another major limitation is the potential confounders that will undoubtedly have had an influence on the metabolic profile of both treatment arms, but which were not controlled for in this analysis. Examples of these include dietary consumption, medications and physical activity which all would have varied prior to study visits thus having an impact on the samples being collected. Patients in the EB group also received high dose PPI for the entirety of treatment with the device; a drug which has already shown to affect the gut microbiome and it is quite foreseeable that the metabolic profile of these patients would also have been affected.[342]

Despite these limitations steps were taken to ensure the collection and analysis of samples was standardised. Biofluids were retrieved from patients who were all fasted, and samples collected in the morning to avoid any diurnal variation, which is particularly a problem with urine samples. Strict protocols were adhered to for the collection, processing and storage of these samples.

4.5 Conclusion

These results indicate that the EB leads to significant perturbations in the metabolic profile of patients with T2DM and obesity allowing discrimination from those individuals who received no device intervention (control group). Analysis of all three biofluids; plasma, urine and stool revealed significant differences between both treatment arms at 6 months and 1 year. There were also significant differences in the metabolic profile of EB patients at 6 months and 1 year in comparison with their samples at baseline.

One of the difficulties in interpreting these changes seen in the metabolic profile of patients receiving the EB and its significance is the current sparsity of data in the literature for any comparisons to be made. All the data presented in this chapter is believed to be novel as no previous studies have explored the impact of the EB on the metabolic profile of obese patients with T2DM. Another strength of this data is the large sample size that has been obtained. It is hoped that with a more in-depth analysis using techniques like MS, further key metabolites can be discovered, and these may be correlated with the clinical outcomes.

Chapter 5: Final Discussion & Conclusions

5.1 Introduction

The incidence and prevalence of obesity and T2DM is increasing at an alarming rate and now poses a global threat to mankind. Causes for this sharp rise are believed to be multifactorial but increasing sedentary lifestyles and poor diets are thought to be major contributory factors. Bariatric surgery has recently come to the forefront as an effective strategy for treating both these conditions when lifestyle interventions such as diet and exercise and anti-diabetic and anti-obesity medications have failed. Surgery can lead to dramatic effects in terms of weight loss and glycaemic improvement, with good long-term data available to support its efficacy and potential to induce diabetes remission. However current demand outstrips supply with less than 1% of patients who qualify for surgery undergoing the procedure each year. With this in mind, there is a greater need to develop alternative therapies to surgery to cope with this added demand and pressures on bariatric services. Recent years have seen the emergence of endoscopic treatments which have been pitched as alternatives or adjuncts to undergoing surgery.

The EB is one such device; a duodenal bypass sleeve liner, designed to mimic the effects of RYGB but up until now, there have been no major RCTs investigating the efficacy of this device. Furthermore, the mechanisms of its action remain unclear although it is postulated that the device elicits its effects by modulating key gut hormones, manipulating bile flow and influencing the gut microbiome. The primary aim of this clinical trial is to explore the efficacy of this device on glycaemic control and weight loss in the setting of nationally funded multicenter RCT. In addition to clinical endpoints, NMR metabolic profiling was also undertaken on biofluids of participants over the course of the study to gain an insight into the metabolic perturbations that occur as a result of the EB device and whether these changes are significant between both patient cohorts.

As the EB is a relatively new device there is less than 10 years of data available on its use, and even less information on its mechanisms of action. Consequently, throughout this thesis comparisons have been drawn between the EB and bariatric surgery as this the gold standard treatment that this device was designed to mimic. This thesis has reported novel data from the first year of the clinical trial from implant to explant of the device. In this final chapter the key take home messages from each chapter will be summarised as well as exploring the wider impact of these results in helping to define the clinical applications of the device in the treatment algorithm of T2DM and obesity.

5.2 Key Clinical Findings

Of the 170 patient randomised in the trial, 75 patients received the device, and 56 of these completed the 12 months of the study. Changes in FPG from baseline were not found to be significant between EB and control groups but significant reduction in fasting levels of insulin was observed between both groups at 6 months and 1 year suggesting that the device may reduce insulin requirements. HBA1c was not analysed at this stage because it is primary endpoint of the RCT so these results are to follow upon conclusion of the trial. The majority of previously published studies on the EB have not found statistically significant differences in FPG or indeed HBA1c.[240] It is possible that the effect of the device may be underestimated due to low numbers and heterogeneity of these previously published studies so the final results of this large RCT are eagerly awaited.

Significant reductions in BMI and weight were observed between EB and control groups with a mean reduction of 12kg from baseline; BMI reduction of 4kg/m^2 at 1 year. This compared with 6kg weight loss and BMI reduction of 2kg/m^2 from baseline in the control group. These differences were greatest at 3 and 6 months. These results provide further compelling evidence to reconsider the optimum implant dwell time to a maximum duration of 6 months rather than 1 year, particularly if the majority of benefit from the device appears to be in this initial period following implantation. Adding weight to

this is the fact that the majority of SAEs appear to occur in the latter stages of device treatment, in particular liver abscesses so shorter treatment periods might negate these risks.

EB therapy was also shown to lead to significant improvements in LFTs, particularly ALT and AST levels which are parameters known to be elevated in non- alcoholic fatty liver disease (NAFLD). NAFLD is a condition with fairly limited treatments available.[343] Furthermore, higher levels of ALT have been associated with subsequent increased mortality risk in a large population based study.[344] Compared with an ALT <20U/L, men with an ALT>100U/L were 3 times more at risk of death from CVD and 59 times more at risk of a death from liver disease. Average baseline ALT levels were 39U/L in the EB group but reduced to 22U/L at one year which would suggest that the EB might be an effective therapy for patients with a diagnosis of NAFLD. Further research in this field would be helpful such as matching the biochemical changes with radiological changes by performing serial liver ultrasounds pre and post implant and monitoring for improvements. However, caution should be taken in deploying the device in any patients with history of liver disease due to the real risk of liver abscesses and the device should be avoided in patients with liver disease from other causes such as viral hepatitis and autoimmune disease.

The EB had significant effects on lipid profile albeit modest, on both fasting total cholesterol and LDL levels which is a similar pattern to that observed post RYGB surgery from 1 month up to 4 years.[345] As with bariatric surgery the potential mechanisms for these changes seen may be as a consequence of alterations in dietary intake, changes in gut hormones, and alterations in the gut microbiota.

5.3 Safety Profile

The EB implant procedure is easy to perform; the average duration was 41 minutes in this trial with no procedure related complications. The commonest reason for unsuccessful implantation is where an anatomical variation exists in the patient, most commonly a short duodenal bulb preventing the

device from being anchored securely. Although explantation of the device is in fact considered easier to perform than implantation (on average it was 10 minutes shorter in duration in this trial) it is associated with a higher risk of procedural related complications. Firstly, there is an increased risk of perforation and bleeding from localized trauma caused by the barbs, so it is imperative that all barbs are contained within the protective hood on removal and remain here throughout the retrieval process. Secondly, findings at endoscopy on explant can be more unpredictable with regards to the location of the device, which may well have migrated more proximally or distally from the duodenal bulb due to peristalsis which may make its removal trickier. Lastly, the degree of the device's adherence to the duodenal wall can vary, as some devices can become tethered or the strings which collapse the device tangled within inflammatory tissue caused by localised trauma and irritation of the duodenal lining by the device. Despite all these factors, the vast majority of devices are removed endoscopically, rarely requiring any surgical intervention (1 in 1000) although patients are informed of this risk during the consenting process. In this trial we did encounter this issue, whereby the device was tethered to the duodenal wall and we were unable to collapse the device and retrieve it endoscopically. In this case laparoscopic removal was required.

The side effect profile from this study was similar to previously published studies of the EB with the major complications being liver abscess and migration of the device with GIB less likely if the patient is prescribed a high dose PPI. In nearly all cases where SAEs have occurred there has been no permanent sequelae and the patient has made a full recovery.

Despite these concerns one of the major advantages of the device is that the procedure is easy to perform as a day case and is minimally invasive. General anaesthetic is not a necessity as it can be performed under sedation. For patients who are not keen on surgery, or who are not fit for surgery it can provide another option when they have exhausted medical options for their diabetes and weight management.

5.4 Key Metabolic Findings

NMR was used to interrogate the plasma, stool and urine of participants in order to identify key metabolic changes over time between the EB and control group and these are summarised in Table 1.24 as well as their comparisons to findings previously reported post RYGB surgery. The potential physiological pathways affected are also listed. Based on these findings, I would hypothesise that some of the key mechanisms of how the EB might elicit its effects on weight loss and diabetes is by altering the gut microbiome, reducing levels of TMAO and increasing anaerobic energy metabolism.

Table 1. 24 Key Metabolic Changes in Biofluids Analysed at 1 Year

	Plasma	Urine	Stool
Endobarrier	⇓ Trimethylamine (TMAO) ⇓ Ascorbate	⇑ Phenylacetylglycine (PAG) ⇑ 3-indoxylsulfate (IS) ⇑ Tyrosine ⇓ Creatinine	⇑ 5-aminopentanoate ⇑ 5-aminovalerate ⇑ lactate ⇓ malate ⇓ fumarate
RYGB Surgery	⇑ Trimethylamine (TMAO) ⇓ Ascorbate	⇑ Phenylacetylglycine (PAG) ⇑ 3-indoxylsulfate (IS) ⇑ Tyrosine ⇓ Creatinine	⇑ 5-aminovalerate ⇑ lactate ⇓ TCA cycle intermediates
Potential Physiological Pathways Implicated	• TMAO is a potential biomarker of CVD.[346]Elevated levels are associated with acute heart failure and left ventricular diastolic dysfunction • Positive association between increased plasma TMAO and T2DM.[347] • Increased susceptibility to Vitamin C deficiency particularly in those with unbalanced diets.	• Increased microbial derived metabolites reflecting gut microbiome changes • Urinary creatinine is used as a surrogate marker of muscle mass so might be indicative of decreased muscle mass. • A reduction in urinary creatinine may also suggest improvements in kidney function.	• Increased microbial derived metabolites reflecting gut microbiome changes • A reduction in TCA metabolites and increased lactate levels suggest altered glycolysis and TCA cycle metabolism leading to altered energy metabolism. • Higher levels of fumarate and malate have may be involved in the pathophysiological pathway of CKD in T2DM.[348]

5.5 Lessons Learnt from the Recruitment campaign

One of the biggest lessons I learnt during this experience of running an RCT is that obtaining a satisfactory outcome in any clinical trial is largely underpinned by a successful recruitment campaign to drive participants numbers and to ensure that the study is adequately powered for the results obtained. The recruitment process posed the greatest challenge in this clinical trial as it has done for other clinical trials in the past.[349] This stimulated me to analyse in more detail, what are the main barriers to recruiting patients to clinical trials, and how can we overcome these. Attempts to negate poor recruitment can include lengthening the recruitment timeline or broadening the screening criteria as what occurred in this trial. Recruitment took a year longer than anticipated, and we also had to broaden some of the screening criteria in order to obtain the full complement of participants. This can have a detrimental impact on the cost of the trial or worse still, in some cases dampen the clinical effect of a particular intervention. Ultimately if recruitment goals are not reached this can potentially lead to the early termination of a trial. A review of the National Cancer Institute Therapy Evaluation Programme (CTEP) sponsored oncology trials found that 38% failed to attain the minimum accrual goals with 71% of phase III trials resulting in poor accruals.[350] A positive correlation was found between poor accrual rates and longer development time of clinical trials – the time from initial concept to commencement of the trial. One potential explanation may be disinterest in the initial research question as newer therapeutic developments become available whilst the trial is being developed.

Often the time taken to recruit patients to a clinical trial is grossly underestimated. A study of 20 multicentre national RCTs funded by the National Health and Medical Research Council (NHMRC) found that the average recruitment period was 4-5 years excluding the period required for patient follow up.[351]

There are ethical implications associated with early trial termination due to inadequate patient recruitment. Firstly, patients already recruited into the study may be exposed to potentially harmful

interventions despite the outcome of the trial being fruitless. Secondly a failed clinical trial will invariably lead to delays in a new treatment or drug therapy being made commercially available for widespread use as outstanding questions may still remain on its efficacy or safety profile. Failed clinical trials not only waste resources and funding but also the time of patients and researchers. Research funding bodies will expect to see evidence of meticulously planned recruitment strategies to ensure that any grants approved are utilised appropriately and that sufficient patient numbers are obtained for a trial in order to address the primary research question.

5.5.1 Barriers to Recruitment

There are numerous barriers to recruitment into clinical trials and these can be divided into four main categories; participant related, researcher related, protocol related and other factors (figure 1.39). The early recognition of these barriers is crucial in order to develop potential solutions that will prevent unnecessary delays in recruitment or negatively impact the integrity of the trial being conducted.

Figure 1. 39 Barriers to Recruitment

PARTICIPANT RELATED

- Age
- Fear of receiving placebo or not receiving treatment intervention
- Fear of side effects
- Lack of awareness of clinical trials
- Language/cultural barriers
- Time constraints
- Travel arrangements and location from study site

RESEARCHER RELATED

- Lack of enthusiasm or belief in study
- Lack of recruitment training or experience
- Language barriers
- Poor communication skills
- Time constraints and competing work loads

PROTOCOL RELATED

- Blinded Trial or Placebo – Participants unaware of what treatment they are receiving
- Invasive testing
- Lengthy study with long follow up period
- Strict eligibility criteria
- Too many study visits or complex study design

OTHER FACTORS

- Lengthy approval processes – obtaining regulatory approval
- No financial incentive
- Poor site selection
- Press and media engagement

There are various participant related factors that will influence successful recruitment to a trial. Some patients are simply unaware that clinical trials and opportunities to take part in research exist or are unsure of how to access the relevant information on research happening in their area. Some patients

may have received correspondence regarding clinical trials but may not understand the language used. Others may be apprehensive of participating due to fears of receiving futile treatment such as placebo medication or undergoing a sham procedure. Open designs are more likely to be popular with patients whereby they know which treatment they are receiving but equally some may be worried about potential side effects associated with an unproven intervention. The location of study site is also important as poor transport links will deter patients from attending. The age of the patient population plays a part as elderly patients are less likely to consent to clinical trials mainly due to fears of the experiment being detrimental to their health.[352]

Researcher related barriers can be often centred around an investigator's personal perception of the trial, their faith in the research being conducted and whether they truly believe of its benefit to the patient.[353] Lack of funding and pressures of time also play a pivotal role on a researcher's potential to recruit successfully to a clinical trial.[354] This is particularly prevalent in primary care recruitment, where general practitioners report difficulties in prioritising research due to perceived demand of the study, lack of support from the research team and time constraints.[355] It is also vital that investigators possess effective communications skills so that they may convey the proposed research in a manner that the patient doesn't feel pressured or coerced in taking part, but rather feels at ease and comprehends the information clearly before consenting to take part in the trial. Some researcher's may be inexperienced in recruiting patients to clinical trials and therefore may lack confidence in approaching potential participants or may not have received the adequate training to be equipped with these tools.

Protocol related factors refer to the study design. It is imperative that study protocols are both realistic and feasible to follow. In a survey of 73 Indian investigators who were asked about the biggest challenge to recruitment and retention of trial subjects; 38% cited the complexity of study

protocol.[356] A complex protocol can lead to participant confusion, generate additional pressures on the trial investigator(s), and increase the likelihood of protocol violations occurring if the protocol is not adhered to. Too many study visits or a lengthy follow up period will deter patients from participating. In addition, if the study is too intrusive or involves invasive procedures to be performed, this might also be unattractive to potential participants. The participant eligibility criteria set should also not be so strict so that difficulties arise in finding suitable subjects.

Other factors to consider include slow lengthy R&D and ethical approval processes which can impact and delay recruitment. Costly clinical trials, with inadequate funding and lack of financial incentives for potential participants make it harder to recruit and retain participants. Poor choice of study site on behalf of the sponsor can be detrimental to the trial, particularly if there is poor engagement from staff or inadequate resources or equipment at the site.

5.5.2 Strategies to Enhance Recruitment

Strategies to enhance recruitment can be subdivided again into the same four categories as for the barriers (figure 1.40).

Figure 1. 40 Factors Enhancing Recruitment

PARTICIPANT RELATED

- Better patient education
- Patient and public engagement forums
- Provide multilingual patient information
- Telephone reminders
- Travel compensation
- Flexible appointment times
- Online data collection

RESEARCHER RELATED

- Clinical research networks
- Electronic patient records to identify patients
- Employing dedicated research staff and assistants
- Recruiter training

PROTOCOL RELATED

- Open trial study design
- Using straight forward data collection
- Broad eligibility criteria
- Pragmatic study design
- Patient engagement in trial design

OTHER FACTORS

- Collaboration with other research centres
- Press and media engagement
- Promotion on social media platforms
- Offering financial remuneration

First and fore most it would be prudent to ensure that information on the current portfolio of clinical trials being offered by a research institution are readily available and easily accessible to the general public. Various portals can be utilised to disseminate this information including clinical trial websites, local and national newspapers, social media platforms, posters and patient information leaflets. Emphasis should also be placed on supplying material that is multilingual to encourage recruitment

from ethnic minorities whom are often poorly represented in clinical trials. Patient and public engagement events can help raise the profile of the different types of research studies offered in the locality as well as providing a forum to educate patients on the benefits of taking part in research for not only them, but society as a whole.

Making travel arrangements or reimbursing travel expenses will further incentivise participation particularly if funding does not stretch to provide financial remuneration for patient involvement. The more convenient a study is for the participant, the more likely they are to commit and adhere to the study protocol. Options may include providing flexible appointment times or online resources to obtain data thus reducing the number of study visits a patient is required to attend.[357]

A strong foundation and infrastructure is fundamental in running a successful recruitment campaign and this is can be provided by government funded local clinical research networks and facilities (e.g. NIHR Biomedical Research Centres and Clinical Research Facilities) providing research coordinators, and research nurses at a local level to support trials. The employment of dedicated research staff to assist in driving recruitment should alleviate some of burden of pressure on the primary study investigator. Developing new technologies such as electronic patient records can also aid clinicians in quickly identifying suitable participants who might fit the study eligibility criteria.[358] Implementing telephone consult reminders prior to clinic visits may also improve study recruitment rates and help build a rapport between doctor-patient prior to face to face meetings.[359]

It should not be assumed that all researchers will be adept in recruiting patients to clinical trials, many will not have any research exposure and therefore will be inexperienced in patient recruitment. Attending a training programme on recruitment has been shown to be well received with some

programs increasing recruiters' self confidence in communicating the components of an RCT to patients, although this has not been shown to improve actual recruitment rates.[360]

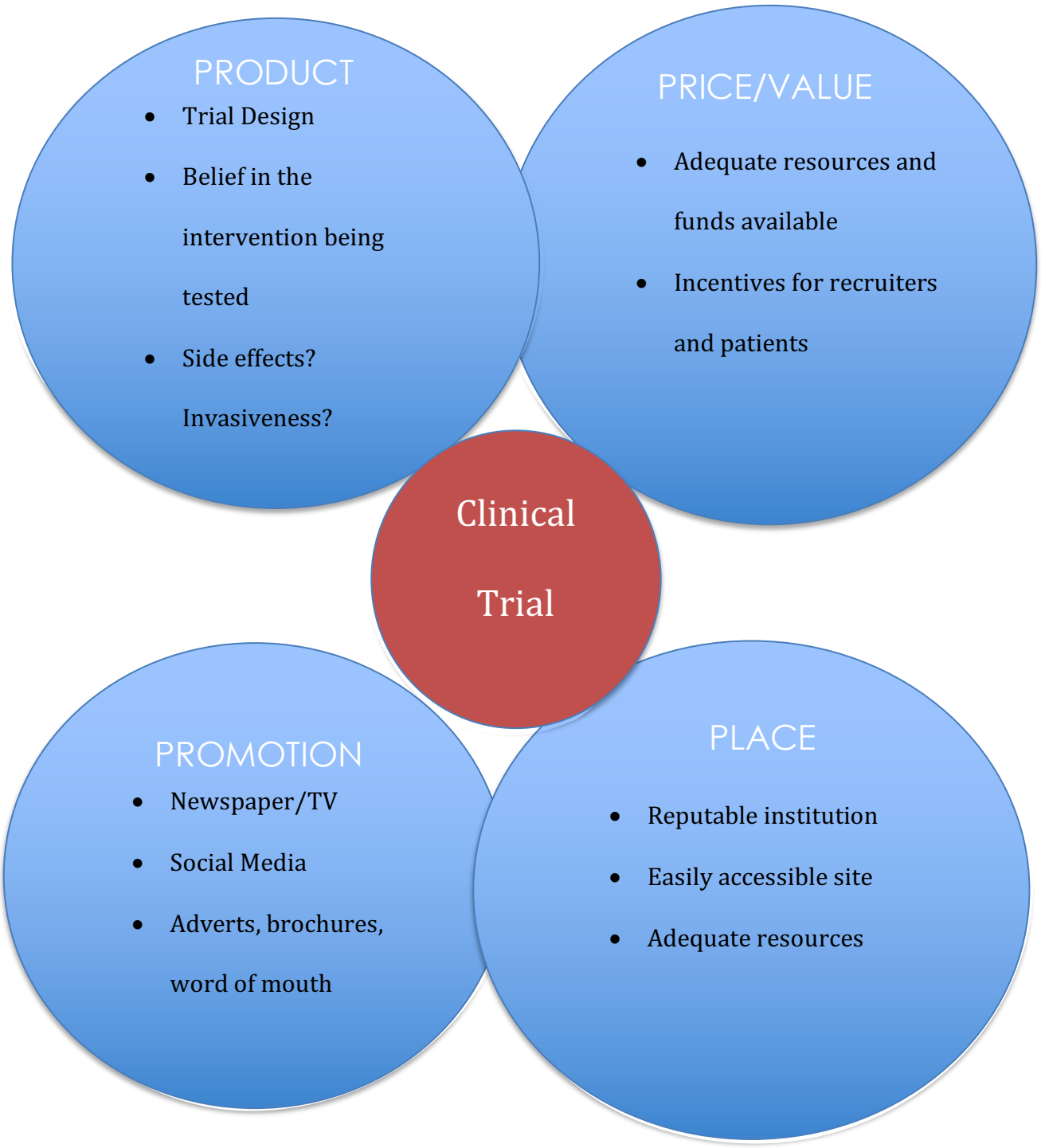
Using open label trials rather than blinded or placebo trials was shown to have a 10% improvement to recruitment in a recent Cochrane review.[361] Collaborating with other research groups and expanding to other research sites may also be beneficial in widening the recruitment net. Patient engagement in research and their involvement in designing of a clinical trial has been shown to increase enrollment rates.[349] Patient and Public Involvement (PPI) groups have an essential role in the designing and writing of protocols, grant applications, patient information sheets and other essential trial documents. They are an effective means of identifying at an early stage potential barriers to recruitment and will decrease attrition rates. Current patient and public involvement in the early stages of clinical trial development is low but adopting a more patient centered approach might help incentivise participation in a particular study.[362, 363]

Internet based recruitment, particularly the use of social media platforms has been shown to be an effective modality for recruitment. Google advertising was found to be successful as well cost effective in recruiting participants to a trial evaluating an online depression intervention.[364] In 2011 Pfizer, a major drug company took this one step further by conducting the first ever RCT of an investigational drug managed solely electronically by creating a "virtual clinical trial".[365] Patients were consented online using a combination of video multimedia and online testing, and any medication was shipped to the patient at home. Researchers managed the study content remotely and no physical clinical visits were required allowing patients to participate in the clinical trial regardless of any geographical restrictions or proximity to clinical sites. In the future we expect to see the ever increasing use of web-based technology both in the promotion and running of clinical trials.

5.5.3 A New Model for Clinical Trial Recruitment

In order to emcompass the key components of a successful clinical trial design I have applied a model which has been widely used in marketing but could equally apply in this context is the 4 P's: Product, Price, Promotion, Place (Figure 1.41).[366] In this scenario, the product is the intervention being tested such as a device or a drug. Is the trial designed appropriately to answer the hypothesis being tested and is there sufficient belief that the intervention will have a clinical benefit with a limited side effect profile. The price, or more appropriately termed the value refers to the grant for the trial - are adequate funds and financial incentives available? Promotion refers mainly to the recruitment process and to increase awareness of the trial. Finally, the place, is the clinical site, and its suitability to conduct a clinical trial.

Figure 1. 41 Four P's of Clinical Trials



The task of recruiting participants into a clinical trial is by far one of the greatest challenges faced by the research team and this trial was no different. Initial strategies of recruitment were heavily reliant on the primary care research network and engagement with GP practices as it was envisaged that the vast majority of patients would be recruited from the primary care setting. This system appeared to work well at UHS site, primary due to well established links between primary and secondary care to facilitate research and the availability of electronic patient records. UHS possessed an extensive database where suitable patients matching the study criteria were identified and invited to participate in the trial with a good response rate. In contrast at the Imperial site, this system failed due to numerous reasons. Some GP practices reported not having the sufficient time and resources to assist in the recruitment process, despite financial incentives being made available for their active participation in this process. Furthermore, when letters were sent out by GP practices to patients who were deemed suitable according to the eligibility criteria, the response rate from these patients was extremely poor. The poor response rate from patient invites was attributed to various factors. These included the high migration rate in and out of London potentially leading to invites being misplaced or not having reached their intended recipient, or that London's multicultural population where English may not always be the native language resulted in the failure to disseminate this information.

The implementation of a local newspaper advertising campaign was instrumental in tapping into a wider audience and raising the profile of the study. Thousands of responses were received from the public registering their initial interest in the study and this kick started a successful recruitment campaign which followed at the Imperial site. This suggests to me that for future clinical trials planning, a greater emphasis should be placed (and therefore funding) on running mass newspaper and social media campaigns which might prove more effective than the traditional methods of recruitment.

5.6 Final Conclusions

The EB is currently unavailable both commercially and in the clinical trial setting. Following the closure of the ENDO trial in the US by the FDA in 2015 the device was withdrawn from the US market, and in the past year, the device manufacturer GID have suffered further setbacks by losing the European market. An increase in the number of device tears recently reported (probably due to a manufacturing defect) culminated in the EB losing its CE mark in November 2017 for non -compliance related to quality control issues. This sequence of events and the timing of the CE suspension is unfortunate particularly as the results of this clinical trial are imminent and are likely to have a major impact on the future of the device.

The current landscape of treatments for obesity are extremely limited and when lifestyle interventions have failed there are only a handful of drugs available, providing modest effects on weight loss. Many patients will therefore be faced with little alternative but to proceed to obesity surgery in order to lose their weight. The EB could be a real option in the treatment algorithm of these patients, particular in those who are not keen on invasive surgery, or whose premorbid function makes them unsuitable for surgery. Furthermore, the improvements seen in liver biochemistry, total cholesterol and LDL is promising. Weight loss is a proven treatment for NAFLD leading to improvements in the histological features of this disease.[367] EB therapy could be an option to consider in these patients coupled with close monitoring of their LFTs and ultrasound imaging to monitor for indicators of improvement.

Based on my findings from this thesis I can make the following conclusions:

- EB therapy is more effective at an inducing weight loss when compared with medical and lifestyle intervention alone, but further evidence is still required to support its benefit as a treatment for diabetes. Although the device did show a significant reduction in fasting insulin

levels at 6 months and one year between both groups, changes in FPG were not significant. Results on HBA1c reduction (the primary end point of the study) are awaited which will be crucial in determining the anti-glycaemic effects of the device.

- It is worth considering a reduction in the implant dwell time from 1 year to 6 months as the device appears to be most efficacious during this initial 6 month period and serious adverse events are more common in the latter 6 months of therapy.

Novel Findings

- *All the metabonomic results presented in this thesis is novel, as no previous studies have investigated the effect of EB therapy on the metabolic profile of participants.*
- The EB leads to a reduction in plasma levels of TMAO and higher levels of this metabolite have been implicated in CVD and T2DM. This might provide an insight into how EB may lead to improvements in diabetes control, although current evidence for this is still lacking in this trial.
- Increased microbial derived metabolites was detected in the stool samples of EB patients which may reflect changes in gut microbiome that occur as a result of duodenal exclusion.

At the end of 2019 the full results of this RCT will be published which will also include the results from the 1 year follow up period following device removal. These results will be vital in determining whether this device can have a future pivotal role to play in the management of diabetes and obesity by answering the question of whether any changes in weight loss and glycaemic improvement observed in the first year are sustained once the device is removed. Fundamentally the endoscopic interventions that are likely to succeed are those devices which are not only easy to adopt but are widely tolerated with an excellent safety profile whilst having a sustained and long-term effect on glycaemic control and weight loss.

5.7 Future Work

5.7.1 Analysis of HBA1c

The main limitation of this study was that I was unable to analyse the results of HBA1c for participants, as stipulated by the NIHR as this was the primary end point of the clinical trial. It was the opinion of the funding body that preliminary analysis of HBA1c results from participants at one year may potentially lead to researcher bias thus jeopardising the primary endpoint and outcomes of the clinical trial. As a consequence, observations of improvements in FPG and insulin levels were used as surrogate markers of glycaemic control in this thesis. This has many flaws as FPG only provides a snap shot of glycaemic control and is unlikely to capture the true variability of glucose control in an individual. Although there is a clear relationship between FPG and HBA1c, the evidence related to lowering FPG and diabetes complications is less secure than with HBA1c. Caution should therefore be applied when making any clinical conclusions as a result of FPG changes between both arms. The final results of the clinical trial are due to be published later this year in 2019 and this will include a detailed analysis of HBA1c results for all participants.

5.7.2 Further Analysis of LFTs, NAFLD and BMD

A key finding in this study was the changes in LFTs observed over time as a result of EB therapy. Significant reductions were observed in ALT and AST levels in the EB group which are parameters associated with NAFLD. If I were to design this study again, I think incorporating a non-invasive liver ultrasound and elastography on participants at baseline, and at six and twelve months would have been extremely useful in determining whether EB therapy has any benefit in patients with NAFLD. This could also be correlated with the calculation of NAFLD scores (a validated scoring system that helps identify patients with NAFLD who may have liver fibrosis) for these patients at baseline, one year and two years.[368] Also of note was the finding that EB therapy leads to significant increases in ALP and it would be pertinent be explore this in future studies. Obtaining ALP iso-enzymes would be

helpful in determining whether the ALP rise observed originated from liver, or bone as suspected in this case. GGT levels did not rise in conjunction with ALP in this study, so it may be safe to assume that the ALP rise originated from bone rather than liver. Serial assessments of BMD could be performed using dual energy x-ray absorptiometry (DEXA) scans at baseline and one year to detect any osteoporotic changes following EB therapy. This is currently the gold standard for assessing BMD although other serum biochemical markers of bone metabolism exist such as CTX-1 and P1NP but there is uncertainty with their use in clinical practice due to the variability of assays used and need to standardized references ranges.[369]

5.7.3 Subgroup Analysis of Metabonomic Data

NMR metabonomic analysis of the various biofluids uncovered distinct differences in the metabolic profile between both patient cohorts over time following EB therapy. However the metabolic data collected could be further interrogated to determine if any relationships exist within each treatment group. For example, in those patients who achieved the greatest weight loss at one year, did they have similar changes in their metabolic profile? Conversely, did their metabolic profile vary widely with those patients who lost little or no weight at all over the year period. Future work should focus on analysing these participant subgroups to uncover if patterns exist in those with the best glycaemic improvements or weight loss outcomes. The hope would be to identify the key metabolites and thus pathways which might be implicated in this process.

5.7.4 Relationship of Metabonomic Changes and Gut Microbiome

The analysis of the metabonomic data uncovered a variety of metabolite pathways, many of which implicated microbial derived metabolites that may potentially reflect gut microbiome changes in these participants. The DNA analysis of the gut microbiome from these participants would help further corroborate and support these findings. This work is currently being undertaken, and whilst

the DNA extraction from stool samples collected from participants has already been conducted by another research fellow, DNA sequencing is being undertaken by a third party. Once the DNA sequencing results are available the next step would be to determine any changes observed in the gut microbiome over time in the control group versus EB. It would then be vital to correlate these results with the metabonomic data to determine if there is an increase in anaerobic bacterial activity as suspected, or other microbial derived metabolites.

5.7.5 Impact of EB therapy on Gut Hormone Modulation

A key concept of EB therapy is that bypassing the proximal small bowel will lead to modulation of enteric gut hormones, including GLP, PYY and ghrelin. Analysis of both fasting and post prandial gut hormone levels from participants is currently being conducted at the University of Dublin and it is envisaged that these results will provide us with further mechanistic information on how the device elicits its effects on weight reduction and glycaemic control.

5.7.6 Comparing EB with RYGB

Bariatric surgery has been proven to be one of the most effective treatments in diabetes and obesity and so it would have been extremely powerful if there had been an additional arm to this study which analysed participants receiving RYGB surgery. This RYGB group could have provided a direct comparison to the EB arm, which the device was designed to mimic. In order to be pragmatic and due to funding constraints, this additional intervention arm was not designed into this study but future work should focus on designing a trial to compare patients receiving EB therapy to those undergoing RYGB. Furthermore, the metabonomic and gut microbiome samples collected from participants in this trial could be compared with a dataset of similarly age-matched participants receiving RYGB (if available) to see if similarities exist over time.

5.7.7 Analysis of Post Explant Data

The EB was licensed for 1 year after which point it should be removed. A certain issue which arises is that the vast majority of patients may then lose the beneficial effects on glycaemic control and weight loss upon removal of the device resulting in a worsening in their diabetes and an increase in their BMI. The results from one year follow up post removal of the device in this trial are due to be published later this year. An Australian study found that in 30 patients who were followed up in the 6 month period immediately post removal of the EB, 72% gained weight with only 5 patients maintaining their weight loss, and 4 patients losing further weight.[316] In the same study 51 patients were followed up for a period of > 6 months following explant, with 69% regaining their weight and only 5 patients maintaining their weight, with 7 patients losing further weight. The study did not report on how these particular patients managed to maintain their weight loss or lose further weight.

GI Dynamics have previously reported data demonstrating the feasibility and safety of re-implantation of the EB in 5 patients who initially completed 12 months of EB treatment but then proceeded to have the device re-implanted after 4 months for another 12 months. HbA1c fell from a baseline of 9.1% to 6.7% after the 1st explant, and from 7.8% upon second implantation to 7.1% at explant with no reported complications.[370] Although small numbers, re-implantation of the EB might be another treatment option to maintain the effect of the device.

Another option may be to alter the device in a way that allows it to remain in situ for longer. A second generation EB device with a 1mm increase in barb length was trialed in 80 patients in Chile. The subjects initially consented to the implant for one year but were then given the opportunity to keep the device in for up to 3 years if tolerated.[371] The %EWL in the completer population at 52 weeks (71 patients), 104 weeks (40 patients), and 156 weeks (11 patients), were 44 ± 16, 40 ± 22, and 39 ± 20, respectively ($p<0.001$). There were 17 T2DM subjects enrolled in the study with baseline HbA1c of

7.1 ± 1.6% which significantly decreased to 6 ± 0.9 and 5.7 ± 0.7% after 12 and 24 months, respectively. Two diabetic subjects managed to complete 36 months of follow-up, and both maintained an HbA1c below 6%.

The ultimate goal is to create a device which is semi-permanent or permanent allowing it to remain in situ for longer thus providing a more long -term solution for these patients. For this to happen one must consider how to combat the unwanted side effects as described above which are associated with keeping an implant in for long periods of time.

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Appendices

A) Telephone Screening Form

EndoBarrier Telephone Screening Form

Date 15.08.2015
Version 3.0

Date: |__|__| / |__|__| / |__|__| (DD/MM/YY)

Introduce yourself and explain purpose of the call. Explain that they will be asked details of their medications so please collect them now or organise another time to call if unavailable.

Personal details

Name: .....

Telephone numbers: **Home** .....
Work .....
Mobile .....
E-mail .....

Date of birth: ____ /____ /_____

Location .....
Too far to travel for patient? Yes ☐⇒ ***STOP*** No ☐

How did you hear about the study?

GP letter/ leaflet	☐	which surgery?.....
Internet Search Engin	☐	which website?.....
Routine Care Provider	☐	who?.....
Poster	☐	where?.....
Newspaper advert	☐	where?.....
Study website	☐	where?.....
Diabetes Research Network	☐	who?.....
Twitter/facebook	☐	who?.....
Word of mouth	☐	who? (optional).....
Other	☐	how?.....

Short explanation of study…..

It is important for you to know that if you do enter the study you are free to withdraw at any time.

Would you like me to explain the study in greater detail for you?

Yes □ No □

Does the EndoBarrier study sound like something you think that you would be able to commit to?

Yes □ No □

If no what reason is given?……
……
……

Screening questions

1. *Are you aged 18-65 years?*
Yes □ No □⇒ ***STOP***

2. *Do you have type 2 diabetes mellitus?* Yes □ No □⇒ ***STOP***
Have you had diabetes for at least 1 year? Yes □ No □⇒ ***STOP***
Are you on any medication for your diabetes? Yes □ No □⇒ ***STOP***

Do you use Insulin? Yes □⇒ ***STOP*** No □

What is your most recent HbA1c? _____ Date of result_____
(if patient does not know, ask patient to contact GP practice for result and to inform you of this. Continue other screening questions)

3. *What is your weight?* _____kg/lbs/stones & oz
What is your height? _____m/cm/feet & inches

Interviewer to calculate BMI: Is BMI: 30-50kg/m2 Yes □
No □
Requires further checks/confirmation □

Details……
……

4. Do you have any medical conditions other than diabetes? (E.g. asthma, hypertension)

Yes ☐ No ☐

If yes, what?……
……..
……

5. Please tell us about all medications you have taken over the last 3 months (list all).

Medications (names only, dosages not required but ask patient specifically if they take aspirin, clopidogrel, warfarin or NSAIDs e.g. ibuprofen)
……..
……
……
……
……

6. Have you ever had surgery on your stomach, intestines or colon/bowel before?

Yes ☐
No ☐
Requires further checks/confirmation ☐
Details……..
……..
……

7. Are you registered with a GP? Yes ☐ No ☐⇒ ***STOP***

Explain that in order to proceed to the face-to-face screening visit, patient will be required to read the full participant information sheet (will be sent to them). Also, if they have not already done so, they must complete and return the consent form to the study team which allows contact with GP. This will allow us to gain essential information on their medications and health prior to the screening appointment.

Are you still interested in taking part in the EndoBarrier study?
Yes ☐ No ☐⇒ ***STOP***

If no what reason is given?……
……
……

If yes - you will need to attend a screening visit, where you will have blood taken. You need to be fasted for this visit. Please do not eat or drink anything on the morning of the visit and do not take any medications on that morning (but bring them with you).

8. Do you consent to do this? Yes ☐ No ☐⇒ ***STOP***
9. If volunteer has consented to face-to-face screening visit and is eligible:

- *Thank the caller for their time and arrange to send a full participant information sheet. They must read this before their screening appointment.*
- *Offer an appointment to attend the clinic to undergo screening and investigations, this will be fasted.*
- *Remind patient to return consent form to all us to contact GP if not already done so.*
- *Please bring along all medications to screening appointment.*

Outcome of pre-screening:

Ineligible to partake ☐ Reason ineligible……
Declined to take part ☐ Reason offered ……
If interested, has a summary patient information sheet(s) been sent?
No ☐
Yes ☐
If interested, has a patient information sheet(s) been sent?
No ☐
Yes ☐
Agreed plan for follow up……
……

B) Poster

Imperial College London

Version 2 (Imperial Version) - 16th March2015

Living with Type 2 Diabetes?
Struggling with your weight?

We are looking for volunteers to take part in a new research study at Imperial College **London** to investigate the effects of a device called an **EndoBarrier.**

This device may help you to **manage your diabetes** and **aid weight loss**.

If you are aged 18-65 years, living with Type 2 Diabetes and have a BMI between 30-50kg/m^2, you may be eligible.

Please contact us for further information.

[Dr Aruchuna Mohanaruban, endobarrier@imperial.nhs.uk, 02075945946 / 078 7285 0052]

Dr Mohanaruban
endobarrier@imperial.nhs.uk
020 331 25745/ 078 7285 0052

C) Consent Forms

Imperial College London

Imperial College Healthcare NHS Trust

EndoBarrier TM Gastrointestinal Liner Diabetes Trial

Participant Consent Form (Main Study)

Title of Project: EndoBarrier TM Gastrointestinal Liner Diabetes Trial
Principal investigator: Prof Julian Teare
Site number: 1
Participant I.D number:

The participant should complete the whole of this sheet him or herself.
(Please initial each statement if it applies to you)

1. I confirm that I have read and understand the Participant Information Sheet **Imperial Version 3.0 (dated 16/03/15)** for the above study. ☐

2. I have had the opportunity to ask questions and discuss this study. All my questions have been answered fully and I have received enough information about the study including the participant information sheet. ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. ☐

4. I agree that my medical notes and data collected from the study may be accessed by individuals involved in the study, or by regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I understand that my personal data will be processed and stored securely in compliance with the 1998 Data Protection Act. ☐

5. I agree that all my samples (blood, urine, faeces, tissue) will be stored for research purposes and this material can only be used with ethical committee approval. All testing of my samples, will be coded such that I cannot be identified by the data. ☐

6. I give permission for the data collected in the questionnaires and computer tasks to be used for the purposes of the study. ☐

7. I give permission for my General Practitioner to be informed of my participation in this study and the results of any medical tests from my visits i.e. blood tests. ☐

8. I give permission for tissue samples to be collected during the implant and removal of the Endobarrier device. ☐

9. I agree for a DNA/RNA sample to be taken and stored to look for changes that may be involved in obesity, diabetes, brain function and the control of appetite and hormones, and understand that the results will not be fed back to me. ☐

10. I give permission for my blood or DNA/RNA samples to be sent to laboratories in the United Kingdom or abroad for analysis as long as all personal information is removed. ☐

11. I give permission for any stored samples that I give during this study, to be used in future studies which have been granted suitable ethical approval. ☐

12. The indemnity arrangements have been discussed with me. ☐

One copy for patient, 1 for site file, 1 for patient notes
Participant Consent Form [Imperial (Main Study)] Version 3.0 –16th March 2015

EndoBarrier TM Gastrointestinal Liner Diabetes Trial

13. I agree to take part in the above study. ☐

14. In the event that I have private medical insurance, I agree to inform my provider of the study. ☐

15. I am happy to be contacted for possible participation in future research studies in the event that I am not eligible for this study. ☐

16. I agree to be contacted by the research team after 4 years in order to provide them with an update on my body weight and health status. ☐

_____	_____	_____
Name of Subject (block capitals)	Signature	Date
_____	_____	_____
Name of Person taking consent	Signature	Date

One copy for patient, 1 for site file, 1 for patient notes
Participant Consent Form [Imperial (Main Study)] Version 3.0 –16th March 2015

D) Patient Information Summary

Imperial College London

Imperial College Healthcare NHS Trust

EndoBarrier TM Gastrointestinal Liner Diabetes Trial

SUMMARY OF RESEARCH STUDY

Study Project Title: EndoBarrier TM Gastrointestinal Liner Diabetes Trial

You are being invited to take part in a research study taking place at Imperial College London, St Mary's Hospital . The study investigates the effect of a new non-surgical device (EndoBarrier) on type 2 diabetes mellitus and weight loss over a period of 2 years. If after reading this you would like more information about the EndoBarrier trial, please complete the attached questionnaire and return in the envelope provided.

What is the purpose of the study?

A new device called the EndoBarrier Gastrointestinal Liner helps patients with diabetes manage their blood sugar levels and lose weight without the need for surgery. This study will compare how effective the EndoBarrier device is compared to standard medical care in the treatment of type 2 diabetes mellitus.

Why have I been invited?

You are being invited because your body mass index (BMI) is between 30-50 kg/ m^2 and you have type 2 diabetes mellitus.

How does EndoBarrier work?

The EndoBarrier has been shown to help control type 2 diabetes mellitus and reduce weight. It is a 60 cm long impermeable sleeve-like device that is inserted through your stomach (endoscopically) and creates a thin plastic layer between food and the wall of the intestine. This could prevent food from coming into contact with the gut until further down the intestine and may alter natural your level of hunger and fullness.

What will happen to me if I take part?

If you are interested in this study we will invite you for a screening visit. If you decide to participate you will be asked to sign an informed consent form. Your doctor will then perform some tests and procedures to determine whether you are eligible for the study.

If you are eligible for the study you will be randomised to either receive the EndoBarrier device for 12 months and subsequently a diet for a further 12 months after the implant, or you will receive a standard medical therapy and a diet for 24 months. All patients will receive specialist support from a doctor specialising in the treatment of diabetes and a dietitian.
Randomisation means that a group of people are split into two groups at random; one group is given one intervention (the EndoBarrier device) and the other is given a different intervention (standard medical therapy/ control group). We then measure how each group is doing and see if one group has achieved its supposed outcome any better.

On your second study visit we will inform you about the treatment for which you have been randomised for the duration of the study. We will further inform you about other tests performed while being on this trial. Your dietitian will assess your diet and give you specific dietary information.

Version 1, 24th April 2014

On some of the study visits, we will also ask you to participate in specific tests which will help us to assess your metabolism, brain activity, insulin sensitivity and food preference. Participation in these tests is entirely optional. More information about these tests can be found in the patient information sheet.

On visit 4 you will either have the EndoBarrier device inserted (EndoBarrier group) or you will see the diabetic specialist doctor or nurse (Medical Therapy group). You will also see the dietitian for review.

During some study visits, you will see the diabetic specialist doctor or nurse, the gastroenterologist (EndoBarrier group only), and the dietitian for review.

If you are in the EndoBarrier group, your EndoBarrier will be removed after 12 months.

What happens if I want to withdraw from the study?

There are no foreseeable reasons why you should end your participation but you may withdraw from the study at any time.

What are the possible advantages and disadvantages of taking part?

Your direct benefit of taking part in this research will be the possible improvement in your blood glucose and HbA1c, blood pressure, weight loss and reduction in long term health risks particularly cardiovascular diseases.

The risks associated with the EndoBarrier procedure include the same risks observed with other upper gastrointestinal endoscopic procedures.

If you are randomised into the EndoBarrier group of the study, the frequent side effects are: cramps/abdominal pain, nausea/vomiting and/ or bloating. Other rare side effects are described in the Participant Information Sheet. If you are randomised into the control arm of the study, no side-effects are expected. More information of potential benefits and risks are outlined in the Participant Information Sheet.

What are the payments for this study?

On each visit, you will be reimbursed for your travel to the hospital.

Contact Information

Dr Prechtl or Dr Mohanaruban can be contacted on 07872850052 or 02075945946.

Thank you for taking the time to read and consider this information sheet.

Version 1, 24th April 2014

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Review Article

The EndoBarrier: Duodenal-Jejunal Bypass Liner for Diabetes and Weight Loss

Aruchuna Ruban, Hutan Ashrafian, and Julian P. Teare

Department of Surgery and Cancer, Imperial College, London, UK

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Abstract

The rapid rise of obesity and type 2 diabetes poses a global threat to healthcare and is a major cause of mortality and morbidity. Bariatric surgery has revolutionised the treatment of both these conditions but is invasive and associated with an increased risk of complications. The EndoBarrier is a device placed endoscopically in the duodenum, which is designed to mimic the effects of gastric bypass surgery with the aim of inducing weight loss and improving glycaemic control. This review outlines the current clinical evidence of the device, its efficacy, potential mechanisms of action, and utility in clinical practice.

1. Introduction

Obesity has reached epidemic proportions with the WHO estimating that approximately 2.3 billion adults worldwide are overweight and more than 700 million are obese [1]. Obesity is associated with the development of other comorbidities, in particular diabetes, which currently affects 422 million adults worldwide [2]. The current favoured treatment for patients with type 2 diabetes (T2DM) who are obese is referral for bariatric surgery. In the 2nd Diabetes Surgery Summit in 2015, several national diabetes societies such as the American Diabetes Association (ADA) and Diabetes UK have recommended the use of bariatric surgery in obese type 2 diabetics reporting diabetes remission rates of between 30–60% following surgery [3]. However, with a greater demand being placed on bariatric surgery, there is a drive to develop nonsurgical alternatives to combat the ever-rising obesity and diabetes epidemic.

One potential alternative is the EndoBarrier, an endoluminal duodenal-jejunal bypass liner (DJBL) developed by GI Dynamics (GID) Inc., Lexington, MA. In this state-of-the-art review, we present the current clinical trial data available on the EndoBarrier and explore its potential mode of action, safety profile, and potential applications in the management of obesity and T2DM.

2. The Device

The EndoBarrier is a single-use endoscopic implant, which consists of the liner, delivery system, and retrieval system. The actual liner portion is an impermeable fluoropolymer that spans 60 cm into the small intestine (Figure 1). Located at the proximal end of the liner are anchors with barbs made of nitinol allowing the device to affix and be secured to the duodenal bulb, proximal to the ampulla of Vater but distal to the pylorus. These anchors also have drawstrings attached to them to facilitate subsequent removal of the device at the end of treatment. Once deployed in the duodenum, the device can remain for a maximum treatment period of 12 months. The liner is open at both ends promoting the passage of chyme from the stomach bypassing the duodenum and into the jejunum. Concurrently, pancreatic juices and bile will enter the duodenum from the ampulla of Vater running along the outside of the sleeve avoiding contact with gastric contents until these exit the sleeve in the jejunum (Figure 2). The desired effect is for the sleeve to mimic the duodenal-jejunal exclusion portion of gastric bypass surgery, thus recreating the beneficial effects seen in postsurgery on glucose homeostasis and energy metabolism, but without enduring permanent alterations to the intestinal anatomy and avoiding the risks associated with undergoing invasive surgery.

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Daily Mail, Saturday, May 14, 2016 VI Page 11

The no-surgery 'gastric band' to beat diabetes

It could help tackle obesity too and save NHS millions

By **Fiona MacRae**
Science Editor

A SIMPLE plastic tube could revolutionise the way the NHS treats diabetes.

The fake intestine lining may provide the benefits of a gastric bypass without the expensive surgery.

Doctors at Imperial College London who have begun a £1.6million trial of the EndoBarrier say the device, which could also combat many problems associated with obesity, could be in use within four years and save the NHS millions.

Britain has the second highest rates of obesity in Europe and the condition costs the economy up to £16 billion a year.

Rates of type 2 diabetes, the form of the condition fuelled by obesity, are soaring and the illness eats up a tenth of the NHS's budget.

It also leads to disabling and life-threatening complications including heart attacks and strokes, blindness and circulatory problems that can lead to amputations.

Trial co-leader Professor Julian Teare said: 'Obesity is a modern pandemic. There is an urgent need for effective and safe non-surgical treatments for the epidemic of obesity and type 2 diabetes.'

The EndoBarrier is a sock-sized tube constructed from a Teflon-like material.

It is inserted down the throat and through the stomach to the small intestine.

Once there, it mimics the effects of gastric bypass surgery by blocking food from being digested.

A gastric bypass is seen as the most effective way to lose weight, with most patients shedding around two-thirds of their excess weight.

It also leads to dramatic improvements in diabetes patients, with many able to stop taking tablets.

However, there are long waiting lists for gastric bypasses, which require major surgery and cost up to £15,000. Some 2.6 million Britons qualify for weight loss surgery but just 6,000 operations are carried out a year.

It is hoped the EndoBarrier, which is made by a US firm, will have a similar effect to a gastric bypass – in which the stomach is made smaller and a section of the intestine put out of action – without the need for surgery.

The new device is inserted in under an hour and patients can go home two hours later.

The two-foot tube reduces the amount of food digested and fools patients into feeling full, meaning most shed a quarter of their excess weight in three months.

'A powerful weapon in fight'

Diabetes symptoms improve quickly after a gastric bypass and the EndoBarrier has a similar effect, trials suggest.

It is thought that tinkering with the digestion raises levels of a substance called GLP, which helps to regulate the production and processing of insulin. Insulin, which helps the body process glucose, stops working properly in patients with diabetes.

The EndoBarrier also somehow affects tastebuds, making patients prefer savoury to sweet foods.

It has to be removed after a year, but it is hoped that the changes to the metabolism will be permanent – meaning it could provide a long-term cure for diabetes.

The latest trial is designed to be big enough and detailed enough to determine whether the device is suitable for widespread use on the NHS.

Some 120 obese men and women with type 2 diabetes will be treated in London and Southampton in studies funded by the NHS's research arm, the National Institute for Health Research, and the Medical Research Council.

Half of the patients will have an EndoBarrier implanted, while the rest will be be given obesity drugs and treated by a dietician.

After a year, the health of the two groups will be compared and more testing will be done a year later to see if the EndoBarrier's effects have persisted after removal. The first patients have already been treated but more volunteers are needed.

Researcher Dr Aruchuna Mohanaruban, of St Mary's hospital in West London, said that if the trial is a success, the EndoBarrier could be in widespread use by 2020.

He added: 'Diabetes and obesity are probably the two biggest epidemics we are facing in the UK.

'Gastric bypass is one of the most effective treatments for diabetes, with 60 to 70 per cent of patients cured.

'But not everyone wants to have surgery, it is not without risks and waiting lists are long. This could potentially be an alternative. The EndoBarrier could be a powerful weapon in the fight against obesity.'

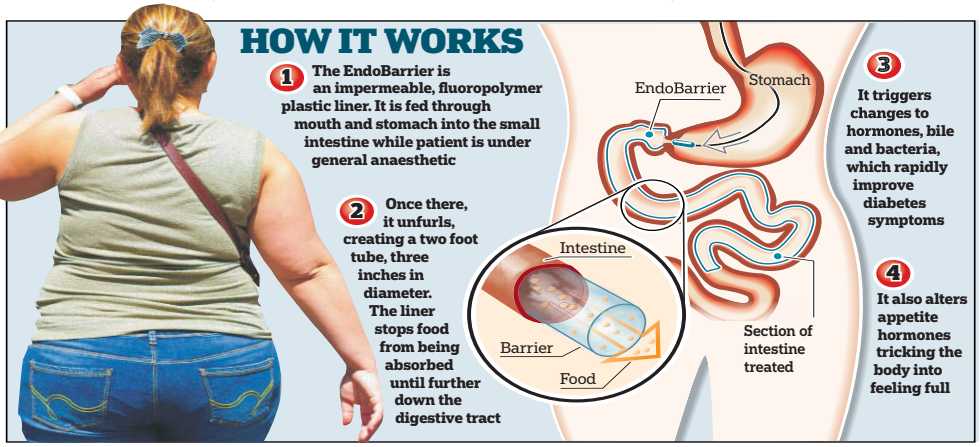
Professor David Haslam, chairman of the National Obesity Forum, said: 'It's very promising but we have to wait for the trial results.'

But Mike Lean, a diabetes expert and professor of human nutrition at Glasgow University, described it as a 'veterinary approach' that 'cannot have long-term benefits'.

He said that at up to £8,000 a procedure, the EndoBarrier is 'fantastically expensive'.

Dr Emily Burns, of the charity Diabetes UK, said: 'It is important to remember that while weight loss surgery for type 2 diabetes is an important treatment option, it should not be seen as a way to fix the type 2 and the obesity epidemic on its own.'

She added: 'We need more measures to prevent people from becoming overweight and obese.'



We've had 2016's only Friday 13th

IF YOU made it through yesterday, then you can breathe a sigh of relief – because it was the only Friday 13th of the year.

There can be as many as three Friday the 13ths in a single year, but this year we had only one to deal with.

The date has been linked to bad luck for centuries, and in the Middle Ages people believed it was because there were 13 people at the Last Supper.

Since then there has been a long-standing myth that if 13 people dine together then one of them will die within a year.

The day's unlucky status was intensified in 1907 with the publication of Thomas W. Lawson's popular novel Friday the 13th, about a stockbroker who uses the superstition to create a Wall Street panic.

Daily Mail Reporter

Studies have shown there are more accidents on Friday the 13th, and some tall buildings and hotels won't call a floor the 13th because of concerns about bad luck.

Often particularly superstitious homeowners avoid putting the number 13 on their door, and the fear even has its own name: 'Triskaidekaphobia.'

But there are some good things associated with the date, as studies have shown that flights are cheaper on the day, as fewer people want to risk travelling.

Dr Caroline Watt, of the psychology department at the University of Edinburgh, said that, ironically, being frightened of the day can put you at risk.

She said: 'If people believe in the superstition of Friday the 13th then they believe they are in greater danger on that day.

'As a result they may be more anxious and distracted and this could lead to accidents. It becomes a self-fulfilling prophecy. It is like telling someone they are cursed. If they believe they are then they will worry, their blood pressure will go up and they put themselves at risk'.

In 2017, Friday the 13th will strike twice. The next year when the date will occur only once is 2021. And the last time there was only one Friday 13th was 2014.

[redacted]

Imperial Medicine Blog

Could the EndoBarrier be the next weapon of mass reduction?

Aruchuna Mohanaruban

28 March 2018

UK obesity rates have continued to rise at an alarming rate, with figures higher than any other developed nation. Strongly associated with obesity is the increased susceptibility to developing type 2 diabetes (T2DM) which currently affects 3.2 million of the UK population. Bariatric surgery – a type of surgery aimed at inducing weight loss – usually by altering the stomach and/or intestines has revolutionised the treatment of these conditions and can lead to a 60% remission in diabetes. However, with demand for this type of surgery outstripping supply, there is a greater need to develop non-surgical alternatives to combat the ever-rising obesity and diabetes epidemic.

What is the EndoBarrier?

One promising alternative comes in the form of an innovative implant: the EndoBarrier, developed by GI Dynamics Inc. This device consists of an impermeable 60cm sleeve, made from a fluoropolymer – a tough and resistant polymer. At one end of the sleeve is a stent anchor allowing the device to affix to the wall of the duodenum. The sleeve then extends 60cm into the small intestine.

How does the EndoBarrier work?

Consequently, digested food passes through the sleeve without being absorbed and bypasses the upper part of the small intestine before coming into contact with pancreatic and bile juices at the other end where it is then absorbed. Cutting out the first part of digestion leads to changes in the metabolism of nutrients and glucose through a variety of mechanisms including:

modulation of gut hormones

alterations in the gut bacteria

disruption of bile flow

Consequently, the patient will begin to feel full quicker due to an increase in satiety hormones which will then decrease the amount they eat. There is also a positive shift in the metabolism of glucose in the body, so more sugar is taken up into cells, and the insulin which a person is naturally producing becomes more effective.

How is the EndoBarrier implanted?

The EndoBarrier is inserted into the small intestine through the mouth using an endoscope (a flexible telescope with optical illumination) and therefore does not require any surgery, unlike a gastric band. Patients can go home within hours of having the procedure performed which takes just under an hour. Another advantage is that general anaesthetic is not always required as the procedure can also be performed whilst giving the patient a sedative, thus reducing the risks associated with anaesthesia.

How is the EndoBarrier removed?

The EndoBarrier is licenced for one year after which point it needs to be removed, but again, this procedure is relatively simple and takes 30 minutes to perform using an endoscope. A specially designed grabber is used to hook the device, collapsing it down in the intestine before removing it safely through the mouth.

How is EndoBarrier being tested for diabetes?

I am a clinical research fellow at the Department of Surgery and Cancer, and along with **Professor Julian Teare** who is the primary investigator, I head the **EndoBarrier trial** – a National Institute for Health Research (NIHR) funded multi-centred randomised control trial being conducted at Imperial College Healthcare NHS Trust and University Hospital of Southampton. This clinical trial is unique in that it is nationally funded and is the first randomised control trial of the EndoBarrier, which compares the device against intensive medical therapy for diabetes and obesity.

Does the EndoBarrier work?

With 170 patients recruited nationally across both sites, the trial has already had a positive

impact on the health of those successfully enrolled in the study. These are all patients with difficult to manage diabetes who are struggling with their weight. Over 35 patients have had the device implanted successfully at Imperial, with exciting changes in their diabetes control and weight loss seen. The result of this study will be published in 2019.

How is the EndoBarrier impacting daily life for patients?

Patient testimonial:

“I have been suffering type 2 diabetes for approximately five years and struggling with my weight for quite some time. As soon as I heard about the EndoBarrier trial I wanted to take part; I had nothing to lose. I was ready to try anything and ready for a change. Over the course of a year, I had lost a considerable amount of weight – I went from 154kg down to 121kg. My sugar levels went from 61 down to 51 and I was very pleased.

“By receiving the EndoBarrier therapy I have been able to make dietary adjustments and completely stopped binge eating. I have increased my exercise regime too, which was virtually zero. I found that my quality of life has improved, my energy levels have increased and I was overall simply a happier person! I personally would recommend the therapy to anyone. Personally, I’ve had a lot of positives impacts from it.”

The clinical trial has already received widespread interest from the national press and has featured in the Daily Mail and Channel 4 who recognised its simple innovative design and exciting results on weight loss and diabetic changes. As the clinical research fellow, it’s very rewarding being involved in the first EndoBarrier randomised trial. Although we recognise that exercise and healthy eating still remain the essential preventative measures for obesity and diabetes, this device could make a big difference in aiding weight loss, or enabling the super obese to reach a weight where they can start exercising. I am hopeful that this device might mimic the effects of restrictive surgery such as gastric bypass but without the risks and complications associated with undergoing surgery, providing another tool in the fight against the obesity and diabetes epidemic.

Dr Aruchuna Mohanaruban is a Clinical Research Fellow at the Department of Surgery & Cancer.

Find out more about the EndoBarrier trial.

By Aruchuna Mohanaruban

Categorised under Department of Surgery and Cancer

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