Portsmouth Hospitals NHS
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Comparison of ambulatory glucose profile prior to and during pancreatic enzyme replacement therapy in patients with diabetes and pancreatic exocrine insufficiency: a single-arm phase IV trial

DRIVE – PEI

Diabetes and Real world investigations into Instability, Variability and Exposure – Pancreatic Exocrine Insufficiency

Short title: Pancreatic replacement therapy and glycaemic control in diabetes

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Original	V1.0	03/04/17	–	–
1 (REC and MHRA changes)	V2.0	22/05/1723/05/17	Dr Katherine Alington	10.4.2 changed definition of childbearing potential and clarified contraception requirements 10.4.5 study visit 4 – confirmed a letter will be sent to GP after AGP review if therapy change recommended 11.2 add questions on dietary habit to GI symptom questionnaire 11.3 all Creon required for study will be provided by hospital pharmacy Appendix 10 removal of GP prescription request letter 12.1.3 removed incorrect definition of unexpected AE 12.1.4 removed due to incorrect definition of related SAE 12.1.5-8 re-numbered to 12.1.4-7 12.3 corrected reporting procedures for SUSARs 12.4 corrected SAE reporting timeframe and Investigator, CI and Sponsor roles

2. SYNOPSIS

Study Title	Comparison of ambulatory glucose profile prior to and during pancreatic enzyme replacement therapy in patients with diabetes and pancreatic exocrine insufficiency: a single-arm phase IV trial
Internal ref. no.	PHT/2017/20
Problem statement	Diabetes is linked to high rates of PEI, which requires PERT. Although PERT is known to alleviate the gastrointestinal symptoms of PEI, the effect that PERT may have on glycaemic control has not been well established by using glycated haemoglobin (HbA1c) and self-monitoring or laboratory glucose testing. Much of the daily glucose variability, instability and hypoglycaemia frequency is missed through these methods, yet these are still contributors towards long-term vascular risk. Further studies are therefore needed to substantiate the probable glucose lowering effect and identify any potential treatment strategies to improve patient care.
Research question / hypothesis	Does treatment of PEI with PERT in individuals with T1DM or T2DM result in improved glycaemic control?
Study Design	Phase IV, single-arm trial

Study Participants	The participant must meet ALL of the following criteria to be considered eligible for the study:
	- Male or Female, aged 18 years or above
	- Diagnosed with Type 1 diabetes or Type 2 diabetes at least 1 year ago
	  o Be receiving oral and / or insulin therapy for diabetes
	- Have 1 or more symptoms of PEI:
	  o Diarrhoea – Bristol Stool Chart (see appendix) type 5, 6 or 7
	  o Steatorrhoea or greasy, pale or offensive smelling stools
	  o Weight loss
	  o Abdominal pain or cramps
	  o Bloating or increased flatulence
	- Low faecal elastase level <200mcg/g within last 2 years
	- Willing and able to give informed consent for participation in the study and for GP to be informed

Planned Sample Size	18-24
Follow-up duration	10 weeks
Planned Study Period	18 months
Primary Objective	To compare glucose variability (represented by mean interquartile range (IQR) over 2 weeks) in patients with diabetes and PEI prior to starting PERT and 6 weeks after starting PERT
Secondary Objectives	To compare the following AGP metrics prior to and 6 weeks after starting PERT

	as collected by the Freestyle Libre flash glucose monitor: - Glucose exposure - Average glucose - Time in hyperglycaemia (>10mmol/L and >15mmol/L) - Time in target range (TIR) (4-10mmol/L) - Time in hypoglycaemia (<3.9mmol/L and <3mmol/L) - Glucose instability - Specific time periods including post-prandial (2 hours after meal) - Estimated HbA1c To compare clinically important measurements including HbA1c, weight and BMI Exploratory comparisons in the following groups: - T1DM and T2DM - Mild/moderate PEI (FE1 100-200mcg/g) and severe PEI (FE1 <100mcg/g) - Responders to PERT and non-responders to PERT based on GI symptom questionnaire
Primary Endpoint	Mean interquartile range over 14 days at weeks 6-8 as measured by the Freestyle Libre flash glucose monitor
Secondary Endpoints	Other AGP metrics averaged over 14 days at weeks 6-8 as measured by the Freestyle Libre flash glucose monitor: - Area under median curve (AUC) - Median - Time above target range (>10mmol/L and >15mmol/L) - Time in target range (TIR) (4-10mmol/L) - Time below target range (<3.9mmol/L and <3mmol/L) - Median curve instability - Specific time periods – including pre-prandial and post-prandial - Estimated HbA1c GI symptom questionnaire at 8 weeks after starting PERT Clinical measurements – HbA1c, weight, BMI at 8 weeks after starting PERT
Intervention(s)	PERT (Creon) at standard dose of 50,000 units per meal and 25,000 units per snack for 8 weeks

3. ABBREVIATIONS

AE	Adverse event
AGP	Ambulatory glucose profile
ANOVA	Analysis of variance
AUC	Area under curve
BMI	Body mass index
CBD	Common bile duct
CCK	Cholecystokinin
CGM	Continuous glucose monitoring
CI	Chief Investigator
CRF	Case report form
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
e-CRF	Electronic case report form
ELISA	Enzyme linked immunosorbent assay
FE1	Faecal elastase 1
FGM / FlashGM	Flash glucose monitoring
FM	Flash monitoring
Freestyle Libre Pro	Freestyle Libre Professional flash glucose monitoring system
GCP	Good clinical practice
GP	General Practitioner
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic hormone
GIT	Gastrointestinal tract
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated haemoglobin
HCP	Healthcare professional
HHS	Hyperglycaemic hyperosmolar state
HRA	Health Research Authority
IBS	Irritable bowel syndrome
IMP	Investigational medicinal product
IQR	Inter-quartile range

MHRA	Medicines and Healthcare Products Regulatory Agency
MDT	Multidisciplinary team
NHS	National Health Service
OGTT	Oral glucose tolerance test
PEI	Pancreatic exocrine insufficiency
PERT	Pancreatic enzyme replacement therapy
PHT	Portsmouth Hospitals NHS Trust
PI	Principal Investigator
PIL	Patient information leaflet
PIS	Participant information sheet
QOL	Quality of life
REC	Research ethics committee
RSI	Reference safety information
SAE	Serious adverse event
SD	Standard deviation
SMBG	Self-monitoring of blood glucose
SmPC	Summary of product characteristics
SOP	Standard operating procedure
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TMF	Trial master file
TMG	Trial management group
TIR	Time in (target) range
TOG	Trial oversight group
UKPDS	UK Prospective Diabetes Study

4. BACKGROUND AND RATIONALE

4.1 Lay summary

Diabetes is a common chronic condition. About 6% of the UK population already have either type 1 diabetes (T1DM) or type 2 diabetes (T2DM), and one in ten are at risk of developing diabetes.

People with diabetes may develop problems including diabetic eye disease, numbness in feet, kidney damage and heart problems. We know how to prevent and treat these conditions. However, diabetes can also cause other problems that we know less about, for example, delayed stomach emptying after meals, and problems with the pancreas not producing enough juices to help digest food.

When the pancreas doesn't produce enough of these digestive juices, patients may have abdominal pain, bloating, diarrhoea and weight loss. This condition is called PEI (pancreatic exocrine insufficiency) and is confirmed by a stool test.

PEI is easily treated by supplementing the digestive juices with a capsule, which contains enzymes for digestion (pancreatic enzyme replacement therapy – PERT). This is taken with every meal and can significantly improve symptoms. This treatment may also improve blood sugar control for people with diabetes, but we are not sure exactly how.

In this study we will monitor sugar levels in patients with diabetes and PEI using a new sensor which sticks to the skin for 2 weeks and measures sugar levels every 15 minutes. We will use this sensor before and after treatment with PERT to give us a better idea of what happens to sugar levels than tests such as HbA1c and fingerprick testing. Patients will continue all their normal medications and diabetes treatments during the study.

Patients will continue to receive PERT from their GP after the study. At the end of the study patients will also be given their sensor results (showing blood sugar levels in more detail), which may help patients to manage their diabetes better in the future.

4.2 Clinical background and definitions

4.2.1 Diabetes mellitus

Diabetes mellitus is a disorder of hyperglycaemia caused by either a deficiency of insulin, or resistance to insulin, or a combination of both. In normal physiological states, insulin is released by the islet cells in the pancreas, stimulated by the production of glucagon-like-peptide-1 (GLP-1) and glucose-dependent insulinotropic hormone (GIP) (know as incretins) by the endocrine cells in the small bowel mucosa in response to carbohydrate and lipid presence in the proximal gastrointestinal tract (GIT). Systemically circulating insulin regulates transport of glucose from blood into cells for storage and use as an energy source. In diabetes, high levels of glucose circulates in the in the blood but is unable to be utilised for energy or storage in muscle and adipose tissue, leading to typical symptoms of hyperglycaemia, metabolic derangement and other complications (1).

In addition to glucagon and somatostatin secretion by the pancreas, the regulation of insulin forms the endocrine pancreatic function.

Type 1 diabetes (T1DM) is characterised by autoimmune destruction of pancreatic islet cells resulting in absolute deficiency of insulin. Type 2 diabetes (T2DM), in contrast, is associated with insulin resistance, often with a degree of insulin deficiency. The cause of T2DM is more varied and multifactorial, with both lifestyle and genetic factors contributing. Approximately 90% of patients with diabetes have type 2, and the remaining 10% have type 1 (1–3) .

Diabetes may be diagnosed when a patient presents with symptoms, but, particularly with T2DM, it may remain asymptomatic for some time and therefore is picked up incidentally, through screening or other routine testing. Diagnostic testing uses one or more of the following; fasting plasma glucose, oral glucose tolerance test and glycated haemoglobin (HbA1c) (3,4).

Treatment depends on the underlying aetiology, and in the case of T2DM, the stage at which a patient is diagnosed may influence initial therapy choice (including the presence of any complications). T1DM is treated with insulin from the time of diagnosis, whereas T2DM can initially be treated with diet and lifestyle modification. Additionally, oral anti-diabetic agents with varying modes of action can be added in. As the disease progresses, patients may be commenced on insulin, as well as newer injectable anti-diabetic agents (3,4).

Daily glucose control is traditionally managed by undertaking finger-prick tests with a handheld glucometer, known as self-monitoring of blood glucose (SMBG). This is undertaken by all T1DM patients and a group of those with T2DM, typically those on insulin, but is not indicated for all. HbA1c is a marker of glycaemic exposure over 2-3 months and is very commonly used for monitoring purposes in diabetes review consultations.

In addition to monitoring and treating glycaemic control, there are a number of recognised complications of diabetes including macrovascular complications (atherosclerosis and cardiovascular disease) and microvascular (neuropathy, nephropathy and retinopathy). Blood pressure control and lipid management are also important. High HbA1c levels are linked to higher risk and progression rate of microvascular complications and myocardial infarction, as demonstrated in both the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) (5,6).

There is growing evidence to show that it is not only high levels of glucose exposure (demonstrated by HbA1c) that is linked to complications. Hypoglycaemia has also been associated with increased morbidity and mortality, related to both the neurological effects of severe hypoglycaemia and, as identified more recently, to cardiovascular events including cardiac arrhythmias and other vascular complications.

Whilst HbA1c is a very useful marker, much of the daily variability in glucose patterns is missed, and patients with similar HbA1c levels can have very different daily glucose patterns, including frequency of hypoglycaemia. Indeed, this variability can often also be missed with SMBG when, for example, four tests might be done in an average day but variability between these tests, including pre- and post-prandial changes and overnight, remains undetected. Whilst glycaemic variability has not been directly shown to cause diabetes complications, it has been shown to predict risk of hypoglycaemia and can therefore be used as an additional and valuable tool.

Continuous glucose monitoring (CGM) technology is an alternative method of measuring glucose levels which provides a much greater frequency of glucose readings than is typically available with SMBG.

4.2.3 Ambulatory glucose profile (AGP)

The glucose data from CGM can be displayed using the AGP. This is a novel way of displaying and interpreting glucose data that uses a visual illustration of an individual's typical day to identify trends in hyperglycaemia, hypoglycaemia and other metrics.

Data collected over multiple days are plotted according to time over 24 hours (from midnight to midnight) to provide a model day which enables rapid qualitative and quantitative visual analysis of trends. In addition, data can be downloaded and analysed in more depth.

In 2012 an expert panel comprising diabetes specialists met with the aim of standardising analysis and display methods of the AGP using CGM data (7). The key glucose metrics that were identified and defined include:

- Target range – can be expressed as time in target range (% or number of hours)
- Glucose exposure – can be evaluated as area under curve (AUC), mean or median
- Glucose variability – expressed using interquartile range (IQR) and inter-decile range (10^{th} – 90^{th} decile)
- Hypoglycaemia – can be expressed in terms of time spent in this range, number of episodes, and risk of episode happening (using glucose instability)

In addition, the panel also determined that 14 days of CGM data can give a 'very accurate, relatively stable reflection of the key glucose metrics' which would be 'highly reflective of what the display would look like after 30 days of CGM' (7). It was determined that 7 to 10 days of data was not necessarily enough to enable accurate interpretation, however some recent studies using CGM have performed analysis of AGPs that have been produced using just 7 days of data (8).

Once the data is downloaded in raw format, a variety of analyses can take place and enable statistical comparison between sets of data, both for the same individual, and across individuals.

4.2.4 Pancreatic exocrine insufficiency

The pancreas plays a vital role in digestion. Gastric acid in the duodenum stimulates the release of secretin from duodenal mucosal cells, which in turn stimulates the release of water and bicarbonate from pancreatic ductal cells. In addition, the presence of fat and protein in the duodenum stimulates cholecystokinin (CCK) release by endocrine cells in the duodenal mucosa, which results in the release of pancreatic enzymes and pro-enzymes from pancreatic acinar cells. Together this combination of water, bicarbonate and enzymes form the pancreatic juices that, once released into the duodenum, enable digestion of fat, carbohydrate and protein. This process is known as the pancreatic exocrine function.

For this process to work, the pancreas requires adequate stimulation, the ability to produce the pancreatic enzymes and a patent pancreatic duct and common bile duct (CBD) to allow flow into the duodenum (9).

There are a number of situations that can lead to a failure of one or more of these steps and subsequently reduced levels of pancreatic enzyme activity within the duodenum, thus resulting in pancreatic exocrine insufficiency (PEI). Of the enzymes released by the pancreas, both amylase

and various proteases are also produced elsewhere in the GIT (such as the salivary gland and the stomach). Lipase is least stable within the gastrointestinal tract and does not have a second site of release, therefore signs and symptoms of fat malabsorption predominate when there is reduced exocrine production from the pancreas. These include weight loss, steatorrhoea (characterised by foul smelling, frothy and floating stool), diarrhoea, abdominal pain and bloating. Weight loss and steatorrhoea are the symptoms most associated with PEI; however these are usually seen in more severe forms when a significant amount of exocrine function has already been lost (typically around 90%). Prolonged PEI can result in malnutrition and fat-soluble vitamin deficiencies if untreated.

The prevalence of PEI amongst individuals without known pre-existing gastrointestinal or pancreatic disease is estimated to be between 11.5 – 21.7%, with approximately 11,000 patients diagnosed in the UK each year (10).

PEI may be caused by intrinsic pancreatic disease and damage (fibrosis and atrophy) such as chronic pancreatitis, following acute pancreatitis, cystic fibrosis and pancreatic malignancy. Other conditions which may result in PEI include; obstructive lesions within the pancreatic duct or CBD such as a tumour or stricture, and anatomical abnormalities such as following upper gastrointestinal (GI) surgery.

It is known that fibrosis, atrophy and destruction of the acinar cells leading to PEI and chronic pancreatitis is associated with the development of diabetes, often known as Type 3C diabetes, or pancreatogenic diabetes, although this loss of endocrine function often occurs late.

There are many different diagnostic tests available to help identify PEI. Previously, invasive pancreatic function tests such as direct duodenal sampling after pancreatic secretin stimulation was considered the gold standard; however these tests are invasive, time consuming, poorly tolerated by patients and not widely available and therefore are not routinely performed in the UK (11). Quantitative analysis of faecal fat content has also been used as a standard test for investigation of malabsorption, however this is difficult and unpleasant to perform; requiring 3 days of total stool collection and analysis (11) and is rarely performed. Pancreatic imaging may be performed, but is more helpful in diagnosing chronic pancreatitis and malignancy than PEI without obvious structural change.

Faecal elastase-1 (FE1) levels can be measured in stool using an enzyme linked immunosorbent assay (ELISA), and is recommended in the UK as the current standard of care for screening for PEI (10,11). FE1 is secreted by the pancreas and undergoes little degradation within the gut lumen before being excreted in faeces, unlike the majority of the other pancreatic enzymes. Despite being an indirect test of pancreatic function, it has been shown to correlate well with other tests of pancreatic exocrine function. FE1 requires a random spot stool sample rather than prolonged sampling. FE1 is not affected by the administration of exogenous enzymes. Reports of exact sensitivity and specificity vary within the literature, however generally accepted reference ranges are: mild to moderate PEI FE1 100-200mcg/g and severe PEI FE1 <100mcg/g (10,12).

Once PEI is diagnosed, the general treatment approach is to normalise digestion and alleviate symptoms. This is achieved through the use of pancreatic enzyme replacement therapy (PERT) plus general supportive advice, including smoking cessation, dietary advice and correction of any related vitamin deficiencies. A low fat diet is no longer recommended (9). PERT is an oral preparation, also known as pancreatin, which is taken at mealtimes and with snacks, with the dose adjusted according to the fat content of the food and on clinical response. A number of different preparations are available commercially; most are enteric coated and all are of porcine origin.

Monitoring is based on clinical response (symptoms, weight change and markers of malnutrition); there is no consensus on repeated testing, particularly given that a change in FE1 would not be expected and other tests such as faecal fat quantification face the same problems as for initial diagnosis (9). A retrospective study has shown that approximately 80% of patients respond to treatment with PERT (10). In patients with no improvement in symptoms, the diagnosis should be questioned and an alternative sought (9).

4.2.5 Diabetes and PEI

High rates of PEI are found in patients with both T1DM and T2DM, although it is relatively underdiagnosed in routine clinical practice, with GI symptoms often attributed to other diabetes complications such as gastroparesis, drug side effects such as metformin, and other co-existing GI disorders such as irritable bowel syndrome (IBS) (13). GI symptoms are experienced frequently in diabetes, with a recent UK survey indicating that over 90% of patients suffer with varying frequency (14).

Studies using FE1 for diagnosis have shown that between 25 – 74% of patients with T1DM have PEI, and between 28 – 54% of patients with T2DM have PEI (15). A recent study performed by the Academic Department of Diabetes and Endocrinology at the Queen Alexandra Hospital, established that 24% of patients attending the specialist clinic experienced one or more GI symptom consistent with PEI. 42% of these patients were found to have a low FE1 (<200mcg/g) consistent with PEI (13). The study also showed that diarrhoea (stool type 5 – 7 on the Bristol Stool scale) was the most common symptom in this cohort, with steatorrhoea second most common and unintentional weight loss third.

Specific factors that can identify patients most at risk of developing PEI are varied, but there is no clear consensus in the literature. These include: duration of diabetes, poorer glycaemic control and high HbA1c, need for insulin (in T2DM) and increased insulin doses, and presence of microvascular or macrovascular complications (15,16).

A number of hypotheses regarding the cause of PEI in diabetes have been suggested, though the exact underlying aetiology, or aetiologies, is still not certain. It has been shown frequently that the pancreas is macroscopically altered in patients with diabetes, with smaller sized organs and evidence of fibrosis and atrophy visible both histologically and on imaging (17). Theories regarding the underlying process leading to these changes include: the reduced trophic effect due to a lack of insulin, the effect of diabetic neuropathy (particularly autonomic neuropathy), fibrosis and atrophy due to microvascular and oxidative stress damage, disregulation due to changes in other islet hormones including glucagon and somatostatin, autoimmune effects, and the presence of underlying pancreatic disease such as chronic pancreatitis that has gone undiagnosed (suggesting that the individual therefore has Type 3c diabetes) (13,17–19). Furthermore, it has been postulated that genetic factors are also involved in development of exocrine dysfunction in diabetes (18).

PEI in diabetes is treated in the same way as PEI due to other conditions; with PERT, dietary and lifestyle advice (smoking and alcohol cessation) and correction of nutritional deficiencies as appropriate. PERT has been shown to be safe in diabetes, without significant adverse effects on glycaemic control (17,20).

4.3 Glycaemic control in diabetes, PEI and PERT

4.3.1 Current understanding

The exact effect of PERT on glycaemic control in patients is not well established. It is known that pancreatic enzyme replacement in PEI enhances the release of GIP in response to oral nutrient ingestion (21). Similarly, post-prandial GLP-1 has also been shown to be increased in patients with PEI who are treated with PERT (21). These findings are thought to represent the fact that GIP and GLP-1 are secreted in response to nutrients that have been digested.

Since release of GIP and GLP-1 leads to a slower rate of gastric emptying (and therefore a more controlled rise in post-prandial glucose) as well as insulin release, it is possible that this enhanced GIP and GLP-1 response in patients with PEI treated with PERT will result in improved glycaemic control (18). However, this outcome has not been substantiated by studies to date.

A study involving adolescents with cystic fibrosis has shown that there is an improvement in post-prandial glycaemia following PERT supplementation (22); results which have also been shown (in addition to an improvement in HbA1c) in a study of patients with tropical calculous pancreatitis (also known as fibrocalcific pancreatic diabetes) (23). In contrast, whilst Ewald et al found no difference in either HbA1c or oral glucose tolerance test, they did find a reduction in mild to moderate hypoglycaemia following PERT (20), though Knop et al found only a non-significant B cell response, in a study involving only a small number of patients (8) (21).

Whilst both cystic fibrosis and chronic pancreatitis, including tropical calculous pancreatitis, are associated with diabetes and pancreatic exocrine insufficiency, the underlying pathological processes leading to these conditions are appreciably different to those of type 1 and type 2 diabetes and the hypothesised causes of PEI in these cases (see section 4.2.5). Furthermore, and particularly in cystic fibrosis, the typical pattern of abnormal glycaemic control differs from that of typical type 1 and type 2 diabetes. As such, the findings in the above studies involving chronic pancreatitis and cystic fibrosis may not be transferrable to the wider diabetes population.

HbA1c, plasma glucose levels and other laboratory measures have been employed in the above studies, however no glucose profiling using CGM techniques have been utilised. This study will aim to observe the glucose control in this cohort of individuals by using CGM, which may provide a better understanding of glycaemic change than has previously been possible to detect with traditional methods.

4.3.2 Current research

A search of clinical trials registers (clinicaltrials.gov, EU Clinical Trials Register and the International Standard Randomised Controlled Trial Number (ISRCTN)) confirms that there are no current studies that are using CGM to investigate individuals with diabetes and PEI. As described above in sections 4.2.5 and 4.3.1, some studies have looked at glucose control in this situation, but using only standard SMBG and HbA1c as markers, which provide very limited insight into glycaemic control.

By using CGM in this study, the aim is to gain a much more detailed understanding of glycaemic control due to the greatly increased frequency of glucose measurements, with readings taken four

times per hour, every hour for 14 days. This will provide a much greater insight than previously shown in any existing or ongoing study by revealing previously undetected patterns in glycaemic control.

The potential outcome and benefits of this study include:

- Increased awareness amongst HCPs regarding
    - Prevalence of PEI amongst individuals with diabetes
    - Importance of treating such individuals with PERT
- Impact to individual participant / other patients with diabetes
    - Reduced symptom burden
    - Improved glycaemic control
    - Potentially improved quality of life of individuals
- Impact to organisations and the NHS as a whole
    - Improved glycaemic control leading to reduced or delayed onset of diabetes complications including microvascular and macrovascular
    - Improved wellbeing of patient cohort and potentially better adherence and engagement due to improved symptomatology
    - Reduced need for other glucose lowering therapies
    - Overall improved cost burden

With these potential benefits in mind, the importance of this study is highlighted; where previous studies using SMBG and HbA1c have failed to substantiate a link between PEI, PERT and glycaemic control in diabetes, it is hoped that through this study it can be shown that CGM and AGP analysis can be used to identify new targets for diabetes care.

4.4 Research questions

The main research question to be answered by this study is: does treatment of PEI with PERT in individuals with T1DM or T2DM result in improved glycaemic control?

4.5 Proposed study

4.5.1 Outline of proposed study

A brief outline of the study is as follows.

Suitable individuals (those with both diabetes and newly diagnosed PEI and associated GI symptoms) will be invited to take part in the study and will be given a PIS. Once consented into the study, a baseline HbA1c will be taken and a Freestyle Libre professional flash glucose monitoring sensor will be applied. This will provide continuous glucose monitoring for 14 days. Participants will

return for a prescription of PERT, which will be issued in accordance with the usual standard of care for patients with PEI. Participants will take PERT for 6 weeks before returning for a second Freestyle Libre sensor to be applied, whilst continuing to take PERT. The data from both periods of CGM will subsequently be analysed using the AGP as per the statistical section in this protocol.

4.5.2 Known and potential risks and benefits

Treating patients diagnosed with PEI with PERT (due to any cause) is part of routine standard care. Participants in this study therefore stand to benefit, by experiencing an improvement or resolution in PEI symptoms. Depending on the outcome of the study, they may also experience an improvement in glycaemic control. PERT is a safe drug with few side effects, and response to treatment is based on clinical symptoms, without the need for additional testing. There are no specific risks associated with taking PERT, with the worst anticipated outcome being that patients have little or no clinical improvement. This may necessitate dose titration, or possible investigation of alternative diagnosis, for which a patient will be directed back to their GP.

The Freestyle Libre flash glucose monitoring system is licenced for use and is available for individuals to purchase in the UK. The Professional version of the Freestyle Libre that will be utilised in this study is blinded to the participant, so that they are not required to make any changes to their usual diabetes monitoring, and they should continue to take their oral medications and insulin, and make adjustments to their insulin doses (if applicable) as they would normally do. The device is safe to use in most settings and environments, and participants will not be placed at any increased risk by using it. The device's usual instructions will be discussed and given to the participant for reference. Participants will benefit from participation and use of the Freestyle Libre Pro through having their glycaemic profile analysed and discussed with them at their final study visit, which will enable personalised advice and behavioural and treatment strategies to improve their glycaemic control.

4.5.3 Potential impact of study

If the study demonstrates a relationship between change glycaemic control and PERT, this could lead to improved treatment strategies for patients with PEI and diabetes, including adjusting timing, dosing or type of medication, and potentially behavioural change particularly if the predominant change in glycaemic control is around prandial and post-prandial glycaemia. This has the potential to benefit individual patients – including those in primary care, and those treated in secondary care in either diabetes gastroenterology services. This could also impact on clinicians; through raising awareness of the benefit of looking for and treating PEI in patients with under-recognised GI symptoms, and identifying specific changes in glycaemic in more detail than previously known. This enables them to treat patients more effectively and to target treatment and / or behavioural change in a more personal fashion than previously was possible.

The use of CGM in this setting may prove beneficial in highlighting changes with PERT and also in identifying problematic or difficult glycaemic control. Significant prandial change in patients is often difficult to detect, as it is not identified using SMBG and HbA1c. This study may therefore influence diabetes care and show that CGM and AGP analysis is a useful and adaptable tool for a number of

different patient groups, for diagnostic purposes rather than its perhaps better known use as an alternative day-to-day substitute for SMBG.

In broader terms, this study has the potential to impact on the NHS and healthcare as a whole. With diabetes being such a vast problem with costly complications, any improvement that can be achieved in glycaemic control is vital. In addition, by showing that CGM is beneficial to individuals and services as a whole, and it could be shown to be a valuable investment that is cost effective.

5. PRELIMINARY STUDIES AND EXPERIENCE OF INVESTIGATORS

Professor Michael Cummings, Chief Investigator, has an extensive research background in the field of diabetes and endocrinology with over 200 abstracts and papers published. With an interest in PEI in diabetes for some time, he has spoken at, and been involved in, a number of educational events on the subject. He has authored relevant papers, including 'Gastrointestinal symptoms and pancreatic exocrine insufficiency in type 1 and type 2 diabetes', published in Practical Diabetes in 2014 (13).

Dr Iain Cranston is a national expert in the use of innovative data analysis techniques for diabetes management. He lectures regarding the application of such techniques in routine clinical practice at conferences on behalf of a number of commercial and academic sponsors including, Roche Diagnostics, Abbott Diabetes Care, Johnson & Johnson, Diabetes UK, Diabetes Wellness and Research Foundation, Eli Lilly, NovoNordisk, Sanofi, Boehringer Ingelheim and Astra Zeneca.

Dr Cranston and Dr Roger Mazze have worked together to establish the AGP Clinical Academy, with the aim of ensuring that the AGP as currently incorporated in to CGM devices is effectively understood and utilised by clinicians worldwide. A number of educational programmes are provided to this end.

The project 'AGP 100' is underway; a local educational program led by Dr Cranston and based at the Queen Alexandra Hospital, Portsmouth. It aims to improve the experience and performance of healthcare professionals (HCPs) in interpretation of continuous glucose monitoring data through structured training around the use of the Freestyle Libre flash glucose monitor in routine clinical practice.

Local expertise has allowed the development of further robust research. This study is one arm of an overarching project to explore the use of diabetic technologies in several vulnerable and at risk populations, others including gestational diabetes, perioperative care, adolescent transition and haemodialysis. Professor Cummings and Dr Cranston will be overseeing and advising on each of these.

Dr Paul Meredith is a principal information analyst with 25 years of experience in the NHS extracting and integrating datasets and more recently performing data analysis on routine care datasets. He has 10 publications in the area of acute hospital care and the deteriorating patient, and is a member of the Wessex CLAHRC Fundamental Care theme. Dr Meredith is a co-investigator on the Wellcome-Trust funded HAVEN project (Hospital Alerting via Electronic Noticeboard), a collaboration between the Universities of Portsmouth and Oxford and hospital trusts in Portsmouth and Oxford, and is also a co-applicant on HSDR grant 13/114/17 studying nurse staffing levels, missed vital signs observations and mortality.

Dr Katherine Alington, Principal Investigator, has clinical experience in the field of diabetes and endocrinology and is undertaking this research as part of an MD at the University of Portsmouth under the supervision of Biochemist and Senior Lecturer Dr Mridula Chopra. Current research interests of Dr Chopra include the effect of dietary and lifestyle factors on blood glucose homeostasis.

6. AIMS AND OBJECTIVES

The aim of this study is to compare the impact of pancreatic enzyme replacement therapy on glycaemic control in patients with both diabetes and PEI by using determinants of glycaemic control and outcomes (the ambulatory glucose profile) that are not fully defined by HbA1c and SMBG.

6.1 Primary Objective

To compare glucose variability (represented by mean interquartile range (IQR) over 2 weeks) in patients with diabetes and PEI prior to starting PERT and 6 weeks after starting PERT

6.2 Secondary Objectives

To compare the following AGP metrics prior to and 6 weeks after starting PERT as collected by the Freestyle Libre flash glucose monitor:

- Glucose exposure
- Mean glucose
- Time in hyperglycaemia (>10mmol/L and >15mmol/L)
- Time in target range (TIR) (4-10mmol/L)
- Time in hypoglycaemia (<3.9mmol/L and <3mmol/L)
- Glucose instability
- Specific time periods including post-prandial (2 hours after meal)
- Estimated HbA1c

To compare clinically important measurements including HbA1c, weight and BMI

Exploratory comparisons in the following groups:

- T1DM and T2DM
- Mild / moderate PEI (FE1 100-200mcg/g) and severe PEI (FE1 <100mcg/g)
- Responders to PERT and non-responders to PERT based on GI symptom questionnaire

7. STUDY DESIGN

7.1 Summary of Study Design

This study is a phase IV single-arm study using Creon (pancreatic enzyme replacement therapy) in accordance with usual standard of care; the decision to prescribe Creon will not be dictated by the protocol. The study will assess the effect of Creon on glycaemic control, but is not looking directly at its indicated clinical effects (which are well established and related to gastrointestinal disturbance).

Potential participants in the study will be newly diagnosed with PEI and will be PERT-naïve. It is anticipated that any patients previously fulfilling the diagnostic criteria of PEI will already have commenced PERT, and therefore will not be eligible to take part.

Potential participants fulfilling the eligibility criteria will be invited to attend the first study visit, where the Freestyle Libre Pro sensor will be applied and left in situ for 14 days. They will attend the second study visit to have the sensor removed and receive a prescription for PERT, to be continued subsequently as a repeat prescription via their GP.

Patients will be asked to inform the research team of any problems with the sensors as soon as possible so that a replacement may be applied if appropriate.

Participants will continue to take PERT as per standard of care for PEI and continue to manage their diabetes as usual, with SMBG as per pre-study. They will then return after 6 weeks for visit 3 (this visit may occur between weeks 5-7 in order to maximise participant convenience and attendance) to have a second Freestyle Libre Pro sensor applied, which will remain in situ for a further 14 days. Participants will continue to take PERT during this time. Patients will attend for the fourth and final visit after 14 days to have the sensor removed.

A letter will be sent to participant's General Practitioner (GP) (see appendix) asking them to continue the PERT prescription and review symptoms as appropriate.

This study involves a total of 4 study visits. The duration of the study will be 10 weeks.

7.2 Primary and Secondary Endpoints

7.2.1 Primary Endpoint

Mean interquartile range over 14 days at weeks 6-8 of PERT therapy as measured by the Freestyle Libre flash glucose monitor.

7.2.2 Secondary Endpoints

Other AGP metrics averaged over 14 days at weeks 6-8 of PERT therapy as measured by the Freestyle Libre flash glucose monitor:

- Area under the median curve (AUC)
- Median
- Time above target range (above 10mmol/L and above 15mmol/L)
- Time in target range (TIR) (4-10mmol/L)
- Time below target range (below 4mmol/L and below 3mmol/L)

- Median curve instability
- Specific time periods – including pre-prandial and post-prandial
- Estimated HbA1c

GI symptom questionnaire at 8 weeks after starting PERT

Clinical measurements – HbA1c, weight, BMI at 8 weeks after starting PERT

8. STUDY PARTICIPANTS

8.1 Study Setting

The study will take place in the Academic Department of Diabetes and Endocrinology at Queen Alexandra Hospital. It will take place on this site only, with no home visits. All study activities will be undertaken by members of the research team within this department.

The participants will be selected from patients attending diabetes clinics within the department. It is anticipated that the required number of patients will be recruited from this source alone; however if the number is inadequate, gastroenterology clinics at Queen Alexandra Hospital will be approached to identify potential participants.

Potential participants must be over the age of 18, as would be expected from all patients attending the department for clinic appointments. They may be male or female, and of any racial or ethnic group.

8.2 Overall Description of Study Participants

Participants will be adults with either T1DM or T2DM diagnosed at least 1 year previously. They must also have one or more symptoms of PEI: diarrhoea, steatorrhoea, weight loss, abdominal pain or bloating. They must have a low faecal elastase level (<200mcg/g) but must not have already started treatment for this with PERT. They must be willing to take part in the study and to attend all required study visits.

8.3 Eligibility Criteria

8.3.1 Inclusion Criteria

The participant must meet ALL of the following criteria to be considered eligible for the study:

- Male or Female, aged 18 years or above
- Diagnosed with Type 1 diabetes or Type 2 diabetes at least 1 year ago
    - Be receiving oral and / or insulin therapy for diabetes
- Have 1 or more symptoms of PEI:
    - Diarrhoea – Bristol Stool Chart (see appendix) type 5, 6 or 7
    - Steatorrhoea or greasy, pale or offensive smelling stools

  - Weight loss
  - Abdominal pain or cramps
  - Bloating or increased flatulence
- Low faecal elastase level <200mcg/g in last 2 years or since diabetes diagnosis, whichever is more recent
- Willing and able to give informed consent for participation in the study and for GP to be informed

8.3.2 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Currently receiving, or have ever received, PERT
- Current prescription of or planning to commence medication (within next 2 months), other than those for diabetes, that may increase or decrease serum glucose levels such as:
  - Oral corticosteroids for more than 7 days
  - Antipsychotics
  - Nutritional supplements such as Fresubin®
  - Weight-loss medication such as orlistat
- Diagnosed with or suspected diagnosis of:
  - Pancreatic malignancy
  - Acute pancreatitis or chronic pancreatitis
  - Type 3c diabetes or other Type 3 secondary diabetes
  - Cystic fibrosis
  - Previous or awaited gastric bypass (within next 2 months), pancreatic or extensive small bowel surgery
  - Other primary pancreatic disorder or uncontrolled liver disorder
    - exception: non-alcoholic fatty liver disease
- Current or recently resolved (within 2 weeks) acute diarrhoeal episode thought likely to be infectious or other gastroenteritis
- Current of previous chronic alcohol excess
- Currently pregnant, recently postpartum (within 6 months) or planning pregnancy before end of study date
- Currently using a modified diet under dietetic supervision, such as FODMAP
- Currently receiving supported nutrition, including via nasogastric tube, gastrostomy tube or parenteral nutrition
- Known allergy to Creon® or any of its components

- Objection to porcine origin of pancreatin
- Known allergy to Freestyle Libre Pro adhesive pad
- Already enrolled, or recently (within 6 weeks) taken part in, another study
    - that may affect glycaemic control
    - that may affect digestion or absorption or another aspect of the GI system or nutrition

9. SAMPLING

We aim to recruit 18-24 participants to the study (see section 14.2, analysis of endpoints for rationale).

In a recent departmental audit into prevalence of PEI, 288 consecutive patients attending diabetes clinic were screened for symptoms of PEI. 24% were found to be symptomatic, with 63% of those providing a stool sample. Of the patients that provided a stool sample, 42% were confirmed as having low FE1 consistent with PEI. This equates to a 6% diagnosis rate for PEI amongst our clinic population. This is somewhat lower than the estimates of PEI prevalence in section 4.2.5, but does make allowances for patients that do not provide a stool sample to allow testing

In real terms, the Academic Department of Diabetes and Endocrinology sees approximately 3000 diabetes patients in clinic per year. This is approximately 250 patients per month. If it is assumed that there is an approximate 50% consent rate for participation in research, this means that there is potential to recruit a maximum of 7 participants per month to this study.

Whilst is hoped that participants will not choose to withdraw from the study, particularly as the treatment they are receiving would be recommended for them as part of standard care even if they were not participating in the study, the research team will be mindful of an assumed withdrawal rate of approximately 20% when recruiting potential participants to reach the target number. This also allows for some attrition of numbers due to sensor device failure or inadequate adherence to Creon therapy.

10. STUDY PROCEDURES

10.1 Recruitment

Participants will be recruited from the cohort of individuals that attend the Academic Department of Diabetes and Endocrinology for a variety of services, including clinic appointments with doctors, diabetes specialist nurses, dieticians and the multidisciplinary foot clinic.

The study will be discussed at a departmental meeting prior to commencing recruitment to make all members of the multidisciplinary team (MDT) aware of the study.

All members of the MDT will continue their routine practice of asking patients about the presence of GI symptoms, and undertake a FE1 stool test if appropriate. The results of this test take approximately 2 weeks, and therefore the diagnosis of PEI cannot be made straight away. Following a FE1 result of <200mcg/g, patients will be informed about the diagnosis of PEI, which may occur via telephone call, follow up clinic visit or by letter – as would happen in routine care.

At this stage, patients will also be invited to take part in the study:

- If a letter is sent to the patient about their diagnosis, then the PIS with a covering letter (see appendix) will be included
- If the diagnosis is disclosed via phone call, the study will be mentioned and the PIS will be sent in the post
- If the diagnosis is discussed face-to-face or in clinic, the PIS will be given then

If a patient expresses a wish not to be involved in the study, they will be prescribed Creon and have follow up arranged as per standard of care. This prescription would routinely be via the patient's GP. Their decision not to be involved in the study will not impact on their treatment of this condition.

Once the PIS has been given to a potential participant, a member of the research team will telephone potential participants or speak to them after an appointment in the department to confirm their interest in the study and to schedule an appointment to attend for study visit 1. A brief screening process will take place prior to or during this patient contact to ensure eligibility criteria are met. Participants will be given at least 24 hours to read and consider the PIS prior to being enrolled into the study.

In addition, posters and advertisements will be placed around the department and individuals will be encouraged to ask about participation in the study.

It is anticipated that through the above method, the appropriate number of patients will be recruited. However, if inadequate numbers of patients are recruited, the gastroenterology clinic at Queen Alexandra Hospital will be approached to assist in identifying potential participants using the same method described above.

The research nurses will be involved and will assist throughout this recruitment, screening and enrolment process to proactively contact potential participants and schedule study visits.

10.2 Screening and Enrolment

Participants will be contacted by a member of the research team inviting them to attend for the first visit once they have had at least 24 hours to read the PIS. A brief screening assessment will take place prior to or during this patient contact to ensure that eligibility criteria are met – for example confirming the results of the FE1 test, confirming the diagnosis of diabetes was made more than 1 year ago. An appointment will be scheduled for visit 1. The full eligibility and exclusion criteria will be discussed face-to-face as part of the detailed medical history when the participant attends for study visit 1, prior to signing the consent form or carrying out any other study-related activities.

Participants will have an opportunity to ask questions and discuss the PIS during this period and at study visit 1 prior to signing the consent form. Consent will be taken by any member of the

research team who is competent to do so and has this skill specified on the delegation log. The record of consent will be kept in the patients' records. Participants will need to be able to give informed consent themselves in order to take part in this study.

10.2.1 Co-enrolment guidelines

Participants are not eligible to take part in this study if they are co-enrolled in another study that has the potential to affect blood glucose levels or the GI system in any way. If a participant wishes to join such a study after enrolling in this study, they are permitted to withdraw from this study if they wish.

10.3 Randomisation

There is no randomisation used in this study.

10.4 Study Assessments

10.4.1 Initial participant contact

- Individual identified as suitable based on diagnosis of diabetes, GI symptoms and FE1 result (see above)
- PIS given

10.4.2 Study visit 1 (week 0, estimated visit length 2 hours)

- Discuss PIS and answer questions
- Detailed medical and drug history
- Confirm eligible to participate using inclusion and exclusion criteria
- Written informed consent
- Baseline venous blood sampling for HbA1c
- Urine pregnancy test performed if female and of childbearing potential with no reliable contraceptive method
    - Childbearing potential includes women who have not undergone the menopause (no menses for 12 months or more)
    - Reliable 'highly effective' contraceptive methods include:
        - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        - Combined (oestrogen and progestogen containing) hormonal contraception (Oral, intravaginal or transdermal)
        - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
        - Female sterilisation (bilateral tubal occlusion) or hysterectomy, or male sterilisation (of partner)

- True abstinence

- GI symptom questionnaire (see appendix) – to be completed on paper by participant; help can be provided if required
- Physical examination
  - Weight
  - Height
  - Calculate BMI
- Freestyle Libre Pro sensor applied
- Participant education regarding sensor and troubleshooting and provide participant with alert card (see appendix)
- Advise participant to contact research team if there are any problems with the sensor, including accidental removal, to allow a replacement sensor to be applied

10.4.3 Study visit 2 (week 2, estimated visit length 1 hour)

- Confirm participant willing to continue with study
- Freestyle Libre Pro sensor removed and data capture confirmed
  - If no data capture, or less than 7 days data capture
    - A new sensor will be applied if the participant agrees, otherwise participant will be withdrawn from the study and prescribed Creon as part of standard care pathway
  - If less than 14 days data capture but more than 7 days
    - Participant will continue in study and data will be used, with reasoning for failure of data capture reviewed in order to minimise risk of re-occurrence (for example accidental early removal, excessive immersion in water)
- Record any changes in drug therapy for diabetes / other comorbidities
- Record any changes in medical history and any problems with the sensor
- Prescribe Creon and educate patient on dosing and administration as per patient information leaflet (PIL) and dosing advice sheet (see appendix)

10.4.4 Study visit 3 (week 8, estimated visit length 30 minutes)

- Confirm participant willing to continue with study
- Assess adherence to Creon therapy
  - Adherence to Creon will be assessed as per section 11.2 Adherence to Study Treatment
- Record any changes in drug therapy for diabetes / other comorbidities
- Record any adverse events or changes in medical history

- Freestyle Libre Pro sensor applied with revision of education

10.4.5 Study visit 4 (week 10, estimated visit length 1 hour)

- Confirm participant willing to continue with study
- Freestyle Libre pro sensor removed and data capture confirmed
    - If no data capture, or less than 7 days data capture
        - A new sensor will be applied if the participant agrees, otherwise the existing sensor data will be reviewed and may be used in subgroup analysis only.
    - If less than 14 days data capture but more than 7 days
        - Participant will continue in study and data will be used
- Venous blood sampling for HbA1c
- Assess adherence to Creon therapy
    - Adherence will be assessed as per section 11.2 Adherence to Study Treatment
- Record any changes in drug therapy for diabetes / other comorbidities
- Record any adverse events, changes in medical history and any problems with the sensor
- Physical examination
    - Weight
    - Calculate BMI
- GI symptom questionnaire (see appendix) – to be completed on paper by participant; help can be provided if required
    - Download and review AGP and discuss potential treatment or behavioural changes with participant. A letter will be sent to the participant's GP if any changes to therapy are recommended
- Ensure continuation of Creon and discharge of participant to GP care

At each screening and study visit, participants will be reimbursed for car parking or bus fare and simple refreshments will be offered.

10.4.6 The Freestyle Libre Professional flash glucose monitoring sensor

Participants will wear a Freestyle Libre Professional sensor twice during the study period; from week 0 to week 2, and from week 8 to week 10.

The sensor consists of a small plastic disc approximately the same size as a £2 coin with a small filament in the centre that is approximately 5mm long and 1mm wide and is inserted beneath the skin. The sensor is applied using a specific application device which is supplied with the device. Members of the research team will be appropriately trained in device application. The sensor will be applied to the back of the participant's arm, and a clear waterproof dressing will be applied to

minimise the risk of accidental removal. Participants will be able to sleep, bath, shower, exercise and swim (up to 1 metre depth for 30 minutes) as normal during the sensor-wear period.

Participants will be provided with an information sheet regarding the sensor and a supply of additional dressings should these be required (personal preference). Since this is a blinded sensor, participants will not be able to interact with the sensor. The sensors will be removed at visit 2 and visit 4, with the data downloaded as specified in this protocol. Participants will continue to perform their usual diabetes monitoring procedures before, during and after each sensor use.

As previously described, the use of the Freestyle Libre flash glucose monitoring sensor is generally safe and well tolerated. There are no anticipated risks involved and participants will not need additional monitoring during the sensor use. The only anticipated problem will be accidental removal of the sensor or failure of the adhesive pad, or failure of the sensor device itself.

In case of premature removal (less than 7 days of sensor wear), participants will be advised to contact the research team to arrange a new sensor to be applied where appropriate. If the original sensor had been in place for at least 7 days prior to removal, this will provide adequate data for interpretation and participants will continue with the standard visit schedule. If less than 7 days worth of data was captured prior to premature removal, participants will be asked to have a new sensor fitted.

A degree of sensor failure can be expected, as with any technology or electrical device. A recent South African study identified a 6% primary sensor failure rate (24).

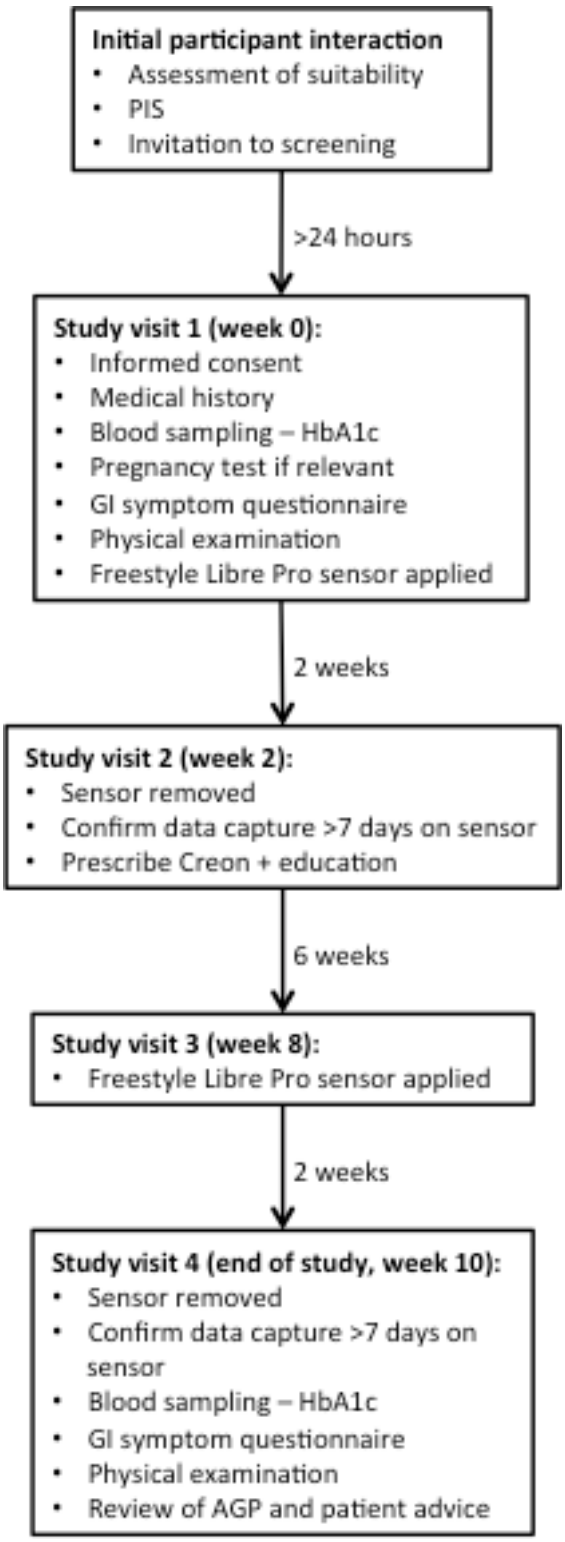
It has been recommended by an expert panel that 14 days of data are collected for analysis, as the resulting AGP would be very similar to that of a prolonged 30 day collection period and provides an ‘acceptable degree of confidence’ on which to base clinical decisions (7). In the view of the expert panel, 7 – 10 days of data may be adequate for analysis (7). Based on these recommendations, this study will require a minimum of 7 days of data to be available for accurate analysis.

Participants will be unaware of a sensor failure until they attend visit 2 or 4 for sensor removal and confirmation of data capture. In case of such sensor failure, if there is at least 7 days of data captured, participants will continue with the standard visit schedule; otherwise participants will be asked to repeat the sensor period where appropriate if there is less than 7 days of data stored on the sensor prior to the sensor failure.

There is no alternative sensor or placebo sensor used in this study; all participants will use the same model of sensor.

The use of Freestyle Libre Professional sensor is not evaluated for use with magnetic resonance imaging (MRI) or X-ray or computed tomography (CT) scanning, therefore the device must be removed prior to any of these being undertaken (25). As above, if less than 7 days of data is collected prior to removal, participants will be asked to have a new sensor applied if appropriate

10.4.7 Study design flowchart



10.4.8 Study visit checklist

Visit	Visit 1 (week 0)	Visit 2 (week 2)	Visit 3 (week 8)	Visit 4 / EOS (week 10)
Assess eligibility	✓			
Informed consent	✓			
Confirm participant willing to continue with study		✓	✓	✓
Detailed medical history	✓			
Blood test – HbA1c	✓			✓
Urine pregnancy test if relevant	✓			
Physical examination – weight, height, BMI	✓			✓
GI symptom questionnaire	✓			✓
Apply Freestyle Libre Pro sensor	✓		✓	
Remove Freestyle Libre Pro sensor		✓		✓
Confirm data capture on sensor		✓		✓
Prescribe Creon		✓		
Record change in drug therapy and medical history	✓	✓	✓	✓
Review AGP and advise participant				✓
Check adherence		✓	✓	✓
Record adverse events		✓	✓	✓

10.5 Discontinuation / Withdrawal of Participants from Study Treatment

Participants may be withdrawn from the study for the following reasons:

- At their own request – they will not be required to provide a reason
- Newly reported intolerance or allergy to Creon or the Freestyle Libre adhesive
- If participants develop a new condition during the study period that may interfere with absorption of Creon or affect their glycaemic control. This includes, but is not limited to, acute pancreatitis, other diarrhoeal or acute gastroenterological conditions, or any emergency admission to hospital lasting more than 24 hours.
- If less than the minimum 7 days of data is captured on the first sensor wear, and participant is unable or unwilling to repeat the sensor period before commencing Creon.
- Women that become pregnant

All withdrawals will be recorded with reason stated, where applicable, in the case report form and medical notes. All withdrawn participants will be followed up to establish whether an adverse event has occurred.

Reasonable attempts will be made to contact any participant that fails to attend all study visits.

10.6 Definition of End of Study

The end of study is the date that the last sensor is removed from the last participant at their last study visit.

11. INTERVENTIONS

11.1 Description of Study Intervention / Treatment

11.1.1 Creon®

Creon® is manufactured by Mylan Products Limited. All participants will be prescribed Creon to commence at the end of the first 14 day sensor period.

Creon consists of a capsule containing gastro-resistant granules which is taken orally at the start of each meal and with snacks. The dose varies depending on the content of the food. Participants will start at 50,000 units with meals and 25,000 units with snacks, in accordance with standard practice. There is specific administration advice regarding chewing and mixing with acidic foods – see summary of product characteristics (SmPC) in appendix. Creon will be dispensed from the pharmacy at Queen Alexandra Hospital.

Participants will take Creon continuously from the date of prescription until the end of the study period (8 weeks). Participants will need to continue Creon beyond this, and will be referred back to their GP for continuation of this prescription. Dose titration upwards may occur at this stage depending on response to treatment – this is again in accordance with standard practice, and will be the responsibility of the receiving primary care team.

There is no routine monitoring required for individuals taking PERT, though participants will answer a GI symptom questionnaire at the end of the study period to assess their response to therapy, to be included in analysis as an exploratory endpoint. As previously described, Creon is generally a safe and well-tolerated drug. There are no anticipated side effects or risks of taking part in this study, though any reported adverse events will be reported according to the protocol procedure.

There are no alternative treatments or placebos used in this study, and all participants will use the same dose guidelines.

The GI symptom questionnaire has been designed specifically for use in this study. There is no existing specific validated questionnaire relating to symptoms of pancreatic exocrine insufficiency, nor an appropriate questionnaire regarding general gastrointestinal symptoms and effect on quality of life.

11.2 Adherence to Study Treatment

Participants will be asked at each study visit about their adherence to Creon. Due to the nature of Creon administration – taken only when eating, and dose dependent on size of meal – it is difficult to assess adherence to Creon with complete accuracy with a simple count of remaining capsules. However, based on an individual participant's typical eating habits in conjunction with a count of remaining capsules, an adequate indication of adherence can be gained, that is appropriate to this study in line with standard clinical care.

Participants' typical eating habits will be assessed using a section of the questionnaire at visit 1 and at visit 4. This will be used to estimate the number of capsules that each participant would be expected to take during the study period. The remaining capsules will be counted at study visits 3 and 4. 80% adherence will be taken as adequate. If adherence is less than this, participants will be allowed to continue in the study but may be analysed in a subgroup and attempts will be made to recruit additional participants to meet the minimum sample size with adequate adherence.

11.3 Accountability of the Study Treatment

Pharmacy will be responsible for supplying all the Creon required for the study, once it has been prescribed by the PI or another member of the research team with appropriate delegation log capabilities. There is no randomisation required.

No additional steps or monitoring will be required by pharmacy above their usual practice. There will be no trial-specific labeling used for Creon in this study as the prescription will be entirely in accordance with standard care and prescription requirements.

It is adequate to assume that the medication will be stored appropriately according the manufacturers guidelines whilst it is located within the pharmacies, and participants will be given standard storage advice according to the patient information leaflet that will be provided with their first prescription.

There is no requirement for return of any unused medication at the end of the study; as participants will be recommended to continue the medication to treat their underlying PEI, they will be encouraged to continue taking any remaining capsules prior to acquiring a further repeat prescription from their GP.

The above approaches to medication management, accountability and labeling are a result of The Sponsor's risk assessment and determination of a low risk Type A clinical trial.

11.4 Concomitant Medication / Therapies

There are no additional supportive medications or therapies that are due to be prescribed as part of the study protocol.

All changes in a participant's drug therapies (both diabetes-related and unrelated) will be recorded at each study visit, but will not affect the individual's continued participation in the study.

Participants taking glucose-altering medications, other than specific medications for diabetes, as specified in the exclusion criteria, will not be eligible to participate.

- Current prescription of, or planning to commence, medication (within next 2 months), other than those for diabetes, that may increase or decrease serum glucose levels such as:
    - Oral corticosteroids for more than 7 days
    - Antipsychotics
    - Nutritional supplements such as Fresubin®
    - Weight-loss medication such as orlistat

12. ASSESSMENT OF SAFETY

The use of Creon in PEI is safe, well tolerated and part of routine practice. Creon is prescribed frequently within the NHS and Portsmouth Hospitals NHS Trust (PHT).

Creon, and other forms of PERT, are regularly prescribed within the NHS and Creon is listed on the PHT formulary. The most serious adverse effect is that of fibrosing colonopathy (strictures of the ileo-caecum and large bowel), which has been reported in patients with cystic fibrosis taking high doses of PERT (over 10,000 units lipase / kg / day). Potential participants with cystic fibrosis will be excluded from this study, and the doses of PERT used will be far below this level of 'high dosing', and as such this outcome is extremely unlikely to occur in the cohort of participants. Other more common undesirable effects include GI symptoms, which are predominantly associated with the underlying condition and cause of PEI, and a rash, which is uncommon.

There are no known medication interactions with PERT, there are no known effects on ability to drive or use machinery, and the only contraindication is that of hypersensitivity to pancreatin of porcine origin or any of the excipients. There is no data exposure during pregnancy, and therefore females who are currently pregnant or planning pregnancy will be excluded.

12.1 Definitions

12.1.1 Adverse event (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a subject enrolled in the study, which does not necessarily have a causal relationship with the study procedures. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal

laboratory result), symptom, or disease that occurs during the subject's participation in the study, whether or not this is considered to be related to the protocol.

12.1.2 Related adverse event

A related AE is defined as an AE which is considered, by the Chief Investigator (CI), Principal Investigator (PI) or the Sponsor, to have a reasonable causal relationship with the subject's participation in the study. This includes any AE that would not ordinarily have occurred but for that subject's participation in the research protocol. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship, namely that the event is 'possibly', 'probably' or 'definitely' caused by the research protocol.

12.1.3 Serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that is both serious and unexpected.

An AE may be considered serious if it:

- Results in death
- Is life-threatening
    - NB: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
    - NB: Hospitalisation for a pre-existing condition, including an elective procedure, which has not worsened, does not constitute an SAE
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Is another important medical event
    - Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

12.1.4 Adverse Incident (AI)

Any event or omission which caused physical or psychological injury to a patient, visitor or staff member, or any event of circumstances arising during NHS care that could have or did lead to unintended or unexpected harm, loss or damage.

12.1.5 Adverse Reaction (AR)

Any untoward and unintended response in a subject to an investigational medicinal product (IMP), which is related to any dose administered to that subject. Any adverse event judged by either the reporting investigator or the sponsor as having reasonable causal relationship to the IMP qualifies as an AR as there is evidence or argument to suggest a causal relationship. All adverse reactions are adverse events.

12.1.6 Suspected Serious Adverse Reaction (SSAR)

Any serious adverse reaction that is suspected (possibly, probably or definitely) to be related to the IMP.

12.1.7 Unexpected Adverse Reaction

An adverse reaction of which the nature and severity is not consistent with the information about the medicinal product in question which is set out in the reference safety information (RSI). The RSI is contained within the summary of product characteristics (SmPC) (see appendix).

12.1.8 Suspected Unexpected Serious Adverse Reaction (SUSAR)

All adverse events that are suspected to be related to the IMP and are both unexpected and serious are considered to be SUSARs.

12.1.9 Serious Breach

A breach which is likely to affect to a serious degree:

- The safety or physical or mental integrity of the subjects of the trial; and / or
- The scientific value of the trial

12.2 Trial specific exceptions to SAE notification and reports

Conditions relating to the course or progression of diabetes will be exempt from SAE notification and reporting (as in section 12.3 below), but will still be recorded on a standardised reporting form (as per section 12.4 below). These include:

- Hypoglycaemia episodes – mild, moderate and severe, including those requiring hospital admission
- Diabetic ketoacidosis (DKA)
- Hyperglycaemic hyperosmolar state (HHS)
- Hyperglycaemia (non-DKA, non-HHS), managed either by individual patient, primary care, secondary care clinic or requiring admission to hospital

- Primary care or secondary care clinic visit related to participant's previously known, or unknown, complications of diabetes such as retinopathy, nephropathy and diabetic foot disease.

12.3 Reporting Procedures for SUSARs

The Sponsor shall expedite all suspected adverse reactions which are both serious and unexpected (SUSARs) to both the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). Fatal or life-threatening SUSARs shall be reported within 7 days and all other SUSARs within 15 days after the Sponsor was first aware of the reaction.

12.4 Recording and Reporting Procedures for All Adverse Events

All AEs and SAEs will be documented using a standardised reporting form and the CRF and will also be documented within the subject's medical notes, in accordance with Good Clinical Practice (GCP) guidelines. The record will include the following as a minimum:

- A verbatim description of the event
- The date of onset
- Intensity (mild, moderate, severe)
- Relatedness to the IMP (unrelated, unlikely, possibly, probably, definitely)
- Serious adverse event (yes, no)
- Action taken
- Outcome of the event
- The date of resolution (if resolved)

All AEs and SAEs will be reported to the Research Sponsor and HRA where appropriate according to the sponsor's standard operating procedure (SOP) for 'Investigators: Recording, Assessing and Reporting Adverse Events in Clinical Research'. AEs and SAEs not immediately reported to the sponsor (as dictated by the SOP) will be collated and regularly reviewed by the Trial Management Group (TMG), which will escalate any issues or concerns to the Trial Oversight Group (TOG).

All SAEs must be reported to the Sponsor within 24 hours of any member of the study team becoming aware of the event. The initial SAE alert (which may be made by phone, email or fax) must be followed up immediately with a detailed written SAE report. If the Investigator does not receive acknowledgement of the SAE report from the Sponsor by the next working day, the Investigator shall contact the Sponsor immediately to confirm receipt.

All reported SAEs will be reviewed by the CI and Sponsor's Research Quality Committee at regular intervals throughout the trial. The CI will inform all investigators concerned of any relevant information about SUSARs and SAEs that could adversely affect the safety of participants.

If the investigator suspects the event to be a SUSAR this will be clearly identified on the report form, and these will be dealt with by the Sponsor as per section 12.3..

12.4.1 The safety recording and reporting period

The period during which any AEs will be recorded and reported (if appropriate) for each participant will be from the date of the first dose of Creon (date of study visit 2), to the date of that participant's final study visit. As all drug treatments in this study are in accordance with usual standard of care, any adverse events occurring after this period while the participant remains on Creon will be the responsibility of the on-going care provider, in accordance with national drug safety reporting guidelines and the Yellow Card Scheme.

12.4.2 Serious Breaches

All serious breaches will be reported to the sponsor in accordance with the sponsor's SOP for 'Reporting Serious Breaches in Clinical Research'.

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Collection Forms

The principal investigator (PI) will be responsible for ensuring the quality and security of all data recorded.

Data collection will be undertaken by the PI, specialist research nurses within the Academic Department of Diabetes and Endocrinology and any other sub-investigators as per the delegation log.

Data will come from a number of sources, and will require a variety of different collection and storage techniques:

Data source	Data collection
Freestyle Libre Pro sensor	Source data is collected and stored on the sensor which is initially worn by the participant for 14 days, and is retained on the sensor once the 14 day period is over. The sensor is identified by a unique identifier number linked to the participant ID. This sensor will be kept as source data, and downloaded as a raw data .csv file and .pdf using the Freestyle Libre software
Medical notes, clinic letters and Diabeta 3 system	Entered onto paper data case report form (CRF) as source data
Consent form	Completed by participant and kept in medical notes
Symptom questionnaire	Completed by participant and kept as source data
Laboratory reports – blood and faecal	Printout from electronic results system (ICE) to be kept as

elastase	source data in medical notes, and results entered onto paper CRF

All CRFs will be kept in the Trial Master File (TMF), locked within the Academic Department of Diabetes and Endocrinology. All data on the CRF and kept within the TMF will be anonymised. Source data which retains personal identifiable data will be stored within the participant medical notes which are also stored and archived according to standard procedures.

All electronic data will be stored anonymously on a secure network folder, accessible via a password-protected Trust computer.

13.2 Data Management

All data will be collected as stated above. The following table summarises the data entry process for types of data:

Data source	Data management
Freestyle Libre Pro sensor	The sensor retains its memory and will be stored in a designated box within the research department, and subsequently archived according to the appropriate SOP. It will continue to be identifiable via a unique code linked to the participant ID. The downloaded .csv raw data will be stored and used within a database and SPSS software for data analysis
Medical notes, clinic letters and Diabeta 3 system Written documentation on CRF of screening and study visits – including medical history, examination and measurements Symptom questionnaire	Data from CRF will be entered onto electronic database for data storage
Symptom questionnaire	Completed by participant, kept as source data and entered onto electronic database
Laboratory reports – HbA1c	Printout from electronic results system (ICE) to be kept as source data and entered onto electronic database

All personal data will be managed in accordance with the principles of the Data Protection Act 1998. Study participants will be assigned a unique participant ID number. No identifiable personal data (name, address, hospital number and date of birth) will be used to identify data.

Study documents (paper and electronic) will be stored within the Academic Department of Diabetes

and Endocrinology. Electronic data will be stored on a secure network folder, accessible from a password-protected Trust computer. Paper copies will be locked within the research room. Access to the department is via a security code protected door, which is alarmed out-of-hours.

Study documents (paper and electronic) will be stored in a secured location following the end of the study period. All source documents will be retained for 15 years after the end date of the study in accordance with the Sponsor's archiving policy. Where trial-related information is documented in the medical records, those records will be identified by a 'DO NOT DESTROY BEFORE dd/mm/yyyy' label where the date is 15 years from the last date that the participant is involved with the study.

In addition to the research team, research regulatory authorities (including the Sponsor and HRA) may have access to all study documents at their request for monitoring and audit purposes.

14. DATA ANALYSIS

14.1 Description of Analysis Populations

The following criteria need to be met for the participant to be included in analysis:

- A minimum of 7 days data (out of a maximum of 14) captured by the Freestyle Libre Pro sensor
- A minimum of 80% compliance with Creon

As there is no randomisation taking place, all participants will be analysed on a per protocol basis.

14.2 Analysis of Endpoints

For each participant and for each sensor period, the mean 24-hour interquartile range will be the primary outcome measure of the study.

There are many components of the AGP (see section 4.2.3). The following parameters will be calculated hourly, over 24 hours and for time-block elements (daytime, night-time, pre-meal and post-prandial) as secondary endpoints, and analysed using the below methods.

- Interquartile range
- Area under median curve
- Median
- Time above target range (above 10mmol/L and above 15mmol/L)
- Time in target range (TIR) (4-10mmol/L)
- Time below target range (below 4mmol/L and below 3mmol/L)
- Median instability
- Estimated HbA1c

The exploratory subgroups groups are:

- Within participant – before and after treatment with PERT

- T1DM and T2DM
- PEI and severe PEI
- Responders to PERT and non-responders to PERT

Simple descriptive statistical analysis will be undertaken to describe the parameters and groups, and will depend on whether the data is normally distributed or not. Within patient comparisons will either be undertaken using Paired t-test or Wilcoxon signed rank test. Across group comparison will be undertaken using either the Two-sample t-test or Mann-Whitney U test.

Additional routine demographic and clinical measures will also be available, including age, sex, BMI, HbA1c and. These will be used to perform additional exploratory comparisons.

For the purposes of this study, a decrease in mean 24-hour IQR of 1mmol/l is considered to be clinically significant. Based on a power of 90% and a significance level of 0.05 to allow for comparison between two dependent means, a sample size of 18 is required, assuming a standard deviation of 1.2mmmol/l for the mean IQR and a repeated measures correlation of 0.5. To allow for a withdrawal rate of 20% and the potential for suboptimal sensor data capture, the recruitment target will be 18-24.

The reduction of 1mmol/l is based on the grand mean of hourly IQRs of a representative group of patients with type 1 diabetes that was evaluated as being 4.3mmol/l, and therefore a reduction of 1mmol/l is clinically meaningful but realistic to achieve. A standard deviation in the mean hourly IQRs of 1.2mmol/l was measured in the same group of patients. There is limited literature on the use of IQR as a marker of glucose variability, because the ambulatory glucose profile (of which glucose variability and IQR are a key component) is a relatively new, although standardised, way to assess such glucose data.

14.3 Procedure for Dealing with Missing, Unused and Spurious Data

As stated above, there are minimum requirements for the number of days' worth of data that is collected. This is to ensure that the data used in analysis is as accurate as possible, and to reduce the impact of spurious or outlier results.

As stated above, attempts will be made to repeat sensor recordings where data is determined as missing.

All data that will be collected from participants will be utilised in the study analysis and will be justified. There is no intention to collect data that will not be analysed.

14.4 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

Any deviations from the planned methods of analysis will be recorded and justified. Any significant deviations will be discussed with the Sponsor and, if appropriate, submitted to the HRA.

14.5 Interim Analysis and Criteria for Early Study Termination

Data capture will be confirmed after each sensor removal (visit 2 and visit 4) but the data not be downloaded or analysed until visit 4.

Preliminary data analysis will take place on an individual participant basis at study visit 4 to review that participant's AGP and offer personalised advice to improve glycaemic control

These preliminary data analyses will be the responsibility of the PI, or the research team member conducting the relevant study visit, provided they have AGP interpretation skills listed on the delegation log.

There are no planned analyses that would result in early study termination, and there are no anticipated events that would necessitate this. Final analysis of all data will be performed by the PI once all participants have completed the study.

15. TRIAL MONITORING

The study will be monitored and audited in accordance with the Sponsor's policy. All trial related documents will be made available on request for monitoring and audit by the Sponsor, the relevant Research Ethics Committee and for inspection by the Medicines and Healthcare products Regulatory Authority or other licensing bodies.

A Trial Management group (TMG) will meet monthly to review the study progress and development. An extended will meet quarterly with additional members present, according to any needs identified. Any concerns not able to be dealt with by the TMG will be escalated to the Trial Oversight Group (TOG) or Research Governance Group (RGG) as appropriate.

16. ETHICS

This study has been designed by following the Clinical Trials Directive and is in application for regulatory authority approval.

16.1 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

16.2 Other Ethical Considerations

The study staff will ensure that the dignity and welfare of each study participant is maintained at all

times. Potential participants that lack capacity to consent to participate in the study will be excluded but will still be advised to commence treatment with PERT according to standard practice. Other vulnerable individuals with capacity to consent will be enabled to participate, with appropriate explanation and use of participant information sheets. Participants will be eligible to take part regardless of their ethnic or other background.

One ethical consideration will be the time between a participant's inclusion in the study, and the time to first prescription of Creon, plus any time prior to study inclusion but after confirmation of a diagnosis of PEI based on the FE1 sample. Whilst participants may continue to experience GI symptoms during this time, the researchers feel that this time before starting PERT will not be harmful to participants. PEI is a chronic condition with is often under-diagnosed, and the FE1 test typically also takes up to two weeks to be reported and therefore in standard practice there is often a similar timescale from suspected diagnosis to treatment. This can be discussed with participants if they wish prior to inclusion in the study.

A further consideration regarding the diagnosis and treatment of PEI is whether the undertaking of this study will lead to a temporary increase in PEI screening and diagnosis, which could potentially fall once the study has closed. All HCPs within the Academic Department of Diabetes and Endocrinology should, and will continue to be encouraged to, routinely ask about GI symptoms and consider testing for PEI as part of their routine diabetes consultations. This should not be affected by the study.

The study has been designed with patient public involvement to provide an end-user opinion regarding the acceptability of the study and of all participant study documents.

16.3 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki.

16.4 ICH Guidelines for Good Clinical Practice

All staff involved in the study will be trained and certified in GCP. Portsmouth Hospitals NHS Trust, as the sponsor, will ensure continued adherence to GCP during the study period.

16.5 Study sponsor

Portsmouth Hospitals NHS Trust Research and Innovation department are acting as the sponsor for this study. Standard NHS indemnity will apply.

17. PATIENT PUBLIC INVOLVEMENT (PPI)

17.1 Study design

This study proposal originated from clinicians within the Academic Department of Diabetes and Endocrinology, with an improvement in patients' health and wellbeing both in the short-term and long-term being the ultimate goal.

PPI have been consulted about the proposal and have reviewed all participant-facing study

documents (consent form, PIS, GI symptom questionnaire, lay summary and waiting room poster). Generally they were happy with the design, readability and wording of all documents. Some small changes were suggested, including:

- GI symptom questionnaire – it was felt that 'often' and 'sometimes' were too subjective, and more clear definitions would be better. The questionnaire has been adjusted to include specific time periods to clarify this.
- Minor grammatical or spelling changes were suggested and have been amended.

17.2 Study implementation

PPI will be involved by the TMG if the researchers experiences difficulties with poor recruitment or retention during the study.

17.3 Dissemination

The aim is to disseminate the study results via conference attendance and publication in a diabetes journal to inform the wider professional diabetes community. In addition, results will be made available to participants, as well as to service users attending the department.

A lay summary will be produced in consultation with PPI, which can be posted on the Trust website and Trust research news publications. In addition, this will also be submitted to charities such as Diabetes UK.

18. FINANCING AND INSURANCE

The study has been costed with input from the Research Finance Officer, and has been sponsor approved.

The study is funded by Mylan® Products Ltd.

19. REGULATORY ISSUES

As a clinical trial, this study is in application for MHRA approval. The study will be carried out according to the EU directive.

20. TRIAL COMMITTEES

This study will have a Trial Management Group (TMG) which will consist of the CI, Professor Cummings, the PI, Dr Katherine Alington, and, where relevant will involve a statistician and PPI input.

21. TIMETABLE AND ORGANISATIONAL CHART

Year	2017	Protocol and data collection tool development PPI	Submit to HRA	HRA and ethics approval granted	Commence screening and recruitment	Commence study visits and data collection	Complete end of study visits and data collection	Data entry	Data analysis	Write up and publication	Dissemination
2017	January	✓									
	February	✓									
	March	✓									
	April		✓								
	May		✓								
	June			✓	✓	✓					
	July			✓	✓	✓	✓	✓			
	August				✓	✓	✓	✓			
	September				✓	✓	✓	✓			
	October				✓	✓	✓	✓			
	November				✓	✓	✓	✓			
	December				✓	✓	✓	✓			
2018	January				✓	✓	✓	✓			
	February					✓	✓	✓			
	March					✓	✓	✓			
	April					✓	✓	✓			
	May					✓	✓	✓	✓	✓	
	June						✓	✓	✓	✓	
	July								✓	✓	✓
	August								✓	✓	✓
	September								✓	✓	✓
	October								✓	✓	✓

22. RESOURCES, EQUIPMENT AND PHYSICAL FACILITIES

The study will take place within the Academic Department of Diabetes and Endocrinology, which has dedicated research space and equipment suitable for participant consultations, physical examination and venepuncture. All study documents will be provided and made available by the research team.

Laboratory facilities will be provided by the pathology service at Queen Alexandra Hospital.

Pharmacy facilities will be provided by the Dispensary at Queen Alexandra Hospital.

The Freestyle Libre Pro glucose monitoring sensors and equipment will be purchased from Abbott Diabetes Care.

Software required is routinely available on PHT computers.

Data management support is provided by Oxford Respiratory Trials Unit.

Statistical support for the protocol design was provided by Paul Meredith, Principal Information Analyst, PHT Research and Innovation Department.

23. DISSEMINATION AND OUTCOME

This study will be incorporated into a larger project that will be submitted to the University of Portsmouth by Dr Katherine Alington for the award of an MD.

In addition, the results of the study will be submitted for publication in a peer-reviewed journal, as well as to national conferences for poster display or oral presentation.

All participants will be informed of the outcome of the study, and results will be displayed within the Academic Department of Diabetes and Endocrinology for visitors and patients to be informed. The study outcome will also be included in the PHT Research and Innovation news publication.

As described above in section 17.3, the results will also be distributed to charities such as Diabetes UK to make the results available to the wider population of individuals with diabetes.

The potential implications of this study include raising awareness of the prevalence of PEI amongst individuals with diabetes, and the importance of treating with PERT, not only on symptom relief, but on improving glycaemic control. This will benefit individuals on a number of levels; improved symptom burden, improved diabetes control and potentially improved quality of life. It may also benefit at a more organisational level, both within PHT and the NHS as a whole; by improving glycaemic control through treating a relatively common and simple-to-treat condition, the need for escalating diabetes treatment to novel and more costly medications may be either unnecessary, or at least delayed. This has implications for potentially reducing or slowing the progression to microvascular and macrovascular complications. Furthermore, by increasing awareness of PEI in individuals with diabetes, it may reduce the need for more costly or invasive initial investigations of individuals with GI symptoms where PEI can be confirmed early, rather than much further down the line once other conditions are excluded, or perhaps not at all, as is frequently the case.

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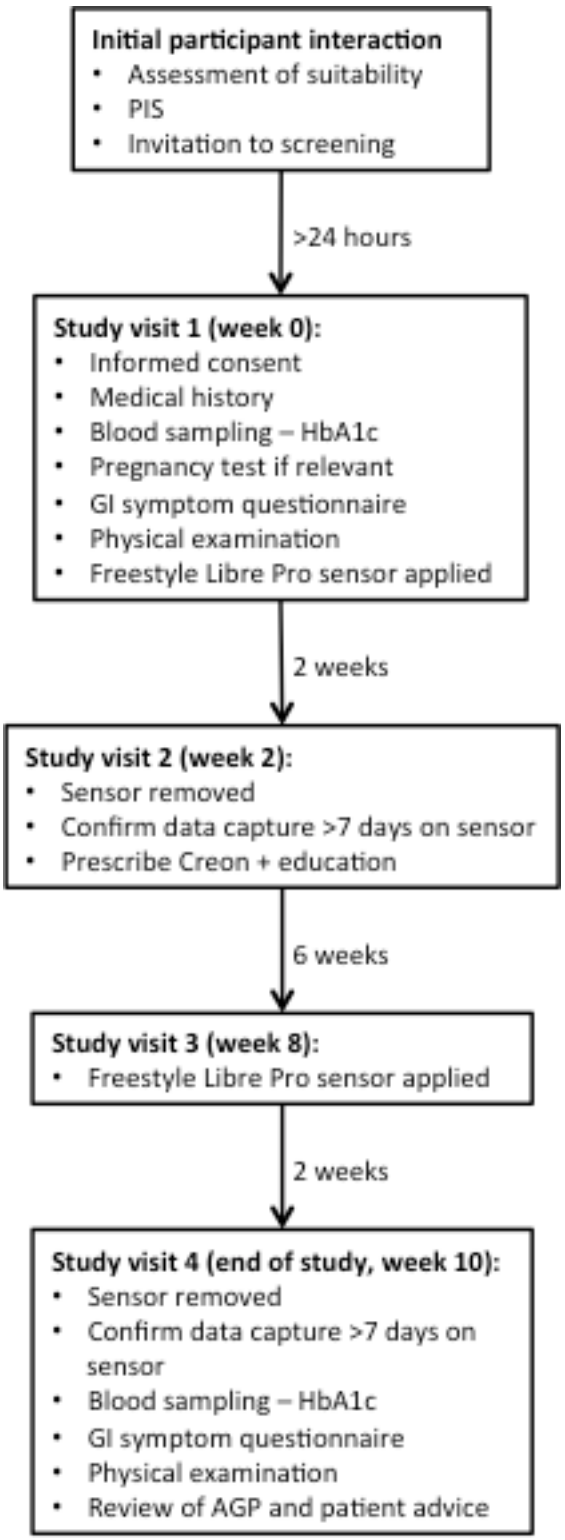
25. APPENDIX 1 SCHEDULE OF PROCEDURES

Visit	Visit 1 (week 0)	Visit 2 (week 2)	Visit 3 (week 8)	Visit 4 / EOS (week 10)
Assess eligibility	✓			
Informed consent	✓			
Confirm participant willing to continue with study		✓	✓	✓
Detailed medical history	✓			
Blood test – HbA1c	✓			✓
Urine pregnancy test if relevant	✓			
Physical examination – weight, height, BMI	✓			✓
GI symptom questionnaire	✓			✓
Apply Freestyle Libre Pro sensor	✓		✓	
Remove Freestyle Libre Pro sensor		✓		✓
Confirm data capture on sensor		✓		✓
Prescribe Creon		✓		
Record change in drug therapy and medical history	✓	✓	✓	✓
Review AGP and advise participant				✓
Check adherence		✓	✓	✓
Record adverse events		✓	✓	✓

26. APPENDIX 2 STUDY FLOW CHART

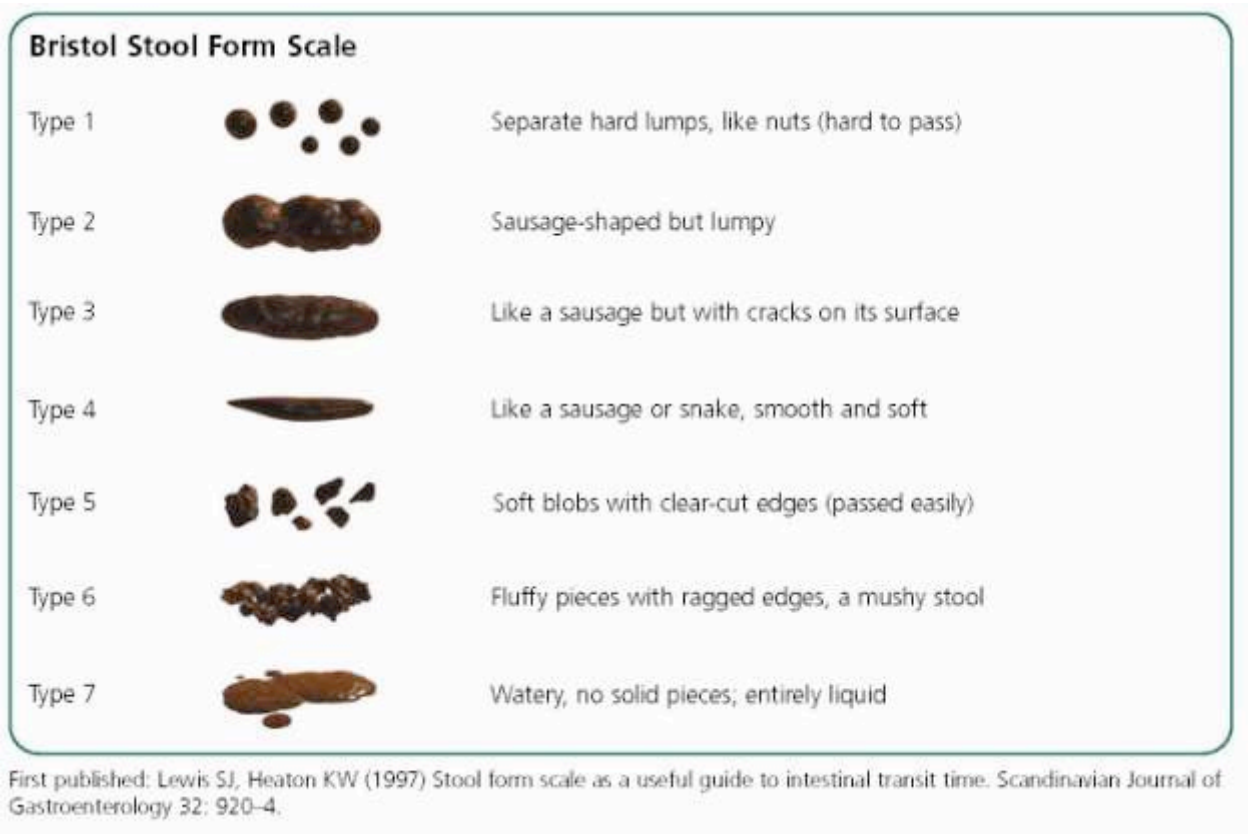


27. APPENDIX 3 PARTICIPANT INFORMATION SHEET

28. APPENDIX 4 INFORMED CONSENT FORM

29. APPENDIX 5 GASTROINTESTINAL SYMPTOM QUESTIONNAIRE

30. APPENDIX 6 BRISTOL STOOL CHART



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31. APPENDIX 7 PARTICIPANT INVITATION LETTER AND REPLY SLIP

32. APPENDIX 8 PARTICIPANT SENSOR INFORMATION CARD

33. APPENDIX 9 PARTICIPANT CREON INFORMATION SHEET

34. APPENDIX 10 GP LETTER

35. APPENDIX 11 WAITING AREA POSTERS

36. APPENDIX 12 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)