Pancreatic enzyme replacement and glucose regulation in Type 1 diabetes

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Protocol

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Impact of Pancreatic Enzyme Replacement in T1D Subjects with Low Pancreas Volume

Daniel J. Moore, M.D., PhD
Assistant Professor of Pediatrics
Ian M. Burr Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics
Vanderbilt University Medical Center

Alvin C. Powers, MD
Professor of Medicine
Division of Diabetes, Endocrinology, and Metabolism
Vanderbilt University Medical Center

Jordan Wright, M.D., PhD
Assistant Professor of Medicine
Division of Diabetes, Endocrinology, and Metabolism
Vanderbilt University Medical Center

Jon M. Williams, PhD
Study Coordinator
Division of Diabetes, Endocrinology, and Metabolism
Vanderbilt University Medical Center

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1.0 Background

Total pancreas volume is decreased in T1D. Recent studies have demonstrated reduced pancreatic volume is present within months of T1D diagnosis in children, adolescents, and adults [1-4]. As the pancreatic beta cells constitute only 1-2% of the pancreas, the degree of reduction in pancreas volume at disease onset

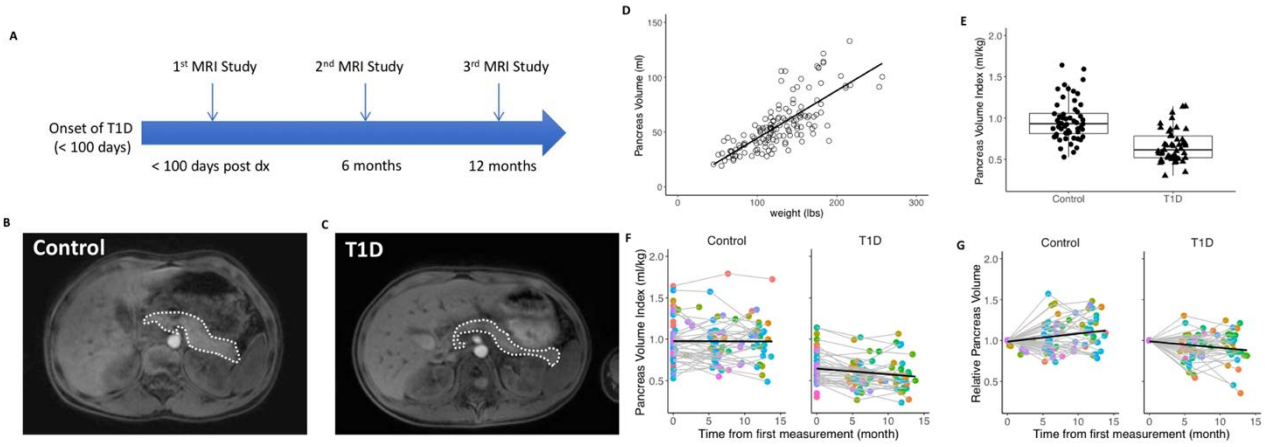

Figure 1. A) Schematic of study design employed to study recent-onset T1D. B) An axial MRI slice through the abdomen of a control participant shows the pancreas (outlined in white). C) An axial MRI slice through the abdomen of a participant with recent-onset T1D shows a smaller, thinner pancreas than seen in the control (outlined in white). D) In the control cohort, pancreas volume correlated with participant weight over the course of adolescent growth. E) Pancreas volume normalized by participant weight, yielding a pancreas volume index in units of [ml/kg], is smaller in participants with T1D than controls. F) Pancreas volume index is unchanged in the control pancreas over a one-year period but declines in participants with T1D over the year after diagnosis. G) When normalized to the baseline measurement for each study participant, pancreas volume increases in the control population but declines in participants with T1D.

suggests exocrine involvement, challenging the established paradigm of T1D being solely a disease of the endocrine pancreas. These unexpected findings raise fundamental questions that challenge our understanding of T1D pathogenesis and point to new questions about management. Especially relevant to the proposed studies, these changes in pancreatic volume and size could reflect deficiency in the exocrine pancreas which could alter food absorption and effect clinical management of glycemia, but this hypothesis has not been investigated.

Our group has developed advanced, standardized approaches to image the pancreas and has applied this approach to understanding the role of whole pancreas pathology in T1D, a disease traditionally thought to only involve the pancreatic islet. An example image of the pancreas of a control participant and participant with recent-onset T1D is shown in Figures 1B and 1C, respectively, with the pancreas outlined in white. Within 100 days of diabetes onset, individuals with T1D (n = 51) had a smaller pancreas (median volume = 29.6 ml) than controls (n = 58, median volume = 47.8 ml, $p < 0.001$), including when normalized by individual weight ($p<0.001$). In multiple autoantibody-positive individuals, the pancreas volume was significantly larger than the T1D cohort ($p=0.014$), but smaller than the control cohort ($p=0.019$). To account for normal adolescent growth, we compared pancreas volume and weight in control study participants. In the control cohort, pancreas volume correlated with participant weight (Figure 1D, $R = 0.76$, $p < 0.001$). Thus, to account for changes in pancreatic volume during normal adolescent growth, pancreas volume was normalized by participant weight yielding what has been termed the pancreas volume index. Normalization by body surface area and BMI were also explored but were inferior to normalizing by weight. At the first study time point, the pancreas volume index was smaller in participants with recent-onset T1D than controls (Figure 1E; median 0.931ml/kg in controls and 0.615 ml/kg in T1D, $p < 0.001$). Pancreas volume index was smaller in participants with T1D when adjusted for age, sex, and BMI (mean difference -0.279 ml/kg with 95% CI -0.352 to -0.205, $p < 0.001$ from linear regression). Key data from these early studies are highlighted in Figure 1 and in our published work. As highlighted in Figure 1, pancreas volume declines over the first year after diagnosis (Figure 1F, G). This finding demonstrates the small

pancreas in T1D and the presence of an underlying process resulting in ongoing changes in the pancreas after diagnosis with T1D; the physiologic consequences of these changes are not known.

Alterations in exocrine biochemical values in T1D. The significant reduction in pancreas size raises questions as to whether there is also a reduction in exocrine pancreas function. Several studies to date have now demonstrated reductions in key markers of exocrine enzymatic activity. These reductions include abnormalities in fecal elastase and reduced measured in the blood of amylase, lipase, and trypsinogen. The degree of these reductions range from slight deviations from normal to more profound losses of 60% or more. To date there has not been a detailed study of clinical symptoms in patients with T1D to determine whether persons living with T1D have symptoms of pancreatic exocrine insufficiency.

Role of Enzyme Replacement in Diabetes Management. To date there has not been an investigation of the potential for pancreatic enzyme replacement therapy in the management of T1D. Related information can be gleaned from treatment of cystic-fibrosis related diabetes (CFRD) which is characterized by a strong component of exocrine insufficiency related to the CFTR mutation. In individuals with CFRD, enzyme replacement has been shown to reduce post-prandial glycemia excursions, which are reflected in improved GLP-1 responses to mixed meal tolerance testing. As post-prandial excursions and glucose variability are a significant challenge in T1D, how enzyme replacement may impact these parameters is an important question.

2.0 Rationale and Specific Aims

We hypothesize that patients with T1DM who have reduced pancreatic volume will have improved glycemic responsiveness, reduced hypoglycemia, and improved symptoms of pancreatic exocrine insufficiency (PEI) when treated with pancreatic enzyme replacement. To test our hypotheses, we will employ a double-blinded crossover study. This study will be a pilot study to gather preliminary information on potential effect size in preparation for a larger study if supported by these results. The study will enroll approximately 15 adult subjects with T1D who will receive both pancreatic enzyme replacement (Creon) or placebo each for 7 days in a random order. The effect of the intervention will be monitored by continuous glucose monitoring, diet recording, capsule counts, a mixed-meal tolerance test, and a survey to assess symptoms of PEI. This study design will allow for estimation of the effect of pancreatic enzyme replacement on the measured parameters.

Aim 1 will provide preliminary estimates of the effect of enzyme replacement on glucose responsiveness, variability, and hypoglycemia. We will download and analyze CGM data to determine changes occurring in measures of glycemic variability and in the duration and severity of hypoglycemia. Data will be divided into 4 7-day blocks including a run-in period, treatment A, a wash out period, and treatment B. Participants will track their meal composition, report daily exercise duration, and a capsule count will be obtained. At the end of treatment A and treatment B, participants will undergo a mixed meal tolerance test (MMTT) in which glucose, C-peptide, GLP-1, GIP, and glucagon will be measured at defined timepoints.

Aim 2 will provide an initial assessment of the effect of enzyme replacement on symptoms of pancreatic exocrine insufficiency in T1D. We will use the PEI-Q to quantitate symptoms of PEI and their relative change during enzyme replacement at each of the 4 intervals. The frequency and degree of PEI symptoms has not been objectively measured in T1D patients previously.

We will obtain information on the adherence to the intervention and will obtain initial information on median and standard deviation for measured variables that will inform future studies. We will perform a paired t-test to provide an initial assessment of outcomes between groups.

This proposed research will be the first study to determine the effect of enzyme replacement therapy on glycemic variability and patient-reported symptoms or PEI in T1D.

3.0 Animal Studies and Previous Human Studies

There have been no previous animal or human studies of the effects of pancreatic enzyme replacement on glucose regulation in T1D. The reported studies to date, as discussed in the background, strongly support that there is pancreatic volume loss and resultant reduction in exocrine enzymes in T1D. However, the clinical impact of this change is not known; an impact of pancreatic enzyme deficiency and enzyme replacement on glucose tolerance/responsiveness in CFRD has been described.

4.0 Inclusion/Exclusion Criteria

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Diagnosed with T1DM for at least 12 months • Age over 18 • Total daily dose of insulin greater than 0.6u/kg/day • Current use of a CGM • Current use of smart phone • Able to read and speak English • Willingness and ability to download and provide CGM and pump (if applicable) data • Reduction of pancreas volume (<0.6mL/kg BW)	• History of celiac disease or inflammatory bowel disease • Unwilling to temporarily discontinue use of medication or supplements other than insulin to control blood glucose • Pregnant or breast feeding • Following a restrictive diet (such as very low carb diet) • History of major bowel or bariatric surgery

5.0 Enrollment/Randomization

5.1 Recruitment

5.1.1 Recruitment Resources

We have previously completed a study of over 70 patients with T1D in which they have received one or more MRI studies. This study group allows us to identify patients with significantly reduced pancreas volume for enrollment in this study.

5.1.2 Initial Contact with Potential Participants

Participants will be contacted by telephone. The initial discussion will provide information about the study and assess whether the subject might be eligible to participate in the study. Study personnel will ask the potential subject to confirm his or her:

- Diagnosis of T1DM
- Age
- Weight
- Height
- Diabetes duration
- Medications
- Food preferences and restrictions
- Use of CGM
- Ability to read and speak English

Inclusion and exclusion criteria are listed in table 1. We will invite eligible subjects to participate in the initial screening visit. The initial screening visit will occur at Vanderbilt University Medical Center. The participant will receive an electronic or paper copy of the informed consent document to review prior to the initial screening visit.

5.2 Enrollment

A member of the study team (i.e. key study personnel, KSP) will obtain written, informed consent at the beginning of the screening visit as detailed in section 6.1.1.1. Once consent is obtained, the participant will be enrolled in the study.

5.3 Randomization

Patients will be randomized for order to receive pancreas enzyme replacement or placebo. The Vanderbilt Investigational Drug Services (IDS) pharmacy will do the randomization. They will dispense the randomized capsule bottles for weeks A and B to the study team to be given to the study participants.

5.4 Participant Compensation

Participants will receive $200 for each completed MMTT for a total of up to $600 for participation in the study.

6.0 Study Procedures

6.1 Research visits

6.1.1 Study Visit 1, Initial Screening Visit

Screening visits will take place in a room designated for research in the Eskind Diabetes Center or in the CRC.

The purpose of the screening visit is to:

- obtain informed, written consent,
- confirm each participant is able to properly upload their continuous glucose monitor (CGM) and pump (if applicable),
- provide participants with blinded treatments (pancreatic enzyme replacement and placebo)
- show participants how to log their food intake on their digital device.

The screening visit will consist of the following:

6.1.1.1 Consent

The PI or designated KSP will obtain consent from all participants. Consent will be obtained in a private room in the Eskind Diabetes Center prior to beginning study procedures. The consent form will be provided to the subject for review prior to the visit. The PI or designated Key Study Personnel will review the consent forms with the participant in detail and provide time for discussing any questions. The study team will provide a copy of the consent form to the participant if applicable.

6.1.1.2 History and Initial Measurements

The PI or designee will review each subject's clinical history and take anthropometric measurements (Height/Weight).

6.1.1.3 Nutritional Tracking App Instructions

The study team will use a nutritional tracking smartphone application, such as Nutrihand, MyFitnessPal, or FatSecret, on which participants will log their daily caloric intake using the software's web-based or Smartphone app interfaces.

Participants will be asked to track intake using this smartphone app throughout the study.

Participants may be asked to use their personal email to send a CSV file containing data files from the smartphone app to the study team. This CSV file does not contain any PHI. The file will be directly uploaded into REDCap, then the email will be deleted.

6.1.1.4 Continuous Glucose Monitor Instructions

The study team will instruct participants in the use of a continuous glucose monitor (CGM) such as Dexcom G6 or Medtronic Guardian or Freestyle Libre for the monitoring of glycemia during the study. The team will then show T1DM participants how to upload CGM data into a HIPAA and FDA-compliant cloud-based, data-integration platform such as Dexcom Clarity or Tidepool.

6.1.1.5 Insulin Instructions

For participants using insulin pumps, the study team will instruct T1DM participants in the transmittal of data derived from an insulin pump such as Medtronic Minimed 670G, Tandem T-Slim, or Omnipod Insulim Management System. Participants will be encouraged to administer all insulin via insulin pump and enter all carbohydrates consumed into the insulin pump. The team will then show T1DM participants how to upload insulin pump data into a HIPAA and FDA-compliant cloud-based, data-integration platform such as Medtronic Careline or Tidepool. Participants not using an insulin pump wil be asked to record their insulin doses given throughout the day.

6.1.1.6 Randomization and Treatment Plan

Participants will be randomized for order in which enzyme replacement or placebo is received. An equal number of participants will receive either order (A/B or B/A). Participants will receive a range of 50,000-100,000 lipase units per meal (approx. 2 Creon 36,000 capsules) and 25,000-50,000 per snack (1 capsule). The participant will be instructed to take same number of capsules of placebo. Participant and provider will be blinded to capsule assignment.

6.1.2 Study visit (baseline)

6.1.2.1 Demographic and history information will be obtained.

6.1.2.2 Participant will be counseled on using and uploading devices and information.

6.1.2.3 Participant will complete a baseline Mixed Meal Tolerance Test (MMTT). The test will be administered according to the well established practices used in the TrialNet clinical T1D research program and described in the included appendix. This baseline visit will take place in the Adult Clinical Research Center (CRC).

6.1.3 Study Visit (end of week A)

6.1.3.1 On last day of week A, subject will have an MMTT at the Adult CRC.

6.1.4 Study Visit (end of week B/end of study)

This visit will include an MMTT at the Adult CRC and will be scheduled on the last day of week B.

6.1.4.1 History and measurements

The PI or designee will review each subject's clinical history and take anthropometric measurements.

6.1.4.2 Continuous glucose monitor and insulin pump data collection

Continuous glucose monitor and insulin pump will be downloaded into a HIPAA and FDA-compliant cloud-based, data-integration platform such as Dexcom Clarity, Medtronic Carelink, or Tidepool.

Information that will be collected from the continuous glucose monitor download will include (but not be limited to):

- Percent of time spent above the glycemic target of 140 mg/dL
- Percent of time spent in the glycemic target of 70 – 140 mg/dL
- Percent of time spent below the glycemic target of 70 mg/dL
- Percent of time spent in hypoglycemia below 50 mg/dL
- Average blood glucose
- Blood glucose standard variation
- All blood glucose values during the study interval

Information that will be collected from the insulin pump download will include (but not be limited to):

- Average total daily dose of insulin
- Average bolus amount of insulin per day
- Average basal amount of insulin per day

6.1.4.3 Nutritional tracking smartphone application data collection

Information that will be collected from the smartphone app will include (but not be limited to):

- Total number of calories consumed
- Average grams of carbohydrates consumed per day
- Average grams of fat consumed per day
- Average grams of protein consumed per day
- Additional macronutrient data

6.1.4.4 Pancreatic Exocrine Insufficiency Questionnaire

Participants will complete the PEI-Q, a validated measure of PEI symptoms at baseline and at end of Week A and Week B. All surveys will be scored by a member of the research team.

6.1.4.5 Diet Instructions

Patients will be instructed to follow their routine diet.

6.1.4.6 Quality Assurance of Interventions

A capsule count will be performed at end of study to assess adherence to treatment assignment.

6.1.4.7 Mixed Meal Tolerance Test

Subjects will participate in an MMTT at baseline and at end of Week A and Week B. The protocol for the MMTT is described in the Appendix; as a slight modification of the Appendix, an additional 8.5 ml tube of blood will be drawn at each time point.

7.0 Risks

7.1 The following risks associated with participation are considered:

7.1.1 Hypoglycemia

Hypoglycemia is encountered intermittently by all patients with T1DM as part of the natural consequence of diabetes management with exogenous insulin administration, and we do not anticipate that this risk will be increased by utilizing enzyme replacement treatment.

We will use the following safety provisions to minimize risk of hypoglycemia: participants will monitor their blood sugar via continuous glucose monitor. Participants will be reminded that if hypoglycemia occurs, the patient should treat hypoglycemia with oral intake (administer 15 grams of carbohydrates in liquid form or with glucose tablets) if the patient is responsive and able to consume the treatment orally. If the patient is unresponsive, the study team would instruct the participant's caretaker to administer intramuscular glucagon. The study team will ensure that the participants have an up-to-date glucagon kit at time of enrollment.

7.2 Discussion of Risks as Part of the Consent Process

The study team will discuss all procedures, risks, and benefits with potential study participants, as part of the consent process. An IRB approved written informed consent document will be required for participation in this study. It is understood that consent is a process and not a discrete event. A participant's decision to withdraw consent will be respected throughout the duration of each subject's participation in this study. It is also understood that there may be as-yet unknown or unanticipated adverse effects of this study. The study team will continually monitor for these effects and consider altering the protocol as needed to ensure patient safety. Changes in the procedures of the study, as well as any change(s) in the risks and/or benefits will be presented to and discussed with the subjects upon approval from the IRB for implementation of such revision(s), and any IRB revised written consent will be signed, as appropriate.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

8.1 Serious Adverse Events

8.1.1 Defining Serious Adverse Events

Consistent with FDA guidelines, serious adverse events (SAEs) will be defined as any untoward medical occurrence that:

- requires inpatient hospitalization
- results in persistent or significant disability
- is suspected to cause a congenital anomaly or birth defect in a subject's unborn child
- is life-threatening
- results in death
- is considered to be an important medical event based on appropriate medical judgement (e.g. bronchospasms requiring emergency department referral, seizures that might not result in hospitalization).

8.2 Assessing relationship between a SAE and relationship to study procedures

An SAE's relationship to the study procedures will be assessed and graded as either: not related, unlikely, possible, probable, or definite.

8.3 Assessing whether an AE is an anticipated problem

Any AE will be assessed for whether or not it was an anticipated problem. In accordance with Department of Health and Human Services guidance and consistent with 45 CFR part 46, an "unanticipated problem" will include any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given
    a. the research procedures that are described in the protocol-related documents, including the IRB-approved research protocol and informed consent document; and
    b. the characteristics of the subject population being studied; related or possibly related to participation in the research; and
2. suggests that the research places subjects or others at a greater risk of harm.
3. related or possibly related to participation in the research;
4. suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

8.4 Hypoglycemia

Hypoglycemia Instances of significant impairment consistent with hypoglycemia and requiring assistance (ie, often referred to as "severe" hypoglycemia), even in the absence of a blood glucose reading, are classified as "Level 3 Hypoglycemia" (IHSG 2017). Level 3 hypoglycemia may include cognitive impartment, altered/loss of consciousness, confusion, seizure, syncope/fainting, or coma, and support may be general assistance, glucagon, or oral carbohydrate (ie, fruit juice or glucose tablets). Such episodes may or may not require medical attention or hospitalization. This study will consider clinically significant hypoglycemia to be Grade 3 or greater hypoglycemia as defined below. Grade 1 and Grade 2 hypoglycemia are expected normal consequences of T1D and will not be recorded as AEs for this protocol. For AE reporting purposes, the severity of a hypoglycemia event should be identified by the Investigator and classified according to CTCAE v5.0 as follows:

- Grade 3 hypoglycemia: 30-39 mg/dL (1.7–2.1 mmol/L). This is considered severe or medically significant but not immediately life-threatening. Hospitalization or prolongation of hospitalization may be indicated. It is likely to be disabling and to limit self-care.
- Grade 4 hypoglycemia: ≤29 mg/dL (1.6 mmol/L). This is considered life threatening (eg, seizures) with urgent intervention indicated.
- Grade 5 hypoglycemia: Hypoglycemia resulting in death.

8.5 Unanticipated, non-serious AEs

All unanticipated, non-serious AEs and the study team's response to the non-serious AE will be included in a report at the time of annual continuing review. The PI will review the AEs and notify the IRB of any changes needed to the protocol. If needed, appropriate changes will be made to the consent form.

8.6 Unanticipated SAEs

In accordance with IRB policy, any unanticipated SAE that is considered possibly related to participation in the study will be reported within 7 calendar days of the PI's notification of the event to the IRB. The study team will continue to follow or obtain documentation of the resolution of any SAE.

8.7 Adverse Event Reporting

The annual summary of all unanticipated adverse events and any audit reports will be sent to the IRB at the time of continuing review.

This protocol will be reviewed annually (at a minimum) by the Vanderbilt IRB. The goal of this process is to determine the risks and benefits of the study in the actual experience of subjects and that measures taken to minimize risks are adequate

9.0 Study Withdrawal/Discontinuation

Subjects will be free to withdraw from the study at any time, which will be made clear at enrollment. Subjects will be withdrawn from the study if:

- Pregnancy is detected
- The PI's (or designated MD, NP, or PA KSP) medical judgement is that participation places the subject at risk for harm.

10.0 Statistical Considerations

10.1 Recruitment

We have targeted an accrual of 15 participants in this pilot study. We will estimate the effect size and variance of the intervention on glycemic variability and symptoms. We will also ascertain the intra-individual variation from comparison between our two non-treatment intervals (run-in and wash-out periods) which will set a lower bound on measurable effects. To estimate the pilot study's optimum accrual, we utilized the method of Whitehead et al. which proposes stepped increases in sample size based on the anticipated standard difference, d, between interventions[1,2]. We defined the minimum important difference (MID) in low blood glucose index, a measure of low blood glucose from CGM data) between enzyme replacement and placebo interventions as 1 (difference in values of 3 for more variable and 2 for less variable as reflected in clinical experience) and estimated a pooled SD of 1.29 based on our review of CGM data from other studies. If d=MID/SDpooled=1/1.29=0.77, a sample size of 15 participants per arm will optimize future sample size calculations for a definitive study.

10.2 Statistical Analysis

Statistical analysis will be performed using a paired samples t-test to compare differences between the two groups.

11.0 Privacy/Confidentiality Issues

A database will be designed for this study using REDCap (Research Electronic Data Capture) tools. REDCap is a secure, web-based application designed to support data capture for research studies, providing validated data entry, audit trails, seamless data downloads to common statistical packages, and mechanisms for importing data from external sources. It will reside on a secure server with access provided exclusively to the research personnel. Subjects will be identified with a study identification number. A key to the subject identification number will be kept in a separate locked file drawer to which only the Principal Investigator and research coordinators have access. Reports will thereby be generated without Protected Health Information (PHI) data, and access will be restricted so that statisticians, etc. don't have access to all data.

Risk of leakage of PHI is minimized by keeping paper records in a locked cabinet and maintaining computerized records in the password protected REDCap data base. The principal investigator and the research staff are trained in HIPAA privacy regulations. The participant's identification is concealed, and a number is used as the identifier instead of the subject's name. Only the principal investigator or members of the research team will have the list of study patient's names as the correlate with the study number.

12.0 Follow-up and Record Retention

The study is anticipated to last for up to eighteen months. The study results will be maintained indefinitely for research purposes.

REFERENCES

1. Bell ML, Whitehead AL, Julious SA. Guidance for using pilot studies to inform the design of intervention trials with continuous outcomes. Clinical epidemiology 2018;10:153-7.
2. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Statistical methods in medical research 2016;25:1057-73.