1.0 Title Page

Full Title

A single site, placebo controlled, double blind randomised clinical trial evaluating the effectiveness of metformin to prevent post-transplant diabetes in a cohort of patients undergoing renal transplantation.

Short Title

The **POWERED** Study: **Pro**phylaxis **w**ith m**e**tformin to p**re**vent PT**D**M

Sponsor

Barts Health NHS Trust

Representative of the Sponsor:

Dr Mays Jawad
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REC Number 18/LO/0958

Sponsor Reference 012280

2.0 Research Reference Numbers

IRAS Number: 203080

EudraCT Number: 2017-004880-11

3.0 Signature Pages

Chief Investigator Declaration

I confirm that the following protocol (Version 1.9, dated 22.06.2020), has been written by me and I, as the Chief Investigator, agree to conduct the trial in compliance with this version of the protocol.

I will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and all subsequent amendments of the clinical trial regulations, current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the study publicly available through publication and/or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator: Kieran McCafferty

Chief Investigator Site: Barts Health NHS Trust

Signature: 

Date: 22/06/2020

Name (please print): Kieran McCafferty

Statistician Declaration

The clinical study as detailed within this research protocol (Version 1.9, dated 22/06/2020), involves the use of an investigational medicinal product and will be conducted in accordance with the current UK Policy Framework for Health & Social Care Research, the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials, ICH E10 - Choice of Control Groups and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Statistician:	Dr Stan Fan
Job title:	Consultant Nephrologist
Statistician Site/Organisation:	Barts Health NHS Trust
Signature:	
Date:	22.06.2020
Name (please print):	Dr Stan Fan

4.0 Key Trial Contacts

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Laboratories	Royal London Hospital Pathology Department Whitechapel E1 1BB
Funder(s)	Diabetic Kidney Disease Centre
Statistician	Dr Stan Fan Consultant Nephrologist Barts Health NHS Trust
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Committees	For membership and contract details please see DMC/TSC document

5.0 Trial Summary

Full title	A single site, placebo controlled, double blind randomised clinical trial evaluating the effectiveness of metformin to prevent post-transplant diabetes in a cohort of patients undergoing renal transplantation.
Short title and/or Acronym	The **POWERED** Study: **Pro**phylaxis **w**ith m**e**tformin to p**re**vent PT**D**M
Trial Design Methodology	Single site, placebo controlled, double blind randomised clinical trial.
Phase of the Trial	II
Study Duration	24 months
Study setting	Single NHS site
Investigational Medicinal Product(s)	Metformin
Medical condition or disease under investigation	Post-Transplant diabetes
Planned Sample Size	57
(Maximum) Treatment duration	3 months
Follow up duration	1 year
End of Trial definition	The last visit of the last subject

6.0 Protocol Contributors

Key Protocol Contributors	Full contact details including phone, email and fax numbers
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7.0 List of Contents

8.0 List of Abbreviations / Glossary of Terms

ABOi	ABO (blood group) incompatible
AE	Adverse event
ATG	Anti-thymocyte globulin
ADM	Anti diabetic medication
BMI	Body mass index
BP	Blood Pressure
CI	Chief investigator
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CRF	Case report form
DBD	Donation after Brain Death
DCD	Donation after Cardiac Death
ECD	Extended Criteria Donor
eCRF	Electronic case report form
eGFR	estimated Glomerular Filtration Rate
GLUT-4	Glucose transporter type 4
HD	Haemodialysis
HDL	High-density lipoprotein
HOMA	Homeostatic model assessment
HRA	Health Research authority
IRAS	Integrated Research Approval System
LDL	Low-density lipoprotein
MALA	Metformin-associated lactic acidosis
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	The National Institute for Health and Care Excellence
OGTT	Oral Glucose Tolerance Test
PD	Peritoneal Dialysis
PTDM	Post Transplant Diabetes Mellitus
REC	Research Ethics Committee
SAE	Serious adverse event
SAR	Serious adverse reaction
SPC	Summary of product characteristics
SUB-I	Sub investigator
SUSAR	Serious unexpected serious adverse reaction

9.0 Introduction

9.1 Background

Kidney transplantation is widely held to be the optimal form of renal replacement therapy for patients with end-stage renal disease, leading to a longer survival and improved quality of life in patients receiving a renal transplant compared to those that remain on dialysis (Reese et al, 2015). However renal transplantation brings with it a new set of challenges for the clinician. One of the most important of these is post-transplant diabetes mellitus (PTDM). The prevalence of PTDM has increased over time and may occur in up to a third of all post-transplant patients making it a critical challenge for transplant physicians (Balla et al, 2009).

PTDM represents a significant risk factor to both patient and graft survival, (Balla et al, 2009; Palepu et al, 2015; Hecking et al, 2012) with some studies suggesting an increase of 60% in graft failure and an almost 90% increase in mortality (Kasiske et al, 2003). This morbidity and mortality is due to the greatly increased risk of cardiovascular disease associated with PTDM (Hecking et al, 2012; Chakkera et al, 1998). In addition to the clinical consequences of PTDM for patients, there is also a huge economic impact on healthcare, with a diagnosis of PTDM doubling the cost of healthcare for a transplant patient (Chakkera et al, 1998).

The precise definition of PTDM varies in the literature: from simply requiring anti-diabetic medications (ADM), to more formalised definitions: a random plasma glucose of ≥11.1 mmol/L, or an 8 hour fasting plasma glucose ≥ 7.0 mmol/L or a glucose concentration of ≥ 11.1 mmol/L following an oral glucose tolerance test (OGTT). In addition, the homeostatic model assessment (HOMA-2 model) of diabetes has been widely used in the diabetic literature. The advantages of this model are both its simplicity; requiring a single set of fasting bloods, and that both insulin resistance and beta cell function (both important in the pathogenesis of PTDM) may be quantified from this model (Levy et al, 1998). In this study, we will use both the formal 2 hour OGTT as the primary end point with the HOMA-2 model as part of the secondary end points.

Important risks factors for PTDM include: Black/Asian race, male sex, older patients, receipt of a 'Donation after cardiac death' kidney, family history of diabetes, BP, raised body-mass index, Hepatitis C disease, Cytomegalovirus (CMV) viraemia, hyperparathyroidism, low HDL cholesterol, and hypomagnesaemia (Palepu et al, 2015; Pilmore et al, 2010).

In addition, PTDM is caused by multiple factors associated with renal transplantation. Steroid use impairs beta-cell function, induces gluconeogenesis and glycolysis, inhibits glycogenesis and leads to insulin resistance (Palepu et al, 2015). Tacrolimus, a calcineurin inhibitor (CNI), has been associated with increased rates of PTDM when compared to other CNIs (cyclosporine) (Margreiter et al, 2002). It leads to hyperglycaemia via reduction of pancreatic insulin secretion and a reduction of GLUT-4 mediated glucose uptake into cells (Palepu et al, 2015). In addition, it may directly cause beta cell toxicity (Chakkera et al, 1998) and down regulate insulin gene expression. However due to its enhanced efficacy in prevention of acute

and chronic rejection it has become the most widely used immunosuppressive in renal transplantation (Margreiter et al, 2002).

PTDM tends to occur early post-transplant, with most patients developing PTDM within the first 3-6 months (Chakkera et al, 1998). A reason for this is the higher doses of immunosuppressive medication used during the early transplant period along with increased incidence of CMV viraemia. Thus, the early post-transplant period represents a crucial window to intervene to reduce the incidence of PTDM.

Recent evidence suggests that basal insulin may protect the pancreas from the pro-diabetogenic stimuli in the first months post-transplantation, thus preventing PTDM (Hecking et al, 2012). However, insulin with its risks of hypoglycaemia and weight gain may not be the ideal therapy for this patient group.

Metformin is a biguanide which leads to a reduction in hyperglycaemia by reducing the expression of gluconeogenesis genes, enhancing the uptake of glucose into cells and reducing free fatty acids which are the substrate for gluconeogenesis (Pilmore et al, 2010). It is recommended as the first line treatment for patients with type 2 diabetes (Pilmore et al, 2012; NICE 2015).

Our hypothesis is that treatment with metformin is safe and will significantly reduce the incidence of diabetes in a post renal transplant cohort of patients in a London Transplant unit.

9.2 Assessment and management of risk

Metformin is licenced as the first line treatment for patients with type 2 diabetes and has been used as an ADM for many decades.

The benefit of metformin over other ADMs to use as prophylaxis against PTDM is that is does not lead to hypoglycaemia, which is a common and potentially dangerous complication of ADMs. It is also 'weight neutral' in that it does not cause weight gain which is a serious and common complication.

Use of metformin also has beneficial effects beyond glycaemic control including reducing BMI, LDL cholesterol and metabolic syndrome and even reducing the incidence of cancer (Pilmore et al, 2010). Metformin use has also been associated with significant reductions in heart failure over other ADMs (Pilmore et al, 2010). Metformin has been shown to prevent diabetes by 30% in a group of high-risk non transplant patients (Knowler et al, 2002).

<u>The known risks to human subjects.</u>
Metformin is generally a well-tolerated medication. From the SPC the most common side effects are gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain and loss of appetite). These symptoms generally occur at initiation of treatment and resolve spontaneously.

The main concern of metformin use in patients with renal disease is the risk of lactic acidosis. Lactic acidosis is a very rare, but serious, metabolic complication that can occur due to metformin accumulation. Metformin-associated lactic acidosis (MALA) has been reported, with a frequency ranging from 1 to 47 cases per 100 000 people. However there remains some debate whether metformin use does indeed correlate with raised lactate levels (Chowdhury et al, 2017). Indeed, recently a Cochrane review concluded that there is no significant evidence that metformin is associated with more lactic acidosis compared to other anti-diabetic therapies (Salpeter et al, 2002).

Metformin is mostly excreted by the kidneys: thus as renal function declines, the plasma concentration of metformin may rise. However recent data in stage 4 CKD patients suggests that even at this level of renal function, the concentrations of metformin did not accumulate (Dissanayake et al, 2017). Because of this concern, NICE guidelines suggest metformin should be reviewed at an eGFR of 45 and stopped at an eGFR of 30ml/min.

How high is the risk compared to normal standard practice?
There is no additional risk to using this product compared to standard practice.
Indeed, because patients will have their renal function measured very frequently as part of routine care, the risk of patients being treated with metformin while their GFR is less than 30ml/min is very low.

Justification for the choice of route of administration, dosage, dosage regimen, and treatment period(s).
Dose: 500mg OD is slightly lower than the standard therapeutic starting dose of metformin (usually either 500mg BD or 850mg OD up to 1g TDS), however: because this is being used as prophylaxis, rather than treatment; and because all patients will have some degree of renal impairment; and NICE recommends lower doses used with renal failure; the lowest standard dose in clinical practice was chosen.

Preclinical & Clinical Data
Metformin has been used for decades to treat many millions of patients with diabetes. In addition to providing good diabetic control in patients with type 2 diabetes, metformin has been shown to have lipid lowering properties, be weight neutral, protect the cardiovascular system, have anti-neoplastic potential, and to attenuate the metabolic syndrome.

In patients at high risk of developing type 2 diabetes it has been shown to prevent the onset of type 2 diabetes (Knowler et al, 2002). In addition, in patients who had gestational diabetes, metformin treatment demonstrated a significant reduction in development of subsequent diabetes (Aroda et al, 2015). All these features make it an ideal therapy for investigating for prophylaxis of PTDM.

How the risk will be minimised/managed.

Because of the perceived small possibility of lactic acidosis metformin use with a GFR of <30ml/min is contraindicated (NICE guidance). Therefore, this medication will only be started in patients with an eGFR of greater than30ml/min, and withheld if the patients' eGFR drops below 30ml/min at any point during the study.

This trial is categorised as: Type B = Somewhat higher than the risk of standard medical care

9.3 Rationale for study design

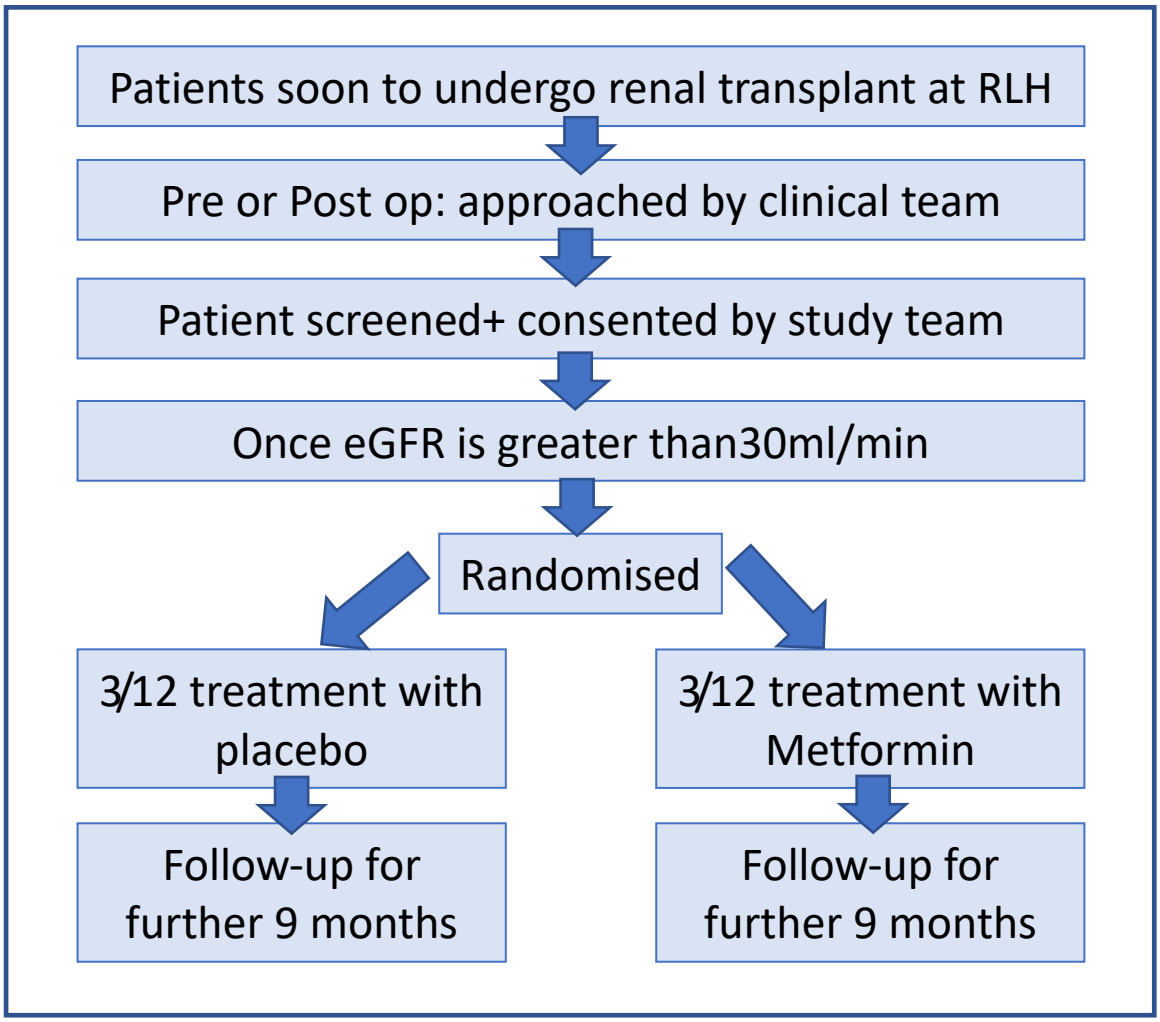
Research Question: Can a 3 month treatment period of metformin prevent PTDM?
The hypothesis of this study is that Metformin could be used to prevent PTDM.

PTDM is a common post-transplant complication, associated with poorer patient and graft survival. Insulin administration has already been shown to be effective in preventing PTDM. However, insulin use has many significant disadvantages: the need for self-injection, weight gain and hypoglycaemia. In contrast, metformin use does not have any of these disadvantages. Metformin has already been shown to be effective in preventing subsequent diabetes both in the context of gestational diabetes, and in patients at high risk of developing diabetes.

The proposed study sets out to use metformin in the first 3 months post renal transplantation. The reason for this time period is that the incidence of PTDM is highest in the early post-transplant period because of the higher burden of immunosuppression. During this time patients are seen very frequently as part of routine care, with frequent checks on their renal function minimising any risk of metformin use with eGFR<30ml/min.

This is a double blind placebo controlled study. The reason for the use of placebo as part of the double blind study is to ensure a lack of bias in the study. It also allows for both the participant and researcher to be blinded to the treatment thus reducing the chance of bias.

10.0 Trial Flowchart



11.0 Trial Objectives and Design

11.1 Primary Objective/s

Will treating post-transplant patients with metformin compared to placebo for 3 months lead to a long-term reduction in post-transplant diabetes? Defined as the presence of PTDM (defined as positive 2hr Oral Glucose Tolerance test) 1 year post-randomisation.

11.2 Secondary Objective/

1) The effect of 3/12 metformin on marker of pancreatic beta cell function using the HOMA test
2) HbA1c level at 3/6/12 months post-randomisation
3) Patient/Graft survival
4) Safety endpoints: SAE, AE
5) Episodes of acute rejection
6) Renal function at 12 months post-randomisation
7) Diagnosis of impaired glucose tolerance (2-hour glucose 7.9-11.1mmol/l)
8) Outcome at 12 months post-transplant of those patients who screen-failed for positive OGTT and were not randomised to the study drug

11.3 Endpoints

11.3.1 Primary Endpoint

The primary end point is the diagnosis of diabetes following a 3 month treatment period of metformin or placebo, defined as a positive 2-hour Oral Glucose tolerance (blood sugar greater than11.1mmol/l) test at 3, 6, or 12 months post-randomisation, or following an OGTT due to suspected new diabetes at other routine clinical visits

11.3.2 Secondary Endpoint

1) The effect of 3/12 metformin on markers of pancreatic beta cell function using the HOMA test at 3,6, and 12 months post-randomisation
2) HbA1c level at 3,6, and12 months post-randomisation
3) Patient/Graft survival
4) Safety endpoints: SAEs, AEs
5) Episodes of acute rejection
6) Renal Transplant function at 12 months post-randomisation
7) Diagnosis of impaired glucose tolerance (as indicated by a 2-hour oral glucose tolerance test result of 7.9-11.1 mmol/L)

8) Incidence of post-transplant diabetes at 12 months post-transplant in those patients not randomised to study drug due to positive OGTT at screening – as defined by the appearance of PTDM on their diagnosis list or the prescription of an anti-diabetic medication on their drug list

11.4 Exploratory or Tertiary endpoints/outcomes

There are no exploratory endpoints in this trial.

11.5 Objectives and End Points Summary

Objective	How objective measured	Outcome
Examine the effectiveness of metformin in preventing PTDM	2hour OGTT glucose level>11.1mmol/l	Diagnosis of PTDM
Examine the effectiveness of metformin on patient safety	Patient/graft survival/SAE/AE/Renal function/Rejection	Is there a significant difference between the placebo and metformin treated groups in terms of number of AE, SAE, Renal function, rejection rates.
Examine the effectiveness of metformin in preventing PTDM	2hour OGTT glucose level 7.9-11.1mmol/l	Diagnosis of impaired glucose tolerance
Examine the effect of metformin on beta cell function	HOMA IR test	Is there a significant difference between the placebo and metformin treated groups

11.6 Trial Design

This is a double blind placebo controlled pilot study to determine if metformin is superior to placebo in preventing post-transplant diabetes.

The expected duration of participation will be 12 months.
The number of study visits will be 5: screening visit, randomisation visit then at 3, 6 and 12 months post-randomisation.
The screening period will be up to 10 days. Where possible, the patients will be randomised within the first 7 days post-transplant. The treatment period will be 3 months; the follow up period will be 9 months.

11.7 Study Setting

This is a single centre study with no patient identification centre sites.

The study will take place in an NHS setting (Barts Health NHS Trust).
Patients will be recruited exclusively from a cohort of patients undergoing renal transplantation at the Royal London Hospital.

12.0 Eligibility Criteria

In order to be eligible for the trial, participants must meet all of the below inclusion criteria and none of the below exclusion criteria.

12.1 Inclusion Criteria

1) Patients (male or female) undergoing renal transplantation under the care of the Barts Health NHS Trust Renal Department
2) Aged 18-75 inclusively
3) Willing to comply with study schedule

12.2 Exclusion Criteria

1) History of Type 1 or type 2 diabetes
2) Clinically significant history of abnormal physical and/or mental health as judged by the investigator other than conditions related to chronic kidney disease
3) Participation in an investigational drug trial in the 3 months prior to administration of the initial dose of study drug
4) Subject with a known hypersensitivity or contraindication to Tacrolimus
5) Subject with a known hypersensitivity or contraindication to Metformin
6) Pregnant or breast feeding

13.0 Trial Procedures

13.1 Participant identification

Participants will be identified by their regular clinical team from those patients admitted or soon to be admitted for a renal transplant. Eligibility decision will be made by the Chief Investigator (CI).

13.2 Informed Consent Procedures

Informed consent will be obtained either pre or post transplantation, but prior to the participant undergoing procedures that are specific to the trial and are outside standard routine care at the participating site (including the collection of identifiable participant data).

13.2.1 Responsibility for obtaining consent

The CI retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent occurs then details must be provided in the Site Delegation Log.

Consent can only be taken by the CI or a medical practitioner trained in the study and delegated on the study log.

13.2.2 Consent Considerations

The right of a patient to refuse participation without giving reasons will be respected.

The participant must remain free to withdraw from the trial at any time without giving reasons and without this compromising his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent, for example if during the trial new Research Safety Information becomes available, or following an amendment that affects the patient, or new information needs to be provided to a participant, it is the responsibility of the CI to ensure this is done in a timely manner.

13.2.3 Population

The patient population will be patients aged 18-75 undergoing renal transplantation under the care of the Renal Department of Barts Health NHS Trust.

13.2.4 Vulnerable participants: considerations

The CI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

13.3.5 Written/ reading / translation considerations

Patients will not have cognitive impairment as this is a standard contraindication to undergoing renal transplantation. Patients who do not speak English will be able to consent to this study using independent advocates where available or standard clinical translation services (Language line). These are readily available during the consent process for the operation itself.

13.3.6 Participants lacking capacity

The clinical team will not approach any patient who is felt not to have capacity to take part in the study.

13.3.7 Minors

Patients under 18 are not eligible to participate in the study.

13.3.8 Consenting process

Patients will be approached by a member of the clinical team and asked if they would like to know more about the study. If the patient is interested, the research team will contact the patient to discuss the trial. They will inform the potential participant or his/her legal representative about the nature and objectives of the trial and possible risks associated with their participation.

In addition, they will receive the PIS and have a minimum of 24 hours to read it and have all their queries satisfactorily answered. The consent process will be documented in the source documents.

13.3.9 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies

Patient samples will be stored as per standard practice. These samples may only be used in future research following a substantial amendment to the protocol and ethical approval.

13.4 Screening Procedures

All participants that undergo screening will be logged into a study specific screening log.

Following consent, and before randomisation takes place the following procedures will be performed:

Inclusion/exclusion criteria
Demographic data
Transplant data
Concomitant medication
Medical history
Weight
Patients will only be randomised if/when eGFR is greater than 30ml/min and their OGTT is negative. If patients do not recover renal function within 10 days from their transplant, they will be screen failed, and will not be randomised to either metformin or placebo. However, their data may be used to monitor their progress during the first year post-transplant.

13.5 Treatment Allocation

13.5.1 Randomisation Method

The method of randomisation will be a simple randomisation using pre filled envelopes with study numbers 1-60 printed on them. The envelopes will be pre-filled by a doctor who is independent to the study and quality control checks will be performed and documented. Inside the envelope there will be a treatment code, which will be sent to pharmacy along with the patient's study number.

Both the patient's study number and the treatment code will be documented in the trial master file.

13.5.2 Randomisation Procedure

A spreadsheet of treatment codes (linked to either active substance or placebo) will be created using an online generator using a block randomisation sequence (Sealed Envelope Ltd. 2016. Create a blocked randomisation list. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists [Accessed 31 Jul 2017].)
This spread sheet will be stored in the pharmacy dispensary.

Each treatment code (for example A1, A2,…A60), will be written on a card and sealed in an envelope.

At randomisation, one of these envelopes will be chosen at random to associate the patient's study ID (e.g. patient 01, or 13) to the treatment code, which will be recorded in the CRF. This linked study code and patient identification will be sent to pharmacy for dispensing. The pharmacist will use their spreadsheet, which links the treatment code with the allocation of IMP or placebo.

Finally, each study participant will have their Study ID linked to their treatment allocation written on a card, which will be sealed in an envelope with their study ID on the front of the envelope (this will be created by an independent doctor). This means that breaking the study allocation will only compromise that individual patient's allocation.

The people who will have access to the envelope section are the CI and Sub-I only. The people who will have access to the treatment code (without the treatment allocation) are the study team. The people who will have access to the treatment code matched to the treatment allocation are the pharmacy team and sponsor office only. Should there be the need to break the treatment allocation, the CI or Sub investigator will open the locked container, and pick out the relevant patient's ID number and open only this envelope.

13.6 Blinding

This is a double blind placebo study: both the patient and the study team will be blinded to the treatment intervention.

Pharmacy staff who dispense the IMP will not be blinded, nor will Sponsor Office staff responsible for reporting unblinded SUSAR reports to the MHRA.

13.7 Unblinding

The code breaks for the trial will be held in the research office of the renal department and are the responsibility of the CI Kieran McCafferty.

If a patient has significant adverse reaction or a SUSAR then they should stop the IMP and be managed by their clinical team as if the patient was on the active drug. Further advice should be sought from the CI as necessary.

In the event a code is required to be broken a request for unblinding will be made by the Chief Investigator or treating health care professional.

If the person requiring the unblinding is not the CI or their team then the healthcare professional will notify the Investigator team that an unblinding is required for a trial subject which will then occur.

On receipt of the treatment allocation details the CI or treating health care professional will continue to deal with the participant's medical emergency as appropriate.

The CI must document the breaking of the code and the reasons for doing so on the CRF/data collection tool, in the site file and medical notes. The CI will ensure it is also documented in the final study report and/or statistical report at the end of the study.

The written information will be disseminated to the Trial Steering Committee.

13.8 Trial Schedule

13.8.1 Schedule of Assessment (in Diagrammatic Format)

Schedule of visits	Screening	Visit 1	Review 1	Review 2	Visit 2	Visit 3	Visit 4
Day/Month	Within 10 days post Tx	Day 1	1 month +/- 7 days	2 months +/- 7 days	3 months +/-14 days	6 months +/-1 month	12 months +/-1 month
Informed Consent	X						
Inclusion/exclusion criteria	X	X					
Demographic data	X						
Transplant data	X						
Medical history	X						
Concomitant medication	X	X			X	X	X
Pregnancy test review	X						
Randomisation		X					
Drug accountability					X		
Study drug dispense		X					
Physical examination		X			X	X	X
Weight	X	X			X	X	X
Vital signs		X			X	X	X
Laboratory bloods	X				X	X	X
OGTT	X				X	X	X
HOMA	X				X	X	X
eGFR Review		X	X	X	X	X	X
AE Review		X	X	X	X	X	X
End-point assessment					X	X	X

Laboratory bloods: Full blood count, urea and electrolytes, bone function test, liver function test, magnesium, fasting lipids and glucose and HbA1c.
A fasting serum C-peptide will be taken in order to perform the HOMA calculation.

13.8.2 Trial assessments

Screening visit
Informed consent
Inclusion/exclusion criteria

Documentation of a negative pregnancy test from post-transplant care in women of childbearing potential: defined as women following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
Demographic data
Transplant data
Concomitant medication
Medical history
Weight
OGTT
HOMA

Visit 1 - to occur within 10 days post screening
Inclusion/exclusion criteria
Concomitant medication
Physical examination
Adverse event reporting
Laboratory bloods: as above. Results from bloods that have been taken as part of routine care may also be included on the case record forms
Vital signs recording
Weight
Randomisation
Study drug dispense

Reviews 1 & 2 (1 and 2 months post randomisation +/- 7 days)
The research team will collect all eGFR results available for the patient, and review all medical records and hospital letters for adverse events. The research team will also telephone the participant to collect any adverse events that may not have been reported in medical records. All eGFR results and adverse events will be reviewed by the Chief Investigator or a medical delegate.

Visit 2 (3 months post randomisation +/- 14 days)
Concomitant medication
Physical examination
Adverse event reporting
Drug accountability
Vital signs recording
Laboratory bloods: as per visit 1.
Weight
OGTT
HOMA
Endpoint assessment

At this visit the patient will stop their IMP, and continue on their standard of care for follow up visits 3 and 4.

13.8.3 Follow up Procedures

Follow up visits will be visits 3 and 4.

Visits 3 & 4 (6 and 12 months post randomisation +/- 1 month)
Concomitant medication
Physical examination
Adverse event reporting
Laboratory bloods: as per visit 1.
Weight
OGTT
HOMA
Vital signs recording
Endpoint assessment

13.9 Withdrawal criteria

Investigational product treatment will be halted if the eGFR falls below 30ml/min. They will still remain on the study and should their renal function recover to greater than30ml/min they will be restarted on the IMP. If however they do not recover function of >30ml/min for 14 days then they will be withdrawn from the IMP for the remainder of the study. They will continue all other study related activities.

Patients may be withdrawn from the study if the investigator feels that individual adverse events or new information gained mean that it is not safe to continue the study, or if it is felt to be in the participant's best interest to stop the study.

Should a participant wish to withdraw from the study treatment the patient will stop the IMP. Patients would be encouraged to continue with the study visits for safety, however should they not want to take part in any further study visits, they will continue to be followed up by their clinical care team as standard. Routine clinical visits will be common for patients in their first year post transplant so it is unlikely any patients will get lost to follow-up, or be put at risk should they withdraw from the study.

Participants will continue to receive follow up procedures unless they specifically opt out.

Routine clinical data collection will continue for patients who have withdrawn from the study unless they specifically opt out of using routine clinical data collection.

Should a patient withdraw from the study this will be documented on the CRF using a study termination form which includes recording reasons for withdrawal and consent for any follow-up information being collected.

13.10 Early withdrawal

If a patient is withdrawn from the study early they will continue with their standard care at the unit.
It will be documented in the CRF and medical notes if the patient is happy to continue on with study visits (without the IMP), or continue to have their clinical data collected or no further data collected.

13.11 End of trial (EOT)

It is the CI's responsibility to submit the EOT notification to REC and MHRA once obtaining sponsor approval. The EOT notification must be received by REC and MHRA within 90 days of the end of the trial.

If the study is ended prematurely, the Chief Investigator will notify the Sponsor, REC & MHRA including the reasons for the premature termination (within 15 days).

End of Trial definition: is after the last patient has completed their last visit.

14.0 Laboratories and samples

14.1 Local Laboratories

Biochemistry and haematology samples will be sent to the Royal London Hospital Laboratory. All the tests that will be performed are part of the standard diagnostic set of tests commonly used to test for diabetes.

14.2 Sample Collection/Labelling/Logging

Samples will be collected by the research nurse or trained phlebotomist as per standard of care.

Samples will be labelled with patient identification and sent to the local labs as per routine care and the results logged on the pathology system and transcribed to the CRF.

The only samples that will be sent to the local lab, which are not part of routine care, are for serum c-peptide. (Glucose samples are sent as part of routine care – just not as part of an OGTT.)

Volume of samples to be collected:
The total volume of blood which will be taken on top of routine care is:
2 teaspoons (10ml) of blood per clinic visit (2x5ml samples of blood) in a serum separating tube provided locally.
2 teaspoons (8ml) of blood per clinic visit and at screening (2x4ml samples of blood) in sodium fluoride/potassium oxalate tubes provided locally.

No tissue or blood will be stored as part of the study.

14.3 Sample Receipt/Chain of Custody/Accountability

Samples will be sent to the lab by the research nurse, where they will be processed per the lab's standard SOPs under their UKAS accreditation. The research team will have responsibility for the custody of the samples until they are handed over the lab technicians at the sample collection point.

14.4 Sample Analysis Procedures

Samples will be taken to the local lab by the research nurse/team after being taken. All samples will be processed in accordance with local procedures.

No samples will be shipped to external labs/sites. No samples will be retained.

14.5 Sample and Data Recording/Reporting

Data will be recorded on the CFR/eCRF.
The CRF will be completed by the CI, Sub-I or research nurse. The CI will counter-sign completed CRFs and these will be stored securely in the study file in the research office.

14.6 End of study

No material will be kept in the department. All biological samples will have been sent to the lab and disposed of as per their routine SOP.

15.0 Trial Medication

15.1 Name and description of investigational medicinal product(s)

Metformin 500mg tablets/ Placebo

15.2 Legal status of the drug

This drug is licensed for use in the UK and other countries for:
The treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control.
In adults, metformin 850mg tablets may be used as monotherapy or in combination with other oral anti-diabetic agents, or with insulin.
In children from 10 years of age and adolescents, metformin tablets may be used as monotherapy or in combination with insulin.
A reduction of diabetic complications has been shown in overweight type 2 diabetic patients treated with metformin as first-line therapy after diet failure.

15.3 Summary of Product Characteristics (SmPC) or IB

The SPC used in this trial is titled Glucophage 500 mg and 850 mg film coated tablets and dated 19.1.17

15.4 Drug storage and supply

The IMP/Placebo will be shipped securely to the clinical trials pharmacy unit from the pharmacy manufacturing unit, where it will be stored until needed. The research nurse will collect the IMP/placebo from the clinical trials pharmacy and dispense this to the study patients. All medicinal products left after study completion will be destroyed

15.5 Supplier

The IMP and placebo will be made by the manufacturing unit at Guy's and St Thomas' NHS Foundation Trust and sent to the clinical trials pharmacy at the Royal London Hospital

The supply is being made specifically for use in the trial, not free of charge, and will not be used for any other purpose then as stated in the trial.

15.6 Manufacturer

Guy's and St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit
13th Floor Tower Wing
Guy's Hospital

Great Maze Pond
SE1 9RT

Telephone: 0207 188 7188 Ext: 51674
Email: elizabeth.lartey@gstt.nhs.uk
Website: www.gsttcommercialservices.co.uk/Pharmaceuticalsmanufacturing/Pharmaceuticalsmanufacturing.aspx

15.7 IMP Storage

The drug should not be stored above 25°C or stored anywhere other than in the original package. The containers should be kept tightly closed. The shelf life of the drug is 3 years. There are no special arrangements needed for the storage of the medication (it can be stored at room temperature).

15.8 Details of accountability

IMP will be dispensed from pharmacy and given to the patient by a member of the research team on the delegation log. An accountability log will be used to record the details of each batch of IMP dispensed to a patient, including subject identification code, drug batch number, date of dispensing and quantity dispenses, date returned and quantity returned, and date destroyed.

15.9 Medication destruction/return and Recall

At month 3 any unused IMP will be returned counted then destroyed as per local policy.
For recall: Guy's Pharmacy has a recall policy SOP number QA-GE-129 for defective medicines.

15.10 Prescription of IMP / Placebo/NIMP

The POWERED prescription form will be used to prescribe IMP or Placebo.

15.11 Preparation and labelling of IMP

The active treatment is Metformin 500mg tablets. The placebo tablet contains no active ingredient and is a visual match to the active. Placebo tablets are manufactured by Guy's and St. Thomas' NHS Foundation Trust (GSTFT PMU). Both active and placebo tablets are re-packaged into identical white plastic patient-packs with an Annex 13-compliant label by GSTFT PMU.

15.12 Preparation and Administration of IMP

The IMP will be dispensed as 500mg tablets. Patients will be counselled on their dose during visit 1.

15.13 Dosage schedules

The patient will be dispensed either placebo or metformin tablets for 3 month supply.

These are 500mg oral tablets to be taken once a day with or after meals.

Missed doses will be permitted: if a patient misses a dose they should take their next dose at the usual time. Drug accountability will be assessed at month 3 where patients will bring back their unused supply with non-adherence defined as less than 80% of medications taken.

15.14 Dispensing of IMP

There will be a dispensing guideline in place within pharmacy. Each member of staff who dispenses the IMP signs the local/pharmacy dispensing log to document appropriate IMP tracking. Any members of the trial team should ensure that they have had study specific training and their involvement should be demonstrated by the study specific trial delegation log.

15.15 Dosage modifications

The dose should be withheld if the EGFR falls to less 30ml/min, and only reinstated again once the eGFR is more than 30ml/min. If the patient's renal function does not recover to >30ml/min within 14 days of stopping the IMP the subject will be withdrawn from the study medication but will continue in the study with other study visits.

15.16 Known drug reactions and interaction with other therapies

Iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. The study drug should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.
CI should be informed if a patient is to undergo a procedure with iodinated contrast agents.

15.17 Prior and Concomitant medication

Any non-study antidiabetic medication is prohibited.

In the event that a patient requires antidiabetic medication then this is an end point and the patient will stop the study medication but will continue to be followed up in the study.

15.18 Assessment of compliance

Compliance will be assessed at visit 2, when the research team will count the number of tablets returned and consider less than 80% adherence to be non-compliant.

15.19 Arrangements for post-trial access to IMP and care

As this study is examining the efficacy of metformin to provide prophylaxis against diabetes, no IMP will be used following completion of the study. If a patient was to develop diabetes metformin would be used as clinically indicated in its licenced form.

16 Equipment and Devices

No equipment or devices will be used outside of standard care.

17 Pharmacovigilance

17.1 General Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity. • Consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI): • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product. • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

17.2 Site Investigators Assessment

The Chief Investigator is responsible for the care of the participant, or in his/her absence a delegated medical practitioner and is responsible for assessment of any event for:

- Seriousness
  Assessing whether the event is serious according to the definitions given in section 17.1.

- Causality
  Assessing the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

- Expectedness
  Assessing the expectedness of all SAEs according to the definition given. If the SAE is unexpected, then it is a SUSAR.

- Severity
  Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

    - **Mild**: Some discomfort noted but without disruption of daily life
    - **Moderate**: Discomfort enough to affect/reduce normal activity
    - **Severe**: Complete inability to perform daily activities and lead a normal life

17.3 Reference Safety Information

Reference Safety Information (RSI) is the information used for assessing whether an adverse reaction is expected.

The reference safety information for this trial is located in section 4.8 of the SPC titled "Metformin 500mg Medley" and dated 29.01.19.

Undesirable effects

(Taken from Medley SPC; revised 29/01/19)

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase the doses slowly.

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common: ≥1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders
Very rare
• Lactic acidosis (see [Special warnings and precautions for use]).
• Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Nervous system disorders
Common
• Taste disturbance

Gastrointestinal disorders
Very common
• Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders
Very rare
• Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders
Very rare
• Skin reactions such as erythema, pruritus, urticaria

Special warnings and precautions for use

Lactic acidosis
Lactic acidosis, a very rare, but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.
In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).
Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function
GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

Cardiac function
Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function.
For patients with acute and unstable heart failure, metformin is contraindicated (see section 4.3).

Administration of iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

Surgery
Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Concomitant use not recommended

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment. Avoid consumption of alcohol and alcohol-containing medicinal products.

Iodinated contrast agents
Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.4.

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics)
More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.
Co-administration of metformin with
• Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
• Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
• Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
• Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.
Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

17.4 Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF.

If as part of the routine care of patients post renal transplant the clinical care team withhold or restart the IMP they must inform the CI/research team. Members of the transplant team will be educated on the protocol and study requirements.

In addition to ensure that all AEs are gathered by the research team during the 3-month treatment period in a timely manner, the research team will review the source documents (clinic letters and or clinical entries on electronic patient record) on a regular basis (maximum every month).

17.5 Notification of AEs of special interest

There are no Adverse Events of Special Interest for this trial.

17.6 Adverse events that do not require reporting

It is standard protocol to stop CMV prophylaxis within the first-year post transplant.

It is also standard practice to wean some patients off prednisolone medication in the first year Therefore, we do not consider these changes an adverse event and they will not be formally reported.

17.7 Notification and Reporting of Serious Adverse Events & SUSARs

All Serious Adverse Events (SAEs) will be recorded in the participants' notes, the CRF, the sponsor SAE form and reported to the sponsor (Joint Research Management Office) within 24 hours of the CI or co-investigators becoming aware of the event. Nominated co-investigators (as listed in the delegation log) will sign the SAE forms in the absence of the CI.

Reporting of SUSARs
Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur during the trial will be reported to the JRMO within 24 hours of the CI or co-investigator becoming aware of the event. The sponsor will then report this to the MHRA.

17.8 Sponsor Medical Assessment

The CI retains overall responsibility for oversight of IMP safety profile and medical assessment of SAEs and SUSARs. The CI must review all SAEs within 48 hours of receipt. This review should encompass seriousness, relatedness and expectedness. Day 0 for all SUSARs is when the SAE/SUSAR is received by the CI and /or coordinating team and /or sponsor whichever is first.

It is expected that the CI will achieve oversight of IMP safety profile through trial committees as per section 28.0.

17.9 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken immediately. In this instance, approval from the Competent Authority prior to implementing these safety measures is not required. However, it is the responsibility of the CI to attempt, where possible, to discuss the proposed measures with the Sponsor and Medical Advisor at the MHRA (via telephone) prior to implementing them if possible.

The CI has an obligation to inform both the MHRA and Research Ethics Committee **in writing within 3 days**, in the form of a substantial amendment. The sponsor (JRMO) must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

17.10 Procedures for reporting blinded SUSARs

The CI as sponsor medical assessor will assess the event blinded, and will assess for active IMP and Placebo. For SUSARS the CI will remain blinded, however the sponsor will be unblinded for reporting to the MHRA.

17.11 Pregnancy

If a patient becomes pregnant while on the IMP the study medication will be withdrawn but the patient will continue on in the study. This is in line with guidance that, while metformin does not have harmful effects in animal studies; clinical guidelines suggest stopping metformin if patients become pregnant. If a patient on the IMP becomes pregnant the CI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. The initial report should be sent within 24 hours and follow up information submitted as and when it becomes available up to agreed follow up time after birth.

18.0 Annual reporting

Development Annual Safety Update (DSUR)
The DSUR will be written by the CI (using the Sponsor's template) and submitted to the sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "notice of acceptance letter" from the MHRA. As delegated Sponsor Medical Assessor the CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial. REC will be sent a copy of the DSUR.

Annual Progress Report (APR)
The APR will be written by the CI (using HRA template) and submitted to the sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the "favourable opinion" letter from the REC.

19.0 Statistical and Data Analysis

19.1 Sample size calculation

We calculated, using data from our cohort that 28% of patients developed diabetes in the first-year post transplant. To demonstrate that metformin reduced this proportion by 50% with a power of 80% and a probability at the 0.5 level we would require 22 patients per group. Accounting for a 20% dropout rate we would need to recruit 57 patients into the study.

19.2 Planned recruitment rate

Based on analysis from the renal unit at the Royal London Hospital (where the study will be based), there were 97 patients who would have met all the inclusion and none of the exclusion criteria and so been eligible to take part in the study within the last 12 months. This would allow a drop of rate of 40% both from refusal to take part (which we estimate to be 15%) and also from screen failures (which we estimate to be 25%). Therefore, it is expected that the recruitment will be complete within 1 year.

19.3 Statistical analysis plan (SAP)

Please refer to SAP for full details

Primary End-Point
The primary end point is the diagnosis of diabetes following a 3 month treatment period of metformin or placebo, defined as a positive 2-hour Oral Glucose tolerance (blood sugar greater than11.1mmol/l) test at 3, 6, or12 months post-randomisation, or following an OGTT due to suspected new diabetes at other routine clinical visits.

Statistical analysis will be by Chi-Square test.
Control vs IMP. P values of < 0.05 will be considered statistically significant.
This will be calculated for Intention to Treat Analysis.
For Intention to treat, we will use the last two available data points for patients that withdrew early from the study.

If patients did not have more than 1 visit after randomisation, they will not be included in analysis.

Secondary End Point:

1) The effect of a 3 month course of metformin on markers of pancreatic beta cell function using the HOMA test at 3, 6, and 12 months
These parameters will be compared on the ITT dataset using 2 way repeated measure ANOVA. P values of < 0.05 will be considered statistically significant.

2) HbA1c level at 3,6, and 12 months

These parameters will be compared on the ITT dataset using 2 way repeated measure ANOVA. P values of < 0.05 will be considered statistically significant.

3) Patient/Graft survival

These parameters will be compared on the ITT dataset using a Kaplan–Meier test statistic P values of < 0.05 will be considered statistically significant.

4) Safety endpoints: SAEs, AEs

Overall AE and SAE rates will be calculated based on the number of each event / duration subject was in the study after randomisation (ITT)

AE and SAE will be categorised into categories as per CRF. The rates of AE/SAE for each category will be calculated.

Control vs IMP rates will be compared using Poisson regression, with no adjustment for multiple events per subject. Statistical significance if P-value <0.05 after Bonferroni correction is applied

5) Episodes of acute rejection

These parameters will be compared on the ITT dataset using Student t-test. P values of < 0.05 will be considered statistically significant

6) Renal function at 12 months

These parameters will be compared on the ITT dataset using Student t-test on the eGFR results at 12 months. P values of < 0.05 will be considered statistically significant

7) Diagnosis of impaired glucose tolerance (as indicated by a 2-hour oral glucose tolerance test result of 7.9-11.1 mmol/L)

These parameters will be compared on the ITT dataset using Chi Sq. P values of < 0.05 will be considered statistically significant.

Baseline Demographics and Biochemical parameters

Continuous variables will be tested for normality using D'Agostino-Pearson normality test. Mean (standard deviation) or median (interquartile ranges) will be displayed. Statistical analysis will be by student t-test (unpaired) or Mann-Whitney U test.

Categorical data will be analysed by Chi Square.

Statistical significance if P-value <0.05 after Bonferroni correction is applied

Baseline Demographic information including:

Transplant operation details

Biochemical parameters (last available result prior to randomisation unless specified)

19.4 Summary of baseline data and flow of patients

Baseline data to be collected will include demographic data, details of transplant, medical history and vital signs.

Groups will be compared using standard statistical methods, continuous data will be reported as mean (SD) or median (IQR) as appropriate. Significance will be analysed using t tests for continuous data and categorical (Chi Square).

There is a plan to produce a consort flow diagram.

19.5 Primary outcome analysis

The primary end point is the diagnosis of diabetes following a 3 month treatment period of metformin or placebo, defined as a positive 2-hour Oral Glucose tolerance (blood sugar greater than11.1mmol/l) test at 3, 6, or 12 months post-randomisation, or following an OGTT due to suspected new diabetes at other routine clinical visits.

The end point data will be analysed on an ITT basis, with no subgroup analysis using unpaired parametric and non-parametric analysis as necessary.

19.6 Secondary outcome analysis

Each of the secondary end points will be analyzed with the null hypothesis that the IMP and placebo are similar in effect on each end point.

19.7 Interim analysis and criteria for the premature termination of the trial

No interim analysis is planned.

19.8 Subject population

The study population will be those patients undergoing a renal transplant at the RLH renal unit. Who satisfy the inclusion criteria and do not meet any of the exclusion criteria.

19.9 Procedure(s) to account for missing or spurious data

As this group of patients attend standard of care clinic visits very frequently post transplantation, it is not expected that they will be lost to follow up. The research team will make every effort to rectify any missing or spurious data.

If a patient should have blood tests, including an OGTT, in the setting of a local primary or secondary healthcare provider, then it will be deemed reasonable to include these results as part of the POWERED Study data set.

20.0 Data Handling & Record Keeping

20.1 Confidentiality

The Chief Investigator has the responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The UK Policy Framework of Health and Social Care Research and Ethics Committee Approval. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) and all subsequent amendments as defined in the JRMO SOP 20 Archiving.

The Chief Investigator and the study team will adhere to these regulations to ensure that the participants' identities are protected at every stage of their participation in the study. To ensure this is done accordingly, at time of consent each participant will be allocated a unique screening number by either the CI or a member of the study team before undergoing any screening procedures.

All investigators and trial site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

20.2 Data Custodian Details

The Chief Investigator Kieran McCafferty, Royal London Hospital, E1 1BB is the 'Custodian' of the research data.

20.3 Pseudononymisation

Data will be in the form of linked anonymised data. Unique study numbers will be used, which are linked to a treatment code. This will be contained in the ISF on the enrolment log.

20.4 Transferring/Transporting Data

All patient-identifiable information will be stored in a locked environment, or on password protected NHS computers on an electronic database.

No data will be transferred out of this environment.

20.5 Data collection tools and source document identification

The source document will be paper medical records and the electronic patient record system Cerner Millennium. Data from the source document will be added to a paper CRF and this will be then uploaded to an eCRF.

20.6 Source Data

The source documents will comprise the site medical notes and health records (paper and electronic), including Barts Health NHS Trust laboratory and pharmacy records.

20.7 Case Report Form

Data will be transcribed from source documents to paper Case Report Forms at the start of the trial with the aim to move to online Electronic Case Report Forms (eCRFs). The eCRFs will be managed by a secure web application, accessible via HTTPS/SSL. Users will be issued with a username and password and will be required to login for web application access; their activity will be tracked using unique user identities and their access to data controlled by defined access roles. Patient Identifiable Data will be encrypted in the database and kept separately from the clinical data. Direct access to the database will be restricted to named users only.

A paper backup system will be established in case of technical failure or for local convenience. Where paper CRFs are used, they should be kept in the investigator file and they will be reviewed as part of source data verification during site monitoring. Patients will be identified only by initials, trial number and day (dd) of birth.

The eCRFs will be completed by the Investigator or suitably trained research staff, as designated in the site delegation log, as accurately and completely as possible throughout the study.

20.8 Data handling and record keeping

Data will be recorded from study visits in the source data and transcribed to the CRF and entered in the database/eCRF. All documents (CRF, signed consent forms etc. will be kept according to the sponsor's requirements. All research staff will be trained on the use the database and CRF.

20.9 Access to Data, Source Data and Documents

Direct access will be granted to authorised representatives from the Sponsor or delegate, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

21.0 Archiving

During the course of research and for archiving period, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Trust Policy that the records are kept for a further 25 years.

Destruction of essential documents will require authorisation from the Sponsor.

Archiving will be authorised by the sponsor following submission of the end of study report.

22.0 Monitoring, Audit and Inspection

22.1 Monitoring

A Trial Monitoring Plan will be developed and signed by the Sponsor and Chief Investigator based on the sponsor's trial risk assessment, which will include on site monitoring. Monitoring procedures are detailed in the Trial Monitoring Plan.

A sponsor monitor will monitor the trial on a regular basis.

22.2 Auditing

The sponsor retains the right to audit the trial. In addition, any part of the trial may be inspected by the regulatory bodies and funders where applicable.

22.3 Notification of Serious Breaches to GCP and/or the protocol

The CI is responsible for reporting any serious breaches to the sponsor (JRMO) **within 24 hours of becoming aware of the breach.**

The sponsor will work with the CI to investigate any potential breach. The sponsor will notify the MHRA, and the CI will notify the REC, within 7 working days of becoming aware of the serious breach.

22.4 Compliance

The CI will ensure that the trial is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and any subsequent amendments of the clinical trial regulations, current UK Policy Framework for Health and Social Care Research, GCP guidelines, the World Medical Association Declaration of Helsinki (1996), the Sponsor's SOPs, and other regulatory requirements as amended.

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA.

22.5 Non-Compliance

Planned deviations or waivers to the protocol and specifically the eligibility criteria are not allowed.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

All deviations will be documented in the patient records, deviation log and CRF.

The CI and the coordinating team should assess the non-compliances and agree on a timeframe in which they need to be dealt with. This assessment should include the need to escalate to the sponsor. Any event with the potential to affect participant safety or data integrity should be reported to the sponsor within 24 hours of the Coordinating team becoming aware.

Where applicable corrective and preventative actions (CAPA) should be taken. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the Sponsor will agree an appropriate action, which could include an on-site audit.

22.6 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA, favourable opinion has been obtained from an NHS REC and HRA Approval.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol participants into the trial, the site will confirm to the CI that it has Capacity and Capability to run the trial, and the CI will activate the site..

The Chief Investigator will obtain approval from the appropriate review bodies before implementing any amendments to the trial.

This study does not involve ionising radiation.

23.0 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator has no financial or other competing interests.

All members of committee will sign a competing interests form.

24.0 Ethical and Regulatory Considerations

Before the start of the trial, approval will be sought from the Research Ethics Committee (REC) and MHRA for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

Decision whether an amendment constitutes a minor or substantial amendment lies with the sponsor.

Substantial amendments that require review by the Sponsor and REC and MHRA (where relevant) will not be implemented until the REC and or MHRA grants a favourable opinion for the study and until Capacity and Capability has been confirmed by the site.

All correspondence with the Sponsor, REC and MHRA will be retained in the Trial Master File at the lead site and Investigator Site File at each site.

The Chief Investigator will notify the REC, MHRA and Sponsor of the end of the study.

25.0 Peer review

This CTIMP trial has undergone independent scientific peer review by a professor of kidney medicine not affiliated with the sponsor. The CTIMP has also undergone local peer review within the Chief Investigator's clinical department.

26.0 Public and Participant Involvement

Haemodialysis patients (who may be potential future recruits) and patients who currently have a renal transplant were involved in reviewing the patient documents to ensure ease of read and clarity. We have engaged with our patient group (The Renal Patient Forum) to invite them to nominate one or more patients to sit on the Trial Study group.

27.0 Indemnity

NHS Indemnity will apply as the Sponsor and site are Barts Health NHS Trust.

27.1 Amendments

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the sponsor must submit a valid notice of amendment to the licencing authority (MHRA) and to the HRA and REC for consideration. The MHRA, REC and HRA will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA, REC and HRA.

If applicable, other specialist review bodies (e.g. Clinical Boards) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Amendments will also be notified to NHS R&D departments of participating sites to assess whether the amendment affects the NHS capability and capacity for that site.

The CI along with the steering committee will be responsible for making the decision to amend the protocol. Amendments will be submitted by the CI to the MHRA, HRA and REC and will inform the Trial registries and local R&D departments. Any changes to study documents will be subject to version control and amendment history.

27.2 Access to the final trial dataset

The steering committee will have access to the final dataset along with the CI.

28.0 Trial Committees

The Trial steering committee/ drug safety monitoring committee will be made up of:

Independent Chair

Trials statistician

Director of DKC

Patient representative

Lead for Transplant Surgery

Consultant in Transplant surgery/renal medicine/diabetic medicine

CI

For the current names of the members please see DMC/TSC document

There will be regular documented management meetings and a trial steering committee with independent representation.

This group will meet every 6 months to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them. This group will review and safety/operational concerns and the have the authority to terminate / prematurely discontinue the trial.

29.0 Publication and Dissemination Policy

29.1 Publication

Publications will occur at the end of the study.

The sponsor retains the right to review all publications prior to submission or publication.

Responsibility for ensuring accuracy of any publication from this study is delegated to the Chief Investigator.

All publications should acknowledge the Sponsor. The correct designation for the sponsor is Barts Health NHS Trust.

The full study report will be accessible via EudraCT.

29.2 Dissemination policy

Data arising from the trial is owned by the sponsor. In all publications arising from this study, the Diabetic Kidney Disease Centre will be acknowledged in the final manuscript.

Participants will be notified of the outcome of the trial in writing. Their non-blinded treatment allocation will be made available to patients on request following publication.
The trial protocol and the full study report will be made publicly available via EudraCT.

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This protocol is based on JRMO CTIMP Protocol Template June 2015 version 4.0.