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Transplantation and Diabetes (Transdiab): A Pilot Randomised Controlled Trial of metformin in pre-diabetes after kidney transplantation

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Abstract

Introduction: New Onset Diabetes after Transplantation (NODAT) is a common complication of kidney transplantion, and is associated with significant morbidity and mortality. In the general population, metformin has been used for diabetes prevention in high risk individuals. Improving insulin sensetivity is one of many proven favourable effects of metformin. Despite the high incidence of NODAT in kidney transplant recipients, there is a lack of evidence for the role of meformin in the prevention of diabetes in this setting. **Methods/Design: Trans**plantation **and Diab**etes **(Transdiab)** is a single-centre, unblinded, pilot randomised controlled trial assessing the feasiblity, tolerability and efficacy of meformin post renal transplantation in patients with Impaired Glucose tolerance (IGT). Participants will undergo an Oral Glucose Tolerance Test (OGTT) in the 4-12 weeks post-transplantation; those with IGT will be randomized to standard care or standard care and Metformin 500mg bid, and followed up for 12 months. The primary outcomes of the study will be the feasibility of recruitment, the tolerability of metformin assessed using the Gastrointestinal Symptom Rating Scale (GSRS) at 3 and 12 months, and the efficacy of meformin assessed by morning glucose and HbA1c at 3,6,9, and 12 months. **Discussion**: Despite the significant morbidity and mortality of NODAT, there are currently no randomized clinical trials assessing pharmacological interventions for its prevention after kidney transplantation. The abnormal renal function and frequent fluctuations of renal clearance are of particular concern in this group of patients, as metformin is more likely to accumulate and causes adverse events. The Transdiab trial will thus provide important data on the feasibility, safety, tolerability and efficacy of Metformin post renal transplantation in IGT patients; this will facilitate undertaking larger multi-centre trials of interventions to reduce the incidence or severity of diabetes after kidney transplantation.

Article summary:

Strengths and limitations of this study:

- Has the potential to address more than one important cause of morbidity and mortality in kidney transplant patients with one simple approach
- Difficult to provide sufficient data for clinical effectiveness of the measure used.
- Safety and tolerability outcomes are likely to be informative and crucial for larger future RCTs

Trial registration: Australian New Zealand Clinical Trials Registry Number: ACTRN12614001171606

Keywords: Kidney transplantation, NODAT, Metformin, prevention, Randomized-controlled trial

Introduction

End-stage kidney disease (ESKD) is a major public health problem with increasing prevalence worldwide. In 2013, there were 4,156 people receiving renal replacement therapy for ESKD in New

Zealand. This represents a population rate of 931 people per million. Of these, 1,572 (38%) had a functioning kidney transplant (1). Kidney transplantation represents the optimal form of renal replacement therapy, and is associated with significantly improved survival (2, 3) quality of life (4), and reduced costs over time (5) compared with dialysis treatment. However, transplant recipients still have increased mortality compared with general population (6). This is predominantly driven by increased cardiovascular disease, as cardiovascular related deaths post-transplant constitutes over 50% of all deaths (7, 8). An important risk factor for this marked risk is New Onset Diabetes after Transplantation (NODAT), previously known as Post-Transplant Diabetes Mellitus (PTDM).

NODAT is a common complication post transplantation, with a reported incidence as high as 50 %(9) and significant impact on morbidity and mortality in transplant recipients. Patients with NODAT have significantly higher rates of cardiovascular disease, cardiovascular death and overall mortality with a doubling in all-cause mortality and a tripling in cardiovascular events (10-12). The mortality risk extends to include other forms of impaired glucose metabolism after transplantation as patients with Impaired Glucose tolerance (IGT) have an increased long-term mortality risk comparable to those with NODAT (13). In addition, NODAT is also associated with increased death censored graft failure (12,14)

In 2003, an expert committee set forth the International Consensus Guidelines for the diagnosis and management of NODAT (15). This was further revised and extended in 2005 to cover recipients of kidney, liver and heart transplants (16). These guidelines are based on those of the World Health Organization (WHO) for the diagnosis of prediabetic states (Impaired Fasting Glucose (IFG) and IGT) and diabetes mellitus (17). Multiple risk factors have been associated with the development of NODAT, the use of diabetogenic immunosuppressive medications (such as corticosteroids (18), Calceniurin inhibitors (12,19) and Mammalian Target of Rapamycin (MTOR) inhibitors (20)) are all associated with impaired glucose metabolism. Furthermore, there is a significant incidence of excess weight gain and obesity in transplant recipients which contributes to insulin resistance, with average post-transplant weight gains of 10-35% reported in the first year (21-23). Possible causes for weight gain include the use of immunosuppressive medications (such as corticosteroids), the relaxation of dietary restrictions and improvements in wellbeing after transplantation (24,25)

Another well-identified risk factor for the development of diabetes in both transplant recipients and the general population is the status of pre-diabetes (IGT or IFG), with impaired fasting glucose (IFG: fasting plasma glucose ≥ 6.1 mmol/L and < 7 mmol/L) or impaired glucose tolerance (IGT: fasting plasma glucose < 7 mmol/L and 2-h plasma glucose after an OGTT ≥ 7.8 mmol/L and < 11.1 mmol/L) define hyperglycemic conditions at risk of the future development of diabetes (12). In nontransplanted patients, some 70 % of individuals with IFG and/or IGT can expect to go on to develop clinical type 2 diabetes at some time in the future (26). That risk is also significant for transplant patients with 15% of patients with IGT developing NODAT over 1 year (27) and 27% over 6 years (28).

Given the significant adverse clinical outcomes associated with diabetes, multiple measures have been introduced to prevent or delay the onset of diabetes in high risk individuals. Current guidelines recommend lifestyle modifications in the management for individuals with prediabetes or diabetes, based on an improved diet and regular moderate physical exercise with the aim of achieving weight loss in overweight or obese patients (29,30).

However, weight loss arising from intensive lifestyle interventions is known to be difficult to maintain over the long term (31). Therefore the current guidelines support the use of pharmacologic antidiabetic therapy immediately after the diagnosis of diabetes for patients considered unlikely to benefit sufficiently from lifestyle intervention alone (32).

Pharmacological therapy (metformin, thiazolidinediones, a-glucosidase inhibitors or basal insulin) have been shown to effectively delay or prevent the conversion of prediabetes to diabetes in non-transplant patients, however metformin is the only pharmacologic agent recommended for the prevention or delay of type 2 diabetes in at-risk subjects due to its effectiveness as demonstrated in well-designed trials, good tolerability and low cost (29,30)

No similar trials have been carried out in transplant recipients, these patients have a high risk of developing NODAT and the subgroup with IGT are likely to be at even greater risk. Therefore, this group might achieve a significant benefit from starting metformin in addition to life style advice.

We will be conducting a pilot randomised controlled trial assessing the safety, tolerability and efficacy of metformin in renal transplant recipients with IGT. The trial will also provide data on the feasibility of recuriting eligible patients with IGT post transplantation to be started on metformin which will help to plan conducting larger trials aiming to reduce the incidence or severity of diabetes after kidney transplantation

Methods/Design

Study design

Transdiab is a single-centre, unblinded, randomised controlled trial. An outline of the study is shown in Figure 1.

Study aims and hypothesis

The primary aim of the NODAT is to evaluate the feasibility, safety, tolerability and efficacy of metformin in kidney transplant patients with Impaired Glucose Tolerance (IGT). The secondary outcomes are those that will help evaluate the additional benefits of metformin on lipid profile, change in weight and cardiovascular events.

We hypothesize that recruiting non-diabetic patients after renal transplantation to have OGTTs in order to identify and pharmacologically manage those with IGT is feasible. We also hypothesize that using metformin within our inclusion criteria is safe with acceptable tolerability in the first year after

renal transplantation. Furthermore, it is likely that metformin will have a favourable effect on HbA1c, morning glucose, lipid profile, excess weight gain and cardiovascular events.

Ethical considerations

Ethical approval has been obtained through the Northern B Health and Disability Ethics Committee of the Ministry of Health in New Zealand. Ethics approval number is **14/STH/129**

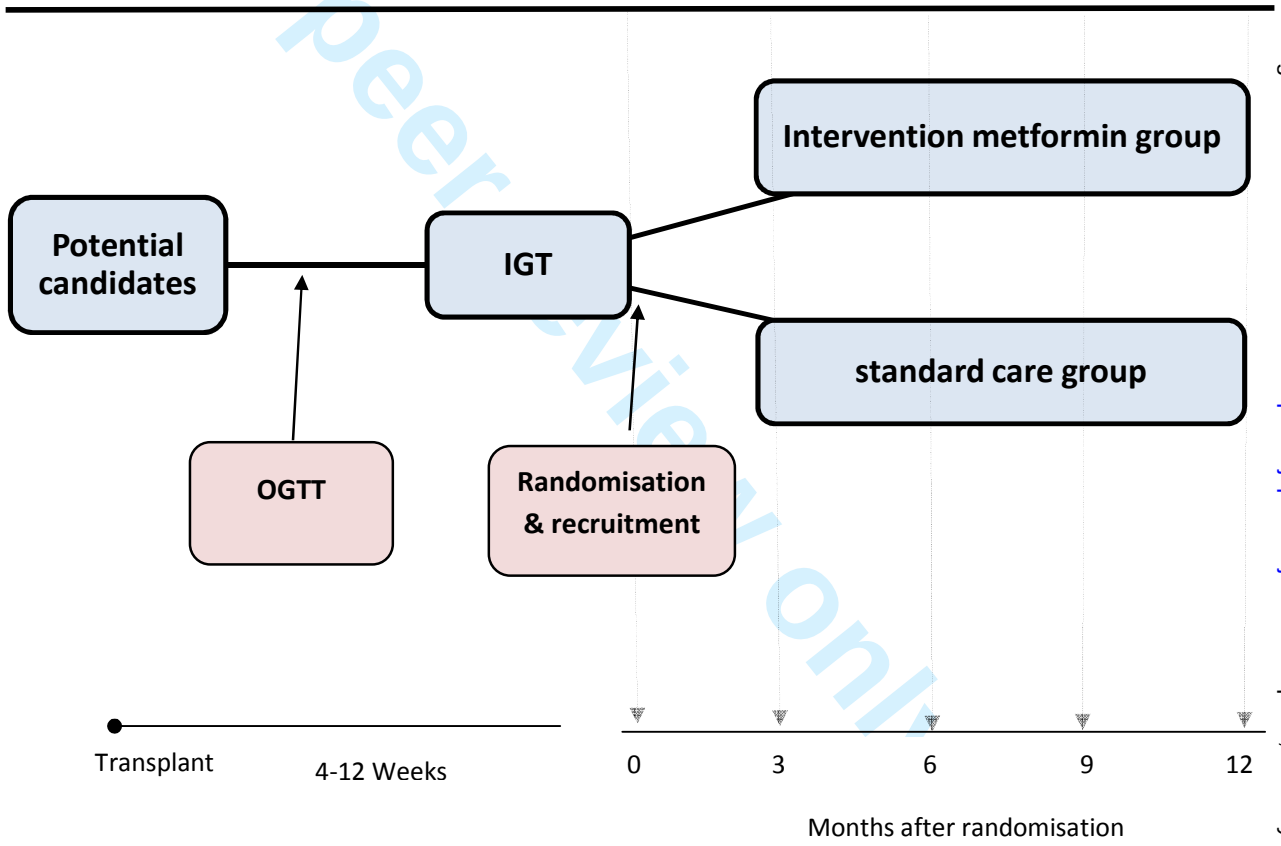

Figure1 .Flowchart of Transdiab trial

Target population and eligibility criteria

The target population for the trial is adult kidney transplant recipients who receive kidney transplantation in our centre between 30/11/2014 and 30/11/2016

Inclusion criteria will include the following: age > 18 years; non-diabetic kidney transplant recipient; willing and able to participate in all trial investigations for the duration of trial follow-up; and ability to provide a written informed consent.

Exclusion criteria will include the following: known diabetes mellitus at the time of transplant (whether on anti-diabetic medications or not); past history of anti-diabetic therapy (oral or insulin); steroid pulse therapy (IV or oral) in the 2 weeks prior to OGTT; estimated Glomerular Filtration Rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula ≤ 30 ml/min/1.73 m^2 BSA; unable to consent; pregnancy or breast-feeding; current alcohol or other substance abuse; and any major illness or comorbidity that may result in death in 12 months as assessed by the treating physician.

Recruitment and randomisation

Potential participants will be identified during their initial inpatient stay following transplantation at Auckland City Hospital, or through the renal transplant outpatient clinic following discharge. Eligible transplant recipients will be invited to participate, given detailed information about the trial and, if agreeable, will be asked to provide a written informed consent. In order to participate, transplant recipients will need to provide informed consent and have the OGTT within 4-12 weeks after the transplant procedure.

Participants who have a 2 hour post-load glucose between 7.8 to 11.1 mmol/L on oral glucose tolerance test (75 g anhydrous glucose dissolved in water) will be randomised. Randomisation will be performed using a computer-generated sequence allocation in blocks of 4 in a 1:1 ratio to receive either standard care or standard care and Metformin 500mg bid.

Standard care group

Participants randomised to the standard care group will receive standard post-transplant care as per usual local practice. This includes immunosuppressive medications to prevent rejection and other treatments under the direction of the treating physician and renal transplant team. Standard immunosuppression includes a calcineurin inhibitor (cyclosporine or tacrolimus as determined by the treating physician), mycophenolate, steroids, and basiliximab as induction therapy.

The current lifestyle standard care after kidney transplantation at Auckland City Hospital includes advice for regular exercise 3 times weekly and a nutritional assessment by a renal dietician during the inpatient stay. The nutrition care involves giving patients resources guiding them on healthy eating and food safety after transplant.

Intervention group

Patients randomised to the intervention group will, in addition to standard care, receive metformin 500mg bid. This will commence at randomisation and continue for 12 months. The decision to continue with Metformin beyond 12 months of follow up is left to the discretion of the caring physician.

Primary outcomes

Feasibility of Recruitment will be assessed by the ratio of the number of randomised patients to the number of patients screened with OGTTs.

Tolerability of Metformin will be assessed using Gastrointestinal Symptom Rating Scale (GSRS), a tool that has been validated to assess symptoms in gastrointestinal disorders such as gastroesophageal reflux disease and irritable bowl syndrome (33,34) at baseline, 3, and 12 months post-randomisation.

Efficacy of Metformin will be assessed by HbA1c and morning glucose levels at baseline, 3, 6, 9, and 12 months post-randomisation

Secondary Outcome:

Secondary outcomes will include the following: Change in body weight, all adverse events, lipid profile at 3, 6, 9 and 12 months, major cardiac events and proportion of patients who revert to normal glucose metabolism on OGTT at 12 months. Also discontinuation of metformin or reduction of dose due to adverse effects will be recorded.

Statistical analysis

The first primary outcome, feasibility of recruitment will be reported as a ratio of the number of randomised patients to the number of patients screened with OGTT at the conclusion of the study.

The second primary outcome, tolerability of metformin will be reported as Gastrointestinal Symptom Rating Scale (GSRS) at 3 and 12 months and compared between the 2 groups using an analysis of covariance (ANCOVA) adjusted for GSRS score at baseline. The third primary outcome, efficacy of metformin will be reported by measuring morning glucose and HbA1c 3, 6, 9, and 12 months post-randomisation and compared between the 2 groups using an analysis of covariance (ANCOVA) adjusted for morning glucose and HbA1c at baseline.

Linear regression will be used to identify significant predictors other than group allocation associated with changes in efficacy, tolerability and metabolic parameters over time. Variables identified as significant will be analysed with pairwise comparisons. Comparisons between groups for differences in categorical variables will be conducted using Chi-square test or Fisher's exact test. All statistical analyses will be performed using appropriate statistical software, such as STATA or SPSS. The level of statistical significance will be set at probability level of <0.05.

Discussion

This trial will provide evidence on the feasibility, safety, tolerability and efficacy of metformin in patients with impaired glucose tolerance after renal transplantation. In addition, the study will also examine in detail changes in other metabolic indices, including BMI, weight change, blood pressure, lipid profile and cardiac events.

The extensive local and international experience with Metformin and the significant potential benefits are likely to encourage patients and physicians to take active part in the study. Based on evidence from the literature, 43% of stable kidney transplant patients (>6 months after transplant)

will have new impaired glucose metabolism after transplantation with new IGT and/or IFG affecting 32% of all recipients (35). Therefore, we hypothesise that performing oral glucose tolerance tests in non-diabetic patients after renal transplantation and subsequently starting those with impaired glucose tolerance on metformin will prove feasible.

Although generally safe, gastrointestinal side effects are not uncommon with the use of metformin, these are generally well tolerated and infrequently cause treatment discontinuation (36). The long term experience with metformin in the diabetic general population has established good tolerability and an acceptable safety profile (37) also in addition to good adherence by patients (38). A major and probably overstated potential side effect is lactic acidosis. Historically, a very low risk of lactic acidosis linked to the use of metformin has been reported (39). More recent high quality evidence has shown no risk related to metformin in general population with type 2 diabetes (40). The risk is probably higher in patients with reduced Glomerular Filtration Rate (GFR) as metformin is more likely to accumulate, but a systematic review found no cases of lactice acidosis despite almost one half of the studies involved allowing inclusion of patients with a serum creatinine above 1.5 mg/dL [133 micromol/L] (41). Given the relative safety of metformin and signficant benefit, the expansion of its use has been recommended to include patients with mild to moderate kidney disease (estimated glomerular filtration rates, 30-60 mL/min per 1.73 m2) (42)

Although physicians might have reservations starting metfomin in renal transplant recipients as they commonly have abnormal GFRs with frequent fluctuations, the recent evidence provides further reassurance in the safety and tolerability of metformin even at moderate renal impairment. Therefore, we hypothesise that the use of metformin in these patients is safe and well tolerated.

Metformin has other favourable effects besides improving insulin sensitivity, some of which can be of substantial benifit to transplant patients. Most notably, the effects on cardiovascular disease (43) and weight gain (44), with current on-going research assessing these benefits even in prediabtic patients (45).

Furthermore, metformin has been shown to reduce the incidence of cancers and cancer-related mortality (46,47). Renal transplant recipients have high cancer related morbidity and mortality with cancer risk almost 3 times higher than general population (48,49).

The outcomes from this research will provide important data on the feasibility of conducting larger multicentre randomised trials of metformin in patients with IGT to reduce the incidence and severity of diabetes in kidney transplant recipients. This study will also provide transplant physicians with more confidence in using metformin in renal transplant recipients if no significant adverse events are encountered. There is a potential risk of bias as the participants are not blinded to the treatment, this could be addressed with the use of placebo in a larger trial.

Measurement of efficacy of the use of metformin is likely to require a large multicentre trial to have a sufficient number of patients for a significant difference (38). We anticipate that by determining feasibility and safety in this pilot study we will pave the way for future larger RCTs.

Conclusions

Transplantation **and Diab**etes **(Transdiab)** study will provide important data on the feasibility, safety and efficacy of metformin in patients with impaired glucose tolerance after renal transplantation. With NODAT being an important cause of morbidity and mortality in renal transplant patients, this study will address a significant gap in current evidence regarding optimal care after kidney transplantation.

Contributorship statements for the authors:

1- Paul manley
   a. The main contributor to the initial design of the research and subsequently acquring ethics approval, registering the study and submitting the proposal for the funding grant.
   b. Substantial contribution to the work draft.
   c. Reviewing and amending the final version for publishing
2- Helen Pilmore
   a. Contributed to the initial conciption of the work and revised the initial design criticially for ingenuity.
   b. Provided further insight in the potential limitations and provided the required support for obtaining the funding grant
   c. Supervised the disegnated fellow in following the study protocol and conducting the appropriate analysis.
   d. Reviewing and amending the final version for publishing
3- Basil Alnasrallah
   a. Substantial contribution to the interpretation of data for the work. Also, drafted the final protocol after reviewing the relevant literature and submitted it for the other authors' comments and amended it accordingly.
   b. Identified the limitations in the study and the practical challenges while carrying out the study and initial analysis.

All authors agreed to be accountable for all aspects of the work in insuring that any issues related to any part of the work are appropriately investigated and resolved.

Conflict of interest

None of the authors had any conflict of interest

Funding

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Data sharing statement

At the time of submitting this protocol, no patients' data were available.

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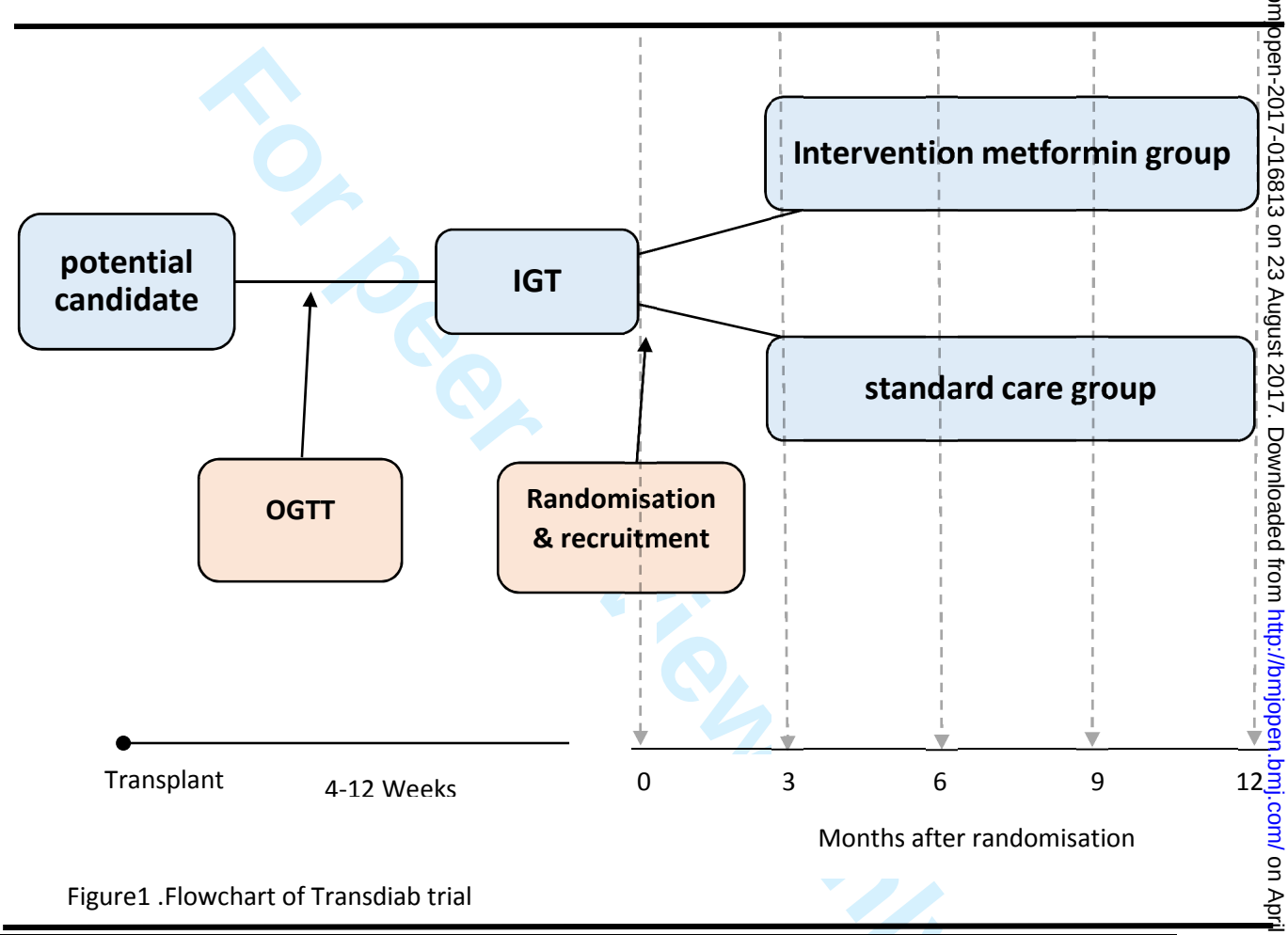

Figure1 .Flowchart of Transdiab trial

A randomised controlled trial of metformin in Impaired Glucose Tolerance (IGT) (TransDiab)

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Study Schema

Consent for screening anytime from post-operative period

⇩

75 g OGTT (as described by WHO) between 4 - 6 weeks after transplant (Up to 12 weeks allowed)

⇩	⇩	⇩
2-hr post-load glucose ≤ 7.8 mmol/L	2-hr post-load glucose 7.8 to 11.1 mmol/L	2-hr post-load glucose ≥ 11.1 mmol/L *or* Fasting glucose ≥ 7.0 mmol/L or DM at any time prior to OGTT if DM
Non-diabetic	**Prediabetes (IGT/IFG)**	**NODAT**
⇩	⇩	⇩
Follow to 12 months	Randomise	Follow for 12 months

.

LifeStyle + Metformin
vs.
LifeStyle

⇩

Minimum follow up 12 months after recruitment of the last patient

Study Outcome Measures:

The primary objectives of this Feasibility Study are to obtain the following feasibility, adverse event and efficacy data:

(i) Feasibility of recruitment in patients with pre-diabetes as defined by impaired glucose tolerance or elevated fasting plasma glucose after kidney transplantation

(ii) Adverse gastrointestinal side effects assessed by Gastrointestinal Symptom Rating Scale (GSRS)

(iii) Efficacy:
   a. Difference in Fasting Plasma Glucose at 3,6,9,12 months
   b. Difference in afternoon glucose at 3,6,9,12 months
   c. Difference in HbA1c at 3,6,9,12 months
   d. Proportion of patients developing New Onset Diabetes after transplantation at 12 month

The secondary objectives of the TRANSDIAB Feasibility Study are to assess the effects of metformin on the following outcome measures:

(i) Discontinuation of the study medication due to adverse events
(ii) All adverse events, including hypoglycemia, lactic acidosis, death
(iii) Absolute changes in weight
(iv) Lipid profile

(v) Fatal and Non-fatal cardiovascular events

(i) Proportion of patients who revert to normal glucose metabolism as defined by OGTT.

Definition of DM

	Glucose concentration, mmol l^{-1}		
	Whole blood Venous	Whole blood Capillary	Plasma* Venous
Diabetes Mellitus:			
Fasting	>=6.1	>=6.1	>=7.0
or			
2-h post glucose load	>=10.0	>=11.1	>=11.1

Study Evaluation Schedule: All patients will have the following investigations regardless of randomisation

Evaluation	Screening	Baseline (Day -7 to -1)	Week 1	Week 2	Week 4	Month 3	Month 6 and 9	Month 12
Glucose Tolerance Test	X							X
eGFR (MDRD)	X		x	x	x	x	x	x
Serum Creatinine	X	X	x	x	x	x	x	x
Serum Glucose		x	x	x	x	x	x	x
HBA_1c		x				x	x	x
Inclusion/Exclusion Criteria	X	X						
Physical Examination +Height		X						x
GI Quality of Life		X				x		x
24 hour urine protein		X				x		x
CNI dosing Record		X	x	x	x	x	x	x
Acute Rejection Episodes	X	X						x
Pm Glucose Level		X				x	x	x
Weight (kg) and BMI		X	x	x	x	x	x	x
Additional Medications		X			x	x	x	x
Serum Cholesterol and TG		X			x	x	x	x
Waist:Hip		X						
Adverse Events			X	X	X	X	X	x
Hypoglycemic med and dose record		x	x	x	x	x	x	X
Endpoint MI, Revascularisation, Death, Graft Loss					x	x	x	x
Blood Pressure	x	x	x	x	x	x	x	x

Inclusion/Exclusion Criteria:

Inclusion criteria

1) Adult (age > 18 years)
1) Incident non-diabetic kidney transplant recipient (deceased or living donor)
2) 2 hour post-load glucose (OGTT 75 g anhydrous glucose dissolved in water), done at 8 to 12 weeks after transplant (up to 16 weeks)
   2 hour PG 7.8 to 11.1 mmol/L for impaired glucose tolerance (IGT) group

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i) Exclusion criteria

In addition, potential participants must have NONE of the following exclusion criteria.

1. Known diabetic at the time of transplant, whether on anti-diabetic medications or not
2. Past history of anti-diabetic therapy (oral or insulin)
3. Steroid pulse therapy (IV or oral) in 2 weeks prior to OGTT*
4. eGFR by MDRD formula ≤ 30 ml/min/1.73 m^2 BSA (in line with the recommendations of Diabetes Australia)
5. Unable to consent
6. Pregnancy/ breast-feeding
7. Any major illness/ comorbidity that may result in death in 12 months as assessed by the treating physician,
8. Current alcohol or other substance abuse.

Study Procedures:

Patient recruitment

1) Patients scheduled for a renal transplant will be approached to discuss the trial. Consent may occur at any time prior to the OGTT

Blinding:

No blinding will occur in this pilot trial.

Dosing Algorithm:

Experimental intervention: Metformin hydrochloride at the starting dose of 500 mg twice a day given with meals, increased to a maximum of 850 mg twice a day after one week.

BMJ Open

Protocol for a Pilot Randomised Controlled Trial of metformin in pre-diabetes after kidney transplantation: The Transplantation and Diabetes (Transdiab) Study

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Primary Subject Heading:	Renal medicine
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Keywords:	new onset diabetes after transplantation, Renal transplantation < NEPHROLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, post transplantation diabetes mellitus

Protocol for a Pilot Randomised Controlled Trial of metformin in pre-diabetes after kidney transplantation: The Transplantation and Diabetes (Transdiab) Study

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Abstract

Introduction: PTDM (post-transplant diabetes mellitus) is a common complication of kidney transplantion, and is associated with significant morbidity and mortality. In the general population, metformin has been used for diabetes prevention in high risk individuals. Improving insulin sensetivity is one of many proven favourable effects of metformin. Despite the high incidence of PTDM in kidney transplant recipients, there is a lack of evidence for the role of meformin in the prevention of diabetes in this setting. **Methods and analysis: Trans**plantation **and Diab**etes **(Transdiab)** is a single-centre, unblinded, pilot randomised controlled trial assessing the feasiblity, tolerability and efficacy of meformin post renal transplantation in patients with Impaired Glucose tolerance (IGT). Participants will undergo an Oral Glucose Tolerance Test (OGTT) in the 4-12 weeks post-transplantation; those with IGT will be randomized to standard care or standard care and metformin 500mg bid, and followed up for 12 months. The primary outcomes of the study will be the feasibility of recruitment, the tolerability of metformin assessed using the Gastrointestinal Symptom Rating Scale (GSRS) at 3 and 12 months, and the efficacy of meformin assessed by morning glucose and HbA1c at 3,6,9, and 12 months. **Ethics and dissemination**: Despite the significant morbidity and mortality of PTDM, there are currently no randomized clinical trials assessing pharmacological interventions for its prevention after kidney transplantation. The abnormal renal function and frequent fluctuations of renal clearance are of particular concern in this group of patients, as metformin is more likely to accumulate and causes adverse events. The Transdiab trial will thus provide important data on the feasibility, safety, tolerability and efficacy of metformin post renal transplantation in IGT patients; this will facilitate undertaking larger multi-centre trials of interventions to reduce the incidence or severity of diabetes after kidney transplantation.

Article summary:

Strengths and limitations of this study:

- Has the potential to address more than one important cause of morbidity and mortality in kidney transplant patients with one simple approach
- Difficult to provide sufficient data for clinical effectiveness of the measure used.
- Safety and tolerability outcomes are likely to be informative and crucial for larger future RCTs

Trial registration: Australian New Zealand Clinical Trials Registry Number: ACTRN12614001171606

Keywords: Kidney transplantation, PTDM, NODAT, Metformin, prevention, Randomized-controlled trial

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry Number: ACTRN12614001171606
Date of registration in primary registry	7/11/2014
Source of material support	Auckland City Hospital, Auckland, New Zealand
Primary sponsor	A+ charitable trust
Contact for public queries	Basil Alnasrallah, MD, FRACP [polbeas@yahoo.com]
Contact for scientific queries	Basil Alnasrallah, MD, FRACP [polbeas@yahoo.com]
Public title	Protocol for a Pilot Randomised Controlled Trial of metformin in pre-diabetes after kidney transplantation
Scientific title	Protocol for a Pilot Randomised Controlled Trial of metformin in pre-diabetes after kidney transplantation: The Transplantation and Diabetes (Transdiab) Study
Countries of recruitment	New Zealand
Health problems studied	Metformin's safety, renal transplantation, diabetes prevention
Intervention	Active comparator: metformin (500mg twice daily) Control comparator: standard therapy (no metformin)
Key inclusion and exclusion criteria	Inclusion criteria: age > 18 years, non-diabetic, kidney transplant recipient, impaired glucose tolerance 4-12 weeks post transplant, and able to consent Exclusion criteria: history of diabetes, steroid pulse therapy prior to OGTT, eGFR ≤ 30 ml/min, pregnancy, and substance abuse.
Study type	Pilot study Interventional Allocation: randomized Intervention model: Parallel assignment Unblinded Primary purpose: safety, tolerability and efficacy
Date of first enrollment	December 2014
Recruitment status	Ongoing recording of results
Primary outcomes	Feasibility of recruitment, tolerability and efficacy of metformin
Key secondary outcomes	Change in body weight, all adverse events, change in lipid profile, major cardiac events and proportion of patients reverting to normal OGTT

Protocol version:

2017-Mar-12	original
2017-May-12	Amendment 01. Primary reasons for amendment: Changing the term New Onset of Diabetes After Transplantation (NODAT) to Post Transplantation Diabetes Mellitus (PTDM). Changes in Section 12. Secondary outcome – reference made to the need of testing lactate levels if clinically indicated (When clinically indicated, lactate levels will be checked)

Funding:

Research grant by A+ Charitable trust for the reasearch fellow salary and stationary costs. No coflict of interest identified in the trial. The funding source had no role in the design of this study and will not have any role during its execusion, analyses, interpretation of the data or decision to submit results.

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Introduction

End-stage kidney disease (ESKD) is a major public health problem with increasing prevalence worldwide. In 2013, there were 4,156 people receiving renal replacement therapy for ESKD in New Zealand. This represents a population rate of 931 people per million. Of these, 1,572 (38%) had a functioning kidney transplant (1). Kidney transplantation represents the optimal form of renal replacement therapy, and is associated with significantly improved survival (2, 3) quality of life (4), and reduced costs over time (5) compared with dialysis treatment. However, transplant recipients still have increased mortality compared with general population (6). This is predominantly driven by increased cardiovascular disease, as cardiovascular related deaths post-transplant constitutes over 50% of all deaths (7, 8). An important risk factor for this marked risk is Post-Transplant Diabetes Mellitus (PTDM), previously known as New Onset Diabetes after Transplantation (NODAT).

PTDM is a common complication post transplantation, with a reported incidence as high as 50 %(9) and significant impact on morbidity and mortality in transplant recipients. Patients with PTDM have significantly higher rates of cardiovascular disease, cardiovascular death and overall mortality with a doubling in all-cause mortality and a tripling in cardiovascular events (10-12). The mortality risk extends to include other forms of impaired glucose metabolism after transplantation as patients with Impaired Glucose tolerance (IGT) have an increased long-term mortality risk comparable to those with PTDM (13). In addition, PTDM is also associated with increased death censored graft failure (12,14)

In 2003, an expert committee set forth the International Consensus Guidelines for the diagnosis and management of PTDM (15). This was further revised in 2013 with The International Expert Panel setting forth the recommendations for PTDM and future directions of research (16). The research recommendations highlighted the need for trials to to help delay or prevent PTDM. The guidelines for PTDM are largely based on those of the World Health Organization (WHO) for the diagnosis of prediabetic states (Impaired Fasting Glucose (IFG) and IGT) and diabetes mellitus (17). Multiple risk factors have been associated with the development of PTDM, the use of diabetogenic immunosuppressive medications (such as corticosteroids (18), Calceniurin inhibitors (12,19) and Mammalian Target of Rapamycin (MTOR) inhibitors (20)) are all associated with impaired glucose metabolism. Furthermore, there is a significant incidence of excess weight gain and obesity in transplant recipients which contributes to insulin resistance, with average post-transplant weight gains of 10-35% reported in the first year (21-23). Possible causes for weight gain include the use of immunosuppressive medications (such as

corticosteroids), the relaxation of dietary restrictions and improvements in wellbeing after transplantation (24,25)

Another well-identified risk factor for the development of diabetes in both transplant recipients and the general population is the status of pre-diabetes (IGT or IFG), with impaired fasting glucose (IFG: fasting plasma glucose ≥ 6.1 mmol/L and < 7 mmol/L) or impaired glucose tolerance (IGT: fasting plasma glucose < 7 mmol/L and 2-h plasma glucose after an OGTT ≥ 7.8 mmol/L and < 11.1 mmol/L) define hyperglycemic conditions at risk of the future development of diabetes (12). In nontransplanted patients, some 70 % of individuals with IFG and/or IGT can expect to go on to develop clinical type 2 diabetes at some time in the future (26). That risk is also significant for transplant patients with 15% of patients with IGT developing PTDM over 1 year (27) and 27% over 6 years (28).

Given the significant adverse clinical outcomes associated with diabetes, multiple measures have been introduced to prevent or delay the onset of diabetes in high risk individuals. Current guidelines recommend lifestyle modifications in the management for individuals with prediabetes or diabetes, based on an improved diet and regular moderate physical exercise with the aim of achieving weight loss in overweight or obese patients (29,30).

However, weight loss arising from intensive lifestyle interventions is known to be difficult to maintain over the long term (31). Therefore the current guidelines support the use of pharmacologic antidiabetic therapy immediately after the diagnosis of diabetes for patients considered unlikely to benefit sufficiently from lifestyle intervention alone (32).

Pharmacological therapy (metformin, thiazolidinediones, a-glucosidase inhibitors or basal insulin) have been shown to effectively delay or prevent the conversion of prediabetes to diabetes in non-transplant patients, however metformin is the only pharmacologic agent recommended for the prevention or delay of type 2 diabetes in at-risk subjects due to its effectiveness as demonstrated in well-designed trials, good tolerability and low cost (29,30)

No similar trials have been carried out in transplant recipients, these patients have a high risk of developing PTDM and the subgroup with IGT are likely to be at even greater risk. Therefore, this group might achieve a significant benefit from starting metformin in addition to life style advice.

We will be conducting a pilot randomised controlled trial assessing the safety, tolerability and efficacy of metformin in renal transplant recipients with IGT. The trial will also provide data on the feasibility of recuriting eligible patients with IGT post transplantation to be started on metformin which will help to plan conducting larger trials aiming to reduce the incidence or severity of diabetes after kidney transplantation

Methods and analysis

Study design

Transdiab is a single-centre, unblinded, randomised controlled trial. An outline of the study is shown in Figure 1.

Study aims and hypothesis

The primary aim of the PTDM is to evaluate the feasibility, safety, tolerability and efficacy of metformin in kidney transplant patients with Impaired Glucose Tolerance (IGT). The secondary outcomes are those that will help evaluate the additional benefits of metformin on lipid profile, change in weight and cardiovascular events.

We hypothesize that recruiting non-diabetic patients after renal transplantation to have OGTTs in order to identify and pharmacologically manage those with IGT is feasible. We also hypothesize that using metformin within our inclusion criteria is safe with acceptable tolerability in the first year after renal transplantation. Furthermore, it is likely that metformin will have a favourable effect on HbA1c, morning glucose, lipid profile, excess weight gain and cardiovascular events.

Ethical considerations

Ethical approval has been obtained through the Northern B Health and Disability Ethics Committee of the Ministry of Health in New Zealand. Ethics approval number is **14/STH/129**

Target population and eligibility criteria

The target population for the trial is adult kidney transplant recipients who receive kidney transplantation in our centre between 30/11/2014 and 30/11/2016

Inclusion criteria will include the following: age > 18 years; non-diabetic kidney transplant recipient; willing and able to participate in all trial investigations for the duration of trial follow-up; and ability to provide a written informed consent.

Exclusion criteria will include the following: known diabetes mellitus at the time of transplant (whether on anti-diabetic medications or not); past history of anti-diabetic therapy (oral or insulin); steroid pulse therapy (IV or oral) in the 2 weeks prior to OGTT; estimated Glomerular Filtration Rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula ≤ 30 ml/min/1.73 m^2 BSA; unable to consent; pregnancy or breast-feeding; current alcohol or other substance abuse; and any major illness or comorbidity that may result in death in 12 months as assessed by the treating physician.

Recruitment and randomisation

Potential participants will be identified during their initial inpatient stay following transplantation at Auckland City Hospital, or through the renal transplant outpatient clinic following discharge. Eligible transplant recipients will be invited to participate, given detailed information about the trial and, if agreeable, will be asked to provide a written informed consent by one of the investigators. In order to participate, transplant recipients will need to provide informed consent and have the OGTT within 4-12 weeks after the transplant procedure. Consented patients' will have their information collected and stored securly by the

reasearch fellow, physically in the research office and electronically on a password protected computer.

Participants who have a 2 hour post-load glucose between 7.8 to 11.1 mmol/L on oral glucose tolerance test (75 g anhydrous glucose dissolved in water) will be randomised. Randomisation will be performed using a computer-generated sequence allocation in blocks of 4 in a 1:1 ratio to receive either standard care or standard care and Metformin 500mg bid.

Standard care group

Participants randomised to the standard care group will receive standard post-transplant care as per usual local practice. This includes immunosuppressive medications to prevent rejection and other treatments under the direction of the treating physician and renal transplant team. Standard immunosuppression includes a calcineurin inhibitor (cyclosporine or tacrolimus as determined by the treating physician), mycophenolate, steroids, and basiliximab as induction therapy.

The current lifestyle standard care after kidney transplantation at Auckland City Hospital includes advice for regular exercise 3 times weekly and a nutritional assessment by a renal dietician during the inpatient stay. The nutrition care involves giving patients resources guiding them on healthy eating and food safety after transplant.

Intervention group

Patients randomised to the intervention group will, in addition to standard care, receive metformin 500mg bid. This will commence at randomisation and continue for 12 months. The decision to continue with Metformin beyond 12 months of follow up is left to the discretion of the caring physician.

Primary outcomes

Feasibility of Recruitment will be assessed by the ratio of the number of randomised patients to the number of patients screened with OGTTs.

Tolerability of Metformin will be assessed using Gastrointestinal Symptom Rating Scale (GSRS), a tool that has been validated to assess symptoms in gastrointestinal disorders such as gastroesophageal reflux disease and irritable bowl syndrome (33,34) at baseline, 3, and 12 months post-randomisation.

Efficacy of Metformin will be assessed by HbA1c and morning glucose levels at baseline, 3, 6, 9, and 12 months post-randomisation

Secondary Outcome:

Secondary outcomes will include the following: Change in body weight, all adverse events, lipid profile at 3, 6, 9 and 12 months, major cardiac events and proportion of patients who revert to normal glucose metabolism on OGTT at 12 months. When clinically indicated, lactate levels will be checked. Also discontinuation of metformin or reduction of dose due to adverse effects will be recorded.

Monitoring:

Interim results will be reviewed and analysed by the lead investigator every 3 months, the decision for early termination of the trial will be considered if serious concerns about patients' saftey are encountered. Full annual analysis of results will be carried out until the completion of the trial. If important changes to the protocol are to take place, they will be conveyed to the sponsor on the annual progress report and also to the affected patients and caring physicians.

Statistical analysis

The first primary outcome, feasibility of recruitment will be reported as a ratio of the number of randomised patients to the number of patients screened with OGTT at the conclusion of the study.

The second primary outcome, tolerability of metformin will be reported as Gastrointestinal Symptom Rating Scale (GSRS) at 3 and 12 months and compared between the 2 groups using an analysis of covariance (ANCOVA) adjusted for GSRS score at baseline. The third primary outcome, efficacy of metformin will be reported by measuring morning glucose and HbA1c 3, 6, 9, and 12 months post-randomisation and compared between the 2 groups using an analysis of covariance (ANCOVA) adjusted for morning glucose and HbA1c at baseline.

Linear regression will be used to identify significant predictors other than group allocation associated with changes in efficacy, tolerability and metabolic parameters over time. Variables identified as significant will be analysed with pairwise comparisons. Comparisons between groups for differences in categorical variables will be conducted using Chi-square test or Fisher's exact test. All statistical analyses will be performed using appropriate statistical software, such as STATA or SPSS. The level of statistical significance will be set at probability level of <0.05.

Ethics and dissemination

This trial will provide evidence on the feasibility, safety, tolerability and efficacy of metformin in patients with impaired glucose tolerance after renal transplantation. In addition, the study will also examine in detail changes in other metabolic indices, including BMI, weight change, blood pressure, lipid profile and cardiac events.

The extensive local and international experience with Metformin and the significant potential benefits are likely to encourage patients and physicians to take active part in the study. Based on evidence from the literature, 43% of stable kidney transplant patients (>6 months after transplant) will have new impaired glucose metabolism after transplantation with new IGT and/or IFG affecting 32% of all recipients (35). Therefore, we hypothesise that performing oral glucose tolerance tests in non-diabetic patients after renal transplantation and subsequently starting those with impaired glucose tolerance on metformin will prove feasible.

Although generally safe, gastrointestinal side effects are not uncommon with the use of metformin, these are generally well tolerated and infrequently cause treatment discontinuation (36). The long term experience with metformin in the diabetic general population has established good tolerability and an acceptable safety profile (37) also in addition to good adherence by patients (38). A major and probably overstated potential side effect is lactic acidosis. Historically, a very low risk of lactic acidosis linked to the use of metformin has been

reported (39). More recent high quality evidence has shown no risk related to metformin in general population with type 2 diabetes (40). The risk is probably higher in patients with reduced Glomerular Filtration Rate (GFR) as metformin is more likely to accumulate, but a systematic review found no cases of lactice acidosis despite almost one half of the studies involved allowing inclusion of patients with a serum creatinine above 1.5 mg/dL [133 micromol/L] (41). Given the relative safety of metformin and signficant benefit, the expansion of its use has been recommended to include patients with mild to moderate kidney disease (estimated glomerular filtration rates, 30-60 mL/min per 1.73 m2) (42)

Although physicians might have reservations starting metfomin in renal transplant recipients as they commonly have abnormal GFRs with frequent fluctuations, the recent evidence provides further reassurance in the safety and tolerability of metformin even at moderate renal impairment. Therefore, we hypothesise that the use of metformin in these patients is safe and well tolerated.

Metformin has other favourable effects besides improving insulin sensitivity, some of which can be of substantial benifit to transplant patients. Most notably, the effects on cardiovascular disease (43) and weight gain (44), with current on-going research assessing these benefits even in prediabtic patients (45).

Furthermore, metformin has been shown to reduce the incidence of cancers and cancer-related mortality (46,47). Renal transplant recipients have high cancer related morbidity and mortality with cancer risk almost 3 times higher than general population (48,49).

The outcomes from this research will provide important data on the feasibility of conducting larger multicentre randomised trials of metformin in patients with IGT to reduce the incidence and severity of diabetes in kidney transplant recipients. This study will also provide transplant physicians with more confidence in using metformin in renal transplant recipients if no significant adverse events are encountered. There is a potential risk of bias as the participants are not blinded to the treatment, this could be addressed with the use of placebo in a larger trial.

Measurement of efficacy of the use of metformin is likely to require a large multicentre trial to have a sufficient number of patients for a significant difference (38). We anticipate that by determining feasibility and safety in this pilot study we will pave the way for future larger RCTs. We intend to communiate our findings via publications and presentations in national and international meetings.

Conclusions

Transplantation **and Diab**etes **(Transdiab)** study will provide important data on the feasibility, safety and efficacy of metformin in patients with impaired glucose tolerance after renal transplantation. With PTDM being an important cause of morbidity and mortality in renal transplant patients, this study will address a significant gap in current evidence regarding optimal care after kidney transplantation.

Contributorship statements for the authors:

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1- Paul manley, Transplant nephrologist – Renal department, Auckland City Hospital, Auckland, New Zealand.
    a. The main contributor to the initial design of the research and subsequently acquring ethics approval, registering the study and submitting the proposal for the funding grant.
    b. Substantial contribution to the work draft.
    c. Reviewing and amending the final version for publishing
2- Helen Pilmore **(lead investigator),** Transplant nephrologist – Renal department, Auckland City Hospital, Auckland, New Zealand. Also seniour lecturer in Auckland University, Auckland, New Zealand.
    a. Contributed to the initial conciption of the work and revised the initial design criticially for ingenuity.
    b. Provided further insight in the potential limitations and provided the required support for obtaining the funding grant
    c. Supervised the disegnated fellow in following the study protocol and conducting the appropriate analysis.
    d. Reviewing and amending the final version for publishing
    e. The steering investigator, conveys annual progress to the funder and review progress with the research fellow
    f. Will have the access to the final database and any related agreements.
3- Basil Alnasrallah, Transplant fellow – Renal department, Auckland City Hospital, Auckland, New Zealand.
    a. Substantial contribution to the interpretation of data for the work. Also, drafted the final protocol after reviewing the relevant literature and submitted it for the other authors' comments and amended it accordingly.
    b. Identified the limitations in the study and the practical challenges while carrying out the study and initial analysis.
    c. Generates the allocation sequence, enrols participants, and assigns participants to interventions. Also, responsible of the entry and storage of the study's data in the research computer.

All authors agreed to be accountable for all aspects of the work in insuring that any issues related to any part of the work are appropriately investigated and resolved.

Conflict of interest

None of the authors had any conflict of interest

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Data sharing statement

At the time of submitting this protocol, no patients' data were available.

Competeing interests

None of the authors had any competeing interests to declare.

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Participant Information Sheet

r letterhead

Study title:	**TRANSDIAB**		
Locality:	**AUCKLAND CITY HOSPITAL**	Ethics committee ref.:	
Lead investigator:	**Helen Pilmore**	Contact phone number:	**09 379 7440**

You are invited to take part in a study looking at diabetes development after kidney transplantation. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 6 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

Diabetes occurs in up to 50% of patients after kidney transplantation and is associated with an increased risk of dying and failure of the kidney transplant. We are undertaking a pilot study of a commonly used drug in diabetes called Metformin compared with usual treatment (dietician review and information about diet and exercise) in patients who develop blood tests suggesting a higher chance of developing diabetes after their kidney transplant. In this study we are going to check the safety of Metformin, how well people are able to tolerate Metformin (by looking at whether people get side effects) and the effect of Metformin on body weight at 12 months after transplantation. We will also look at how commonly diabetes occurs after transplantation in our population of kidney transplant recipients.

Metformin has been shown to prevent the development of diabetes in people with a high risk of diabetes in the general population. Additionally it does not cause hypoglycaemia (low blood sugars) and has beneficial effects on survival. In the Auckland Renal Transplant Group we have been using Metformin in patients who develop diabetes after their kidney transplantation. There is evidence that people who are pre-diabetic will benefit from Metformin and that this drug will prevent diabetes from occurring. This has not been tested after kidney transplantation.

All consenting patients will undergo an oral glucose tolerance test when they are well with stable blood tests at 4 – 12 weeks after kidney transplantation. This involves fasting and then getting a blood test followed by a sugary drink. Patients then have 2 more blood tests each an hour apart. Patients who have an elevated fasting glucose, or impaired glucose

tolerance will be randomised to Metformin in addition to standard advice regarding diet and exercise, or standard advice alone. This means you have a 50% chance of being given Metformin if you consent to the study and have blood tests suggesting you have a higher chance of diabetes. We will also check your kidney function and your blood sugars for 12 months.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

All patients who are over the age of 18 and not already diabetic who have a kidney transplant done but the Auckland Renal Transplant Group will be asked to participate in the study. Being in the study will involve an oral glucose tolerance test and then if you have a high glucose and are pre-diabetic in that test, you will be randomised (chosen by a random computer generated program) to have either standard advice on diet and exercise or Metformin in combination with advice on diet and exercise. You will also have a questionnaire on potential side effects of Metformin to answer at 1 month and 12 months after starting the study. If you are no longer in Auckland at this time we will contact you by phone to do the questionnaire. All other blood tests done will be your usual blood tests done at standard time.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

Potential risks of being in the study are the possible side effects of Metformin.

Very Common -occurring in more than 10% (10/100) people taking Metformin

- Nausea
- Vomiting
- Diarrhoea
- Abdominal pain
- Loss of appetite

Common - affecting between 1 to less than 10% (1/ 10 to 1 /100) people taking Metformin

- Taste disturbance, usually a metallic taste

Very rare - affecting under 0.01% (1 in 10,000) people taking Metformin

- Elevated levels of lactic acid in the blood (lactic acidosis)
- Decreased absorption of vitamin B12 during long-term use
- Skin reactions such as rash, itching or flushing

Metformin can rarely cause a serious disorder called lactic acidosis. This results in too much acid in the blood and occurs in about 5 out of 100 000 people on this medication and can be very serious resulting in admission to intensive care units, dialysis and even death. Lactic acidosis may occur more commonly in people with poor kidney function. Hence we will only use this medication in people who have at least 30% of normal kidney function. People with

lactic acidosis feel very unwell, short of breath and notice rapid breathing. It can occur if people become unwell for any other reason such as having a bad flu or other infection. If you feel very unwell and are on Metformin you need to seek medical help urgently. Additionally all patients who become unwell with a fever or require admission to hospital will have the use of Metformin re-evaluated.

Potential benefits of Metformin are that patients on this medication may have a lower risk of developing diabetes and a lower risk of heart disease and cancer. Additionally Metformin has been shown to prevent weight gain in most populations. Weight gain is very common after kidney transplantation and associated with more diabetes and worse outcomes.

All patients who have a glucose tolerance test will be followed for 12 months to check to see if they have developed diabetes over that period. All of the data collected on you will be stored safely and you will not be identified in any way.

WHO PAYS FOR THE STUDY?

This study is funded by the A+ Trust. All of your study visits will be done during usual clinic visits. If you are no longer in Auckland for your follow up after transplantation we will contact your caring team to find out your blood results.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

Entry into this study is entirely voluntary. Choosing not to take part in this study will not affect your treatment or care in any way. The doctors will continue to treat you with the best means available.

If you agree to participate in this study you will be asked to sign a consent form. However you may withdraw from the study at any time without giving a reason. This will not affect your treatment or care in any way.

All the information collection in the study will be kept confidential.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

After the study we will send you information about the results of the study. Any patient can take Metformin if it is prescribed by their doctor so if the medication is working for you, you will be able to remain on Metformin.

All study data will be stored for at least 15 years and will be stored on a password locked computer by the primary investigator.

It is anticipated that the results of the study will be available by 2017 and we will send you the results. We hope to publish the results in a peer reviewed journal. You will not be identifiable in any publication.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Name,	**Associate Professor Helen Pilmore; Renal Physician**
Telephone number	**09 379 7440**
Email	**hpilmore@adhb.govt.nz**

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone:	0800 555 050
Fax:	0800 2 SUPPORT (0800 2787 7678)
Email:	advocacy@hdc.org.nz

If you require Māori cultural support talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 2324

If you have any questions or complaints about the study you may contact the Auckland and Waitematā District Health Boards Māori Research Committee or Maori Research Advisor by telephoning 09 4868920 ext 3204

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS

Email: hdecs@moh.govt.nz

Consent Form

Your letterhead

If you need an INTERPRETER, please tell us.
If you are unable to provide interpreters for the study, please clearly state this in the Participant Information Sheet

Please tick to indicate you consent to the following *(Add or delete as appropriate)*

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	No ☐
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	No ☐
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.	Yes ☐	No ☐
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	Yes ☐	No ☐
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	Yes ☐	No ☐
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	No ☐
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.	Yes ☐	No ☐
I understand that there may be risks associated with the treatment in the event of myself or my partner becoming pregnant. I undertake to inform my partner of the risks and to take responsibility for the	Yes ☐	No ☐

prevention of pregnancy.		
I agree to my (type of tissue) samples being sent overseas and I am aware that these samples will be disposed of using established guidelines for discarding biohazard waste.	Yes ☐	No ☐
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.	Yes ☐	No ☐
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.	Yes ☐	No ☐
I understand the compensation provisions in case of injury during the study.	Yes ☐	No ☐
I know who to contact if I have any questions about the study in general.	Yes ☐	No ☐
I understand my responsibilities as a study participant.	Yes ☐	No ☐
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

Declaration by participant:

I hereby consent to take part in this study.

Participant's name:

Signature:	Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date:

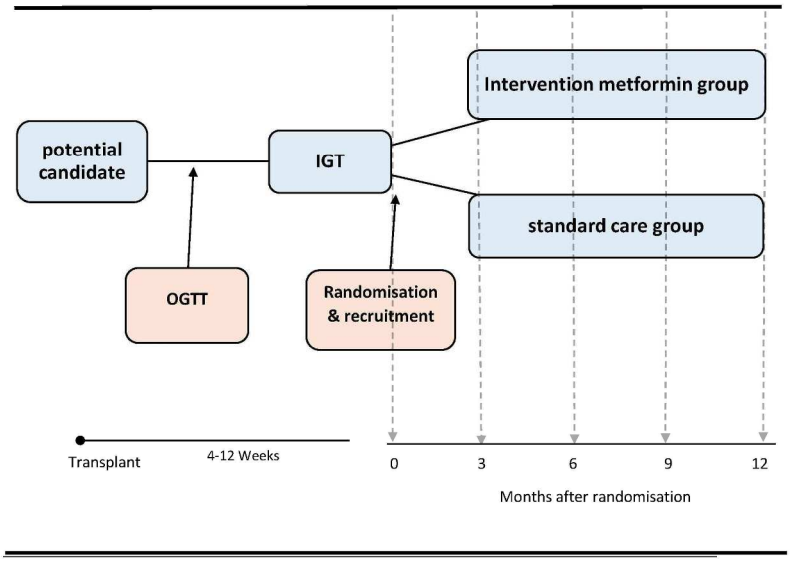

Figure 1. Flowchart of Transdiab trial

215x279mm (300 x 300 DPI)

A randomised controlled trial of metformin in Impaired Glucose Tolerance (IGT) (TransDiab)

Principal Investigator

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Study Schema

Consent for screening anytime from post-operative period

⇩

75 g OGTT (as described by WHO) between 4 - 6 weeks after transplant (Up to 12 weeks allowed)

⇩	⇩	⇩
2-hr post-load glucose ≤ 7.8 mmol/L	2-hr post-load glucose 7.8 to 11.1 mmol/L	2-hr post-load glucose ≥ 11.1 mmol/L *or* Fasting glucose ≥ 7.0 mmol/L or DM at any time prior to OGTT if DM
Non-diabetic	**Prediabetes (IGT/IFG)**	**NODAT**
⇩	⇩	⇩
Follow to 12 months	Randomise	Follow for 12 months

.

LifeStyle + Metformin
vs.
LifeStyle

⇩

Minimum follow up 12 months after recruitment of the last patient

Study Outcome Measures:

The primary objectives of this Feasibility Study are to obtain the following feasibility, adverse event and efficacy data:

(i) Feasibility of recruitment in patients with pre-diabetes as defined by impaired glucose tolerance or elevated fasting plasma glucose after kidney transplantation

(ii) Adverse gastrointestinal side effects assessed by Gastrointestinal Symptom Rating Scale (GSRS)

(iii) Efficacy:
   a. Difference in Fasting Plasma Glucose at 3,6,9,12 months
   b. Difference in afternoon glucose at 3,6,9,12 months
   c. Difference in HbA1c at 3,6,9,12 months
   d. Proportion of patients developing New Onset Diabetes after transplantation at 12 month

The secondary objectives of the TRANSDIAB Feasibility Study are to assess the effects of metformin on the following outcome measures:

(i) Discontinuation of the study medication due to adverse events
(ii) All adverse events, including hypoglycemia, lactic acidosis, death
(iii) Absolute changes in weight
(iv) Lipid profile

(v) Fatal and Non-fatal cardiovascular events

(i) Proportion of patients who revert to normal glucose metabolism as defined by OGTT.

Definition of DM

	Glucose concentration, mmol l^{-1}		
	Whole blood Venous	Whole blood Capillary	Plasma* Venous
Diabetes Mellitus:			
Fasting	>=6.1	>=6.1	>=7.0
or			
2-h post glucose load	>=10.0	>=11.1	>=11.1

Study Evaluation Schedule: All patients will have the following investigations regardless of randomisation

Evaluation	Screening	Baseline (Day -7 to -1)	Week 1	Week 2	Week 4	Month 3	Month 6 and 9	Month 12
Glucose Tolerance Test	X							X
eGFR (MDRD)	X		x	x	x	x	x	x
Serum Creatinine	X	X	x	x	x	x	x	x
Serum Glucose		x	x	x	x	x	x	x
HBA_1c		x				x	x	x
Inclusion/Exclusion Criteria	X	X						
Physical Examination +Height		X						x
GI Quality of Life		X				x		x
24 hour urine protein		X				x		x
CNI dosing Record		X	x	x	x	x	x	x
Acute Rejection Episodes	X	X						x
Pm Glucose Level		X				x	x	x
Weight (kg) and BMI		X	x	x	x	x	x	x
Additional Medications		X			x	x	x	x
Serum Cholesterol and TG		X			x	x	x	x
Waist:Hip		X						
Adverse Events			X	X	X	X	X	x
Hypoglycemic med and dose record		x	x	x	x	x	x	X
Endpoint MI, Revascularisation, Death, Graft Loss					x	x	x	x
Blood Pressure	x	x	x	x	x	x	x	x

Inclusion/Exclusion Criteria:

Inclusion criteria

1) Adult (age > 18 years)
1) Incident non-diabetic kidney transplant recipient (deceased or living donor)
2) 2 hour post-load glucose (OGTT 75 g anhydrous glucose dissolved in water), done at 8 to 12 weeks after transplant (up to 16 weeks)
   2 hour PG 7.8 to 11.1 mmol/L for impaired glucose tolerance (IGT) group

.

i) Exclusion criteria

In addition, potential participants must have NONE of the following exclusion criteria.

1. Known diabetic at the time of transplant, whether on anti-diabetic medications or not
2. Past history of anti-diabetic therapy (oral or insulin)
3. Steroid pulse therapy (IV or oral) in 2 weeks prior to OGTT*
4. eGFR by MDRD formula ≤ 30 ml/min/1.73 m^2 BSA (in line with the recommendations of Diabetes Australia)
5. Unable to consent
6. Pregnancy/ breast-feeding
7. Any major illness/ comorbidity that may result in death in 12 months as assessed by the treating physician,
8. Current alcohol or other substance abuse.

Study Procedures:

Patient recruitment

1) Patients scheduled for a renal transplant will be approached to discuss the trial. Consent may occur at any time prior to the OGTT

Blinding:

No blinding will occur in this pilot trial.

Dosing Algorithm:

Experimental intervention: Metformin hydrochloride at the starting dose of 500 mg twice a day given with meals, increased to a maximum of 850 mg twice a day after one week.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	10
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____N/A_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____N/A_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____7_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____7____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____10____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____N/A____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____N/A____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____9_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____N/A_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	15-22
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a Pilot Randomised Controlled Trial of metformin in pre-diabetes after kidney transplantation: The Transplantation and Diabetes (Transdiab) Study

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	new onset diabetes after transplantation, Renal transplantation < NEPHROLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, post transplantation diabetes mellitus

Protocol for a Pilot Randomised Controlled Trial of metformin in pre-diabetes after kidney transplantation: The Transplantation and Diabetes (Transdiab) Study

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Abstract

Introduction: PTDM (post-transplant diabetes mellitus) is a common complication of kidney transplantation, and is associated with significant morbidity and mortality. In the general population, metformin has been used for diabetes prevention in high risk individuals. Improving insulin sensitivity is one of many proven favourable effects of metformin. Despite the high incidence of PTDM in kidney transplant recipients, there is a lack of evidence for the role of meformin in the prevention of diabetes in this setting. **Methods and analysis: Trans**plantation **and Diab**etes **(Transdiab)** is a single-centre, unblinded, pilot randomised controlled trial assessing the feasibility, tolerability and efficacy of meformin post renal transplantation in patients with Impaired Glucose tolerance (IGT). Participants will undergo an Oral Glucose Tolerance Test (OGTT) in the 4-12 weeks post-transplantation; those with IGT will be randomized to standard care or standard care and metformin 500mg bid, and followed up for 12 months. The primary outcomes of the study will be the feasibility of recruitment, the tolerability of metformin assessed using the Gastrointestinal Symptom Rating Scale (GSRS) at 3 and 12 months, and the efficacy of meformin assessed by morning glucose and HbA1c at 3,6,9, and 12 months. **Ethics and dissemination**: Despite the significant morbidity and mortality of PTDM, there are currently no randomized clinical trials assessing pharmacological interventions for its prevention after kidney transplantation. The Transdiab trial will thus provide important data on the feasibility, safety, tolerability and efficacy of metformin post renal transplantation in IGT patients; this will facilitate undertaking larger multi-centre trials of interventions to reduce the incidence or severity of diabetes after kidney transplantation. This study has been approved by the Northern B Health and Disability Ethics Committee of the Ministry of Health in New Zealand. On study completion, results are expected to be published in a peer-reviewed journal.

Article summary:

Strengths and limitations of this study:

- Has the potential to address more than one important cause of morbidity and mortality in kidney transplant patients with one simple approach
- Difficult to provide sufficient data for clinical effectiveness of the measure used.
- Safety and tolerability outcomes are likely to be informative and crucial for larger future RCTs

Trial registration: Australian New Zealand Clinical Trials Registry Number: ACTRN12614001171606

Keywords: Kidney transplantation, PTDM, NODAT, Metformin, prevention, Randomized-controlled trial

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry Number: ACTRN12614001171606
Date of registration in primary registry	7/11/2014
Source of material support	Auckland City Hospital, Auckland, New Zealand
Primary sponsor	A+ charitable trust
Contact for public queries	Basil Alnasrallah, MD, FRACP [polbeas@yahoo.com]
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Public title	Protocol for a Pilot Randomised Controlled Trial of metformin in pre-diabetes after kidney transplantation
Scientific title	Protocol for a Pilot Randomised Controlled Trial of metformin in pre-diabetes after kidney transplantation: The Transplantation and Diabetes (Transdiab) Study
Countries of recruitment	New Zealand
Health problems studied	Metformin's safety, renal transplantation, diabetes prevention
Intervention	Active comparator: metformin (500mg twice daily) Control comparator: standard therapy (no metformin)
Key inclusion and exclusion criteria	Inclusion criteria: age > 18 years, non-diabetic, kidney transplant recipient, impaired glucose tolerance 4-12 weeks post transplant, and able to consent Exclusion criteria: history of diabetes, steroid pulse therapy prior to OGTT, eGFR ≤ 30 ml/min, pregnancy, and substance abuse.
Study type	Pilot study Interventional Allocation: randomized Intervention model: Parallel assignment Unblinded Primary purpose: safety, tolerability and efficacy
Date of first enrollment	December 2014
Recruitment status	Ongoing recording of results
Primary outcomes	Feasibility of recruitment, tolerability and efficacy of metformin
Key secondary outcomes	Change in body weight, all adverse events, change in lipid profile, major cardiac events and proportion of patients reverting to normal OGTT

Protocol version:

2017-Mar-12	original
2017-May-12	Amendment 01. Primary reasons for amendment: Changing the term New Onset of Diabetes After Transplantation (NODAT) to Post Transplantation Diabetes Mellitus (PTDM). Changes in Section 12. Secondary outcome –

	reference made to the need of testing lactate levels if clinically indicated (When clinically indicated, lactate levels will be checked)

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Introduction

End-stage kidney disease (ESKD) is a major public health problem with increasing prevalence worldwide. In 2013, there were 4,156 people receiving renal replacement therapy for ESKD in New Zealand. This represents a population rate of 931 people per million. Of these, 1,572 (38%) had a functioning kidney transplant (1). Kidney transplantation represents the optimal form of renal replacement therapy, and is associated with significantly improved survival (2, 3) quality of life (4), and reduced costs over time (5) compared with dialysis treatment. However, transplant recipients still have increased mortality compared with general population (6). This is predominantly driven by increased cardiovascular disease, as cardiovascular related deaths post-transplant constitutes over 50% of all deaths (7, 8). An important risk factor for this marked risk is Post-Transplant Diabetes Mellitus (PTDM), previously known as New Onset Diabetes after Transplantation (NODAT).

PTDM is a common complication post transplantation, with a reported incidence as high as 50 %(9) and significant impact on morbidity and mortality in transplant recipients. Patients with PTDM have significantly higher rates of cardiovascular disease, cardiovascular death and overall mortality with a doubling in all-cause mortality and a tripling in cardiovascular events (10-12). The mortality risk extends to include other forms of impaired glucose metabolism after transplantation as patients with Impaired Glucose tolerance (IGT) have an increased long-term mortality risk comparable to those with PTDM (13). In addition, PTDM is also associated with increased death censored graft failure (12,14)

In 2003, an expert committee set forth the International Consensus Guidelines for the diagnosis and management of PTDM (15). This was further revised in 2013 with The International Expert Panel setting forth the recommendations for PTDM and future directions of research (16). The research recommendations highlighted the need for trials to to help delay or prevent PTDM. The guidelines for PTDM are largely based on those of the World Health Organization (WHO) for the diagnosis of prediabetic states (Impaired Fasting Glucose (IFG) and IGT) and diabetes mellitus (17). Multiple risk factors have been associated with the development of PTDM, the use of diabetogenic immunosuppressive medications (such as corticosteroids (18), Calceniurin

inhibitors (12,19) and Mammalian Target of Rapamycin (MTOR) inhibitors (20)) are all associated with impaired glucose metabolism. Furthermore, there is a significant incidence of excess weight gain and obesity in transplant recipients which contributes to insulin resistance, with average post-transplant weight gains of 10-35% reported in the first year (21-23). Possible causes for weight gain include the use of immunosuppressive medications (such as corticosteroids), the relaxation of dietary restrictions and improvements in wellbeing after transplantation (24,25)

Another well-identified risk factor for the development of diabetes in both transplant recipients and the general population is the status of pre-diabetes (IGT or IFG), with impaired fasting glucose (IFG: fasting plasma glucose ≥ 6.1 mmol/L and < 7 mmol/L) or impaired glucose tolerance (IGT: fasting plasma glucose < 7 mmol/L and 2-h plasma glucose after an OGTT ≥ 7.8 mmol/L and < 11.1 mmol/L) define hyperglycemic conditions at risk of the future development of diabetes (12). In nontransplanted patients, some 70 % of individuals with IFG and/or IGT can expect to go on to develop clinical type 2 diabetes at some time in the future (26). That risk is also significant for transplant patients with 15% of patients with IGT developing PTDM over 1 year (27) and 27% over 6 years (28).

Given the significant adverse clinical outcomes associated with diabetes, multiple measures have been introduced to prevent or delay the onset of diabetes in high risk individuals. Current guidelines recommend lifestyle modifications in the management for individuals with prediabetes or diabetes, based on an improved diet and regular moderate physical exercise with the aim of achieving weight loss in overweight or obese patients (29,30).

However, weight loss arising from intensive lifestyle interventions is known to be difficult to maintain over the long term (31). Therefore the current guidelines support the use of pharmacologic antidiabetic therapy immediately after the diagnosis of diabetes for patients considered unlikely to benefit sufficiently from lifestyle intervention alone (32).

Pharmacological therapy (metformin, thiazolidinediones, a-glucosidase inhibitors or basal insulin) have been shown to effectively delay or prevent the conversion of prediabetes to diabetes in non-transplant patients, however metformin is the only pharmacologic agent recommended for the prevention or delay of type 2 diabetes in at-risk subjects due to its effectiveness as demonstrated in well-designed trials, good tolerability and low cost (29,30)

No similar trials have been carried out in transplant recipients, these patients have a high risk of developing PTDM and the subgroup with IGT are likely to be at even greater risk. Therefore, this group might achieve a significant benefit from starting metformin in addition to life style advice.

We will be conducting a pilot randomised controlled trial assessing the safety, tolerability and efficacy of metformin in renal transplant recipients with IGT. The trial will also provide data on the feasibility of recruiting eligible patients with IGT post transplantation to be started on

metformin which will help to plan conducting larger trials aiming to reduce the incidence or severity of diabetes after kidney transplantation

Methods and analysis

Study design

Transdiab is a single-centre, unblinded, parallel group, randomised controlled trial. An outline of the study is shown in Figure 1.

Study aims and hypothesis

The primary aim of the PTDM is to evaluate the feasibility, safety, tolerability and efficacy of metformin in kidney transplant patients with Impaired Glucose Tolerance (IGT). The secondary outcomes are those that will help evaluate the additional benefits of metformin on lipid profile, change in weight and cardiovascular events. This will be done in a superiority framework.

We hypothesize that recruiting non-diabetic patients after renal transplantation to have OGTTs in order to identify and pharmacologically manage those with IGT is feasible. We also hypothesize that using metformin within our inclusion criteria is safe with acceptable tolerability in the first year after renal transplantation. Furthermore, it is likely that metformin will have a favourable effect on HbA1c, morning glucose, lipid profile, excess weight gain and cardiovascular events.

Target population and eligibility criteria

The target population for the trial is adult kidney transplant recipients who receive kidney transplantation in our centre between 30/11/2014 and 30/11/2016

Inclusion criteria will include the following: age > 18 years; non-diabetic kidney transplant recipient; willing and able to participate in all trial investigations for the duration of trial follow-up; and ability to provide a written informed consent.

Exclusion criteria will include the following: known diabetes mellitus at the time of transplant (whether on anti-diabetic medications or not); past history of anti-diabetic therapy (oral or insulin); steroid pulse therapy (IV or oral) in the 2 weeks prior to OGTT; estimated Glomerular Filtration Rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula ≤ 30 ml/min/1.73 m^2 BSA; unable to consent; pregnancy or breast-feeding; current alcohol or other substance abuse; and any major illness or comorbidity that may result in death in 12 months as assessed by the treating physician.

Recruitment and randomisation

Potential participants will be identified during their initial inpatient stay following transplantation at Auckland City Hospital, or through the renal transplant outpatient clinic following discharge. Eligible transplant recipients will be invited to participate, given detailed information about the trial and, if agreeable, will be asked to provide a written informed consent by one of the investigators. In order to participate, transplant recipients will need to provide informed consent and have the OGTT within 4-12 weeks after the transplant

procedure. Consented patients will have their information collected and stored securely by the research fellow, physically in the research office and electronically on a password protected computer. The research fellow will also generate the allocation sequence, enroll participants and assign the groups.

Participants who have a 2 hour post-load glucose between 7.8 to 11.1 mmol/L on oral glucose tolerance test (75 g anhydrous glucose dissolved in water) will be randomised. Randomisation will be performed using a computer-generated sequence allocation in blocks of 4 in a 1:1 ratio to receive either standard care or standard care and Metformin 500mg bid.

Standard care group

Participants randomised to the standard care group will receive standard post-transplant care as per usual local practice. This includes immunosuppressive medications to prevent rejection and other treatments under the direction of the treating physician and renal transplant team. Standard immunosuppression includes a calcineurin inhibitor (cyclosporine or tacrolimus as determined by the treating physician), mycophenolate, steroids, and basiliximab as induction therapy.

The current lifestyle standard care after kidney transplantation at Auckland City Hospital includes advice for regular exercise 3 times weekly and a nutritional assessment by a renal dietician during the inpatient stay. The nutrition care involves giving patients resources guiding them on healthy eating and food safety after transplant.

Intervention group

Patients randomised to the intervention group will, in addition to standard care, receive metformin 500mg bid. This will commence at randomisation and continue for 12 months. The decision to continue with Metformin beyond 12 months of follow up is left to the discretion of the caring physician.

Primary outcomes

Feasibility of Recruitment will be assessed by the ratio of the number of randomised patients to the number of patients screened with OGTTs.

Tolerability of Metformin will be assessed using Gastrointestinal Symptom Rating Scale (GSRS), a tool that has been validated to assess symptoms in gastrointestinal disorders such as gastroesophageal reflux disease and irritable bowl syndrome (33,34) at baseline, 3, and 12 months post-randomisation.

Efficacy of Metformin will be assessed by HbA1c and morning glucose levels at baseline, 3, 6, 9, and 12 months post-randomisation

Secondary Outcome:

Secondary outcomes will include the following: Change in body weight, all adverse events, lipid profile at 3, 6, 9 and 12 months, major cardiac events and proportion of patients who revert to normal glucose metabolism on OGTT at 12 months. When clinically indicated, lactate levels will be checked. Also discontinuation of metformin or reduction of dose due to adverse effects will be recorded.

Monitoring:

Interim results will be reviewed and analyzed by the lead investigator every 3 months, the decision for early termination of the trial will be considered if serious concerns about patients' safety are encountered. Full annual analysis of results will be carried out until the completion of the trial. If important changes to the protocol are to take place, they will be conveyed to the sponsor on the annual progress report and also to the affected patients and caring physicians. The access of the final trial dataset will be available to the primary investigator.

Statistical analysis

The first primary outcome, feasibility of recruitment will be reported as a ratio of the number of randomised patients to the number of patients screened with OGTT at the conclusion of the study.

The second primary outcome, tolerability of metformin will be reported as Gastrointestinal Symptom Rating Scale (GSRS) at 3 and 12 months and compared between the 2 groups using an analysis of covariance (ANCOVA) adjusted for GSRS score at baseline. The third primary outcome, efficacy of metformin will be reported by measuring morning glucose and HbA1c 3, 6, 9, and 12 months post-randomisation and compared between the 2 groups using an analysis of covariance (ANCOVA) adjusted for morning glucose and HbA1c at baseline.

Linear regression will be used to identify significant predictors other than group allocation associated with changes in efficacy, tolerability and metabolic parameters over time. Variables identified as significant will be analysed with pairwise comparisons. Comparisons between groups for differences in categorical variables will be conducted using Chi-square test or Fisher's exact test. All statistical analyses will be performed using appropriate statistical software, such as STATA or SPSS. The level of statistical significance will be set at probability level of <0.05.

Ethical considerations

Ethical approval has been obtained through the Northern B Health and Disability Ethics Committee of the Ministry of Health in New Zealand. Ethics approval number is **14/STH/129**

Discussion

This trial will provide evidence on the feasibility, safety, tolerability and efficacy of metformin in patients with impaired glucose tolerance after renal transplantation. In addition, the study will also examine in detail changes in other metabolic indices, including BMI, weight change, blood pressure, lipid profile and cardiac events.

The extensive local and international experience with metformin and the significant potential benefits are likely to encourage patients and physicians to take active part in the study. Based on evidence from the literature, 43% of stable kidney transplant patients (>6 months after transplant) will have new impaired glucose metabolism after transplantation with new IGT and/or IFG affecting 32% of all recipients (35). Therefore, we hypothesise that performing oral glucose tolerance tests in non-diabetic patients after renal transplantation and subsequently starting those with impaired glucose tolerance on metformin will prove feasible.

Although generally safe, gastrointestinal side effects are not uncommon with the use of metformin, these are generally well tolerated and infrequently cause treatment discontinuation (36). The long term experience with metformin in the diabetic general population has established good tolerability and an acceptable safety profile (37) also in addition to good adherence by patients (38). A major and probably overstated potential side effect is lactic acidosis. Historically, a very low risk of lactic acidosis linked to the use of metformin has been reported (39). More recent high quality evidence has shown no risk related to metformin in general population with type 2 diabetes (40). The risk is probably higher in patients with reduced Glomerular Filtration Rate (GFR) as metformin is more likely to accumulate, but a systematic review found no cases of lactic acidosis despite almost one half of the studies involved allowing inclusion of patients with a serum creatinine above 1.5 mg/dL [133 micromol/L] (41). Given the relative safety of metformin and significant benefit, the expansion of its use has been recommended to include patients with mild to moderate kidney disease (estimated glomerular filtration rates, 30-60 mL/min per 1.73 m2) (42)

Although physicians might have reservations starting metfomin in renal transplant recipients as they commonly have abnormal GFRs with frequent fluctuations, the recent evidence provides further reassurance in the safety and tolerability of metformin even at moderate renal impairment. Therefore, we hypothesize that the use of metformin in these patients is safe and well tolerated.

Metformin has other favourable effects besides improving insulin sensitivity, some of which can be of substantial benefit to transplant patients. Most notably, the effects on cardiovascular disease (43) and weight gain (44), with current on-going research assessing these benefits even in prediabtic patients (45).

Furthermore, metformin has been shown to reduce the incidence of cancers and cancer-related mortality (46,47). Renal transplant recipients have high cancer related morbidity and mortality with cancer risk almost 3 times higher than general population (48,49).

The outcomes from this research will provide important data on the feasibility of conducting larger multicentre randomised trials of metformin in patients with IGT to reduce the incidence and severity of diabetes in kidney transplant recipients. This study will also provide transplant physicians with more confidence in using metformin in renal transplant recipients if no significant adverse events are encountered. There is a potential risk of bias as the participants are not blinded to the treatment, this could be addressed with the use of placebo in a larger trial.

Measurement of efficacy of the use of metformin is likely to require a large multicentre trial to have a sufficient number of patients for a significant difference (38). We anticipate that by determining feasibility and safety in this pilot study we will pave the way for future larger RCTs. We intend to communicate our findings via publications and presentations in national and international meetings.

Conclusions

Transplantation **and Diab**etes **(Transdiab)** study will provide important data on the feasibility, safety and efficacy of metformin in patients with impaired glucose tolerance after

renal transplantation. With PTDM being an important cause of morbidity and mortality in renal transplant patients, this study will address a significant gap in current evidence regarding optimal care after kidney transplantation.

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Contributorship statements for the authors:

1- Paul manley, Transplant nephrologist – Renal department, Auckland City Hospital, Auckland, New Zealand.
   a. The main contributor to the initial design of the research and subsequently acquring ethics approval, registering the study and submitting the proposal for the funding grant.
   b. Substantial contribution to the work draft.
   c. Reviewing and amending the final version for publishing
2- Helen Pilmore **(lead investigator),** Transplant nephrologist – Renal department, Auckland City Hospital, Auckland, New Zealand. Also seniour lecturer in Auckland University, Auckland, New Zealand.
   a. Contributed to the initial conciption of the work and revised the initial design criticially for ingenuity.
   b. Provided further insight in the potential limitations and provided the required support for obtaining the funding grant
   c. Supervised the disegnated fellow in following the study protocol and conducting the appropriate analysis.
   d. Reviewing and amending the final version for publishing
   e. The steering investigator, conveys annual progress to the funder and review progress with the research fellow
   f. Will have the access to the final database and any related agreements.
3- Basil Alnasrallah, Transplant fellow – Renal department, Auckland City Hospital, Auckland, New Zealand.
   a. Substantial contribution to the interpretation of data for the work. Also, drafted the final protocol after reviewing the relevant literature and submitted it for the other authors' comments and amended it accordingly.
   b. Identified the limitations in the study and the practical challenges while carrying out the study and initial analysis.
   c. Generates the allocation sequence, enrols participants, and assigns participants to interventions. Also, responsible of the entry and storage of the study's data in the research computer.

All authors agreed to be accountable for all aspects of the work in insuring that any issues related to any part of the work are appropriately investigated and resolved.

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Data sharing statement

At the time of submitting this protocol, no patients' data were available.

Conflict of interest

None of the authors had any conflict of interest

Competing interests

None of the authors had any competing interests to declare.

Figure1 .Flowchart of Transdiab trial

Participant Information Sheet

AUCKLAND DISTRICT HEALTH BOARD Te Toka Tumai

r letterhead

Study title: **TRANSDIAB**

Locality: **AUCKLAND CITY HOSPITAL**

Ethics committee ref.:

Lead investigator: **Helen Pilmore**

Contact phone number: **09 379 7440**

You are invited to take part in a study looking at diabetes development after kidney transplantation. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 6 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

Diabetes occurs in up to 50% of patients after kidney transplantation and is associated with an increased risk of dying and failure of the kidney transplant. We are undertaking a pilot study of a commonly used drug in diabetes called Metformin compared with usual treatment (dietician review and information about diet and exercise) in patients who develop blood tests suggesting a higher chance of developing diabetes after their kidney transplant. In this study we are going to check the safety of Metformin, how well people are able to tolerate Metformin (by looking at whether people get side effects) and the effect of Metformin on body weight at 12 months after transplantation. We will also look at how commonly diabetes occurs after transplantation in our population of kidney transplant recipients.

Metformin has been shown to prevent the development of diabetes in people with a high risk of diabetes in the general population. Additionally it does not cause hypoglycaemia (low blood sugars) and has beneficial effects on survival. In the Auckland Renal Transplant Group we have been using Metformin in patients who develop diabetes after their kidney transplantation. There is evidence that people who are pre-diabetic will benefit from Metformin and that this drug will prevent diabetes from occurring. This has not been tested after kidney transplantation.

All consenting patients will undergo an oral glucose tolerance test when they are well with stable blood tests at 4 – 12 weeks after kidney transplantation. This involves fasting and then getting a blood test followed by a sugary drink. Patients then have 2 more blood tests each an hour apart. Patients who have an elevated fasting glucose, or impaired glucose tolerance will be randomised to Metformin in addition to standard advice regarding diet and exercise, or standard advice alone. This means you have a 50% chance of being given Metformin if you consent to the study and have blood tests suggesting you have a higher chance of diabetes. We will also check your kidney function and your blood sugars for 12 months.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

All patients who are over the age of 18 and not already diabetic who have a kidney transplant done but the Auckland Renal Transplant Group will be asked to participate in the study. Being in the study will involve an oral glucose tolerance test and then if you have a high glucose and are pre-diabetic in that test, you will be randomised (chosen by a random computer generated program) to have either standard advice on diet and exercise or Metformin in combination with advice on diet and exercise. You will also have a questionnaire on potential side effects of Metformin to answer at 1 month and 12 months after starting the study. If you are no longer in Auckland at this time we will contact you by phone to do the questionnaire. All other blood tests done will be your usual blood tests done at standard time.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

Potential risks of being in the study are the possible side effects of Metformin.

Very Common -occurring in more than 10% (10/100) people taking Metformin

- Nausea
- Vomiting
- Diarrhoea
- Abdominal pain
- Loss of appetite

Common - affecting between 1 to less than 10% (1/ 10 to 1 /100) people taking Metformin

- Taste disturbance, usually a metallic taste

Very rare - affecting under 0.01% (1 in 10,000) people taking Metformin

- Elevated levels of lactic acid in the blood (lactic acidosis)
- Decreased absorption of vitamin B12 during long-term use
- Skin reactions such as rash, itching or flushing

Metformin can rarely cause a serious disorder called lactic acidosis. This results in too much acid in the blood and occurs in about 5 out of 100 000 people on this medication and can be very serious resulting in admission to intensive care units, dialysis and even death. Lactic acidosis may occur more commonly in people with poor kidney function. Hence we will only use this medication in people who have at least 30% of normal kidney function. People with lactic acidosis feel very unwell, short of breath and notice rapid breathing. It can occur if people become unwell for any other reason such as having a bad flu or other infection. If you feel very unwell and are on Metformin you need to seek medical help urgently. Additionally all patients who become unwell with a fever or require admission to hospital will have the use of Metformin re-evaluated.

Potential benefits of Metformin are that patients on this medication may have a lower risk of developing diabetes and a lower risk of heart disease and cancer. Additionally Metformin has been shown to prevent weight gain in most populations. Weight gain is very common after kidney transplantation and associated with more diabetes and worse outcomes.

All patients who have a glucose tolerance test will be followed for 12 months to check to see if they have developed diabetes over that period. All of the data collected on you will be stored safely and you will not be identified in any way.

WHO PAYS FOR THE STUDY?

This study is funded by the A+ Trust. All of your study visits will be done during usual clinic visits. If you are no longer in Auckland for your follow up after transplantation we will contact your caring team to find out your blood results.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You

will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

Entry into this study is entirely voluntary. Choosing not to take part in this study will not affect your treatment or care in any way. The doctors will continue to treat you with the best means available.

If you agree to participate in this study you will be asked to sign a consent form. However you may withdraw from the study at any time without giving a reason. This will not affect your treatment or care in any way.

All the information collection in the study will be kept confidential.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

After the study we will send you information about the results of the study. Any patient can take Metformin if it is prescribed by their doctor so if the medication is working for you, you will be able to remain on Metformin.

All study data will be stored for at least 15 years and will be stored on a password locked computer by the primary investigator.

It is anticipated that the results of the study will be available by 2017 and we will send you the results. We hope to publish the results in a peer reviewed journal. You will not be identifiable in any publication.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Name, **Associate Professor Helen Pilmore; Renal Physician**

Telephone number **09 379 7440**

Email **hpilmore@adhb.govt.nz**

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

If you require Māori cultural support talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 2324

If you have any questions or complaints about the study you may contact the Auckland and Waitematā District Health Boards Māori Research Committee or Maori Research Advisor by telephoning 09 4868920 ext 3204

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS

Email: hdecs@moh.govt.nz

Consent Form

Your letterhead

If you need an INTERPRETER, please tell us.
If you are unable to provide interpreters for the study, please clearly state this in the Participant Information Sheet

Please tick to indicate you consent to the following *(Add or delete as appropriate)*

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	No ☐
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	No ☐
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.	Yes ☐	No ☐
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	Yes ☐	No ☐
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	Yes ☐	No ☐
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	No ☐
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.	Yes ☐	No ☐
I understand that there may be risks associated with the treatment in the event of myself or my partner becoming pregnant. I undertake to inform my partner of the risks and to take responsibility for the	Yes ☐	No ☐

prevention of pregnancy.		
I agree to my (type of tissue) samples being sent overseas and I am aware that these samples will be disposed of using established guidelines for discarding biohazard waste.	Yes ☐	No ☐
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.	Yes ☐	No ☐
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.	Yes ☐	No ☐
I understand the compensation provisions in case of injury during the study.	Yes ☐	No ☐
I know who to contact if I have any questions about the study in general.	Yes ☐	No ☐
I understand my responsibilities as a study participant.	Yes ☐	No ☐
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

Declaration by participant:

I hereby consent to take part in this study.

Participant's name:

Signature:	Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date:

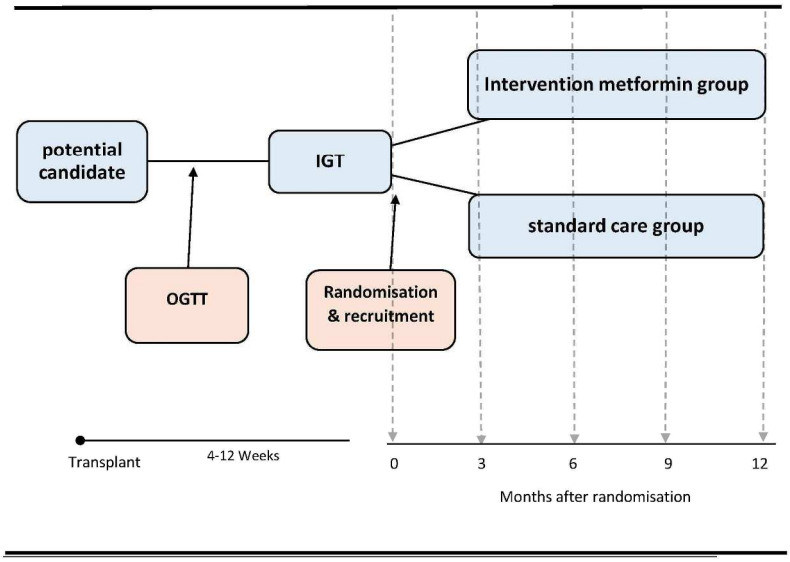

Figure 1. Flowchart of Transdiab trial

215x279mm (300 x 300 DPI)

A randomised controlled trial of metformin in Impaired Glucose Tolerance (IGT) (TransDiab)

Principal Investigator

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Study Schema

Consent for screening anytime from post-operative period

⇩

75 g OGTT (as described by WHO) between 4 - 6 weeks after transplant (Up to 12 weeks allowed)

⇩	⇩	⇩
2-hr post-load glucose ≤ 7.8 mmol/L	2-hr post-load glucose 7.8 to 11.1 mmol/L	2-hr post-load glucose ≥ 11.1 mmol/L *or* Fasting glucose ≥ 7.0 mmol/L or DM at any time prior to OGTT if DM
Non-diabetic	**Prediabetes (IGT/IFG)**	**NODAT**
⇩	⇩	⇩
Follow to 12 months	Randomise	Follow for 12 months

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LifeStyle + Metformin
vs.
LifeStyle

⇩

Minimum follow up 12 months after recruitment of the last patient

Study Outcome Measures:

The primary objectives of this Feasibility Study are to obtain the following feasibility, adverse event and efficacy data:

(i) Feasibility of recruitment in patients with pre-diabetes as defined by impaired glucose tolerance or elevated fasting plasma glucose after kidney transplantation

(ii) Adverse gastrointestinal side effects assessed by Gastrointestinal Symptom Rating Scale (GSRS)

(iii) Efficacy:
   a. Difference in Fasting Plasma Glucose at 3,6,9,12 months
   b. Difference in afternoon glucose at 3,6,9,12 months
   c. Difference in HbA1c at 3,6,9,12 months
   d. Proportion of patients developing New Onset Diabetes after transplantation at 12 month

The secondary objectives of the TRANSDIAB Feasibility Study are to assess the effects of metformin on the following outcome measures:

(i) Discontinuation of the study medication due to adverse events
(ii) All adverse events, including hypoglycemia, lactic acidosis, death
(iii) Absolute changes in weight
(iv) Lipid profile

(v) Fatal and Non-fatal cardiovascular events

(i) Proportion of patients who revert to normal glucose metabolism as defined by OGTT.

Definition of DM

	Glucose concentration, mmol l^{-1}		
	Whole blood Venous	Whole blood Capillary	Plasma* Venous
Diabetes Mellitus:			
Fasting	>=6.1	>=6.1	>=7.0
or			
2-h post glucose load	>=10.0	>=11.1	>=11.1

Study Evaluation Schedule: All patients will have the following investigations regardless of randomisation

Evaluation	Screening	Baseline (Day -7 to -1)	Week 1	Week 2	Week 4	Month 3	Month 6 and 9	Month 12
Glucose Tolerance Test	X							X
eGFR (MDRD)	X		x	x	x	x	x	x
Serum Creatinine	X	X	x	x	x	x	x	x
Serum Glucose		x	x	x	x	x	x	x
HBA_1c		x				x	x	x
Inclusion/Exclusion Criteria	X	X						
Physical Examination +Height		X						x
GI Quality of Life		X				x		x
24 hour urine protein		X				x		x
CNI dosing Record		X	x	x	x	x	x	x
Acute Rejection Episodes	X	X						x
Pm Glucose Level		X				x	x	x
Weight (kg) and BMI		X	x	x	x	x	x	x
Additional Medications		X			x	x	x	x
Serum Cholesterol and TG		X			x	x	x	x
Waist:Hip		X						
Adverse Events			X	X	X	X	X	x
Hypoglycemic med and dose record		x	x	x	x	x	x	X
Endpoint MI, Revascularisation, Death, Graft Loss					x	x	x	x
Blood Pressure	x	x	x	x	x	x	x	x

Inclusion/Exclusion Criteria:

Inclusion criteria

1) Adult (age > 18 years)
1) Incident non-diabetic kidney transplant recipient (deceased or living donor)
2) 2 hour post-load glucose (OGTT 75 g anhydrous glucose dissolved in water), done at 8 to 12 weeks after transplant (up to 16 weeks)
   2 hour PG 7.8 to 11.1 mmol/L for impaired glucose tolerance (IGT) group

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i) Exclusion criteria

In addition, potential participants must have NONE of the following exclusion criteria.

1. Known diabetic at the time of transplant, whether on anti-diabetic medications or not
2. Past history of anti-diabetic therapy (oral or insulin)
3. Steroid pulse therapy (IV or oral) in 2 weeks prior to OGTT*
4. eGFR by MDRD formula ≤ 30 ml/min/1.73 m^2 BSA (in line with the recommendations of Diabetes Australia)
5. Unable to consent
6. Pregnancy/ breast-feeding
7. Any major illness/ comorbidity that may result in death in 12 months as assessed by the treating physician,
8. Current alcohol or other substance abuse.

Study Procedures:

Patient recruitment

1) Patients scheduled for a renal transplant will be approached to discuss the trial. Consent may occur at any time prior to the OGTT

Blinding:

No blinding will occur in this pilot trial.

Dosing Algorithm:

Experimental intervention: Metformin hydrochloride at the starting dose of 500 mg twice a day given with meals, increased to a maximum of 850 mg twice a day after one week.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6,7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5,6

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____N/A_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____N/A_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____5,6_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____5,6____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____6____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____N/A____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____N/A____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____7_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____N/A_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12,13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	14-21
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.