removal

TYPE 1 DIABETES

REducing with MetfOrmin Vascular Adverse Lesions in type 1 diabetes (REMOVAL)

REMOVAL Investigators

Version 3.0 (9th November 2015)

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

Document	**STUDY PROTOCOL**
Title, version number & date	**REMOVAL study** Version 3.0; 09/11/2015
Compound	Metformin (Glucophage 500mg)
Full Title	**REducing with MetfOrmin Vascular Adverse Lesions in T1DM** **(REMOVAL)**
Study Numbers	EudraCT nr : 2011-000300-18 Clinical Trials.gov identifier : NCT01483560 Sponsor's protocol code nr: GN10DI406 REC reference nr: 11/WS/0012
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Contents 3

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Location:

Australia, Canada, Denmark, Netherlands, UK

Abbreviations used in protocol

AE adverse event
bd twice daily
β-HCG β -human chorionic gonadotrophin
BHF GCRC British Heart Foundation, Glasgow Cardiovascular Research Centre
CCA common carotid artery
CCA cIMT intima-media thickness of the distal common carotid artery
CI chief investigator
cIMT carotid intima-media thickness
CHD coronary heart disease
CRF case report form
CRP C-reactive protein
CTA clinical trials authorisation
CV coefficient of variation
DCCT Diabetes Control and Complications Trial
DICOM document imaging and storage service provider
DM diabetes mellitus
DSMB data and safety monitoring board
ECG electrocardiogram
eGFR estimated glomerular filtration rate
ETDRS early treatment diabetic retinopathy study
FBC full blood count
FDA Food and Drug Administration (United States)
FPG fasting plasma glucose
GCTU Glasgow Clinical Trials Unit
GMP good manufacturing practice
HbA1c glycated haemoglobin A1c
HBGM home blood glucose monitoring
IL-6 interleukin 6
IRB Institutional Review Board
IMP investigational medicinal product
IVRS Interactive Voice Response System
IWS Interactive Web System
LFT liver function tests
MDRD modification of diet in renal disease
MedDRA Medical Dictionary for Regulatory Activities
MI myocardial infarction
MHRA Medicines and Healthcare products Regulatory Agency
NYHA New York Heart Association
OGTT oral glucose tolerance test
PI principal investigator
PV pharmacovigilance
QP qualified person
RCB Robertson Centre for Biostatistics, University of Glasgow
SAE serious adverse event
sICAM-1 soluble intercellular adhesion molecule-1
SmPC summary of product characteristics
SDRN Scottish Diabetes Research Network
SUSAR suspected unexpected serious adverse reaction
T1DM type 1 diabetes
t-PA tissue plaminogen activator
U&E urea and electrolytes
ULN upper limit of normal
UKPDS United Kingdom Prospective Diabetes Study

1. STUDY SYNOPSIS

Title of Study:	**REducing with MetfOrmin Vascular Adverse Lesions in T1DM (REMOVAL)**
Brief Title:	**REMOVAL**
National Coordinating Centres	British Heart Foundation: Glasgow Cardiovascular Research Centre, Glasgow; Steno Diabetes Center, Gentofte; University of Western Ontario, London, Ontario; NHMRC Clinical Trials Centre, Sydney Medical School, Australia; University of Maastricht, Netherlands
Duration of Study:	Three month run-in period (third month with single-blind placebo); 3 years double-blind randomized treatment.
Primary Objective:	To assess in a randomized controlled trial the effects of three years metformin added to titrated insulin therapy (towards target HbA1c 7.0%/ 53 mmol/mol) on progression of atheroma as measured by progression of averaged mean far wall common carotid artery intima-media thickness (cIMT) in adults with type 1 diabetes at risk of cardiovascular disease.
Secondary Objectives:	Change in: (i) HbA1c; (ii) LDL cholesterol; (iii) albuminuria and estimated glomerular filtration rate; (iv) retinopathy stage (two-field photographs); (v) weight; (vi) insulin dose; (vii) endothelial function
Tertiary Objectives:	Change in: (i) frequency of hypoglycaemia; (ii) treatment satisfaction; (iii) markers of endothelial function (t-PA, sE-selectin, sICAM-1); (iv) progression of mean maximal distal common carotid artery cIMT; (v) vitamin B12 status.
Rationale:	Intensive glucose control reduces long term rates of cardiovascular disease (CVD) in people type 1 diabetes (T1DM) but the majority of individuals affected by the condition do not currently achieve glucose targets with standard insulin therapy. Upward insulin dose titration may lead to weight gain, hypoglycaemia and dyslipidaemia. Metformin has potential for addressing these issues as it may: (i) reduce insulin dose for a given achieved HbA1c; (ii) promote weight stabilization; (iii) be associated with low rates of hypoglycaemia; and (iv) reduce LDL cholesterol - even on a background of statin therapy. It may also have direct and potentially beneficial cardiovascular effects. Progression of carotid artery intima-media thickness (cIMT) is the primary endpoint as this is accelerated in type 1 diabetes. cIMT reliably predicted cardiovascular events in DCCT and has been successfully targeted by metformin in a number of small studies in conditions other than type 1 diabetes. The secondary endpoint is a composite of clinically-relevant markers of microvascular and macrovascular prognosis.
Product, Dose, Modes of Administration:	**Single-blind placebo Run-In:** One tablet once daily with the evening meal. **Double-blind treatment period:** Oral metformin (as Glucophage 500 mg x 2 twice daily) titrated from initial 500 mg to target 2000 mg daily/ matching placebo.
Sample Size:	500 enrolled participants.
Randomisation:	By telephone call to the study Interactive Voice Response System (IVRS) or electronically via the portal providing the study electronic Case Report Form (as provided by the Robertson Centre for Biostatistics, University of Glasgow).

Inclusion Criteria (abbreviated)	Type 1 diabetes (defined in Section 7.1) for five years or more; age ≥ 40 years; 7.0 ≤ HbA1c < 10.0% (53-86 mmol/mol) **AND *three or more*** of the following ten CVD risk factors: (i) BMI ≥ 27 kg/m^2 (ii) current HbA1c > 8.0% (64 mmol/mol) (iii) known CVD/ peripheral vascular disease (iv) current smoker (v) eGFR < 90 ml/ min/ 1.73 m^2 (vi) confirmed micro- (or macro-) albuminuria [according to local assays and reference ranges] (vii) hypertension (BP≥140/ 90 mmHg; or established on antihypertensive treatment) (viii) dyslipidaemia [total cholesterol ≥ 5.0 mmol/L (200 mg/dL); or HDL cholesterol < 1.20 mmol/L (46 mg/dL) [men] HDL cholesterol < 1.30 mmol/L (50 mg/dL) [women]; or fasting triglycerides ≥ 1.7 mmol/L (150 mg/dL); or established on lipid-lowering treatment (ix) strong family history of CVD (at least one parent, biological aunt/ uncle, or sibling with myocardial infarction or stroke aged < 60 years) (x) duration of diabetes > 20 years.
Exclusion Criteria (abbreviated)	(i) eGFR < 45 ml/ min/ 1.73m^2 (ii) woman of childbearing age not on effective contraception – see Appendix 4 (iii) pregnancy and/or lactation (iv) Acute Coronary Syndrome or Stroke/ TIA within the last 3 months (v) NYHA stage 3 or 4 heart failure (vi) uncontrolled angina (vi) significant hypoglycaemia unawareness (vii) impaired cognitive function/ unable to give informed consent (viii) previous carotid surgery/ inability to capture adequate carotid images (ix) gastroparesis (x) history of lactic acidosis (xi) other contraindications to metformin - hepatic impairment - known hypersensitivity to metformin - acute illness (dehydration, severe infection, shock, acute cardiac failure) - suspected tissue hypoxia (xii) Any coexistent life threatening condition including prior diagnosis of cancer within two years (xii) history of alcohol problem or drug abuse
Duration of Treatment:	Three years per participant (plus one month placebo single-blind in third month of three month Run-In period)
Statistical Analysis Primary:	Mixed effects regression model estimates of between-group cIMT differences over time, with 95% confidence intervals and p-values. Primary outcome regression model extended to assess whether metabolic effects could explain differences in progression of cIMT.

2. SCHEDULE OF ASSESSMENTS

Protocol: REMOVAL																						
	Pre-screening	Run-in Period				Treatment																
*telephone visit only R routine clinic visit F fasting visit	Visit 0 R	Visit R1	Visit R2*	Visit R3*	Visit R4*	Visit 1 F	Visit 2*	Visit 3*	Visit 4*	Visit 5 R	Visit 6 R	Visit 7*	Visit 8 F Yr 1	Visit 9*	Visit 10 R	Visit 11*	Visit 12 F Yr 2	Visit 13*	Visit 14 R 1	Visit 15* 1	Visit 16 F Yr 3	Visit 17 2 Close out
Treatment month (±2 weeks; or see Appendix 6)		-3		-2	-1	0			1	3	6	9	12	15	18	21	24	27	30	33	36	38
Treatment week (±3 days)			-10	-8	-4		1	2														
Provide information	x																					x
Informed consent		x																				
Eligibility criteria		x																				
Medical/ Disease History		x																				
Concomitant medications		x				x			x	x	x	x	x		x		x		x		x	
Weight R		x				x				x	x		x		x		x		x		x	
Waist circumference		x				x				x	x		x		x		x		x		x	
Height R		x																				
BP and heart rate R		x				x					x		x		x		x		x		x	
Dispense study medication		x				x				x	x		x		x		x		x			
Collect/ count unused medication						x				x	x		x		x		x		x		x	
Titrate study medication							x	x	x													
Give out new diary		x				x					x				x				x			
Adjust insulin to HbA1c (review glucose diary) R		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Record insulin dose						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Steno hypoglycaemia questionnaire		x				x			x	x	x	x	x	x	x	x	x	x	x	x	x	
Treatment satisfaction questionnaire		x				x			x				x				x				x	
Other adverse events (including cardiovascular)			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Full blood count, vitamin B12 R		x				x							x				x				x	
U+E, local lab HbA1c, LFT, routine lipids R		x				x				x	x		x		x		x		x		x	
Pregnancy test		x				x	Only in women of childbearing age – repeated if clinically indicated in prompted discussion with participant															
C-peptide		x																				
Carotid IMT (±4 weeks except Visit 1: see below**)						x							x				x				x	
Retinal images (±4 weeks except Visit 1: see below**)						x															x	
Endothelial function (ENDOPAT) (±4 weeks except Visit 1: see below**)						x							x								x	
LDL sample for central analysis		x				x							x				x				x	
Microalbumunuria R		x				(x)							x				x				x	
Lactate						x				x			x				x				x	
Plasma biomarker samples		x				x							x				x				x	
Urine aliquot		x				x							x				x				x	
	** N.B. All Visit 1 assessments [including carotid IMT, retinal imaging and ENDOPAT] MUST be completed within 4 weeks PRIOR TO randomization** [1] VISIT 14 and VISIT 15 time windows altered or omitted for participants randomized after the end of March 2014 – see Appendix 6 [2] VISIT 17 must be at least one week after Visit 16																					

3. INTRODUCTION

Cardiovascular disease (CVD) is the commonest cause of premature death in type 1 diabetes (T1DM).[1-4] Population-based data from 19,248 individuals with the condition in Scotland indicate ten year absolute CVD event rates of 16.7% and 12.7% respectively in men and women aged 40-60 years (Colhoun, unpublished data presented at JDRF Complications Prevention Workshop, Washington, April 2010), rising to 49% and 39% in those aged over 60 years. These rates are 3-5 fold higher than in the general population. While relative risk is even higher in younger individuals, 95% of actual CVD events occur in those above 40 years of age. The major risk factors are male gender, hypertension, dyslipidaemia, cigarette smoking, hyperglycaemia and nephropathy.

Few randomized controlled trials (RCTs) have directly addressed myocardial infarction (MI) and stroke prevention in T1DM. It is acknowledged in the 2010 American Diabetes Association "Standards of Medical Care"[5] that recommendations for people with the condition to be prescribed statin therapy to prevent CVD are based on extrapolation from type 2 diabetes,[6] and on meta-analysis of trials involving a total of 651 people with T1DM in whom CVD event reduction was not statistically significant.[7] A period of intensive glycaemic control in the Diabetes Control and Complications Trial (DCCT) was associated in later post-randomisation follow up in the Epidemiology of Diabetes and Its Complications (EDIC) study with a reduction in CVD events.[8,9] Achievement of target glycaemic control is essential for preventing the complications of T1DM, but many years after the DCCT achieving tight glycaemic control remains a challenge for many people living with T1DM. The figures are stark: in the UK, no more than 20% of people with the condition achieve HbA1c < 7.5% and about a third typically have an HbA1c >9% (Scottish Diabetes Survey 2009).[10] With intensified insulin therapy, insulin up-titration aimed at achieving target glycaemia can result in more frequent hypoglycaemia, and - in a significant subpopulation - weight gain, hypertension and dyslipidaemia.[11,12]

Metformin has many of the properties desirable for an adjunct oral agent to be added in with insulin therapy to improve metabolic control.[13,14] Data from ourselves and others show that it may: (i) reduce insulin dose (by 6 units) for a given achieved HbA1c; (ii) promote weight stabilization; (iii) be associated with low rates of hypoglycaemia; and (iv) reduce LDL cholesterol – by 0.5 mmol/L (20 mg/dL) - even on a background of statin therapy.[15-18] There is considerable evidence that it may also provide direct and potentially beneficial cardiovascular effects at least in type 2 diabetes - particularly as demonstrated in the UK Prospective Diabetes Study (UKPDS).[19,20]

Metformin undergoes active transport into cells via the OCT-1 transporter[21] and activates the AMP-activated protein kinase (AMPK), resulting in decreased hepatic glucose production, increased muscle fatty acid oxidation and improved whole-body insulin sensitivity.[22-24] A meta-analysis of its effects in non-diabetic individuals indicates reductions in weight (5%), insulin resistance (23%), LDL cholesterol (6%), and triglycerides (5%).[25] In some countries, metformin is relatively frequently co-prescribed with insulin for people with T1DM, particularly those who are overweight. For example, in Tayside, Scotland (2008 data), 9.7% of people with T1DM and BMI>27 kg/m^2 were currently prescribed metformin, rising to 15.9% for those with BMI>30 kg/m^2 *(unpublished data)*, even although this is not mentioned or advocated in local or national guidelines.

3.1 Work leading up to this proposal

The investigators have long-standing interests in the cardiovascular effects of metformin. NS and JP previously conducted an RCT in non-diabetic women with chest pain and normal coronary arteries which demonstrated a pronounced effect of metformin on vascular endothelial function and parameters of exercise tolerance/ sub-maximal cardiopulmonary exercise testing.[26] On the basis of these results, NS initiated the ongoing CAMERA trial to test the effect of 18 months' metformin treatment on carotid intima media thickness (IMT) in 200 non-diabetic adults with stable coronary heart disease.[27] Recently, in a collaborative epidemiological study between JP (Chief Investigator) and cardiology colleagues, positive effects of metformin were observed on mortality in people with type 2 diabetes and heart failure (in comparison with sulphonylureas).[28]

In 2008, colleagues at the Steno Diabetes Center (SL and PR) reported the largest and longest RCT to date of adjunct metformin in T1DM in 100 participants over one year of follow-up.[18] This trial, conducted at the Steno Diabetes Center, demonstrated the safety of metformin in this context and contributed important data on metabolic endpoints: for example, sustained and statistically significant reductions in mean weight (1.74 kg) and total cholesterol (0.37 mmol/L) were reported despite stable HbA1c - which may have been a feature of the study design. The mean reduction in total cholesterol associated with randomisation to metformin tended to be larger in patients on stable statin therapy (mean 0.50 mmol/L).[29] This trial was a major contributor to the recent systematic review of the RCT evidence base for metformin therapy in T1DM conducted by JP and HC,[15] although, like the other previous studies, did not examine cardiovascular endpoints or surrogates. In formal meta-analysis of all appropriate published RCT data, consisting of only eight smaller studies and fewer than 200 patient years of follow-up, we concluded that metformin was associated with a reduction in insulin dose by 6.6 units/ day. There were insufficient data to be confident regarding pooled effects on HbA1c, weight and cholesterol.[15] It was clear: (i) that there are insufficient cardiovascular data, and (ii) that few studies have titrated insulin doses back up towards an HbA1c target after metformin therapy has been initiated.

Finally, CS published in 2009 a major metformin RCT in people with type 2 diabetes (n=390) treated with insulin therapy (the HOME trial).[17] This study demonstrated a reduction in cardiovascular disease (prespecified as a secondary endpoint) over 4.3 years follow-up (hazard ratio, 0.61 (95% CI, 0.40-0.94; *P*=.02). HbA1c fell significantly (mean 0.4%) in participants randomized to metformin even although the protocol did not specify measures aiming to achieve intensive glycaemic control. Like the UKPDS, which involved randomisation of 342 participants to metformin therapy, these data cannot be directly extrapolated to T1DM. However, they contribute to the literature recently reviewed by Anfossi et al,[14] which suggests that metformin may have direct and potentially beneficial cardiovascular effects in a variety of conditions, including non-diabetic individuals, which may be independent of (or additional to) effects mediated via glycaemia.[30-31]

4. STUDY RATIONALE – HYPOTHESIS

Hypothesis: Does metformin added to titrated insulin therapy [towards target HbA1c 7.0% (53 mmol/mol)] reduce progression of atheroma as measured by carotid artery intima-media thickness (cIMT) in adults with T1DM at risk of cardiovascular disease?

Secondary and tertiary objectives: to examine the effect of metformin on other markers of diabetic micro- and macrovascular complications and intermediate disease-related biomarkers.

The primary endpoint - progression of carotid IMT - is widely used as a surrogate of CVD morbidity and mortality in studies evaluating the efficacy of interventions targeting atherosclerosis.[32,33] Thickness of the blood-intima and media-adventitia interfaces (IMT) is highly correlated between the carotid and coronary arteries whether measured using ultrasound or quantitative angiography.[34] In people with T1DM aged 40 years, mean common carotid artery (CCA) IMT is similar to in controls 20 years older.[35,36] In DCCT-EDIC, a reduction in carotid IMT was reported[36] six years before CVD outcome benefit was demonstrated.[9] A recent consensus statement including a pooled analysis of more than 30 RCTs which used carotid IMT as a primary outcome supported its use in intervention trials and its treatment as a linear variable in studies of populations across a wide range of CVD risk.[37] In small clinical trials, metformin has been reported to reduce carotid IMT progression in both metabolic syndrome and T2DM.[38-40]

We acknowledge the ultimate importance of demonstrating effects of metformin on hard clinical endpoints but such a study would necessarily be very expensive and lengthy. A study establishing the effectiveness of metformin on a meaningful surrogate endpoint of carotid IMT study is timely and feasible now, will bring results much sooner, and will establish whether an endpoint study is fully justified. If adding metformin to insulin therapy in T1DM has favourable cardiovascular, metabolic, and/ or microvascular effects - whether via glucose-lowering or other mechanisms - many more people with T1DM could benefit from more widespread use given that it is a safe and already-marketed oral agent. At the recent JDRF Complications Prevention workshop (April 2010), there was a near consensus that its potential to reduce macrovascular and microvascular complications in T1DM should be tested further.

Current practice. People with T1DM aged over 40 years should be treated with insulin and lifestyle recommendations to achieve and maintain target glycaemic control (HbA1c < 7.0%/ 53 mmol/mol).[6] Blood pressure lowering therapy is usually commenced according to international guidelines where BP is > 140/ 90 mmHg with a target systolic BP < 130 mmHg (lower where there is microalbuminuria/ proteinuria).[6] HMG-CoA reductase inhibitor (statin) therapy is recommended for those with known cardiovascular disease (CVD) but as there is no hard clinical trial evidence to guide cholesterol-lowering in primary CVD prevention there is considerable geographical variation in practice. For example, T1DM is excluded from some guidelines (e.g. in the Netherlands) but in others (e.g. UK) statins are suggested independent of cholesterol levels for some aged over 40 years, including those with CVD risk factors or long duration of disease.

5. OBJECTIVES

Primary objective: to test for the first time in a double-blind randomized, placebo controlled trial whether three years treatment with metformin 1000 mg bd added to titrated insulin therapy (towards target HbA1c 7.0%/ 53 mmol/mol) reduces atherosclerosis, as measured by progression of carotid IMT, in adults with confirmed T1DM aged 40 years and over and at increased risk for CVD.

Secondary and tertiary objective: to examine over this period the effect of metformin on other markers of diabetic micro- and macrovascular complications and intermediate disease- related biomarkers. The composite secondary endpoint will provide clinically meaningful information on the potential of metformin to influence clinical practice in this condition. The REMOVAL study will be five times larger and three times longer than any previously-conducted trial of metformin in T1DM.

In REMOVAL, participants will be provided with the best care possible throughout the five-year follow-up period. They will be encouraged and supported to work towards and maintain target glycaemic control (HbA1c < 7.0%/ 53 mmol/mol) independent of the randomization (i.e. metformin or placebo). This will be achieved by: (i) increased attention to lifestyle measures; (ii) careful supported adjustment of insulin doses; and (iii) intensifying insulin regimens and doses where necessary.

The primary, secondary and tertiary endpoints are defined below.

Primary endpoint: progression of averaged mean far wall common carotid artery IMT (CCA cIMT, measured in mm, at baseline, 12, 24 and 36 months).

Secondary endpoints:
(i) HbA1c;
(ii) LDL cholesterol;
(iii) albuminuria & estimated glomerular filtration rate
(iv) retinopathy stage (ETDRS stage = Early Treatment Diabetic Retinopathy Study);
(v) weight
(vi) insulin dose;
(vii) endothelial function (in some centres).

N.B. We will consider a statistically significant improvement in two or more of these secondary endpoints to be a clinically meaningful result with the potential to influence clinical practice.

Tertiary endpoints: To compare between treatment groups, as above, change in:
(i) frequency of hypoglycaemia;
(ii) treatment satisfaction;
(iii) markers of endothelial function (t-PA, sE-selectin, sICAM-1);
(iv) progression of averaged maximal distal common carotid artery IMT (CCA cIMT, measured in mm, at baseline, 12, 24 and 36 months).
(v) vitamin B12 status

6. STUDY DESIGN

a) Type of study
Randomized, double-blind, placebo controlled trial

b) Assessments
Carotid IMT measurements and analysis will be led and coordinated by Professor Nish Chaturvedi and Professor Alun Hughes at University College, London, UK where there is extensive experience in running large clinical vascular research studies. Data will be

acquired using a standard ultrasound scanning protocol.[41] Both sonographer and participant will be positioned to facilitate high quality, reproducible images. The same ultrasound system and preset image parameter settings (e.g. depth, gain, persistence, dynamic range, post processing) will be used throughout the study. Ultrasound equipment will be calibrated before commencement and every six months subsequently using an ultrasound phantom or as part of each site's local annual service/ calibration.

Right and left carotid arteries will be interrogated in B mode with a 7.0 MHz or higher broadband linear array transducer with concurrent recording of 3-lead ECG. A plaque screen (defined as focal thickening ≥1.5 mm or 50% greater than surrounding IMT) of the near and far walls of the common carotid artery (CCA), bulb and internal carotid artery segments will be performed. Then longitudinal images of the common carotid artery will be obtained at anterior, lateral and posterior angles, using Meijer's arc to standardize the transducer angle.

If a participant is found to have asymptomatic high grade carotid stenosis (i.e. >50%) on scanning, cardiovascular risk factor management will be reviewed and arrangements made by their site Principal Investigator (with verbal consent) to facilitate further investigation and treatment as appropriate - usually via the participant's primary care physician. However, our experience, including in older populations with established angiographic coronary disease, suggests that significant stenosis affected <1% of the study population.[42] Participants will be eligible to enter and remain in the trial unless cIMT measurements of adequate quality cannot be obtained e.g following carotid artery surgery. Incidental findings, such as tumours or dissection of the carotid artery, will also be reported to the site PI.

Cineloops and images from at least five cardiac cycles will be saved in DICOM format. They will be uploaded on to the study web-based management system for digital archiving; as such they will be accessible to the reading centre at Imperial College London for evaluation and analysis. cIMT measurements will be taken from the distal 1 cm of the CCA (i.e. immediately proximal to the bulb). Measurements will be performed in triplicate, and the mean of three readings used in analysis. The primary assessment will be the within-person change in the averaged mean far wall common carotid artery (CCA) IMT as this is the most reproducible measure. All measurements will be performed by one trained assessor at Imperial College London under the supervision of Professor Nish Chaturvedi and Professor Alun Hughes (AH) using a validated semi-automated program (Wendelhag et al., 1997).[43] The assessor will also undergo repeated 'masked' QC cycles to assess repeatability within scans at a given timepoint, and within scans over time.

The group has the necessary experience and expertise to carry out the required high level of training and standardization with the technical staff at the study sites – e.g. NC with the SABRE study (NC; www.sabrestudy.org) and JP with the RISC study (www.egir.org).[44] NC and AH will be responsible for running the core-lab for blinded analysis of the cIMT study data and directing ongoing quality control of the ultrasound data acquisition at all study sites. The numbers of sonographers at each field site will be kept to a minimum (≤2) and all sonographers will undergo initial training and certification at the core laboratory to ensure standardization and high quality of imaging prior to commencement of the study.

Carotid IMT QC: (i) Accreditation – after training by the Carotid IMT reading centre at Imperial College London, each sonographer will be asked to submit five accreditation scans to demonstrate understanding and adherence to the carotid IMT protocol (these can be performed on healthy volunteers); (ii) Reproducibility – sonographers will also be asked to perform a repeat baseline carotid IMT measurement on six of the first willing study participants on a second occasion. This can be performed at visit 1 or within a week of visit 1. Sonographers will be expected to demonstrate an intra-operator coefficient variation (CV) of <10% in these 6 individuals; (iii) On-going QC – sonographers will invite the same study participants to continue to undergo repeat carotid IMT measurements at visits 8, 12 and 16 in order to assess for any measurement drift. Results of Quality Control (QC) will be fed back to centres on a regular basis with follow up re-training/ certification as necessary.

HbA1c will be measured in accredited local laboratories participating in DCCT-aligned quality control programmes.

Lipids: samples of 7 ml EDTA plasma will be collected at Baseline, 0, 12, 24 and 36 months for centralised total cholesterol, HDL-cholesterol, direct LDL-cholesterol and triglycerides assay – participants will be asked to fast from midnight for all of these samples except Baseline (Visit R1). Aliquots will be stored at - 80ºC for transport to the laboratory in Glasgow for central assay. Total and HDL cholesterol and triglycerides will also be measured as per routine care in local routine laboratories to guide the requirement for and optimisation of statin therapy: the most recent values (within three months) will be recorded on Case Report Forms at the time of annual visits.

Microalbuminuria: status (positive or negative - see Appendix 5) as per routine care screening systems in local centres will be recorded annually in CRFs. At the same visits, aliquots of urine will be frozen and stored at -80ºC (for later shipment to Glasgow) in case later centralised analysis is indicated.

eGFR: serum creatinine concentrations measured in local laboratories will be reviewed at least annually and checked against safety criteria. Values from annual review (within three months) will be recorded on CRFs and used to calculate estimated glomerular filtration rate using the MDRD equation [eGFR ml/min/ $1.73m^2$ = 186 x serum creatinine$^{-1.154}$ x age$^{-0.203}$ x (1.210 if Black) x (0.742 if female)]. In addition, we will retain aliquots of plasma in order to have the possibility later to measure cystatin C using laser immunonephelometry (Dade Behring).

Retinopathy stage: two color 45° field retinal photographs (fields 1 and 2) will be taken in each eye at 0 and 36 months and graded at the University of Wisconsin Ocular Epidemiology Reading Center (OERC) using the modified Airlie House classification scheme and the Early Treatment Diabetic Retinopathy Severity scale.[45] This is an ordinal scale based on the presence and severity of a combination of retinal lesions determined by comparison with standard photographs. Component retinal lesions are evaluated individually and then are used in assigning the diabetic retinopathy severity level.

Images captured in each eye at the study site will be uploaded on to the study web-based management system for digital archiving; as such they will be accessible to the OERC in Wisconsin for evaluation. These images will consist of a 45 degree image centered on the optic disc (field 1) and a 45 degree image centred on the macula (field

2). Each set of images will be graded using custom designed computer software with built in completeness and consistency checks. The grading system includes a preliminary and detailed grading followed by an edit and adjudication if necessary. (Two different graders must agree on the retinopathy severity for the grading to be considered "final".) The preliminary grading will assess photo quality and will provide an overview of the retinopathy status as well as provide an opportunity to evaluate any imminent pathology that needs immediate attention. If significant retinal pathology (e.g. retinal vein branch occlusion) exists, notification will be made to the site Principal Investigator with a copy sent to the coordinating centre.

After preliminary grading, images will be sent to a second masked grader for a detailed evaluation of all diabetic lesions and other common conditions. A comparison will then be made between the preliminary grading and the detailed grading for agreement on absence and/or presence and severity of diabetic retinopathy. If there is a disagreement in the retinopathy severity level assigned, the eye will be sent to a third masked grader for an edit grade. A similar comparison between the edit grade and the preliminary grade and detail grade will then be done. If the edited grade still does not agree with either the preliminary or detailed retinopathy severity score, the eye will be sent to the consulting ophthalmologist for adjudication. Additionally, since each study participant will have a baseline and closeout visit a longitudinal review will also be done towards the end of the study to ensure that any change in retinopathy status across visits represents real change and not an artifact of photo quality or grader error.

If a participant is found by the Reading Center to have a previously-undetected retinal abnormality (at baseline) or an as-yet-undetected significant progression of retinopathy (at follow-up), this will be fed back to the site Principal Investigator in order that the participant (with verbal consent) can be referred locally for appropriate assessment and treatment - if necessary via the participant's primary care physician.

Blood pressure: will be measured in triplicate with at least 3 minutes between recordings and according to Standard Operating Procedures developed by the Scottish Diabetes Research Network http://www.sdrn.org.uk/sites/default/files/sop08_physicalmeasuresbloodpressure.pdf (using a validated semi-automatic device).

Weight: will be measured using calibrated weighing scales (kg).

Insulin dosage and frequency of hypoglycaemia: Insulin dose and home blood glucose monitoring (HBGM) will be extracted by study nurses from the Study Diary and reported on the study CRF using dedicated fields including the Steno Hypoglycaemia Questionnaire (Appendix 3).

Treatment satisfaction: the Diabetes Treatment Satisfaction Questionnaire [status and change (DTSQs/ DTSQc)] will be administered at baseline and annual assessments.[46]

Biomarker plasma samples: samples of plasma and serum will be stored at baseline, 0, 12, 24 and 36 months according to the study Sample Handling Protocol. In total, we will withdraw 7 mls serum at each of these time-points (stored in five aliquots of around 0.5 mls each), and will repeat this procedure for 7 mls EDTA plasma; thus, in total, we will retain 10 aliquots (5 serum, 5 plasma) of samples for biomarker tests. All will stored at -80ºC for later transport to the central laboratory in Glasgow. Lipids, hsCRP, t-PA, sE-

selectin, sICAM-1 and apoproteins will initially be measured on two such aliquots. hsCRP and apoproteins will be measured on automated platforms in NHS Glasgow laboratories. Other assays will be run using established ELISAs with all samples run at the same time to minimise variability. Eight aliquots at each timepoint will be retained for future assays of interest as prioritised by the Steering Committee. Transport on to other laboratories will be covered by separate Material Transfer Agreements. These will include markers of endothelial function (t-PA, sE-selectin, sICAM-1), vitamin B12 status (homocysteine, holotranscobolamin-II, S-adenosylmethionine), and Advanced Glycosylation End-products. As novel genes are currently being identified determining therapeutic response to metformin, we will also retain buffy coat for later DNA extraction.

Endothelial function: will be measured using ENDOPAT (Itamar ®) as Reactive Hyperaemia Peripheral Arterial Tonometry (RH-PAT), a non-invasive measurement of peripheral microvascular endothelial function using changes in digital pulse volume during reactive hyperaemia, at 0, 12 and 36 months (in approximately 400 of the 500 patients i.e. in 80% of the study centres). This method has been validated in children with T1DM in whom it has been shown to detect endothelial dysfunction.[47] As Raynaud's phenomenon and treatment with α-blockers are contraindications to ENDOPAT, any affected individuals will be excluded from these assessments.

Other assessments: Serum C-peptide will be measured in local laboratories at the screening visit: participants will be withdrawn before randomisation in cases where this is > 200 pmol/L (= 0.2 nmol/L or 0.6 ng/ml). Although the risk of lactic acidosis is almost negligible,[48] plasma lactate will be monitored according to the Schedule of Assessment in local laboratories; participants with values > 3.0 mmol/L (>27 mg/dL) will be recalled for clinical assessment within one week and treatment discontinued if this level is sustained: where possible, blood samples for lactate will be performed without a tourniquet ("uncuffed)" and following minimal exertion (this approach will be adopted for all repeat lactate measurements). Full blood count and serum vitamin B12 (cobolamin) concentrations will also be monitored during the study in view of the small risk of metformin induced B12 deficiency identified in recent papers by the applicants (CS/ SL): concentrations fell by 80 pmol/L with prolonged therapy, although rarely outwith the reference range (150-550 pmol/L).[18,49] Any individuals whose levels do fall below the reference range (<150 pmol/L) and who do not wish to discontinue therapy will be referred to their primary care physician for consideration of replacement therapy.

Long-term follow-up: The primary and secondary outcomes of the study are robust, but they are surrogates for long-term CVD risk. Where national competent authorities permit, we will seek informed consent from all participants to "flag" them in national systems using national health numbers to permit outcome assessment and to receive notifications of deaths. This will be led by applicant IF who has particular expertise in this area.

c) Sample handling storage and shipping

Following pre-processing and aliquoting, blood and urine samples will be stored locally at –70ºC or –80ºC according to the study Sample Handling Plan prior to shipping to the central laboratory in Glasgow (Applicant NS). All study samples will be sent on dry ice using contracted couriers at annual intervals. All samples will be stored on arrival at –80ºC.

d) Statistical considerations/ number of subjects to be included in the study

Primary endpoint cIMT: For the primary endpoint of cIMT there will be a baseline measurement and repeat measurements at year 1, 2 and 3 (visits 8, 12 and 16). All those with a baseline and at least one follow up measurement will be included in analysis.

We intend to analyse IMT data using repeated measures regression analysis assuming a linear progression in IMT measurements. We expect a mean progression of 0.044mm over 3 years (in the control arm) and a standard deviation (SD) for progression of 0.05 mm; therefore a final sample size of 200 per treatment arm will provide 90% power (at 5% significance level) to detect a difference of at least one third of an SD (0.0167mm) in 3 year progression of averaged mean cIMT between treatment arms - an effect size more conservative than reported for acarbose, statins, and TZDs on cIMT.

We therefore aim to recruit 500 patients (allowing for around 20-25% treatment discontinuation/ drop-out) and making the very conservative assumption that all those discontinuing treatment/ and withdrawing consent would not even have one follow up measurement (in reality this may occur after one or more follow up cIMT measurements so power will be more than this estimate).

Rates of progression and variation of common carotid artery IMT vary widely between different studies and data from T1DM patients, other than the patients in DCCT/EDIC who are younger than this trial participants, are sparse. Our estimate of progression rate over three years (0.044 mm) is at the lower boundary of that reported by Bots in a meta-analysis of cIMT progression rates of control groups (almost all non-diabetic) from published RCTs.[50] In that analysis the annual rate of change in mean cIMT was 0.0176 mm (95% CI, 0.0149 to 0.0203). Whilst many of the control group participants in this pooled analysis were not on statins (in contrast to many REMOVAL participants with T1DM) almost all were non-diabetic so that their progression rate would be expected to be lower than in diabetes.

Other endpoints: The sample size for the study is based on the primary endpoint as described above. This sample size also yields 90% power at 5% significance level to detect differences of approximately 0.3 SD in continuous outcomes i.e. lipid, metabolic and endothelial function parameter changes from baseline at follow up. To put this into context, in the largest trial of metformin in T1DM to date the reported effects on LDL-C were considerably larger than this at (0.46 SD) so that we have ample power to replicate and refine the precision of this treatment effect. For other endpoints we acknowledge that power is lower but emphasize that the sample size is appropriately based on the primary endpoint, and that we are stating *a priori* that we will consider a change in two of the seven secondary endpoints to be clinically meaningful. Thus, for retinopathy progression, based on recent data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (Co-applicant Klein) we expect three year two-step progression in categorical ETDRS retinopathy stage to be 13.7%. Assuming follow-up retinal photographs in 400 participants, treatment with metformin would have to be associated with a hazard ratio of 0.40 to have 80% power to declare significance for this specific secondary endpoint (at $p<0.05$). Given the relatively low marginal cost of acquiring the retinal photographs, many of which will be captured from routine screening, we believe incorporation of this endpoint in the study is an opportunity to acquire at least a useful point estimate for likely effect size (albeit with wide confidence intervals). This may be

useful in assessing the statistical power of any future retinopathy intervention trials with metformin.

e) Feasibility of achieving required sample size
Based on an analysis of the current living population of people with T1DM in Scotland with available risk factor data (n=22,891), we estimate that approximately 52% are aged 40 years and upwards and meet our HbA1c entry criteria. Of these 25% have at least three additional risk factors as per our criteria, such that an overall 13% of all adult clinic (≥16 years) attendees meet our entry criteria. Assuming a response rate of 25% (as was achieved in the largest metformin trial in T1DM) to date,[18] we therefore need to recruit from sites that have a total adult attendee list of about 19,000. It is on this basis that we have approached the participating sites which together have the appropriate base population. We will retain the opportunity to extend recruitment rapidly to satellite sites in case rates of accrual are lower than expected.

f) Duration of study and timelines
Following the three month Run-In Period (taking placebo in the third month), participants will remain on therapy as randomized for three years (see Appendix 6). All of the 22 study visits on the Schedule of Assessments (page 10), are timed to coincide with three-monthly appointments in routine care except nine which are "telephone-only" assessments. Recruitment will be completed within 12 months. Data analysis will be conducted at the end of the trial.

g) Number of sites
18 sites with the capabilities to deliver all the assessments required are signed up to recruit into REMOVAL following regulatory and ethical approval. This follows a detailed feasibility exercise in the five countries involved: Australia, Denmark, Canada, Netherlands and the UK. Five "reserve" sites in the UK have also been identified by way of contingency planning.

7. STUDY POPULATION

7.1 Inclusion Criteria:

1. Type 1 diabetes for five years or more*****
2. age ≥ 40 years
3. 7.0 ≤ HbA1c < 10.0% (53-86 mmol/mol)

*defined as diagnosis below age 40 years AND insulin use within 1 year of diagnosis

AND *three or more* of the following ten CVD risk factors:

(i) BMI > 27 kg/m^2

(ii) current HbA1c > 8.0% (64 mmol/mol)

(iii) known CVD/ peripheral vascular disease

(iv) current smoker

(v) estimated glomerular filtration rate < 90 ml/min per 1.73 m^2 (MDRD equation)

(vi) confirmed micro- or macroalbuminuria [according to local assays and reference ranges - see Appendix 5]

(vii) hypertension (BP ≥ 140/ 90 mmHg or established on antihypertensive treatment)

(viii) dyslipidaemia:
- total cholesterol ≥ 5.0 mmol/L (200 mg/dL);
- OR HDL cholesterol < 1.2 mmol/L (46 mg/dL) [men] or < 1.3 mmol/L (50 mg/dL) [women];
- OR triglycerides ≥ 1.7 mmol/L (150 mg/dL); or established on lipid-lowering treatment

(ix) strong family history of CVD (at least one parent, biological aunt/ uncle, or sibling with myocardial infarction, coronary artery bypass graft or stroke aged < 60 years)

(x) duration of diabetes > 20 years.

7.2 Exclusion Criteria:

(i) Women of childbearing age (i.e. continuing menstrual cycle) not using effective contraception – see Appendix 4.

(ii) Pregnancy and/or lactation; planning to get pregnant or not using effective contraception

(iii) Patients with Acute Coronary Syndrome or Stroke/ Transient Ischaemic Attack within the last three months

(iv) Symptomatic angina on mild or moderate exertion

(v) Stage 3 or 4 heart failure defined according to the NYHA criteria

(vi) Estimated glomerular filtration rate < 45 ml/min/1.73m^2 (MDRD)

(vi) Contraindications to metformin
- hepatic impairment (ALT > 3.0 times ULN)
- known hypersensitivity to metformin
- acute illness [dehydration, severe infection, shock, acute cardiac failure]
- suspected tissue hypoxia

(vii) Metformin treatment for more than three months within last two years

(viii) Anaemia (haemoglobin < 10.0 g/dL)

(ix) Ongoing treatment with oral steroids, pramlintide or GLP-1 agonist therapy

(x) Hypoglycaemia unawareness confirmed as significant by site Principal Investigator

(xi) Impaired cognitive function/ unable to give informed consent

(xii) Previous carotid surgery or inability to capture adequate carotid images

(xiii) Gastroparesis (on gastric emptying studies) confirmed as significant by site Principal Investigator OR more than two hospital admissions with unexplained vomiting in last year

(xiv) history of biochemically-confirmed acidosis (with lactate > 5.0 mmol/L)

(xv) Any coexistent life-threatening condition including diagnosis of cancer within prior two years

(xvi) history of alcohol problem or drug abuse

(xvii) diabetes other than type 1 diabetes (e.g. secondary to pancreatitis, pancreatectomy or primary pancreatic disease)

(xviii) Involvement in a clinical trial involving an investigational medicinal product within the last six months

7.3 Identification of participants and Informed Consent.

a) Pre-screening: Procedures may vary between sites, but all have systems in place for identifying potentially eligible participants in secondary and tertiary care. In many sites, participating investigators will systematically review their clinical record systems for potentially eligible patients and invite them to specific screening visits. In other sites, clinical visit lists will be pre-reviewed in order that potentially eligible individuals can be sent an information sheet by post one week before their routine scheduled review visit. Eligibility criteria of those indicating agreement to be approached will then be checked at the routine visit, and the information sheet and study procedures explained. Potential participants will be given a Patient Information Sheet and an Expression of Interest Form (with prepaid envelope) at this time and will be asked for permission to contact again to discuss further and (if appropriate) arrange a screening visit

b) Screening: A separate non-fasting visit will then be arranged within two weeks at which potential participants will have further time to discuss with the study nurse and doctor. Eligibility criteria will be checked by the study doctor and a research nurse. Risks and side-effects of the active trial medication will be explained. Metformin is long established in clinical practice and has a good safety profile. The main side effects are gastrointestinal disturbances that are dose dependent see below. The procedures for management of hypoglycaemia will be discussed: (http://www.sdrn.org.uk/sites/default/files/sop27_managementofhypoglycaemia.pdf).

c) Pregnancy: Women of childbearing age will be asked about pregnancy status and contraceptive usage and a urine pregnancy test will be conducted (following informed consent – see below – and prior to entering the Run-In Period). There have been

several recent trials of metformin use in pregnancy, especially for treatment of gestational diabetes mellitus. Systematic review of these trials concludes no adverse effects of metformin as compared with insulin therapy.[51,52] Nonetheless in this trial we will not recruit those wanting to become pregnant and will discontinue study drug in women who become pregnant. All such pregnancies will be notified to the pharmacovigilance sponsor using the standard pregnancy notification form of the sponsor and the pregnancy followed to outcome.

d) Run-in Period: Those who choose to participate will be invited to give informed consent as per Good Clinical Practice standards and will be invited to enter the three month Run-In Period. They will be given a unique identifying number based on the country of origin, specific site and sequence of recruitment; this will be used for all subsequent correspondence, transfer of samples and data input. They will be encouraged to conduct frequent home blood glucose monitoring (HBGM) and record the results in a standardised Study Diary designed to record (and permit easy extraction) of changes in insulin dosages and episodes of hypoglycaemia (severe or symptomatic). Technique will be reinforced by study nurses. "Sick day rules" as in usual clinical care will be reinforced and supplemented using information printed in the Study Diary.

Individuals with higher glucose/ HbA1c concentrations at the time of enrolment will be carefully reviewed. Where possible any major changes to insulin regimen thought to be necessary at this time or during study follow-up (e.g. switch from multiple daily injections to pump therapy) will be discussed and implemented in the Run-in Period. BP control will also be reviewed in detail for each participant and any additional assessments necessary scheduled (e.g. 24 hour ambulatory BP monitoring). If these confirm that new therapy is indicated according to the above criteria, this will be discussed and explained. Where there is agreement, such therapy will be initiated (with any additional monitoring required) during the Run-in Period. Cardiovascular risk factors and cholesterol levels will be reviewed with the aim of identifying participants for whom statin therapy may be indicated at present (or in the near future). As in clinical practice, a final decision will be reached in discussion with individual participants.

It is recognised that during the years followed up in the trial many participants will require further changes to be made in their regimens in order to achieve glucose (and other) targets: such changes will be encouraged, supported and implemented.

During the third month of the Run-in Period, participants will be asked to take one tablet of run-in medication (i.e. placebo matching metformin 500 mg) once daily with their evening meal.

e) Baseline assessments: see Schedule of Assessments (page 10). At the beginning of the Run-in Period, relevant items from past medical history, concomitant medications (including duration, type and dose of any previous statin therapy) will be extracted from routine health records and validated with the participant. HbA1c, liver function tests, albuminuria and renal function results will also be captured into the electronic Case Report Form from the recent clinic visit. Where liver function tests and FBC were not performed in routine care within the previous 90 days, or where there are missing data, these will be requested from local laboratories as additional tests.

Height, body weight, ethnicity, and smoking status will be extracted where possible from routine clinic data and validated with patient. The Investigator/ study nurse will be

responsible for extracting validation information from clinical records. Adherence will be assessed by tablet counts 3-6 monthly (which will be documented on the electronic Case Report Form).

f) Randomisation visit: At the end of the three-month Run-In Period, participants will attend after avoiding strenuous exercise and having fasted from 10 pm the previous evening including avoidance of smoking and caffeine (free water intake permitted). This visit will include: (i) check of adherence to study medication over the third month (tablet counts); (ii) measurement of the primary endpoint (carotid IMT); and (iii) repeat anthropometric and metabolic assessments (see Schedule of Assessments – Section 2). Pregnancy testing will be conducted if indicated.

Participants with: (i) less than 70% adherence on tablet counts who are non-adherent in the view of site staff; or (ii) inadequate quality carotid images in the view of the local sonographer will be withdrawn at this stage i.e. before randomization. Those who met HbA1c criteria at the screening visit (R1) but who now have HbA1c < 7.0% (53 mmol/mol) will not be excluded at this visit.

Participants remaining eligible, who satisfy the study inclusion/ exclusion criteria and have provided written informed consent can then be randomized to metformin or placebo by telephone via a call to the study Interactive Voice Response System (IVRS) or electronically via the study portal for the study electronic CRF, see section 14.1.

g) Follow up: see Schedule of Assessments (page 10) and Section 10 (page 31). Participants will then have visits at one month, three months and 3-6 monthly thereafter until study cessation. As almost all patients will be attending for routine clinic care, we envisage that most visits will be conducted by study nurses in the same location and time as usual care and include:

- assessment of adherence
- capture of data on prespecified clinical events (see Section 13)
- safety questionnaire
- Diabetes Treatment Satisfaction Questionnaire
- routine clinic bloods and additional trial specific bloods
- capture of data on prespecified concurrent medications
- capture of data held in Study Diary to be used by patient to record hypoglycaemic episodes and insulin dose

h) Insulin dose titration: At the beginning of the Run-in Period, insulin regimen will be reviewed by the Investigator and optimized against standard of care [target HbA1c < 7.0% (53 mmol/L)] according to local practice under national guidelines. For example, participants may be referred into existing structured education programmes and insulin regimens may be changed e.g. from twice daily biphasic injections to multiple dose injections (MDI), or from MDI to insulin pump therapy.

Study nurses will arrange to telephone participants at 2, 4 and 8 weeks to reinforce frequent HBGM recording and monitoring, encourage hypoglycaemia reporting, discuss ongoing titration of insulin and reinforce concordance with any additional therapies prescribed. Email may be used to facilitate communication and exchange of data as an adjunct to telephone communication when convenient for participants and permitted by the relevant IRBs and Ethics Committees; however, in the UK communications of recommended changes of insulin doses will be by telephone only. Telephone visits will continue in the first four weeks following randomization with calls at 1, 2, 4 and 8 weeks between study nurse and participant during which HBGM results will be discussed.

The need to optimize glycaemic control in all participants will be emphasized at the initial Investigator Meeting and subsequent regular Investigator Teleconferences. To this end, HbA1c data, blinded to randomized therapy, will be reviewed by study centre at the University of Glasgow and fed back to Investigators three monthly with their own site performance plotted against the other sites (anonymised). Therapeutic strategies will be discussed at a teleconferences three and six months after "first-patient, first visit" and six monthly thereafter (or more frequently if required). In those centres in which average glucose control is higher than in other centres, a Steering Committee member (Dr Irene Hamriak) with particular expertise in achievement of glucose targets within trials (including DCCT and ACCORD) will lead on supporting local investigators and participants to achieve targets with every available means.

i) Hypoglycaemia management plan: Symptoms of hypoglycaemia include paleness, shaking, perspiration, a feeling of weakness, increased heart rate, hunger, agitation, difficulty in concentrating, irritability, fatigue, blurred vision, temporary loss of consciousness, confusion, convulsions and coma (see http://www.sdrn.org.uk/sites/default/files/sop27_managementofhypoglycaemia.pdf).

Participants will be asked to record all hypoglycaemic episodes on the relevant page in their Study Diary. Throughout the trial they will be encouraged to check their blood sugar if they feel hypoglycaemic and record the result. However, they should not delay treating symptoms if their blood sugar meter is not readily available. All major (severe) hypoglycaemia should be reported to the Investigator/ nurse team within 24 hours during the metformin dose titration phase of the study (see page 27 below). Contact should be maintained with the participant so that insulin dose can be adjusted appropriately. A hypoglycaemic event will be defined as "an event which causes the symptoms of hypoglycaemia at any level of blood glucose measurement or a blood glucose measurement of less than 2.8.mmols/l with or without symptoms."

Hypoglycaemic events will be categorised into minor, major episodes and any involving unconsciousness as follows:

- **Minor episodes** are treated by the participant and will be resolved by eating some short acting glucose source, followed by a longer acting carbohydrate.
- **Major (or severe) episodes require assistance from** one or more other persons to resolve the event e.g. another family member or paramedic.
- **Major (or severe) episodes involving unconsciousness** (self-reported)

All episodes of severe hypoglycaemia should be reported to study nurses as soon as possible in order that the hypoglycaemia management plan can be followed.

As in the study by Lund et al,[18] we will also record information on self-reported blood/ plasma glucose levels during hypoglycaemic events as captured from the Study Diary.

Following an episode of severe hypoglycaemia, standard causes of hypoglycaemia will be reviewed in order to identify an obvious precipitating factor (insulin dosing error, accidental intravascular injection or other injection site problem, excessive unplanned exercise, missed meal, alcohol consumption, renal impairment, loss of warning signs). HbA1c will be repeated where the most recent available value is more than six weeks previously. Where no obvious reversible precipitant is identified, participants will be advised to reduce insulin dose by 10% over the following month and perform more intensive HBGM. At review, after one month, the aim will be to uptitrate insulin dose once again, *unless* glycaemic target HbA1c < 7.0%/ 53 mmol/mol continues to be met on the reduced dose *or* there have been further episodes of major or unacceptable minor hypoglycaemia.

If the participant has a major hypoglycaemic event and is brought into the Emergency Department, this will only be considered an SAE if the hospital stay is longer than 12 hours. Minor hypoglycaemic episodes (i.e those not requiring assistance from another individual) will not be recorded as an AE.

j) Participant discontinuation: Participants will be free to discontinue study medication at any point during the study. Where possible, follow up in the trial will be continued with continuing titration of insulin doses to target. If informed consent for follow-up is withdrawn, data collected up to self-withdrawal will be included in the study unless the participant wishes otherwise. Clinical samples will be destroyed at their request.

k) Source documents: Participants will be asked to provide informed consent for investigators to obtain copies of official documentation (discharge letter or clinic letter) of any cardiovascular events which will be made available at the request of study monitors. This will also apply for Severe Adverse Event reporting (Section 13, page 34 for which we will obtain copies of official documentation (discharge letter or clinic letter).

l) Long term follow-up: Informed consent will be sought from participants for later long-term follow-up for events occurring following completion of the trial via linkage to national databases (e.g. cardiovascular events/ mortality). Where permitted by ethics/ IRB committees in the various national territories, consent will also be sought for up to 20 years for: (i) contacting the participant's primary care practitioner; (ii) contacting by telephone to complete questionnaire(s); (iii) sending out questionnaire(s); and/or (iv) inviting to follow-up visit(s).

8. MEDICATIONS

Formulation, source and labelling of study medication. The Investigational Medicinal Product (IMP) in the study is metformin 500mg or matching placebo tablets. The metformin tablet is identical in chemical composition to Glucophage 500mg licensed in the UK. See the Summary of Product Characteristics for further details.[53] The matched placebo will be formulated as film-coated tablets matching Glucophage 500 mg tablets (tablet core - cellactose, calcium hydrogenphosphate, magnesium stearate; film coating – hypromellose). Metformin 500mg and placebo tablets will be manufactured in accordance with Good Manufacturing Practice. Both active and placebo medication will be packaged and distributed by Merck-Serono® and supplied to study sites free-of-charge.

The single-blind run-in packs will contain sufficient supplies for 28 days treatment. For the double-blind treatment period, metformin 500 mg and matching placebo tablets, will be packed in matching packs so as to maintain the blind. Each pack contains sufficient supplies for 90 days' treatment with a small overage (excess). Packs will be labelled with a unique pack number that will be used to assign treatment to the patient via the IVRS/IWS system whilst maintaining the blind. Packs will be labeled in accordance with Good Manufacturing Practice and local regulatory requirements. Labelling text will include protocol identification reference, storage caution statements, dosing instructions, batch number and expiry date. A tear-off label will be attached for dispensing purposes.

Drug storage and stability. All study drug must be stored in the original container below 30ºC in a secure location. Although the investigator is ultimately responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study this should be delegated to an appropriately trained pharmacist at the site who will be responsible for the accountability of all used and unused trial supplies. The study drug must be stored in accordance with the study medication label. The study medication provided for use in the study will be used only as directed in the study protocol and only for trial participants.

Drug ordering. Study drug will only be released to the study site once all the appropriate regulatory and governance approvals are in place. The IVRS/IWS will track drug supplies at individual study sites and trigger additional drug supply shipments when required.

Drug accountability. A record of study drug movements will be maintained for accountability purposes. Delegated pharmacy staff will be required to receipt the drug via the IVRS/IWS system and record the dispensing of the study drug to participants on appropriate drug accountability forms. Study drug should not be dispensed or supplied to patients without the appropriate IVRS/IWS notifications being completed. Drug accountability records will include the use by each patient**,** disposal of patient returned medicines and any unused study medication. Accountability records will include dates, quantities, batch numbers, expiration dates and the unique code numbers assigned to the investigational medicinal product and study participants.

Only those supplies intended for use in the study will be dispensed to study participants. Unused study drug will be disposed of in accordance with the guidance in the "Disposal" section below. Study drug will not be used for any purpose other than the present study. Study participants must be instructed to return all original containers including empty, partially filled or unused medication at the end of each treatment period in order that an assessment of medication adherence can be performed.

Accountability logs will be made available for inspection by the study sponsor or their designee and regulatory inspectors. Sites may be required to send anonymised accountability log information to permit remote site monitoring. Study sites will be provided with appropriate drug accountability logs and further detailed written information on study drug management.

Maintaining blinding. Study medication will be assigned electronically or by IVRS (Interactive Voice Response System) supplied by the Robertson Institute for Biostatistics, see section 14.1.

Unblinding. Ceasing treatment, rather than unblinding, will be carried out as far as possible. In any case of hospitalisation with acute illness participants will be advised to discontinue the study medication and inform the relevant clinician. However, where knowledge of treatment may assist emergency treatment, unblinding will be supported. Study participants will be provided with a Patient Alert Card indicating the name of the investigational study drug, the study number, the investigator's name, a 24-hour contact number and information on how to unblind in an emergency: a freephone number will be provided which permits this via a telephone menu system. Several prompts in the system warn the user that they require to be a health professional and to record their name and other pertinent information. For each unblinding an email alert is generated to the Study Coordinator and Chief Investigator. Requests are set at a maximum of 2-3 per 24 hours in case of malicious unblinding. The most likely scenarios for unblinding will be:

confirmed pregnancy, overdose/ accidental ingestion, development of acute renal failure. The Patient Alert Card will be collected from patients at the end of their involvement in the study.

Route of administration. Tablets should be taken orally and swallowed with a glass of water and food (at mealtime).

Double-blind treatment periods dose and dose titration. Metformin as Glucophage 500mg two tablets twice daily (= 1000mg twice daily) or matching placebo tablets. Participants will be asked to titrate up the medication according to usual practice with metformin i.e. they will take one tablet with the evening meal for one week; this will then be increased to additional tablets at weekly intervals with the morning meal, evening meal and then morning meal until a dose of 1000 mg twice daily is achieved. This dose titration, and any insulin adjustment required, will be supported by the weekly telephone calls and guidance printed in the Study Diary. Participants will also be able to call study nurses. If it is found that a participant is only able to tolerate a lower daily dose of study medication, in particular due to gastrointestinal side-effects (see below), this will be permissible and will be documented accordingly.

Risks of treatment. Please refer also to the SmPC.[53]

- Lactic acidosis (blood pH <7.35 with plasma lactate >5.0 mmol/L): This condition has been associated with metformin, usually in cases of acute renal failure, but there remains no evidence that metformin causes lactic acidosis in stable individuals with adequate renal function.[23,24] The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years) and in 8.4 vs 9.0 cases per 100,000 patient years MF vs other diabetes medications of placebo (www.ahrq.gov – Johns Hopkins). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Risk factors are significant renal insufficiency, liver dysfunction, severe acute congestive heart failure and any state where there is risk of hypoperfusion and hypoxaemia.
- Hypoglycaemia: metformin without concomitant diabetes medications has not been shown to cause hypoglycaemia. However, in combination with insulin therapy, there may be a small additional risk, although neither minor or major overall hypoglycaemia risk was statistically elevated in the largest previous trial.[18] Participants will be informed of the symptoms of hypoglycaemia, namely skin pallor, trembling, perspiration, a feeling of weakness and/or hunger, blurred vision and advised to take appropriate corrective measures e.g. sugar-containing drink or food.
- Pregnancy and lactation: metformin is increasingly considered safe in pregnancy[25] but will be an exclusion criterion in this study [see Section 7.3(c)].
- Renal dysfunction: Metformin is excreted renally and may therefore accumulate during significant renal dysfunction. Therefore renal function will be assessed by regular U&E analyses during the trial. Intravascular administration of iodinated contrast agents in particular (e.g. coronary or peripheral angiograms, contrast imaging such as CT scans) may precipitate renal failure with resultant accumulation of metformin. Therefore standard procedures will be followed in such circumstances: the study drug will be discontinued prior to the test and not reinstated until >48 hours later only after it has been verified that renal function has returned to pretest levels.

Choice of eGFR threshold (45mL/min/1.73m^2) in study: Metformin is commonly used safely in patients with moderate chronic renal impairment. In one example in Tayside,[54] 4.8% of patients on metformin in Tayside had a serum creatinine >150umol/L with one case of lactic acidosis in 4600 patient years; that case was related to acute myocardial infarction with secondary acute renal failure and not due to metformin therapy. In another study from Edinburgh,[55] researchers concluded that an eGFR threshold between 36 – 40mL/min/1.73m2 would be useful and safe. The UK National Institute for Clinical Excellence published criteria for use of metformin in chronic renal impairment in 2008.[56] This guidance states that metformin is contraindicated with a serum creatinine >150 micromol/L or eGFR <30 ml/minute/1.73 m^2. Furthermore the guideline recommends that the dose of metformin be reviewed if the serum creatinine exceeds 130 micromol/L or the eGFR is below 45 ml/minute/1.73 m^2.
Accordingly, we have selected a baseline eGFR threshold of 45mL/min/1.73m^2 in this study below which participants will not be recruited. If during participation a subject's eGFR falls to <45mL/min/1.73 m^2 consideration will be given to IMP dose reduction. If during participation a subject's eGFR falls to <30mL/min/1.73 m^2 IMP will be discontinued.

Side effects. Please refer also to the SmPC.[53]
- Very rare (<1/10 000): Chest discomfort, palpitation. These should only be recorded as AEs if associated with an SAE, or if they result in discontinuation of study medication or dose reduction.
- Common (>1/100): taste disturbance, abnormal stools, hypoglycaemia (see below), myalgia, lightheadedness, dyspnoea, nail disorder, rash, sweating increased, chills, flu syndrome, flushing, skin reactions. These should only be recorded as AEs if they result in discontinuation of study medication or dose reduction.
- Common (> 1/100): Decreased vitamin B12 absorption has been reported in long term use, however although plasma levels fell significantly in the HOME trial over 4.3 years,[17] actual levels usually remained within standard reference ranges. Vitamin B12 Serum levels falling below the local assay reference range (150 pmol/L or equivalent) should be recorded as AEs.
- Very common (>1/10): Gastrointestinal effects are most common and may include nausea, vomiting, diarrhoea, abdominal discomfort, headache and loss of appetite. It is well recognised that these side-effects usually resolve spontaneously following initiation of therapy and are minimised if the dose is titrated upwards (as will be done in the study). These events should only be recorded as AEs if they result in discontinuation of study medication or treatment dose reduction.

Serious Adverse Reactions that are expected (<0.5%)
- Lactic acidosis may occur extremely rarely (see page 28 above). It will usually be associated with hospitalisation and reported as an SAE.

Abnormal Laboratory Findings
The following will be specifically recorded as AEs on CRF pages:
- LFTs: any abnormal results of >2.5 times upper limit of normal
- Reduction in eGFR to < 45 ml/min/1.73 m^2 and < 30 ml/min/1.73 m^2
- Hb < 10.0 g/dL AND fall of >1.5 g/dL from baseline
- MCV > 105 fL

Other. Participants will be advised to avoid alcohol excess during the study though this is not an exclusion criteria. Their primary care physician (where applicable) will be

advised that if commencing a medication which may lead to a deterioration in renal function, such as NSAIDs, they should monitor renal function and advise the study doctor of any deterioration.

Interruption of treatment: in preference to permanent treatment withdrawal or withdrawal from the study, investigators will permit treatment interruption of any duration (which will be documented) in any participant who develops any of the following:
- Acute illness: severe infection, shock, acute or clinically unstable cardiac failure
- Acute myocardial infarction or other acute coronary syndrome
- Surgery: treatment will be discontinued 48 hours prior to elective surgery with general anaesthesia and will be recommenced no earlier than 48 hours following surgery and only when it has been confirmed that renal function has returned to pre-operative levels.
- Requirement for investigation involving intravascular iodine-containing contrast agent (as per national guidelines): treatment will be discontinued 48 hours prior to investigation and recommenced no earlier than 48 hours afterwards.
- Anaemia (Hb<10.0 g/dL AND fall of >1.5 g/dL from baseline) considered by the local investigator to be potentially related to study medication.

In these cases, treatment will be restarted where possible in accordance with the Investigator's clinical judgement, local practice, standard-of-care, and national guidelines (renewed titration from a lower starting dose is not usually required unless interruption has been prolonged e.g. more than four weeks). Where treatment interruption has persisted for four weeks or more it will be documented as permanent.

Withdrawal of treatment: Investigators will withdraw from treatment any participant who develops any of the following:
- Pregnancy: discontinue if participant becomes, or intends to become, pregnant
- Development of new contraindications to metformin
    - hepatic impairment (ALT > 3.0 ULN)
    - renal impairment with eGFR <30 mL/min/1.73m^2 during study – see page 28
- Biochemically-confirmed severe lactic acidosis (>5.0 mmol/L with acidosis)
- Hypersensitivity to metformin

Dose reduction of treatment: Where eGFR falls below 45 ml/min/ 1.73m^2 on any measurement Investigators should permanently reduce metformin dose to 500 mg twice daily.

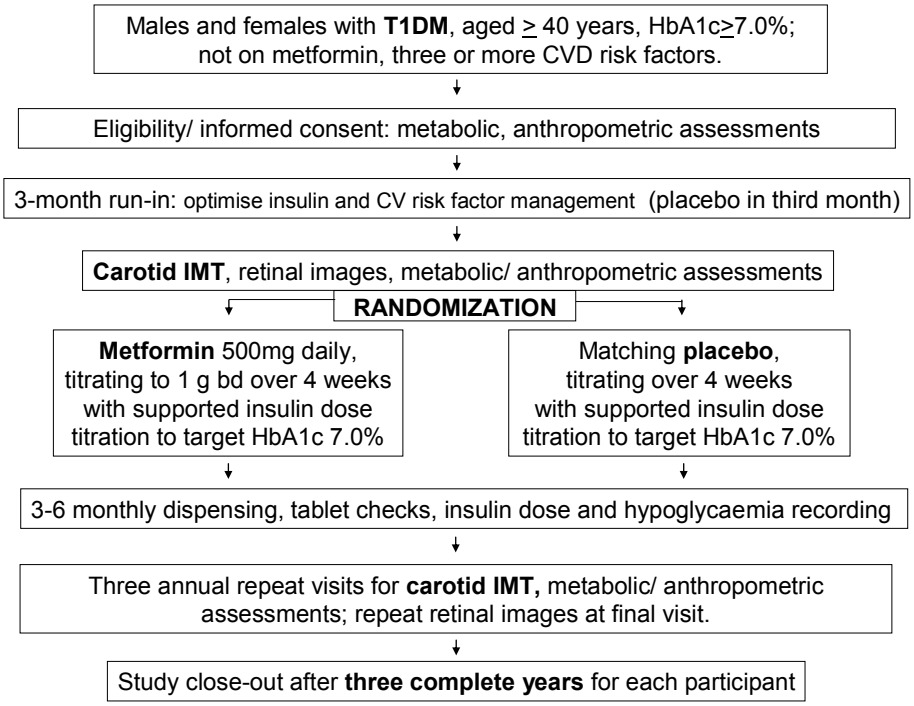
Withdrawal from study: Investigators will withdraw from the study any randomized participants with:
- confirmed pregnancy
- withdrawal of consent for follow-up
- any other reason agreed between the participant and the site Principal Investigator

At the end of the study: No further study medication will be provided.

Assessment of adherence: Tablet counts will be carried out by study nurses following at relevant study visits, including the final clinic visit, to assess adherence. This will be documented in the eCRF. Site medical and nursing staff will also discuss and reinforce adherence to study medication with participants.

Concomitant medication. No concomitant medication is specifically excluded.

9. TIMELINE FOR PARTICIPANT IN STUDY



10. CLINICAL MEASUREMENTS AND EXAMINATIONS AT EACH VISIT

Prescreening visit. Provision of Patient Information Sheet and Expression of Interest form. Request for permission to contact.

Screening Visit (R1 start of Run-in Period) – non-fasting: Informed consent requested: if provided, full medical history, vital signs, weight, waist circumference, height measurements. Dispense study medication (which will be commenced following telephone prompting at visit R4). Give out diary. Treatment satisfaction questionnaire. Hypoglycaemia questionnaire. Titrate insulin. Blood samples (U&E, LFT, HbA1C, local laboratory total cholesterol, HDL and triglycerides, FBC, vitamin B12, C-peptide. microalbuminuria status. Samples for LDL, plasma biomarkers. Urine aliquot. Pregnancy testing if appropriate. Concomitant medications recorded. Review requirement for statin or ACE inhibitor against local practice, national guidelines and standard-of-care.

Telephone visits (R2-R4): insulin dose titration. Questions on adverse events. Visit R4 only: commence study medication.

Study Visit 1 (randomization): Vital signs, weight, waist circumference. Carotid IMT (can be done during last four weeks of Run-In). Retinal imaging. Endothelial function. Collect/ count unused medication. Dispense study medication with advice on dose titration. Give out diary. Hypoglycaemia questionnaire. Treatment satisfaction

questionnaire. Insulin dose titration/ record insulin dose. Blood samples (U&E, LFT, HbA1C, local laboratory total cholesterol, HDL and triglycerides, FBC, vitamin B12, microalbuminuria status if not available from Screening visit R1). Samples for LDL, plasma biomarkers. Lactate. Urine aliquot. Pregnancy testing if appropriate. Concomitant medications recorded. Questions on adverse events. Randomisation.

Telephone Visits 2-4 (0–1 month). Insulin dose titration/ record insulin dose, study medication dose titration (except at telephone visit 4). Questions on adverse events. Concomitant medications and Hypoglycaemia questionnaire (visit 4 only).

Study Visit 5 (3 months). Weight, waist circumference; U&E, LFTs, HbA1c as per routine care. Lactate. Insulin dose titration/ record insulin dose. Hypoglycaemia questionnaire. Dispense study medication. Collect unused medication. In some subjects it will be clear by this stage whether they will only tolerate a single daily dose of study medication. This will be documented and subsequent prescriptions will be reduced accordingly. Remaining study medication will be sent to pharmacy for tablet count. Any change in concomitant medications will be recorded. Questions on adverse events.

Study Visit 6 (6 months). Vital signs, weight, waist circumference; U&E, LFTs, HbA1c as per routine care. Hypoglycaemia questionnaire. Insulin dose titration/ record insulin dose. Give out diary. Dispense study medication. Collect unused medication. Any change in concomitant medications will be recorded. Questions on adverse events.

Telephone Visit 7 (9 months). Insulin dose titration/ record insulin dose. Hypoglycaemia questionnaire. Any change in concomitant medications will be recorded. Questions on adverse events.

Study Visit 8 (12 months). Vital signs, weight, waist circumference. Carotid IMT. Endothelial function. Dispense study medication. Collect unused medication. Hypoglycaemia questionnaire. Treatment satisfaction questionnaire. Insulin dose titration/ record insulin dose. Blood samples (U&E, LFT, HbA1c, local laboratory total cholesterol, HDL and triglycerides, FBC, Vitamin B12, lactate), microalbuminuria status. Samples for LDL, plasma biomarkers. Urine aliquot. Pregnancy testing if appropriate. Concomitant medications recorded. Questions on adverse events.

Telephone Visit 9 (15 months). Insulin dose titration/ record insulin dose. Hypoglycaemia questionnaire. Questions on adverse events.

Study Visit 10 (18 months). Vital signs, weight, waist circumference; U&E, LFTs, HbA1c as per routine care. Insulin dose titration/ record insulin dose. Give out diary. Hypoglycaemia questionnaire. Dispense study medication. Collect unused medication. Any change in concomitant medications will be recorded. Questions on adverse events.

Telephone Visit 11 (21 months). Insulin dose titration/ record insulin dose. Hypoglycaemia questionnaire. Questions on adverse events.

Study Visit 12 (24 months). Vital signs, weight, waist circumference. Carotid IMT. Dispense study medication. Collect unused medication. Hypoglycaemia questionnaire. Treatment satisfaction questionnaire. Insulin dose titration/ record insulin dose. Blood samples (U&E, LFT, HbA1C, local laboratory total cholesterol, HDL and triglycerides, FBC, vitamin B12, lactate), microalbuminuria status. Samples for LDL, plasma

biomarkers. Urine aliquot. Pregnancy testing if appropriate. Concomitant medications recorded. Questions on adverse events.

Telephone Visit 13 (27 months). Insulin dose titration/ record insulin dose. Hypoglycaemia questionnaire. Questions on adverse events.

Study Visit 14 (30 months – omitted for participants randomized after September 2014 as per Appendix 6). Vital signs, weight, waist circumference; U&E, LFTs, HbA1c as per routine care. Insulin dose titration/ record insulin dose. Give out diary. Hypoglycaemia questionnaire. Dispense study medication. Collect unused medication. Any change in concomitant medications will be recorded. Questions on adverse events.

Telephone Visit 15 (33 months – omitted for participants randomized after June 2014 as per Appendix 6). Insulin dose titration/ record insulin dose. Hypoglycaemia questionnaire. Questions on adverse events.

Study Visit 16 (36 months - earlier for participants randomized after March 2014 as per Appendix 6). Vital signs, weight, waist circumference. Carotid IMT. Retinal imaging. Endothelial function. Hypoglycaemia questionnaire. Treatment satisfaction questionnaire. Insulin dose titration/ record insulin dose. Blood samples (U&E, LFT, HbA1C, local laboratory total cholesterol, HDL and triglycerides, FBC, vitamin B12, lactate), microalbuminuria status. Samples for LDL, plasma biomarkers. Urine aliquot. Pregnancy testing if appropriate. Collect all unused medication. Concomitant medications recorded. Questions on adverse events.

Close out Visit 17 (at least one week after Visit 16 but within two weeks). Insulin dose titration following withdrawal of randomized medication. Provide information. Remaining study medication will be sent to pharmacy for tablet count. Questions on adverse events.

Unscheduled visit (at any time): Adverse event reporting; treatment dose reduction or discontinuation; lost medication.

11. MONITORING & EVALUATIONS

Monitoring will be carried out by the study Co-sponsor and out with the UK by delegated organizations with sponsorship equivalent and study insurance responsibilities in Australia, Canada, Denmark and Holland. Remote monitoring will be used as appropriate. The level of monitoring will be based on the outcome of the completed risk assessment; however the minimum requirement per site will be: (i) an initiation visit following the issue of all approvals and prior to the start of recruitment; (ii) a full monitoring visit when the first few patients have been randomized; and (iii) a close-out visit at each site after the last patient has completed the last visit. All Informed Consent Forms will be reviewed; a minimum of 10% of subjects will be reviewed for Source Data Verification (SDV). These will be chosen at random and will consist of both subjects with reported SAEs and those without any reported SAEs. Greater Glasgow and Clyde R&D Governance will agree a Monitoring Plan which will form the template for delegated organizations. The sponsor will obtain and review the monitoring tools and processes of delegated organizations to ensure they satisfy the minimum requirements of the sponsor.

12. ASSESSMENT AND REPORTING OF ADVERSE EVENTS / SERIOUS ADVERSE EVENTS

12.1 Definitions

These are in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004(as amended)**:**

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any adverse event or adverse reaction that

a. results in death
b. is life threatening
c. requires hospitalisation or prolongation of existing hospitalisation
d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect
f. is otherwise considered medically significant by the investigator.

i.e. important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above

Suspected Serious Adverse Reaction (SSAR)
Any adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC).[53]

Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out in the SmPC.[53]

13. RECORDING and REPORTING AEs/SAEs

Adverse events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and as defined within this protocol. (See flow chart)

Metformin is widely available and has been used in the treatment of type 2 diabetes in the UK for more than 50 years, and in the US for more than 10 years. We will therefore collect specific Adverse Events of Medical Interest (see list below): (i) of specific relevance to its potential use in T1DM; (ii) related to the complications of T1DM; and (iii)

related to the study endpoints. All Serious Adverse Events with exception of planned routine hospitalisations and outpatient hospital visits will be collected within the eCRF.

Adverse Events of Medical Interest

- **Hypoglycaemia:** as per the Steno Hypoglycaemia Questionnaire (Appendix 3) administered at study visits as per the Schedule of Assessments
- **Gastrointestinal:** Diarrhoea, abdominal pain, nausea and vomiting, constipation, loss of appetite resulting in discontinuation of study medication or dose reduction.
- **Cardiovascular:** chest discomfort, palpitations resulting in discontinuation of study medication or dose reduction
- **Any revascularisation:** coronary (angioplasty/ stent/ CABG); carotid (endarterectomy); peripheral (angioplasty/ stent/ surgical)
- **Foot:** ulceration; lower limb surgical procedure: amputation (digit/ below knee/ above knee); ulcer debridement.
- **Eye:** laser treatment; vitrectomy; cataract surgery; vitreous haemorrhage; retinal vein or artery occusion; loss of vision in one eye.
- **Neurological:** headache resulting in discontinuation of study medication or dose reduction
- **Metabolic:** biochemically-confirmed unexplained acidosis with lactate > 5.0 mmol/L, abnormal LFTS results >2.5 times upper limit of normal, or reduction in eGFR of > 25%
- **Other:** hypersensitivity reaction to metformin, overdose"

As outlined above, the following symptoms **should only be reported as AEs if leading to an SAE or treatment dose reduction/ discontinuation:**

- diarrhoea, abdominal pain, nausea and vomiting, constipation, loss of appetite
- taste disturbance, abnormal stools, nail disorder, rash
- increased sweating, chills, flu syndrome, flushing, skin reactions
- chest pain, palpitations
- headache, myalgia, light-headedness

At all study visits patients will be questioned about any illnesses, hospitalisations and the expected adverse reactions/ events listed above. Completion of patient diaries will aid the research team to elicit adverse events. In addition to adverse event data, at annual visits we will measure liver function tests (AST, ALT and γGT) and a Full Blood Count.

Full details of AEs of medical interest and SAEs including the nature of the event, start and stop dates, severity, relationship to study drug and outcome will be recorded in the subject's medical records and in the eCRF. AEs will be monitored and followed up until satisfactory resolution or stabilization.

All Serious Adverse Events must be assessed for seriousness**,** causality, severity (which will be undertaken by Principal Investigators at each site) and expectedness (which is the responsibility of the Chief Investigator).

Severity. This should be assessed and described using the following categories:

Mild	awareness of event but easily tolerated
Moderate	discomfort enough to cause some interference with usual activity
Severe	inability to carry out usual activity.

All SAEs arising during the clinical trial will be reported by entering the details into the eCRF as soon as reasonably practicable and in any event within 24 hours of first becoming aware of the event. Any follow up information should also be reported.

Serious adverse events recorded in the eCRF will be transferred to the Glasgow Pharmacovigilance database.

SAEs that occur at any time after the inclusion of the subject in the study (defined as the time when the participant signs the informed consent) up to 30 days after the subject completed or discontinued the study will be reported.

The participant is considered to have completed the study after the completion of the last visit when any remaining medication will be collected. The date of discontinuation is when a subject and/or investigator determines that the subject can no longer comply with the requirements for any further study visits or evaluations.

All **SUSARS** will be reported an expedited fashion to the MHRA and other relevant regulatory authorities as well as to the relevant IRBs and Ethics Committees.

Fatal or life threatening SUSARs. Not later than 7 days after the CI had information that the case fulfilled the criteria for a fatal or life threatening SUSAR, and any follow up information within a further 8 days.

All other SUSARs. Not later than 15 days after the CI had information that the case fulfilled the criteria for a SUSAR. The Glasgow Clinical Trials Unit Pharmacovigilance (PV) Office will report SUSARs on behalf of the CI to the MHRA and other relevant regulatory authorities via the eSUSAR reporting system and to the Ethics committee in paper format.

A copy of the SUSAR report will be forwarded by the PV Office to the sponsor's representative in other host countries for submission as appropriate to the national ethical and regulatory authorities.

The Principal Investigator at each site will be informed about any SUSARs which have occurred during the study by the Pharmacovigilance Office in liaison with the Project Manager. A report will also be placed on the study web portal.

Unblinding. In the event of a SUSAR, participant treatment will be unblinded by the sponsor before reporting to the MHRA and REC. SUSAR reporting to the participating investigators will be blinded.

Pregnancy is not considered an AE or SAE. However, Principal Investigators will report pregnancy information on any female participant or female partner of a male participant who becomes pregnant while participating in the Trial to the sponsor within two weeks of

first becoming aware of the pregnancy. This report should be provided to the PV office on the Pregnancy Notification Form provide by the sponsor (on www.glasgowctu.org) The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded by the PI to the PV Office.

Annual Safety Report

As required by the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), an annual safety report will be prepared by the CI in liaison with the PV Office.

This report will be submitted to the UK ethical and regulatory authorities within 60 days of the anniversary of the issue of the Clinical Trials Authorisation (CTA) by the PV Office on behalf of the CI. A copy of the report will be forwarded by the PV Office to the sponsor's representative in other host countries for submission as appropriate to the national ethical and regulatory authorities.

14. CRF REPORTING AND DATA COLLECTION

14.1 Randomisation

A central randomisation facility based at the Robertson Centre for Biostatistics, University of Glasgow will be contacted either by telephone or by a web-based service and randomised therapy will be assigned. Randomisation will be stratified by study site and based on randomly permuted blocks allocated within each trial centre.

14.2 Emergency Unblinding Procedures

Breaking of the study blind will be performed only: (i) for SUSARs; and, (ii) where knowledge of the treatment is considered by local health personnel absolutely necessary for further management of the patient. A central unblinding facility based at the Robertson Centre for Biostatistics, University of Glasgow, will be available by telephone (see Section 8, page 26). Notification of all unblinding will be sent to the Chief Investigator.

14.3 Case Report Forms / Electronic Data Record

An electronic case report form (e-CRF) will be used to collect study data at each site. The e-CRF will be developed by the study Data Centre at the Robertson Centre for Biostatistics, University of Glasgow. Access to the e-CRF will be restricted, with only authorised site-specific personnel able to make entries or amendments to their patients' data. It is the investigator's responsibility to ensure completion and to review and approve all data captured in the e-CRF.

Data will be validated at the point of entry into the e-CRF and at regular intervals during the study. Data discrepancies will be flagged to the study site coordinator and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

14.4 Data Handling

The Robertson Centre for Biostatistics at the University of Glasgow will be responsible for collating, cleaning and analysing the data for the study. The Robertson Centre will also be responsible for data back-up and security. This centre will also manage the electronic reporting of SUSARS on behalf of the sponsor.

14.5 Data Transfers

Data for IMT and retinal image data analysis will be transferred at agreed intervals during the study via the study web portal. A data transfer protocol will be developed and approved by the study team involved in the generation of these data/images and the Robertson Centre for Biostatistics.

14.6 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigators agree to keep records, including the identity of all participating subjects (sufficient information to link records, all original signed informed consent forms serious adverse event forms, source documents, and detailed records of treatment disposition. The records should be retained by the study country coordinators and investigator according to ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

15. STATISTICAL ANALYSIS

Prof Ian Ford and Prof H Colhoun will draft the Statistical Analysis Plan (with the study statistician). Primary analysis will be done at the Robertson Centre/ University of Glasgow CTU with University of Dundee receiving copy of stable dataset on study database lock. University of Dundee will maintain a copy of the endpoint and safety datasets and will write data analysis code that mirrors the CTU analyses as validation.

Professor Ian Ford, Director of the Robertson Centre for Biostatistics (RCB) at the University of Glasgow, a co-investigator on the study, has calculated that we need to recruit 500 participants (see Section 6; statistical considerations, page 18). Data management, statistical analysis and other aspects of clinical trial support will be supervised by Professor Ford.

The data for the CCA cIMT (cIMT) will be analysed using repeated measures regression analysis using all data available for each subject. The hypothesis is that all participants have individual regression lines defining their own disease progression over time and that, on average, the slopes of these regression lines will be reduced by metformin (Glucophage 500 mg bd) treatment. The analysis will be adjusted for cardiovascular risk factors which are strong predictors of IMT progression over and above the baseline measurement to minimise the residual standard deviation and thereby maximise the power of the study. Regression model effect estimates with 95% confidence intervals and associated p-values will be calculated to compare patterns of CCA cIMT progression (primary end-point).

The primary analysis will be extended to determine if the metabolic effects of metformin could potentially explain differential effects on progression of cIMT.

We will report baseline characteristics by treatment group to determine whether randomization was successfully achieved. We will tabulate SARs and SUSARS and the adverse reactions, including hypoglycaemic episodes listed above. The effect of

metformin on the primary endpoint and secondary endpoints will be evaluated using standard mixed linear and survival analysis methods.

Premature withdrawal, treatment non-adherence and other protocol deviations will be summarised by treatment group without formal statistical comparison. The primary analysis will be repeated for the subgroup of patients that completed the study according to the protocol. Adverse events will be summarised by treatment group, as a whole and by MedDRA system organ class and preferred term, without formal statistical comparison. For the purposes of analysis, visit attendance out with three weeks of the intended study visit date will constitute a protocol deviation.

A full Statistical Analysis Plan covering all study outcomes will be created and signed off before study close-out and unblinding.

The RCB and the Glasgow Clinical Trials Unit (GCTU) within which it sits, have significant experience of coordinating and analysing clinical trials. All aspects of the study will be conducted to satisfy GCTU standard operating procedures that are compliant with existing guidelines and regulations for the conduct of clinical trials. GCTU has UKCRN registration and all aspects of data management and statistical analysis will be conducted in accordance with ISO 9001:2008 for quality systems and TickIT for software development.

16. PUBLICATION & ARCHIVING

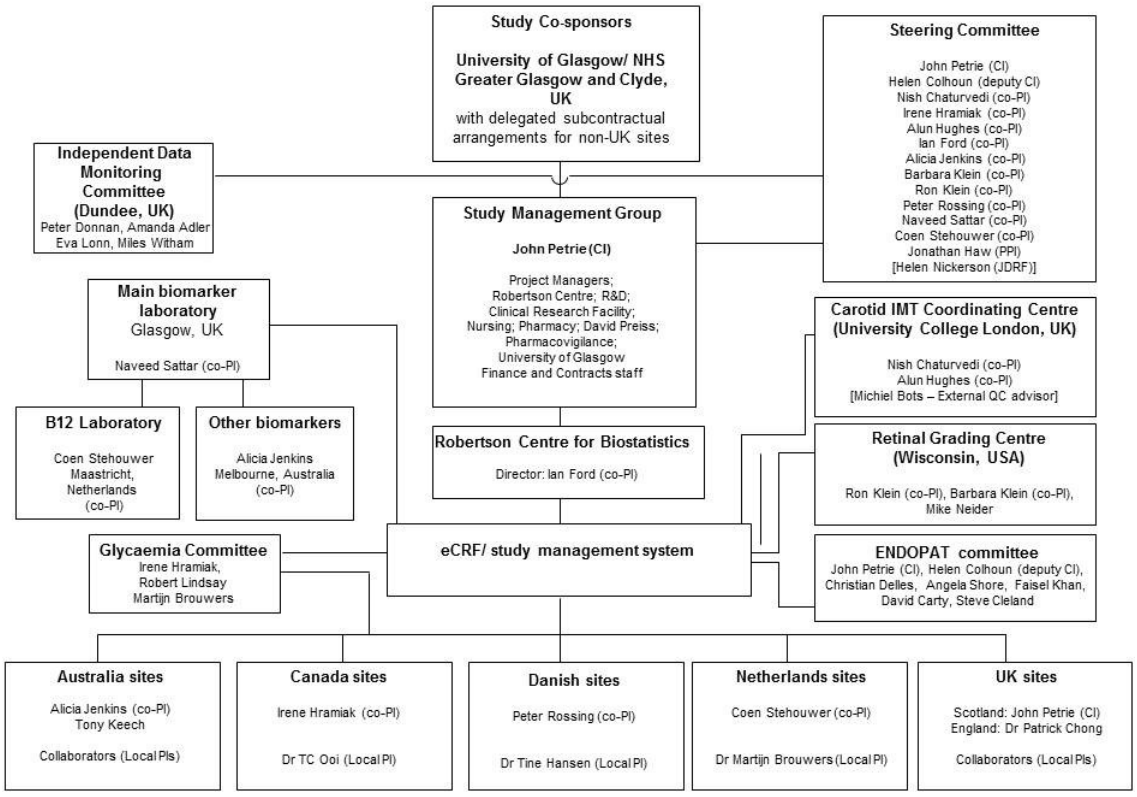
Results from this study will be submitted for publication in a peer reviewed journal at a maximum of 6 months post database lock. Given the importance of the subject we anticipate publication in high ranking journals. The work will also be presented at major international and national meetings. Data from the study will be stored by the Chief Investigator for a minimum of 10 years. A final report of the study will be provided to the MHRA and CSO as per requirements.

17. CHANGES TO PROTOCOL

Any changes to the protocol will be submitted to the Sponsor and, if considered substantial, will be submitted thereafter to the MHRA and to the relevant Ethics Committee.

18. MANAGEMENT AND COMMITTEE STRUCTURE

A Steering Committee will oversee the progress of the trial. It will consist of key investigators, key nominated collaborators, a patient representative, and a (non-voting) funding body representative. Its functions will be to provide oversight of the protocol, study progress, study analysis and dissemination of results. It will meet at least annually and will take any final decision on study termination based on DSMB recommendation. The Study Coordinator will be in attendance at Steering Committee meetings.



A Study Management Group will consist of the Chief Investigator and representatives of the Project Management Unit, the Sponsor, the Robertson Centre for Biostatistics, research pharmacy, the Pharmacovigilance Office, the Study Monitoring Team and other relevant personnel as appropriate. Its functions are to manage the trial day-to-day, oversee recruitment, and progress towards analysis and dissemination of trial results. Minutes will be disseminated to non-UK National Coordinators.

A Data and Safety Monitoring Board (DSMB) will be established by the University of Dundee with an independent statistician who will be provided with a cleaned but blinded dataset every six months. The study statistician will write the code for running DSMB analyses but the unblinding and running of analyses will be done by DSMB statistician. The DSMB will make recommendations to the Steering Committee on any safety issues.

All study committees will have formal Charters describing the roles and responsibilities of the members.

REFERENCES

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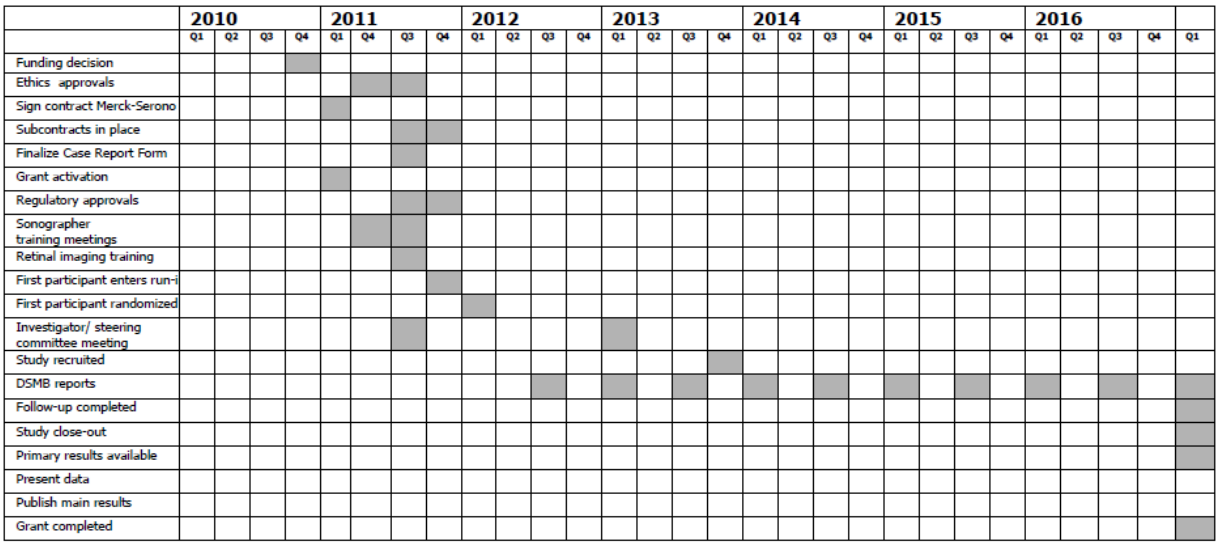
Appendix 1

REMOVAL study national Principal Investigators

Country (City)	National PI	Address
Australia	Alicia Jenkins	NHMRC Clinical Trials Centre, Sydney Medical School, Levels 4-6 Parramatta Road, Camperdown, NSW 2050, Australia
Canada	Irene Hramiak	St. Joseph's Health Care, 268 Grosvenor Street, London, Ontario N6A 4V2, Canada
Denmark	Peter Rossing	Steno Diabetes Center A/S, Niels Steensens Vej 2, DK-2820, Gentofte, Denmark
Netherlands	Coen Stehouwer	Maastricht University Medical Centre, PO Box 5800, 6202 AZ Maastricht, The Netherlands
UK	John Petrie	BHF Cardiovascular Research Centre, University of Glasgow 126 University Place Glasgow G12 8TA, UK

Appendix 2

Planned study timelines



Appendix 3: Steno Hypoglycaemia Questionnaire

HYPOGLYCAEMIA

Minor events |__||__| no. of events
(since last contact)

Major events (without coma*) |__||__| no. of events (since last contact) BG: |__||__|,|__| mmol/l (average)

- Potential cause:

Too little food ☐ 1 Physical activity ☐ 2 Alcohol ☐ 3 Betablocker ☐ 4 Insulin ☐ 5 Unknown ☐ 6

- Treatment:

Carbohydrate ☐ 1 Glucagon ☐ 2 Glucose iv ☐ 3 Other ……. ☐ 4

Major events (with coma*) |__||__| no. of events (since last contact) BG: |__||__|,|__| mmol/l (average)

- Potential cause:

Too little food ☐ 1 Physical activity ☐ 2 Alcohol ☐ 3 Betablocker ☐ 4 Insulin ☐ 5 Unknown ☐ 6

- Treatment:

Carbohydrate ☐ 1 Glucagon ☐ 2 Glucose iv ☐ 3 Other ……. ☐ 4

* Coma is defined as unconsciousness during a hypoglycaemic event.
Major event is one requiring assistance for recovery

Appendix 4: Contraception

For women of childbearing potential in REMOVAL, acceptable forms of effective contraception include:*

1. Established use of oral, injected or implanted hormonal methods of contraception (note oestrogens may decrease glucose-lowering effect of oral glucose-lowering medications including metformin)

2. Placement of an intrauterine device (IUD) or intrauterine system (IUS). *[Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g. steel or copper wire]*

3. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) – must be combined with spermicidal foam/gel/film/cream/suppository.

4. Sole male partner has been sterilised with appropriate post-vasectomy documentation of the absence of sperm in ejaculate.

5. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

***See MHRA "Clarification of contraceptive wording in clinical trials conducted in the UK - Version 2 amended 21st May 2010"**

Appendix 5: Microalbuminuria definitions

For the presence or absence of microalbuminuria to be judged in relation to the inclusion criteria, the results of local assays conducted on at least two separate urine specimens must be available. The final decision will lie with the site Principal Investigator according to local protocols, guided by the following criteria.

Units	Definition	
	Male	**Female**
First morning sample		
mg/ mmol[1]	≥ 2.5	≥ 3.5
mg/g[1]	≥ 25	≥ 35
μg/ mg[1]	≥ 25	≥ 35
mg/L*	≥30	
Timed		
μg/ min	>20	
mg/ 24 hours	>30	
[1]ACR = albumin: creatinine ratio; *simple concentration (not preferred method)		

Occurrence of new microalbuminuria during the trial will be judged according to local assays, the results of which will be recorded in the eCRF.

Central assays may later be performed on stored urine aliquots to support the microabuminuria secondary endpoint analysis.

Appendix 6: Abbreviated follow up (final 50 participants)

Calendar month randomized	Number of participants affected	Visit window adjustment	Abbreviation of follow-up (months)
Up to end March 2014	(379)	Visit 15 – Visit 16 window 3 months (per protocol)	0 (per protocol)
April 2014	8	Visit 15 – Visit 16 window reduced to 2 months	1
May 2014	8	Visit 15 – Visit 16 window reduced to 1 months	2
June 2014	12	Visit 15 omitted (i.e. Visit 14 – Visit 16 window reduced to 3 months)	3
July 2014	7	Visit 14 – Visit 16 window reduced to 2 months	4
August 2014	6	Visit 14 – Visit 16 window reduced to 1 month	5
September 2014	7	Visit 14 and 15 omitted (i.e. Visit 13 – Visit 16 window reduced to 3 months)	6
October 2014	1	Visit 13 – Visit 16 window reduced to 2 months	7
November 2014	1	Visit 13 – Visit 16 window reduced to 1 month	8
	50		

Please refer to Schedule of Assessments (page 10) for visit windows "per protocol"

These arrangements affect a total of 50 participants at the following sites *(site number)*:
Canada: Ottawa *(12)*
Australia: Royal Melbourne *(16)*, Prince Alfred, Sydney *(17)*
Denmark: Steno Diabetes Center *(13)*
Netherlands: Maastricht *(14)*
UK: Aberdeen *(21)*, Aintree *(7)*, Ayr *(24)*, Royal Infirmary Edinburgh *(19)*, Hull *(6)*, London(UK)*(8)*