Study Protocol

The iDiabetes Platform: Enhanced Phenotyping of Patients with Diabetes for Precision Diagnosis, Prognosis and Treatment

Study Acronym	iDiabetes
Sponsor	University of Dundee
Sponsor/R&D Number	2-026-22
Funder	Chief Scientist Office, Scottish Government
Chief Investigator	Professor Ewan Pearson
REC Number	23/ES/0008
ISCRTN Number	18000901
Version number and date	V4, 21st March 2024

This protocol has regard for the HRA guidance and order of content V1.2 March 2016

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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

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

Chief Investigator: Prof Ewan Pearson

Signature: Date:

27/03/2024

I. LIST OF ABBREVIATIONS

A&E	Accident and Emergency department
ACE	Angiotensin Converting Enzyme inhibitors
AE	Adverse Event
ACR	Albumin-to-creatinine ratio
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blockers
AST	Aspartate Transaminase
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CI	Chief Investigator
CPIC	Clinical Pharmacogenetics Implementation Consortium
DOCMAN	Document Management System
DPWG	Dutch Pharmacogenetics Working Group
ECHO	Echocardiogram
eGFR	estimated Glomerular Filtration Rate
ECG	Electrocardiogram
EDTA	EthyleneDiamine Tetraacetic Acid
ELF	Enhanced Liver Fibrosis score
FIB-4	Fibrosis-4 Score
GCP	Good Clinical Practice
HbA1c	Haemoglobin A1c
HCA	Health Care Assistant
HIC	Health Informatics Centre
HF	Heart Failure
ICE	Integrated Clinical Environment (order comms)

iDiabetes	Intelligent Diabetes – an enhanced precision approach to diabetes care
iLFT	Intelligent Liver Function Tests
ISRCTN	International Standard Randomised Controlled Trial Number
ISO	International Standards Organisation
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
MB	Management Board
MWDH	My Way Digital Health
MDMW	My Diabetes My Way
MI	Myocardial Infarction
MODY	Maturity-onset diabetes of the young
NAFLD	Non-alcoholic fatty liver disease
NFS	NAFLD Fibrosis Score
PCI	Percutaneous Coronary Intervention
PPI	Patient and Public Involvement
PRS	Polygenic Risk Score
REC	Research Ethics Committee
SAB	Scientific Advisory Board
SAS	Scottish Ambulance Service
SCI Diabetes	The national clinical diabetes system used across Scotland for all primary and secondary diabetes care.
SCI Store	SCI Store is an information repository that provides clinicians with secure access to patient information at the point of care
SH	Severe Hypoglycaemia
SHARE	The Scottish Health Research Register and Biobank
SLD	Steatotic Liver Disease
SOP	Standard Operating Procedure
SU	Sulphonylurea
TMF	Trial Master File
TRE	Trusted Research Environment

T1D	Type 1 diabetes
T2D	Type 2 diabetes
UKCA	UK Conformity Assessed
UKPDS	UK Prospective Diabetes Study

II. STUDY SUMMARY

Study Title	The iDiabetes Platform: Enhanced Phenotyping of Patients with Diabetes for Precision Diagnosis, Prognosis and Treatment	
Short Title	iDiabetes	
Study Design	Cluster randomised controlled study	
Study Participants	Patients with diabetes	
Planned Sample Size	7,500 Usual care 7,500 iDiabetes care 7,500 iDiabetesPlus care	
Study duration	4 years with up to 15 years long term follow up	
Planned Study Period	15-month study entry period	
	Objectives	Outcome Measures
Primary	Does the implementation of a multifactorial precision platform improve outcomes for patients with diabetes?	Hierarchical: 1) All-cause mortality 2) All-cause hospitalisations 3) >40% fall in eGFR 4) Absolute HbA1c reduction >0.5% at 2 years

III. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Chief Scientist Office, Scottish Government	Financial support and support in kind

IV. ROLE OF STUDY SPONSOR AND FUNDER

The roles and responsibilities of the Sponsor and Funder will be detailed in the Clinical Research Agreement.

V. ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

The study will be coordinated by a Study Management Board, consisting of the grant holders, including the CI, collaborators, and programme manager. Details of membership of the SMB will be held in the TMF. The Study Management Board will meet regularly to ensure all practical details of the study are progressing and working well and everyone within the study understands them. Minutes of the MB meetings will be maintained in the TMF.

A Scientific Advisory Board will be convened for this study composed of independent experts which will meet at least annually. The board will monitor and supervise the project to its overall objectives. A Terms of Reference has been agreed.

The CI will be responsible for the conduct of the study. Site delegate(s) will oversee the study and will be accountable to the CI.

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP).

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from an NHS REC. Appropriate NHS R&D permissions will be obtained prior to commencement of the study.

VI. PROTOCOL CONTRIBUTORS

Chief Investigator, Professor Ewan Pearson: Review and final approval

Co-investigator, Professor Rory McCrimmon, Review

Co-Investigator, Professor John Dillon, Review

Co-Investigator, Professor Chim Lang, Review

Co-Investigator, Dr Samira Bell, Review

Co-Investigator, Professor Tim Croudace, Review

Co-Investigator, Dr Scott Cunningham, Review

Co-Investigator, Dr Cameron Munro, Review

Co-Investigator, Professor Mandy Ryan, Review

Co-Investigator, Professor Colin Palmer, Review

Co-Investigator, Dr Ify Mordi, Review

Co-Investigator, Dr Alexander Doney, Review

Co-Investigator, Professor Peter Donnan, Review

Co-Investigator, Professor Sam Philip, Review

Co-Investigator, Dr Albert Farre, Review

Co-Investigator, Gerry Tosh, Review

Co-Investigator, Dr Susan Morrow, Review

Clinical Research Fellow, Dr Damien Leith, Review

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Clinical Research Fellow, Dr Rachael Barrrett, Review

Clinical Research Fellow, Dr Mya Lelt Win, Review

Programme Manager, Stephanie McKenzie, Review

VII. KEY WORDS: DIABETES, PRECISION MEDICINE, PHENOTYPING

1. STUDY OVERVIEW

iDiabetes (intelligent Diabetes) will provide a precision approach to diabetes care. This will be achieved by making better use of the health data that is already routinely collected for patients with diabetes across Scotland, supplemented by additional blood tests that are taken to enable better risk prediction for diabetes complications. iDiabetes will be fully implemented within the NHS environment, with near-real time access to anonymised data to evaluate efficacy and cost effectiveness, and to support new discovery and model development.

iDiabetes will be implemented for 15,000 patients with diabetes in Tayside, using a cluster randomised design. GP practices will be randomised to usual care, iDiabetes care or iDiabetesPlus care, with evaluation to see if the iDiabetes care approaches result in better outcomes and whether they are cost effective. Patients will be informed if their GP practice has been randomised to iDiabetes care or iDiabetesPlus care and will be given the option to opt out if they would rather receive usual care.

iDiabetesPlus patients will have additional blood tests performed on the bloods taken at their annual review screening visit. These additional blood tests will measure insulin sensitivity and beta-cell function, cardiac biomarkers (NT-proBNP and hsTroponin I), liver fibrosis markers (utilising non-invasive fibrosis scores [FIB-4, NAFLD Fibrosis Score] and Enhanced Liver Fibrosis [ELF] test) and a genotyping array to determine Type 1 diabetes genetic risk where needed and coronary artery disease (CAD) polygenic risk score. These blood tests will be used in combination with a patient's health records to predict risks and guide treatment choice. The diabetes care team will receive treatment or management recommendations and the patients will be able to see their results and recommendations on My Diabetes My Way. iDiabetes will only make recommendations – it is up to the patient and diabetes care team to agree whether to accept these recommendations.

We will evaluate the efficacy of the programme using a hierarchical outcome as our endpoint to evaluate reduction in mortality, hospitalisation, renal function decline and HbA1c. A comprehensive health economic model will be developed to assess cost effectiveness of this approach.

The iDiabetes IQ engine (providing the decision support) developed by the University of Dundee iDiabetes developers, will be registered as a Class 1 medical device (under the UK Medical Device Directive) prior to the study start by the iDiabetes group. The device manufacturer will be Tayside Health Board.

1.1. Assessment and Management of Risk

OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Hypothesis

Implementation of a precision medicine platform will improve outcomes of patients with diabetes.

Justification for the composite primary outcome

The primary outcome will be a hierarchical outcome similar to that utilised in the ATTR-ACT study (Maurer et al., 2018). In this method, which can be applied to a cluster randomised design (Zhang & Jeong, 2021) outcomes are ranked in order of 'loss', based on clinical priorities, and a hierarchical win ratio method is applied (Pocock et al., 2012). The approach uses a hierarchical composite as the primary outcome giving greater statistical power, with the win-ratio providing an easily calculated and understood outcome metric. The approach also allows combination of time to event, as well as physiological measures (Redfors et al., 2020). We can only use measures that are available in the enhanced phenotyping group and the usual care group, so results such as liver fat, or quality of life cannot be used, therefore in decreasing order of importance, we rank: 1) All-cause mortality as this is a big 'loss' and failure to consider mortality can introduce issues of competing risk – i.e. those that die can't have any of the other events. 2) All-cause hospitalisations as these are common – occurring in 33.2/100 patient years for patients with T2DM – and a major burden to patients and healthcare systems. 3) Renal function decline as a major morbidity. In keeping with clinical trials for focusing on renal outcomes we will use an eGFR fall of >40% as the endpoint (in an unselected population this is seen in 2% of the population over 2 years). 4) HbA1c change as HbA1c is a major driver of both micro and macrovascular disease in diabetes; here we choose an HbA1c reduction >0.5% (5.5mmol/mol) as a clinically significant win (this occurs in about 25% of a population with T2D over 2 years). We do not rank HbA1c higher despite its importance in diabetes as many of our interventions (for HF, CAD, Renal disease, NAFLD) are HbA1c independent where HbA1c lowering is not our primary goal.

1.2. Table of objectives/outcomes

Objectives	**Outcome Measures**
Does the implementation of a multifactorial precision pipeline improve outcomes for patients with diabetes?	A composite hierarchical outcome (in decreasing order or importance)
	1) All -cause mortality
	2) All-cause hospitalisations
	3) >40% reduction in eGFR

	4) Absolute HbA1c deterioration >0.5% (>5.5mmol/mol) at 2 years
Secondary Objectives	**Outcome Measures**
	Individual components of primary composite outcome
	Heart Failure hospitalisation
	Adherence to medication
	Severe hypoglycaemia (including SAS paramedic)
	Proportion of people treated according to guidelines

2. STUDY DESIGN

2.1. Study design

This is a cluster randomised controlled study, with each GP practice forming a cluster. Up to 60 GP practices in Tayside will be randomised to usual care, iDiabetes care or iDiabetesPlus care. Randomisation will occur prior to the project start. The intervention is an implementation of a diabetes clinical decision support system, implemented and evaluated over a 3-3 year period. The decision support system may need to be changed in line with changing clinical care standards over this period.

Usual care: Patients will attend for their annual diabetes review appointment and receive their usual standard of care. No action is needed for the study by the practice team or patient.

iDiabetes care: Patients will attend for their annual review appointment and be entered into iDiabetes. Using the patient data from SCI-Diabetes and routine blood results, the iDiabetes platform will promote the implementation of guideline-based care. Results and recommendations will be made available to patients' health care teams via the Diabetes dashboard and patients can access these via MyDiabetesMyWay or their HCP.

iDiabetesPlus care: As for the iDiabetes group above, but with the addition of enhanced blood testing (see 2.3). It includes the use of precision prediction models to predict best drug and risk of hypoglycaemia, and with the inclusion of biomarkers to improve the diagnosis of diabetes, the allocation of treatment to those with cardiorenal or liver risk, and monitoring of renal function decline.

15,000 patients will enter the two iDiabetes care pathways and all groups will be followed up using their routine health record data for ~2 years to the primary end point. Ongoing analysis will continue using linked data for up to 15 years.

Patients at iDiabetes and iDiabetes Plus practices will receive a flyer in the mail or by email from their practice prior to their annual review appointment. These will also be available in each of the intervention GP practices and care and treatment centres along with iDiabetes posters.

In addition to the flyer, there will be a dedicated website, www.idiabetes.org.uk, where there is more detailed study information and an FAQ section covering all aspects of the study. This website will also have contact details for the study team..

Patients within either of the iDiabetes groups will have the option to opt out and receive usual care at any time (see 5.10).

2.2. Annual Review: Entry into iDiabetes

Patients with diabetes will enter the iDiabetes care pathways when they attend for their routine diabetes screening visit within primary care. This will either be at their GP practice or at a primary care 'Care and Treatment Centre'. .

HCPs will use the primary care page, which collects routine patient and clinical data, within Sci-Diabetes for all patients attending for their annual diabetes review. If a patient is from an iDiabetesPlus practice, the page will alert the HCP to request the iDiabetesPlus bloods. This page also includes an option for patient opt out and to provide the patient's email address so information on how to sign up to MDMW can be sent (see 2.4) if agreeable.

2.3. Blood samples

Patients in all three groups will have their routine bloods taken at their annual review visit.

Only patients in iDiabetesPlus practices will undergo additional testing; biochemistry and genetics for all and, for patients with type 1 diabetes only, immunology (see details below).

NHS Tayside Laboratory Tests – iDiabetesPlus patients

a. Biochemistry
   Blood taken will be cascade tested in a similar way to the iLFTs that are now standard across NHS Tayside.
   All patients will have c-peptide and glucose measured – to determine HOMA B and HOMA S (measures of beta-cell function and insulin sensitivity) in Type 2 diabetes and for use in the Type 1 diabetes diagnostic pathway for Type 1 diabetes.
   All patients over the age of 40 years will have NT-proBNP and hsTroponin I measured. A modified version of the iLFT pathway will be performed in all iDiabetesPlus patients, with those with an ALT level >30 automatically cascading non-invasive fibrosis scoring (Fib-4, NAFLD Fibrosis Score +/- ELF score) and a limited liver aetiology screen (hepatitis B & C and markers suggestive of hereditary haemochromatosis).

b. Immunology

In line with the recently introduced Type 1 diagnostic pathway in Scotland, all patients with Type 1 diabetes diagnosed within the last 3 years will have pancreatic autoantibodies measured. Those with type 1 diabetes with a duration of >3 years who have a c-peptide between 200 and 900 pmol/L will proceed to pancreatic autoantibody testing.

c. Genetics

All patient samples will be analysed with a genotyping array. This array measures ~1M variants across the genome and will be imputed against the latest imputation platform (currently Haplotype Reference Consortium). This will be used to derive a Coronary Artery Disease Polygenic Risk Score and a Type 1 diabetes polygenic risk score.

The use of genetic testing in this way has been discussed and agreed with our PPI group. They were reassured by the following:

1. We are doing genotyping not sequencing. Sequencing analyses every base pair in the genome (or a targeted gene region) and is the method required to identify almost all severe genetic conditions e.g., Huntington disease or BRCA1 breast cancer risk. The genotyping array focuses on more common genetic risk variants, where each variant may be associated with limited risk. This genotyping array can be used to determine someone's polygenic risk score, which is essentially a single number that conveys their genetic risk for a trait. For clinical purposes we will be focusing on the genetic risk of coronary artery disease and Type 1 diabetes, and a limited set of genetic variants that alter how people respond to, or have side effects from, common drug treatments.
2. We will not look at the rest of the genome data as part of our clinical iDiabetes implementation. If new evidence emerges regarding the clinical utility of other polygenic risk scores or genetic variants then these will be discussed by the iDiabetes management board, with advice from the iDiabetes Scientific Advisory Board and the PPI group before any decision is made to use this new evidence to inform on patient care.
3. Research use of the genetic information – where we will use the genetic data and other clinical data to learn more about diabetes risk and complications, and drug response – will be undertaken using anonymised data in a secure Trusted Research Environment.

2.4. Study Results

Patients will receive their results and recommendations within 4 weeks of their review appointment. A follow up appointment with the practice nurse or GP to discuss their review will be provided but it may be later than usual for the iDiabetesPlus group. This is to allow for the completion of all the laboratory tests. As per normal practice, blood results will be made available on clinical systems as they are reported. Those patients with type 1 diabetes will have a follow up appointment in secondary care within 6-8 weeks.

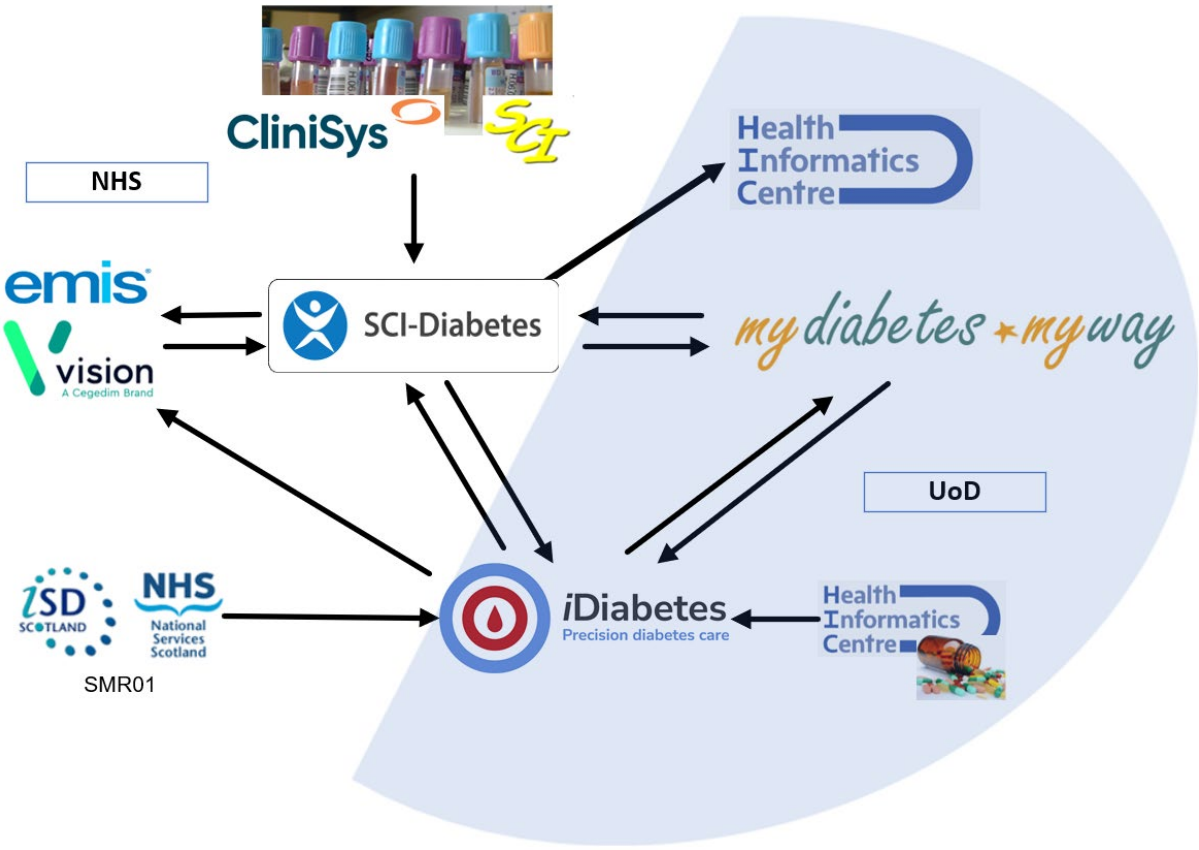
If a patient needs to be referred for further tests (iDiabetesPlus group), e.g., ECHO or Fibroscan, they will be contacted by the iDiabetes clinical team. Clinical consent will be obtained for additional tests.

My Diabetes My Way (MDMW)

In order to access their own results and recommendations, patients will be encouraged to sign up to https://mydiabetesmyway.scot.nhs.uk. MDMW is an established patient portal currently used by >60,000 patients in Scotland, where they can find information about diabetes in general and their own diabetes and individual test results. Results from iDiabetes will feed into MDMW.

If a patient does not wish to sign up for MDMW they do not have to. All iDiabetes results and recommendations are shared with the health care team who will discuss these with their patients.

2.5. Data Flows



SCI-Diabetes is the clinical system used across Scotland for clinical management of all patients with diabetes, and this will be the route whereby clinical data are pulled in from, and fed back to, primary care, as well as routed to MDMW and the iDiabetes IQ engine for decision support. An iDiabetes Dashboard will be generated that is linked to from within SCI-Diabetes and MDMW. All the above

links are already in place as part of existing clinical and research pipelines, other than the iDiabetes IQ engine and iDiabetes Dashboard which will be created prior to initiation of the iDiabetes platform. All data flows and hosting will be managed according to GDPR requirements with approval from NHS Tayside Information Governance and Caldicott guardians.

2.6. Decisions and Recommendations – iDiabetes (guideline supported) care

The iDiabetes platform will prompt the diabetes care team to deliver guideline supported care. The guidelines are based upon the 2022 ADA/EASD guidelines for management of Type 2 diabetes, and the Tayside MCN guidelines for the management of diabetes (including both type 1 and type 2 diabetes). The implementation of decision support advice to 'nudge' clinicians to guideline supported care have been discussed and agreed by the iDiabetes management board, and the iDiabetes PPI group, and endorsed by the Scientific Advisory Board.

2.6.1. Low Adherence Alert

Prescription encashment data is provided to each health board. A feed of this data will be passed to SCI-Diabetes via the Dundee Health Informatics centre, and this will be used to determine percentage adherence for each of:

Diabetes drugs

Statins

Antihypertensives

An adherence dashboard will be available on the iDiabetes dashboard for use by clinicians when reviewing treatment response; and for patients on MDMW. Automated alerts may be sent to the diabetes care team if adherence drops below an agreed threshold.

2.6.2. Treatment intensification, monitoring and cessation

Treatment intensification. HbA1c will be measured at the initial annual review visit (entry to iDiabetes) and then at recommended intervals. Treatment intensification will be recommended based upon individualised HbA1c targets.

If drug adherence is poor to any diabetes treatment, then treatment intensification could include reinforcement of drug adherence.

At all intensification stages, diet and lifestyle measures will be reinforced.

Non-glycaemic indication for treatment. If a patient has existing cardiorenal disease, or is at risk for cardiorenal disease, they will be treated with SGLT2i or GLP-1RA as indicated by the ADA/EASD 2022 guideline, irrespective of HbA1c.

Monitoring and Cessation. In keeping with usual care, HbA1c will be measured at 6-month intervals (likely at 5 months after treatment intensification). If HbA1c has not improved sufficiently then a drug switch may be recommended.

De-intensification. If HbA1c is low or the risk of SH is high, then dose reduction and or cessation of drug may be recommended.

Medicines Optimisation. Where a patient has renal disease, cardiovascular disease or liver disease advice will be provided to optimise statins to target cholesterol, ACE/ARB for proteinuria, antihypertensives to target blood pressure, beta-blocker for HF, Finnerone for proteinuria, antiplatelets for established CVD.

2.7. Decisions and Recommendations – iDiabetesPlus (enhanced guideline supported) care

For iDiabetesPlus, the platform will provide guideline support similar to that provided to the iDiabetes group. In addition, it will include precision prediction models for best drug and risk of hypoglycaemia, with the inclusion of biomarkers to improve the diagnosis of diabetes, the allocation of treatment to those with cardiorenal or liver risk and monitoring of renal function decline. The precision modules being implemented are outlined here:

2.7.1. Type 1 Diabetes and Monogenic Diabetes Diagnosis

A diagnostic pipeline will be implemented in line with the currently agreed Scotland wide approach to confirmation of diagnosis of type 1 diabetes and selection for monogenic gene sequencing (with additional clinical consent).

This will be applied to everyone with a clinical diagnosis of Type 1 diabetes and those with non-type 1 diabetes who have a high MODY risk probability.

Patients with a clinical diagnosis of type 1 diabetes will be managed in accord with the current Scotland wide type 1 diabetes pipeline.

Patients without a clinical diagnosis of type 1 diabetes will be managed in accord with the Scotland genetics laboratory criteria for monogenic diabetes testing, currently:

1. They are diagnosed under the age of 35 years (in White Europeans) or ≤30 years in high prevalence ethic groups **AND EITHER**
2. A BMI <30 kg/m2 AND a parent with diabetes (if White) OR A BMI<27kg/m2 AND a parent with diabetes (High prevalence ethnic group) **OR**
3. MODY probability ≥20%

For patients who proceed to monogenic testing then they will need clinical consent for monogenic sequencing. The iDiabetes clinical team will contact the patient to discuss the potential likelihood of MODY and in line with good clinical practice will obtain clinical consent and a further genetic sample for monogenic gene sequencing. The outcomes will be: 1) A diagnosis of Type 1 diabetes, 2) A diagnosis of probable Type 2 diabetes, 3) Possible monogenic diabetes – needs clinician review and consent for monogenic testing, 4) Needs adjudication review by iDiabetes clinician and possible secondary care review.

2.7.2. Hypoglycaemia Risk

A prediction model has been developed in Tayside and validated in Fife, which provides the individual risk for severe hypoglycaemia for those with type 2 diabetes who are insulin treated or sulphonylurea treated. In addition, there is already a link between the Scottish Ambulance Service and SCI-Diabetes that has been used clinically. An incident severe hypoglycaemic (SH) event and SH risk will be used in people with T2D as follows:

- An incident SH event will be alerted to the diabetes specialist nurses (for insulin treated patient) or primary care (for SU treated patients).

- An individual is calculated to be high risk for incident SH. SH risk will be displayed on the iDiabetes dashboard and alerted if high risk at consultation. An automated alert will be triggered if risk is high (10% per year, as agreed with the iDiabetes PPI group) but subject to review. High risk patients will be flagged to the diabetes care team with a recommendation to review the dose or consider alternative treatment.

- As part of 'best drug prediction' (see 2.7.9) the predicted risk of SH will be provided for the patient should they be started on a sulphonylurea or insulin. This information will be available to patients on MDMW and to the diabetes care team on the iDiabetes page of SCI-Diabetes.

2.7.3. MWDH Risk Models

MWDH have developed and validated a set of meta-models for all-cause mortality, incident MI – Male & Female. These will be made available on the clinician facing iDiabetes dashboard.

Causal models

MWDH have developed a composite risk score with patient and clinician involvement. Using published models of lifestyle and drug intervention they have developed a patient facing tool that allows patients to see how their risk changes with weight loss, stopping smoking or lowering HbA1c. These will be made available to both clinicians and patients on the iDiabetes dashboards.

2.7.4. Targeted Drug Treatment

Several targeted drug treatment modules will be used. Suggestion for the best drug treatment will depend on an individual's risk – with cardiac, renal, or liver risk in those aged over 40 years prompting specific targeted intervention. For those who do not have a cardiac, renal, or liver indication a 'best drug prediction' model will be applied to provide predicted HbA1c for a range of available treatment options.

2.7.5. Renal Risk

Patients at high renal risk will be identified based upon eGFR and urine ACR. If an elevated ACR is new (within the last 2 years) then the GP will be prompted to repeat an early morning ACR on two more occasions, with the ACR considered elevated if two of three readings are above a threshold.

Those with T2D and high renal risk will be recommended to start SGLT2i and to Add/Optimize ACE/ARB and Statin.

For people with T1D and high renal risk SGLT2i are not licensed and will not be recommended. ACE/ARB and Statin optimization will be recommended.

Patients will be referred to renal services if there is a rapid deterioration in renal function. We will use the Kidney Failure Risk equation as recommended by NICE.

2.7.6. Heart Failure

Those with known HF will be identified using GP read codes (for HF). SGLT2i will be recommended for these patients, along with recommendations to optimize ACE/ARB and Beta-blocker (if known HfrEF) and optimize blood pressure treatment.

For those without known HF, a BNP>400pg/ml is suggestive of HF. Clinical follow up and ECHO will be requested.

For those without known CVD and mild elevation of NT-proBNP SGLT2i will be initiated.

ECHO will be offered with a US2.ai supported ECHO at the Research ECHO laboratory that allows automated real time ECHO reporting, see Appendix 3.

For those with T1D, there is no licensed diabetes treatment other than insulin. The focus will be on optimizing ACE/ARB and adding/optimizing beta-blocker (for HfrEF) and risk factors such as hypertension for HfpEF.

2.7.7. Cardiovascular disease and risk for cardiovascular disease

Those with prior CVD (MI, CABG, PCI, ACS, Stroke, TIA, PVD) will be identified using GP read codes. For those without prior CVD, high risk individuals will be identified as those with age >55 and two or more of (obesity, smoking, hypertension, Dyslipidaemia, Albuminuria) OR with a high genetic risk.

Treatment recommendation in T2D will be for SGLT2i in those with a history of CVD or risk for CVD, with (elevated BNP or urine ACR AND no evidence of liver fibrosis (from FIB-4, NFS, ELF or Fibroscan). Those not recommended for SGLT2i will receive GLP-1RA.

Additional recommendation will be to add/optimize statins and, for those with prior CVD to ensure that the patient is treated with antiplatelets and ACE/ARB.

SGLT2i and GLP-1RA are not licensed in T1D. Patients with T1D and prior CVD or high risk for CVD will have optimization of ACE/ARB, antiplatelets and statins recommended.

2.7.8. Liver Fibrosis Risk

Patients at high liver risk (ie. SLD with or without advanced fibrosis) will be identified based on: all patients will receive a streamlined version of the iLFT test – those with ALT >30 will automatically be cascaded to receive a liver aetiology screen (HbSAg, HCV antibody and ferritin/transferrin saturations) and liver fibrosis screen (FIB-4 and NFS score with an ELF test for those with indeterminate or high fibrosis markers).

Patients with a high risk of advanced fibrosis or cirrhosis (FIB-4 >3.25/ NFS >0.675/ ELF >9.8) will be invited to a dedicated iDiabetes liver clinic for further assessment including Fibroscan. Those found to have incidental liver cirrhosis will be referred on to secondary care hepatology services for long term management including, where appropriate, variceal and HCC screening.

Where patients with type 2 diabetes have not received treatment indicated by renal disease or cardiac disease, patients at high risk of SLD with or without fibrosis (ALT >30) will start Semaglutide PLUS Pioglitazone if BMI>30 kg/m^2 or Pioglitazone alone if BMI ≤30 kg/m2.For those with T1D the same algorithm will be followed, however the only treatment for SLD licensed in T1D would be weight loss.

2.7.9. Best Drug Prediction

For those with T2D who have no specific risks to drive treatment choice, the choice of next drug will be recommended based upon validated prediction models. These will use clinical measures (e.g., age, sex, BMI, creatinine, diabetes duration and current medication) to predict HbA1c and weight at 6 months and 1 year. These predictions will be presented to the diabetes care team on the iDiabetes dashboard. If there is a clear best drug this will be indicated, although the choice of drug will be made by the patient and diabetes team.

The diabetes care team will receive a recommendation for treatment escalation if the patient's HbA1c is above their individual target.

2.8. Mixed-methods Implementation and Process Evaluation (IPE)

Qualitative evaluations are detailed in Appendix 2.

2.9. Cost effectiveness

Alongside clinical effectiveness, the iDiabetes platform must represent value for money to the health care system. To assess this, a health economic evaluation will be conducted. A model-based cost-effectiveness analysis of the iDiabetes and iDiabetesPlus platforms versus standard diabetes care will be conducted. The cost per complication avoided and Quality-Adjusted Life Year gained (QALYs – the standard health economic utility measure) for each strategy will be predicted by incorporating the trial data into an existing diabetes simulation model. To estimate the resource implications of introducing the iDiabetes platform at scale in NHS Scotland, a budget impact analysis will be conducted. This will assess whether the recommendations from the cost-effectiveness analysis model are affordable to NHS Scotland.

If implemented, the iDiabetes platform will affect treatment plans for patients. For any predicted improvement in health outcomes to be achieved, patient adherence to the treatment plan is essential.

To gauge uptake of and adherence to the iDiabetes platform, patient preferences will be explored using the discrete choice experiment (DCE) methodology. DCEs have been widely used in health economics to assess patient, public and clinician preferences, including preferences for personalised medicine. The DCE data will be used to: (i) assess the relative importance of attributes in the delivery of personalised diabetes care; (ii) predict patient uptake and acceptability of alternative treatment plans and (iii) estimate benefit-risk trade-offs associated with the risk of adverse outcomes. The DCE data will complement the cost-effectiveness evidence, ensuring that the iDiabetes platform is valued by service users.

3. STUDY SETTING

The study will take place within GP practices and secondary care in NHS Tayside.

4. PARTICIPANT ELIGIBILITY CRITERIA

4.1. Inclusion criteria

For GP practices

- A commitment to participate for the duration of the study

For patients

- Registered patients with a diagnosis of diabetes
- Age >18 years

4.2. Exclusion criteria

Only practices who choose not to take part in the study will be excluded.

5. STUDY PROCEDURES

5.1. Recruitment

All GP practices in Tayside (approx. 60) will be invited to take part in the study.

Practices will be randomised to usual care, iDiabetes and iDiabetesPlus care with stratification by deprivation and practice size.

5.2. Randomisation

The design will be a three-arm cluster randomised trial of iDiabetes Plus, iDiabetes (guidelines), and usual care. The three main comparisons are iDiabetes Plus vs. usual care, iDiabetes (guidelines) vs. usual care and iDiabetes Plus vs. iDiabetes (guidelines).

Stratification will be carried out by **practice** size (<7000, 7000+) and deprivation index (Yes, No) according to the marker of over one third of practice patients in the most deprived Scottish quintile of deprivation.).

Randomisation will initially be in a ratio of 40 iDiabetes: 20 usual care (so 2: 1.0) using up to 60 total clusters (and approximately 400 patients per cluster).

Then a second randomisation for iDiabetes only, 20 iDiabetesPlus and 20 iDiabetes in a 1:1 ratio.

This will be carried out by a University of Dundee statistician initially, stratifying the randomisation as above. giving 4 strata in total.

If GP recruitment is slow then randomisation will be undertaken in two batches. An initial batch of at least 30 GP practices, and a second group of up to 30 GP practices randomised within 3 months of the full study roll out.

5.3. Patient identification

Within practices allocated to receive iDiabetes care, all patients aged 18 years and over with diabetes will be included.

5.4. Screening

iDiabetes care practices will identify their own patients. Patient numbers entering the iDiabetes care process will be recorded within SCI-Diabetes. There will be no separate subject logs kept at individual cluster practices.

5.5. Ineligible patients

All patients identified as meeting the inclusion criteria will be included in the analysis.

5.6. Consent

iDiabetes will be implemented in a cluster randomised design, randomised by GP practice with consent at GP practice level but without explicit consent by each patient (see below re. consent for genetic testing). Cluster randomisation will enable robust evaluation of efficacy and cost effectiveness of the iDiabetes care approaches vs usual standard of care. This will be required before iDiabetes care can be rolled out across Scotland. Failure to randomise with a comparator group would not attain an evidence level for national implementation.

The justification for a cluster randomised implementation with practice level consent is as follows:

1) **Standard within-license treatment recommendations**. All treatments being recommended by iDiabetes are standard treatments currently used in Scotland for the treatment of diabetes, cardiovascular disease, and renal disease. Treatment choice is currently largely at random (with considerable variation in what practices give what diabetes drug for second- and third-

line therapy). iDiabetes is using existing and new data to advise which would be the best of these drugs to prescribe.

2) **iDiabetes does not allocate treatment, it recommends a treatment**. The choice of the drug will be decided by the diabetes care team in consultation with the patient. This will allow the diabetes care team to ensure a reason not to give the recommended treatment has not been overlooked.
3) **Representativeness of the real world.** An individual level consent design will inevitably result in a non-representative group of study participants which raises concerns about the translation of the findings to the real-world. Consent at the GP practice level is close to a real-world implementation, and any findings from this study will be ready to implement at scale across Scotland.
4) **Practicality.** It is not practical to randomise 24,000 patients with diabetes with individual level consent – this would be cost prohibitive.
5) **The option to opt out.** All patients who will be receiving iDiabetes care and treatment recommendations will be written to in advance and given the option to opt out at any point (see 5.10)
6) **Patient involvement.** This study has been co-designed with a representative patient panel, including involvement in the design of the information leaflet and details on how to opt-out.

iDiabetes Group – Explicit Consent for Genetics

In order to comply with the requirements of the Human Tissue Act 2004 explicit consent for genetics testing will be obtained from patients in the iDiabetes Plus group. When the patient attends to have their review bloods taken, the health care worker will ask the patient to confirm that they are agreeable to having the genetic tests completed. The SCI-Diabetes primary care page will prompt for this question and make it mandatory to check the appropriate box, agree/do not agree. The patient flyer, which they will receive in advance of the visit, has details of the genetic tests with a link to the website where there is further information in FAQs. The flyer states that the patient will be asked to confirm at the visit that they agree for the genetic tests to be completed. If they decline the genetic testing, they can still participate in the study.

5.7. Study assessments

This is a cluster randomised study of patients attending for routine annual reviews so there are no research specific visits.

5.8. Long term follow-up assessments

Data from patients in the study will be linked using a unique community health index number (CHI) to electronic medical records to allow for long term follow-up for up to 15 years.

5.9. Qualitative assessments

Qualitative evaluations are detailed in Appendix 2.

5.10. Opt out criteria

Patients at iDiabetes practices are free to opt out at any time and are not obliged to give a reason(s).

Firstly, they will receive an information leaflet if their GP practice is randomised to iDiabetes or iDiabetesPlus care. This will inform them about the iDiabetes project and will let them know how they can opt out. They will be able to opt out by email or by telephone.. The study team will aim to respond to patient contacts within two working days.

Secondly, when patients attend for their routine diabetes annual review, they can opt out with the HCA/practice nurse.

Finally, the patient will have an option to opt out at any interaction with the Diabetes Care team over the course of the study.

Patient's wishes to opt out, and a reason if volunteered, will be recorded in the national diabetes clinical care system (SCI-Diabetes).

The CI or delegate will make a reasonable effort to ascertain the reason(s), both for those who express their right to withdraw and for those lost to follow up, while fully respecting the individual's rights.

5.11. Patients moving GP practice

If a patient moves GP practice during the study to a different randomisation group within Tayside, the patient will continue to receive iDiabetes or iDiabetesPlus care if their annual review visit has already taken place. The study team will liaise with their new GP practice where necessary.

5.12. Storage and analysis of clinical samples

Samples taken are part of routine clinical care and will be managed by the usual NHS clinical procedures.

All patients who are part of iDiabetes will be encouraged to sign up to SHARE. This will enable research use of their samples and consent to recontact in line with the SHARE processes. Patients will have been informed about SHARE in their iDiabetes information leaflet in advance of attending for their diabetes screening visit.

5.13. End of study

The end of study is defined as completion of follow up data collection for all participants. The Sponsor and/or CI have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor, REC and NHS R&D Office(s) within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

The End of Trial report will be sent within one year of the End of Trial declaration to the Sponsor and REC. Study results will be posted on the study website for patients.

6. SAFETY REPORTING

As all the patient care and management is part of clinical care by the diabetes care teams then there will be no adverse event reporting.

7. STATISTICS AND DATA ANALYSIS

7.1. Health Informatics Centre

Data will be analysed within the HIC trusted research environment (TRE). Data linkage will include:

Demography
Deaths
GRO Death Certification
SMR01
Biochemistry
Haematology
Community Dispensed Prescribing
SCI Diabetes: Diabetes Diagnosis, BMI, Blood pressure, Smoking
SAS hypoglycaemia
ECHO
Fibroscan
iDiabetesPlus blood results
Renal register

7.2. Sample size calculation

We will use a composite outcome (See 7.4.1.)

For the composite primary outcome, no standard method has yet been developed for sample size estimation but Zhang and Jeong (2021) have developed R-code which simulates the cluster win ratio (cWR) and we have adapted this for our design. The code uses two outcomes of fatality and non-fatal outcome of hospitalisation, and it should be noted that with four outcomes in iDiabetes we will have greater power as power increases with the number of outcomes in the composite, though with diminishing returns for very common outcomes.

Simulation of power for composite

Simulations utilised the R program developed by Zhang and Jeong (2021). In the simulations 10% of the actual numbers were used (as one simulation took 40 mins using 24,000) so that we had 60 clusters

and 2,400 subjects i.e., 40 per cluster and 80 person-years. The gamma frailty parameter beta for shape and rate was set at 20 which is equivalent to an ICC = 0.05.

The results of 500 simulations gave the proportion of statistically significant results ($p<0.05$) as 413 so power was 413/500 = 82.6% to detect a mean WR = 1.20. Hence power is excellent using the total number of clusters (60) but only 10% of the proposed trial number of subjects.

Power for individual outcomes

In addition, for the individual components of the composite, power is given below. Difference in Poisson rate or incidence rate ratio was used in these calculations as this is similar to HR in a time to event analysis especially with low censoring and mortality. Note also that the WR = ~ 1/HR. No sample size is given for mortality as the event rate is likely to be very low. All sample sizes were estimated using PASS 2023Sample2023 Sample Size and Power analysis software.

Hospitalisation. For the outcome of hospitalisation comparing 7,500 iDiabetesPlus vs 7,500 controls over two years gives a total of 29982 person-years. With 38 clusters (allowing for 19 practices per arm) 79%% power is achieved to detect a difference in Poisson rate of 8% or more (53% reduced to 45%) assuming an ICC = 0.03 and alpha = 0.05. The same applies to iDiabetes vs iDiabetesPlus.

For the same outcome comparing 7,500 iDiabetesPlus vs 7,500 iDiabetes (guidelines) power is 78 % to show a difference in event rate of 8% (45% to 37%) assuming an ICC = 0.03 and alpha = 0.05

Time to eGFR reduction > 40% from baseline. For the main comparison (7,500 vs 7,57,500) power is 77% to reduce the assumed usual care level of 2.6% to 2% or more (a drop of 0.6%) .assuming ICC = 0.03 and alpha = 0.05.

HbA1c fall > 0.5% at two years. For this outcome we assumed a usual care rate of 25% and power was 84% to detect a difference of 0.5% (5.5mmol/mol) or more assuming ICC = 0.03 and alpha = 0.05.

7.3. Planned recruitment rate

A phased start will be in place for GP practices within the iDiabetes and iDiabetesPlus group. This is to allow a test of all processes, with opportunity to refine the process before a full roll out. An initial group of 4-6 practices will begin, with the additional practices starting within 4 months. iDiabetes patient entry will continue for up to 15 months in each practice. Recruitment to iDiabetes and iDiabetesPlus will be stopped when 7500 patients have entered these arms. Recruitment in the usual care arm will be allowed to increase up to 9000 if recruitment to usual care is quicker than to the iDiabetes arms.

7.4. Statistical analysis plan

A statistical analysis plan (SAP) will be finalised prior to initial data lock.

7.4.1. Primary outcome analysis

A hierarchical outcome using a win-ratio (in decreasing order or importance) – 1) All-cause mortality 2) All-cause hospitalisations 3) >40% decline in eGFR, and 4) Absolute HbA1c deterioration >0.5% (>5.5mmol/mol) over 2 years.

For the three comparisons of iDiabetesPlus vs. usual care, iDiabetes (guideline only) vs usual care and iDiabetesPlus vs iDiabetes (guideline only) the Hochberg procedure (Vickerstaff et al., 2019) or (FDA 2017) will be used to assess type I error as it is recommended for positively correlated interventions and retains more power where multi-arm comparisons are used.

7.4.2. Secondary outcome analysis

Individual Components of the composite endpoint

All-cause mortality

Hospitalisation rate over 2 years

Number with eGFR>40% reduction from baseline, or ESKD by 2 years

Number with absolute HbA1c reduction >0.5% (5.5mmol/mol) at 2 years

HF hospitalisation

Drug Adherence

Rate of severe hypoglycaemia

Proportion of people treated according to guidelines

Weight change

7.4.3. Exploratory analysis

Renal

AKI rate over 2 years – with AKI defined as an increase in serum creatinine to 1.5-times a recent historical value (which is presumed to have increased within a week); OR initiation of RRT for acute kidney injury

Number with ACR>20mg/mmol at 2 years

Number with ACR>3mg/mmol at 2 years

Mean annual rate of change in eGFR from baseline to final follow-up measure (in those with eGFR<60ml/min at baseline)

Cardiac (total, and within iDiabetesPlus stratified by NT-proBNP <125pg/ml, 125-400pg/ml, >400pg/ml)

Cardiovascular mortality (by treatment allocation (SGLT2i, GLP-1RA, ACEI/ARB, beta-blockers, mineralocorticoid antagonists, antiplatelets, statins)

Hospitalisation for MACE (ACS, MI, revascularisation, stroke, TIA) (by treatment allocation (SGLT2i, GLP-1RA, ACEI/ARB, beta-blockers, mineralocorticoid antagonists, antiplatelets, statins)

Number diagnosed with HFpEF and HFrEF based on echocardiography and clinical findings

Liver

Progression/regression of liver stiffness (Fibroscan) by treatment allocation (SGLT2i, GLP-1RA, Pioglitazone) (within iDiabetesPlus)

Number with ALT >30 at 2 years

Number of patients newly diagnosed as having SLD or other aetiologies of liver disease. (iDiabetesPlus vs iDiabetes vs standard of care group). Number of referrals to secondary care liver services (iDiabetesPlus vs non-iDiabetesPlus).

Number of new diagnoses of SLD with advanced fibrosis or cirrhosis

Glycaemia

HbA1c at 2 years

Treatment inertia – HbA1c at initiation of new treatment

Number stopping due to poor response

HbA1c reduction at 6 months after new drug initiation (non-insulin)

General

Persistence of new drug for more than 6 months

Change of diagnosis (from baseline to 2 years, as documented in SCI-Diabetes)

Change in cardiovascular risk (UKPDS 10-year CV risk)

Progression of retinopathy (number with new onset background retinopathy, number with new onset referrable retinopathy or maculopathy)

Hospitalisation with foot disease (foot ulcer, any lower limb amputation)

Social inequalities

Impact of socio-economic deprivation (based upon SIMD), comparing between iDiabetes and usual care, on: primary composite endpoint; reduction in hospitalisation, uptake of recommended treatment, HBA1c at 2 years, Treatment inertia, number with eGFR decline>40%

Covid-19: We do not expect this will be an ongoing concern, as the study will not commence until August 2023, and randomisation should remove any confounding related to covid exposure. However, we will adopt two sensitivity analyses – we will remove those hospitalised due to covid from the analysis and we will include covid status as a covariate in any models.

7.5. Criteria for the premature termination of the study

The Sponsor may decide to terminate the study prematurely. If this occurs, written notification of the study termination is required. Some conditions that may warrant study termination include the following:

• Discovery of an unexpected, significant, or unacceptable risk to the participants in the study

• Decision on the part of the funder to suspend or discontinue the study

• Decision by the Sponsor to stop the study at any time, where applicable

8. DATA MANAGEMENT

8.1. Data collection tools

Data used is that collected routinely via clinical care interactions and laboratory measures and captured within SCI-Diabetes.

8.2. Access to Data

The CI will permit study-related monitoring, audits, REC review, and regulatory inspection. In the event of an audit, the CI will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all study records.

8.3. Archiving

Archiving of study documents will comply with Sponsor SOPs. All study documentation, electronic and paper, will be retained for at least 15 years. The CI will be responsible for archiving all study documents, electronic and paper.

9. MONITORING, AUDIT & INSPECTION

9.1. Monitoring

A study risk assessment will be conducted by the Sponsor prior to Sponsorship approval being granted. The Sponsor has determined the appropriate extent and nature of monitoring for the study and will appoint appropriately qualified and trained monitors independent to the study team as required.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1. Research Ethics Committee (REC) review & reports

Before the start of the study, approval will be sought from a research ethics committee.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study.

All correspondence with the REC will be retained in the Study Master File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. It is the Chief Investigator's responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

A copy of all REC reports will be submitted to the Sponsor.

10.2. Peer review

This project is funded by the CSO, Scottish Government and therefore has been subjected to its peer review process for funding applications. This includes an external peer review followed by a review by the funding panel members.

10.3. Primary and Secondary Care Involvement

GPs and the primary care team have been consulted extensively on the design and set up of the study. A GP is a work package lead and grant holder. The project has been discussed at consultation meetings with primary care staff, at the Tayside Diabetes MCN network conference and with the Tayside Local Medical Committee GP sub-group. The group will engage throughout the project with the Diabetes MCN network, the NHS Research Scotland Diabetes Network and with NHS diabetes policy via the Scottish Diabetes Group.

Training will be provided to staff within GP practices by the study team. This will be delivered by a combination of methods including written resources, online/recorded sessions and in person meetings. Ongoing updates will be provided by further training as required and study newsletters.

10.4. Public and Patient Involvement

Patients have been involved throughout the study concept and design phase. Two patients are grant holders and provide expert patient involvement on the MB and SAB. The study and patient materials have also been developed following regular input from the Dundee Diabetes PPI group and interaction with this group will continue for the duration of the study.

10.5. Regulatory Compliance

The study will not commence until a Favourable REC opinion has been granted. The Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place.

10.6. Device Regulation Compliance

In the UK, the Medical Device Directive (MDD) is the legal basis for regulation of software as a medical device. This is under review and the current plan is to align with the EU Medical Device regulations (MDR), with this implementation recently deferred to March 2024 at the earliest. The exact requirements of the UK MDR when implemented are not yet defined. It is anticipated that software registered under UK MDD will be subject to a grandfather clause for 3 years to enable transition across to the new UK MDR.

Supported by Innoscot Health (funded by Scottish Government) we will register the iDiabetes IQ engine as a Class 1 medical device under the current UK Medical Device Directive and this will be in place prior to implementation of the iDiabetes platform. The iDiabetes IQ engine will be low risk (Class 1) because: 1) all treatment recommendations are for standard treatments within licensed indication that could be prescribed by the diabetes care team anyway; and 2) the treatment is a recommendation and the decision on what treatment to provide will be decided by the health care professional.

For each component of the iDiabetes platform, we will:

1) Define the intended use of the software and the requirements
2) Undertake a risk assessment
3) Establish what evidence we need to collect during the study to ensure that we can establish safety and efficacy of each recommendation.

We will work to the following standards:

BS EN ISO 13485:2016+A11:2021 Medical devices – Quality management systems – Requirements for regulatory purposes

BS EN ISO 14971: 2019+A11:2021 Medical devices. Application of risk management to medical devices.

This defines a risk management framework that should be applied throughout the lifecycle of the device, i.e., an initial risk assessment should be performed when the requirements have been established and it should be updated periodically, in particular when design changes are made, and in response to experience gained from using the device. Following 14971 will lead to production of a Risk Management File.

BS EN 62304: 2006+A1: 2015 Medical device software. Software life-cycle processes.

This defines a series of processes that should be followed throughout the life cycle of the device. For example:

- Planning
- Requirements capture
- System Design
- Unit implementation
- Verification and Validation

• Installation and maintenance

BS EN 62366-1: 2015+A1: 2020 Medical devices. Application of usability engineering to medical devices.

This provides a series of processes to follow, to adequately capture any usability risks associated with the device.

10.7. Protocol compliance

All protocol deviations, non-compliance and breaches shall be notified to the Sponsor on identification. The REC shall be notified of any Serious Breaches of GCP. Any deviation from the protocol is considered as a potential breach that must be reported to the Sponsor using a breach report.

10.8. Data protection and participant confidentiality

The CI and study staff will comply with the requirements of the General Data Protection Regulation (EU) 2016/679 (GDPR) and the UK Data Protection Act 2018 or any subsequent amendment or replacement thereof with regard to the collection, storage, processing and disclosure of personal data and will uphold the principles of GDPR in Article 5.

The CI and study staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or local equivalent.

Personal data or data concerning health will not be released without the existence of a legal basis for processing under Articles 6 and 9 of GDPR, such as official authority 6(1)e or substantial public interest 9(2)g. The CI and study staff will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated participant data will be restricted to the CI and appropriate delegated study staff.

Where data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

10.9. Indemnity

The University of Dundee are Sponsoring the study.

Insurance – The University of Dundee will obtain and hold Professional Negligence Clinical Studies Insurance cover for legal liabilities arising from the study.

Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity - The Sponsor does not provide study participants with indemnity in relation to participation in the Study but has insurance for legal liability as described above.

10.10. Amendments

Amendments to the protocol will be conducted in compliance with Sponsor SOPs. The decision to amend the protocol will lie with the CI after consultation with the study management team. The CI will seek Sponsor approval for any amendments to the Protocol or other approved study documents. The Sponsor will decide whether an amendment is substantial or non-substantial. The CI will be responsible for submitting the amendment to the appropriate regulatory authorities and communicating amendments to sites. Amendments to the protocol or other study documents will not be implemented without approval from the Sponsor and subsequent approval from the appropriate REC and NHS R&D Office. The amendment history will be detailed in an Amendment Log.

10.11. Post-study care

Ongoing medical care will be provided to the patients by their usual medical practitioners.

10.12. Access to the final study dataset

The CI and study statistician will have access to the final study dataset. Additional access to the final study dataset will be approved by the CI and appropriate data transfer agreement put in place.

11. DISSEMINATION POLICY

11.1. Dissemination policy

Details of the study and clinical study final report will be published with the intention to submit a manuscript for publication no later than 12 months after the end of study. The report will be made available to the Funder. The report can be used for publication and presentation at scientific meetings. Study investigators have the right to publish orally or in writing the results of the study. The criteria for authorship will follow the criteria of the International Committee of Medical Journal Editors.

Publications will be reviewed according to the agreed contractual terms but will not restrict the general rights outlined above for the Investigators to publish the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

A newsletter giving a summary of the results of the study will be made available to patients on the study website. There will be involvement with local and social media so patients with diabetes in Tayside are aware of the initiative and what it delivers.

11.2. Authorship eligibility guidelines and any intended use of professional writers

The data arising from this study resides with the study team and ownership with the University of Dundee. The criteria for authorship will follow the criteria of the International Committee of Medical Journal Editors. On completion of the study, the study data will be analysed and tabulated, and a clinical study final report will be prepared. The CI will be responsible for authorship of the final report.

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13. APPENDICES

13.1. Appendix 1: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
AM001	3	22-09-2023	Stephanie McKenzie	Updated list of names of those who have reviewed protocol.
			Damien Leith	Secondary objectives – Addition of new diagnosis of NAFLD
			Damien Leith	Additions throughout the protocol of details relating to the liver pathway, liver fibrosis risk and related blood tests
			Damien Leith	Update to liver diagnosis definitions
			Ify Mordi Mya Win	ECHO. Addition of details of US2.ai technology used to allow real time ECHO reporting Appendix 3
			Ewan Pearson	Update to the sample size calculations
			Chim Lang	Update to cardiac exploratory analyses
			Stephanie McKenzie	Addition of standard BS EN ISO 13485:2016+A11:2021 Medical device QMS
			Albert Farre	Addition of qualitative work in Appendix 2

13.2. Appendix 2 Qualitative research

Aims and objectives

The aim of this embedded qualitative study is to explore the views and experiences of those delivering and receiving iDiabetes and iDiabetesPlus care.

This study will address the following objectives:

1. To understand the organisational context and practices involved in the implementation and delivery of iDiabetes and iDiabetesPlus care
2. To explore the impact of implementing iDiabetes and iDiabetesPlus on primary and secondary care provision from the perspective of patients and health professionals

Methods

Study design

This is an embedded qualitative study using semi-structured interviews, documentary analysis and PPI/stakeholder engagement activities.

Study setting

This study will be conducted in primary and secondary Diabetes care settings in NHS Tayside randomised to the intervention arms of the study, iDiabetes and iDiabetesPlus.

Participants

Inclusion criteria - staff:

- Clinical and non-clinical staff involved in the design, implementation, and delivery of iDiabetes/iDiabetesPlus care in community and hospital settings.

Inclusion criteria - patients:

- Patients aged 18 years and over receiving iDiabetes and iDiabetesPlus care in community and hospital settings

Exclusion criteria:

- Refusal of consent
- Anyone without capacity to consent for inclusion

Data collection and data analysis

We will focus on how health professionals and patients across the two intervention arms of the study make sense of and experience *iDiabetes and iDiabetesPlus* care.

This study will be informed by Normalisation Process Theory (May and Finch, 2009) – a sociological theory which explains the processes involved in implementing and/or making a new intervention work in practice to allow for the intervention to become 'normalised' or embedded in individuals/groups

everyday practices. Four core constructs describe generative mechanisms that facilitate normalisation: coherence (work to make sense of an intervention), cognitive participation (work to engage with an intervention), collective action (work to enable an intervention to happen) and reflexive monitoring (work to appraise an intervention).

Data collection will be organised in three iterative stages with concurrent data analysis, which will inform further refinement of interview topic guides and, where needed and feasible, development of additional measures for any key intervention activities to be implemented in subsequent rounds of data collection:

1. During phased implementation: A clear understanding of the causal assumptions underpinning an intervention is vital to enable a robust evaluation of how interventions work in practice (Skivington *et al.*, 2021). We will undertake interviews with key informants (e.g. intervention developers/planners, implementation/oversight teams, clinical leads) and staff and patients from the initial set of 4-6 iDiabetes/iDiabetesPlus practices where the interventions will be first introduced. The primary focus at this stage will be on exploring the early acceptability of the interventions as well as identifying any emerging problems and solutions as the interventions are refined and implemented.

2. After the first annual review: Once iDiabetes and iDiabetesPlus practices proceed to full rollout, we will undertake two further rounds of data collection. First, we will conduct follow-up interviews with key informants and a subset of stage 1 participants, and then we will conduct an additional round of interviews with staff and patients from the wider set of iDiabetes/iDiabetesPlus practices across Tayside. The primary focus at this stage will be on understanding how those involved in delivering and receiving iDiabetes and iDiabetesPlus care feel about the interventions, and how they make them work in practice, at the point of their first annual review appointment under iDiabetes/iDiabetesPlus care.

3. After the second annual review: This stage will focus on exploring how the views and experiences of those involved in delivering and receiving iDiabetes and iDiabetesPlus care in practice evolve over time, following up on any issues identified in the previous stage, as the interventions become more embedded in clinical practice and participants become more experienced in using them. We will first conduct a round of follow-up interviews with key informants and a subset of stage 2 participants, and then we will conduct a further additional round of interviews with staff and patients from iDiabetes/iDiabetesPlus practices following their second annual review under iDiabetes/iDiabetesPlus care.

There is a potential for participants to become distressed during interviews if these touch on personally sensitive or triggering topics (e.g. if patients have experienced anxiety or concerns about their condition, or if they experienced any medication related issues or any adverse health outcomes or co-morbidities). Likewise, staff might become upset when recalling difficult experiences. In such instances participants would be encouraged to seek support and signposted to sources of support available for patients and staff.

If a researcher is informed about potential malpractice, misconduct, or that someone is in danger of harm, the researcher must take appropriate steps. Local protocols will be followed, and appropriate personnel contacted.

These obligations are described in the Participant Information Sheets and in the consent forms, where participants will indicate that they have read and understood this part.

Audio-recorded data from qualitative interviews will be transcribed verbatim, anonymised then subjected to thematic analysis (Boyatzis, 1995; Braun and Clarke, 2006). Qualitative data collection and analysis will take place concurrently to enhance rigour and trustworthiness of findings. Additional techniques to enhance trustworthiness will be put in place, including independent coding triangulation and group-based data analysis critique and data interpretation sessions with the rest of the research team and the study's PPI group.

Any relevant documentary data will be included in the qualitative dataset and analysed using techniques from textual analysis (Rapley, 2007). The qualitative analysis will be aided by QSR NVivo software.

Sampling and recruitment

A purposeful, maximum variation sampling strategy will be employed (Patton, 2002). We will initially account for characteristics relating to setting, including type of intervention (iDiabetes/iDiabetesPlus settings), practice size (<6000, 6000+) and deciles of deprivation (1-3, 4-7, 8-10); and participants, including staff (e.g. seniority, professionals group, role) and patients (age, T1D/T2D) to maximise variation and will subsequently refine our criteria as data collection and analysis progress. The overall estimated sample is 20-25 health professionals and 38-46 patients across the three data collection stages.

Eligible participants will be identified and asked permission to be contacted by the research team using multiple strategies:

- Patients: In primary care, a sub-set of selected iDiabetes/iDiabetesPlus practices relevant to the qualitative sampling criteria will give out information to eligible participants attending for their annual review results appointment. In secondary care, Diabetes Clinicians and Clinical Research Fellows will give out information to eligible participants when patients attend for their review appointment or for ECHO or Fibroscan. Any eligible patients who express an interest in taking part in the study will be asked to provide their preferred contact details and permission to be contacted by the research team. The research team will then follow up with potential participants who agreed to be contacted and offer to respond any questions they might have about the study documents before seeking consent (giving participants at least 24 hours to consider their participation) and agreeing a suitable time for an interview. Participants will be informed that consent will be confirmed in writing (if interviewed in person) or verbally by audio recording a consent statement (if interviewed via Microsoft Teams).

Alongside this, a study recruitment advert will be disseminated via the iDiabetes website and the iDiabetes page on My Diabetes My Way, providing contact details for the research team. If further participants are needed within the required study timeframes, we will use SHARE (Scottish Health Research Register and Biobank) as an additional source of recruitment of participants who have already consented to be contacted for participation in research. A separate SHARE application form will be completed with a view to identify patients in the register meeting relevant combinations of our sampling criteria. Any eligible participants identified via SHARE will then be by SHARE staff in the first instance and then invited to take part in the study following the same process and study documents as for those identified by clinical teams.

- Health professionals: NHS Tayside diabetes care professional networks and internal email lists will be used to invite eligible health professionals in primary and secondary care to take part in the study. At the time of invitation, the researcher will provide relevant information about the study and the voluntary and anonymous nature of their participation, provide a copy of the participant information sheet, and offer to respond to any queries about the study. Invitations will be made well in advance so that consent can be sought after giving participants at least 24 hours to consider their participation. Participants will be informed that consent will be confirmed in writing (if interviewed in person) or verbally by audio or video recording a consent statement (if interviewed via Microsoft Teams).

Data management

Following each interview, we will transfer the audio recordings onto a secure University server with encryption and password protection and delete them from any other device. We will then securely transcribe the audio recordings and anonymise the transcripts. Once the transcriptions have been checked for accuracy, we will permanently delete all audio recordings.

We will only use interview data for the purpose of this study. We will allocate each study participant with a unique study identifier and we will refer to participants using such anonymous codes only. We will remove any other personally identifiable information from the transcripts; therefore, transcripts will not include any personal data. We will store anonymised transcripts in a secure University server.

Consent forms and any further participant details will be stored in a secure University server in line with the General Data Protection Regulation (GDPR) and associated legislation. For participants choosing to be interviewed remotely (via telephone or Microsoft Teams) the researcher will read out the consent statements and ask them to provide verbal confirmation of their agreement. This will be recorded separately from the interview and this consent audio file will be stored in a secure University server, separate from the study data. All participant materials will be securely destroyed at the end of the study. Transcripts and reports will not include personal data or any personally identifiable information.

References

Boyatzis, R.E. (1995) *Transforming Qualitative Information: Thematic Analysis and Code Development*. First Printing edition. Thousand Oaks, CA: Sage Publications, Inc.

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Patton, M.Q. (2002) *Qualitative research & evaluation methods*. 3rd edition. London: Sage.

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13.3. Appendix 3 ECHO scanning

Aims and objectives

The measurement of NT-proBNP in patients allows the opportunity for early identification of cardiac abnormalities, in particular the diagnosis of heart failure. This could allow the opportunity for patients to have their cardiac management optimised. The use of NT-proBNP as a screening test in this manner is well-established in clinical guidelines, with low levels excluding the presence of cardiac abnormalities without the need for further tests. Individuals with elevated NT-proBNP levels are recommended to have an echocardiogram to further evaluate cardiac structure and function.

This study will address the following objectives:

1. To determine the prevalence of cardiac abnormalities in iDiabetesPlus patients with elevated NT-proBNP.
2. To measure the proportion of these patients who have a treatment change based on the echo results.
3. In patients with significantly elevated NT-proBNP, to compare the utility of an AI-supported echo compared to a standard echo.

Methods

Study design

This is an embedded study where iDiabetesPlus patients with proBNP levels exceeding 400pg/ml will be identified. Subsequently, echocardiography will be employed to evaluate heart failure features in these patients using echocardiography parameters analysed through Us2.ai software.

Study setting

This study will be conducted in the Division of Molecular and Clinical Medicine in Ninewells Hospital in Dundee.

Participants

Inclusion criteria

- Patients aged 18 years and over receiving iDiabetesPlus care in community and hospital settings
- Patients not known to have HF with a proBNP>400pg/ml

Exclusion criteria:

- Refusal of consent
- Anyone without capacity to consent
- Patients who have had echocardiography in the last 12 months, where the result showed insignificance, and they remain asymptomatic

Data collection and data analysis

Patients will have been identified as requiring an Echocardiogram (echo) following measurement of proBNP.

As part of the iDiabetes patient dashboard patients will already be aware that the cardiology team will be in contact with them to discuss the NT-proBNP result and arrange an echo.

All patients with proBNP exceeding 400pg/ml will receive a phone call from the iDiabetes cardiology team advising of the need for an echo. The approach to patients will be stratified based on their NT-proBNP level.

NTproBNP >2000pg/ml

These individuals will have an urgent echo requested through the standard clinical pathway (in the NHS rather than research). These patients are higher-risk and are more likely to have significant pathology that could require ongoing cardiology management, therefore it is imperative that the echo result is available to any treating clinician. Currently patients with such NT-proBNP levels typically have an echo performed within ~4 weeks. ss

They will also be asked if they are willing to attend for an AI-supported research echo. If feasible this will be performed on the same day as their clinical scan. This will be optional however. If they are interested in taking part in the study, they will be sent a PIS and ICF with contact details for the study team to make an appointment.

NT-proBNP 400-2000pg/ml

Current clinical pathways mean that patients with NT-proBNP in this range will be appointed for a routine echo. Current waiting times mean that the wait for a routine echo is in some cases over 12 months. We will therefore offer all of these patients the opportunity to attend for an iDiabetes research echo as their sole echo study (rather than an NHS echo).

The echo study will be performed by the iDiabetes cardiology team. Echocardiographic images will be obtained using echocardiography machines in the cardiology research lab, Ninewells Hospital, Dundee. Measurements will be analysed through state-of-the-art echocardiography software called Us2.ai software to facilitate the detection of heart failure.

Patients who do not wish to take part in the study will be referred for an NHS echo through the standard care pathway. All patients with a proBNP exceeding 2000pg/ml will be referred for an NHS echo regardless of whether they participate in the study.

Data Management

After analysing all the ECHO data, echocardiography reports will be shared with the iDiabetes team and a results summary uploaded into their NHS medical records. A treatment recommendation letter will be sent to primary care for optimisation of heart failure according to standard heart failure guidelines. If required, onward management and/or referral onto secondary care services will be facilitated by the iDiabetes team (either direct referral or advice to the primary care practitioner).

Anonymised DICOM images will be stored on a secure University server. Consent forms and any further participant details will be stored in a secure University server or locked filing cabinet in line with the General Data Protection Regulation (GDPR) and associated legislation.