TRIAL PROTOCOL

IMPROVE DKD TRIAL

Digital multi-component intervention to IMPROVE the care of older people living with Diabetes and Chronic Kidney Disease

A type 2 hybrid effectiveness-implementation cluster randomised trial

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

En of

Version Number: **V 1.0**

Version Date: **17th September 2025**

PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

Funding and support in kind

Funder(s)/Supporting Organisations	Financial and non-financial support given:
National Institute for Health and Care Research (NIHR)	Fully funded project grant
Funding scheme	NIHR Health and Social Care Delivery Research
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The Funder of the trial will have no role in the data collection, data analysis or data interpretation. This project is funded by NIHR 158442. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the 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 trial 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 from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	**IMPROVE DKD**
Protocol version number:	Version: __ __
Protocol version date:	__ __ / __ __ / __ __ __ __
CI name:	Professor Indranil Dasgupta
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor statement

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance statement

This protocol describes the IMPROVE DKD trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the IMPROVE DKD trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the 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.

Trial name:	IMPROVE DKD
Protocol version number:	Version: __ __
Protocol version date:	__ __ / __ __ / __ __ __ __
PI name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

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IRAS reference number	332287

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ABBREVIATIONS

A&E	Accident and Emergency
ABCD-UKKA	The Joint Association of British Clinical Diabetologists & UK Kidney Association Committee
APC	Admitted Patient Care
BCTU	Birmingham Clinical Trials Unit
BEAR	Birmingham Environment for Academic Research
BMI	Body Mass Index
BP	Blood Pressure
CCGs	Clinical Commissioning Groups
CI	Chief Investigator
CIG	Co-Investigator Group
CKD	Chronic Kidney Disease
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
CVD	Cardiovascular Disease
DCEA	Distributional Cost-Effectiveness Analysis
DExtER	Data Extraction for Epidemiological Research
DKD	Diabetic Kidney Disease
DSA	Data Sharing Agreement
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Record
ESKD	End Stage Kidney Disease
EVPI	Expected Value of Perfect Information Analysis

EVPPI	Expected Value of Perfect Parameter Information
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GLP1	Glucagon Like Peptide 1
GP	General Practitioner
HbA1c	Haemoglobin A1c
HCPs	Healthcare Professionals
HES	Hospital Episode Statistics
HRA	Health Research Authority
HSDR	Health and Social Care Delivery Research
ICC	Intraclass Correlation Coefficient
IMD	Index of Multiple Deprivation
ISF	Investigator Site File
ITT	Intention to Treat
JOC	Joint Oversight Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial Infarction
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
ONS	Office for National Statistics
PI	Principal Investigator
PPI	Patient and Public Involvement
PSA	Probabilistic Sensitivity Analysis

PSS	Personal Social Services
QALY	Quality Adjusted Life Year
RAASi	Renin Angiotensin Aldosterone System Inhibitors
RCTs	Randomised Controlled Clinical Trials
RDN	Research Delivery Network
REC	Research Ethics Committee
ROST	Recruitment Optimisation Support Team
SAP	Statistical Analysis Plan
SCr	Serum Creatinine
SGLT2i	Sodium Glucose Co-transporter-2 Inhibitor
SWAT	Study Within a Trial
T2D	Type 2 Diabetes
TMF	Trial Master File
TMG	Trial Management Group
UACR	Urine Albumin Creatinine Ratio
UK	United Kingdom
UoB	University of Birmingham

TRIAL SUMMARY

Title

Digital multi-component intervention to IMPROVE the care of older people living with diabetes and chronic kidney disease: a type 2 hybrid effectiveness-implementation cluster randomised trial.

Objectives

Effectiveness

1. To evaluate the effectiveness of the digital management tool for general practice, developed for this trial to promote adherence to Joint Association of British Clinical Diabetologists and UK Kidney Association (ABCD-UKKA) guideline recommendations, at slowing Diabetic Kidney Disease (DKD) progression compared to usual care.
2. To evaluate the cost-effectiveness of the digital management tool compared to usual care.

Implementation

3. To use routine data to evaluate GP adherence to five ABCD-UKKA guideline recommendations: (optimising 1. blood pressure, 2. glycaemic control, and the use of optimum doses of 3, RAASi, 4. SGLT-2i and 5. Statins).

4. To adopt mixed methods to explore and better understand the influences of fidelity, mechanisms of action and context on the implementation and effectiveness of the digital management tool.

Trial design

Type II hybrid effectiveness-implementation cluster randomised trial. The trial includes a study within a trial (SWAT) to assess the value of modelling trial outcomes using process of care data only, compared with intermediate outcome data and later clinical outcomes.

Setting and Clusters

60 Primary Care General Practices (GP) across England. This will be the randomisation unit.

Cluster eligibility criteria

GP practices that use Optum (previously branded as Egton Medical Information Systems electronic patient record systems [EMIS]) and software and share data with Clinical Practice Research Datalink (CPRD).

Research participants

Healthcare professionals (HCPs) managing the clinical care of patients with type 2 diabetes (T2D).

Patient main eligibility criteria

Patients with T2D, aged ≥60 years with estimated glomerular filtration rate (eGFR) between 30-59 ml/min/1.73m^2 (CKD Stage 3).

Sample size

Both co-primary outcomes are powered at 90% (alpha=0.05) with 30 GP practices (clusters) per arm and each GP practice size (cluster size) being approximately 25. This equates to 750 patients in each group (1500 patients in total).

Interventions

Multicomponent intervention based on the Joint ABCD-UKKA Guidelines recommendations. The intervention has two parts:

1. Digital management tool: HCP-facing automatic point-of-care computer reminders, developed in an earlier work package of the trial, reinforcing five guideline recommendations:

1) optimising blood pressure control (target systolic <130 mmHg)2) optimising glycaemic control (target Haemoglobin A1c (HbA1c) <58 mmol/mol); 3) use of an optimum dose of a RAASi

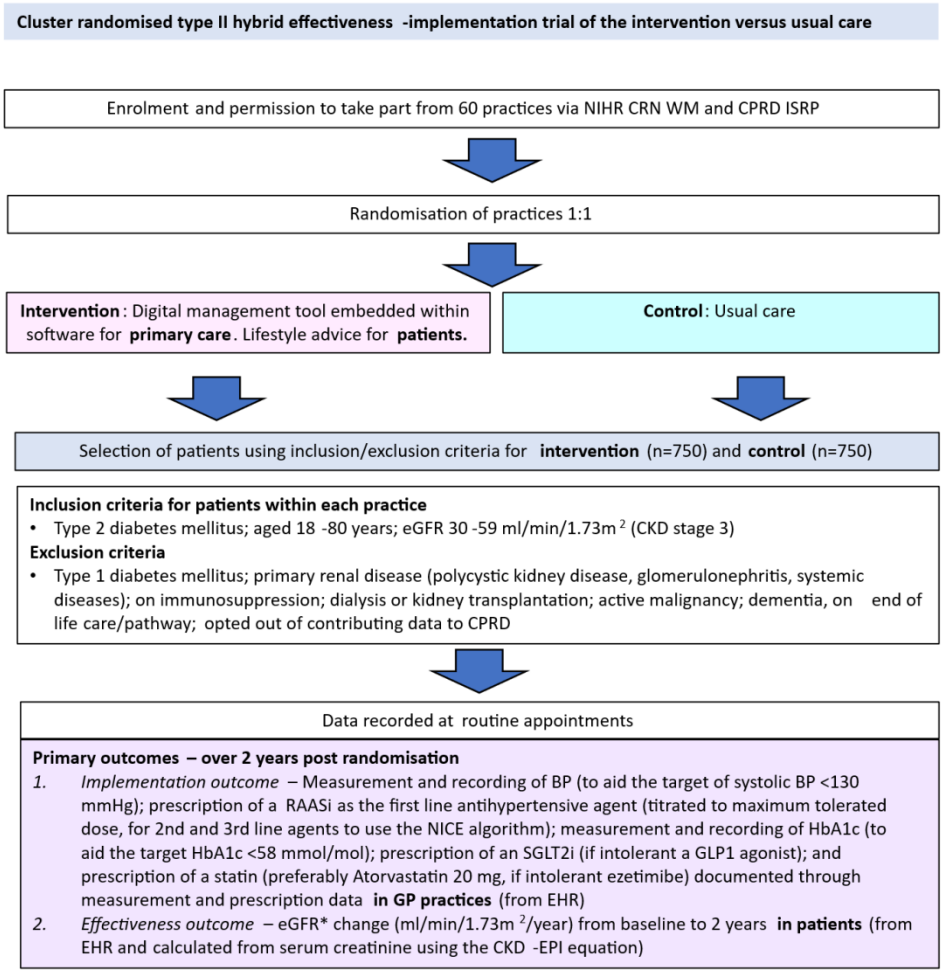
4) use of a sodium glucose co-transporter-2 inhibitor (SGLT2i) and 5) use of an optimum dose of a statin.

2. Provision of patient-facing multimedia lifestyle advice. Developed in an earlier work package of the trial, promoting /reinforcing the following lifestyle recommendations for people with DKD: low salt intake (<5 g/day), moderate alcohol intake (<14 units/ week), regular moderate intensity physical exercise (150 min/ week), smoking cessation, maintaining healthy body mass index (BMI) (18.5 – 25 Kg/m^2).

Outcome measures

- Effectiveness outcome: Change in eGFR over a period of 2 years obtained via routine data collection.
- Implementation outcome: GP adherence to the five key ABCD-UKKA guideline recommendations: optimising blood pressure (BP) and glycaemic control, and the use of optimum doses of RAASi, SGLT-2i and statin. This will be determined via routine data collection at 12 months post randomisation.

TRIAL SCHEMA



Process evaluation	Cost-effectiveness evaluation	Study within a trial (SWAT)
• Mixed-methods approach (survey and qualitative methods) using MRC guidance for process evaluations of complex interventions • Evaluate intervention fidelity, mechanisms of action and contextual barriers and facilitators to implementation of the digital management tool and to patient engagement with the lifestyle components of the intervention.	• Decision model-based economic evaluation undertaken from an NHS/Personal Social Services perspective • Modelling approach – decision model to estimate the longer -term costs and outcomes from the implementation of guidelines • Use of distributional cost -effectiveness analysis (novel exploratory method) alongside decision modelling to incorporate health inequality issues (e.g. sex, age, ethnicity, social deprivation).	• Assess the value of modelling trial outcomes using process of care data only, compared with intermediate outcome data and later clinical outcomes. • Use of the same model structure and cost and utility inputs, but different estimates of process outcomes and effectiveness at three time points: 1) early economic modelling using baseline trial data; 2) at trial completion; and 3) base-case economic analysis.

Figure 1. Flow chart of IMPROVE DKD project
Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CPRD, Clinical Practice Research Datalink; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; EHR, electronic health records; GP, general practice; HbA1c, glycosylated haemoglobin; NIHR CRN WM, National Institute for Health Research Clinical Research Network West Midlands; RAASI, renin-angiotensin-aldosterone system inhibitor; SGLT2, sodium-glucose cotransporter-2.

Contents

1 BACKGROUND AND RATIONALE

1.1 Background

Diabetes is one of the fastest growing health challenges of the 21st Century, costing the National Health Service (NHS) £10 billion per year, 80% of which is spent on treating complications, placing significant demand on health and social care services [1]. Kidney failure is a major complication of type-2 diabetes (T2D) accounting for 30% of patients starting dialysis in the United Kingdom (UK) [2, 3]. In the UK, 7 million people have chronic kidney disease (CKD) (>10% of population), 50% of which is caused by diabetes [1, 3, 4].

CKD is associated with ~45,000 premature deaths and over 100,000 hospital admissions a year, mainly for cardiovascular (CV) events [4-6], which exponentially increases with CKD progression [7]. The NHS annual direct cost of managing CKD is currently £6.4 billion, most of which is spent on dialysis, and it is predicted to increase to £13.9 billion in the next 10 years [4]. Most people with diabetes-related CKD or diabetic kidney disease (DKD) are managed in primary care; over 70% of them are aged over 70 years [3, 8]. Our 2024 analysis of primary care data revealed a stark unmet need and inequality in the management of DKD [8]. DKD is a substantial health problem faced by older people living with diabetes. Slowing the progression of DKD, and thereby avoiding dialysis and CV events, is a significant challenge for service providers.

There is a large body of trial evidence demonstrating that it is possible to slow the progression of DKD and reduce CV risk by early interventions that include lifestyle measures, good glycaemic (HbA1c <58 mmol/mol) and blood pressure (BP) (systolic <130 mmHg) control, and use of renin-angiotensin-aldosterone system inhibitors (RAASi) and statins [9]. A robust evidence base underpins the clinical practice guidelines issued by the Joint Association of British Clinical Diabetologists & UK Kidney Association Committee (ABCD-UKKA) and National Institute for Health and Care Excellence (NICE) [10-13].

Trials have also shown that sodium glucose co-transporter-2 inhibitors (SGLT2i) reduce the risk of CKD progression (by up to 40%), CV events and mortality in DKD [14-16]. Furthermore, Finerenone, a non-steroidal, selective mineralocorticoid receptor antagonist, has been shown to reduce the risk of progression of DKD by 18% and the risk of CV events by 14% [17]. These have informed the 2022 and

2024 updates in the guidelines, which endorse multicomponent treatment recommendations tailored to the needs of patients [10, 11, 18].

Although guidelines contribute to the improvement of care and act as a bridge between routine care and trial evidence, implementation of guidelines in primary care can be challenging and is influenced by complexities in care and pressures on the health professional's time [19]. The randomised controlled trials (RCTs) that provided the evidence for the clinical guidelines tended to examine single interventions in presentative patient populations. They do not determine the effectiveness or implementation of multi-component interventions delivered as a package in the context in which they are used. The IMPROVE DKD trial will evaluate a low-cost digital management tool to improve the delivery of DKD treatment recommendations in primary care.

This trial recognises the working environment of general practice. It provides a time-efficient, simplified mechanism to support general practitioners (GPs) to deliver effective, evidence-based care to people with DKD, who present with complex multi-morbid conditions. The aim is to improve their health, clinical outcomes and quality of life, through reducing risk of kidney failure and CV events, and potentially saving costs to the NHS.

1.2 Trial rationale

National Diabetes Audit data from 2007 – 2008 demonstrated significant unmet needs in the management of DKD in primary care [20]. Data from 2019 unfortunately shows little improvement over the past decade, despite several iterations of the NICE and ABCD-UKKA guidelines over this period. A cross-sectional analysis of ECLIPSE primary care data from 13 Clinical Commissioning Groups (CCGs) in the UK (212,000 diabetes patients, 25% DKD) shows a stark unmet need in the clinical management of DKD in primary care, including inadequate coding for CV disease, glycaemic target being achieved in only 9-16%, BP target in 28-40%, lipid target in 40-60%, and only 7.4% with DKD and heart failure receiving an SGLT2 inhibitor [21].

This is further supported by our 2024 cross-sectional analysis of primary care data (IQVIA Medical Research Data) [8] showing health inequalities in the management of DKD. Of the 2.3 million adults, prevalence of diabetes was 7.2%, and of these 20% (n=32,905) had DKD (median age 76 years). While most (93%) patients had had their BP measured in the past year, women, the most socially deprived and older people were less likely to have had their BP measured. Of those who had their BP measured, 61% did not achieve the target (<130/80 mmHg); with the most deprived and women less likely to achieve the target. More than 90% had HbA1c measured in the past year, but older people and women were less likely to have their HbA1c measured. Around 58% were at or below target (<58 mmol/mol); with the most deprived less likely to be on target.

As for appropriate medication use, older people, the most deprived and women were less likely to receive RAASi. Whilst 78% of DKD patients were prescribed a statin, those of Black ethnicity (compared to White) and women were less likely to have these prescribed. These results show a lack of improvement in the achievement of targets since the decade-old National Diabetes Audit. They also suggest that failure to implement evidence-based recommendations are intensified in certain patient populations, including women, older people, some ethnic groups, and socially deprived people [8].

The NHS is under tremendous financial and operational pressures, making it challenging to maintain standards of care [22]. This is a particular challenge for primary care with the increasing demand on limited resources. This is reflected in an inability to consistently deliver evidence-based care. As workloads and care complexity increase, time constraints impact adherence to the multiplicity of clinical guidelines in general practice [23]. Fundamental changes in care delivery, including methods and tools, are required to continuously improve care, as recommended by the Lancet Commission on Diabetes [24]. To this end, point-of-care computer reminders have been shown to be effective in delivering multiple clinical recommendations in several studies, including a large cluster randomised trial in UK primary care [25].

In people with T2D, there are several studies showing that multicomponent risk interventions (lifestyle measure, glycaemic and BP control, use of RAASi and statins) reduce complications including kidney failure and CV mortality [26-28]. In a DKD trial, a multicomponent risk factor intervention delivered over two years led to a threefold increase in the achievement of multiple treatment targets and a 50% lower risk of kidney failure and death [29]. These studies were conducted in secondary care, but subsequent economic analysis supported the cost-effectiveness of multifactorial interventions when implemented in primary care [30].

There is a growing evidence base for interventions to promote the implementation of evidence-based clinical guidelines. Amongst these, point-of-care computerised prompts and reminders embedded within electronic health record (EHR) systems offer a potentially efficient, scalable, and sustainable way to improve care [31]. However, they need to be carefully designed and implemented to minimise unintended consequences, such as alert fatigue and distracting clinicians and patients from consultation agendas [32]. There is also growing evidence to support the use of patient-mediated interventions in promoting the uptake of recommended practice. These include patient information (informing or reminding patients about recommended care) and patient education (increasing patient knowledge about their condition and options for care) [33].

In the IMPROVE DKD trial, a digital management tool, comprising computerised reminders for health care professionals and multimedia patient-facing advice, developed in an earlier work package, will

be evaluated to improve adherence to and outcomes of guideline-recommended kidney care for older people with T2D.

1.2.1 Justification for design.

The IMPROVE DKD trial is a type II hybrid effectiveness-implementation cluster-randomised trial [34] in primary care that will assess a digital management tool (developed by the team as part of the National Institute for Health and Care Research [NIHR] grant) with embedded cost-effectiveness and process evaluations. This choice reflects the fact that our intervention is focused on both NHS staff (to implement guideline recommended care) and patients (to self-assess and manage a range of lifestyle behaviours). A cluster-randomised design has been utilised given there would be potential for contamination (receiving aspects of the intervention in question) in the control group under an individual patient randomised design [35].

1.2.2 Justification for choice of clusters

For this trial, the participants are the healthcare professionals managing the clinical care of patients with T2D [8]. The GP practices will be the clusters and will be selected from the Clinical Practice Research Datalink (CPRD) Aurum database. The justification for this is twofold: the digital management tool will be developed and embedded within Optum patient management software, and all study related data will be collected through the EHR contributing to CPRD Aurum. The study will be conducted in England for the ease of trial administration; the practices will be recruited strategically to ensure that the trial participants are broadly representative of UK practices in terms of socioeconomic factors, ethnic diversity, and rurality.

1.2.3 Justification for choice of patient population

Patients in each cluster meeting the inclusion criteria: age between 18 – 80 years with type-2 diabetes and eGFR between 30 – 59 ml/min/1.73 m^2 (Stage 3 CKD) will be selected. The intervention is based on the ABCD-UKKA guidelines, which are more likely to benefit type-2 diabetic patients with a moderate degree of CKD than those with advanced CKD (Stages 4 and 5) with regards to slowing the progression of kidney disease.

Type-1 diabetics with CKD will be excluded because DKD secondary to T2D is the main cause of kidney failure in the UK and the numbers are steadily rising with the progressive increase of T2D in the general population. Further, SGLT2-inhibitors, the use of which is recommended by the ABCD-UKKA guidelines, has not been tested in trials in this population. Additionally, type-2 diabetic patients with another known primary cause of CKD, those on immunosuppressive treatment, on dialysis or had a kidney transplant are excluded because the ABCD-UKKA recommendations are not

applicable to them. Type-2 diabetic patients with active malignancy, known dementia, or on end of life care are less likely to benefit from the intervention and hence excluded from the trial.

1.2.4 Justification for choice of intervention

The intervention is based on the current ABCD-UKKA guidelines [18] on the management of DKD which is informed by evidence from several RCTs demonstrating that adequate BP and glycaemic control and the use of RAAS inhibitors, SGLT-2i and statins can slow progression of DKD. The guidelines endorse multicomponent treatment recommendations tailored to the needs of patients [18]. Although guidelines contribute to the improvement of care and act as a bridge between routine care and trial evidence, implementation of guidelines in primary care can be challenging and is influenced by complexities in care and pressures on health professional time. Carefully designed point-of-care computerised prompts and reminders embedded within EHR systems offer a potentially efficient, scalable, and sustainable way to improve care [31].

The intervention is a low-cost digital management tool, consisting of a computer prompt embedded in the GP EHR system, to help improve the delivery of DKD guideline recommendations in primary care. Our approach recognises the working environment of general practice. The digital management tool provides a time efficient, simplified mechanism to support GPs to deliver effective, evidence-based care to people with DKD, who present with complex multi-morbid conditions. The aim of the research is to improve the health and clinical outcomes of people with DKD, through reducing the risk of kidney failure and CV events, and thereby potentially saving cost to the NHS.

Although for the trial, the intervention has been developed within the Optum system, it can easily be adapted for other GP practice EHR systems used in the UK, e.g. Vision and System One. This means it can potentially be rolled out nationally at an anticipated low cost and could help all primary care physicians to deliver evidence-based management, which can benefit hundreds of thousands of people with DKD across the country.

1.2.5 Justification of choice of primary outcomes

As this is a type II hybrid effectiveness-implementation trial, there are two primary outcomes of the trial (an implementation outcome and an effectiveness outcome):

1.

This will assess the implementation of the digital management tool in the intervention arm. Success at the patient level will be measured by adherence to the five key recommendations of the Joint ABCD-UKKA guidelines as listed below 1-5.

1. **Measurement and recording** of BP (to aid the target of systolic BP <130 mmHg).
2. **Prescription** of a RAASi as the first line antihypertensive agent titrated to the maximum tolerated dose. If BP remains uncontrolled, suggest adding a calcium channel blocker or a diuretic as the 2nd and 3rd line agents as per NICE guidelines.
3. **Measurement and recording** of HbA1c (to aid the target HbA1c <58 mmol/mol).
4. **Prescription** of an SGLT2i (if intolerant exception coded).
5. **Prescription** of a statin (preferably atorvastatin 20 mg, and if intolerant to statin, of ezetimibe).

Evidence of adherence to each recommendation will be recorded as an action in the EHR (e.g., measurement taken and/or prescription given) for each eligible patient seen in the 12 months since GP practice randomisation.

We will assess full adherence as a binary measure based on either adherence or non-adherence to all the 5 points above. Further analysis will consider whether there is a difference between intervention and standard of care clusters in terms of adherence score (between 0 [zero adherence] and 5 [full adherence to each of the guideline recommendations). Adherence will also be assessed between months 13 and 24 to allow us to explore whether there is evidence of sustained adherence in practice.

1.3 Effectiveness outcome:

This is to assess the success of the digital management tool in improving clinical outcomes, i.e. slowing the progression of kidney disease. We will collect routinely measured serum creatinine data at baseline (within 12 months prior to randomisation) and over 2 years post-randomisation of the cluster, from which estimated glomerular filtration rate (eGFR; ml/min/1.73m^2/year) will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2021) [36]. Change in eGFR is a validated and well-accepted measure of change in kidney function in clinical trials [37].

2 AIMS AND OBJECTIVES

2.1 Main trial objectives

To evaluate the effectiveness and implementation of a digital management tool to improve evidence-based care and outcomes for people with DKD in general practice.

2.1.1 Clinical aims and objectives

To evaluate the digital management tool:

- In slowing DKD progression compared to usual care (effectiveness objective).

- For promoting adherence to ABCD-UKKA guidelines for the management of DKD in primary care (implementation objective).

2.1.2 Economic aims and objectives

- To evaluate the cost-effectiveness of the digital management tool compared to usual care.
- To assess the relative costs and benefits of using process of care outcomes to estimate costs, outcomes and cost-effectiveness compared with using intermediate and later clinical outcomes in the trial.

2.1.3 Process evaluation aims and objectives

- To explore and better understand the influences of fidelity, mechanisms of action and context on the implementation and effectiveness of the digital management tool.
- To evaluate patient engagement with the lifestyle components of the intervention.

3 TRIAL DESIGN AND SETTING

3.1 Trial design

Type II hybrid effectiveness-implementation cluster randomised trial with economic and process evaluations. The trial includes a Study within a Trial (SWAT; see below).

3.2 Trial setting

Sixty Primary Care GP Practices in England.

3.3 Sub-study

A SWAT will also be undertaken to assess the value of modelling trial outcomes using only process of care data compared with intermediate and later clinical outcomes.

3.4 Assessment of risk

All clinical trials can be considered to involve an element of risk. In accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures, this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation: No higher than the risk of standard medical care

4 ELIGIBILITY

4.1 Cluster

4.1.1 Inclusion Criteria:

General practices will be eligible to take part in the research if they are:

- Using Optum software for patient care record
- Signed up and reporting data to CPRD

4.1.2 Exclusion Criteria:

Any CPRD Aurum practices that were involved in the optimisation of the IMPROVE-DKD digital tool.

4.2 Research Participants

Any healthcare professional managing the clinical care of patients with T2D.

4.3 Cluster Patients

Eligible patients at each practice will be automatically determined through patient coding using the Recruitment Optimisation Support Team (ROST) system linked to CPRD data where they meet the following criteria.

4.3.1 Inclusion Criteria:

- Type 2 diabetes mellitus
- Aged 18-80 years (although a subset of these patients ≥60 will inform the main analysis data-set – see section 14.3)
- eGFR 30-59 ml/min/1.73m^2 (CKD stage 3)

4.3.2 Exclusion Criteria:

- Type 1 diabetes mellitus, known primary renal disease (e.g., glomerulonephritis, vasculitis, adult polycystic kidney disease)
- On immunosuppression therapy
- On dialysis or received a kidney transplantation
- Active malignancy
- On end-of-life care/pathway
- Dementia
- Opted out of contributing data to CPRD

4.4 Process evaluation questionnaires and interviews

Both HCPs delivering the intervention and patients receiving the intervention will participate in the process evaluation. *Inclusion /exclusion: HCPs*

All HCPs involved in delivering the IMPROVE-DKD intervention will be invited to complete a feedback questionnaire

4.4.1 Data collection for HCPs

An email invitation will be sent to the practice manager to circulate to the relevant staff in each practice (those staff involved in seeing patients with DKD). The invitation makes it clear that it is only for those who delivered the IMPROVE DKD intervention.

The survey will give the option to consent to take part in an interview. We will purposively sample and invite to interview those HCPs who consent to be interviewed, based on their profession, length of time in current role, length of time since qualified, age and gender (sampling will be based on data in their questionnaire responses). We will then contact the selected individuals via the contact details they provide in the questionnaire to invite them to be interviewed.

Inclusion /exclusion: Patients: All patients receiving the IMPROVE-DKD intervention in the intervention cluster (inclusion and exclusion criteria as per sections 4.3.1 and 4.3.2) will be given the opportunity to access the lifestyle advice website (they will be provided with a link to the website via text, email or letter as part of the intervention).

4.4.2 Data collection for Patients

The IMPROVE-DKD lifestyle advice website is hosted on the secure NIHR Hub server gives participants the opportunity to fill in a feedback survey (via a link on the home page) this links to a Secure Microsoft Form (which is hosted on University of Birmingham servers). The survey will give the option to consent to take part in an interview. We will purposively sample and invite to interview those patients who consent to be interviewed, based on their age and gender (sampling will be based on data in their questionnaire responses). We will then contact the selected individuals via the contact details they provide in the questionnaire, to invite them to be interviewed.

4.5 Co-Enrolment

GP practices are allowed to undertake additional clinical trials related to diabetes management. We will request that they inform the Trial Management Group (TMG) if they do so.

5 CONSENT

The leadership at the General Practice will grant permission for participation in the study by completing a site agreement to become a trial cluster. Health care professionals employed at health facilities randomised to the intervention group will also be asked to sign an agreement to adhere to the trial protocol in lieu of a formal consent form.

The justification for cluster level consenting is because the intervention (digital management tool) is targeted at the health care provider. Patients are not the research participants in this study [38]; there will be no direct contact between the tool and individual patients for the purpose of the data collection, all outcomes will be obtained from anonymised, routinely collected, data.

5.1 Consent for process evaluation qualitative interviews

5.1.1 Primary care Health care professionals

At 6-12 months following recruitment, all primary care practice health care professionals involved in the delivery of the IMPROVE DKD intervention will be sent a feedback questionnaire, the initial page of which will take electronic informed consent. The questionnaire will also ask if they are happy to take part in an interview about their experience. If they answer yes, the questionnaire will ask for their contact details. The contact details will be kept separately from the questionnaire data to ensure anonymity of the questionnaire data is maintained.

From those who indicated that they are willing to be interviewed, a purposive sampling frame will be used to ensure that a representative sample of healthcare professionals involved in intervention delivery are selected. Interviews will stop when data saturation has been reached or 30 healthcare professionals have been interviewed, whichever happens first. Participants will be able to choose where the interview will take place from: online or via telephone. A participant information sheet will be emailed to participants at least 1 week prior to further contact (by phone or email) to organise the interview time. Informed consent will be taken verbally from each individual who takes part in the interviews, at the time of the interview. To do this, the HCP Interview Consent Form will be read out to the participant, asking for agreement to each point in turn. All interviews will be recorded either on an encrypted audio recorder or via the record function of the platform the online meeting is taking place on Teams. The audio recordings of consent will be taken separately to the interview and stored on a secure (University of Birmingham) server for 10 years. After this period, the audio recordings will be deleted. Recordings will be deleted from the recorder once transferred. The interview audio file will be sent securely to a specialist transcription company (with whom a confidentiality agreement will be made) and will be handled in accordance with the Data Protection Act 2018.

5.1.2 Intervention cluster patients

The IMPROVE-DKD lifestyle advice website will include as invite on the home page for patients to take part in a feedback survey (questionnaire). The first page of the questionnaire will take informed consent for completion of the questionnaire. The questionnaire also asks (at the end) if they are willing to be interviewed about their experience of using the IMPROVE-DKD lifestyle advice website. If they answer yes, the questionnaire will ask for their contact details. The contact details will be kept separately from the questionnaire data to ensure the anonymity of the questionnaire data is maintained.

From those who indicated that they are willing to be interviewed, a purposive sampling frame will be used to ensure that a representative sample of up to 30 participants will be interviewed.

Participants will choose where the interview will take place from: online or via telephone. A participant information sheet will be sent to the participant (by email or letter (their preferred means of contact)) and informed consent will be taken verbally, at the time of the interview. To do this, the Patient Interview Consent Form will be read out to the participant, asking for agreement to each point in turn.

All interviews will be recorded either on an encrypted audio recorder or via the record function of the platform the online meeting is taking place on Teams. The audio recordings of consent will be taken separately to the interview and stored on a secure (University of Birmingham) server for 10 years. Recordings will be deleted from the recorder once transferred. The interview audio file will be sent securely to a specialist transcription company (with whom a confidentiality agreement will be made) and will be handled in accordance with the Data Protection Act 2018.

6 ENROLMENT, RANDOMISATION and BLINDING

6.1 Identification of GP practices

CPRD will be responsible for identifying and inviting all practices to take part in the study. Prior to any practices being contacted, the research team will discuss with CPRD the key practice demographics that we are aiming to reach i.e. range of deprivation scores, to allow them to target who they approach strategically. Prior to the cluster randomised trial, an optimisation study will take place to understand and enhance the GP experience for the cluster trial. This will involve a small number of GP practices, ideally ones that are non-CPRD. If any CPRD Aurum practices are included in the optimisation study, they will not be eligible to participate in the study at the cluster level.

6.2 Screening and enrolment

The number of individual GP practices approached about the trial will be provided by CPRD. Once a practice has agreed to take part in the trial, their details will be passed onto the Research Delivery

Network (RDN) who will start their R&D process. BCTU will also be provided with the GP practice details, and arrangements will be made regarding contract signature (which will act as cluster consent), delivering trial specific training, registration and randomisation.

6.3 Randomisation method

GP practices will be randomised in a 1:1 ratio to either the intervention or usual care group. A minimisation algorithm will be used within the randomisation system to ensure balance in the intervention allocations over the following variables:

- Size of GP practice
    - (≥10,000/<10,000 registered patients)
- Location using the Office for National Statistics (ONS) Output Areas classification according to postcode [39]
    - (Urban: ≥10,000 people/Rural: <10,000 people)
- Deprivation index as per the index of multiple deprivation (IMD) [40] according to postcode
    - (Decile rank: 1-4/5-7/8-10)

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Randomisation of the GP practices will be performed by BCTU. Requests for centre allocation will be sent from the Trial Manager to an independent statistician not involved in the trial who will perform the randomisation using the 'rct-minim' function in Stata [41]. The resulting allocation will be communicated to the trial team via email using a standardised template. Output from the algorithm will be securely stored to generate an audit trail of the process.

6.4 Blinding

Due to the nature of the intervention, the healthcare professionals within the cluster cannot be blinded. The main effectiveness outcome is eGFR, which is an objective measure and is not influenced by knowledge of the intervention group. To encourage maintenance of usual care provision in the control group, only the leadership team who signed the consent will be made aware that their GP practice has been allocated to the control group; no further action will be required at this centre. Patients are not the research participants in this study and so do not need to be made aware of any alerts or recommendations from the ROST system to the healthcare professional, which are aimed at encouraging best practice. There is no substantial risk and the intervention will adhere to the policies and quality standards of the participating local trusts/local authorities/health boards.

7 TRIAL INTERVENTION

7.1 Trial intervention

The intervention is (1) a digital management tool comprising computerised reminders for health care professionals and (2) the provision of patient-facing advice, to improve adherence and the lifestyle of people with T2D needing kidney care.

The multicomponent intervention is based on the five key recommendations of the Joint ABCD-UKKA guideline recommendations [10-12].

- Optimisation of BP control, target systolic BP <130 mmHg,
- Optimisation of glycaemic control, target HbA1c ≤58 mmol/mol,
- The use of a RAASi as the first line antihypertensive agent– titrated to maximum tolerated dose. If BP remains uncontrolled, suggest adding a calcium channel blocker or a diuretic as the 2nd and 3rd line agents as per the NICE guideline,
- The use of an SGLT2i, if intolerant to use a Glucagon Like Peptide 1 (GLP1) agonist,
- The use of a statin – preferably Atorvastatin 20 mg, if intolerant to use ezetimibe.

The tool will be embedded in the GP EHR system in the clusters randomised to deliver the intervention. It will identify patients meeting the inclusion criteria and automatically generate a prompt at every contact with the patient. It will highlight the recommendations that are yet to be met. It will also include exception coding for previous intolerance to any of the medications.

The patient facing, multimedia, lifestyle advice will be generated at the first contact with the GP and will focus on five key self-care targets [18].

1. Low salt intake (<5 g/ day)
2. Moderate alcohol intake (<14 units/ week)
3. Regular moderate intensity physical exercise (building to at least 150 min/week)
4. Smoking cessation
5. Working towards and maintaining a healthy body mass index (BMI; 18.5–25 Kg/m^2)

Patients will be sent a link via email, text or letter from their GP practice. The link will take them to a website where they can view and engage with online lifestyle advice materials (a paper version will be available for those who cannot access the online materials). Initially patients will be guided through an assessment of their current lifestyle (the factors listed above), which will help them to decide what they can do to optimise the management of their DKD. Patients will then choose which

aspects to focus on and work through a downloadable workbook, which helps them to understand the importance of the issue and what they can do to improve their situation, along with suggestions and planning, self-monitoring and problem-solving tools to support changes in their lifestyle behaviours. No patient data will be stored during the self-assessment process or through their engagement with the lifestyle advice workbooks.

For participants who do not have easy access to the internet they will be given a one-page summary of the lifestyle advice. In addition to English the lifestyle advice summary document will also be available in Urdu, Bengali, Bulgarian, Mandarin, Polish and Punjabi for those who would prefer a non-English version.

7.1.1 Continuation of the intervention after the trial

In the intervention practices, the digital management tool will remain operative after the completion of the trial. If the trial demonstrates success in terms of implementation and effectiveness, we will seek to offer the digital tool to GP practices across the UK, including those in the control arm of the trial. Patients who have been sent the lifestyle advice website link will have access for 12 months after the trial ends.

7.1.2 Criteria for discontinuing allocated interventions

No pre-specified criteria for practice withdrawal are planned. If necessary, practices can withdraw from the trial after discussion with the chief investigator (CI). Data collected up to that time-point will still be used in analysis.

7.1.3 Adherence

GP staff' adherence to recommendations contained in the digital management tool will be assessed as part of the implementation outcome at 13 and 24 months as described in Section 8.1.1 below.

Individual patient adherence to the lifestyle advice will be assessed via the process evaluation (see below).

8 OUTCOME MEASURES

8.1 Main trial outcomes

8.1.1 Primary outcomes

1. Effectiveness outcome:

Change in eGFR (ml/min/1.73m^2) (calculated from the serum creatinine (SCr) value using the CKD-Epi Creatinine Equation) over a period of 2 years post-randomisation obtained via routine data collection [37].

2. Implementation outcome:

GP adherence to all five Joint ABCD-UKKA guideline recommendations (listed below) will be assessed using anonymised routine data, initially recorded in the EHR which will include documentation and/or recorded action taken (e.g. measurement and/or prescription).

Specifically, for each eligible patient, the following actions will be required for this binary outcome to be classified as achieved (or not) within 12 months of centre randomisation:

i. **Measurement and recording** of BP (to aid the target of systolic BP <130 mmHg).

ii. **Measurement and recording** of HbA1c (to aid the target of HbA1c <58 mmol/mol).

iii. **Prescription** of a RAASi as the first line antihypertensive agent (titrated to maximum tolerated dose. If BP remains uncontrolled, suggest adding a calcium channel blocker or a diuretic as the 2nd and 3rd line agents as per the NICE guideline.

iv. **Prescription** of an SGLT2i (to be exception coded).

v. **Prescription** of a statin (preferably atorvastatin 20 mg, if intolerant ezetimibe).

The above criteria will be coded based on a decision algorithm to objectively determine the success from these criteria. The algorithm will be approved and signed off prior to data analysis and will also be embedded within the Statistical Analysis Plan (SAP).

Sensitivity analysis will consider whether there is a difference between groups in terms of adherence score (between 0 and 5). Adherence will also be assessed between months 13 and 24 to allow us to explore whether there is evidence of sustained change in practice.

8.1.2 Secondary outcomes

Any continuous outcomes (e.g. BP control) will be assessed over a period of 2 years post-randomisation. Any composite or categorical outcomes will be considered as a result of the outcome occurring at any point in time over the two years post-randomisation. Data will be obtained from CPRD primary care and linked secondary care and area-based datasets.

- A composite of eGFR decline >50%, end-stage kidney disease (ESKD) and all-cause mortality
- Non-fatal myocardial infarction (MI), non-fatal stroke, hospitalisation for heart failure
- Components of the implementation endpoints – BP control, glycaemic control and the use of RAASi, SGLT2I and statin

8.1.3 Exploratory outcomes

- Urine albumin creatinine ratio (UACR) measurement (% in each arm)
- UACR reduction of >30% between baseline and 2 years
- Use of Finerenone and proportion of participants who would have benefitted from the drug i.e. those with UACR >30 mg/mmol despite the use of optimal doses of RAASi and SGLT2i.

8.1.4 Process evaluation outcomes

- Process evaluation to understand the influences of fidelity, mechanisms of action and context on the use of the digital management tool.

8.1.5 Health Economic Outcomes

- To estimate the cost-effectiveness of the implementation strategy (digital tool) for the management of DKD versus usual care.
- To assess the value of modelling trial outcomes using only process of care data compared with intermediate and later clinical outcomes

9 TRIAL PROCEDURES

9.1 Baseline and follow-up data collection

An overview of the data being collected within the IMPROVE DKD trial is given below in Table 1. EHR data will be collected directly through the CPRD system and linked data, and so there is no requirement for Investigators or Health Care Professionals in Primary Care to complete case report forms to record demography and patient characteristics. The data will include medical history (such as previous BP/eGFR, diabetes and other comorbidities, medications, clinical measurements and tests, and blood results etc). The SAP will detail each variable collected and relevant descriptions/determinants. Baseline individual-level data and follow-up data on patients will be received through CPRD yearly. No follow-up visits are required as data linkage will occur through CPRD of primary care and linked secondary care and area-based datasets. Safety outcomes will be collated from CPRD.

Table 1: Routine data to be collected through CPRD Aurum

Visit	Cluster eligibility	Baseline (patient appointment)	Data collected over 24 Months (at patient appointments)

Eligibility check	x		
Cluster consent via mNCA	x		
Randomisation	x		
Measuring a recording of BP		x	x
Prescription of a RAASi		x	x
Measurement and recording of HbA1c		x	x
Prescription of an SGLT2i		x	x
Prescription of a statin		x	x
Serum creatinine (SCr) reading to *calculate eGFR*		x	x
Non-fatal MI, non-fatal stroke, heart failure hospitalisation (also via linkage with hospital episode statistics; HES)		x	x
Urine albumin: creatinine ratio		x	x
UACR			x
Prescription of Finerenone		x	x

10 ADVERSE EVENT REPORTING

10.1 Adverse event recording

As the interventions being tested as a bundle in this trial are recommended by ABCD-UKKA and NICE, and the participants in this trial are the GPs, there are no adverse events that would be anticipated as a unique consequence of participation in the trial. No expedited reporting of adverse events is proposed.

When looking at the outcomes for the patients within a cluster, we are anticipating that there will be deaths. However, most of these deaths will be a consequence of their co-morbidities. It is possible that there may be a difference in the rate of death in cluster patients between the two arms of the trial if the IMPROVE DKD intervention reduces deaths in the intervention arm. However, this will not be detected by expedited reporting because (i) the proportion of deaths due to the trial intervention will be small compared to the background risk of death and differences will be difficult if not impossible to detect by reporting of individual deaths, and (ii) this is a cluster randomised trial so adjustment for the clustering will be required to explore whether crude differences in death rates are due to the intervention.

11 DATA HANDLING AND RECORD KEEPING

11.1 Source data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). To allow for the accurate collection of the data, source data will be accessible and maintained by health care professionals. Source data are generally kept as part of the medical records generated and maintained at site. The source data for IMPROVE DKD trial will include routine data of cluster patients received from CPRD and linked secondary care and area-based datasets, their medical records and for GP participants, their interview transcripts. In addition, for this trial, if a blood test or blood pressure check is performed then the source data will be routine data.

11.2 Data Management

The University of Birmingham (UoB) holds a multi-study licence with the Medicines and Healthcare products Regulatory Agency (MHRA) for use of the CPRD database. Any study that the University undertakes will need to have a protocol approved by the Research Data Governance Scientific Committee at CPRD. All information that identifies an individual patient has been removed from the

database, so neither CPRD nor the UoB will hold any patient identifiers. Data collected in the CPRD Aurum database is covered under the NHS national opt-out, so that patients who do not want their data used for purposes beyond their direct care that is, for research and planning can opt-out. Their data will not be available in the CPRD Aurum database, and they will not be selected as being eligible for the study for the practices that are randomised. Anonymised EHR data will be available through the CPRD Aurum database, and so there is no requirement for investigators or front-line NHS healthcare professionals in Primary Care to complete case report forms to record demographic and patient characteristics. This includes demographic information (year of birth, sex, ethnicity), medical history, medications, clinical measurements and tests, and blood results. Furthermore, appropriate data from linked datasets that include the IMD, admissions to hospital and accident and emergency (A&E) through the hospital episode statistics (HES) admitted patient care (APC) and A&E and cause of death will also be available through CPRD for practices that have given permission for linkage.

On an approximately annual basis, CPRD will transfer data for the practices that have been randomised as part of the trial using a secure file transfer service (e.g., Progress® MOVEit® Transfer). The University has developed Data Extraction for Epidemiological Research (DExtER), a software tool that applies standardised methods to generate extracts of anonymised EHRs. DExtER is currently being used with the CPRD Aurum primary care dataset, and systems have already been developed to automatically integrate this data into the DExtER platform. When the dataset for the trial is made available for UoB, DExtER will be used to efficiently extract the relevant data for the target population of this study based on the specified eligibility criteria. The SAP will detail each variable collected and relevant descriptions/determinates.

No follow up visits are required as only data that is routinely collected through CPRD Aurum (primary care data), linked to secondary care data (HES), data on cause of death from the Office for National Statistics (ONS), and area-based datasets will be used for the analysis of the trial. Efficacy outcomes will be collated from these sources based on a pre-specified clinical code set. CPRD only extracts the minimal amount of data required on a by-study basis and employs over 60 data quality checks covering data integrity and format. CPRD has access to data provided by multiple GP software providers including Optum software. CPRD accesses the most up-to-date information across all contributing practices, thereby enabling: (1) Pre-screening searches to be carried out at scale and standardised according to the trial protocol; (2) Contemporaneous application of selection criteria with regular refreshes; (3) In-built recording of serious adverse events according to Good Clinical Practice (GCP) and regulatory/ethics requirements; and (4) Regular, restricted, safety-focused data downloads to monitor safety directly from the EHR, configurable to provide regular updates to the

Joint Oversight Committee (JOC) (see section 18.5). These processes will be detailed in the trial specific Data Management Plan.

11.3 Data Security

11.3.1 Data processing for questionnaire and interview data

Data entered in response to the feedback questionnaires (for both HCP and patient participants) will be stored on University of Birmingham servers.

Data entered will include informed consent for completion of the questionnaire, questionnaire responses and, where the participant agrees to be contacted to take part in an interview, the participant's preferred contact details (email or physical address and phone number). Once collected, the data will be downloaded to a secure University of Birmingham server, where the contact details will be kept separately from the questionnaire data to ensure anonymity of the questionnaire data during analysis.

All interviews will be recorded either on an encrypted audio recorder or via the record function of the platform the online meeting is taking place on Teams with data being stored only on secure University of Birmingham servers (and not in other cloud locations). The audio recordings of consent will be taken separately to the interview (or separated from the interview data post-recording) and stored on a secure (University of Birmingham) server for 10 years. After this period the audio recordings will be deleted. Any recordings on digital recorders will be deleted from the recorder once transferred. The interview audio files will be sent securely to a specialist transcription company, with whom a confidentiality agreement will be made, and will be handled in accordance with the Data Protection Act 2018.

11.3.2 Data security at the University of Birmingham

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The university's data protection and information security documents is available here:
https://www.birmingham.ac.uk/documents/university/legal/university-of-birmingham-data-protection-policy.pdf (last accessed 20/03/2025)

CPRD data will be stored on a secure server called the Birmingham Environment for Academic Research (BEAR Research Data Store. More information is available here: https://www.birmingham.ac.uk/research/arc/bear/rds/research-data-store.aspx) (last accessed 20/03/2025)

The data can only be accessed on campus or through remote access service, all access is via a two-factor authentication process.

The IMPROVE DKD qualitative interview records (section 5.1) will be transferred from the encrypted audio recorder to UoB servers and then deleted from the recorder and permanently deleted at the end of the study. If the interview takes place over teams then the recording will be treated in the same way as an audio file and follow the same process as above. Once the recording has been transcribed, the transcription will be saved on a password protected UoB server, within a folder with restricted access.

Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The UoB's Data Protection Registration number is Z6195856.

11.3.3 Data security at CPRD

CPRD is a Data Processor for IMPROVE DKD. CPRD standard operating procedures and policies are in place that define the policies and procedures for data access and external data transfer. A full list is defined in the trial Data Management Plan.

11.3.4 Data Security for NHS clinical systems

Optum Recruit is an application that draws data from contracted GP practices in England that are hosted in the Patients who use the lifestyle intervention website will be offered a feedback questionnaire. (and a patient information leaflet, explaining the aims of the study, how the questionnaire data will be used and seeking consent for these uses). data centre. The data are a copy of the coded record and exclude artefacts such as documents, imaging files and other peripheral data. Data transit is over https and is encrypted in transit. EXA is built on Amazon web servers, which is encrypted at rest and is accredited with the Data Centre Alliance Class 3 Facility European Code of Conduct.

Optum Group is certified to ISO 27001:2013, has implemented 14 cloud security policies in line with NCSC Cloud Principles; are NHS Digital Data Security and Protection Toolkit compliant; and are certified to Cyber Essentials Plus. Optum Group operates an internal audit program alongside a program of staff training and awareness to ensure people, processes and technology maintain compliance to all applicable Data Protection rules and regulations, including the Data Protection Act 2018 and the UK General Data Protection Regulations (GDPR). In terms of the Network and Information Systems Regulations, Optum do not provide critical infrastructure, so we are not required to demonstrate compliance, however Optum Group has taken steps to ensure compliance to the regulations by reviewing and tracking their alignment to each area of the National Cyber

Security Centre Cyber Assessment Framework guidance. Insofar as Optum Recruit is concerned, Optum, as the supplier, shall implement and maintain appropriate technical and organisational measures to preserve the confidentiality and integrity of the Patient Contact Data and/or Patient Trial Data and prevent any unlawful processing or disclosure or damage, taking into account the state of the art, the costs of implementation, the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of the Data Subjects (the Security Measures).

11.4 Archiving

Archiving will be authorised by BCTU on behalf of the Sponsor following submission of the end of trial report and will include the relevant trials documents. The final dataset will be stored for at least 10 years in accordance with UK Policy Framework for Health and Social Care Research 2017. No documents should be destroyed without prior approval from the BCTU. The Trial Master File (TMF) will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 10 years. Archiving and destruction of documents will follow the Sponsor's Standard Operating Procedures.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Site set-up and Initiation

All those identified at the GP practice from the leadership team to be the named person for that site will be asked to sign the necessary agreements including a Site training log and Delegation Log and supply a current Curriculum Vitae (signed and dated) and GCP certificate to BCTU.

Each GP practice will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design and protocol procedures. GP practices will be provided with an Investigator Site File (ISF) containing essential documentation, instructions, and other documentation required for the conduct of the trial. The IMPROVE DKD Trial Office must be informed of any change in the GP practice team.

12.2 Monitoring

The monitoring requirements for this trial have been developed following a trial-specific risk assessment by BCTU. Monitoring visits will be only conducted where issues are identified by remote monitoring and on-site investigation is required (e.g., if there is a lack of response to remote monitoring requests or where deemed appropriate by the sponsor). On-site monitoring may be carried out as required following a trial-specific risk assessment and as documented in the Monitoring Plan. Any monitoring activities will be reported to the research team and any issues

noted will be followed up to resolution. If a monitoring visit is required, the Trial Office will contact the GP practices to arrange a date for the proposed visit and will provide the GP practice with written confirmation. The Principal Investigator at the GP practices will allow designated BCTU staff access to source documents as requested. The monitoring will be conducted by staff from BCTU/the sponsor. The Trial office will be in regular contact with the GPs practices to check on progress and address any queries that they may have.

12.3 Audit and inspection

The Principal Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The Investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

12.4 Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial. Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action. GP practices may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

13 END OF TRIAL DEFINITION

The end of the trial is defined as the date on which the last participant completes their final follow-up visit and all protocol-required data have been collected and verified. The end of trial will be six months after the last data capture. The IMPROVE DKD Trial Office will notify the Research Ethics Committee (REC) and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the REC and sponsor within 15 days of the end of trial. The Trial Office will provide the REC and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

14 STATISTICAL CONSIDERATIONS

14.1 Sample size

As we have co-primary outcomes, two sample size calculations have been performed, and we have selected the larger of the two as our target. For both outcomes, power was chosen to be 90% (alpha=0.05) and cluster size assumed to be 25. Our previous study data suggest that cluster sizes will be larger, on average 45 patients per practice. We have modelled the impact of this in terms of power and difference to detect but felt it was best to assume conservative values. Larger cluster sizes will be beneficial in terms of power, with only limited impact on resource given data collection will be automated. Furthermore, to account for any differences in cluster size, a coefficient of variation of 0.2 has been incorporated.

For the clinical effectiveness outcome (change in eGFR), the trial is powered to detect a small to moderate difference between groups of 0.25 standard deviations. Assuming a conservative intraclass correlation coefficient (ICC) of 0.04 and accounting for 5% attrition will require data on 750 patients per group (1500 patients in total). Given the above assumptions around cluster size, this would require 30 GP practices per group (60 in total).

For the implementation outcome, the control group rate for correct implementation of the guidelines has been assumed to be 50%, as a conservative measure as this is where the sample size is maximised; lower control group rates of compliance are certainly possible and will enable us to detect smaller differences with higher power. To detect an absolute improvement of 20% (i.e. going from 50% to 70%) with the same assumptions as above in terms of practice size and attrition would require 650 patients per group (1300 in total). Our previous study on T2D in primary care has shown the ICC for the different components of implementation outcomes could potentially be lower and in the range of 0.02-0.04. If this is the case, we would be able to detect absolute improvements as small as 10%.

14.2 Analysis of outcomes

A separate SAP will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those randomised to intervention versus those randomised to no intervention. In the first instance, all analyses will be based on the intention to treat (ITT) principle, i.e., all clusters and patients will be analysed in the intervention group to which they were randomised irrespective of adherence to randomised intervention or protocol deviations. For all outcomes, appropriate summary statistics and differences between groups, (e.g.

proportions/percentages, mean/standard deviation or median/interquartile range) will be presented. Intervention effects will be adjusted for the minimisation variables listed in Section 6. Since this is a cluster randomised trial, the randomisation algorithm uses the cluster specific minimisation criteria. However, for the analysis we will be analysing individual patient data and so we will adjust for the individual patient specific criteria as fixed effects. GP practice will be adjusted for in the model as a random effect parameter to allow for the cluster design. For outcomes where baseline value is available, this will also be adjusted for in the model as fixed effects. No adjustment for multiple comparisons will be made.

14.3 Primary outcome(s)

For the change in eGFR over 2 years co-primary outcome, this data is continuous and so mean and standard deviation along with minimum and maximum values will be presented by group. Least squares mean difference at 2 years along with the corresponding 95% confidence interval and p-value will be estimated from a mixed effects linear regression model. All available eGFR over the 2 years will be included in the model and time will be included as a continuous variable. Model will also adjust for the baseline eGFR value as well as intervention by time interaction parameter. A general 'unstructured' covariance structure will be assumed.

For the implementation outcome, data will be binary (adherent Yes/No). Therefore, the number and percentage of patients that were managed with a complete set of guideline recommendations will be reported by group. Full details on how adherence to this outcome will be coded is provided in the SAP. An adjusted relative risk, 95% confidence interval and p-value, as well as the adjusted risk difference, 95% confidence interval and p-value will be estimated from first fitting a mixed effects logistic regression model (with robust standard error), followed by marginal standardisation method.

Note: Although the eligibility criteria for patients in the trial is stated to be 18-80 years old, for the main analysis, only patients aged 60 years or more will be included. Patients<60 are expected to be relatively rare but will be included as a supportive analysis, which will give us extra information on the effect of the intervention on a broader population.

14.4 Secondary outcomes

For the secondary outcome components of the implementation outcome, each component (i.e. BP control, glycaemic control and the use of RAASi, SGLT2I and statin) will be analysed separately and data for each component will be treated as binary (yes/no) data where yes indicates if the guideline was adhered to for each individual component. The adherence to each individual component of the guideline will be analysed separately using the same methods as described for the overall guideline adherence to the implementation outcome.

Similarly, the secondary outcome “composite of eGFR decline >50%, end-stage kidney disease (ESKD) and all-cause mortality” will be treated as binary (yes/no) data and again analysed using the same methods as described for the implementation outcome.

Secondary outcomes non-fatal myocardial infarction (MI), non-fatal stroke and hospitalisation for heart failure will be analysed separately and data for each will be treated as time-to-event. Each outcome will be compared between the groups using survival analysis methods and Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event comparisons. A shared frailty Cox proportional hazard model will be fitted separately for each, and results will be expressed as the adjusted hazard ratio with 95% confidence intervals.

14.5 Planned subgroup analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see Section 6) and performed on the primary outcomes only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the implementation outcome regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. For the change in eGFR outcome, the effects of these subgroups will be examined by adding the subgroup by intervention group interaction parameters to the mixed effects linear regression model. To allow for the possibility of differential changes over time within the different subgroups, time by subgroup and the three-way interaction between intervention, time and subgroup will also be included in the model. Least squares mean differences between intervention groups within subgroups will be estimated at 2 years through the fitted model that includes the relevant interaction parameter. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.6 Missing data and sensitivity analyses

Analysis will be completed on observed data in the first instance, utilising models that make assumptions about the mechanism of missing data being missing at random. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this may include simulating missing responses using a multiple imputation approach. Full details will be included in the SAP.

14.7 Planned final analyses

The primary analysis for the trial will occur two years after the last patient recruited from the final practice that has been randomised, and the corresponding datasets have been received from CPRD.

15 ECONOMIC EVALUATION

A decision model-based economic evaluation will be undertaken to evaluate the cost-effectiveness of an implementation strategy (digital management tool) for the management of DKD versus current care from an NHS/Personal Social Services (PSS) perspective.

The model will extrapolate intermediate clinical effectiveness outcomes from routine collected data over a 2-year period to DKD progression, risk of cardiovascular disease (CVD) and mortality over patient lifetime. The cost-utility analysis will discount costs and quality-adjusted life years (QALYs) at 3.5%.

15.1 Model-based economic evaluation

A decision model will be constructed to estimate the longer-term costs and outcomes from the implementation of guidelines and the subsequent impact on clinical measures such as blood pressure, eGFR and HbA1c. Existing literature will be reviewed to determine the most appropriate model type [42]**,** however a microsimulation model is likely to be proposed as it can simulate individuals, their demographics, disease status and risk factors and short-term outcomes and costs (from the trial data), and extrapolate these over a remaining lifetime. The model will include CVD outcomes (e.g. stroke, MI) and DKD progression (e.g. dialysis, transplant).

15.2 Cost-utility analysis (cost per quality-adjusted life-year (QALY) gained)

The purpose of the model is to estimate the effect of the likely increase in adherence to guidelines which will improve the management of DKD and risk factors including the management of hypertension, diabetes and lipids and therefore potentially reduce adverse clinical events. Costs will include the costs related to the implementation of the strategy, management of risk factors and health conditions (medication, referrals, investigations), and acute and long- term costs of clinical events. Outcomes will be as QALYs which combine quality of life and mortality. Quality of life estimates (utilities) for baseline status and clinical events will be sourced from existing literature.

Baseline individual-level data on participant demographics, risk factors and existing health conditions will be provided by the trial to characterise the population simulated by the model. Follow-up data at 24 months will provide information on whether guidelines have been implemented, including medication changes, changes in clinical outcomes (e.g. BP, eGFR, HbA1c) investigations and referrals. These data will allow forward projection of health care resource use, risk of clinical events, quality of life and mortality.

Data on costs and resources required to implement the intervention including upfront costs of development and training (and retraining), additional consultation time and health care use to deliver guideline-based management will be sourced from trial and included in the analysis. Ongoing

medication costs, disease management costs and costs related to acute and long-term health care use from clinical events will be sought from previously published work (e.g. NICE guidelines, DKD models) and standard NHS unit costs. A review of the literature and existing DKD models will provide baseline utility (quality of life) values related to the characteristics of the trial population and disutility values for acute clinical events e.g. stroke, long-term disease (e.g. stages of DKD). Estimates from published papers will be sought to link management of risk factors and changes in intermediate clinical outcomes to the risk of clinical events, including fatal events.

The model will be subject to extensive deterministic and probabilistic sensitivity analysis (PSA). The former will include changing individual parameter values (one way), changing model assumptions, as well as multi-way analysis, threshold analysis and optimistic/pessimistic scenario analysis. PSA will simultaneously assess global parameter uncertainty; model parameters will be inputted as distributions to reflect uncertainty around the base-case estimates. Cost-effectiveness planes and cost-effectiveness acceptability curves will be presented to show the probability the strategies are cost-effective at different cost/QALY thresholds. The probabilistic output also facilitates expected value of perfect information analysis (EVPI). EVPI values the expected monetary gain from an allocation decision made based upon perfect information with no uncertainty in input parameters. The Expected Value of Perfect Parameter Information (EVPPI) can also be estimated, which provides an estimate of the gain from reducing the decision uncertainty attributable to eliminating the uncertainty regarding a particular parameter.

15.3 Distributional cost-effectiveness analysis (DCEA) - health inequalities

Distributional cost-effectiveness analysis (DCEA) is a novel exploratory method used alongside decision modelling to incorporate health inequality issues such as sex, age, ethnicity and socioeconomic status into an economic evaluation [43]. The method provides information on the impact of an intervention on equity and trade-offs between equity and efficiency. We will explore the feasibility of including equity considerations in the distribution of costs and effects using this method, and aspects of inequity included in the DCEA will be dependent on data availability.

16 HEALTH ECONOMICS SUB-STUDY

A SWAT will be undertaken to assess the value of modelling trial outcomes using only process of care data compared with intermediate outcomes and later clinical outcomes. If modelling using process of care data alone represents a good prediction of the final model, this may suggest that the assessment of later clinical outcomes may be less necessary. This ‘proof of principle’ work will help researchers, reviewers and funders elaborate and justify decisions and costs of collection of trial outcomes in the future.

17 PROCESS EVALUATION

17.1 Process Evaluation aims

The aims of the process evaluation will be to assess how the intervention was implemented (Intervention fidelity) and to identify other mechanisms or contextual factors that influence intervention outcomes. We will also seek to identify possible refinements that will facilitate future implementation of the IMPROVE DKD intervention.

17.2 Process Evaluation Methods

We will use a mixed-methods approach (electronic process data, survey and qualitative methods), consistent with Medical Research Council (MRC) guidance [44] for process evaluations of complex interventions [45]. We will evaluate intervention fidelity, mechanisms of action and contextual barriers and facilitators to implementation of the digital management tool. We will also evaluate patient engagement with the lifestyle components of the intervention. Participants included in this process evaluation will mainly be GPs and other health care professionals (e.g. specialist nurses) who were involved in the implementation of the tool and patients who received the lifestyle intervention. Participant selection is discussed below.

17.3 Healthcare professional recruitment

At 6-12 months following recruitment of each GP practice, everyone involved in the delivery of the IMPROVE DKD intervention at the practice will be sent a brief feedback questionnaire and asked if they are willing to be interviewed regarding their experiences of the IMPROVE DKD intervention.

A purposive sample of up to 30 primary care health care professionals will be selected (to maximise diversity in job/role, experience (years in role), age and gender) to take part in semi-structured interviews. A topic guide will be developed and further refined during the initial interviews. The interviews will take place online, orby telephone and at a time and location of the interviewee's choosing. The interviews will be stopped once data saturation is reached.

17.4 Patient recruitment

Patients who use the lifestyle intervention website will be offered a feedback questionnaire (and a patient information leaflet, explaining the aims of the study, how the questionnaire data will be used and seeking consent for these uses). Patients will be recruited via a questionnaire on the website that asks if they are happy to fill in a feedback questionnaire about the lifestyle advice materials that are on the website. The questionnaire will identify potential strengths of the intervention, areas for improvement and if behaviour change has occurred. The feedback questionnaire will also ask if they are willing to be interviewed about their experience of the intervention. Of the participants who say that they are, a purposive sample of up to 30 participants will be interviewed.

17.5 Intervention fidelity assessment

The following data will be collected to assess the extent to which a) the ROST prompt was activated b) practices took the actions recommended by the ROST prompt and c) patients signposted to the lifestyle intervention component engaged with the lifestyle materials.

At the practice level, the following electronic process data will be collected (where possible /depending on the capabilities of the prompt-tool and the practice system).

- Number of distinct patients for whom the ROST prompt appeared at least once during each year of intervention delivery
- Number of times per patient the ROST prompt appeared
- Number of patients for whom each component of the ROST prompt (each clinical care recommendation) was marked as "completed" (including the lifestyle advice prompt).
- (If possible) Number of patients sent letters or emails to prompt access to the lifestyle intervention.

For patients using the lifestyle website, the following electronic process data will be collected (where possible /depending on the capabilities of the web interface used for the lifestyle component). This will be aggregated data on total website usage, rather than individual-level data:

- Number of times intervention material accessed within the following subcategories:
    - Main page
    - Blood Pressure management
    - Alcohol advice
    - Physical activity advice
    - Salt advice
    - Smoking advice
    - Weight loss /healthy eating advice
    - Stress management

- Number of distinct IP addresses used to access intervention material divided into the following subcategories:
    - Main /landing page
    - Blood Pressure Advice
    - Alcohol advice
    - Physical activity advice
    - Salt advice
    - Smoking advice
    - Weight loss advice

17.6 Process Evaluation Data Analysis

Qualitative data will be analysed using framework analysis, using the IMPROVE-DKD programme theory as an initial coding framework. Survey data and intervention fidelity data will be summarised using descriptive statistics (e.g. means, or proportions with standard deviations or 95% confidence intervals).

18 TRIAL ORGANISATIONAL STRUCTURE

18.1 Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

18.2 Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

18.3 Trial Management Group

The Trial Management Group (TMG) comprises individuals responsible for the day-to-day management of the trial: the CI, statistician(s), trial team leader, trial manager, research nurse, data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to ensure the quality of the trial. The TMG will meet sufficiently frequently to fulfil its function.

18.4 Co-Investigator group

The Co-Investigator Group (CIG) will comprise the CI, all co-investigators (clinical and non-clinical) and members of the TMG. The CIG will ensure all practical details of the trial are progressing and working well and everyone within the trial understands them. The CIG will convene at approximately 3 monthly intervals.

18.5 Independent Joint Oversight Committee (JOC)

The role of the JOC is to provide overall supervision of the trial. The JOC will meet at least annually and will monitor trial progress and conduct and advise on scientific credibility. The JOC also carries the responsibility for deciding whether the trial needs to be stopped on the grounds of safety or efficacy. The JOC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety.

19 FINANCE

The National Institute for Health and Care Research (NIHR) Health and Social Care Delivery Research (HSDR) is funding this trial (Project number 158442).

20 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include Data Protection Act 2018 (and subsequent amendments), and the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments). The protocol will be submitted to and approved by the REC prior to the start of the trial. It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

21 CONFIDENTIALITY AND DATA PROTECTION

All investigators and health care professionals must comply with the requirements of the Data Protection Act 2018 (and subsequent amendments) and GDPR with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access will be limited to the minimum number of individuals necessary for quality control, audit and analysis. The controller of the data is the UoB, and all staff are expected to comply with this institution's Standard Operating Procedures.

In brief, all data will be used in line with the Act, for example the principles of: (1) Fair, lawful and transparent use by only using anonymised data for analysis; (2) Explicit use of this data for the purposes of health improvement in specified patient subgroups; (3) Relevant and limited use of data to what is necessary to answer the research questions; (4) Applying of our established data pipelines to ensure accuracy, and identify and rectify anomalies; (5) Keeping data for no longer than is necessary and permit collaboration/data sharing with other research groups, where applicable, to ensure the full extent of value from the data obtained; (6) Handling data in a way that ensures security and prevents loss or misuse; and (7) Technical and organisational procedures in place to ensure accountability, in addition to Patient and Public Input (PPI) input on research questions and data use.

22 FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the Joint Oversight Committee are required to provide declarations on potential competing interests as part of their membership of the committee. Authors are similarly required to provide declarations at the time of submission to publishers.

23 INSURANCE AND INDEMNITY

The UoB has in place clinical trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to patients.

With respect to the conduct of the trial at GP practices and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the clinical recruitment centre and is therefore indemnified through the NHS Litigation Authority.

24 ACCESS TO FINAL TRIAL DATASET

Requests for data generated during this study will be considered by BCTU. Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in the absence of the CI) any of the following: the Trial Sponsor, the relevant TMG, and independent Joint Oversight Committee.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once the release of the data is approved and before data can be released. Any data transfer will use a secure and encrypted method. The datasets for the main trial will include anonymous data only. Data from the process evaluation will include pseudonymised data.

25 PUBLICATION PLAN

Outputs from this trial will be submitted for publication in peer reviewed journals and the findings of the trial will be made public. Manuscripts will be prepared by the writing group as defined in the trial publication plan. Manuscripts should be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review.

In all publications, authors should acknowledge that the trial was performed with the support of the NIHR and the UoB and BCTU. Intellectual property rights will be addressed in the project agreement between the UoB and collaborating universities. A plain English summary will be available via the study website.

26 REFERENCE LIST

1. *Diabetes UK*. Diabetes statistics; Available from: https://www.diabetes.org.uk/about-us/about-the-charity/our-strategy/statistics.
2. Xie, Y., et al., *Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016.* Kidney Int, 2018. **94**(3): p. 567-581.
3. *UK Renal Registry (2022) UK Renal Registry 24th Annual Report*. Available from: https://ukkidney.org/audit-research/annual-report/24th-annual-report-data-31122020.
4. *Kidney Disease. A UK public health emergency. The health economics of kidney disease to 2033. Kidney Research UK.* June 2023; Available from: https://www.kidneyresearchuk.org/wp-content/uploads/2023/06/Economics-of-Kidney-Disease-full-report_accessible.pdf.
5. *PHE. CKD prevalence model 2014*. Available from: https://assets.publishing.service.gov.uk/media/5a82c379e5274a2e8ab593af/ChronickidneydiseaseCKDprevalencemodelbriefing.pdf.
6. *National Chronic Kidney Disease Audit//National Report: Part 2*. December 2017; Available from: https://www.lshtm.ac.uk/media/9951.
7. Go, A.S., et al., *Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization.* N Engl J Med, 2004. **351**(13): p. 1296-305.
8. Phillips, K., et al., *Inequalities in the management of diabetic kidney disease in UK primary care: A cross-sectional analysis of a large primary care database.* Diabet Med, 2024. **41**(1): p. e15153.
9. Zac-Varghese, S. and P. Winocour, *Managing diabetic kidney disease.* British Medical Bulletin, 2017. **125**(1): p. 55-66.
10. Banerjee, D., et al., *Management of Hypertension in Patients With Diabetic Kidney Disease: Summary of the Joint Association of British Clinical Diabetologists and UK Kidney Association (ABCD-UKKA) Guideline 2021.* Kidney Int Rep, 2022. **7**(4): p. 681-687.
11. Karalliedde, J., et al., *Clinical practice guidelines for management of hyperglycaemia in adults with diabetic kidney disease.* Diabet Med, 2022. **39**(4): p. e14769.
12. *(ABCD-RA) Clinical Practice Guidelines for Management of Lipids in Adults with Diabetes Mellitus and Nephropathy and/or Chronic Kidney Disease*. Available from: https://ukkidney.org/sites/renal.org/files/management-of-lipids-in-adults-with-diabetes-mellitus-and-nephropathy-and-or-chronic-kidney-disease.pdf.
13. *NICE guideline [NG28]. Type 2 diabetes in adults: management*. Available from: https://www.nice.org.uk/guidance/ng28/chapter/Recommendations.
14. Perkovic, V., et al., *Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy.* N Engl J Med, 2019. **380**(24): p. 2295-2306.
15. Heerspink, H.J.L., et al., *Dapagliflozin in Patients with Chronic Kidney Disease.* N Engl J Med, 2020. **383**(15): p. 1436-1446.
16. Herrington, W.G., et al., *Empagliflozin in Patients with Chronic Kidney Disease.* N Engl J Med, 2023. **388**(2): p. 117-127.
17. Bakris, G.L., et al., *Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes.* N Engl J Med, 2020. **383**(23): p. 2219-2229.
18. Dasgupta, I., et al., *Current management of chronic kidney disease in type-2 diabetes-A tiered approach: An overview of the joint Association of British Clinical Diabetologists and UK Kidney association (ABCD-UKKA) guidelines.* Diabet Med, 2024: p. e15450.

19. *Clinical Practice Guidelines: Closing the gap between theory and practice*. Available from: https://assets.ctfassets.net/zlnfaxb2lcqx/7dALXR9DWAIXC9I1mLm66s/eea1bc19f809f4aa1205420e9afb62af/JCI-Whitepaper_cpgs-closing-the-gap_compressed.pdf.
20. Hill, C.J., et al., *Chronic kidney disease and diabetes in the national health service: a cross-sectional survey of the U.K. national diabetes audit.* Diabet Med, 2014. **31**(4): p. 448-54.
21. P., W., *Diabetes Professional Conference, London 2021. Personal communication.*
22. *Understanding pressures in general practice. The King's Fund.*

. Available from: https://www.kingsfund.org.uk/publications/pressures-in-general-practice.

23. Tsiga, E., et al., *The influence of time pressure on adherence to guidelines in primary care: an experimental study.* BMJ Open, 2013. **3**(4).
24. Chan, J.C.N., et al., *The Lancet Commission on diabetes: using data to transform diabetes care and patient lives.* The Lancet, 2020. **396**(10267): p. 2019-2082.
25. Coma, E., et al., *Effectiveness of electronic point-of-care reminders versus monthly feedback to improve adherence to 10 clinical recommendations in primary care: a cluster randomized clinical trial.* BMC Med Inform Decis Mak, 2019. **19**(1): p. 245.
26. Gaede, P., et al., *Effect of a multifactorial intervention on mortality in type 2 diabetes.* N Engl J Med, 2008. **358**(6): p. 580-91.
27. Griffin, S.J., et al., *Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial.* Lancet, 2011. **378**(9786): p. 156-67.
28. Oellgaard, J., et al., *Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits.* Kidney Int, 2017. **91**(4): p. 982-988.
29. Chan, J.C., et al., *Effects of structured versus usual care on renal endpoint in type 2 diabetes: the SURE study: a randomized multicenter translational study.* Diabetes Care, 2009. **32**(6): p. 977-82.
30. Gaede, P., et al., *Cost-effectiveness of intensified versus conventional multifactorial intervention in type 2 diabetes: results and projections from the Steno-2 study.* Diabetes Care, 2008. **31**(8): p. 1510-5.
31. Kwan, J.L., et al., *Computerised clinical decision support systems and absolute improvements in care: meta-analysis of controlled clinical trials.* BMJ, 2020. **370**: p. m3216.
32. Jani, Y.H. and B.D. Franklin, *Interruptive alerts: only one part of the solution for clinical decision support.* BMJ Qual Saf, 2021. **30**(12): p. 933-936.
33. Fønhus, M.S., et al., *Patient-mediated interventions to improve professional practice.* Cochrane Database of Systematic Reviews, 2018(9).
34. Curran, G.M., et al., *Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact.* Med Care, 2012. **50**(3): p. 217-26.
35. Hemming, K. and M. Taljaard, *Key considerations for designing, conducting and analysing a cluster randomized trial.* International Journal of Epidemiology, 2023. **52**(5): p. 1648-1658.
36. (CKD-EPI), C.K.D.E.C., C.-E.C.E. (2021), Editor. 2009. p. Recommended method for estimating GFR in adults.
37. Levey, A.S., et al., *Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of CKD: A Scientific Workshop Sponsored by the National Kidney Foundation in Collaboration With the US Food and Drug Administration and European Medicines Agency.* Am J Kidney Dis, 2020. **75**(1): p. 84-104.
38. Weijer, C., et al., *The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials.* PLoS Med, 2012. **9**(11): p. e1001346.

39. Statistics, O.f.N.; Available from: https://www.ons.gov.uk/methodology/geography/geographicalproducts/areaclassifications.

40. GOV.UK. *Accredited official statistics English indices of deprivation 2019*. Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019.

41. Ryan, P., *RCT_MINIM: Stata module to assign treatments to subjects in a controlled trial.* 2009/Apr.

42. Brennan, A., S.E. Chick, and R. Davies, *A taxonomy of model structures for economic evaluation of health technologies.* Health Econ, 2006. **15**(12): p. 1295-310.

43. Asaria, M., S. Griffin, and R. Cookson, *Distributional Cost-Effectiveness Analysis: A Tutorial.* Med Decis Making, 2016. **36**(1): p. 8-19.

44. Skivington, K., et al., *A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance.* BMJ, 2021. **374**: p. n2061.

45. Borrelli, B., *The Assessment, Monitoring, and Enhancement of Treatment Fidelity In Public Health Clinical Trials.* J Public Health Dent, 2011. **71**(s1): p. S52-s63.