FULL/LONG TITLE OF THE STUDY
PERsonalised Medicine for Intensification of Treatment (PERMIT): the case of type 2 diabetes mellitus

SHORT STUDY TITLE / ACRONYM
PERMIT

PROTOCOL VERSION NUMBER AND DATE

Version 1.0

RESEARCH REFERENCE NUMBERS

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor
I also confirm that I will make the findings of the study publically 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 planned in this protocol will be explained.

For and on behalf of the Study Sponsor:
Signature: Date: .....
.....
Name (please print):
.....
Position:
.....

Chief Investigator:

Date: ...27./.11../.2024 .....

Signature:
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Name: (please print): Richard Grieve
.....

KEY STUDY CONTACTS

Chief Investigator	Professor Richard Grieve 15-17 Tavistock Place, London, England, WC1E 7HT Email: richard.grieve@lshtm.ac.uk
Sponsor	Mrs Patricia Henley Head of Research Governance and Integrity London School of Hygiene & Tropical Medicine Keppel Street London England WC1E 7HT
Funder(s)	National Institute for Health and Care Research NIHR128490
Committees	Study Steering Committee: Professor Kenneth Paterson ken.paterson@dsl.pipex.com Professor Stephen Evans Stephen.evans@lshtm.ac.uk Professor Jim Lewsey jim.lewsey@glasgow.ac.uk Professor Ewan Pearson e.z.pearson@dundee.ac.uk Dr Sarah Finer s.finer@qmul.ac.uk Dr Rahul Mohan rahulmohan@doctors.org.uk

STUDY SUMMARY

Study Title	PERsonalised Medicine for Intensification of Treatment (PERMIT): the case of type 2 Diabetes Mellitus
Internal ref. no. (or short title)	PERMIT
Study Design	An advanced Instrumental Variable method and a microsimulation model adapted to the UK setting to provide unbiased estimates of relative effectiveness according to the individual patients' risk profile.
Study Participants	People with T2DM, aged over 18 years, prescribed SU, DPP4i or SGLT2i for 1st-stage intensification
Planned Study Period	01/01/2020 – 30/11/2023 (47 Months)
Research Question/Aim(s)	The aim is to evaluate the relative effectiveness of alternative drug regimens for first-stage treatment intensification for T2DM, and provide evidence to target treatments for individual patients. The objectives are: 1. To assess disparities in the initiation of second-line antidiabetic treatments prescribed among people with

	T2DM in England according to ethnicity and social deprivation 2. To compare the effectiveness of SU, DPP4i, and SGLT2i added to metformin for people T2DM who require second-line treatment in routine clinical practice. 3. To examine heterogeneity effectiveness of SU versus DPP4i combined with metformin on levels of haemoglobin A1c (HbA1c) across the entire target population and subpopulations of decision-making relevance. 4. To assess the comparative effectiveness of SU, DPP4i or SGLT2i added to metformin according to age, baseline HbA1c, and individual risk-factor profiles of multiple long-term conditions (MLTCs). 5. To calibrate the RAPIDS microsimulation model to UK data and then use the resultant RAPIDS-UK model to predict probabilities of long-term complications for people with T2DM in England after second-line treatment with SU, DPP4i or SGLT2i added to metformin.

Title: PERsonalised Medicine for Intensification of Treatment (PERMIT): the case of type 2 diabetes mellitus

1. Summary of Research

The aim of this study is to evaluate the relative effectiveness of alternative oral drug regimens as second-line treatment (first-stage treatment intensification) for people with type 2 diabetes mellitus (T2DM), and provide evidence to help choose the right treatment for individual patients. In T2DM, there is great uncertainty about which drug to choose as an 'add on' to metformin for individual patients.

The objectives are:

1. To assess disparities in the initiation of second-line antidiabetic treatments prescribed among people with T2DM in England according to ethnicity and social deprivation
2. To compare the effectiveness of SU, DPP4i, and SGLT2i added to metformin for people with T2DM who require second-line treatment in routine clinical practice.
3. To examine heterogeneity in the comparative effectiveness of SU versus DPP4i combined with metformin on levels of haemoglobin A1c (HbA1c) across the entire target population and subpopulations of decision-making relevance.
4. To assess the comparative effectiveness of SU, DPP4i or SGLT2i added to metformin according to age, baseline HbA1c, and individual risk-factor profiles of multiple long-term conditions (MLTCs).
5. To calibrate the RAPIDS microsimulation model to UK data and then use the resultant RAPIDS-UK model to predict probabilities of long-term complications for people with T2DM in England after second-line treatment with SU, DPP4i or SGLT2i added to metformin.

Overview of Methods

This proposal addresses a gap in knowledge about targeting appropriate drug treatments for T2DM. The target population is people with T2DM on metformin, who are then prescribed either a sulfonylurea (SU), dipeptidyl peptidase-4 inhibitor (DPP4i) or sodium-glucose cotransporter-2 inhibitor (SGLT2i) which in the UK NHS are most frequently chosen as an 'add on' to metformin. This study will access linked Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) data on baseline characteristics, biomarker levels, concomitant medications, and also on long-term outcomes (micro- and macro- vascular complications including death, and related hospital admissions). As a starting point, we will assess disparities in the choice of second-line treatment for people in England with T2DM according to ethnicity and social derivation (Obj 1). We will then estimate the comparative effectiveness of the different drugs prescribed in routine clinical practice on outcomes including haemoglobin A1c (HbA1c) (Obj 2). We will examine heterogeneity in comparative effectiveness for two of the common second-line treatments (SU and DPP4i) on levels of haemoglobin A1c (HbA1c) at 12 months across the entire target population and subpopulations of decision-making relevance (Obj 3). We will then assess the comparative effectiveness of second-line treatment with SU, DPP4i or SGLT2i added to metformin according to age, baseline HbA1c and individual risk-factor profiles of multiple long-term conditions (MLTCs) (Obj 4). Finally, we will calibrate the RAPIDS microsimulation model to UK data and then use the resultant RAPIDS-UK model to predict probabilities of long-term complications for people with T2DM in England after second-line treatment with SU, DPP4i or SGLT2i added to metformin.

A crucial aspect of the overall study design is that it recognizes that observational studies that adjust only for measured confounding variables are liable to report biased estimates of treatment effectiveness. We therefore propose an instrumental variable (IV) study design as this can provide accurate estimates of effectiveness, even when there are unmeasured differences between the comparison groups[1, 2]. A valid IV encourages treatment receipt, in this case of alternative drugs, but does not have a direct effect on the outcome, for example level of HbA1c. Our study draws from literature which shows that clinicians' prescribing history can be an IV when it strongly predicts the treatment offered, but does not have an independent effect on the outcome[2].

Our pilot study found that the proportions of patients prescribed SU, DPP4i or SGLT2i varied across NHS Clinical Commissioning Groups (CCG). We will exploit this unexplained variation in prescribing to estimate the relative effectiveness of alternative second-line treatment regimens for T2DM. We will recognise that

the extent to which people with T2DM benefit from alternative treatments, may well depend on their individual risk profiles, including their age, gender, whether they have CVD and their baseline biomarker levels. We will report the effects of second-line treatments on long-term outcomes in particular the incidence of micro- and macro- vascular complications. We will provide evidence on the relative effectiveness of these second-line treatments by using CPRD-HES linked data to adapt an individual-level simulation model to the NHS context.

The research design has been informed by our PPI co-applicant, and by people with T2DM who support the emphasis on generating evidence to personalise drug choice and reporting long-term outcomes which have been designated a priority research area by Diabetes UK. Panels of health care professional who manage patients with T2DM, and PPI representatives will advise on which aspects of personalization patients find most important, and the best way to present the study results to inform changes to clinical practice. We will provide evidence on long-term effectiveness according to individual-level risk profiles. The co-applicants with direct experience of influencing NICE recommendations for technology appraisals (Adler, chair of Technology Appraisal committee) and clinical guidelines for T2DM (Khunti and Smeeth), have driven the study design to help ensure that the results can directly change practice.

2. **Background and Rationale**

In the UK around 3.5 million people have been diagnosed with T2DM, accounting for ~10% of NHS expenditure[3] which is expected to rise to ~17% by 2035-36[4]. T2DM is a progressive disease and international clinical guidelines recommend additional drugs if glycemic control is inadequate following metformin monotherapy[3, 5]. This second-line treatment can be with a SU, or newer, more costly classes of drugs[3, 6, 7], most commonly DPP4is or SGLT2is. An international consensus statement does not specify a single preferred drug class for intensification, but recommends that treatment choice is 'personalised' to individual characteristics and risk profile. However, as NICE recognised when developing the guidelines for T2DM, for many patients there is insufficient evidence to inform these decisions[8'3].There is wide variation across NHS CCGs in the proportion of people with T2DM prescribed either SU, SGLT2is or DPP4is in addition to metformin[7].

The aim of precision medicine is to target the right treatment to the right patient at the right time. This requires evidence about the relative effectiveness of alternative treatments related to the individual's risk profile. The availability of large-scale routine datasets of sufficient quality, such as the CPRD[9], can provide the requisite data on individual risk factors, treatment pathways and outcomes for relevant target populations[9]. However, to provide useful evidence on comparative effectiveness, studies must address biases, especially confounding by indication and informative censoring, and report long-term outcomes[10].

Brief literature review

There is unresolved controversy about the safety and relative effectiveness of SUs[11] and the routine prescription of DPP4i and SGLT2i for second-line treatment has recently increased. We reviewed the literature to investigate the relative effectiveness of the three alternative drug classes for second-line treatment, and to generate hypotheses about which baseline characteristics or concomitant medications may moderate or mediate relative effectiveness. Our initial review found that most studies assessing the effectiveness and safety of SGLT2is or DPP4is compared patients randomised to 'placebo' or to 'clinician choice'[12] which makes the results difficult to interpret.

To investigate the existing literature on the relative effectiveness of the alternative second-line treatments of interest, we undertook a systematic search of published clinical trials with active comparators for people with T2DM. Our PubMed search on 15 Mar 2019 had the following criteria "Diabetes Mellitus, Type 2"[Mesh] AND "Metformin"[Mesh] AND ("Sulfonylurea Compounds"[Mesh] OR "Dipeptidyl-Peptidase IV Inhibitors"[Mesh] OR ("Sodium-Glucose Transporter 2"[Mesh] AND Inhibitor*) OR Gliflozin*) AND (Dual OR Combination) AND "Clinical Trial"[Publication Type]. This search was supplemented by a bibliographic review and advice from clinical experts. We found 393 studies but excluded those judged irrelevant after title and abstract (n=371), and full text review (n=12). A total of 10 studies were judged relevant to the study question: 6 compared DPP4is with SU [13, 14], 3 compared SGLT2is versus SU[15], and only one directly

compared SGLT2is to DPP4is. This study found that compared to treatment with a DPP4i, treatment with a SGLT2 achieved greater reductions in HbA1C, weight and SBP, but these results were from post-hoc analyses.

Several meta-analyses have reported that compared to other antidiabetic drugs, second- or third-generation SUs were not associated with higher risk of death, or CVD events[16]. The ongoing CAROLINA trial recently reported that the safety profile of SUs was similar to DPP4is[17]. In a recent placebo-controlled trial, SGLT2is were found to reduce major CVD events in patients with established CVD. While head-to-head randomised controlled trials (RCTs) could provide unbiased estimates of relative effectiveness, the range and number of patients included in previous and ongoing RCTs are insufficient to provide reliable estimates of long-term safety and effectiveness according to individual-level risk profiles[18, 19].

Our literature review identified observational studies that compared outcomes across second-line drug regimens. These studies found that SUs, DPP4is and SGLT2is were each associated with HbA1c reductions when combined with metformin[20, 21], but that SUs were associated with higher risk of CVD events[22]. However, these studies did not recognise that patients who received SUs may have been of more severe case mix, according to unmeasured prognostic variables (e.g. frailty)[23]. An IV design, much like randomisation, can provide accurate estimates of treatment effectiveness even when there are unmeasured differences between the comparison groups[1, 2]. In T2DM, previous studies have used provider prescribing as an IV to compare SUs with TZDs as second-line treatments [24], and metformin versus SUs for drug initiation [25]. However, these studies did not provide evidence on relative effectiveness according to patient risk profiles.

Previous research has raised several hypotheses about risk factors that could modify the relative effectiveness of alternative second-line drugs. First, SGLT2is may be more effective than SUs or DPP4i in reducing subsequent events in patients with pre-existing CVD. Second, for patients with chronic kidney disease (CKD), SGLT2is may be relatively effective in reducing disease progression[26].
Third, for patients with MLTCs the relative effectiveness of the alternative drug classes for second-line treatments may be mediated by the concomitant use of antihypertensive and lipid lowering drugs. For example, SGLT2is could be of greater benefit for patients with chronic heart failure (CHF) as they might augment the effects of diuretics in reducing the risks of CVD and End-Stage Renal Disease (ESRD). However, there is limited evidence about the synergistic effects of combining oral antidiabetic therapies with other drugs (polypharmacy).

To provide evidence-based personalised care, further research is therefore required to report relative effectiveness of second-line treatment according to individual patient's risk profiles. The risk profiles will use baseline measures drawing from the hypotheses about subgroup effects raised by the literature review, and advice from clinical experts and the PP representatives. The measures will include age, gender, ethnicity, established CVD, HbA1c, cholesterol levels, estimated glomerular filtration rate (eGFR), body mass index (BMI) and MLTC. Where the literature raises hypotheses about the relative effectiveness for subgroups of patients with particular risk factor combinations, for example that for patients with pre-existing CVD, the relative effectiveness of SGLT2is may be modified by the patients baseline renal function, we will consider the relative effectiveness according to combinations of baseline risk factors.

Why this research is needed now

A recent statement by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) emphasised that evidence was urgently required about the benefits and risks of alternative second-line drugs. The joint report recommends that this choice of treatment should reflect whether or not the patient has CVD, CHF or CKD, and emphasised the need for more evidence on relative effectiveness according to multiple risk factors. NICE's guidelines for T2DM encourage clinicians and patients to: "Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes."[3]

Decision-makers at NICE, leading diabetologists, GPs and PPI representatives have all indicated that further evidence is urgently required to tailor the choice of second-line treatment according to risk factors.

These measures of risk must be routinely measured in primary care. SU is a low cost alternative, and the patent for drugs in the DPP4i class expires in 2022, which will leave SGLT2i as the relatively high cost alternative.

Building on existing work

First, we will access large-scale data on prescribing patterns from the CPRD-HES linked data, and extend a previous study that described prescribing patterns following second-line treatment[7]. These data contain information on individual demographic characteristics, risk factors, 'polypharmacy', biomarkers and also on long-term outcomes[27]. Our study will be required to develop new drug codes to categories the concomitant medications as well as each antidiabetic regimen over each patient's follow-up (up to 9 years). The codes developed will have to be that general to CPRD but also the Veterans Affairs (VA) electronic medical record data used to build the long-term diabetes model that this study will extend. Second, we will extend an IV method that can fully address confounding and provide person-level treatment effects. The method was originally developed by co-applicant Basu, and recently applied by Grieve and colleagues[28]. Third, we will extend a T2DM microsimulation model developed by Basu to the UK context[29]. We will use the CPRD data, and the IV estimates within the model to provide estimates of the long-term effectiveness of alternative intensification regimens, according to the individual's baseline line of HbA1C, age and presence of MLTC.

Generalisable findings and prospects for change

The choice of second-line treatment for patients with T2DM, and how best to target treatments for individual patients is an important challenge world-wide. The study will provide evidence on which second-line treatments are most effective, overall and according to patients risk factors prior to second-line treatment, namely their baseline HbA1c, age and presence of MLTC.

The PI (Grieve) has registered the proposed study with NICE to inform updates to their clinical guidelines for T2DM. The study design, including for example the choice of treatment regimens, has been shaped by our PP representatives and is supported by Diabetes UK. The study's prospects for influencing practice 'on the ground' will be enhanced by the active engagement of health care professionals (GPs, practice nurses, service commissioners and diabetologists), and PPI representatives throughout the project.

Our study will provide evidence to inform individual choices by applying advanced modelling methods to a large-scale administrative dataset. These insights will help inform future approaches to inform patient care for other chronic diseases, and help decision makers target the right treatments for the right patients.

3. Aims and Objectives

The aim is to evaluate the relative effectiveness of alternative drug regimens for first-stage treatment intensification for T2DM, and provide evidence to target treatments for individual patients.

The objectives are:

1. To assess disparities in the initiation of second-line antidiabetic treatments prescribed among people with T2DM in England according to ethnicity and social deprivation
2. To compare the effectiveness of SU, DPP4i, and SGLT2i added to metformin for people T2DM who require second-line treatment in routine clinical practice.
3. To examine heterogeneity in the comparative short-term (12 month) effectiveness of SU versus DPP4i combined with metformin on levels of haemoglobin A1c (HbA1c) across the entire target population and subpopulations of decision-making relevance.
4. To assess the comparative effectiveness of SU, DPP4i or SGLT2i added to metformin according to age, baseline HbA1c, and individual risk-factor profiles of multiple long-term conditions (MLTCs).
5. To calibrate the RAPIDS microsimulation model to UK data and then use the resultant RAPIDS-UK model to predict probabilities of long-term complications for people with T2DM in England after second-line treatment with SU, DPP4i or SGLT2i added to metformin.

4. Research Plan/Methods

Overview

This project will evaluate the effectiveness of alternative second-line treatment according to patient-level measures routinely recorded in primary care data. We will use CPRD-HES data to develop a model to provide accurate estimates of the long-term incidence of macro- and micro- vascular complications for patients with T2DM in England. The CPRD is an exceptional source of anonymised population-based electronic health records. These primary care records combining both GOLD and Aurum datasets comprise a representative sample of ~20% of the UK population and contain comprehensive high quality data on clinical diagnoses, prescribing, referrals, tests and demographic/lifestyle factors[9, 30]. Linkage between the primary care records in CPRD and HES is well established for >70% of practices in the CPRD, providing a data set augmented with detailed secondary care diagnostic and procedural records. Our group is experienced in using these data to conduct high quality studies, including of evaluating treatments for T2DM[27].

Instrumental variable design

Studies which apply traditional risk adjustment approaches when there is little information on case-severity are liable to provide biased estimates of treatment effectiveness. We therefore propose an IV study design[1, 2]. A valid IV design can provide accurate estimates of treatment effectiveness even when there are unmeasured differences between the comparison groups[1, 2]. An IV encourages receipt of the treatment, in this case first-stage treatment intensification, but does not have a direct effect on the outcome, for example HbA1c, except through the treatment prescribed (Fig. 1).

The IV for the prescription of each first-stage treatment intensification regimen is the CCG's prescribing history, which reflects that the choice of second-line treatment may involve the hospital diabetologist, the GP, other health-care professionals, and the patient. We will define 'CCG prescribing history' as the proportion of patients prescribed each first-stage treatment intensification in the CCG for the last complete calendar year prior to the treatment intensification of the patient currently under consideration.

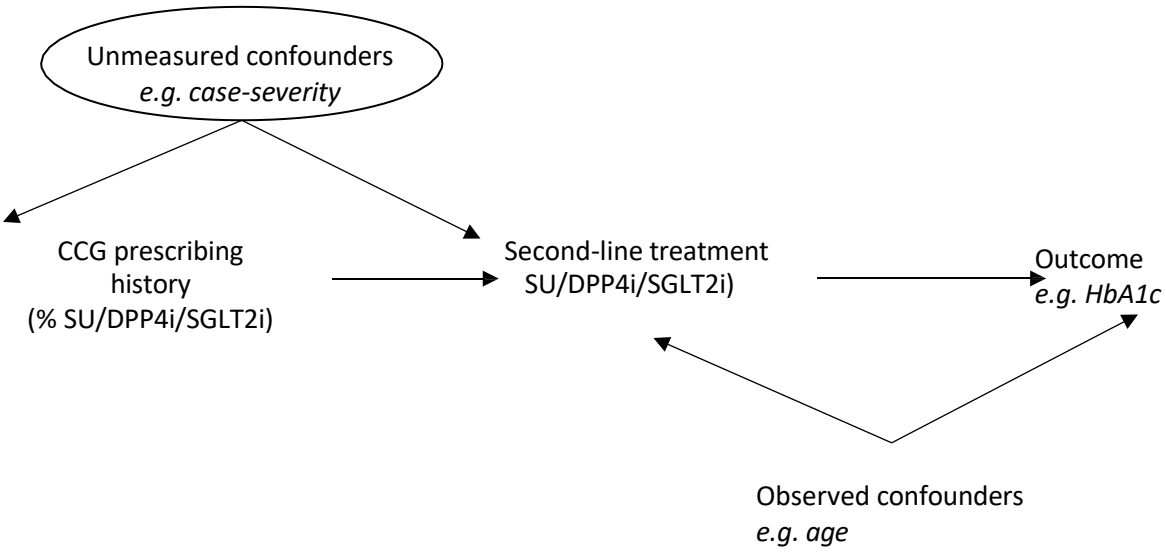


Fig. 1. Instrumental variable design.

In our pilot CPRD data the proportions of patients prescribed each second-line treatment varied widely; for example in 2014, the ranges across CCGs were 5-100% (SU), 0-90% (DPP4i) and 0-35% (SGLT2i). These proportions have changed over time (2014-2018) (Fig. 2), but similar patients received different first-stage treatment regimens simply according to CCG prescribing preference, or time period.

This study's design will exploit this wide variation in the choice of second-line treatment. Our CPRD pilot data suggest that 'CCG prescribing history' is a valid IV for the second-line treatment regimen prescribed. The CCG prescribing history is a strong, independent predictor of the choice of first-stage treatment intensification[31], and balances key prognostic variables like age and baseline HbA1c. We will use this IV to estimate the relative effectiveness of alternative second-line treatments for T2DM while minimising bias from unobserved confounding. We will use an IV approach, the 2-stage residual inclusion (2SRI) which can report the appropriate estimand, the average treatment effect (ATE) for the overall population and subpopulations of interest for the three way treatment comparison (SU vs DPP4i vs SGLTis) required for objectives 2 and 4. For Objective 2, which requires a two-way comparison (SU vs DPP4i) we will use a 'Local IV estimator' which can allow for heterogeneity according to unobserved (e.g. lifestyle choices) as well as observed (e.g. baseline HbA1C) factors when reporting the relative effectiveness of the alternative second-line treatments according to individual patient risk profiles.

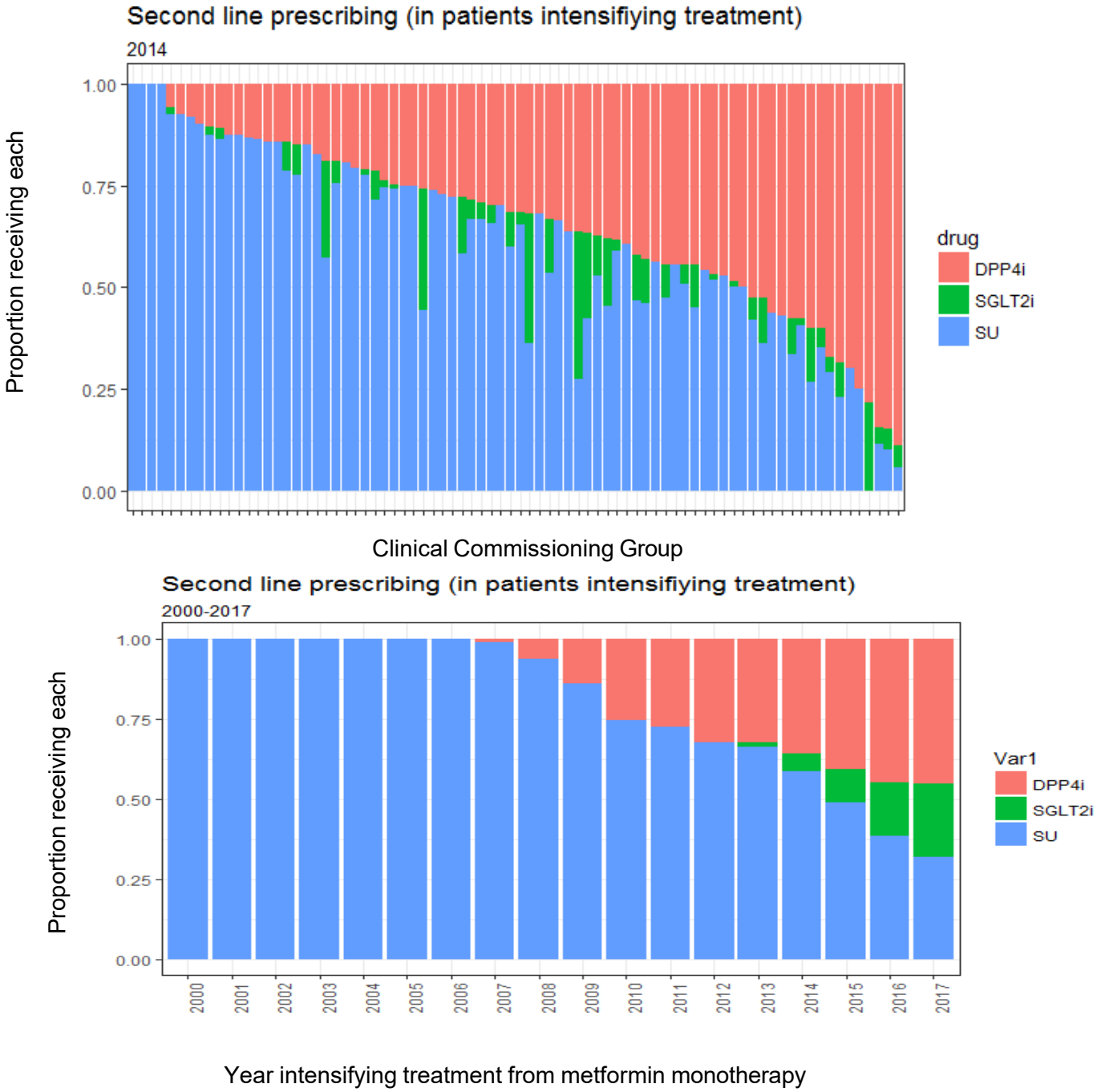
Overall population

We will identify a prevalent cohort of patients aged ≥ 18 years old with a diagnosis of T2DM, included in the CPRD between 1 Jan 2011 and 31 Dec 2019. We will exclude those aged <18 years who are much more likely to have type 1 DM. We will include only patients who intensify treatment with a second oral treatment after a previous period of metformin monotherapy, the recommended drug for initiation. We will define 'baseline' as the date of the first prescription for second-line treatment. To help ensure that the study includes only those patients who have received metformin prior to second-line treatment we will includeonly patients registered at a General Practitioner (GP), for at least twelve months prior to second-line treatment. We will exclude patients who start more than one new antidiabetic treatment on the same day, those who discontinue metformin prior to 'baseline', and those without the HES linkage required for information on long-term outcomes.

Comparators and second-line treatment cohorts
We will include patients prescribed the three most common classes of drugs for second-line treatment. In our 2016 CPRD pilot data, the most frequently prescribed drug classes for second-line treatment were DPP4i (41.4 %), SU (35.4%) and SGLT2i (15.4%), which have all been recommended by NICE and SIGN. We will group patients according to which class of therapy they started at second-line treatment. We will exclude other comparators that were used infrequently in the pilot data, namely thiazolidinedione (TZDs, 2.5%), and injectable insulin (2.7%), and Glucogen-like peptide-1 agonists, (GLP-1,1.8%), because patients tend to prefer non-injectable therapies when offered the choice.

We will define a *'long-term outcomes cohort'* as eligible patients who initiated second-line treatment any time 1.1.2011-31.12.2019, providing the long-term follow-up of up to 7.6 years required for the RAPIDS- UK model. Our feasibility count suggest that this cohort will contain approximately 38,000, 29,000 and 8,000 patients who had second-line treatment with SU, DPP4i and SGLT2i respectively which is the pertinent sample for objective 5. We will also define a subsample of patients for the '*comparative effectiveness cohort*' (objective 2) limited to patients prescribed second-line treatment between 1.1.2016-31.12.2019 (SU=6,000; DPP4i, 13,000 and SGLT2i=6,700).

Fig. 2. Proportion of patients receiving each treatment in CPRD pilot data.
a) By Clinical Commissioning Group in 2014 (n = 4,450 patients).
b) By year across all Clinical Commissioning Groups (n = 61,787 patients).



Patient-level covariates (see also outcomes)
For the one-year period *prior* to second-line treatment, we will extract information on patient characteristics (age, gender, ethnicity, index of multiple deprivation, marital status, approximate duration of diabetes), comorbidities (e.g. established CVD, CHF, CKD), and biomarker levels (HbA1c, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, other systolic blood pressure (SBP), diastolic blood pressure (DBP), eGFR, body weight, and BMI). Each of these measures will be considered as part of the measurement of the baseline risk profile, and following the findings of the literature review and the design workshop, will be considered as variables for the subgroup analysis and in reporting results according to baseline risk profiles. The list of patient-level covariates

includes all those that will be required by the RAPIDS-UK model for predicting long-term effectiveness (see objective 5).

Treatment use
To address the research questions, the RAPIDS-UK model will require information on each patient's full longitudinal patterns of antidiabetic treatments, and those of concomitant medications for lipid lowering and anti-hypertensives. First, the model requires information on the drugs prescribed for the period *prior* to first-stage intensification. Second, the study requires data on the dates of prescription of second-line treatment, and those of lipid-lowering and antihypertensive medications *during* the period of second-line treatment. Third, for the period *after* clinicians have stopped prescribing second-line treatment, we require information on the prescription of subsequent anti-diabetic drugs and insulin, including newer alternatives such as Glucagon-like peptide-1s (GLP1s)

We will extract all the required information on prescriptions by extending previous algorithms developed to identify antidiabetic regimens from CPRD, [7] to extract all the required information on concomitant medications. A major challenge is that for each drug, the definitions will be required to consistent with those applied to the United States Department of Veterans Affairs (VA) electronic medical record and Medicare Claims databases in building the original RAPIDS model. The study will therefore develop general codes to identify all the anti-diabetic, anti-hypertensives and lipid lowering drugs based on British National Formulary chapter and drug codes. We will use these codes to identify the second-line treatment, and extract the dose and estimated dates of initiation and cessation for each treatment. To provide measures of long-term effectiveness requires that information on all relevant prescriptions is extracted for the maximum follow-up time for each patient.

Outcomes
From the onset of second-line treatment until the maximum duration of follow-up, the study will extract information from the CPRD on biomarkers (HbA1c, HDL, LDL and total cholesterol, triglycerides, SBP, DBP, eGFR, body weight, and BMI). Follow-up for all patients will be censored at the date of death, transfer out of the practice or end of data collection, whichever is earliest. We will report the time to cessation of first-line intensification. From the HES-linked data, we will use ICD10 diagnostic codes as primary or secondary diagnoses, to identify inpatient hospital admissions associated with T2DM including hypoglycaemia, MI, CHF, unstable angina, stroke, ESRD, and lower limb amputation. We will extract information on mortality, including date of death, from linkage to ONS mortality data.

Missing data in the CPRD-HES linked cohort

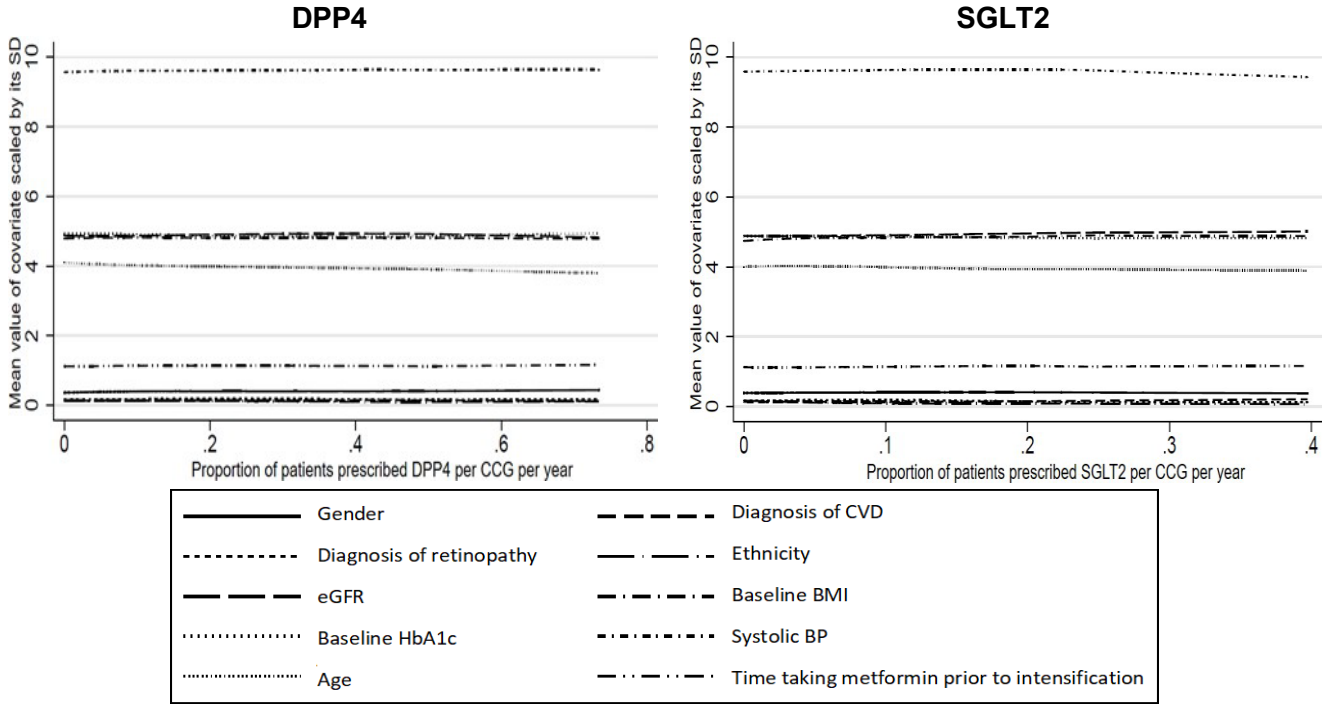
The main potential issues are missing values for baseline case-mix variables and biomarkers at particular time-points. Drawing on the precedent study we expect <5% of patients will have missing values for baseline variables such as BMI, with the exception of ethnicity (c10%), for which missing data will be minimised by using HES admission data from linked episodes.

For the main comparative effectiveness analysis (obj 2) we will handle all missing baseline and longitudinal outcome data by multiple imputation[32] with chained equations.[33] This approach assumes data are missing at random. The imputation of each long36itudinal outcome at a given time point will use all relevant information, including measurements of the same outcome at other time points. This use of auxiliary information can help the study recover more accurate estimates of the unknown outcome values.[34] This will help ensure our study population is comparable across the second-line treatments at each time point. Partially observed covariates and outcomes[35 36] will be multiple imputed by predictive mean matching with 10 donors, producing five imputed datasets. The number of imputations will be driven by the need to balance computational time with improved inference from increasing the number of imputations (see supplementary methods for further details). The imputation models developed for each covariate will be congenial with the form of outcome[37] (continuous or time to event). For the time-to-event endpoints, we will assume that there are no missing outcome data. All imputation models will be stratified by second line treatment (DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas) and by whether the individual died or was censored before the relevant study end date.

Instrumental variable
Our proposed IV design follows research in pharmaco-epidemiology[2] that uses provider preference as an instrument for treatment prescribed. The IV will be the prescribing history in each CCG. This will be defined as the proportion of relevant prescriptions within the CCG for each first-stage treatment intensification in the last complete calendar year prior to the treatment intensification of the patient currently under consideration.

The key assumptions
For the CCG prescribing history to be a valid instrument for the treatment prescribed, it has to: i) strongly predict the treatment prescribed; ii) be independent of baseline covariates; and iii) only affect the outcome through the treatment prescribed[1]. The IV design will lead to bias if the prescribing history of the CCG has a direct effect on the outcome. We carefully assessed whether the CCGs prescribing history met the criteria for an IV, and found that in the pilot data it was strongly associated with the second-line treatment regimen prescribed (assumption 1);[38] also found that prescribing history balanced the observed covariates (assumption 2) (Fig. 3).[39,40] Although we cannot assess empirically whether clinicians' prescribing history is independent of unmeasured confounders, the assumption is justified in this study, since the vast majority of patients will attend their local GP without considering their prescribing history. For assumption iii) it seems unlikely that the CCGs prescribing history would have a direct effect on the outcomes. For example, it is unlikely that just because a CCG shows a preference for prescribing SUs the patients' outcome would be better (or worse) regardless of the treatment actually taken. We will re-consider each assumption for the full CPRD dataset (see analysis section).

Fig. 3. Covariate balance across levels of the Instrumental Variables (IVs) (2014-2017). These demonstrate that clinician choice of different drugs used for intensification shows remarkably little relationship with clinical risk factors, strongly suggesting the IV approach will produce balanced valid comparison groups. A) Preference for prescription of DPP4i (prescriptions of DPP4i excluding current patient / total prescriptions) by year & CCG. B) Preference for prescribing SGLT2i (prescriptions of SGLT2i excluding current patient/ total prescriptions) by year & CCG.



Objective 1: *Inequalities*

Design

We will describe the cohort who meet the study inclusion criteria. We will include people aged 18 years or older with a T2DM diagnosis who were prescribed one of the three second-line oral antidiabetic treatments of interest between 1 January 2014 and 31 March 2020 after first-line antidiabetic treatment with metformin monotherapy. We will use a cross-sectional study design to investigate the association of the patients' ethnicity and level of deprivation in their area of residence, with the choice of second line oral antidiabetic treatment prescribed. We will use mixed-effects multivariable, multinomial logistic regression models (using a random effect to account for clustering at the CCG level) to compare the odds of initiating SGLT2i and DPP4i versus SU, and SGLT2i versus DPP4i. The covariates considered in this model will include: sex, age, time on first-line oral antidiabetic treatment (metformin monotherapy), number of patients registered at the individual's general practice, geographic region, co-prescriptions for renin-angiotensin system inhibitors (RASi) and/or statins, histories of proteinuria and hypoglycaemia, BMI (kg/m^2), HbA1c (mmol/mol), smoking status, alcohol intake, and relevant comorbidities at the time of second-line antidiabetic initiation. The model will also mutually adjust for ethnicity and deprivation (using the index of multiple deprivation (IMD)). We will use this model to report any disparities in the initiation of second-line antidiabetic treatments according to ethnicity and social deprivation level.

Outputs: We will provide an assessment of whether there are inequalities in the use of second-line treatment according to ethnicity and levels of deprivation.

Objective 2: *Comparative effectiveness*

Design

We will describe the baseline characteristics of the 'effectiveness' cohort, and the second-line treatment pathways. We will evaluate the relative effectiveness of each second-line treatment strategy incorporating the subsequent treatments that patients receive in current practice. This aspect of the study will be designed according to the target trial framework.[41] In brief, a target trial is a hypothetical RCT for assessing comparative effectiveness from observational data which requires the definition of the main elements of a trial's protocol, including eligibility criteria and the respective treatment strategies. We will apply target trial principles[41] to primary care data in England between 2015-2021 from the CPRD to identify people with T2DM who had similar prognosis prior to initiating any of the three second-line antidiabetic drug treatments under comparison.

Workshop
We will convene a design workshop to inform the proposed analysis. The panel of health care professionals and PPI representatives will advise on: the definition of personalisation; the choice of subgroup variables, building on those identified in the literature review; the communication of the risks and benefits of the alternative treatments; and the prioritisation of the different outcome measures. The clinical panelists will include diabetologists, GPs and practice nurses involved in care for people with T2DM. The majority of the PPI panellists will be people with T2DM who have experienced second-line treatment. Diabetes UK and local PPI panels convened by the co-applicants have agreed to support the study and participate in the workshops (see PPI section for full details).

Outcomes
The primary outcome will be the absolute change in HbA1c (mmol/mol) between baseline and 1-year following each second-line treatment prescription (HbA1c at 1-year – HbA1c at baseline). Treatment groups will be compared according to the mean change in HbA1c. We will use the measurement closest in time to the 1-year follow-up timepoint and allow for measures within ±90 days, otherwise the measure will be designated as missing.

Secondary outcomes will include: change in HbA1c at 2-years, and change in BMI, SBP, and eGFR all at 1- and 2-years. We also reported the time to the following first events before 2-years follow-up: (a) a 40% decline in eGFR from baseline, which could be a marker for the rarer end-stage kidney disease (ESKD) outcome,[22] (b) a major adverse kidney event (MAKE), a composite outcome for the earliest of a decline in eGFR from baseline of 40%, ESKD, and all-cause mortality,(c) heart failure hospitalisation, (d) 3-point major adverse cardiovascular event (MACE), a composite outcome for the earliest of myocardial infarction, stroke, and CVD death, and (e) all-cause mortality. We also reported time to myocardial infarction and stroke individually.

Sample size calculation
The study will include approximately 25,700 (SU=6000, DPPi4=13,000, SGLT2i=6,700) patients who meet the eligibility criteria. The FDA recommends that an average between-treatment difference in the HbA1c change from baseline of 0.4% (e.g. from 8.0% to 7.6%) is of clinical significance[42]. The assumed standard deviation of 2.4 is taken from a previous study of patients with T2DM recruited from CPRD[43]. We follow methodological recommendations for sample size calculations with IV designs, by assuming a 'base case' level of non-compliance of 10%, but also consider scenarios with alternative levels[1]. We require 90% power at the 5% (2-sided) level of statistical significance. We follow methodological recommendations for sample size calculations with IV designs by recognising that while the proposed IV is strong, it will not perfectly predict the treatment received, and so we assume the 'base case' compliance (the proportion of patients in who actually receive the treatment predicted by the IV) is 80%, but also consider scenarios where the V is weaker (70% compliance) and stronger (90%). Table 1 shows the requisite sample sizes for the two treatment groups projected to have fewest patients (SU and SGLT2i). The anticipated sample sizes will be more than sufficient across these scenarios for detecting whether the overall estimates of treatment effectiveness are statistically significant.

With the projected sample sizes, we can also report estimates of treatment effectiveness with sufficient precision for major subgroups of prime interest, for example according to established CVD (or not), and broad categories by age, and levels of baseline HbA1c, and eGFR.

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Table 1: Required sample size (N) for the IV design according to instrument strength (level of compliance) and magnitude of effect size at 90% power and 2.5% (2-sided) level of statistical significance

	Level of compliance (IV strength)					
	70%		80%		90%	
Effect size: between-treatment difference in mean HbA1c reduction baseline to 12 months	SU	SGLT2i	SU	SGLT2i	SU	SGLT2i
0.3	3416	1464	2615	1121	2066	886
0.4	1921	823	1471	630	1162	498
0.5	1230	527	941	403	744	319

Analysis

An instrumental variable (IV) analysis will address confounding by indication. The instrumental variable approach taken will be the two-stage residual inclusion (2SRI) method.[23] This approach will enable us to report comparative effectiveness across the full study populations of interest, that is, to report average treatment effects, while addressing the risk of bias from unmeasured confounding. The first stage models will estimate the probabilities for each person to be prescribed each treatment given their baseline covariates and their CCG's tendency to prescribe (TTP) that treatment. The second-stage outcome models will include generalised residuals from the first stage (propensity score) models. The outcome models will be estimated by ordinary least squares (OLS) for continuous outcomes (e.g. 1-year HbA1c), and Cox proportional hazards models for time-to-event outcomes.[45] All standard errors will be calculated with non-parametric bootstrapping, and will account for clustering of individuals within practices, and within- individual correlation introduced by repeated measures of outcomes.

Sensitivity analyses

We will undertake sensitivity analyses to consider data issues, for example by applying alternative exclusion criteria for when there is doubt about the clinical coding of T2DM[46] or the second-line treatment regimen. We will consider different assumptions about missingness patterns, for example by undertaking complete records analysis[47]. We will examine the robustness of the findings to alternative statistical models including those that use traditional IV designs and risk-adjustment.

Output

We will provide estimates of the comparative effectiveness of second-line treatments with SUs vs DPP4is vs SGLT2is.

Objective 3: *To examine heterogeneity in the comparative effectiveness of DPP4i versus SU*

We will design a second target trial to examine if comparative effectiveness of alternative second-line treatments for people with T2DM differs across patient subgroups (treatment effect heterogeneity). We will limit the scope of this investigation to the comparison of SU vs DPP4is and for the primary outcome (mean change in HbA1c between baseline and 1-year follow-up). The rationale for these choices are that it will enable us to compare the estimated treatment effects with those from a published RCT.[48] We will limit the cohort inclusion criteria to presenting for second-line treatment in years 2011 to 2015, as over this period the use of SGLT2i is low, and the vast majority of prescriptions for second-line treatment for T2DM in England are for SU or DPP4i.

We will again combine the target trial design with an IV analysis that could reduce the risk of confounding and assess treatment effect heterogeneity. We will use a different form of IV approach to the previous paper, in that we will use a local instrumental variable (LIV) method.[49,50] This approach will enable us to fully examine treatment effect heterogeneity including treatment effect modification according to levels of unobserved covariates (essential heterogeneity) across subpopulations that would –and would not– have met the eligibility criteria for the published RCT. Using the CCG's TTP DPP4i as instrument and the same covariates as in the 2SRI case in WP2, the LIV method can identify individualised treatment effects. These individual effects will then be aggregated to report average treatment effects across the full target population (defined by a national

clinical guideline), and for the 'RCT-eligible' and 'RCT-ineligible' subpopulations. Within the LIV estimation, the first-stage models will estimate the probability that each person is prescribed DDP4i given their baseline covariates and their CCG's TTP. The second-stage outcome models will then include the predicted probabilities from the first-stage (propensity score) models, covariates, and their interactions. For the RCT-eligible population we will compare the average treatment effect to those from the published RCT.

Output

We will provides assessments of heterogeneity in the comparative effectiveness of second-line treatments with SUs vs DPP4is across whole populations of interest, including those who do not meet RCT eligibility criteria

Objective 4: Comparative effectiveness according to age, baseline HbA1c, and individual risk-factor profiles of multiple long-term conditions (MLTCs).

To further assess treatment effect heterogeneity, we will assess the extent to which the relative effectiveness of the alternative second-line treatments differs according to age, baseline HbA1c, and the presence of different MLTC. It is possible that factors related to living with MLTC, for example, polypharmacy, could modify the treatment effects estimated in RCTs which tend to include healthier people living with fewer long-term conditions (LTC) compared with the general population of people with T2DM. Thus, we will investigate heterogenous treatment effects for the three second-line oral antidiabetic treatments of interest in the PERMIT study (SU, DPP4i, and SGLT2i, all added to metformin monotherapy) according to diverse MLTC and patient characteristics.

We will revert back to the three-way comparison of second-line treatments, since the potential for heterogeneous treatment effects is of interest for all three comparisons, particularly SGLT2i versus DPP4i and SU. The LIV approach cannot be used for the three-way treatment comparison and so we will use the 2SRI approach (see also objective 2). We will use the same primary outcome as for the overall comparative effectiveness study that is the mean change in HbA1c between baseline and 1-year follow-up.

Output

We will provide further assessments of heterogeneity in the comparative effectiveness of alternative second-line treatments according to age, baseline HbA1c and presence of MLTCs.

Objective 5: *Calibrate RAPIDS microsimulation model to UK data and use resultant RAPIDS-UK model to predict probabilities of long-term complications for people with T2DM in England after second-line treatment with SU, DPP4i or SGLT2i added to metformin*

The RAPIDS model predicts levels of intermediate outcomes over time, including HbA1c; BMI; serum high-density lipoprotein (HDL); low-density lipoprotein (LDL); and total cholesterol; serum triglycerides; SBP; DBP and eGFR (see Figure 4).[29] This model estimates probabilities of all-cause death and other clinical events, such as advanced diabetic eye disease, hypoglycaemia, myocardial infarction (MI), unstable angina, stroke, heart failure (HF), lower-extremity amputation (LEA), and ESKD. The inputs required by RAPIDS to estimate such probabilities include a mixture of constant risk factors (sex and ethnicity), and time-updated (over each 90-day quarter) risk factors, such as age, duration of diabetes, treatments prescribed (glucose-lowering agents, statins, and blood pressure-lowering drugs), and histories of CVD and hypoglycaemia.

We will extend the RAPIDS microsimulation model for a T2DM population in England to predict long-term outcomes following the initiation of one of the three second-line antidiabetic therapies of interest. This model will recognise diverse treatment patterns observed in routine clinical practice. We will calibrate predicted values and assess the external validation of RAPIDS when the model is applied to CPRD data.[51] We will compare the predicted outcomes across the alternative second-line treatments over a maximum follow-up of 7.6 years. We will calculate the between-treatment differences in the means of these predictions together with 95% CI. We will report the comparative effectiveness of these alternative second-line treatments on these long-term

outcomes, both overall and stratified by baseline CVD status. We will implement RAPIDS in R 4.3.1.

Outputs

We will provide an individual-level simulation model for T2DM that accurately predicts long-term outcomes according to the risk profile of general populations of people with T2DM in the UK presenting for second-line treatment. We will provide estimates of the comparative effectiveness of the alternative treatments according to long-term outcomes.

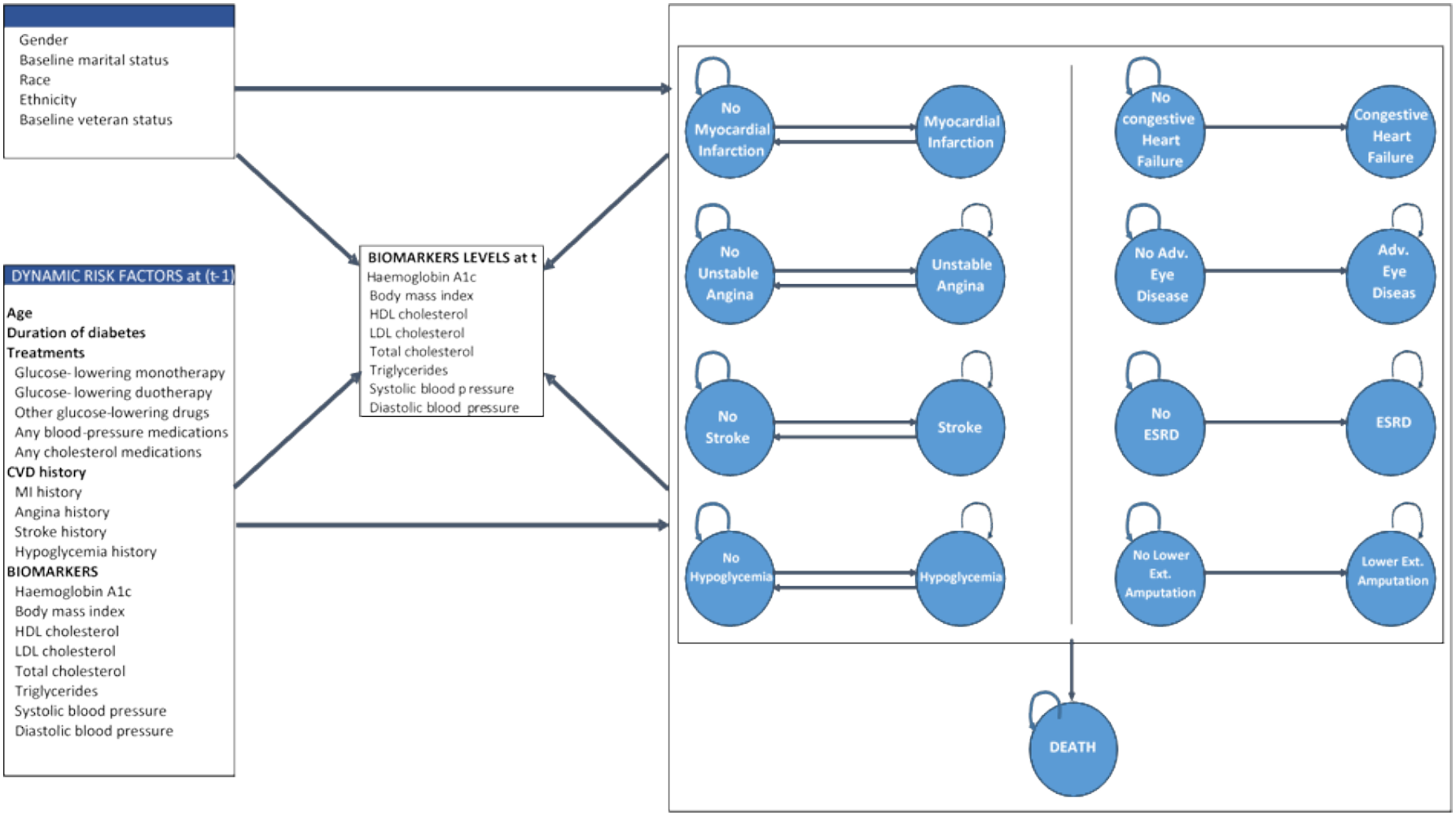

Fig. 4. The real-world progression in diabetes (RAPIDS) model. Glucose-lowering duotherapy includes dual combinations of oral antidiabetic drugs. The right hand box represents transitions over time periods. For particular events (e.g. Myocardial Infarction) the model allows patients to progress to a healthy state in the period following the event (left hand column). For other sequelae (e.g ESRD) the patient remains in that chronic disease state in the period following the event.

5.Dissemination, knowledge mobilisation and pathways to impact

Findings will be presented at UK and international conferences about diabetes care. The design and translation workshops will draw on the views of patient representatives, GPs, practice nurses, national policy makers (e.g. NICE, NHS England), to help ensure the study can inform future clinical guidelines and care for patients with T2DM. We will work closely with colleagues at NICE from the outset to ensure that the study design is defined to ensure the results can input directly into future clinical guidelines for T2DM. The research will provide recommendations via the Academic Health Sciences Networks to commissioners and providers of T2DM care on targeting second-line treatment regimens to individual patients, and those patient groups where additional evidence would be of greatest value.

While the study will use CPRD-HES data from the UK, we will ensure that both the empirical and methodological insights have wider relevance. We will work with an advisory panel (see below) to consider carefully the implications of the findings to other countries. The methods will be discussed at academic meetings, in particular, the international conference in Medical Decision-Making and the UK Health Economists' Study Group.

We will develop a study website that will be an important repository of information about the study methods and findings, for both lay and professional audiences. It will include study protocols, and early 'heatmaps' conveying the study findings. We will make a version of the long-term effectiveness model available on the project website. The website will reside within the main LSHTM website (e.g. permit.lshtm.ac.uk) and will be developed by the research manager, and then maintained by the research administrator.

6.Plans to engage patients, NHS and wider population about the work

The application has benefited from the input of co-applicant Paul Charlton, a Patient Research Ambassador Initiative member, and member of the NIHR HTA commissioning board, and Bill Huston, a patient with T2DM. The PPI representatives felt that the study design and interpretation should be informed by experiences of patients with T2DM, and have supported plans for two workshops which will include PP representatives. The first (design) workshop will inform the way personalisation is defined, and the prioritisation of the different outcome measures, and the second (translation) workshop will focus on interpretation and communication of results.

We will work with the LSHTM media department, and our lay representatives to ensure the findings are accessible to the broader public. The study website will be an important repository of information about the study methods and findings, for both lay and professional audiences. A full and complete account of the research will be made available by open access as a publication in the NIHR HTA Journal. Research papers will be published in peer-reviewed journals.

7.Project/research timetable

Grant Start date: January 2020

6 Months prior to grant start	Development of initial study protocols University ethics application and approval
Months 0-9	Application and receipt of CPRD data Data cleaning, testing of provisional drug coding algorithms consistent with GOLD and Aurum CPRD data, and VA data (US) Extraction of HES admissions according to ICD-10 codes Preparation of summary data for discussion at clinical/PPI panel
Month 6	*Clinical/PPI panel* to refine subgroup definitions, prioritisation of outcomes (*Design workshop)*
Month 9	*Advisory Group Meeting* Finalisation of study protocols and analysis plans Approval of final amendments to ethics applications
Months 9-12	Application of final coding algorithms to full CPRD-HES linked data Submission of paper to Health Economics Study Group on IV design Final study protocols, study design publications in open access journals
Months 13-18	Inequalities analysis (obj 1) Submit paper I
Month 12	*Interim report to NIHR*
Months 13-28	comparative effectiveness analysis (obj 2) submit paper II
Month 24	*Interim report to NIHR*
Month 27	*Advisory Group meeting*
Month 29-36	Heterogeneity analysis (obj 3) Submit paper III
Month 36	*Interim report to NIHR*
Month 37-44	MLTC analysis (obj 4) Submit paper IV
Month 45	*Clinical PPI panel (Translation workshop);* Advisory Group meeting

Months 46-48	Population of RAPIDS-UK model with final cut of CRPD and estimation of long-term relative effectiveness (obj 5) Submit paper V
Month 48	Presentation at international diabetes conferences
Month 48	*Draft final report to NIHR*

8. Project management

RG will take overall responsibility for project delivery (12.5% WTE over the project); he will guide the team, ensure close collaboration between the methodological and clinical inputs, monitor progress against timelines. RG will be assisted in managing this complex project by a project manager (10% WTE), who will help ensure key project milestones and deliverables are met, and by a project administrator (5%), who will both help ensure smooth collaboration between LSHTM and the project partners, and in planning workshops, advisory group meetings, and with key translation activities such as the development and maintenance of the project website. The study management group will consist of RG, ID, SoN, the Associate Professor, RA, AB, and the post-doctoral researcher based at the UoW (by Skype, years 2-3 only). The study management group will meet bi-weekly in person, and will report to the study advisory group.

The study advisory panel will be chaired by Dr Ken Patterson, Diabetologist and ex-Chair of the Scottish Medicines Consortium, and members (LSHTM unless stated) will include Profs Stephen Evans, Martin Gulliford (Kings College London), Sebastian Schneeweiss (Harvard Medical School), Alan Brookhardt (University of North Carolina), James Carpenter, Karla Diaz-Ordaz, and Gabriel Rogers (NICE). The meetings of the study advisory group will be at months 9, 27 and 45. These timings have been chosen to ensure key strategic input, and so that the advisory group can offer an overall assessment of the project's progress to help ensure timely delivery of each project component.

9. Ethics approval

The project involves the use of routinely allocated anonymous administrative data, and discussions with PPI and clinical representatives. The project will not require approval by NHS ethics committees, but will require approval by our local university ethics committee, and an application will be submitted in advance of the project start date. It is anticipated that a minor amendment to the ethics approvals will be required once the study protocols have been finalised. We will also require CPRD Independent Scientific Advisory Committee approval in order to access CPRD data.

10. Team expertise and justification of resources (see also costing section)

Prof Richard Grieve (RG) is a health economist with over 20 years of experience including in advancing quantitative methods to estimate treatment effectiveness from observational data; RG will lead the project. Prof Anirban Basu is an economist who has developed the IV method and the RAPIDS model. Basu will provide guidance throughout the project (average 7.5% WTE throughout), and specific technical input during year 2 in supervising the postdoctoral researcher develop the RAPIDS-UK model. Prof Andrew Briggs has expertise in developing T2DM models and will advise on how best to customise the RAPIDS model to the UK (1% WTE). Dr Stephen O'Neill is an econometrician and will provide the specialist skills required to undertake the LIV analysis (average 4.5% throughout).

Prof Ian Douglas (2%) and Assistant Prof Richard Silverwood (2%, no financial cost) have extensive experience in using electronic health records (EHRs) and will advise on preparing the CRPD/HES data, developing drug coding algorithms for extracting the prescription data. The research assistants (50% months 1-18) and Assistant Professor (80% throughout) will work together to extract the CPRD-HES data, develop the required coding algorithms, and extract each data item including baseline information biomarkers over time, drug use, and events from the HES linked data. The Assistant Professor will be required to develop the IV design, provide descriptive statistics, and early analyses for each workshop, lead the analyses, and help draft key papers and the final report. The post-doctoral researcher and Assistant Professor will work together to extend the RAPIDS model to the UK.

Essential clinical input into the study design, and the translation of results will be provided by Prof Liam Smeeth (2%), a clinical epidemiologist with an outstanding record in the use of EHRs, and a practicing GP; Prof Kamlesh Khunti who is Professor of Primary Care Diabetes and Vascular Medicine and past chair of NICE Guidelines on Prevention of Diabetes, and Dr. Amanda Adler, who is a diabetologist, an epidemiologist, former chair of NICE diabetes guidelines, former chair of NICE Quality Standards for Diabetes, and current chair of a NICE Appraisal Committee. Paul Charlton (PC) is a PPI representative on the NIHR HTA commissioning board and will lead the PPI input including the design and translation workshops. PC (2.5% WTE) will be actively involved throughout the project to provide oversight from the public perspective.

We have also included costs to run two PPI/clinical panels to inform the design/translation workshops, and resources for the researchers at LSHTM/UoW to meet to ensure that the key design and analysis steps are undertaken in a consistent and timely way.

11. Success criteria, barriers/risks and mitigation strategies

Success criteria	Barriers/Risks	Mitigation
Obtaining the CPRD-HES data	Access to the data can be delayed while all the approval processes are granted	Research team highly experienced in accessing CPRD-HES data. Application will be submitted prior (October 2019) to the study start date (January 2020)
Consistency of drug codes across 'new' and 'old' versions of CPRD and VA data	The definitions of each drug may differ by data source. The no. requisite drug classes is large and includes antihypertensive and antiplatelet drugs	Our teams have previously prepared and tested coding algorithms on CPRD and VA data. The research teams at LSHTM and UoW will work together closely to ensure definitions are consistent. We have costed travel between the sites, and management time to ensure careful co-ordination.
Appropriate approach to missing biomarker data	Biomarker data will not be available at three monthly intervals for all patients	We will draw on our expertise in preparing CPRD data for analysis, and specifically in handling missing data. Specifically, we will use multiple imputation to make reasonable assumptions about the missing data
IV design is judged valid	There could be insufficient variation in the prescription of the alternative drugs for first-stage intensification across CCGs or time periods	We have assessed the major IV assumptions using the pilot data, and found that they are reasonable. We will further investigate these assumptions in the full CPRD data and undertake rigorous sensitivity analyses
The study's results help inform changes to service provision	Clinical and health service decision-makers are reluctant to use evidence from an observational design to change treatment choice	Leading clinicians including those who influence guidance for T2DM have shaped this research. We will work closely with those who develop NICE guidelines those who make clinical decisions 'on the ground'

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