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Randomised cross-over trial of vildagliptin and pioglitazone as add-on therapy in patients with type 2 diabetes: predicting Which One is Right Here (WORTH) study protocol

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ABSTRACT

Introduction There is emerging evidence for stratified glucose-lowering responses to certain oral medications for type 2 diabetes (T2D) by individual characteristics. The objective of this study was to test whether glycaemic response to representative treatments of dipeptidyl peptidase-4 inhibitors (vildagliptin) and thiazolidinediones (pioglitazone) varies according to ethnicity, gender, baseline obesity, triglyceride level or genetic variation.

Methods This is a multicentre, two-period, two-treatment, open-label, randomised cross-over trial of vildagliptin and pioglitazone as second-line or third-line therapy in patients with T2D who have suboptimal glycaemic control on metformin and/or sulfonylurea therapy. It is conducted in New Zealand with a target of 300 patients (40% with Māori or Pacific ancestry) eligible if aged ≥18 and ≤80 years, with T2D for more than 1 year, on stable doses of metformin and/or sulfonylurea for at least 3 months, with HbA1c between 59 and 110 mmol/mol inclusive. Participants are assigned to complete 4 months of vildagliptin 50 mg per day or pioglitazone 30 mg per day, followed by 4 months of the other medications in randomly allocated sequences. Participant characteristics, including ethnicity, obesity, lipid profile and candidate genotypes are collected at baseline. Primary outcome variable is on treatment HbA1c. Secondary outcomes include weight change, frequency of side effects and patient preference.

Ethics and dissemination Ethical approval of the trial has been obtained from the New Zealand Health and Disability Ethics Committee (18/STH/242). The trial commenced in February 2019 and recruitment is expected to be completed by March 2020. Results will be reported in articles submitted to peer-reviewed journals, as well as in presentations at national and international meetings.

Trial registration number ACTRN12618001907235.

Strengths and limitations of this study

- ► This is the first randomised trial that aimed to test potential stratification of glycaemic response to vildagliptin and pioglitazone according to ethnicity, obesity, lipid profile and genetics.
- ► Two-period, two-treatment, cross-over trial design allows subjects to act as their own controls and thus limits confounders.
- ► Limitations include open-label treatment allocation and relatively short treatment duration on submaximal therapy.

INTRODUCTION

Type 2 diabetes (T2D) is a heterogeneous condition characterised by various underlying defects in insulin resistance, renal glucose reabsorption, impairment in pancreatic alpha and beta cell functions,[1] each of which are targeted by a range of mechanistically discrete T2D medications.[2] Although there are multiple oral agents used to treat T2D, individual glucose-lowering responses to these agents vary greatly. Hence, there is a need to develop a stratified/personalised approach that will result in more effective use of glucose-lowering therapy.

While agents from the sodium–glucose transport protein 2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) class are recommended in many cases due to their superior cardiorenal outcomes beyond glucose-lowering effects,[3] the utility of dipeptidyl peptidase-4 inhibitors (DPP4i, collectively known as gliptins, such as vildagliptin) and thiazolidinediones (such as pioglitazone), is clearly only realised through the magnitude of their glucose lowering-related benefits. Hence, identifying which subgroups of people with T2D are most likely to obtain the most glucose-lowering benefit from pioglitazone or vildagliptin therapies is

important for the patient, who can avoid side effects and time wasted from ineffective glucose-lowering therapy, thereby achieving better outcomes at reduced medication burden.

Currently, neither SGLT2i and GLP-1RA are funded in New Zealand. Prior reports indicate that sulfonylurea therapy is the most common second line-therapy after first-line metformin use in New Zealand.[4] Vildagliptin has been funded since October 2018, as the only medication in the DPP4i class (https://bpac.org.nz/2018/docs/vildagliptin.pdf), and its use is rapidly increasing as both second and third line therapy. While pioglitazone, as the only medication in the thiazolidinedione class, is also funded in New Zealand, it is prescribed infrequently, in approximately 3% of patients.[4] Currently, vildagliptin and pioglitazone are two of only three oral agents (the other being acarbose) which are funded for treatment of T2D in New Zealand, beyond metformin and sulfonylureas. Once SGLT2i and GLP1RA are funded in New Zealand, identifying subgroups who have the greatest glucose-lowering responses to these agents would also be relevant.

Routinely assessed individual patient characteristics such as ethnicity,[5 6] obesity status,[7 8] baseline triglycerides,[7] and gender[8] have been shown to predict glucose-lowering responses to DPP4i and thiazolidinediones. With respect to ethnicity, vildagliptin, (a DPP4i which acts to increase endogenous insulin production in a glucose dependent way), has been associated with greater glucose-lowering efficacy in Japanese patients.[5] This is thought to be due to more preservation of beta-cell function,[5] however, these agents may result in greater body weight gain in Asian patients.[9] Pioglitazone, (a thiazolidinedione which increases peripheral insulin sensitivity), has been associated with the least improvement in HbA1c among Indian patients.[6] Re-analysis of randomised controlled trials,[8] showed that while sulfonylureas produce similar glucose lowering among men and women of different body mass, obese women achieve greater and more durable HbA1c reduction with thiazolidinediones than sulfonylureas, while non-obese men achieve less Hba1c reduction with thiazolidinediones than sulfonylureas.[8] A recent UK study has shown, using both a prospective study and retrospective analysis of routinely collected general practice data, that those with obese range body mass index (BMI) and high triglycerides (>2.3 mmol/L) had a poorer response to DPP4i when compared with patients with lower BMI and triglycerides (11.3 mmol/mol vs 5.3 mmol/mol reduction in HbA1c, p=0.01).[7]

Genetic predictors of glycaemic response to these two T2D medication classes have also been described. Greater response to rosiglitazone has been described among Scottish patients carrying combined genotypes (SLC01B1 521T>C variant which putatively transports thiazolidinediones into the liver, and the wild-type CYP2C8 which metabolises this medication), with up to 4 mmol/mol greater Hba1c reduction (p=0.006).[10] Previous studies have shown that polymorphisms in DPP4[11 12] and GLP1R,[13 14] which are directly involved in the mechanism of action of DPP4i were associated with glycaemic response to these medications. A Taiwanese study also found that single nucleotide polymorphisms in several genes implicated in beta cell function were strongly associated with lower response to DPP4i.[15]

In New Zealand, we have identified that the derived allele of a missense variant (rs373863828, p.Arg457Gln) in the *CREBRF* gene is uniquely present in approximately 24% of those with Māori and Pacific ancestry, and is associated with 40% lower odds of T2D, yet an increase in BMI by 1.4 kg/m^2, per allele.[16] Our unpublished work suggests this genetic variant is associated with retained early insulin response. This suggests that the aetiology of T2D among those who carry the *CREBRF* variant is distinct from those without the variant, and hence such people may respond differentially to specific T2D medications. In New Zealand, T2D and its complications are more common in Māori and Pacific people.[17–19] As a result, a precision medicine approach to T2D medication selection requires particular investigation in Māori and Pacific patients in order to improve equity of diabetes related health outcomes. Knowledge of which of the T2D therapies are proven to work best in this population may improve patient outcomes and medication adherence, as there is a tendency to attribute medication non-response solely to non-adherence which can reduce engagement with care and delays timely T2D medication escalation in the presence of inadequate glycaemic response.

Trial objectives and hypotheses

This randomised cross-over trial aims to test potential stratification of glycaemic response to vildagliptin and pioglitazone according to New Zealand ethnicity, obesity, lipid profile and genotype. The primary objective is to evaluate whether people of Māori or Pacific ethnicity respond differently to vildagliptin and pioglitazone compared with non-Māori/non-Pacific people. We hypothesise that those of Māori or Pacific ethnicity will have a greater fall in HbA1c with pioglitazone compared with vildagliptin, because of greater obesity associated insulin resistance.

Self-defined ethnicity as a social construct measure of cultural affiliation, is a poor proxy for the biological or genetic determinants of drug response. Therefore, we will directly investigate factors that may underpin such differences. The secondary objectives are (a) to test potential stratification of glycaemic response according to obesity, lipid profile, CREBRF and other genotypes associated with altered response to diabetes medications (b) to develop a bioresource for the assessment of various biomarkers (including other genetic markers) and diabetes medication response.

We hypothesise that:

a. Obese patients with BMI >30 kg/m^2 and/or those with high triglycerides (TG >2.3 mmol/L) at baseline will achieve a greater lowering in HbA1c when receiving pioglitazone than vildagliptin, because pioglitazone works as an insulin sensitiser, as opposed to vildagliptin

which works through stimulating endogenous insulin secretion post-prandially.

b. Patients with the derived *CREBRF* genetic variant,[16] will respond less well to pioglitazone, which is thought to work through enhancing insulin sensitivity, and will respond better to vildagliptin which promotes insulin secretion.

METHODS AND ANALYSIS

Trial design

A multicentre, two-period, two-treatment, open-label, randomised cross-over trial. A cross-over design was chosen for this study because the within-patient variation is less than the between patient variation and thus required fewer patients than the parallel group design. This study was prospectively registered with Australian New Zealand Clinical Trials Registry (ANZCTR 12618001907235) in November 2019. The trial registration data set is available in online supplementary table 1, which includes the latest protocol version updates. Sponsor and key personnel details are available in online supplementary table 2. Ethical approval to conduct this study from the New Zealand Health and Disability Ethics committee (number 18/STH/242) was received on 12 February 2019, after which the trial commenced. Recruitment is expected to continue until March 2020 and follow-up is expected to be completed by November 2020.

Study setting

This is a multicentre study, conducted in several general practices, (primary care) and diabetes clinic sites across New Zealand, including both urban and rural regions, and includes patients from widely differing socioeconomic circumstances. These include Auckland, Waikato, Turangi, Kaitaia and Tairāwhiti through contacts established by the principal investigator (RM) on the basis of previous collaborative research or other clinical meetings.

Eligibility criteria

Patients are eligible to participate if they (1) are aged 18–80 years inclusive, with T2D for more than 1 year; (2) are on stable doses of metformin and/or sulfonylurea for at least 3 months; (3) have an HbA1c of >58 and <111 mmol/mol; (4) have never been on DPP4i or thiazolidinedione; (5) have no recent insulin use, atleast in the last 3 months; (6) have no active infection requiring antibiotics; (7) no history of active liver disease with ALT/AST above three times upper limit of normal; (8) no history of heart failure above New York Heart Association class 2, bladder cancer, macroscopic haematuria, pancreatitis or diabetic ketoacidosis; (9) not pregnant or breastfeeding or planning a pregnancy, (10) not on rifampicin, gemfibrozil, phenytoin, oral steroids or carbamazepine; and (11) able and willing to give informed consent. Women of childbearing potential must be willing to use an effective method of contraception from the time consent is signed until 7 days after treatment discontinuation. Patients are considered not of childbearing potential if they are surgically sterile (ie, they have undergone a hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or if they are postmenopausal (defined as no menstrual period for 12 months without an alternative medical cause).

Interventions

Each participant will complete 4 months of vildagliptin 50 mg per day followed by 4 months of pioglitazone 30 mg per day, or vice versa. The time to maximum efficacy and a 4-week washout period was incorporated into the treatment duration period of 4 months before the end of treatment HbA1c assessment. A drug-free washout period was deemed inappropriate as the rebound in hyperglycaemia was deemed detrimental to participants. To minimise any carry-over effects, we chose the 4-month treatment period as this was sufficient to allow for washout of the first treatment. Since both drugs have no continuing glucose-lowering effect 4 weeks after discontinuation, the end of treatment HbA1c taken at 4 months is expected to reflect glycaemia over the preceding period of 8–12 weeks.

Randomisation and blinding

Eligible participants who provide written informed consent will be randomised in a 1:1 ratio to one of the two sequences, by the central study pharmacist via a secure study database. Randomisation lists are prepared by the study statistician, using permuted block randomisation with variable block sizes (2 or 4) and stratified by recruiting region and ethnicity (Māori/Pacific vs non-Māori, non-Pacific). This is an open-label trial where both participants and research staff are aware of the treatment sequences after randomisation. The open-label nature of the study was selected for lower cost, lower complexity, higher recruitment rates and greater external validity.

Primary and secondary outcomes

The primary outcome measure is HbA1c after 4 months on each of the two drugs. Secondary outcomes include body weight, blood pressure, frequency of side effects, including hypoglycaemia, Diabetes Treatment Satisfaction Questionnaire (DTSQ)[20] total scores and change in scores, and patient preference at the end of each 4 month period. Adverse and serious adverse events will be collected throughout the trial period.

Participant timeline and visit schedule

Screening and baseline assessment (research visit 1)

Patients will be identified from primary care and research databases across multiple sites. Existing research cohorts, with permission to confirm eligibility and contact for future research, will be used in line with relevant database permissions. Primary care sites will be invited to undertake a simple database search of eligible patients, who will be contacted by their clinician and any interested people will be followed up by the research team.

After informed consent is obtained, the research team will assess these patients and those who meet the eligibility criteria will be enrolled in the study. Baseline clinical data will be collected, including age at diagnosis and

Table 1 Study timeline and investigations

Written informed consent	Screening/Baseline	4 months	8 months
Eligibility check	x		
Clinical history, ethnicity and medications	x		
Height	x		
Weight	x	x	x
Waist circumference	x	x	x
Hip circumference	x	x	x
Blood pressure	x	x	x
Laboratory Test*	x	x	x
Sample for DNA extraction†	x		
C-peptide	x		
Diabetes autoantibodies	x		
Medication dispensing	x	x	
Medication return and accountability	x	x	x
DTSQs‡	x	x	x
DTSQc§			x
Patient-reported side effects		x	x
Patient overall study medication preference			x

*blood sample for creatinine, lipid profile, liver enzymes, glucose, HbA1c
†Genotyping for CREBRF and other genetic variants associated with glucose lowering response to diabetes medications
‡Diabetes treatment satisfaction questionnaire (status version)
§Diabetes treatment satisfaction questionnaire (change version)

duration of diabetes, height, weight, waist-hip ratio, blood pressure, ethnicity, current treatment, family history and co-morbidities (see table 1). Baseline data on patient preference and priorities about therapy will be collected in the form of the DTSQ. This covers eight items with regard to the diabetes treatment over the past few weeks and measures overall satisfaction, convenience, flexibility, understanding of diabetes, willingness to recommend current treatment to others and willingness to continue the current treatment. The participant will score each item from a scale from 0 (very dissatisfied) to 6 (very satisfied), and each score (except item 2 and 3) are added to produce the total DTSQ score. Higher total score indicates higher treatment satisfaction and vice versa. Fasting blood test will be done to assess for baseline Hba1c, fasting glucose, lipids, renal and liver function tests, genetic test, C-peptide and diabetes autoantibodies (see table 1). Participants are then randomised to complete 4 months of vildagliptin followed by 4 months of pioglitazone or vice versa.

Participants will be asked not to change their usual diabetes treatment (ie, metformin and/or sulfonylurea) for the duration of the study, unless required for hypoglycaemia. The study team will manage only the study medications for the duration of the participant's involvement in the study. A text reminder for starting the study medication and for promoting adherence will be sent to participants by Zoom pharmacy. The general practitioner or secondary care diabetes team will manage other aspects of diabetes care in line with standard clinical practice.

Follow-up visit 2 and visit 3

Participants are followed up at the end of each 4-month treatment period (research visit 2 and visit 3). Fasting blood tests will be taken to measure glycaemic response (HbA1c), fasting glucose, liver enzymes and lipids . Weight, waist and hip circumferences, blood pressure and data about patient experience will also be collected including perceived side effects, and preparedness to remain on this therapy as part of the DTSQs. Participants will also complete the Diabetes Treatment Satisfaction Questionnaire Change (DTSQc) version [21] at research visit 3 to assess for change in satisfaction after trialling both study medicines. The DTSQc also overcomes potential ceiling effects of DTSQs where respondents who score maximum or near-maximum satisfaction at baseline and can show little or no improvement at follow-up if DTSQs was used alone.[21] Medication adherence will be assessed using self-reported adherence and pill count.

At the end of the study (research visit 3), patient treatment preference will be recorded after ascertaining their HbA1c, weight change, frequency of hypoglycaemia and any patient-reported side effects. Each participant will then be asked which treatment they would prefer to take long term and the reason for their preference.

Sample size

This trial aimed to assess whether one patient group responds differently to two test drugs compared with other patient groups. A target sample size of 300 participants will be recruited between 1 February 2019 and 30 March 2020, with a target of 40% Māori or Pacific participants (n=120). This sample size will provide 80% power at 5% significance level to detect a minimal effect size of 0.35 SD between two patient groups on the difference in HbA1c between two test drugs, allowing for 10% loss to follow-up. The study may recruit beyond the target sample size of 300 (up to a maximum of 400 participants) as long as it is still within the recruitment period.

In a cross-over trial of metformin versus repaglinide[22] (an insulin secretagogue), the SD of change in HbA1c on two different therapies in a cross-over trial setting is 8.7 mmol/mol. Data from Clinical Practice Research Datalink shows obese patients respond better to thiazoledinediones, and non-obese patients respond better to DPP4i, with an overall difference in response between strata of 3.1 mmol/mol (equivalent to 0.36 SD).[7]

Data management

All study data will be collected and managed using Research Electronic Data Capture electronic research management database, which is password-protected. Participant files will be securely stored on site at the participating sites. The final anonymised study dataset will be available to the investigative team.

Statistical analysis

Statistical analysis will be performed using SAS V.9.4. All statistical tests will be two-sided at 5% significance level. The primary analysis will follow the principle of intention to treat, including all randomised participants in the allocated treatment sequences for two drugs. Per protocol analysis will be conducted on those participants with no major protocol deviations. Baseline characteristics will be summarised by patient group. Continuous variables will be presented as mean, SD, median and range. Categorical variables will be presented in frequencies and percentages. The primary hypothesis about whether the difference in achieved HbA1c for the two drugs is different between Māori/Pacific patients and non-Māori non-Pacific patients will be tested using linear mixed model regression with both fixed and random effects. The fixed effects will include the baseline outcome value, stratification factors, cross-over period, drug class, patient group and its interaction with the drug. The random effect will include patients as the cluster. Model-adjusted difference in HbA1c between two test drugs will be estimated for each patient group with 95% CIs. Missing data on the outcome measure will be considered in maximum likelihood estimates assuming missing at random. Sensitivity analysis on the primary outcome using different imputation methods on the missing data will be used to test the robustness of main findings. Similar regression analysis will be carried out to test secondary hypotheses. An overall model without patient groups will also be considered to determine whether there is a difference between two drugs in achieved HbA1c after 4 months on each of the drugs. Period effects will be assessed as part of the final analysis. Generalised linear mixed models will be used on other secondary outcomes measured at the end of each 4-month period using an appropriate link function. All adverse events collected during the study period will be summarised descriptively.

In the secondary analysis, any effect of the CREBRF genetic variant (A-allele of rs373863828) on drug response will be tested by linear regression testing for association of the A-allele with magnitude of change in HbA1c. In addition to standard covariates, ancestral informative markers and multidimensional scaling will be included to account for stratification owing to admixture (primarily with people of European ancestry).[16]

Data safety monitoring committee

An independent data safety monitoring committee was not deemed necessary by the Health research council data safety monitoring committee who reviewed the study protocol. While it considered that the study involved randomisation, the medications used in the study were all in current clinical use in these patients. Nonetheless, a less formal independent data safety monitoring committee was assembled to be responsible for safeguarding the interests of trial participants. The committee are tasked with assessing the safety of the interventions during the study period, and to monitor the overall progress and conduct of the trial. No interim analyses, stopping guidelines or audits of trial conduct are planned.

Study intervention safety

Vildagliptin is well tolerated with infrequent short-term side effects and is weight neutral with a low risk of hypoglycaemia in comparison to other therapies.[23] The most common reported side effects include hypoglycaemia (where cotreated with insulin/sulfonylurea), asthenia, fatigue, oedema, gastrointestinal disturbance and headache. However, many of these have similar incidence to placebo on meta-analysis of published trials.[23] Large cardiovascular outcome trials and meta-analysis of this drug class demonstrate cardiovascular safety.[24] Due to an excess of case reports and animal data, there has been concern that DPP4i may cause pancreatitis. This association has not been supported by recent large cohort studies, meta-analysis of published trials or recent large interventional trials.[25–27]

Major side effects of pioglitazone include gastrointestinal disturbances, weight gain (mean 2.8 kg at 1 year) and fluid retention, which may lead to oedema and exacerbation of existing heart failure. In patients with pre-existing cardiovascular disease, and therefore high heart failure risk, heart failure requiring hospitalisation occurred in 5.7% pioglitazone vs 4.1% of placebo participants, but mortality and subsequent morbidity were not different.[28] Pioglitazone appears to have modest favourable effects on cardiovascular outcomes.[29] The risk of hypoglycaemia is low but may occur in patients also treated with insulin or a sulfonylurea. Long-term treatment is associated with an increased risk of fracture in women (OR 1.94)[29] and an increase in the risk of bladder carcinoma (HR 1.23 or 5 additional cases per 100 000 patient years in meta-analysis of randomised controlled trials).[30 31] There have been rare reports of hepatocellular dysfunction; therefore, pioglitazone should not be initiated in patients with active liver disease.

The study eligibility criteria ensure that patients will be excluded if they have contraindications to vildagliptin or pioglitazone based on their New Zealand Medicines and Medical Devices Safety Authority (Medsafe) registration data. Participants are also closely monitored throughout the study for any adverse events.

Patient and public involvement

A group of eight patients with T2D, including three of Māori and Pacific ethnicity, were consulted about the study rationale and study design in a group meeting held at the Auckland Diabetes Centre in November 2018,

prior to seeking ethics approval for this study. They all expressed enthusiasm about the focus of the research aims and provided input into the recruitment strategy. They advised on the appropriateness and burden of the data collection plan, checked comprehension and provided edits on the participant information sheet. Their comments and feedback were incorporated into the final study design and ethics application. The consent process includes opportunity for discussion with family (whanau), and option for karakia (Māori prayers) when research blood samples are disposed.

DISCUSSION

Various studies in European and Asian patients with T2D have demonstrated that certain clinical characteristics such as ethnicity, body mass index (BMI), gender and genotype may predict an individual's response to various hypoglycaemic agents.[5 7–9 16] These findings need evaluation in a randomised, prospective trial setting in the New Zealand population, particularly among Māori and Pacific patients who have a greater burden of disease and complications related to T2D,[17–19] as well as a distinct genetic background, with 25% prevalence of CREBRF variant, which has the largest impact on BMI and T2D for a common genetic variant to date.[16 32]

One of the limitations of our study design is the potential for carry-over effects of the first study medication on the second study medication. We elected against a washout period because of the risks of hyperglycaemia; however, our choice of 4-month treatment period was designed to minimise carry-over effect from the first medication beyond the first 1-month of crossing over. Since Hba1c reflects glycaemic control over the preceding period of 8–12 weeks only, and both drugs have no glucose-lowering effects beyond 4 weeks after discontinuation, there would have been little carry-over effects after a treatment period of 4 months on each medication.[33] It is possible the 4-month treatment duration may be shorter than the duration required to reach the maximum glucose-lowering effect. However, it appears that near-maximal HbA1c lowering with both vildagliptin and pioglitazone is realised at 3 months of treatment.[34 35] Although non-maximal doses of both vildagliptin and pioglitazone will be evaluated in this study, there is modest additional HbA1c lowering with either vildagliptin given at a dose of 50 mg two times per day compared with once a day[36] or with pioglitazone 45 mg compared with 30 mg.[37] A further limitation is that the open-label use of the two medications could introduce some bias in the reporting and assessment of outcomes. Nevertheless, this is a pragmatic study design assessing the ability to predict side effects and efficacy associated with real-world use of these medications.

Overall, this study should provide novel data on the potential utility of baseline clinical characteristics in predicting glucose-lowering response to either pioglitazone or vildagliptin, providing a more rational approach to selection of T2D medication in the New Zealand population.

Ethics and dissemination

Ethics approval has been granted by the New Zealand Health and Disability Ethics Committee (18/STH/242). This study was prospectively registered at ANZCTR and all protocol modifications have been updated through both the ethics committee and the ANZCTR. The trial commenced in February 2019 and recruitment is still ongoing. The results of this study will be reported back to participants and health providers in each site as summary statements, in manuscripts submitted to peer-reviewed journals, as well as in presentations at national and international meetings.

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Contributors RY wrote the first draft of the manuscript based on the study protocol written by RM, who conceived the study idea, obtained the funding and is the guarantor of the study. YJ is primarily responsible for the statistics analysis plan. TRM is responsible for the genetic analysis plan. DG contributed to the study design as lead pharmacist. Trial implementation, conduct and data acquisition were conducted by RB, AM, GD, RP, JHH, BO-W and KM-S). All authors read and approved the final version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

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