TriMaster - a research study to help improve treatment of type 2 diabetes, by learning how individuals respond to different blood sugarlowering drugs

Submission date	Recruitment status	[] Pro
02/11/2016	No longer recruiting	[X] Pr
Registration date	Overall study status	[X] St
30/11/2016	Completed	[X] Re
Last Edited 12/12/2022	Condition category Nutritional, Metabolic, Endocrine	[] Inc
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Plain English summary of protocol

Background and study aims

Type 2 Diabetes is a common health condition where the sufferer has difficulty controlling their blood sugar (glucose) as they do not produce enough insulin to function properly (insulin deficiency), or that the body's cells don't react to insulin as they should do (insulin resistance). Over 4% of the population has Type 2 diabetes. It is a major cause of illness and accounts for around 10% of the money spent in the NHS. Good control of blood sugar with appropriate life style and medication makes patients feel better and reduces the risks of complications of diabetes. The current guidelines for treatment of patients with Type 2 diabetes list a large number of drugs without giving clear guidance on which patients should have which drugs. This makes it difficult for patients and their health care professionals to know which drugs are likely to suit them best. In type 2 diabetes, it is common for additional treatments to be added over time to maintain, or lower, blood sugar levels. Responses to this change of treatment can vary between individuals, but little is known about why this happens. If it was possible to predict which medicine is likely to work for a person, the most effective treatment could be chosen from the start, avoiding ineffective medicines and unnecessary side effects. This study is looking at three standard diabetes treatments which can be added when two existing medicines stop maintaining good blood sugar levels. The aim of this study is to compare how patients with different blood sugar levels, weight and kidney function respond, and which treatment each patient prefers.

Who can participate?

Adults aged between 30 and 80 who have Type 2 Diabetes and are currently taking two oral diabetes medications but whose blood sugar levels mean they need an additional (third) medication.

What does the study involve?

Participants are assigned to undergo treatment with three different study drugs in a random order for 16 weeks. Before each medicine cycle, participants attend a study visit with a research nurse, where they undergo repeated blood sampling after drinking a 'meal' drink (like a milkshake) to test the pattern of their blood sugar levels. At the end of visit the participants are given their first pot of study medication. All of the medications are in the form of a plain capsule to be taken once a day in addition to existing diabetes medications. The participant is also be given them a card to carry with them in case a doctor needs to know which treatment they are taking in an emergency. While they are taking the medications, participants are asked to keep a note of any new symptoms they. At the end of all three medicine cycles, participants are interviewed to find out which medication they preferred. In addition, their blood sugar tests before and after each cycle are compared to see which medication was most effective for them.

What are the possible benefits and risks of participating?

The main benefit for research participants is that future care could be informed and improved by results from the study which show which patients may do best on which treatment. In addition, we are recruiting patients who need another (third) therapy to maintain good blood sugar levels. These participants will be able to 'test' the 3 available drugs that their doctor could prescribe, in a trial setting, with support from the research team. At the end of their study involvement, participants and their clinicians will receive un-blinded results of blood sugar tests, weight, and frequency of side effects. Clinicians will be able to use this data alongside the participant's medical history, their own clinical judgement and the patient's preference to make an informed decision about recommended future treatment. The main risk to participants is the risk of low blood sugar (hypoglycaemia) and other side effects from the study drugs. If a participant has a very good response to a study drug they could be at some risk of low blood sugar. Long term hypoglycaemia can lead to complications but the brief period which would be possible in the study is of very low risk. By taking a standard diabetes drug in a trial setting participants will receive equal if not better care and support than if this was prescribed by their usual doctor. We will take steps to make sure participants are closely monitored and have instructions for what to do should they experience low blood sugar. Participants may also experience some side effects whilst taking the study drugs. These drugs are all licensed, well-established medications recommended by NICE for these patients. They will be prescribed as per usual clinical care guidelines in a standard dose. All medications can result in side effects and participants will be provided with a list of common, uncommon and serious potential side effects and what to do should they occur before they choose to take part.

Where is the study run from?

Royal Devon and Exeter Hospital (lead centre) and 19 other hosptials in England, Scotland and Wales (UK)

When is the study starting and how long is it expected to run for? August 2016 to December 2021

Who is funding the study? Medical Research Council (UK)

Who is the main contact? Ms Catherine Angwin c.angwin@exeter.ac.uk

Study website https://www.diabetesgenes.org/current-research/trimaster/

Contact information

Type(s)

Public

Contact name Ms Catherine Angwin

ORCID ID http://orcid.org/0000-0002-0935-5284

Contact details University of Exeter Medical School and NIHR Exeter CRF RILD, L3 Rm 2.15 Royal Devon and Exeter Hospital (Wonford) Barrack Road Exeter United Kingdom EX2 5DW +44 1392 408181 c.angwin@exeter.ac.uk

Additional identifiers

EudraCT/CTIS number 2015-002790-38

IRAS number 183044

ClinicalTrials.gov number NCT02653209

Secondary identifying numbers 31613, IRAS 183044

Study information

Scientific Title

TriMaster: Randomised Double-Blind Crossover study of a DPP4 inhibitor, SGLT2 inhibitor and thiazolidinedione as third line therapy in patients with type 2 diabetes who have suboptimal glycaemic control on dual therapy with metformin and a sulphonylurea

Acronym

TriMaster

Study objectives

Hypotheses:

1. Patients with insulin resistance, characterised clinically by a raised BMI (>30 kg/m2), compared to non-obese patients, will:

1.1. Respond well to pioglitazone, a thiazolidinedione that works as an insulin sensitiser

1.2. Respond less well to sitagliptin, a DPP4i, which works through stimulating endogenous insulin secretion post-prandially.

2. Patients with modestly reduced estimated glomerular filtration rate (eGFR 60-90 mls/min/1. 73m2), compared to those with eGFR >90 mls/min/1.73m2, will:

2.1. Respond poorly to canagliflozin, a SGLT2 inhibitor, which works through inhibiting the active reabsorption of glucose in the proximal tubule, as the reduced eGFR will reduce the glucose-lowering efficacy

2.2. Respond well to sitagliptin, a DPP4i that is renally cleared, as the reduced eGFR will increase plasma DPP4i concentrations

Ethics approval required

Old ethics approval format

Ethics approval(s) South Central - Oxford A Research Ethics Committee, 09/05/2016, ref: 16/SC/0147

Study design Randomised; Interventional; Design type: Treatment, Drug

Primary study design Interventional

Secondary study design Randomised controlled trial

Study setting(s) Hospital

Study type(s) Treatment

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied

Type 2 diabetes mellitus

Interventions

All participants receive all three treatments in random order, according to one of six possible treatment order ABC, ACA, BAC, BCA, CAB, CBA.

The treatment study drugs are over-encaspulated capsules taken once a day for 16 weeks (16-18 week window).

- 1. Pioglitazone 30mg
- 2. Sitagliptin 100mg
- 3. Canagliflozin 100mg

Following screening and confirmation of eligibility, participants are randomises by the trial database and allocated a treatment order. They then receive the three treatments for 16-18 weeks at a time, with no washouts between treatment periods.

At the end of each treatment period participants attend a research visit for sample and data collection. A final follow-up visit is conducted 2-4 weeks after all study treatments have concluded.

Intervention Type

Other

Primary outcome measure

Glycated haemoglobin (HbA1c) is measured using a HbA1c test on blood samples collected at baseline, 8 and 16 weeks of each treatment cycle.

Secondary outcome measures

Patient treatment preference will be recorded through participant interviews at the end of the study.

Overall study start date

01/08/2016

Completion date

14/12/2021

Eligibility

Key inclusion criteria

1. Clinical diagnosis of Type 2 diabetes

2. Age ≥30 and ≤80

3. Currently treated with two classes of oral glucose-lowering therapy (given either as separate or combined medications), that do not include a DPP4-inhibitor, a SGLT2-inhibitor or a thiazolidinedione. This is likely to be metformin and sulphonylurea but may include prandial glucose regulators nateglinide or repaglinide.

4. No change in diabetes treatment (new treatments or dose change) within previous 3 months 5. HbA1c > 58mmol/mol (7.5%) – confirmed at screening visit

- 6. eGFR \geq 60mls/min/1.73m² confirmed at screening visit
- 7. Able and willing to give informed consent

Participant type(s) Patient

Age group

Adult

Sex Both

Target number of participants Planned Sample Size: 600; UK Sample Size: 600

Total final enrolment 525

Key exclusion criteria

1. Changes in glucose-lowering therapy or dose within last 3 months

- 2. HbA1c ≤ 58mmol/mol (7.5%)
- 3. eGFR 2.5 x upper limit of the assay normal range or known liver disease, specifically >30 µmol
- /L that is associated with other evidence of liver failure.
- 4. Currently treated with corticosteroids
- 5. Active infection (any infection requiring antibiotics at present)

6. Active foot ulcer

7. Recent (within 3 months) significant surgery or planned surgery (excluding minor procedures)

8. Acute cardiovascular episode (angina, myocardial infarction, stroke, transient ischemic episode) occurring within the previous 3 months

- 9. History of heart failure or current use of loop diuretic therapy (Furosemide or Bumetanide)
- 10. History of bladder carcinoma or current/ongoing investigation for macroscopic haematuria
- 11. History of Diabetic Ketoacidosis or pancreatitis
- 12. Pregnant, breastfeeding or planning a pregnancy over the study period
- 13. Concurrent Participation on another Clinical Trial of an Investigational Medicinal Product
- 14. Unable or unwilling to give informed consent

Date of first enrolment

01/11/2016

Date of final enrolment 31/01/2020

Locations

Countries of recruitment England

Scotland

United Kingdom

Wales

Study participating centre Royal Devon and Exeter Hospital Royal Devon and Exeter NHS Foundation Trust Barrack Road Exeter United Kingdom EX2 5DW

Study participating centre Ninewells Hospital & Medical School NHS Tayside Dundee United Kingdom DD1 9SY

Study participating centre

BHF Glasgow Cardiovascular Research Centre Greater Glasgow & Clyde Health Board - BHF CGRC Institute of Cardiovascular & Medical Sciences University of Glasgow 126 University Place Glasgow United Kingdom G12 8TA

Study participating centre Musgrove Park Hospital

Taunton and Somerset NHS Foundation Trust Taunton United Kingdom TA1 5DA

Study participating centre

Royal Sussex County Hospital

Brighton and Sussex University Hospitals NHS Trust Eastern Road Brighton United Kingdom BN2 5BE

Study participating centre Manchester Royal Infirmary

Central Manchester University Hospitals NHS Foundation Trust Oxford Road Manchester United Kingdom M13 9WL

Study participating centre Churchill Hospital

Oxford University Hospitals Old Road Headington Oxford United Kingdom OX3 7LE

Study participating centre

Northern General Hospital Sheffield Teaching Hospitals NHS Foundation Trust Herries Road Sheffield United Kingdom S5 7AU

Study participating centre Freeman Hospital

The Newcastle Upon Tyne Hospitals NHS Foundation Trust Freeman Road High Heaton Newcastle Upon Tyne United Kingdom NE7 7DN

Study participating centre Queen Alexandra Hospital

Portsmouth Hospitals NHS Trust Southwick Hill Road Portsmouth United Kingdom PO6 3LY

Study participating centre Southmead Hospital

North Bristol NHS Trust Southmead Road Westbury-on-Trym Bristol United Kingdom BS10 5NB

Study participating centre Derriford Hospital Plymouth Hospitals NHS Trust

Derriford Road Plymouth United Kingdom PL6 8DH

Study participating centre Prince Philip Hospital

Hywel Dda University Health Board Bryngwyn Mawr Dafen United Kingdom SA14 8QF

Study participating centre

Morriston Hospital

Abertawe Bro Morgannwg University Health Board Heol Maes Eglwys Morriston Swansea United Kingdom SA6 6NL

Study participating centre

Royal Cornwall Hospital Royal Cornwall Hospitals NHS Trust Treliske Truro United Kingdom TR1 3LJ

Study participating centre University Hospital of Wales Cardiff and Vale University Health Board

Heath Park Cardiff United Kingdom CF14 4XW

Study participating centre Guy's Hospital Guy's and St Thomas' NHS Foundation Trust Great Maze Pond London United Kingdom SE1 9RT

Study participating centre East Surrey Hospital Surrey and Sussex Health NHS Trust Canada Avenue Redhill United Kingdom RH1 5RH

Study participating centre Queen Elizabeth The Queen Mother Hospital East Kent Hospitals University NHS Foundation Trust St Peters Road Margate United Kingdom CT9 4AN

Sponsor information

Organisation Royal Devon and Exeter NHS Foundation Trust

Sponsor details

Royal Devon and Exeter Hospital Research & Development Office 3rd Floor, Noy Scott House Barrack Road Exeter England United Kingdom EX2 5DW

Sponsor type Hospital/treatment centre

ROR

https://ror.org/03085z545

Funder(s)

Funder type Research council

Funder Name Medical Research Council

Alternative Name(s) Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type Government organisation

Funding Body Subtype National government

Location United Kingdom

Results and Publications

Publication and dissemination plan

Data and results related to protocol-derived outcomes will be published by the MASTERMIND consortium. A lay summary of results will be provided to all participants. Analysis will be conducted from recruitment end with results intended for publication from early 2020 onwards.

Intention to publish date

30/06/2022

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from the Chief Investigator Andrew Hattersley (A.T.Hattersley@exeter.ac.uk)

IPD sharing plan summary

Available on request

Study outputs

Study Outputs					
Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<u>Protocol article</u>	protocol	01/12/2020		Yes	No
<u>Statistical Analysis Plan</u>	version 9	11/03/2021	24/03/2021	No	No
<u>Results article</u>	prespecified secondary endpoint data	07/12/2022	12/12/2022	Yes	No
<u>Results article</u>	primary endpoint results	07/12/2022	12/12/2022	Yes	No
HRA research summary			28/06/2023	No	No