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

Submission date
02/11/2016

Recruitment status
No longer recruiting

Registration date
30/11/2016

Overall study status
Completed

Last Edited
12/12/2022

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

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
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2015-002790-38

Integrated Research Application System (IRAS)
183044

ClinicalTrials.gov (NCT)
NCT02653209

Protocol serial number
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

Study type(s)
Treatment

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

Key secondary outcome(s))

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

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

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

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
United Kingdom

England

Scotland

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
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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
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S5 7AU

Study participating centre
Freeman Hospital
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freeman Road
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NE7 7DN

Study participating centre
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Portsmouth Hospitals NHS Trust
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PO6 3LY

Study participating centre
Southmead Hospital
North Bristol NHS Trust
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Derriford Hospital
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Study participating centre
Prince Philip Hospital
Hywel Dda University Health Board
Bryngwyn Mawr
Dafen
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SA14 8QF

Study participating centre
Morriston Hospital
Abertawe Bro Morgannwg University Health Board
Heol Maes Eglwys
Morriston
Swansea
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SA6 6NL

Study participating centre
Royal Cornwall Hospital
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TR1 3LJ

Study participating centre
University Hospital of Wales
Cardiff and Vale University Health Board
Heath Park
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CF14 4XW

Study participating centre
Guy's Hospital
Guy's and St Thomas' NHS Foundation Trust
Great Maze Pond
London
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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

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, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

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

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	prespecified secondary endpoint data	07/12/2022	12/12/2022	Yes	No
Results article	primary endpoint results	07/12/2022	12/12/2022	Yes	No
Protocol article	protocol	01/12/2020		Yes	No
HRA research summary			28/06/2023	No	No
Statistical Analysis Plan	version 9	11/03/2021	24/03/2021	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes