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Magnetic resonance imaging (MRI) for abdominal aortic aneurysms to predict rupture or surgery: the MA3RS trial

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Registration date 04/03/2013	**Overall study status** Completed	
Last Edited 10/10/2019	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
The aorta is the main blood vessel that comes out of the heart and rapidly distributes blood to the whole body. In some people, the aorta becomes swollen (an aneurysm) especially as it passes through the abdomen. These abdominal aortic aneurysms (AAA) usually grow slowly without causing any symptoms, but they can sometimes burst or need to be fixed by an operation. Currently aneurysms are monitored by ultrasound scanning. The aim of this study is to see whether magnetic resonance imaging (MRI) might be a better way of following patients who have an aneurysm. To do this, a contrast agent (Ferumoxytol) will be used that contains tiny iron filings that are eaten up by cells (called macrophages) in the wall of the aneurysm. The MRI scanner can then be used to get a picture of the aneurysm. In a small
group of patients, it has been found that this MRI scan can be used to detect 'hotspots' in the wall of some aneurysms that seemed to grow more quickly than others. The aim of the current study is to confirm these findings in a larger group of patients and also to see whether MRI scanning can identify patients with aneurysms at risk of bursting or those that go on to need an operation.

Who can participate?
Patients who are more than 40 years old with an AAA

What does the study involve?
At the start of the study, participants come to the hospital on two separate days. On the first day they are asked about any existing or previous medical conditions, give a blood sample (about 4 teaspoonfuls - 20 ml) and their blood pressure is checked. They have an MRI scan of their abdomen to look at their aneurysm. Through a drip in their arm they receive a drug called Buscopan which helps stop the
digestive movements in the abdomen so that the MRI scanner can get a clear picture. If they are unable to have this drug it will not be given but the scan goes ahead. They also have a CT scan of their abdomen at this appointment. Computed Tomography (CT) scanning uses an x-ray machine to give a detailed 3D picture. In order for the scanner to give a clear picture, participants are given an injection of a standard contrast agent into the drip in their arm. CT scanning is often

used to assess aneurysms, for example if an operation is being considered. As part of this study, participants have a CT scan when they enter the study and two years after entry into the study to provide detailed information about whether the aneurysm has changed in size. After both the scans, participants receive Ferumoxytol through the drip in their arm and their blood pressure is monitored for 30 minutes after this. This visit will last about three hours. The following day participants return to the hospital to have a further MRI scan of their abdomen to look at their aneurysm. Participants need to have a drip in their arm again, as they need to have buscopan before the scan (as they did on the first day). The second visit takes about 40 minutes.
Either on day 1 or day 2 the stiffness of your arteries is measured by recording blood pressure from the arm and leg. This is called pulse wave analysis. For this part of the study participants are asked not to eat anything and avoid caffeine (water is fine) for 4 hours before their appointment time. In addition they should avoid alcohol for 24 hours before this appointment. A small number of patients (40) are asked to return for a further two visits, one month and one year after the original visit to redo the scans with repeated doses of ferumoxytol and buscopan. Participants get two extra MRI scans at 1 month plus ferumoxytol and buscopan and two extra MRI scans at 1 year plus ferumoxytol and buscopan. This determines how repeatable the scan is.
As participants have an AAA, they routinely attend the hospital every 6 months for an ultrasound scan of their aneurysm so it can be monitored. This still happens when they take part in this study. A blood sample is taken(about 4 teaspoons - 20 ml, which would not normally be done). In addition pulse wave analysis is also repeated at these 6 monthly visits. This adds about 40 minutes onto the visit. If participants require surgery to treat their aneurysm during their involvement in the study, a sample of tissue is taken from the wall of the aneurysm after it has been repaired. This tissue would normally be discarded. The sample is tested to assess the strength of the wall and its structure. Participants are part of the study for 2 years.

What are the possible benefits and risks of participating?
It is hoped that the findings of this study will benefit other patients with aneurysms in the future. It is unlikely that there will be any side effects from taking part in this study. MRI scanners do not use X-rays but instead use strong magnets which do not cause any problems for the vast majority of people, but for a small number (such as those who have a pacemaker for their heart) it is advisable to avoid having one of these scans. A CT scan is a routine medical procedure and it is possible that participants would require CT scans to assess their AAA even if they were not part of this study. The scan itself is associated with very few side effects. The most important potential side effect, as with any x-ray scan, is the use of radiation. The amount of radiation used during the scan varies but is around 2 to 3 times the amount that participants would normally receive in a year from background natural sources of radiation, such as from rocks in the Earth's crust. The lifetime risk of developing cancer from the x-rays involved in the CT scan is very small. Before giving participants the CT contrast agent, the function of their kidneys is checked and they are asked if they have any known allergies to this contrast agent. If there are any concerns regarding either of these two factors, they are not be given the contrast agent. Ferumoxytol is routinely used to treat people who have low levels of iron in their blood. The iron filings are absorbed into the body's general iron stores. Whilst most people do not have any symptoms when receiving the contrast agent, a small minority of people experience mild side effects. These are uncommon (affecting between 1 to 3 in every 100 patients) and include: nausea, vomiting, abdominal or chest pain, dizziness, low blood pressure, headache, shortness of breath, cough, skin rash or itch, swelling of the ankles and muscle cramps. As with any medication, serious side effects such as severe allergies are possible but are extremely rare. Blood pressure is monitored 30 minutes after you are given the Ferumoxytol.
Most people do not have any symptoms when receiving buscopan, but a minority of people experience mild side effects. These are very uncommon (affecting 1 in 1000) and include: dry mouth, a fast heart rate, a skin rash or itch, constipation. As with any medication, serious side effects, such as severe allergies can happen but are rare. There is a possibility that the scans

performed in this study could reveal an incidental health problem. If this were to happen this would be discussed and appropriate further tests and treatments arranged as necessary. This may be viewed as a positive thing but it must be remembered that this could affect insurance policies. Participants should also understand that there may be other conditions that do not show up on this kind of scan.

Where is the study run from?
The study is being run by the University of Edinburgh and will be taking place in Edinburgh, Glasgow and Forth Valley (UK)

When is the study starting and how long is it expected to run for?
September 2012 to September 2016

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

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2012-002488-25

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
11/20/03

Study information

Scientific Title
Magnetic Resonance Imaging using ultrasmall supermagnetic particles of iron oxide in patients under surveillance for abdominal aortic aneurysms to predict rupture or surgical repair

Acronym
MA3RS

Study objectives
Ruptured Abdominal Aortic Aneurysms (AAA) is the thirteenth commonest cause of death in the United Kingdom and accounts for 6,800 deaths each year in England and Wales. Population screening halves the mortality associated with AAA, and has led to the establishment of national screening and surveillance programmes. However, AAA surveillance is complex because of the non-linearity and unpredictability of expansion rates. Although the best predictor of aneurysm expansion is the aneurysm diameter, up to one fifth of ruptured AAA are less than 55 mm in diameter, and many patients present with diameters considerably greater than 55 mm without prior symptoms or rupture. There is therefore a major unmet clinical need to predict aneurysm growth and rupture more accurately so that surgeons can better target preventative potentially life-saving surgery. We have developed a novel magnetic resonance imaging method that is based upon the known biological processes underlying aneurysm expansion and rupture. For the first time, this study proposes to assess this novel approach to identify aneurysms that are likely to expand more rapidly and potentially rupture. This technique would provide potentially important additional information to the current simplistic gold-standard of ultrasound measurement of aneurysm diameter.

The primary objective of the study is to determine whether mural uptake of ultrasmall supermagnetic particles of iron oxide (USPIO) provides incremental risk prediction in addition to standard risk markers such as aneurysm diameter, smoking and blood pressure.

The secondary objectives is for patients under surveillance for abdominal aortic aneurysms, to determine whether mural uptake of USPIO:
1. Correlates with the rate of aneurysm expansion
2. Occurs more commonly in patients who progress to surgery or whose aneurysm subsequently ruptures
3. Co-localises with, or relates to, areas of biomechanical stress
4. Occurs in a reproducible manner

This study will investigate other inter-related mechanisms associated with aneurysm growth. It will specifically explore the added value of biomechanical stress modeling as we suspect co-localisation of both USPIO uptake and areas of high mechanical stress could act synergistically and cause more marked aneurysm growth. It will also examine correlates with other blood biomarkers including regulators of extracellular matrix turnover (such as matrix metalloproteinases and tissue inhibitors of metalloproteinases) and vascular inflammation (such as C-reactive protein and interleukin-6).

Ethics approval required
Old ethics approval format

Ethics approval(s)
East of Scotland Ethics Research Service REC 1 (EoSRES REC 1), 28/08/2012, ref: 12/ES/0068

Study design
Prospective observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Screening

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

Health condition(s) or problem(s) studied
Abdominal Aortic Aneurysm

Interventions
All patients will have a full formal and standardized clinical assessment at the first study visit that will include history, examination, documentation of cardiovascular risk factor profile (smoking status, family history, hypertension, hyperlipidaemia, diabetes mellitus) and concomitant medications (antihypertensive medication, etc). This assessment will be updated at each clinic attendance (standard clinical care is 6 monthly appointments).

Blood pressure, pulse wave analysis and velocity will be performed at the first and last study visit. In Edinburgh, patients will undergo these investigations at each 6 monthly appointment.

Pulse wave velocity involves the blood flow in the artery in the neck and the artery in the groin being checked using a noninvasive probe and the distance between the 2 sites recorded. Pulse wave analysis involves the blood flow in the artery in the arm being assessed, again with a noninvasive probe.

Blood samples:
Blood samples (20 mL on each visit) will be collected at the first and last study visits. Patients recruited from Edinburgh will have blood samples collected every 6 months for analysis of markers of inflammation in the blood.

Ultrasound of the abdominal aorta
Patients will undergo 6 month ultrasound imaging as part of standard care for the surveillance programme to measure the maximal anteroposterior diameter of the aneurysm.

Computed tomography (CT) of the abdominal aorta:
CT scans will occur at the first study visit and at 24 months. In cases where study participants undergo emergency repair of a ruptured abdominal aortic aneurysm then a CT scan may not be performed.

Magnetic resonance imaging (MRI) of the abdominal aorta
Magnetic resonance imaging will be conducted and Ferumoxytol administered at the first study visit. 24-36 hours after administration of Ferumoxytol a repeat MRI scan will be performed. The MRI scanning protocol will be completed prior to the procedure.

Analysis of tissue from the abdominal aortic wall
Patients recruited in Edinburgh who undergo elective repair of their abdominal aortic aneurysm will have tissue sampled from the discarded part of the aneurysm. This tissue will be stored and analysed for mechanical testing and then discarded in accordance with the human tissue act.

Duration of appointments
The first study visit is expected to take 34 hours. 6 monthly appointments for ultrasound scans are part of routine clinical care. The final CT scan at 2 years will take 30 minutes.

Follow up
Patients will be recruited over an 18 month period and followed up for 24 months.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
The composite of aneurysm rupture or aortic aneurysm repair

Secondary outcome measures
1. The rate of aneurysm rupture
2. The rate of surgical repair of the aneurysm
3. Aneurysm growth rate
4. All-cause and aneurysm-related mortality
5. We will conduct exploratory analyses examining the interactions between mural USPIO uptake, biomechanical stress, clinical risk factors and serum biomarkers of extracellular matrix turnover and inflammation.

Clinicians involved directly with patient surveillance and care will be blinded to the magnetic resonance imaging findings of mural USPIO uptake.

Overall study start date
07/09/2012

Completion date
07/09/2016

Eligibility

Key inclusion criteria

1. Abdominal aortic aneurysms measuring ≥40 mm in anteroposterior diameter on ultrasound scanning
2. Age ≥40 years. Patients with abdominal aortic aneurysms less than 40 years may have a connective tissue disorder and a different aetiology to their disease

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
350

Total final enrolment
342

Key exclusion criteria
1. Patients expected to, or already received, imminent elective or emergency surgical or endovascular repair
2. Contraindication to magnetic resonance imaging scanning identified from magnetic resonance imaging safety questionnaire
3. Patients refusing or unable to give informed consent
4. Woman with child-bearing potential and who are breastfeeding will not be enrolled into the trial (woman who have experienced menarche, are pre-menopausal, have not been sterilised or who are currently pregnant)
5. Intercurrent illness including patients with a systemic inflammatory disorder or underlying malignancy (life expectancy < 2 years)
6. Renal dysfunction (eGFR ≤30 mL/min/1.73m2)
7. Polycythemia
8. Contraindication to ferumoxytol (evidence of known iron overload, hemochromatosis, known hypersensitivity to ferumoxytol or its components or anaemia not caused by iron deficiency)
9. Contraindication to Iodine

Date of first enrolment
07/09/2012

Date of final enrolment
07/09/2016

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
University of Edinburgh
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Sponsor information

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Sponsor type
University/education

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ROR
https://ror.org/01nrxwf90

Funder(s)

Funder type
Research council

Funder Name
Efficacy and Mechanism Evaluation Programme (MRC UK) ref: 11/20/03

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, EME

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/06/2016		Yes	No
Results article	results	29/08/2017		Yes	No
Results article	results	06/02/2018	16/07/2019	Yes	No
Results article		09/10/2019		Yes	No
HRA research summary			28/06/2023	No	No