Fenofibrate in the management of AbdoMinal aortic anEurysm (FAME): study protocol for a randomised controlled trial

Sophie E. Rowbotham 1,2, Doug Cavaye 3, Rene Jaeggi 4,5, Jason S. Jenkins 6, Corey S. Moran 4,5, Joseph V. Moxon 4,5, Jenna L. Pinchbeck 4,5, Frank Quigley 7, Christopher M. Reid 8,9 and Jonathan Golledge 4,5,10*

Abstract

Background: Abdominal aortic aneurysm (AAA) is a slowly progressive destructive process of the main abdominal artery. Experimental studies indicate that fibrates exert beneficial effects on AAAs by mechanisms involving both serum lipid modification and favourable changes to the AAA wall.

Methods/design: Fenofibrate in the management of AbdoMinal aortic anEurysm (FAME) is a multicentre, randomised, double-blind, placebo-controlled clinical trial to assess the effect of orally administered therapy with fenofibrate on key pathological markers of AAA in patients undergoing open AAA repair. A total of 42 participants scheduled for an elective open AAA repair will be randomly assigned to either 145 mg of fenofibrate per day or identical placebo for a minimum period of 2 weeks prior to surgery. Primary outcome measures will be macrophage number and osteopontin (OPN) concentration within the AAA wall as well as serum concentrations of OPN. Secondary outcome measures will include levels of matrix metalloproteinases and proinflammatory cytokines within the AAA wall, periaortic fat and intramural thrombus and circulating concentrations of AAA biomarkers.

Discussion: At present, there is no recognised medical therapy to limit AAA progression. The FAME trial aims to assess the ability of fenofibrate to alter tissue markers of AAA pathology.

Trial registration: Australian New Zealand Clinical Trials Registry, ACTRN12612001226897. Registered on 20 November 2012.

Keywords: Abdominal aortic aneurysm, Fenofibrate, Clinical trial, Osteopontin, Macrophage

Background

An abdominal aortic aneurysm (AAA) is defined as a progressive dilation of the infrarenal aorta, and is associated with a risk of fatal rupture which increases at larger AAA diameters [1, 2]. The incidence of AAA increases with advancing age, with approximately 5% of men and approximately 1% of women aged over 65 years having an AAA [3–7]. Other risk factors include smoking, hypertension, Caucasian ethnicity and a positive family history [8, 9]. Small AAAs (30–54 mm in diameter) are typically asymptomatic and may be detected as an incidental finding on imaging performed for other purposes, or as a pulsatile abdominal mass on routine physical examination. AAA screening programmes using ultrasound have been introduced in the United Kingdom, the United States and Sweden and are expected to reduce aneurysm-related mortality [10–13]. There is no recognised medical therapy for AAAs, with current management comprising regular ultrasound surveillance, until a diameter threshold is reached (typically 55 mm), at which point surgical repair is considered as the risk of aortic rupture is considered to be high for most patients [14].

Identification of an effective drug therapy to limit AAA progression would represent a significant advancement in clinical management. Clinical trials in humans have yet to report convincing benefit of any tested agent in slowing AAA growth [15–18]. However, preclinical
studies continue to hold promise. Studies employing two rodent models reported that the peroxisome proliferator activator alpha (PPARα) ligand fenofibrate can reduce AAA development [19, 20]. Notably, in one study, fenofibrate-mediated protection against AAA formation was associated with the concomitant reduction of the proinflammatory protein osteopontin (OPN) and reduced recruitment of macrophages to the aortic wall [19]. Osteopontin (OPN) is a phosphorylated acidic glycoprotein that is implicated in many processes integral to AAA development including inflammation, proteolysis and atherosclerosis [21–26]. OPN deficiency has been shown to protect against AAA formation in angiotensin-II-infused apolipoprotein-e-deficient mice [27], and serum OPN has been shown to be independently associated with AAA presence and growth in humans [28]. Of significant importance to the development and progression of AAA in experimental models is the ability of OPN to promote macrophage accumulation within the aorta [27, 29]. Macrophages are implicated in aortic destruction as a result of the production of a range of proteolytic enzymes, such as matrix metalloproteinases (MMPs) [30], and marked macrophage infiltration is a consistent feature of human AAA [31].

PPARα ligands have been shown to downregulate OPN expression in human macrophages in vitro [32]. Fibrates are well-known PPARα ligands and are indicated in the treatment of hypertriglyceridaemia [33]. Previous studies in rodent models suggest that fenofibrate downregulates OPN expression in hypertrophied left ventricle and dysfunctional renal cells [34, 35]. Furthermore, treatment of diabetic patients with bezafibrate for 4 weeks has been shown to reduce circulating concentrations of OPN by approximately 40% [32]. The ability of fenofibrate to downregulate OPN may be critical in reducing macrophage infiltration and the associated release of proteolytic enzymes, thus potentially limiting AAA expansion. Additionally, fenofibrate is known to elevate serum high-density lipoprotein (HDL) which has been associated with protection from AAA [31].

Collectively, the above findings lead to the hypothesis that a short course of fenofibrate will exert beneficial effects on AAA by mechanisms involving both serum lipid modification and favourable changes to the AAA wall. The aim of the current study is to assess the effect of fenofibrate taken daily for a minimum of 2 weeks in participants scheduled for elective open AAA repair. This group of patients is particularly suitable since the AAA will be replaced with a prosthetic graft enabling the AAA wall and thrombus to be removed for biological assessment. The primary aim of the study is to determine whether fenofibrate will reduce the relative number of AAA-wall macrophages, reduce the relative concentration of AAA-wall OPN and also reduce the serum concentrations of OPN. The effect of fenofibrate on secondary parameters, including inflammatory cell (neutrophils, B-and T-lymphocytes) number, MMPs and proinflammatory cytokines within the AAA wall, periaortic fat and intramural thrombus, and circulating concentrations of AAA biomarkers, including osteoprotegerin, resistin, D-dimer and fasting lipids, will also be assessed [31, 36–38].

Methods/design
Study design and participants
Fenofibrate in the management of Abdominal aortic aneurysm (FAME) is a multicentre, randomised, double-blind, placebo-controlled clinical trial to assess the effect of orally administered therapy with fenofibrate on key pathological markers of AAA in patients undergoing open AAA repair. The trial will be conducted at four sites in Australia: The Royal Brisbane and Women’s Hospital, Brisbane; The Holy Spirit Northside Private Hospital, Brisbane; The Townsville Hospital, Townsville and The Mater Hospital, Townsville. The trial will be reported according to the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) (see Additional files 1 and 2). Only research personnel who are directly involved in the recruitment and data collection aspect of the study will have access to patients’ personal details. All Case Report Forms (CRFs), source documentation and samples will be stored de-identified where personal information has been removed and coded with a study number.

The FAME trial will include participants recruited from specialist vascular outpatient clinics who have an asymptomatic infrarenal AAA with a maximum orthogonal diameter ≥50 mm. FAME will not include individuals who require emergency or urgent AAA repair due to the requirement for a minimum 2 weeks of treatment with trial medication prior to surgery. Furthermore, participants will only be included if it is determined that they have a high likelihood of treatment compliance according to the treating physician or local study coordinator. Additional exclusion criteria include current treatment with fibrates, known contraindications to fenofibrate treatment and previous aortic surgery. A full list of inclusion and exclusion criteria is given in Table 1.

Randomisation and follow-up
The overall design of the FAME trial is shown in Fig. 1. At the initial visit, potential participants booked for an elective open repair of an AAA will be assessed against the eligibility criteria (Table 1) and, if appropriate, informed consent will be obtained. Individuals will undergo a medical examination, resting blood pressure and heart rate assessments, and collection of blood samples for measurement of full blood count (haemoglobin, white cell count, platelets, neutrophils, lymphocytes, monocytes,
eosinophils, basophils), urea and electrolytes (sodium, potassium, creatinine, estimated glomerular filtration rate, urea, chloride, bicarbonate), liver function tests (Albumin, total bilirubin, alanine transaminase, aspartate aminotransferase, gamma-glutamyl transpeptidase, lactate dehydrogenase), fasting lipids (cholesterol, triglyceride, HDL cholesterol, low-density lipoprotein (LDL) cholesterol), fasting glucose and C-reactive protein. Serum, plasma and whole blood will also be collected for the later assessment of circulating concentrations of protein (such as cytokines) and genetic (deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)) markers. Investigational blood samples will be collected into the following tubes: 2 × 5-mL SST, 2 × 4-mL EDTA tubes, 1 × 4-mL sodium citrate tube and 1 × 2.5-mL PaxGene tube. Blood samples will be processed according to site-specific standard operating procedures (SOPs) and shipped to the study centre in Townsville. Eligible participants will be randomised to receive 145 mg fenofibrate or placebo, administered once a day for a minimum of 2 weeks directly prior to surgery, in a parallel-group design. Randomisation to fenofibrate or placebo will be stratified by study centre. Random allocation sequences will be computer-generated by a statistician and provided to each study centre’s clinical trial pharmacist, ensuring both investigators and participants are blinded to drug assignment. Trial medication will be allocated and dispensed by the local study centre’s clinical trials pharmacist. Allocation concealment will be achieved by using identical packaging of the intervention and placebo. In the case of an emergency situation where breaking of the group allocation blinding would be required, the local study centre clinical trial pharmacist will be contacted. To facilitate compliance, participants will be provided with the phone number of the local study coordinator with instructions to contact them in the event of possible medication-related problems or consideration of discontinuation. In this event arrangements will be made for the participant to be reviewed by the study physician to ascertain whether discontinuation is required.

Table 1 Patient eligibility criteria

| Inclusion criteria                                                                 | Exclusion criteria                  |
|-----------------------------------------------------------------------------------|-------------------------------------|
| Ability to provide written informed consent                                      | Currently taking fenofibrate or related fibrates |
| Diagnosis with an asymptomatic AAA which is infrarenal in location and measures ≥50 mm on CTA | Contraindication to fenofibrate treatment: |
| Scheduled for an elective open repair of an AAA                                   | - Liver impairment as demonstrated by abnormal AST or ALT tests (>1.5 × ULN) |
| High likelihood of medication compliance within the 2-week period prior to surgery | - Renal impairment as demonstrated by an elevated serum creatinine level (>150 μM) |
|                                                                                    | - Symptomatic gallbladder disease    |
|                                                                                    | - Previous reaction to any lipid-modifying medication |
|                                                                                    | - Previous infrarenal abdominal aortic surgery |
|                                                                                    | - Mycotic AAA                        |
|                                                                                    | - Requirement for emergency or urgent open AAA repair |
|                                                                                    | - Current participation in another drug trial |

CTA computed tomographic angiography, AAA abdominal aortic aneurysm, AST aspartate aminotransferase, ALT alanine transaminase, ULN upper limit of normal
On the day of surgery, further blood samples will be collected (as per initial visit). Adverse and clinical events will be recorded, changes to usual medication noted, and compliance with the study drug regimen analysed by capsule counting. During open surgery, biopsies will be taken from the following sites: (1) subcutaneous fat at the incision site, (2) periaortic fat near the AAA, (3) AAA neck, (4) AAA body (opposite the inferior mesenteric artery) and (5) AAA thrombus. To preserve RNA and protein integrity, tissue samples will be collected into liquid nitrogen immediately upon harvest for subsequent genetic and protein analysis. An additional AAA body sample will be collected and immediately stored in 10% (v/v) paraformaldehyde and wax-embedded for immunohistochemical analysis. All collection of tissues will be performed according to site-specific SOPs and shipped to the study centre in Townsville.

Outcome assessment
Outcome assessment will be performed at the study centre in Townsville on the tissue and blood samples collected. All outcome assessment will be conducted by scientists blinded to the treatment allocation of the participants.

Primary outcome assessment
To assess AAA-wall macrophage number, serial cryostat sections 7 μm thick will be cut from each AAA wall sample for subsequent macrophage staining, as previously described [19]. All samples will be stained simultaneously using identical reagents and incubation times. Serial frozen sections will be air-dried, fixed in acetone for 10 min at −20 °C, air-dried and rehydrated with phosphate-buffered saline (PBS) before being incubated in 3% H2O2/0.1% sodium azide/PBS to block endogenous peroxidase. For macrophage detection, sections will be blocked in 2% (v/v) normal goat serum in PBS followed by staining using pan-macrophage antibody (Abcam) and goat anti-rat HRP (Chemicon). An IgG (Sigma) will be used as isotype control. Slides will be incubated in the peroxidase substrate 3,3′-diaminobenzidine (ImmPACT DAB, Vector Laboratories), counterstained in Mayer’s haematoxylin, dehydrated, cleared in xylene and mounted in Depex mounting medium. Stained sections will be photographed using a Leica BMLB microscope fitted with a SPOTTM CCD Camera (Diagnostic Instruments, Inc., Sterling Heights, MI, USA) and digital images captured to a PC supported with SPOT32TM software (version 2.1.2; Diagnostic Instruments, Inc., Sterling Heights, MI, USA). Identical exposure times and settings will be used for sections. Image analysis will be performed on digital tiff images using Adobe Photoshop CS6 Extended software. For each section, the total tissue area and area of macrophage staining will be measured using the ‘Selection Tool’ and ‘Record Measurements’ functions. Macrophage staining will be expressed as macrophage number and also as a percentage of total tissue area.

AAA-wall OPN will be determined using an enzyme-linked immunosorosent assay (ELISA) and immunohistochemistry. For determination by ELISA, protein will be extracted from individual frozen AAA wall biopsies by homogenising in buffer (10 mM cacodylic acid, 60 mM L-arginine, 0.25% (v/v) Triton x-100 in PBS, pH 7.2) and centrifuging at 18,000 × g for 20 min. Supernatant protein will be quantified by the Bradford technique (Protein Assay, Bio-Rad, Hercules, CA, USA). OPN concentration will be measured by ELISA (Quantikine, R&D Systems for OPN) and expressed as pg/mg of protein. Excellent reproducibility of similar assays has previously been reported [39]. For determination by immunohistochemistry, slides will be incubated in 2% (v/v) normal goat serum (Vector Laboratories) in PBS and endogenous avidin and biotin-blocked using an Avidin/Biotin blocking kit (Vector Laboratories), then 2 μg/mL rabbit anti-human OPN (Immuno Biological Laboratories), biotinylated goat anti-rabbit IgG (Vector Laboratories) and Vectastain Elite ABC-HRP. Rabbit IgG (Vector Laboratories) will be used as isotype control antibody.

Serum OPN concentration will be measured using blood collected from participants following an overnight fast. Serum will be stored at −80 °C until later batch assessment using ELISA according to the manufacturer’s instructions, and expressed as ng/mL (R&D Systems). This assay has previously demonstrated excellent intra- and inter-assay reproducibility [39].

Secondary outcome assessment
Additionally, inflammatory cells (neutrophils, B- and T-lymphocytes), MMPs and proinflammatory cytokines will be assessed by immunohistochemistry and ELISA as previously described [40, 41]. Circulating concentrations of other AAA biomarkers, including osteoprotegerin, resistin, D-dimer and fasting lipids, will be assessed by ELISA and automated assays as previously described [31, 36–38]. Whole genome microarrays and real-time polymerase chain reaction will be used to examine gene expression levels based on findings from ongoing expression arrays and biomarker studies.

Study population and power calculation
Estimated outcomes for the control group are based on assessments performed in human AAA biopsies or blood samples from previous studies [28, 32, 42–44]. Estimated effect sizes for fenofibrate therapy are based on previous rodent and human studies, and the consideration of outcomes likely to be required for clinical efficacy [19, 28, 32, 42–44]. To significantly influence the natural
history of aortic destruction, it is estimated that a reduction in all primary outcomes assessed within AAA biopsies of at least 50% is likely to be required. In a rodent model, 4 weeks’ treatment with fenofibrate reduced aortic OPN concentration and macrophage infiltration by a median of 95% and 70%, respectively, suggesting that this treatment effect size is realistic [19]. For serum OPN, it has previously been reported that a fibrate reduced circulating OPN concentration by approximately 40% after 4 weeks of treatment [32]. Based on these data, the estimated mean values for control and treatment groups were calculated and are given in Table 2. Sample sizes were calculated using GPower3.1, based on a t test as the statistical analysis test. Since there are three primary outcomes, alpha was set at .017, adjusted from .05 for multiple testing. Sample size was estimated based on a power of 80% and equal numbers of participants in each treatment arm. As a result, 20 participants receiving fenofibrate and 20 participants receiving placebo are required. Assuming a dropout rate of 5%, a total of 42 participants will be required.

Safety

Participant safety will be assessed prior to the administration of the medication and at the end of the study period. At the initial visit, a consultation with a physician will occur, during which the participant will be informed about known side effects including symptoms of abdominal/back pain, chest pain, and renal and liver dysfunction. Pathology tests consisting of full blood count, fasting lipids, glucose, inflammation markers, liver and renal function will be performed. The participant will undergo a physical assessment which will include blood pressure and heart rate measurements that will be reviewed by a physician along with the results of pathology tests prior to randomisation. At the final visit, pathology tests as per the initial visit will be performed and reviewed by a physician. Any adverse event will be reported to the coordinating centre and carefully monitored throughout the study. Serious adverse events (SAEs) will be defined as death, requirement for inpatient hospital treatment and persistent or significant disability. All SAEs will be reported by the site principle investigator to the HREC and reviewed by the chief principle investigator, where a decision regarding withdrawal of trial medication will be made. Where a decision to withdraw trial medication is made, participants will be encouraged to remain on the study protocol. Previous studies suggest that fenofibrate is a relatively safe medication [45, 46]. Participants who are concurrently on warfarin will have two additional safety assessments after randomisation. Current routine care for patients on warfarin involves ongoing measurement of International Normalised Ratio (INR) levels, which in turn dictates the dose of medication required to manage clotting without increasing the risk of excessive bleeding. Participants will be instructed to have their INR concentrations assessed via their usual system at 3–5 days and again at 14–21 days post first dose so that warfarin dosage may be adjusted accordingly.

Data management and analysis

Trial documentation including protocols, SOPs and CRFs will be shared electronically with participating study centres. Protocol amendments will be submitted to the Royal Brisbane and Women’s Hospital HREC and local site research governance offices and disseminated to the relevant parties at each study site. Data recorded on printed CRFs will be scanned to the study centre in Townsville where it will be entered centrally and examined for data quality. This will allow confirmation of entry criteria and collection of set entry and outcome data. Examples of important baseline data which will be collected include age, gender, presence of diabetes and/or dyslipidaemia, concurrent medications and maximum aortic diameter. At completion of the trial the database will be checked for errors and data confirmed with source documentation where required. Analysis of primary and secondary endpoints will be based on intention-to-treat at the time of randomisation. All participants who meet the eligibility criteria, provide written informed consent and are enrolled in the study will be included in the primary analysis, regardless of adherence to medication allocation.

To identify potential confounders, collected clinical and demographic data will be compared between groups via univariate statistics. The distribution of all continuous data variables will be assessed for normality using the Kolgorov-Smirnov test. Normally distributed continuous variables will be compared between test groups via t test; non-normally continuous distributed variables will be compared between groups using the Mann-Whitney U test. Nominal data will be compared using the chi-squared test. Characteristics showing a p value < 0.100 on univariate tests will be considered as potential confounders and will be entered as covariates in subsequent

| Primary outcome                                      | Measurement method | Estimated outcomes Placebo | Estimated outcomes Fenofibrate |
|-----------------------------------------------------|--------------------|----------------------------|-------------------------------|
| AAA-wall OPN concentration (pg/mg)                  | ELISA              | 210 ± 145                  | 84 ± 87                       |
| AAA-wall macrophages (per mm² section)              | IHC                | 4.9 ± 1.8                  | 2.4 ± 1.8                     |
| Serum OPN concentration (ng/mL)                     | ELISA              | 77 ± 32                    | 46 ± 32                       |

AAA abdominal aortic aneurysm, ELISA enzyme-linked immunosorbent assay, IHC immunohistochemistry, OPN osteopontin
binary logistic regression models assessing the association of each of the outcome measures with treatment allocation. Following binary logistic regression, the association of all covariates with treatment allocation will be reported as odds ratios and 95% confidence intervals. For all analyses, \( p \) values <0.05 will be considered to be significant. Data will be published in a peer-reviewed journal with copies of the paper available to participants if required.

### Discussion

The estimated global prevalence rate of AAA per 100,000 in 2010 has been reported to range from approximately 8 in individuals aged 40–44 years to approximately 2,275 in individuals aged 75–79 years [47]. Prevalence is reported to be higher in developed versus developing nations, and in 2010 was highest in Australasia [47]. The global death rate due to AAA per 100,000 has been reported to have increased from 2.49 in 1990 to 2.78 in 2010, with the highest mean death rate found to occur in Australasia [48]. At present there is no known effective medical therapy to limit AAA progression, and large randomised trials have failed to provide evidence that early elective endovascular repair (EVAR) or open surgery for patients with AAAs measuring 40–54 mm reduces mortality [49–52]. Current management of patients with small AAAs involves regular repeat imaging since most small AAAs slowly increase in size, with approximately 70% of 40–54-mm AAAs requiring surgical repair [49–53]. AAA surgery is associated with significant mortality (1–5%) and perioperative complications (approximately 20%) [50, 52, 54, 55]. Whilst EVAR has gained popularity in recent years due to reduced length of inpatient stay and reduced intensive care unit admissions, total hospital costs are significantly greater than those associated with open repair (approximately AUS$23,000 versus approximately AUS$18,500 for preoperative, operative, postoperative and 1-year follow-up costs) in part due to the requirement for lifelong surveillance and the high rate of need for reintervention [54].

In the current study the effect of a promising new medical therapy will be assessed to determine whether a short course of fenofibrate will inhibit AAA-OPN expression and associated macrophage-based inflammation, whilst inducing other potential beneficial effects such as raising HDL.

### Trial status

At the time of submission, recruitment was ongoing.

### Additional files

Additional file 1: SPIRIT 2013 Checklist. (DOC 122 kb)
Additional file 2: SPIRIT figure. Schedule of enrolment, interventions and assessments. (DOC 60 kb)

### Abbreviations

AAA: Abdominal aortic aneurysm; ALT: Alanine transaminase; AST: Aspartate aminotransferase; CRF: Case Report Form; CT: Computed tomographic angiography; ELISA: Enzyme-linked immunosorbent assay; EVAR: Endovascular repair; FAME: Fenofibrate in the management of Abdominal aortic aneurysm; HDL: High-density lipoprotein; HREC: Human Research Ethics Committee; MMP: Matrix metalloproteinase; NHMRC: National Health and Medical Research Council; OPN: Osteopontin; PPARα: Peroxisome proliferator activator alpha; SAEC: Serious adverse event; SOP: Standard operating procedure; SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials; ULN: Upper limit of normal

### Acknowledgements

The authors would like to acknowledge the following vascular consultants: Dr. Allan Kruger, Dr. Nicolas Boyne, Dr. Simon Quinn, Dr. Danella Favot and Dr. Murray Ogg from the Royal Brisbane and Women’s Hospital; and Dr. Ramesh Velu and Dr. Nile Allaf from The Townsville Hospital.

### Funding

This trial is funded by project grants from the National Health and Medical Research Council (NHMRC) of Australia (102095S) and a Centre of Research Excellence grant from the NHMRC of Australia (1000967). JG holds a Practitioner Fellowship from the NHMRC, Australia (1019921) and a Senior Clinical Research Fellowship from the Queensland Government. CMR holds a Senior Research Fellowship from the NHMRC (1045862). The sponsors had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript.

### Availability of supporting data

Not applicable.

### Authors’ contributions

The protocol for the trial was developed by JG, CM and PW who were investigators on the funding application. CR participated in the design of the trial. JM will lead the data analysis. SR and JP are the site coordinators. RJ is responsible for management of the trial across all sites. The paper was written based on the protocol by SR and edited by all other authors. The site principal investigators are JG (The Townsville Hospital), JJ (The Royal Brisbane and Women’s Hospital), DC (The Holy Spirit Northside Private Hospital) and FQ (The Mater Medical Centre). All authors read and approved the final manuscript.

### Competing interests

The authors declare that they have no competing interests.

### Consent for publication

Not applicable.

### Ethical approval and consent to participate

The protocol (version 6.1, dated 3 November 2015) was approved by: the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC) for the Royal Brisbane and Women’s Hospital and The Townsville Hospital sites (HREC/10/QRBW/421); the St. Vincent's Health and Aged Care HREC for the Holy Spirit Northside Hospital (HREC/13/SVHAC/04); and the Mater Health Services Townsville HREC for The Mater Hospital, Townsville (HREC/MH520110101-01). The trial will be conducted in agreement with the principles of the Declaration of Helsinki. All participants will be informed about the purpose of the trial, the risks and benefits, and written informed consent will be obtained by the local study coordinator prior to entry into the trial.

### Notes

Professor Philip J Walker, who was an investigator on the funding application for the FAME trial and helped to develop the protocol, is now deceased.

### Author details

1The University of Queensland, School of Medicine, Herston, QLD 4006, Australia. 2Department of Vascular Surgery, The Royal Brisbane and Women’s...
References

1. Khosla S, et al. Meta-analysis of peak wall stress in ruptured, symptomatic and intact abdominal aortic aneurysms. Br J Surg. 2014;101(11):1530–7. discussion 1537.
2. Moxon JV, et al. Diagnosis and monitoring of abdominal aortic aneurysm: current status and future prospects. Curr Probl Cardiol. 2010;35(10):512–48.
3. Ashton HA, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet. 2002;360(9345):1531–9.
4. Ashton HA, et al. Fifteen-year follow-up of a randomized clinical trial of ultrasonographic screening for abdominal aortic aneurysms. Br J Surg. 2007;94(6):696–701.
5. Lindholm JS, et al. Screening for abdominal aortic aneurysms: single centre randomised controlled trial. BMJ. 2005;330(7494):750.
6. Norman PE, et al. Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm. BMJ. 2004;329(7477):1259.
7. Scott RA, Bridgewater SG, Ashton HA. Randomized clinical trial of screening for abdominal aortic aneurysm in women. Br J Surg. 2000;89(3):283–5.
8. Chakof EL, et al. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg. 2009;50(4):880–96.
9. Moll FL, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:558–8.
10. NHS Abdominal Aortic Aneurysm Screening Programme 2011–2012. Available from: http://www.screening.nhs.uk/getdata.php?id=1362. Accessed 1 June 2016.
11. SAAVE Act Background [22 June 2016]. Available from: www.vascularweb.org/healthpolicyandgovernmentrelations/Pages/saave-act-background.aspx. Accessed 1 June 2016.
12. Force, U.S.P.S. Screening for abdominal aortic aneurysm: recommendation statement. Ann Intern Med. 2005;143(2):198–202.
13. Wanhainen A, Block M. The Swedish experience of screening for abdominal aortic aneurysm. J Vasc Surg. 2011;53(4):1164–5.
14. Roose TW, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;58(19):2020–45.
15. Golledge J, Norman PE. Current status of medical management for abdominal aortic aneurysm. Atherosclerosis. 2011;217(1):57–63.
16. Meijer CA, et al. Doxycycline for stabilization of abdominal aortic aneurysms: a randomized trial. Ann Intern Med. 2013;159(2):185–23.
17. Propanolol Aneurysm Trial I. Propanolol for small abdominal aortic aneurysms: results of a randomized trial. J Vasc Surg. 2002;35(1):72–9.
18. Rughani G, Robertson L, Clarke M. Medical treatment for small abdominal aortic aneurysms. Cochrane Database Syst Rev. 2012;CD009536.
19. Golledge J, et al. Peroxisome proliferator-activated receptor ligands reduce aortic dilatation in a mouse model of aortic aneurysm. Atherosclerosis. 2010;210(1):51–6.
20. Krishna SA, et al. Fenofibrate increases high-density lipoprotein and sphingosine 1 phosphate concentrations limiting abdominal aortic aneurysm progression in a mouse model. Am J Pathol. 2012;181(2):706–18.
21. Denhardt DT, et al. Osteopontin as a means to cope with environmental insults: regulation of inflammation, tissue remodeling, and cell survival. J Clin Invest. 2001;107(9):1055–61.
22. Golledge J, et al. Osteoprotegerin and osteopontin are expressed at high concentrations within symptomatic carotid atherosclerosis. Stroke. 2004;35(7):1636–41.
23. Isoda K, et al. Osteopontin transgenic mice fed a high-cholesterol diet develop early fatty-streak lesions. Circulation. 2003;107(5):679–81.
24. Lai CF, et al. An osteopontin-NADPH oxidase signaling cascade promotes pro-matrix metalloproteinase 9 activation in aortic mesenchymal cells. Circ Res. 2006;98(12):1479–89.
25. Matsui Y, et al. Osteopontin deficiency attenuates atherosclerosis in female apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol. 2003;23(6):1029–34.
26. O’Reagan A, Berman JS. Osteopontin: a key cytokine in cell-mediated and granulomatous inflammation. Int J Exp Pathol. 2000;81(6):373–80.
27. Brummer D, et al. Angiotensin II-activated atherosclerosis and aneurysm formation is attenuated in osteopontin-deficient mice. J Clin Invest. 2003;112(9):1318–31.
28. Golledge J, et al. Association between osteopontin and human abdominal aortic aneurysm. Arterioscler Thromb Vasc Biol. 2007;27(3):655–60.
29. Gaviria D, et al. Vitamin E inhibits abdominal aortic aneurysm formation in angiotensin II-infused apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol. 2005;25(8):1671–7.
30. Golledge J, et al. Abdominal aortic aneurysm: pathogenesis and implications for management. Arterioscler Thromb Vasc Biol. 2006;26(12):2605–13.
31. Golledge J, et al. Association between serum lipoproteins and abdominal aortic aneurysm. Am J Cardiol. 2010;105(10):1480–4.
32. Nakamachi T, et al. PPAR-alpha agonists suppress osteopontin expression in macrophages and decrease plasma levels in patients with type 2 diabetes. Diabetes. 2007;56(16):1662–70.
33. Balakumar P, Rohilla A, Mahadevan N. Pleiotropic actions of fenofibrate on the heart. Pharmacol Res. 2011;63(1):8–12.
34. Ichihara S, et al. Attenuation of cardiac dysfunction by a PPAR-alpha agonist is associated with down-regulation of redox-regulated transcription factors. J Mol Cell Cardiol. 2006;41(2):318–29.
35. Park CW, et al. Accelerated diabetic nephropathy in mice lacking the peroxisome proliferator-activated receptor alpha. Diabetes. 2006;55(4):885–93.
36. Golledge J, et al. Obesity, adipokines, and abdominal aortic aneurysm: Health in Men study. Circulation. 2007;116(20):2275–9.
37. Golledge J, et al. Evaluation of the diagnostic and prognostic value of plasma D-dimer for abdominal aortic aneurysm. Eur Heart J. 2011;32(3):354–64.
38. Moran CS, et al. Association of osteoprotegerin with human abdominal aortic aneurysm progression. Circulation. 2005;111(13):3119–25.
39. Clancy P, et al. Assessment of a serum assay for quantification of abdominal aortic calcification. Arterioscler Thromb Vasc Biol. 2006;26(11):2574–6.
40. Clancy P, Koblar S, Golledge J. Involvement of angiotensin II type 1 and 2 receptors in gelatinase regulation in human carotid atheroma in vitro. J Atheroscler Thromb. 2016;23(7):773–91.
41. Lindeman JH, et al. Clinical trial of doxycycline for matrix metalloproteinase-9 inhibition in patients with an abdominal aneurysm: doxycycline selectively depletes aortic wall neutrophils and cytotoxic T cells. Circulation. 2009;119(16):2209–16.
42. Golledge J. et al. The novel association of the chemokine CCL22 with abdominal aortic aneurysm. Am J Pathol. 2010;176(5):2098–106.
43. Golledge J, et al. Reduced expansion rate of abdominal aortic aneurysms in patients with diabetes may be related to aberrant monocyte-matrix interactions. Eur Heart J. 2008;29(10):665–72.
44. Moran CS, et al. Interaction between angiotensin II, osteoprotegerin, and peroxisome proliferator-activated receptor-gamma in abdominal aortic aneurysm. J Vasc Res. 2009;46(3):209–17.
45. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibrin acid derivatives. Am J Med. 1987;83(5B):26–36.
46. Keech A, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9,955 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366(9500):1849–61.
47. Sampson UK, et al. Estimation of global and regional incidence and prevalence of abdominal aortic aneurysms 1990 to 2010. Glob Heart. 2014;9(1):159–70.
48. Sampson UK, et al. Global and regional burden of aortic dissection and aneurysms: mortality trends in 21 world regions, 1990 to 2010. Glob Heart. 2014;9(1):171–80.
49. Cao P, et al. Comparison of surveillance versus aortic endografting for small aneurysm repair (CAESAR): results from a randomised trial. Eur J Vasc Endovasc Surg. 2011;41(1):13–25.
50. Lederle FA, et al. Immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med. 2002;346(19):1437–44.
51. Ouriel K, et al. Endovascular repair compared with surveillance for patients with small abdominal aortic aneurysms. J Vasc Surg. 2010;51(5):1081–7.
52. United Kingdom Small Aneurysm Trial Participants. Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med. 2002;346(19):1445–52.
53. Lindholt JS, et al. Long-term benefit and cost-effectiveness analysis of screening for abdominal aortic aneurysms from a randomized controlled trial. Br J Surg. 2010;97(6):826–34.
54. Hayter CL, et al. Follow-up costs increase the cost disparity between endovascular and open abdominal aortic aneurysm repair. J Vasc Surg. 2005;42(5):912–8.
55. Trial Participants EVAR. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet. 2005;365(9478):2179–86.